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The chemistry of

hydroxyl, ether and peroxide groups

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–C–OH; –C–O–C–; –C–O–O–H(R)

Supplement E2
The chemistry of
hydroxyl, ether and peroxide groups

Edited by

SAUL PATAI

The Hebrew University, Jerusalem

1993

JOHN WILEY & SONS

CHICHESTER–NEW YORK–BRISBANE–TORONTO–SINGAPORE

An Interscience® Publication

Other Wiley Editorial Offices

John Wiley & Sons, Inc., 605 Third Avenue,
New York, NY 10158-0012, USA

Jacaranda Wiley Ltd, G.P.O. Box 859, Brisbane,
Queensland 4001, Australia

John Wiley & Sons (Canada) Ltd, 22 Worcester Road,
Rexdale, Ontario M9W 1L1, Canada

John Wiley & Sons (SEA) Pte Ltd, 27 Jalan Pemimpin #05-04,
Block B, Union Industrial Building, Singapore 2057

Library of Congress Cataloging-in-Publication Data

The chemistry of hydroxyl, ether and peroxide groups / edited by Saul Patai.
p. cm.—(The Chemistry of functional groups. Supplement ; E)
'An Interscience publication.'
Includes bibliographical references and index.
ISBN 0 471 93045 8
1. Hydroxides. 2. Ether. 3. Peroxides. I. Patai, Saul.
II. Series.
QD305.E7C484 1993 92-4325
547'.63—dc20 CIP

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN 0 471 93045 8

Typeset in Thomson Press (India) Ltd, New Delhi, India.
Printed and bound in Great Britain by Biddles Ltd, Guildford, Surrey

This volume is dedicated to my good friend and devoted physician,

Professor Avinoam Zlotnick

'A faithful friend is the medicine of life',
(*Ecclesiasticus*—Ben Sira 6.16)

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Foreword

Supplement E, published in 1980, contained new material relating to chapters which appeared in the main volumes on *The Ether Linkage* (1967), on *The Hydroxyl Group* (1971) and on *The Thiol Group* (1974). Since then, another main volume has been published on an oxygen-containing functional group, namely *The Chemistry of Peroxides* (1983), as well as several other main volumes on sulphur-containing functional groups ($\overset{+}{S}R_3$, SO, SO_2, —SOH, —SOOH, $—SO_3H$). Hence a supplementary volume treating all the above groups together would have been too large and it was decided to include in the present *Supplement E2* only material on the hydroxyl, ether and peroxide groups, while another supplementary volume, *Supplement S*, is already in the press and will deal with sulphur-containing functional groups and will be published, hopefully, in the late summer of 1993.

Unfortunately, several chapters planned for the present volume did not materialize, such as 'Acidity, basicity and complex formation', 'Alcohols, phenols, ethers and peroxides as synthones', 'Thermal decompositions', 'Reaction mechanisms involving peroxides and polyoxides' and, finally and most regrettably, 'Safety and toxicity'. I hope sincerely that these subjects will be dealt with according to their merit in a future supplementary volume.

Jerusalem
November 1992

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 and complex-forming ability.

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

(d) Additional chapters deal with special topics such as electrochemistry, photochemistry, radiation chemistry, thermochemistry, syntheses and uses of isotopically labelled compounds, as well as with biochemistry, pharmacology and toxicology. Whenever applicable, unique chapters relevant only to 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 authors and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, some volumes may be published without giving consideration to the originally planned logical order of the chapters.

Since the beginning of the Series in 1964, two main developments 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, and my sincere thanks are due to all of them. Finally, I wish to render hearty thanks to Professor Zvi Rappoport who, for many years, has shared the work and responsibility of the editing of this Series.

The Hebrew University
Jerusalem, Israel

SAUL PATAI

Contents

List of abbreviations used

Ac	acetyl (MeCO)
acac	acetylacetone
Ad	adamantyl
Alk	alkyl
All	allyl
An	anisyl
Ar	aryl
Bz	benzoyl (C_6H_5CO)
Bu	butyl (also *t*-Bu or Bu^t)
CD	circular dichroism
CI	chemical ionization
CIDNP	chemically induced dynamic nuclear polarization
CNDO	complete neglect of differential overlap
Cp	η^5-cyclopentadienyl
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_3)
Hex	hexyl (C_6H_{13})
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 and Pr^i)
PTC	phase transfer catalysis
Pyr	pyridyl (C_5H_5N)
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 or Ts	tosyl (*p*-toluenesulphonyl)
Trityl	triphenylmethyl (Ph_3C)
Xyl	xylyl ($Me_2C_6H_3$)

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

CHAPTER 1

General and theoretical aspects of the —OH, —O— and —O—O— groups: Integration of theory and experiment

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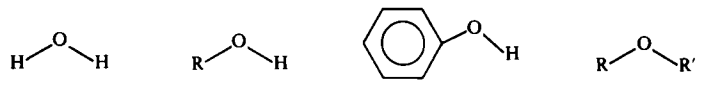
Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

I. INTRODUCTION

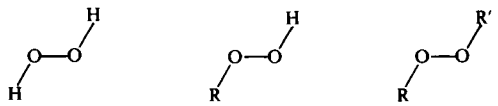
The purpose of this chapter is to discuss recent general and theoretical advances related to the —OH, —O— and —O—O— groups in organic molecules. In previous volumes of this series, they have been discussed separately and/or in conjunction with their sulphur analogues[1-4]. In the present work, our focus is on the single-bonded-oxygen functional groups. Our general theme is the integration of theory and observed chemical behaviour, with the aim of rationalizing the differences that are found in the chemical reactivities of these linkages despite their inherent similarities.

Water (**1**) is the simplest hydroxyl-containing molecule. Alcohols (**2**) and phenols (**3**) are organic derivatives of water in which one hydrogen is replaced by an alkyl group and an aromatic ring, respectively; ethers (**4**) have both hydrogens replaced by organic groups. Derivatives of hydrogen peroxide (**5**) with one and two hydrogens replaced by organic moieties are classified as hydroperoxides (**6**) and peroxides (**7**), respectively. The



(1) (2) (3) (4)

R = alkyl group



(5) (6) (7)

physical properties and chemical reactivities of these compounds are largely determined by: (a) the presence of the single-bonded oxygen(s) with their lone pairs of electrons; and (b) in the case of the OH-containing systems (**1–3, 5, 6**), a relatively labile hydrogen that can participate in hydrogen bonding and/or be replaced. The importance of these factors in determining physical properties is reflected in the boiling points, densities and solubilities listed in Table 1. It can be seen that within groups of compounds of similar molecular weight, the alcohols (and hydroperoxide) invariably have significantly higher boiling points and densities than the hydrocarbons and ethers; the former can act as both hydrogen bond donors and acceptors, and thus have the ability to self-associate in the liquid state. Ethers and peroxides, on the other hand, can only be hydrogen bond acceptors and consequently do not normally self-associate. Their boiling points are similar to those of the aliphatic hydrocarbons of comparable molecular weight. However, the presence of the hydrogen-bond-accepting oxygen in the ethers allows them to dissolve in water to varying degrees, whereas alkanes are insoluble in water (see Table 1).

In this chapter we will address many topics relevant to the understanding of the chemical and physical properties of organic molecules containing the —OH, —OR, —OOH and —OOR groups. First we will consider the roles of electronegativity and charge capacity in determining molecular properties. This will be followed by an overview of theoretical models for obtaining the geometries of these groups, with an emphasis on *ab initio* Hartree–Fock methods. Electrostatic potentials of molecules containing —OH, —OR, —OOH and —OOR will be discussed in relation to chemical reactivity, hydrogen-bonding tendencies and local polarity, and substituent effects will be examined. The relevance of these computed results to the overall chemical behaviour of the systems will be brought out in brief overviews of their reactive properties. An analysis of factors related to the enhanced reactivity of three- and four-membered-ring ethers and peroxides

TABLE 1. Some physical properties of compounds containing single-bonded oxygens[a]

Name	Formula	Mol. wt.	Boiling pt. (°C)	Density ($g\,cm^{-3}$)	Solubility in water
Water	H_2O	18	100	1.00	∞
Ethane	CH_3CH_3	30	−89	[b]	i
Methanol	CH_3OH	32	65	0.791	∞
Hydrogen peroxide	HOOH	34	150	1.442	∞
Propane	$CH_3CH_2CH_3$	44	−42	[b]	i
Ethanol	CH_3CH_2OH	46	78	0.789	∞
Dimethyl ether	CH_3OCH_3	46	−24	[b]	s
Butane	$CH_3(CH_2)_2CH_3$	58	0	[b]	i
Ethyl methyl ether	$CH_3OCH_2CH_3$	60	7	[b]	s
1,2-Ethanediol	$HOCH_2CH_2OH$	62	198	1.12	∞
Ethyl hydroperoxide	CH_3CH_2OOH	62	93–97	0.933	∞
1-Propanol	$CH_3(CH_2)_2OH$	62	97	0.804	v
Isopropanol	$CH_3CHOHCH_3$	62	82	0.786	∞
Pentane	$CH_3(CH_2)_3CH_3$	72	36	0.626	i
Butanol	$CH_3(CH_2)_3OH$	74	118	0.810	s
t-Butyl alcohol	$(CH_3)_3COH$	74	83	0.789	∞
Diethyl ether	$(CH_3CH_2)_2O$	74	35	0.714	s
Hexane	$CH_3(CH_2)_4CH_3$	86	69	0.659	i
Diethyl peroxide	$(CH_3CH_2O)_2$	90	58–59	0.824	δ
Glycerol	$HOCH_2CHOHCH_2OH$	92	290	1.26	∞
Phenol	C_6H_5OH	94	182	1.07	s
Heptane	$CH_3(CH_2)_5CH_3$	100	98	0.684	i
Isopropyl propyl ether	$(CH_3)_2CHO(CH_2)_2CH_3$	102	83	0.747	δ

[a]These properties are taken from: R. C. Weast (Ed.), *Handbook of Chemistry and Physics*, 49th ed., CRC Press, Baton Rouge, 1968. The symbols relating to solubility are as follows: i, insoluble; δ, slightly soluble; s, soluble; v, very soluble; ∞, miscible.
[b]This compound is a gas at normal temperature and pressure.

will be presented. Finally, there will be a brief discussion of the role of the —O— linkage in molecular recognition.

II. ELECTRONEGATIVITY AND CHARGE CAPACITY IN RELATION TO MOLECULAR PROPERTIES

A. General Background

As a starting point for understanding the properties of organic molecules containing single-bonded oxygen-containing linkages, we begin with a discussion of electronegativity and charge capacity. These concepts are particularly important in understanding the molecular properties of oxygen-containing systems.

Pauling first defined electronegativity, χ, as the power of an atom in a molecule to attract electrons to itself[5,6]; since then this defined concept has been widely used to rationalize the rearrangements of electrons when atoms interact to form molecules. In an important development, χ was identified as being related to the electronic chemical

potential[7], μ, as given by equation 1,

$$\chi = -\mu = -\left(\frac{\partial E}{\partial N}\right)_{v(\mathbf{r})} \tag{1}$$

where E and N are the electronic energy and the number of electrons in the system, and $v(\mathbf{r})$ is the nuclear potential.

In view of the very close link between electronegativity and chemical potential, $\chi = -\mu$, it is to be anticipated that the electronegativity should be uniform throughout any molecular system at equilibrium. This has indeed been shown to be true[7-9], confirming the principle of electronegativity equalization that had been postulated much earlier by Sanderson[10,11].

In order for the principle of electronegativity equalization to be fulfilled, the electronegativity of an atom must be a variable function. In writing and using equation 1, it is being assumed that E is differentiable with respect to N, even though N has only integral values for isolated atoms and molecules. The validity of doing so continues to be discussed and analysed[12-20]. As has been pointed out[20], the existence of continuous energy functions $E(N)$ for the various individual atoms can be regarded as a consequence of acknowledging the physical significance of the concept of atoms in molecules, with their associated non-integral numbers of electrons. While there is no unique definition of an atom in a molecule[21-23], the concept is certainly a well-established and extremely useful one.

It is indeed widely assumed to be reasonable and appropriate to write atomic energies as continuous functions of N. These are often taken to be power series of the form[24-31]

$$E(N) = E(N_0) + \alpha(N - N_0) + \beta(N - N_0)^2 + \gamma(N - N_0)^3 + \cdots \tag{2}$$

in which N_0 is the number of electrons corresponding to the neutral atom. (It is clear that the energy could alternatively be written as a function of the net charge Q, where $Q = N_0 - N$.) Equation 2 is equivalent to expanding $E(N)$ in a Taylor series around the point $N = N_0$[20,32-37]:

$$E(N) = E(N_0) + (N - N_0)\left(\frac{\partial E}{\partial N}\right)_{N_0} + \frac{1}{2}(N - N_0)^2\left(\frac{\partial^2 E}{\partial N^2}\right)_{N_0} + \frac{1}{6}(N - N_0)^3\left(\frac{\partial^3 E}{\partial N^3}\right)_{N_0} + \cdots \tag{3}$$

It has been cautioned, however, that these expansions are not necessarily convergent[20,33], and other formulations for $E(N)$ have been proposed[20,31,35,38,39].

From equations 2 and 3, which are most often truncated after the quadratic term[20,21-33,36,37], it follows that

$$\alpha = \left(\frac{\partial E}{\partial N}\right)_{N_0} \tag{4}$$

and

$$\beta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{N_0} \tag{5}$$

From equation 1 and the truncated form of equation 2,

$$\chi = -\left(\frac{\partial E}{\partial N}\right) = -\alpha - 2\beta(N - N_0) \tag{6}$$

Electronegativity expressions analogous to equation 6, sometimes written in terms of the net charge Q, have appeared many times in the past[12,24,26-28,30,36-45]. Replacing α and β in accordance with equations 4 and 5, and recognizing from equation 1 that α

is the negative of the electronegativity of the neutral atom, leads to

$$\chi(N) = \chi(N_0) + (N_0 - N)\left(\frac{\partial^2 E}{\partial N^2}\right)_{N_0} \tag{7}$$

Equation 7 predicts how the electronegativity of an atom will change as it gains or loses electronic charge. Such a relationship makes it possible to apply the principle of electronegativity equalization. It should be noted, however, that equation 7 takes only charge transfer into account; it does not consider, for example, polarization of the atom. Thus equation 7 implies that the atoms in homonuclear molecules have the same electronegativities as they do in the free state (or, that the chemical potential of the molecule is the same as that of the free atoms). Numerical estimates presented earlier indicate that this is not so[46], and data compiled more recently by Parr and Yang[12] lead to the same conclusion.

The quantity $(\partial^2 E/\partial N^2)_{N_0}$ in equation 7 evidently a measure of the responsiveness of an atom's electronegativity (or chemical potential) to a gain or loss of electronic charge. It has been studied extensively and used to interpret a great deal of chemical behaviour, from two different (but related[45]) points of view. Huheey argued that the coefficient of the net charge $(N_0 - N)$ in equation 7 [which had not yet been identified as $(\partial^2 E/\partial N^2)_{N_0}$] is related inversely to the atom's ability to absorb or yield electronic charge, its 'charge capacity', which shall be designated by κ[42,47,48]. Accordingly,

$$\left(\frac{\partial^2 E}{\partial N^2}\right)_{N_0} = \frac{1}{\kappa} \tag{8}$$

Since $\chi(N_0) = -(\partial E/\partial N)_{N_0}$ and $Q = N_0 - N$, equation 8 can also be written in terms of the electronegativity and net charge[45]:

$$\left(\frac{\partial \chi}{\partial Q}\right)_{Q=0} = \frac{1}{\kappa} \tag{9}$$

More recently, Parr and Pearson[49] have proposed that 'hardness', η, which had originally been introduced as a basis for rationalizing a large number of chemical reactions[50,51], be defined as

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{v(\mathbf{r})} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{v(\mathbf{r})} \tag{10}$$

The implications of equation 10 have been explored in a number of studies[2,19,20,31,43,52–62]. For neutral atoms, clearly

$$2\eta = \frac{1}{\kappa} \tag{11}$$

It has been shown that this relationship can be reached without needing to stipulate the functional form of $E(N)$[45].

Inserting equation 8 into equation 7 gives

$$\chi(N) = \chi(N_0) + \frac{N_0 - N}{\kappa} \tag{12}$$

Quantities $\chi(N_0)$ and κ can be assigned values by using the truncated $E(N)$ relationship to represent the atom's first ionization energy I and electron affinity A[12,24–27,31,41,42]. This leads to

$$\chi(N_0) = -\mu(N_0) = \frac{I + A}{2} \tag{13}$$

TABLE 2. Electronegativities, charge capacities and polarizabilities of main group elements

I	II	III	IV	V	VI	VII	Inert gases
Li	Be	B	C	N	O	F	Ne
3.01	<4.66	4.29	6.26	⩽7.27	7.54	10.41	<10.78
0.210	<0.107	0.125	0.100	⩽0.0688	0.0823	0.0713	<0.0464
164	37.8	20.4	11.9	7.42	5.41	3.76	2.67
Na	Mg	Al	Si	P	S	Cl	Ar
2.84	<3.82	3.22	4.77	5.61	6.22	8.29	<7.88
0.218	<0.131	0.181	0.148	0.103	0.121	0.107	<0.0635
159.3	71.5	56.3	36.3	24.5	19.8	14.7	11.1
K	Ca	Ga	Ge	As	Se	Br	Kr
2.42	<3.06	3.1	4.5	5.31	5.89	7.59	<7.00
0.260	<0.164	0.18	0.15	0.111	0.129	0.118	<0.0714
293	168	54.8	41.0	29.1	25.4	20.6	16.7
Rb	Sr	In	Sn	Sb	Te	I	Xe
2.33	<2.85	3.0	4.30	4.85	5.49	6.76	<6.07
0.271	<0.176	0.180	0.164	0.132	0.142	0.135	<0.0824
319	186	(30)	(30)	(27)	(26)	(26)	27

Atom
a
b
c

a: electronegativity, $\chi(N_0)$.
b: charge capacity, κ.
c: polarizability, α (bohr^3)[a].

[a]The values in parentheses have estimated accuracies of only 50%.
Experimental atomic polarizabilities have been taken from T. H. Miller and B. Bederson, *Adv. At. Mol. Phys.*, **13**, 1 (1977).

and

$$\kappa = \frac{1}{I - A} \tag{14}$$

Since there are some problems associated with the $E(N)$ functions, as mentioned above, it is reassuring that equations 13 and 14 can also be obtained within the frameworks of Xα and Hartree–Fock theories[34]. It is noteworthy that equation 13 is identical in form to Mulliken's electronegativity expression[63,64], which he reached by directly considering the energies involved in electron transfer. In Mulliken's formula, however, I and A refer to the valence state of the atom, whereas equations 13 and 14 have more recently often been used with ground-state values[12,39,45,49,65].

κ and η are two ways of viewing one aspect of an atom's response to a gain or loss of electronic charge. It seems intuitively reasonable that they should be closely related to the polarizability of the atom; indeed this was anticipated for κ some years ago[52,53], and it was subsequently confirmed for subgroups of atoms from the first four rows of the perodic table[45]. Since then, with a complete set of data for the main group elements in the first four rows (Table 2), we have found that within each of the vertical columns, charge capacity is linearly related to polarizability, with correlation coefficients ranging from 0.99 to 1.00[66]. There have been several analyses of relationships between charge capacity, polarizability, hardness and other atomic properties[67–70].

B. Atomic and Molecular Properties

Table 2 lists values of $\chi(N_0)$ and κ for the main group elements of the first four rows of the periodic table, obtained via the formulas given in equations 13 and 14 using experimentally determined ionization potentials[71] and electron affinities[72]. The values listed for $\chi(N_0)$ and κ of the group II elements, the inert gases and nitrogen reflect electron affinities given as < 0 ($\leqslant 0$ for nitrogen)[72].

Our purpose in presenting Table 2 is to put into perspective certain unique properties of oxygen in relation to the other main group elements. As can be seen, there is a general trend that as the neutral atom electronegativity $\chi(N_0)$ increases, the charge capacity decreases. (This can of course of predicted from equations 13 and 14 and the fact that I is usually an order of magnitude larger than A.) This trend is closely followed in the vertical columns of the main group elements, and in a general way in the horizontal rows as well, although these do show deviations[66,70]. Also evident in Table 2 is the close relationship between charge capacity and polarizability, mentioned earlier.

There are marked decreases in intrinsic electronegativity and increases in charge capacity in going from first to second row atoms, especially in groups IV–VII and the inert gases. For example, $\chi(N_0)$ decreases from 7.54 to 6.22 in going from oxygen to sulphur, while κ increases from 0.0823 to 0.121, respectively. These changes are important in explaining certain discontinuities that exist in many chemical and physical properties in going from the first to succeeding rows of atoms[66,73–78].

Nitrogen, oxygen and fluorine stand out because of their relatively high intrinsic electronegativities and low charge capacities. These atoms show a pronounced initial tendency to attract electrons; however, this is rapidly balanced by the strong repulsion between their growing electronic populations (which are highly concentrated due to the small sizes of the atoms) and the remaining external electrons in a molecule[79,80]. As a result, nitrogen, oxygen and fluorine do not develop as large negative charges as would be expected simply on the basis of their intrinsic electronegativities; this is evident in both ionic and covalent systems.

The 'anomaly' of the surprisingly low electron affinities of N, O and F can be attributed to the factors mentioned above: their small sizes and charge capacities and the resulting

strong repulsive interactions between their electrons and the added one[79,80]. Thus, the experimentally determined electron affinities of the group VI elements show a gradual increase in going from polonium (1.9 eV) to sulphur (2.07 eV), but then a sharp decrease for oxygen (1.46 eV)[72]. In contrast, the ionization potentials increase monotonically through the same series, including oxygen[71]. For the elements Po–S, there is an excellent linear relationship between electron affinities and ionization potentials[80]. However, oxygen deviates markedly; its electron affinity is 21 kcal mol^{-1} (0.91 eV) lower than what would be predicted by extrapolation[80].

The factors that give rise to anomalously low electron affinities for fluorine, oxygen and nitrogen should cause ionic and covalent bonds involving these elements to be weaker than would be anticipated due to the anomalously strong repulsions between their electrons and those contributed to the bonds by their partners. For ionic and covalent fluorides, the gas-phase dissociation energies are indeed about 26 kcal mol^{-1} lower than would be predicted on the basis of extrapolation from the heavier halides[79]. (This is the same magnitude as the deviation in the electron affinity of fluorine.) In the case of F_2, the effect is approximately doubled[79]. Covalent bonding has also been shown to be destabilized in some oxygen and possibly nitrogen molecules, including the homopolar O—O and N—N bonds[80]. In the case of oxygen, this destabilizing contribution is approximately 21 kcal mol^{-1} for each oxygen atom[80], the same magnitude as the deviation in its electron affinity.

While the first electron affinity of oxygen is low, its second electron affinity is actually negative[72]. The oxide ion, O^{-2}, could not form in isolation; it would spontaneously eject an electron to achieve a lower energy. This is due to the repulsion between the mononegative ion, O^{-1}, and the second electron added to form O^{-2}. The latter is stable only in the presence of counterions and solvating molecules that stabilize the charge.

Indeed, a high variability of electronegativity with charge has been shown to occur in oxide crystals[81] (in terms of equation 12, this is equivalent to saying that oxygen has a low charge capacity). It has been suggested[81] that the *effective* electronegativity of oxygen is less when bonded to more highly electropositive metals; this can be attributed to its small charge capacity which allows it to accept only a limited amount of electronic charge from these high-κ metals[66]. The reluctance of oxygen to accept a -2 charge may be a factor in the tendency of the heavier high-κ alkali and alkaline earth metals to form peroxides and superoxides[82] where the charge can be spread over the diatomic anion.

The importance of oxygen's low charge capacity in determining the distribution of electronic charge in molecular systems is evident in the following examples. Crystallographic studies of coesite (a high-pressure form of quartz, SiO_2) and forsterite (Mg_2SiO_4) have led to the surprising conclusions that the charges on the oxygen atoms are about the same in both compounds, despite the presence in the latter of magnesium, with its tendency to give up electrons[83]. Apparently the oxygen atoms are 'saturated'; i.e., they cannot accommodate more negative charge than they already have in SiO_2, and so any additional electron density lost by the magnesium atoms goes to the larger silicon.

The same effect can be seen in calculations on simple molecules. For example, in the cyanate and thiocyanate ions, OCN^- and SCN^-, the sulphur is found to be more negative than the oxygen[84,85]. This would be paradoxical in a one-parameter representation of electronegativity, since oxygen is intrinsically more electronegative than sulphur, but it is readily understandable in terms of the low charge capacity of the small oxygen atom. That this is truely due to a charge capacity effect and not to some artifact of the computational method may be seen from similar calculations on the neutral CO_2 and SCO molecules[84]; without the increased burden of the anionic charge, the oxygen is indeed more negative than the sulphur.

The importance of charge capacity in determining acidities can be seen when comparing the acidities of HF and H_2O with those of HCl and H_2S (Table 3). Though fluorine and

TABLE 3. Experimentally determined pK_a values[a]

Molecule	pK_a
HCl	−7
HF	3
H_2S	7
C_6H_5SH	8
C_6H_5OH	9–11
CH_3SH	12
$C_6H_5C(OOH)(CH_3)_2$	13[b]
H_2O	16
CH_3OH	16
CH_3CH_2OH	18
$(CH_3)_3COH$	19

[a]References 86.
[b]The experimentally determined pK_a values of the hydroperoxide was taken from I. M. Kolthoff and A. I. Medalia, *J. Am. Chem. Soc.*, **71**, 3789 (1949).

oxygen are more electronegative than chlorine and sulphur, respectively, the former are more reluctant to accept a full negative charge due to their small charge capacities. Thus, HF and H_2O are weaker acids than their respective second row analogues HCl and H_2S. The same trend holds for the organic —OH and —SH derivatives shown in Table 3[86]. It is interesting to note that alkyl hydroperoxides are stronger acids than the corresponding alcohols; the ROO^- anion can apparently better accept the full negative charge than can the RO^- ion.

It is not only the charge capacity of the atom from which the proton is being extracted that is important in determining the acidity of a protic acid, but also the charge capacity of what is bonded to the atom. The inherent basicities of the hydroxide and alkoxide ions are an example of this point. In this gas phase, the basicity order is[87]

$$HO^- > CH_3O^- > CH_3CH_2O^- > (CH_3)_2CHO^- > (CH_3)_3CO^-$$

The larger charge capacity of the alkyl group(s) stabilizes the anions by accepting electron density from the small, low-κ oxygen. Thus, alcohols are inherently stronger acids than water. The reversal of behaviour in solution (Table 3) is a solvation effect; this explanation is now given in organic textbooks[86,88,89]. (The solution basicity order of the hydroxides and alkoxides had traditionally been explained in terms of the electron-donating power of the alkyl groups increasing the electron density of the oxygen atom in the more highly substituted ions.)

C. Concluding Remarks

Our purpose in Section II has been to give a theoretical basis for some of the seemingly anomalous observed characteristics of oxygen as an atom and as a component of molecular systems. While oxygen has a strong initial tendency to attract electrons, its capacity for absorbing them is limited due to its small size, which concentrates the electronic charge already present and thereby produces a strong repulsive interaction with any additional charge. Thus, because of its low charge capacity, oxygen cannot always become as negative as might be anticipated simply on the basis of its intrinsic electronegativity. We have shown that these concepts are important for understanding

the distributions of charge in oxygen-containing systems and the acidities of molecules with —OH and —OOH groups. We will refer to them again in later sections.

III. STRUCTURAL CHARACTERISTICS

Complete theoretical determination of equilibrium structure involves minimization of the energy of the system with respect to each independent geometrical parameter[90], resulting in an 'optimized' structure. The latter is necessarily somewhat dependent upon the methodology and basis set used to perform the optimization. In this section we will discuss the effectiveness of two first-principles approaches for obtaining bond lengths and angles of prototypical organic —OH, —OR, —OOH and —OOR groups: *ab initio* self-consistent-field molecular orbital (SCF-MO) methods[90,91] and local density functional (LDF) procedures[12,92,93]. We will begin with brief discussions of each technique, and then focus on their capabilities for providing structures of systems containing singly-bonded oxygens.

In both *ab initio* SCF-MO and density functional methods, the initial step is usually to apply the Born–Oppenheimer, or adiabatic, approximation[94], according to which the movement of the electrons may be treated separately from that of the nuclei; the latter are viewed as occupying stationary positions.

In an *ab initio* treatment, the objective is to solve the Schrödinger equation for the system of interest, $\hat{H}\Psi(\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N) = E\Psi(\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N)$, in which $\hat{H}$ is the Hamiltonian operator for an N-electron system having total electronic energy E and described mathematically by Ψ, which is a function of the positions of the electrons. If Ψ can be determined, then it can be used to obtain any desired electronic property of the system; for example, its electronic density $\rho(\mathbf{r})$ is given rigorously by equation 15:

$$\rho(\mathbf{r}) = \rho(\mathbf{r}_1) = N \int \Psi^*(\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N)\Psi(\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N)\, d\mathbf{r}_2 \cdots d\mathbf{r}_N \tag{15}$$

The Hamiltonian operator is the sum of kinetic and potential energy operators, $\hat{H} = \hat{T} + \hat{V}$, where (in atomic units)

$$\hat{T} = -\frac{1}{2}\sum_{i=1}^{N} \nabla_i^2 \tag{16}$$

and

$$\hat{V} = -\sum_i \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}_i|} + \sum_{i<j} \frac{1}{|\mathbf{r}_j - \mathbf{r}_i|} \tag{17}$$

Z_A is the charge on nucleus A, located at $\mathbf{R}_A$. The summations are over all of the electrons and all of nuclei. The second term on the right side of equation 17 represents the instantaneous repulsion between two electrons. It is the presence of this term that has prevented the exact analytical solution of the Schrödinger equation[95]. The total energy of the system is given by

$$E_T = E + \sum_{A<B} \frac{Z_A Z_B}{|\mathbf{R}_A - \mathbf{R}_B|} \tag{18}$$

In order to obtain at least reasonable approximations to Ψ and E, two simplifications are frequently introduced. First, Ψ is expressed in determinantal form in terms of one-electron functions called 'molecular orbitals', which are usually written as linear combinations of basis functions centered at the various nuclei. During the past thirty years, gaussian-type functions have come to be the most widely used for the latter purpose. The larger the basis set of gaussians, the better will be the representation of Ψ; however, the time and space requirements of the computations also increase markedly.

The second simplification is that each electron is treated as moving in the *average*

potential of all of the other electrons; computationally, this is handled by going through an iterative process until self-consistency is achieved. Hence this is known as a 'self-consistent-field' molecular orbital (SCF-MO) procedure. By increasing the size of the basis set (or by seeking numerical rather than analytical representations of Ψ), one can approach a limiting case, the Hartree–Fock solution. (The term Hartree–Fock is often applied, loosely, to any *ab initio* SCF-MO calculation.)

The primary deficiency of the Hartree–Fock (HF) method is that it overestimates the repulsive interactions between electrons; by dealing with an average rather than the instantaneous potential, it does not properly reflect the correlation between their movements that tends to diminish the repulsive effect. There are two general 'post-Hartree–Fock' approaches that have been developed to take account of this electron correlation. In the 'configuration-interaction' (CI) procedure, Ψ is expressed as not just a single determinant but rather a linear combination of several, each corresponding to a different distribution (configuration or 'excitation') of the electrons among the molecular orbitals. In the other post-Hartree–Fock method, which is based on many-body, or Møller–Plesset (MP), perturbation theory, the Hartree–Fock wave function is taken to be the zero-order solution, with the perturbation being the difference between the exact Hamiltonian and the Hartree–Fock operator. Solving the perturbation theory equations then produces the first-, second- and higher-order corrections to the wave function and correspondingly the second-, third- and higher-order corrections to the energy (MP2, MP3, MP4, etc.). (It should be noted that the nth-order wave function is sufficient to obtain perturbation energies up to order $2n + 1$.)

In density functional theory, the focus is on the electronic density, $\rho(\mathbf{r})$, rather than an electronic wave function, $\Psi(\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N)$[12,92,93]. The Hohenberg–Kohn theorem states that all of the electronic properties of a chemical system are determined by the electronic density[96]; in particular, the energy is a functional of $\rho(\mathbf{r})$: $E = F[\rho]$. The nature of the functional F is not specified by the theorem, and a great deal of work has gone into its elucidation[12]. In general

$$F[\rho] = T[\rho] + \sum_{\mathrm{A}} \int \frac{Z_{\mathrm{A}}\rho(\mathbf{r})\,d\mathbf{r}}{|\mathbf{R}_{\mathrm{A}} - \mathbf{r}|} + \frac{1}{2}\int\int \frac{\rho(\mathbf{r})\rho(\mathbf{r}')\,d\mathbf{r}\,d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} + V_{\mathrm{xc}}[\rho] \tag{19}$$

terms, T is the kinetic energy functional and V_{xc} represents exchange and correlation effects.

Due to the problems associated with determining the natures of T and especially V_{xc}, an approximate procedure is frequently used, based on the formalism developed by Kohn and Sham[97]. The electronic density $\rho(\mathbf{r})$ is written as the sum of one-electron orbitals (equation 20)

$$\rho(\mathbf{r}) = \sum_{i=1}^{N} |\phi_i|^2 \tag{20}$$

which are obtained by solving the Kohn–Sham equations:

$$\left[-\frac{\nabla_i^2}{2} + v_{\mathrm{eff}}(\mathbf{r}_i) \right] \phi_i, \quad i = 1, 2, \ldots, N \tag{21}$$

The exchange/correlation contribution to the effective potential, v_{eff}, is often expressed by a formula derived for a uniform (i.e. constant density) gas; a number of such formulas have been proposed and investigated[12,93,98]. This overall approach is known as the local density approximation.

Local density functional (LDF) theory is currently in a period of considerable activity designed to explore its capabilities and limitations[92,93]. A particular advantage is that it requires less computer time and space than do *ab initio* procedures, largely because

TABLE 4. Some calculated[a] (HF) and experimentally determined[b] structural parameters

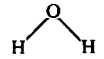
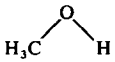
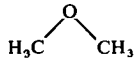
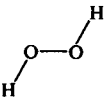
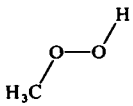
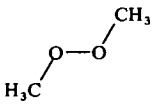
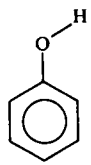
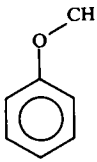
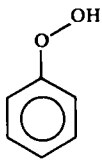
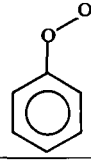
Molecule	Geometrical parameter	HF/STO-3G	HF/3-21G	HF/6-31G*	Exp.
Saturated —OH, —OCH_3					
	r(OH)	0.990	0.967	0.947	0.958
	∠(HOH)	100	108	106	105
	r(CO)	1.433	1.441	1.400	1.421
	r(OH)	0.991	0.966	0.946	0.963
	∠(COH)	104	110	110	108
	r(CO)	1.433	1.433	1.391	1.410
	∠(COC)	109	114		112
Saturated —OOH, —$OOCH_3$					
	r(OO)	1.396	1.473	1.393	1.452[c]
	r(OH)	1.001	0.971	0.949	0.965[c]
	∠(OOH)	101	99	102	100[c]
	∠(HOOH)	125	180	115	119[c]
	r(OO)	1.397	1.469	1.394	—
	r(CO)	1.447	1.445	1.399	—
	r(OH)	1.002	0.971	0.950	—
	∠(COO)	106	104	107	—
	∠(OOH)	101	100	102	—
	∠(COOH)	113	180	119	—
	r(OO)	1.402	1.465	1.399	1.469[d]
	r(OC)	1.446	1.444	1.397	—
	∠(COO)	105	104	106	—
	∠(COOC)	122	180	180	—
Aromatic —OH, —OCH_3					
	r(CO)	1.395	1.377	1.353	1.364
	r(OH)	0.989	0.964	0.947	0.956
	∠(COH)	105	113	111	109
	r(C_{ar}—O)	1.400	1.372	—	1.370[d]
	r(O—CH_3)	1.432	1.435	—	1.424[d]
	∠(COC)	115	121	—	—
Aromatic —OOH, —$OOCH_3$					
	r(OO)	1.402	1.460	—	—
	r(CO)	1.413	1.397	—	—
	r(OH)	0.999	0.972	—	—
	∠(COO)	108	110	—	—
	∠(OOH)	99	99	—	—
	∠(COOH)	180	142	—	—

TABLE 4. (*continued*)

Molecule	Geometrical parameter	HF/STO-3G	HF/3-21G	HF/6-31G*	Exp.
	r(OO)	1.406	1.459	—	—
	$r(C_{ar}—O)$	1.413	1.391	—	—
	$r(O—CH_3)$	1.445	1.452	—	—
	$\angle(C_{ar}—OO)$	108	110	—	—
	$\angle(OO—CH_3)$	104	104	—	—
	$\angle(COOC)$	180	175	—	—

[a]Calculated HF structural parameters of the first four molecules were obtained from Reference 90. Others were taken from geometry optimizations carried out for the purposes of this work.
[b]Experimentally determined structures were obtained from M. D. Harmony, V. W. Laurie, R. I. Kuczkowski, R. H. Schwendeman, D. A. Ramsay, F. J. Lovas, W. J. Lafferty and A. G. Maki, *J. Phys. Chem. Ref. Data*, **8**, 619 (1979) unless otherwise indicated.
[c]D. Cremer and D. Christen, *J. Mol. Spectrosc.*, **74**, 480 (1979).
[d]F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, S1 (1987).

many of the most difficult electron repulsion integrals are avoided. For example, the time needed for LDF calculations increases with the third power of the number of basis functions, compared to the fourth and fifth powers for HF and MP2, respectively.

Table 4 lists some calculated *ab initio* HF and experimentally determined structural parameters (when available) for some prototypical saturated and aromatic molecules containing —OH, $—OCH_3$ and —OOH and $—OOCH_3$. Several significant trends emerge which are important in selecting a basis set for HF geometry optimizations of molecules containing these groups. (The term 'basis set' refers to the functions used to build up the molecular orbitals. The ones that will be mentioned in this discussion are designated as STO-3G, 3-21G and 6-31G*. They increase in size and flexibility in the order given.)

For the saturated —OH- and $—OCH_3$-containing molecules in Table 4, it is seen that the STO-3G, 3-21G and 6-31G* basis sets all provide reasonable C—O and O—H bond lengths and COH and COC angles, with errors not exceeding 0.03 Å or 5°, respectively. (However, the calculated twist angles around the O—O bond are seen to cover a wide range.) It is interesting to note that for CH_3OH, the STO-3G basis yields a C—O bond length (1.433 Å) close to experiment than does either the 3-21G or the 6-31G* basis set. In fact, the 6-31G* consistently underestimates the C—O bond lengths. The COH and COC bond angles are slightly underestimated with the STO-3G basis set, and slightly overestimated with the others. This phenomenon has been discussed in detail elsewhere[90]. (It is important to emphasize that increasing the size of the basis set guarantees improvement only in the energy of a system, and not in any other of its properties, some of which may be given more accurately at lower computational levels.)

Table 4 shows that the STO-3G aromatic C—O bond lengths of phenol and anisole are too long by about 0.03 Å; the 3-21G and 6-31G* basis sets, on the other hand, provide $C_{ar}—O$ bond distances within 0.015 Å of experimental values. The inability of the STO-3G to accurately handle some types of conjugation is well known[90], and should be considered when choosing a basis set suitable for geometry optimizations of unsaturated alcohols and ethers. If one or more of the organic groups (R or R') is, for example, aromatic or a vinyl derivative, it is advisable to choose a more flexible basis set (e.g. 3-21G) to obtain a geometry.

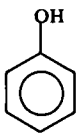
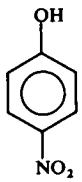
In looking at the computed and experimentally determined geometries of H_2O_2 in Table 4, it is seen that the STO-3G and 6-31G* basis sets both underestimate

TABLE 5. Calculated (post-HF and LDF) and experimentally determined structural parameters for H_2O, CH_3OH and H_2O_2

Molecule	Geometrical parameter	MP2/6-31G*[a]	DMol/DNP[b]	Experimental[c]
H_2O	r(OH)	0.969	0.988	0.958
	∠(HOH)	104.0	103.7	104.5
CH_3OH	r(CO)	1.423	1.415	1.421
	r(OH)	0.970	0.980	0.963
	∠(COH)	107.4	109.7	108.0
HOOH	r(OO)	1.468	1.466	1.452[d]
	r(OH)	0.976	0.988	0.965[d]
	∠(OOH)	98.7	98.8	100.0[d]
	∠(HOOH)	121.1	119.9	119.1[d]

[a]Carnegie-Mellon Quantum Chemistry Archive.
[b]Reference 99.
[c]Experimentally determined structures were obtained from M. D. Harmony, V. W. Laurie, R. I. Kuczkowski, R. H. Schwendeman, D. A. Ramsay, F. J. Lovas, W. J. Lafferty and A. G. Maki, *J. Phys. Chem. Ref. Data*, **8**, 619 (1979) unless otherwise indicated.
[d]D. Cremer and D. Christen, *J. Mol. Spectrosc.*, **74**, 480 (1979).

TABLE 6. Calculated and experimental X—OH rotational barriers[a]

Molecule	Barriers to Rotation (kcal mol^{-1}) HF/STO-3G	HF/3-21G	HF/6-31G*	MP2/6-31G*	Experimental
CH_3CH_3	2.9	2.7	3.0	3.1	2.9
CH_3OH	2.0	1.5	1.4	1.5	1.1
	5.2	2.4[b]	—	—	3.3
	6.2	3.7[b]	—	—	4.3
HOOH,					
cis barrier	9.1	11.7	9.2	9.4	7.0
trans barrier	0.2	—	0.9	0.6	1.1

[a]The values in this table are taken from Reference 90, unless otherwise indicated. Except for ethane which is included as a reference, the rotational barriers are for rotation of the —OH group.
[b]Reference 104.

the O—O bond length by more than 0.05 Å, while the 3-21G predicts an O—O bond distance wthin 0.02 Å of the experimental value. This general trend is seen throughout Table 4 for the molecules containing —OOH and —$OOCH_3$ linkages.

Proceeding now to calculations that include electron correlation, Table 5 lists MP2/6-31G* and local density functional (LDF) structural data for H_2O, CH_3OH and H_2O_2. The LDF results[99] were obtained using the program DMol[100] with the DNP basis set. The latter is a double numerical basis set augmented by polarization functions. Both the MP2/6-31G* and DMol/DNP values are in excellent agreement with experimental data. The agreement between the MP2/6-31G*, LDF/DNP and experimental structures of H_2O_2 is particularly noteworthy, illustrating again that obtaining reliable structures for molecules containing oxygen linked to highly electronegative atoms (fluorine, oxygen and/or nitrogen) requires that electron correlation be taken into account[90,101–103].

Our results in Tables 4 and 5 indicate that good structures can be obtained for molecules containing —OH and —OR groups by means of HF geometry optimizations carried out with a judicious choice of basis set, as well as with methods including electron correlation. However, the latter appear to be better suited for the —O—O— linkage.

It has been pointed out elsewhere that the magnitude of the C—OH rotational barrier of methanol is very slightly overestimated by the HF/STO-3G, HF/3-21G, HF/6-31G* and MP2/6-31G* methods[90] (see Table 6). However, the trend in the X—OH rotational barriers among several molecules is reproduced well by all of these approaches[90,104]. Table 6 shows that the X—OH rotational barriers in CH_3OH, C_6H_5OH, p-$O_2NC_6H_4OH$ and H_2O_2 consistently increase in that order.

IV. ELECTROSTATIC POTENTIALS OF SINGLE-BONDED OXYGEN-CONTAINING MOLECULES IN RELATION TO CHEMICAL REACTIVITY

B. Definition and General Features

The electrostatic potential $V(\mathbf{r})$ that the nuclei and electrons of a molecule create in the surrounding space has emerged in the past two decades as an effective tool for studying the reactive behaviour of molecules in both electrophilic and nucleophilic processes and in intermolecular recognition interactions[105–109]. The quantity $V(\mathbf{r})$ is defined rigorously by equation 22:

$$V(\mathbf{r}) = \sum_{\mathrm{A}} \frac{Z_{\mathrm{A}}}{|\mathbf{R}_{\mathrm{A}} - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')\, d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \tag{22}$$

where Z_{A} is the charge on nucleus A, located at $\mathbf{R}_{\mathrm{A}}$, and $\rho(\mathbf{r})$ is the electronic density function. $V(\mathbf{r})$ is a real physical property that expresses the net electrical effect of the nuclei and electrons of a molecule; it can be determined experimentally by diffraction methods as well as computationally[108].

In this section we will present characteristic features of the electrostatic potentials of molecules containing —OH, —OR, —OOH and —OOR groups. These will subsequently be discussed in relation to overall chemical reactivity, including hydrogen bonding tendencies, and molecular charge separation, or local polarity.

The sign of $V(\mathbf{r})$ in any particular region depends upon whether the effects of the nuclei or the electrons are dominant there. An approaching electrophile will be attracted initially to those regions in which $V(\mathbf{r})$ is negative, and in particular to the points where $V(\mathbf{r})$ has its most negative values (the local minima, $V_{\min}$). Using $V(\mathbf{r})$ to predict sites susceptible to nucleophilic attack is not as straightforward as for electrophilic attack, due to the fact that $V(\mathbf{r})$ maxima are found only at the positions of the nuclei[110]; they

reflect the magnitudes of the nuclear charges and cannot be assumed to indicate relative reactivities toward nucleophiles. However, we have demonstrated that when $V(\mathbf{r})$ is examined on three-dimensional molecular surfaces significantly removed from the nuclei[110], then buildups of positive potential do reflect relative affinities for nucleophiles[109,111,112].

The electrostatic potentials of molecules containing single-bonded oxygen are largely dominated by the extensive negative regions associated with these oxygens, indicating them to be sites attractive to electrophiles (including hydrogen bonds)[104,107,109,113–118]. This can be seen in Figures 1–4, which show two-dimensional $V(\mathbf{r})$ contour plots for CH_3OH, H_3COCH_3, $HOOCH_3$ and H_3COOCH_3, respectively. The values of the V_{min} in the vicinities of the oxygens are listed in Table 7. These occur above and below the planes of Figures 1–4, and reflect the lone pairs of electrons associated with each oxygen.

Although oxygen is normally depicted as having two lone pairs and these are often reflected by two separate $V(\mathbf{r})$ minima, as in CH_3OH, H_3COCH_3, $HOOCH_3$, H_3COOCH_3, H_2O, H_2O_2 and many other molecules[107,113–116], it should be noted that this is not always the case[107,109,115]. For example, the peroxide oxygen closest to the $F_3CC{=}O$ group in peroxytrifluoroacetic acid (**8**) has but a single V_{min}, whereas the other two oxygens have two[115].

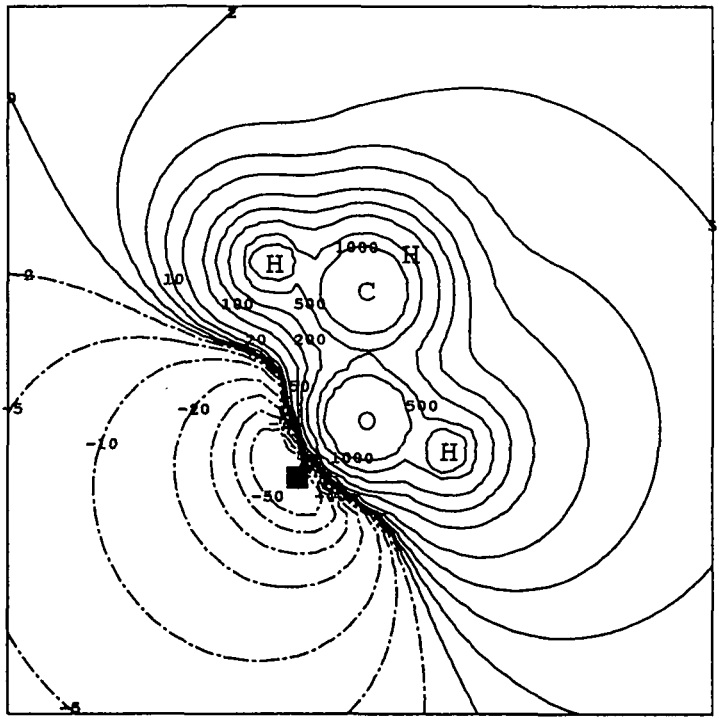


FIGURE 1. Calculated STO-5G electrostatic potential of CH_3OH, in kcal mol^{-1}, in a plane passing through the carbon and the —OH group. The projections of other nuclear positions are shown by their atomic symbols. Dashed contours correspond to negative potentials. The position of the most negative potential is indicated; the value is: ■ −68.1

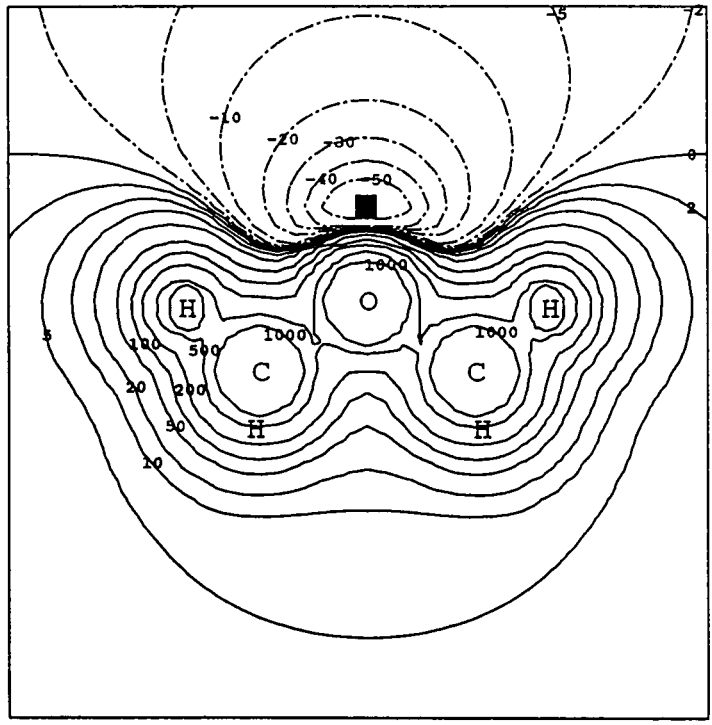
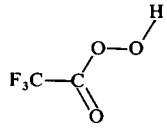


FIGURE 2. Calculated STO-5G electrostatic potential of H_3COCH_3, in kcal mol^{-1}, in a plane passing through the carbons and oxygen. The projections of other nuclear positions are shown by their atomic symbols. Dashed contours correspond to negative potentials. The position of the most negative potential is indicated; the value is: ■ −65.5



(8)

For perspective, it is interesting to compare the V_{min} values in Table 7 to those of some other molecules containing single-bonded oxygens (Table 8). The most negative V_{min} in Tables 7 and 8 is that of H_2O, −75 kcal mol^{-1}. The values for the aliphatic alcohols are somewhat smaller in magnitude, while the ethers cover a wide range, with the cyclic ones tending to be the less negative. It should be noted that phenol has a weaker V_{min} that the other alcohols, reflecting resonance donation of charge from the OH to the aromatic ring.

Consistent with the −1 oxidation state of oxygen in the —O—O— linkage, the potential minima of $HOOCH_3$, H_3COOCH_3 and the molecules containing —O—O— linkages in Table 7[115,116], tend to be less negative than those of many of the other molecules in Tables 7 and 8. This doubtless reflects, at least in part, the fact that two oxygens are now competing for the polarizable electronic charge.

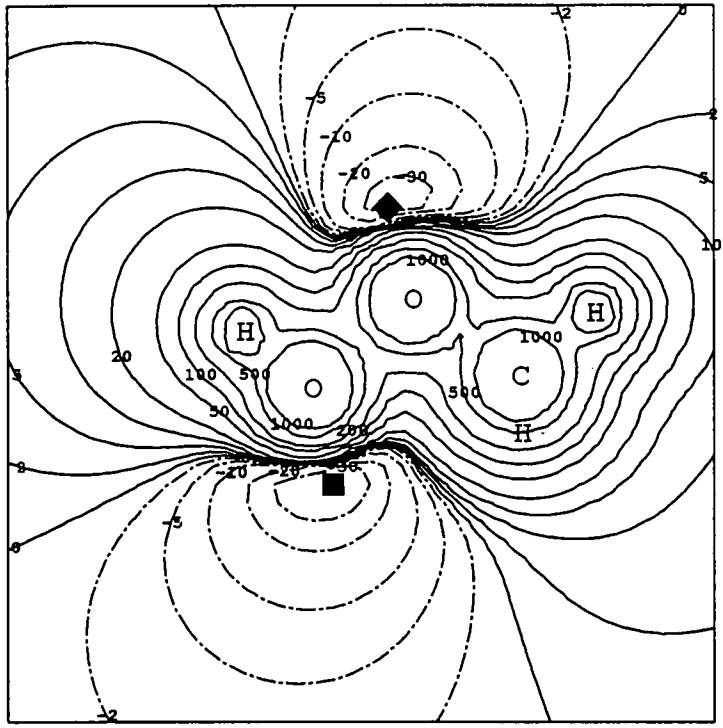
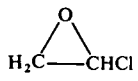
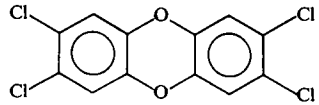


FIGURE 3. Calculated STO-5G electrostatic potential of $HOOCH_3$, in kcal mol^{-1}, in a plane passing through the carbon and —OOH group. The projections of other nuclear positions are shown by their atomic symbols. Dashed contours correspond to negative potentials. The positions of the most negative potentials are indicated; the values are: ■ −42.7; ◆ −36.0

The negative regions of electrostatic potential associated with —O— and —O—O— linkages in hydrocarbon frameworks are diminished in size and magnitude by the introduction of electron-withdrawing groups such as —F, —Cl, $—CF_3$ and NO_2[113–116]. For example, the oxygen V_{min} of chlorooxirane (**9**) and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (**10**) are −38[113] and −29[114] kcal mol^{-1}, respectively, compared to −51 kcal mol^{-1} for the parent compounds (Table 8). The net effect of the substitution of electron-withdrawing groups is thus to reduce the basicities of the oxygens, e.g. as sites for protonation and/or hydrogen bonding.



(**9**)



(**10**)

An alternative to showing $V(\mathbf{r})$ in planes passing through the space of a molecule, as is done in Figures 1–4, is to compute it on three-dimensional surfaces encompassing the molecule. One way of defining such a surface is by means of a particular contour of the

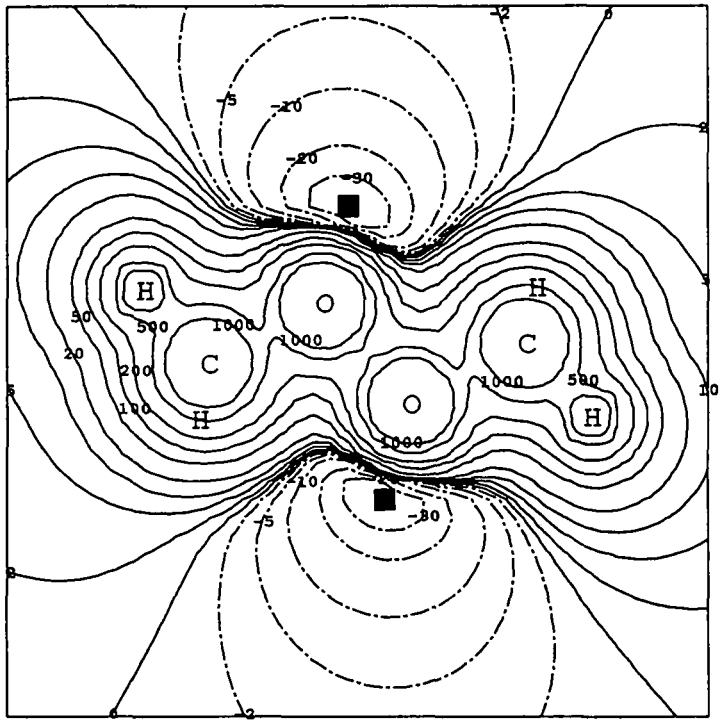


FIGURE 4. Calculated STO-5G electrostatic potential of H_3COOCH_3, in kcal mol^{-1}, in a plane passing through the carbons and oxygens. The projections of other nuclear positions are shown by their atomic symbols. Dashed contours correspond to negative potentials. The positions of the most negative potentials are indicated; the value is: ■ −41.0

electronic density $\rho(\mathbf{r})$. This has the advantage that the surface is established in terms of a property of the actual molecule, rather than by superposing atomic spheres.

Plates 1–4 present the electrostatic potentials computed on molecular surfaces defined by the 0.001 electron/bohr^3 contour of $\rho(\mathbf{r})$ for the same four molecules as in Figures 1–4. The large negative regions associated with the oxygens are very much in evidence. A

TABLE 7. Calculated electrostatic potential data[a]

Molecule	V_{min}	$V_{S,max}$
CH_3OH	−69.9	29.4
H_3COCH_3	−65.9	11.5
$HO_aO_bCH_3$	O_a: −50.2	28.6
	O_b: −45.3	
H_3COOCH_3	−48.0	12.2

[a]Electrostatic potentials were computed at the STO-5G level using 3-21G optimized structures. Units are kcal mol^{-1}.

TABLE 8. Calculated STO-5G electrostatic potential minima of miscellaneous molecules

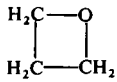
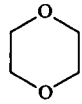
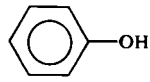
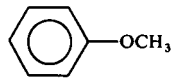
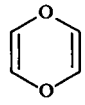
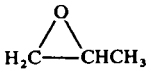
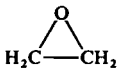
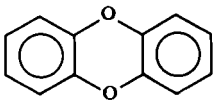
Molecule	V_{min}(kcal mol^{-1})
—OH and —OR linkages	
H_2O	−75[a]
$[CH(CH_3)_2]_2O$	−71[b]
$CH_3CHOHCH_3$	−68
CH_3CH_2OH	−67
$[CH_3(CH_3)_2]_2O$	−66[b]
$[CH_3CH_2]_2O$	−65[b]
	−65
$H_3COCH_2CH_2OCH_3$	−60[b]
	−59
	−58
	−58
	−56
	−54[c]
	−53[d]
	−51[d]
	−51[e]
—O—O-linkages	
H_2O_2	−55, −43[a]
	−50
	−47[c]

TABLE 8. (*continued*)

Molecule	V_{min}(kcal mol^{-1})
	−37[a]

[a]Reference 115.
[b]Reference 117.
[c]Reference 116.
[d]Reference 113.
[e]Reference 114.

striking feature of plates 1 and 3 as compared to Figures 1 and 3 is the very positive nature of the electrostatic potential in the vicinity of the —OH and —OOH hydrogens. The most positive surface potentials ($V_{S,max}$) in these regions are 29.4 and 28.6 kcal mol^{-1}, compared to 11.5 and 12.2 kcal mol^{-1} for the methyl hydrogens of dimethyl ether and dimethyl peroxide (Table 7). As mentioned earlier, a particular advantage of presenting electrostatic potentials on surfaces is the possibility of quantitatively comparing portions of molecules that may be susceptible to nucleophilic interactions[111,112], e.g. hydrogens to be donated in hydrogen bonds[112,118] or transferred. The first of these will now be discussed in more detail.

B. Hydrogen Bonding Tendencies

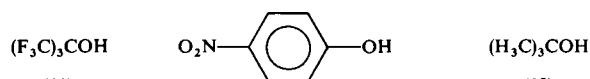
We have recently demonstrated, for several families of molecules, that the local minima V_{min} and surface maxima $V_{S,max}$ correlate well with empirical parameters designed to indicate hydrogen-bond-accepting and -donating tendencies, respectively, in solute–solvent interactions[112,117,118]. For example, within a series of alkyl ethers, the more negative is V_{min}, the better able is the oxygen to accept a hydrogen bond[117]. For a group of aliphatic alcohols and *para*- substituted phenols, we showed that the more positive is $V_{,max}$, the stronger hydrogen-bond donor is the molecule[112,118].

In the spirit of these correlations[117], our V_{min} results in Tables 7 and 8 suggest that hydrogen-bond-accepting tendencies for aliphatic single-bonded-oxygen systems decrease, in general, in the order

alcohols, ether > hydroperoxides, peroxides

With regard to hydrogen-bond-donating powers, the marked contrast of the $V_{S,max}$ values of CH_3OH and $HOOCH_3$ to those of H_3COCH_3 and H_3COOCH_3, as evident in Table 7 and brought out vividly by Plates 1–4, is fully consistent with the well-known hydrogen-bond-donating abilities of alcohols and hydroperoxides and the absence of such behaviour in, for example, ethers.

The $V_{S,max}$ values of —OH-containing systems cover a range of values, depending upon the molecular framework and the presence of substituent groups[112,118]. For example, the $V_{S,max}$ values of perfluoro-*t*-butanol (**11**), *p*-nitrophenol (**12**), phenol (**3**) and *t*-butanol (**13**), computed on molecular surfaces defined by the 0.001 electron/bohr^3 contour of the electronic density, are 49, 46, 35 and 26 kcal mol^{-1}[118], respectively. The general



(11) (12) (13)

trend is that $V_{S,max}$ increases upon the substitution of electron-attracting groups, indicating a corresponding increase in hydrogen-bond-donating tendencies.

It is interesting to note that the gas-phase acidities[87] and the hydrogen-bond-donating tendencies[119] of the aliphatic alcohols follow opposite trends. This may reflect the fact that hydrogen bonding does not involve the loss of a proton and the subsequent formation of an anion. As we have discussed earlier, the gas-phase acidities of the aliphatic alcohols can be interpreted in terms of the charge capacity of the alkyl group to which the oxygen is bonded; the tertiary alkyl groups are better able than the secondary and primary to delocalize the negative charge imposed upon the low-charge-capacity oxygen. The hydrogen-bond-donating tendencies[119] and $V_{S,max}$ values[112,118], however, increase in general with decreasing carbon-to-oxygen ratio.

C. Charge Separation in Molecules

The presence of oxygen in an organic molecule introduces some degree of charge separation, or local polarity, into the system, due to the high intrinsic electronegativity of oxygen; this occurs even if the symmetry of the molecule is such that the overall dipole moment is zero. The final distribution of charge is of course dependent upon both the intrinsic electronegativities and the charge capacities of the constituent atoms. The electrostatic potential results that we have presented for molecules containing —O— and —O—O— linkages provide some indications of the charge separation within these systems. Indeed $V(\mathbf{r})$, as defined by equation 22, is a physical manifestation of the distribution of electronic and nuclear charge in a chemical system.

In order to have a quantitative measure of the local polarity that may be present even in a zero-dipole-moment molecule, we have recently introduced a polarity index Π, defined in terms of the electrostatic potential as given in equation 23[120]:

$$\Pi = \frac{1}{A}\int_S |V(\mathbf{r}) - \bar{V}_S|\, dS \tag{23}$$

The integral represents the total amount by which the electrostatic potential on the molecular surface deviates from its average value, $\bar{V}_S$; this is divided by the surface area A in order to permit comparisons between molecules of different sizes.

For practical convenience, equation 24 can be written in the form

$$\Pi = \frac{1}{n}\sum_{i=1}^{n} |V_i(\mathbf{r}) - \bar{V}_S| \tag{24}$$

where $V_i(\mathbf{r})$ is the potential at the ith point on the surface and

$$\bar{V}_S = \frac{1}{n}\sum_{i=1}^{n} V_i(\mathbf{r})$$

As n increases, equation 24 approaches equation 23. We have proposed equation 24 as the working formula for Π[120], which can be viewed as the average deviation of the electrostatic potential on the molecular surface. We have computed Π for molecules of a variety of types[120], and demonstrated its relationship to an empirical polarity–polarizability parameter and also to the dielectric constant, an experimentally determined property[120].

Table 9 lists our calculated Π values for some representative saturated alcohols, hydroperoxides, ethers and peroxides, including also cyclohexane and water for perspective. An emerging general trend is that Π increases as the carbon to —O— or —O—O— linkage ratio decreases. In cases where alcohols, hydroperoxides, ethers and peroxides

TABLE 9. Some calculated and experimental molecular properties

Molecule	Π^a (kcal mol)	π^{*b}	ε^c
$c\text{-}C_6H_{12}$	2.2	0.00	2.02
$CH_3CH_2OCH_2CH_3$	6.7	0.27	4.34
$(H_3C)_3COH$	7.7	0.41	10.9
$H_3CCHOHCH_3$	8.7	0.48	18.3
H_3COCH_3	9.1	—	5.02
H_3COOCH_3	9.2	—	—
CH_3CH_2OH	10.1	0.54	24.3
$HOOCH_3$	11.7	—	—
CH_3OH	12.8	0.60	32.63
H_2O_2	19.1	—	84.2
H_2O	21.6	1.09	75.54

[a]Π values were computed at the STO-5G level using STO-3G geometries, and are taken from Reference 120, except for those of H_2O_2, H_3COCH_3, $HOOCH_3$ and H_3COOCH_3, which were computed specifically for this chapter. For the latter three, Π was computed at the STO-5G level using 3-21G structures. For H_2O_2, an experimental structure was used.
[b]Reference 119.
[c]Experimentally determined dielectric constants are taken from: R. C. West (Ed.), *Handbook of Chemistry and Physics*, 60th ed., The Chemical Rubber Co., Cleveland OH, 1979/80. All data correspond to temperatures between 20 and 30 °C.

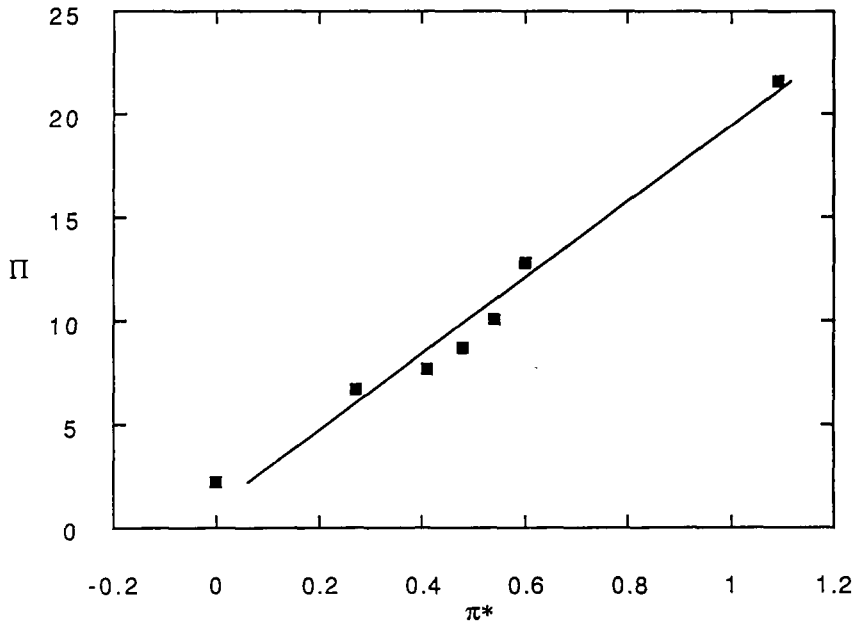


FIGURE 5. Relationship between Π, in kcal mol^{-1}, and the empirical polarity/polarizability parameter π^* for the molecules in Table 8; the linear correlation coefficient is 0.99

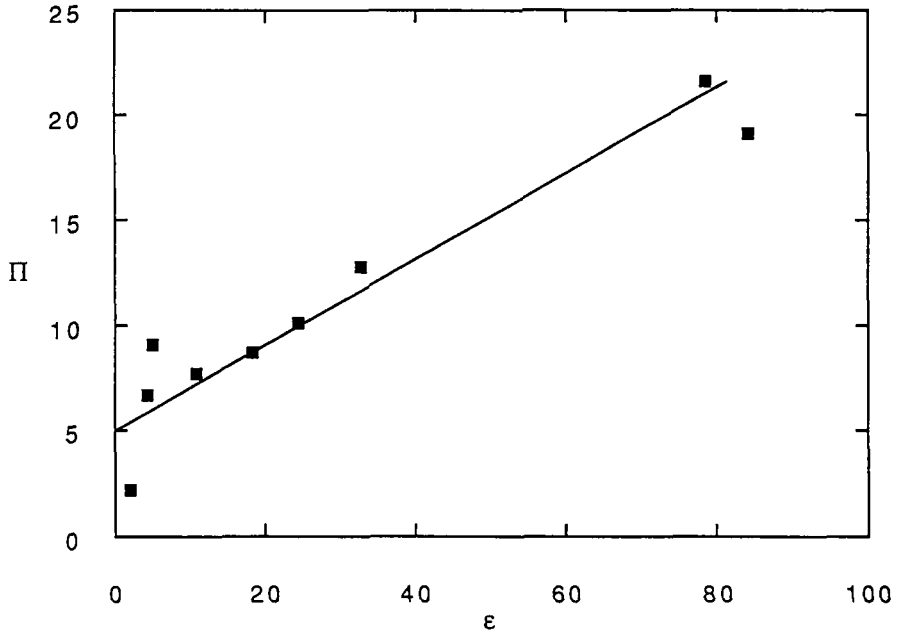


FIGURE 6. Relationship between Π, in kcal mol^{-1}, and the dielectric constant ε for the molecules in Table 8; the linear correlation coefficient is 0.95

have the same C to —O— or —O—O— ratio, the alcohol invariably has the highest Π values, presumably reflecting in part the presence of local regions of highly positive surface electrostatic potential associated with the —OH hydrogen.

It can be seen that there are general correlations between Π and the empirical polarity–polarizability parameter π^* [119] and also the dielectric constant ε for the group of molecules in Table 9. These relationships are shown in Figures 5 and 6; the linear correlation coefficients are 0.99 and 0.95, respectively.

D. Concluding Comments Regarding the Electrostatic Potential

The molecular electrostatic potential $V(\mathbf{r})$ is an effective tool for characterizing sites and relative reactivities for electrophilic and nucleophilic interactions (including hydrogen bonding) of molecules containing —O— and —O—O— linkages. $V(\mathbf{r})$ minima and surface $V(\mathbf{r})$ maxima identify probable initial sites for electrophilic and nucleophilic attack, respectively; the magnitudes of these values reflect relative tendencies for such interactions.

Alcohols and hydroperoxides have relatively strong negative regions of $V(\mathbf{r})$ associated with their oxygens and also highly positive potentials in the vicinities of their —OH and —OOH hydrogens, indicating them to be likely candidates for both electrophilic and nucleophilic interactions, as is found experimentally to be the case[86]. The electrostatic potentials of ethers and peroxides, on the other hand, are dominated by the negative oxygen regions, reflecting the tendencies of these molecules to interact with electrophiles. These $V(\mathbf{r})$ features are fully consistent with observed physical properties of these compounds (e.g. see Table 1). The strongly negative and positive regions of alcohols and

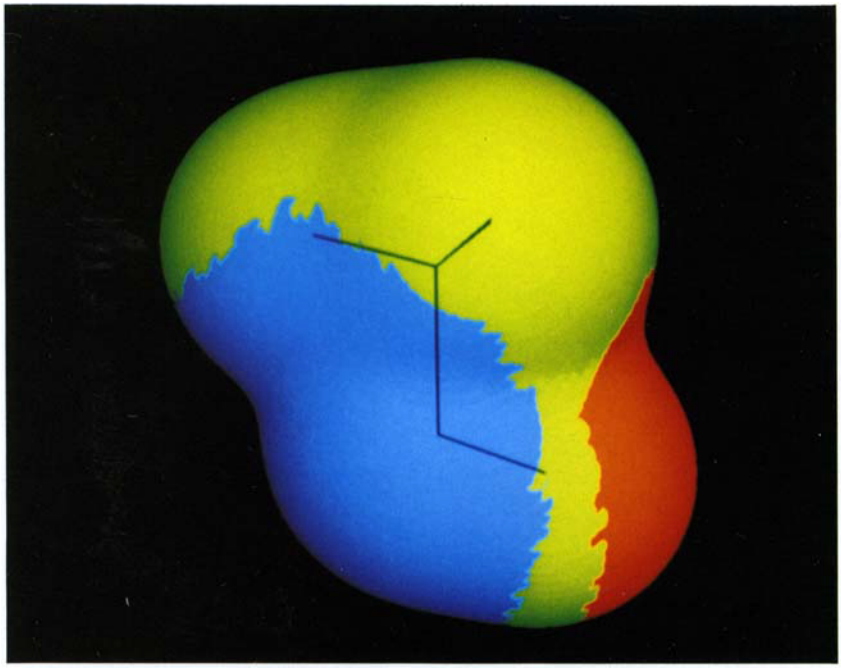


PLATE 1. Calculated STO-5G electrostatic potential on the molecular surface of CH_3OH. Color ranges, in kcal mol^{-1}: red > 13; 13 > yellow-green > 0; blue < 0

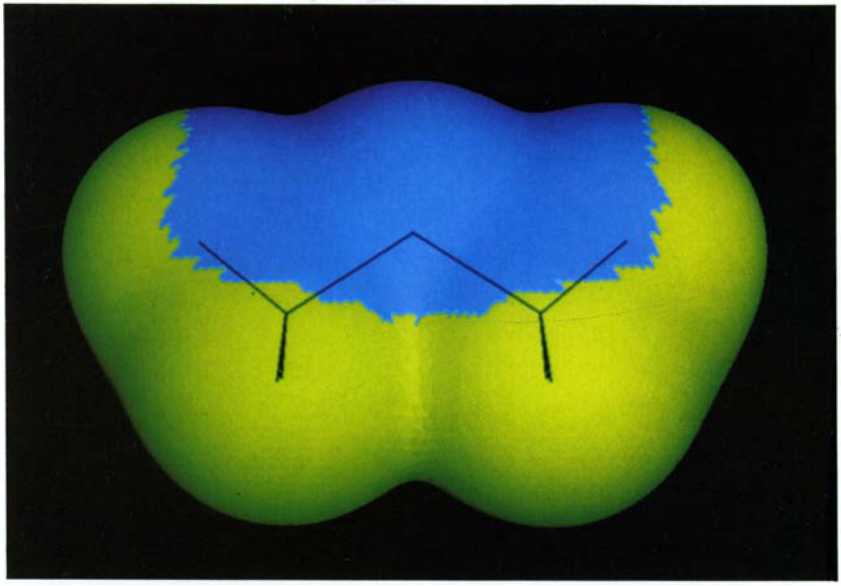


PLATE 2. Calculated STO-5G electrostatic potential on the molecular surface of H_3COCH_3. Color ranges, in kcal mol^{-1}: 13 > yellow-green > 0; blue < 0

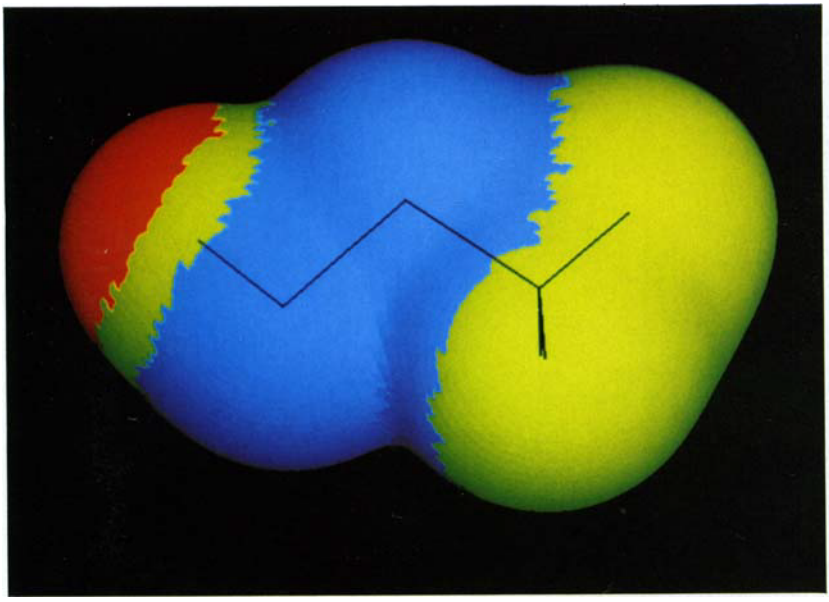


PLATE 3. Calculated STO-5G electrostatic potential on the molecular surface of $HOOCH_3$. Color ranges, in kcal mol^{-1}: red > 13; 13 > yellow-green > 0; blue < 0

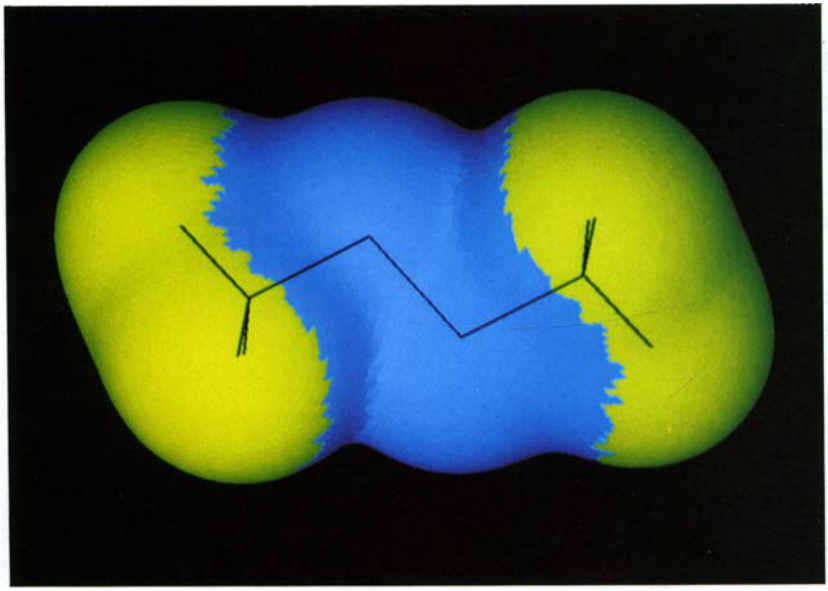


PLATE 4. Calculated STO-5G electrostatic potential on the molecular surface of H_3COOCH_3. Color ranges, in kcal mol^{-1}: 13 > yellow-green > 0; blue < 0

hydroperoxides (e.g. as shown in plates 1 and 3) are indicative of tendencies for self-association in the liquid state, resulting in high boiling points relative to the ethers and peroxides, and also high solubilities in aqueous solution. Likewise, the lower solubilities of ethers and peroxides in water are consistent with their inabilities to act as hydrogen-bond donors (compare plates 2 and 4 to plates 1 and 3). The relevance of these computed results to the chemical behaviour of these systems will be discussed further in Section VI and VII.

We have shown that the average deviation of the electrostatic potential on the surface of a molecule is a meaningful measure of charge separation, or local polarity. The values of our polarity index, Π, for a number of molecules containing —O— and —O—O— groups correspond well with intuitive notions of polarity, and are linearly related to the empirical polarizability parameter π^* and also the experimentally determined dielectric constant.

V. SUBSTITUENT EFFECTS OF —OH, —OCH_3, —OOH AND —$OOCH_3$ GROUPS

Substituent parameters derived from reaction rate and equilibrium studies are one of the many tools available to the physical organic chemist[121,122]. They provide a means of characterizing the electronic effects that substituents generally have upon molecular systems. For example, the —OH and —OCH_3 groups are classified as fairly strong resonance donors and inductive attractors of electronic charge[121,122]. However, the net effect is dependent upon the framework to which the substituent is bonded. For example, —OH and —OCH_3 act as electron-donating groups when substituted on benzene rings; in acetic acid, on the other hand, they are overall electron attractors[121].

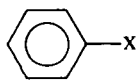
The substituent effects of the —OH and —OCH_3 groups have been well documented[120–122]. Their Hammett constants, σ_m and σ_p, and their inductive and resonance parameters, σ_I and σ_R, are listed in Table 10. However, such data are not available for —OOH and —$OOCH_3$. In this section we will briefly discuss recent theoretical methods that we have developed which allow predictions of substituent parameters[123–126], and which we will apply to the —OOH and —$OOCH_3$ groups.

We have discovered some useful relationships between substituent constants and (a) the calculated electrostatic potential $V(\mathbf{r})$ (equation 22) and (b) the average local ionization energy $\bar{I}(\mathbf{r})$[123–126]. The latter is defined by equation 25[124]:

$$\bar{I}(\mathbf{r}) = \sum_i \frac{\rho_i(\mathbf{r})|\varepsilon_i|}{\rho(\mathbf{r})} \tag{25}$$

where $\rho_i(\mathbf{r})$ is the electronic density of the ith molecular orbital, ε_i is the orbital energy, and $\rho(\mathbf{r})$ is the total electronic density.

We interpret $\bar{I}(\mathbf{r})$ as the average energy required to ionize an electron at any point $\mathbf{r}$ in the space of a molecule[124]. We have demonstrated in a series of studies that the pattern of $\bar{I}(\mathbf{r})$ on a molecular surface reveals sites and relative reactivities toward electrophiles[124,126–130]. For example, we have shown that the lowest values of $\bar{I}(\mathbf{r})$ on the molecular surfaces of monosubsitituted benzenes (**14**) provide a quantitative measure of the activating/deactivating and the directing tendencies of the various substituents with regard to electrophilic aromatic substitution[124,126], and correlate well with the Hammett constants σ_m and/or σ_p. This lowest surface $\bar{I}(\mathbf{r})$, designated as $\bar{I}_{S,\min}$, can also be used to predict aqueous acidities[126,128–130].



(14)

X = H, or a substituent group,
e.g. NH_2, CH_3, F, CHO, NO_2

TABLE 10. Some calculated STO-5G V_{min} and $\bar{I}_{S,min}$ values and some experimentally derived[a] and predicted substituent constants

Molecule	Amine nitrogen V_{min}[b] (kcal mol^{-1})	$\bar{I}_{S,min}$[b,c] (eV)	Substituent constants[a]			
NH_2—X systems			σ_I	σ_R		
NH_2—H	−109.3	N:11.91	0.00	0.00		
NH_2—CH_3	105.9	N:11.88	−0.01	−0.11		
NH_2—NH_2	−91.5	N:12.53	0.17	−0.48		
NH_2—$OOCH_3$	−91.3	N:12.84	(0.23)[d]	(−0.41)[e]		
NH_2—OOH	−90.2	N:12.90	(0.25)[d]	(−0.33)[e]		
NH_2—OCH_3	−87.0	N:12.82	0.30	−0.45		
NH_2—OH	−84.8	N:12.85	0.24	−0.62		
NH_2—CF_3	−82.3	N:13.18	0.40	0.08		
NH_2—Cl	−75.9	N:13.82	0.47	−0.23		
NH_2—CN	−64.8	N:14.15	0.57	0.13		
NH_2—NO_2	−59.9	N:14.47	0.67	0.15		
C_6H_5—X systems					σ_m	σ_p
C_6H_5—NH_2	—	C_{para}:13.72			−0.09	−0.57
C_6H_5—OCH_3	—	C_{para}:14.09			0.10	−0.28
		C_{meta}:14.44				
C_6H_5—OH	—	C_{para}:14.13			0.13	−0.38
		C_{meta}:14.53				
C_6H_5—$OOCH_3$	—	C_{para}:14.17			(0.18)[f]	(−0.18)[f]
		C_{meta}:14.51				
C_6H_5—CH_2CH_3	—	C_{para}:14.19			−0.06	−0.13
C_6H_5—OOH	—	C_{para}:14.26			(0.28)[f]	(−0.08)[f]
		C_{meta}:14.61				
C_6H_6	—	C:14.32			0.00	0.00
C_6H_5—F	—	C_{para}:14.34			0.34	0.06
C_6H_5—CHO	—	C_{meta}:14.58			0.41	0.47
C_6H_5—NO_2	—	C_{meta}:15.11			0.71	0.81

[a] σ_I, σ_R, σ_m and σ_p are taken from Reference 121. The values in parentheses are predictions based on correlations that we have developed, and are discussed in References 123–126 and in the text.
[b] The STO-5G amine nitrogen V_{min} and $\bar{I}_{S,min}$ values are taken from Reference 125, except for those of NH_2—OCH_3, NH_2—OOH and NH_2—$OOCH_3$, which were calculated for this chapter.
[c] The STO-5G ring carbon $\bar{I}_{S,min}$ values are taken from Reference 126, except for those of C_6H_5—OH, C_6H_5—OCH_3, C_6H_5—OOH and C_6H_5—$OOCH_3$, which were calculated for this chapter.
[d] This value is the average obtained from our V_{min} vs σ_I and $\bar{I}_{S,min}$ vs σ_I correlations.
[e] This value is estimated from the relationship $\sigma_p \approx \sigma_I + \sigma_R$.
[f] This value is obtained from our $\bar{I}_{S,min}$ vs σ_m, σ_p relationship.

We have earlier presented direct computational means for obtaining a measure of a substituent's total electron-attracting tendency[123]. We showed that both the V_{min} and the $\bar{I}_{S,min}$ values of the amine nitrogens in NH_2—X molecules correlate well with the inductive substituent constant σ_I (or the quantity $\sigma_I + \sigma_R$ when the substituent is electron-withdrawing through resonance)[123,125].

In Table 10 we list the calculated amine nitrogen V_{min} and $I_{S,min}$ values of some NH_2—X systems, including NH_2—OOH and NH_2—$OOCH_3$, and the ring carbon $\bar{I}_{S,min}$ values of some monosubstituted benzenes, including C_6H_5—OOH and C_6H_5—$OOCH_3$. (The structures of NH_2—OOH and NH_2—$OOCH_3$ were optimized

at the STO-3G level with the O—O bond distances set to 1.46 Å; those of C_6H_5—OOH and C_6H_5—$OOCH_3$ were optimized at the 3-21G level.) Consistent with our earlier findings[123,125], the amine nitrogen V_{min} and $\bar{I}_{S,min}$ values of the NH_2—X systems in Table 10 are linearly related to σ_I, with correlation coefficients of 0.98 and 0.99. Using these relationships, we estimate the σ_I values of —OOH and —$OOCH_3$ to be 0.25 and 0.23, respectively.

Looking next at the ring carbon $\bar{I}_{S,min}$ of the monosubstituted benzenes in Table 10, Figure 7 shows a linear relationship (as before[124,126]) between the $\bar{I}_{S,min}$ at the *meta* and *para* positions and the corresponding Hammett constants σ_m or σ_p; the linear correlation coefficient is 0.97. Using this correlation we predict the σ_p values of —OOH and —$OOCH_3$ to be −0.08 and −0.18, respectively, and the σ_m to be 0.28 and 0.18. Our data suggest that in C_6H_5—OOH and C_6H_5—$OOCH_3$, the *para* (and *ortho*) positions are slightly activated toward electrophilic attack relative to benzene, while the *meta* positions are deactivated.

Substituents for which σ_m is greater than σ_p, such as —NH_2, —OH and —OCH_3, are classified as resonance-donating and inductive-withdrawing groups[121]. Our Hammett constant and σ_I predictions suggest that the —OOH and —$OOCH_3$ groups fit into this category. Furthermore, since $\sigma_p \approx \sigma_I + \sigma_R$[121], where σ_R describes resonance effects, we are able to estimate the σ_R values for —OOH and —$OOCH_3$ to be approximately −0.33 and −0.41, respectively. These σ_R predictions are fully consistent with the above interpretation.

Our relationships involving the electrostatic potential $V(\mathbf{r})$ and the average local ionization energy $\bar{I}(\mathbf{r})$ have allowed us to characterize the —OOH and —$OOCH_3$ groups

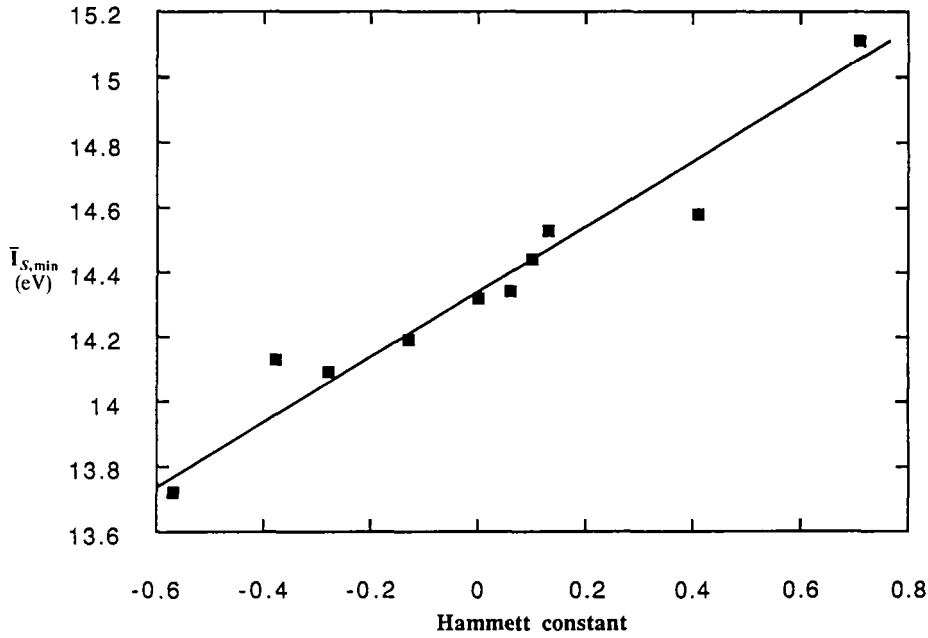


FIGURE 7. Relationship between STO-5G ring carbon $\bar{I}_{S,min}$ of some monosubstituted benzenes and the Hammett constants σ_p and/or σ_m; the linear correlation coefficient is 0.97

as moderately strong inductive attractors and resonance donors of electronic charge, as are also —OH and —OCH_3. The ring carbon $\bar{I}_{S,min}$ data in Table 10 suggest that —OOH and —$OOCH_3$ are weaker than —OH and —OCH_3 as activators of the benzene ring toward electrophilic substitution; this is consistent with the less negative σ_R values predicted for the former two.

VI. OVERVIEW OF THE REACTIONS OF ALCOHOLS, PHENOLS AND ETHERS

Alcohols are highly versatile chemical species which can be converted to many kinds of aliphatic compounds: ethers, alkyl halides, alkenes, esters, aldehydes, ketones and carboxylic acids. Despite the great variety and selectivity involved in alcohol reactions, these can be divided into three major types[86].

(1) the alcohol acting as an acid and the O—H bond being cleaved;
(2) the alcohol oxygen acting as a base, and the C—O bond being cleaved (normally resulting in the elimination of water); and
(3) oxidations, by agents such as H_2CrO_4 or $KMnO_4$.

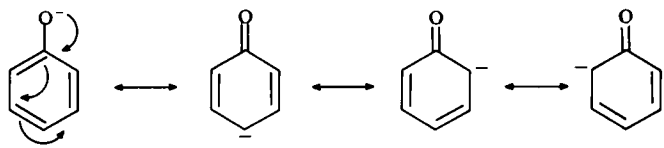
Reactions of the first two types do not result in a change in oxidation number of the alcohol oxygen (although this oxygen is not always retained in the reaction product), while the third of course does. It was pointed out in Section IV.A that the key features of the electrostatic potentials of alcohols are strongly positive and negative regions associated with the hydroxyl hydrogen and oxygen. These are fully consistent with the first two reaction categories of alcohols, i.e. acidity of the hydrogen and basicity of the oxygen.

Phenols are also used widely in synthesis. Their reactions can again be classified into three main types[86]:

(1) substitution of the aromatic ring;
(2) the phenol acting as an acid and the O—H bond being cleaved; and
(3) oxidation to quinones.

As is well known, —OH activates the benzene ring toward electrophilic attack, and phenol is therefore useful for forming *para*- and *ortho*-substituted aromatic derivatives.

Phenol (**3**) is a stronger acid than the aliphatic alcohols (**2**), which can be rationalized by the high degree of resonance stabilization afforded the phenoxide ion (**15**) (equation 26) by the presence of the aromatic ring[86]. In essence, this reflects the higher charge capacity of an aromatic ring relative to the alkyl groups of aliphatic alcohols. Unlike the latter, which require more rigorous basic conditions to form alkoxides, phenols can form phenoxide ions by reaction in aqueous sodium hydroxide. Both alkoxides and phenoxides are used in the preparation of ethers.



(26)

(**15**)

As a class, ethers are relatively inert compounds. (An important exception are the epoxides and, to a smaller degree, the oxetanes, which will be discussed separately.) Ethers are generally unreactive in the presence of bases (unlike alcohols and phenols), and both oxidizing and reducing agents. Their main reaction is C—O bond cleavage,

in which the ether oxygen acts as a base[86]. Reactions such as these require acid catalysis, normally under fairly strenuous conditions.

The importance of oxygen basicity in ether chemical behaviour could be inferred from their electrostatic potentials, in which the dominant feature is the extended and strong negative region due to the oxygen (plate 2 and Tables 7 and 8). It is also evident that the ether hydrogens are much less positive and hence less susceptible to nucleophiles (or bases) than are the hydroxyl hydrogens of alcohols and phenols (e.g. see plates 1 and 2 and Table 7), in agreement with ether molecules' general unreactivity toward bases[86].

VII. OVERVIEW OF THE CHEMICAL REACTIVITY OF HYDROPEROXIDES AND PEROXIDES

Many of the physical and some of the chemical properties of alkyl hydroperoxides and peroxides are similar to those of the corresponding alcohols and ethers, respectively (e.g. see Tables 1, 3, 4 and 7–10). These similarities include a general susceptibility toward interactions with electrophiles and, in the cases of the alcohols and hydroperoxides, slightly acidic hydrogens. The additional presence of the —O—O— linkage in hydroperoxides and peroxides introduces significant instability into these compounds and virtually dominates their chemistry[86,131].

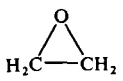
Alkyl hydroperoxides and peroxides are usually unstable, and many, e.g. $HOOCH_3$ and H_3COOCH_3, are highly explosive. In general, the violence of decomposition decreases as the C to —O—O— ratio increases[131]. These types of compounds are not normally used as explosives, however, due to their extreme instabilities. The latter is reflected in the fact that commercially available organic peroxides are labelled with their ten-hour half-life temperatures[131].

A major use of organic peroxides in synthesis is as a source of free radicals, $RO\cdot$. They are used in the polymer industry as initiators of free radical polymerization, and as curing and crosslinking agents[131]. Transfer of an oxygen atom from organic peroxides via cleavage of an O—O bond can also be a highly significant biochemical process[132], e.g. in catalysis by flavoenzymes, although the mechanistic details are not well understood[133]. Bach and coworkers have pointed out the importance of the inclusion of electron correlation in studies of the 1,2-hydrogen shift in H_2O_2 and CH_3OOH[133,134].

VIII. THREE- AND FOUR-MEMBERED-RING ETHERS AND PEROXIDES

Three- and four-membered ring saturated ethers and peroxides, derivatives of ethylene oxide (oxirane, **16**), oxetane (**17**), dioxirane (**18**) and 1,2-dioxetane (**19**), differ significantly in both physical and chemical properties from their aliphatic and larger alicyclic analogues[86,135]. A key characteristic of these molecules is the small endocyclic bond angles imposed by the three- and four-membered rings; for tetracoordinate carbon and dicoordinate oxygen, normal bond angles are in the neighbourhood of 109°. This feature is a destabilizing factor, contributing to the overall strain inherent in these systems[135].

Three- and four-membered heterocyclic rings are normally classified as strained molecules. The term 'molecular strain' is viewed generally in a broad sense to include all factors that are destabilizing in a molecule, such as unfavourable conformations and distortions of bond distances, as well as the perhaps more common notion of bond angle



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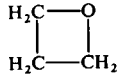

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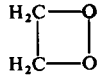
(18)



(19)

strain. (A detailed discussion of strained organic molecules has been presented by Greenberg and Liebman[135].)

We have earlier developed an index which provides an effective basis for characterizing individual strained bonds[136], based on the 'bond path' concept[137,138]. A bond path is the path between two bonded nuclei that goes through the saddle point in the internuclear density and follows the maximum density gradient to each nucleus. It can be viewed as the ridge of highest electron density that links the two nuclei. For many bonds, such as those between the carbons in propane and cyclohexane, the bond path is essentially identical with the internuclear axis; in other cases, such as molecules with strained bonds, there can be a significant difference between the two[116,136,138–142]. Our 'bond deviation' index was introduced as a numerical measure of the degree to which a given bond path differs from a defined reference path[136], and can be viewed as reflecting bond angle strain. A thorough discussion of this index has been given elsewhere[141].

We have shown for ethylene oxide (**16**)[136], dioxirane (**18**)[115] and a variety of strained aza systems[121] that the introduction of oxygen or nitrogen into strained rings diminishes the bond deviation index of the C—X bond (where X is O or N) relative to the parent hydrocarbon C—C bond, suggesting a slight decrease in bond angle strain. For example, the bond deviation indices of the C—O bonds in **16** and **18** are 0.06 and 0.05, respectively, compared to 0.08 for the C—C bonds in cyclopropane; that of the O—O bond in **18** is 0.05[115,136]. (To provide further perspective, the values for cyclobutane and cyclohexane are 0.02 and 0.00[141].)

The slightly stabilizing effect of the introduction of oxygen and nitrogen into strained ring systems is reflected in the individual bonds, as was just discussed, and also in the molecule as a whole; this can be inferred from calculated isodesmic reaction energies (Table 11). The isodesmic reaction procedure[91,143] is a means of studying anomalous energy effects in molecules. An isodesmic reaction is a hypothetical chemical process in which the number of bonds of each formal type remains the same on each side of the equation, but their mutual relationships are changed. Representative isodesmic reactions for propane (C_3H_8) and cyclopropane (C_3H_6) are given in equations 27 and 28, respectively. These relationships were designed so that the total numbers of C—C and C—H bonds are the same in the products as in the reactants. If the energies of these bonds also remained the same, then ΔE for each reaction would be zero. Hence the ΔE values reveal any deviations from bond energy additivity and are therefore interpreted as being due to special energy effects associated with the molecule being investigated, e.g. strain, steric effects, resonance stabilization, etc. ($\Delta E < 0$ indicates the presence of stabilizing factors, while $\Delta E > 0$ implies destabilization.)

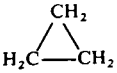
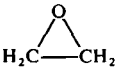
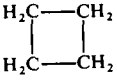
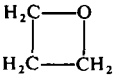
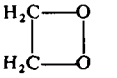
$$2C_2H_6 \longrightarrow C_3H_8 + CH_4 \tag{27}$$

$$3C_2H_6 \longrightarrow C_3H_6 + 3CH_4 \tag{28}$$

Table 11 shows that the calculated isodesmic reaction energies of cyclopropane, cyclobutane and **16–19** are positive, with values ranging from 18 to 31 kcal mol^{-1}; this is consistent with the conception of three- and four-membered rings as being strained. It is noteworthy that the calculated 3-21G $\Delta E_{\text{isodesmic}}$ values of cyclopropane and cyclobutane are fairly close to their widely quoted strain energies of 28 and 27 kcal mol^{-1}[135], respectively.

For each ring size, there is a small decrease in $\Delta E_{\text{isodesmic}}$ upon the replacement of one or two CH_2 groups by oxygens, indicating that this is having a stabilizing effect. We have found similar trends when substituting nitrogen in both strained and unstrained hydrocarbons[144,145]. We attribute this stabilization to σ-conjugation of the oxygen and nitrogen lone pairs[146,147], in which the lone-pair electronic density is delocalized to some extent through the σ-bond framework. A small degree of such stabilization is also

TABLE 11. Calculated 3-21G molecular energies and isodesmic reaction energies

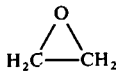
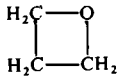
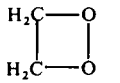
Molecule	Total energy (hartrees)	$\Delta E_{isodesmic}$ (kcal mol^{-1})
CH_4	−39.97688	0.0
H_2O	−75.58596	0.0
CH_3CH_3	−78.79395	0.0
CH_3OH	−114.39802	0.0
	−116.40121	31.4
$CH_3CH_2CH_3$	−117.61330	−1.4
H_2O_2	−149.94582	0.0
	−152.00070	31.3
H_3COCH_3	−153.21321	−2.0
	−155.23100	23.4
	−187.55208	25.7
	−190.83891	17.8
	−226.37886	19.6
H_3COOCH_3	−227.58031	−6.5

observed in the unstrained molecule CH_3OCH_3 (Table 11). The absence of a significant decrease in $\Delta E_{isodesmic}$ in going from cyclopropane to ethylene oxide, **16** (and also to its nitrogen counterpart, aziridine[145]), may reflect an opposing, destabilizing factor; the heteroatoms may be disrupting to some extent the 'σ-aromaticity' that has been attributed to cyclopropane[148]. (Detailed analyses of the contributions to overall molecular strain in cyclopropane and cyclobutane are given elsewhere[135,148,149].)

In the preceding paragraphs we have discussed the effects of imposing three- and four-membered-ring frameworks upon ethers and peroxides. Despite the evidence that oxygen may actually have some stabilizing influence upon the individual strained bonds and the molecules as a whole, the net result is that **16–19** and their derivatives are inherently destabilized, relative to their aliphatic non-cyclic analogues, by the structural constraints of their frameworks. It can be seen in Table 12 that the C—O and O—O bond lengths of **16–19** are in all instances slightly longer (and weaker[115]) than the corresponding bond distances in their aliphatic analogues (Table 4). This is another reflection of their relative instability, suggesting enhanced tendencies for C—O and/or O—O bond cleavage in **16–19**.

Unlike aliphatic and larger alicyclic ethers, **16** and **17** undergo both acid- and base-catalyzed C—O bond cleavage[86,135]. Thus nucleophiles to which tetrahydrofuran and

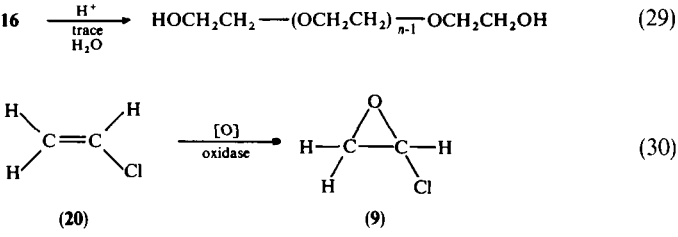
TABLE 12. Calculated and experimental structural parameters of some strained monoethers and peroxides

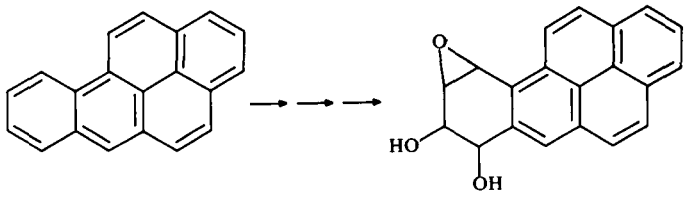
Molecule	Structural parameter	HF/3-21G	Experimental
	r(OC)	1.469	1.434[a]
	r(CC)	1.474	1.470
	∠(COC)	60	61.4
	∠(CCO)	60	59.3
	r(OC)	1.476	1.449[b]
	r(CC)	1.558	1.549
	∠(COC)	92	92
	∠(CCO)	91	92
	r(OO)	1.522	1.516[c]
	r(OC)	1.428	1.388
	∠(COO)	58	57
	∠(OCO)	64	66
	r(OO)	1.497	
	r(OC)	1.486	[d]
	r(CC)	1.535	
	∠(COO)	91	
	∠(OCC)	89	

[a]G. L. Cunningham, A. W. Boyd, R. J. Meyers, W. D. Gwinn and W. I. LeVan, *J. Chem. Phys.*, **19**, 676 (1951).
[b]S. I. Chan, J. Zinn and W. D. Gwinn, *J. Chem. Phys.*, **34**, 1319 (1961).
[c]R. D. Suenram and F. J. Lovas, *J. Am. Chem. Soc.*, **100**, 5117 (1978).
[d]Not available.

diethyl ether are inert, e.g. CH_3O^- and NH_3, cleave C—O bonds in **16** and **17**. In view of the greater strain in the C—O bonds in **16** compared to **17**, implied by the differences in the bond deviation indices of three- and four-membered rings[141] (as mentioned earlier), it is not surprising that **16** is generally more reactive than **17**[135]. For example, the OH^- catalyzed cleavage of a C—O bond in **16** proceeds 10^3 times more rapidly than in **17**[150]. These experimental observations suggest that the effects of bond angle strain are an important factor in determining the relative reactivities of epoxides and oxetanes.

Cleavage reactions of epoxides are extremely useful in organic synthesis[86], e.g. in making polyethylene glycol (equation 29). In addition, epoxides are believed to be responsible for the carcinogenicities of a number of olefins and halogenated olefins[151–153], e.g. the notorious vinyl chloride (**20**) (equation 30), and polycyclic aromatic hydrocarbons[154–156], e.g. benzo(*a*)pyrene (**21**) (equation 31). (It has been shown that chlorooxirane, **9**, and the diol epoxide **22** are the ultimate carcinogenic forms of **20** and



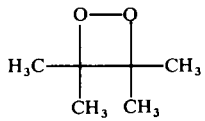


(31)

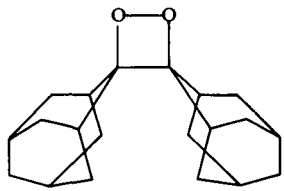
(21) (22)

21[151–156].) Because of their importance, the epoxides and their possible reaction intermediates and pathways have prompted a variety of theoretical investigations; see, for example, references 113 and 156–173. Many of these have sought to elucidate the mechanisms through which they exert their biological effects[113,158,160,162,164–171,173].

Dioxiranes and 1,2-dioxetanes are in general highly unstable species[135], as might be anticipated due to the presence of the —O—O— linkage and considerable strain. The results of experimental studies have been interpreted as indicating that dioxiranes are intermediates in some reactions of peroxy compounds, and that they can serve as oxygen transfer agents[174–181]. This interesting class of oxidants has been analysed in several theoretical studies; see, for example, references 115 and 182–185. A number of 1,2-dioxetanes, e.g. **23** and **24**, have been isolated[135,186–188]; many of these luminesce upon standing or heating[187]. Compound **24** possesses unusual thermal stability, and has provided some insight into the mechanism for the thermal decomposition of 1,2-dioxetanes[135,188]



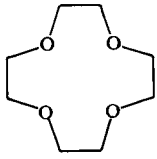
(23)



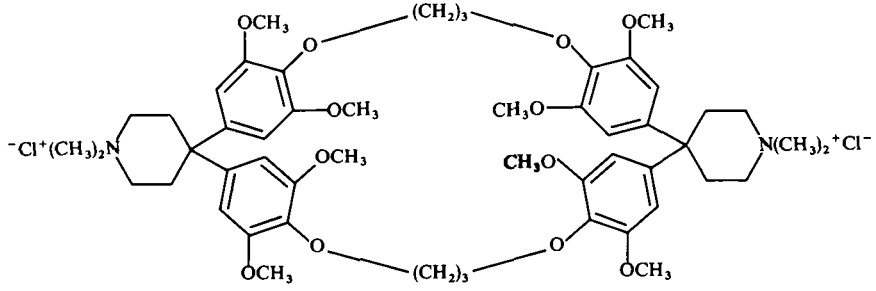
(24)

IX. THE ETHER LINKAGE IN MOLECULAR RECOGNITION

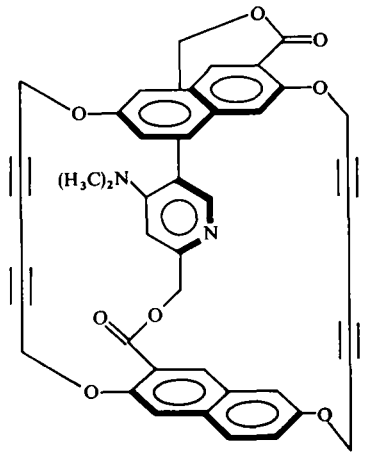
The —O— linkage is a component of crown ethers[3,189], e.g. 1,4,7,10-tetraoxacyclododecane or '12-crown-4' (**25**), and of many cyclophanes[190], e.g. **26**[191] and **27**[192,193]. These classes of compounds are of particular interest in the area of molecular recognition[190,194–196] because of their abilities to complex smaller chemical species, thus acting as 'hosts' for 'guest' molecules by means of favourable intermolecular interactions.



(25)



(26)



(27)

Crown ethers form complexes primarily with positive ions[3,189,197]; in most cases, the cations are held tightly in the centre of the cavity. The size of the cavity determines the ions which can be complexed; for example, **25** binds Li^+ but not K^+[197]. Crown ethers are accordingly useful in separating mixtures of cations, and also as phase-transfer catalysts in synthesis[197]. Thus, the oxygens in the crown ethers apparently play at least two key roles: they interact favourably with positively charged guest ions, and they also provide solubility in aqueous solutions. Several conformational studies of crown ethers have been carried out, using *ab initio*[198–200], semi-empirical[201] and molecular mechanics[202–204] procedures. A recent *ab initio* SCF-MO study has reported a fourth, previously unreported conformation of 12-crown-4, **25**[200].

The cyclophanes **26** and **27** were designed specifically for the inclusion of substituted aromatic molecules[191] and phenols[192,193], respectively. The methoxy groups in **26** are believed to provide depth to the binding site and to prevent the formation of aggregates of **26** in aqueous solution[190]. The pyridine nitrogen in **27** can act as a hydrogen-bond acceptor for an —OH hydrogen of the guest molecule[192,193]. A major role of the ether oxygen in cyclophanes such as **26** and **27** is presumably to aid solubility in aqueous solution, although other weak intermolecular interactions involving the —O— linkage undoubtedly influence the complexing ability of the cyclophane. The identification and elucidation of these present a challenge to the theoretical chemist.

X. ACKNOWLEDGEMENT

We thank Mr. Tore Brinck for computational assistance. The support of this work through DARPA/ONR Contract No. N00014-91-J-1897, administered by ONR, is greatly appreciated.

XI. REFERENCES

1. D. Peters, in *Chemistry of the Functional Groups, The Chemistry of the Ether Linkage* (Ed. S. Patai), Chap. 1, Wiley, London, 1967.
2. R. F. W. Bader, in *Chemistry of the Functional Groups, The Chemistry of the Hydroxyl Group* (Ed. S. Patai), Chap. 1, Wiley, London, 1971.
3. J. Royer, in *Chemistry of the Functional Groups, Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulphur Analogues* (Ed. S. Patai), Chap. 1, Wiley, Chichester, 1980.
4. D. Cremer, in *Chemistry of the Functional Groups, The Chemistry of the Peroxides* (Ed. S. Patai), Chap. 1, Wiley, Chichester, 1980.
5. L. Pauling, *J. Am. Chem. Soc.*, **54**, 3570 (1932).
6. L. Pauling, *The Nature of the Chemical Bond*, 3rd ed., Cornell University Press, Ithaca, New York, 1960.
7. R. G. Parr, R. A. Donnelly, M. Levy and W. E. Palke, *J. Chem. Phys.*, **68**, 3801 (1978).
8. R. A. Donnelly and R. G. Parr, *J. Chem. Phys.*, **69**, 4431 (1978).
9. P. Politzer and H. Weinstein, *J. Chem. Phys.*, **71**, 4218 (1979).
10. R. T. Sanderson, *Science*, **114**, 670 (1951).
11. R. T. Sanderson, *J. Am. Chem. Soc.*, **74**, 272 (1952).
12. R. G. Parr and W. Yang, *Density-Function Theory of Atoms and Molecules*, Oxford University Press, New York, 1989.
13. L. J. Bartolotti, S. R. Gadre and R. G. Parr, *J. Am. Chem. Soc.*, **102**, 2945 (1980).
14. M. S. Gopinathan and M. A. Whitehead, *Isr. J. Chem.*, **19**, 209 (1980).
15. J. Katriel, R. G. Parr and M. R. Nyden, *J. Chem. Phys.*, **74**, 2397 (1981).
16. J. P. Perdew, R. G. Parr, M. Levy and J. L. Balduz, Jr., *Phys. Rev. Lett.*, **49**, 1691 (1982).
17. T. T. Nguyen-Dang, R. F. W. Bader and H. Essén, *Int. J. Quantum Chem.*, **22**, 1049 (1982).
18. R. G. Parr and L. J. Bartolotti, *J. Phys. Chem.*, **87**, 2810 (1983).
19. J. Robles and L. J. Bartolotti, *J. Am. Chem. Soc.*, **106**, 3723 (1984).
20. P. Fuentealba and R. G. Parr, *J. Chem. Phys.*, **94**, 5559 (1991).
21. P. Politzer, J. D. Elliott and B. F. Meroney, *Chem. Phys. Lett.*, **23**, 331 (1973).
22. R. F. W. Bader, *Acc. Chem. Res.*, **18**, 9 (1985).
23. J. Rychlewski and R. G. Parr, *J. Chem. Phys.*, **84**, 1696 (1986).
24. R. P. Iczkowski and J. L. Margrave, *J. Am. Chem. Soc.*, **83**, 3547 (1961).
25. C. K. Jørgensen, *Orbitals in Atoms and Molecules*, Academic Press, New York, 1962.
26. J. Hinze, M. A. Whitehead and H. H. Jaffé, *J. Am. Chem. Soc.*, **85**, 148 (1963).
27. G. Klopman, *J. Am. Chem. Soc.*, **86**, 1463 (1964).
28. J. L. Reed, *J. Phys. Chem.*, **85**, 148 (1981).
29. R. E. Watson, L. H. Bennett and J. W. Davenport, *Phys. Rev. B*, **27**, 6428 (1983).
30. L. L. Lohr, Jr., *Int. J. Quantum Chem.*, **25**, 211 (1984).
31. L. Komorowski, *Chem. Phys.*, **114**, 55 (1987).
32. G. P. Lawes, N. H. March and M. S. Yusaf, *Phys. Lett. A*, **67**, 342 (1978).
33. N. H. March, *J. Chem. Phys.*, **76**, 1869 (1982).
34. J. L. Gázquez and E. Ortiz, *J. Chem. Phys.*, **81**, 2741 (1984).
35. W. J. Mortier, K. V. Genechten and J. Gasteiger, *J. Am. Chem. Soc.*, **107**, 829 (1985).
36. M. S. Wilson and S. Ichikawa, *J. Phys. Chem.*, **93**, 3087 (1989).
37. A. K. Rappé and W. A. Goddard III, *J. Phys. Chem.*, **95**, 3358 (1991).
38. L. Komorowski, *Chem. Phys.*, **76**, 31 (1983).
39. R. G. Parr and L. J. Bartolotti, *J. Am. Chem. Soc.*, **104**, 3801 (1982).
40. L. Komorowski, *Chem. Phys. Lett.*, **103**, 201 (1983).
41. R. Ponec, *Theor. Chim. Acta*, **59**, 629 (1980).
42. J. E. Huheey, *J. Phys. Chem.*, **69**, 3284 (1965).

43. L. C. Balbas, L. A. Vega and J. A. Alonso, *Z. Phys. A*, **319**, 275 (1984).
44. D. Datta, *J. Phys. Chem.*, **90**, 4216 (1986).
45. P. Politzer, *J. Chem. Phys.*, **86**, 1072 (1987).
46. P. Politzer and B. A. Zilles, *Croat. Chem. Acta*, **57**, 1055 (1984).
47. J. E. Huheey and J. C. Watts, *Inorg. Chem.*, **10**, 1553 (1971).
48. J. E. Huheey, *J. Org. Chem.*, **36**, 204 (1971).
49. R. G. Parr and R. G. Pearson, *J. Am. Chem. Soc.*, **105**, 7512 (1983).
50. R. G. Pearson, *J. Am. Chem. Soc.*, **85**, 3533 (1963).
51. R. G. Pearson, *Science*, **151**, 172 (1966).
52. R. F. Nalewajski, *J. Am. Chem. Soc.*, **106**, 944 (1984).
53. W. Yang, C. Lee and S. K. Ghosh, *J. Phys. Chem.*, **89**, 5412 (1985).
54. M. Berkowitz, S. K. Ghosh and R. G. Parr, *J. Am. Chem. Soc.*, **107**, 6811 (1985).
55. L. Komorowski, *Chem. Phys. Lett.*, **134**, 536 (1987).
56. L. Komorowski, *Z. Naturforsch*, **42a**, 767 (1987).
57. M. Berkowitz and R. G. Parr, *J. Chem. Phys.*, **88**, 2554 (1988).
58. R. F. Nalewajski, J. Korchowiec and Z. Zhou, *Int. J. Quantum Chem., Quantum Chem. Symp.*, **22**, 349 (1988).
59. L. Bauer, G. Sala and G. Sello, *J. Comput. Chem.*, **11**, 694 (1990).
60. P. K. Chattaraj, H. Lee and R. G. Parr, *J. Am. Chem. Soc.*, **113**, 1855 (1991).
61. M. K. Harbola, R. G. Parr and C. Lee, *J. Chem. Phys.*, **94**, 6055 (1991).
62. R. G. Parr and P. K. Chattaraj, *J. Am. Chem. Soc.*, **113**, 1854 (1991).
63. R. S. Mulliken, *J. Chem. Phys.*, **2**, 782 (1934).
64. R. S. Mulliken, *J. Chem. Phys.*, **3**, 573 (1935).
65. P. Politzer, D. R. Murphy and R. G. Parr, *J. Chem. Phys.*, **79**, 3859 (1983).
66. P. Politzer, J. E. Huheey, J. S. Murray and M. Grodzicki, *J. Mol. Struct. (THEOCHEM)*, in press.
67. A. Vela and J. L. Gázquez, *J. Am. Chem. Soc.*, **112**, 1490 (1990).
68. K. D. Sen, M. C. Bohm and P. C. Schmidt, *Struct. Bond.*, **66**, 99 (1987).
69. J. K. Nagle, *J. Am. Chem. Soc.*, **112**, 4741 (1990).
70. P. Politzer, J. S. Murray and M. E. Grice, in *Chemical Hardness* (Ed. K. D. Sen), Springer-Varlag, in press.
71. C. E. Moore, *Natl. Stand. Ref. Data Ser. Natl. Bur. Stand.*, **34** (1970).
72. H. Hotop and W. C. Lineberger, *J. Phys. Chem. Ref. Data*, **4**, 539 (1975).
73. E. S. Gould, *Inorganic Reactions and Structure*, 2nd ed., Holt, Rinehart and Winston, New York, 1962, p. 211.
74. R. T. Sanderson, *Inorganic Chemistry*, Reinhold, New York, 1967, pp. 285–292.
75. P. Politzer, in *Homoatomic Rings, Chains and Macromolecules of Main-Group Elements* (Ed. A. L. Rheingold), Chap. 4, Elsevier, New York, 1977.
76. F. A. Cotton and G. Wilkinson, in *Advances in Inorganic Chemistry*, 4th ed., Wiley–Interscience, New York, 1980, pp. 208–211.
77. J. E. Huheey, *Inorganic Chemistry: Principles of Structure and Reactivity*, 3rd ed., Harper and Row, New York, 1983.
78. B. E. Douglas, D. H. McDaniel and J. Alexander, in *Concepts and Models of Inorganic Chemistry*, 2nd ed., Wiley, New York, 1983, pp. 45–47, 226.
79. P. Politzer, *J. Am. Chem. Soc.*, **91**, 6235 (1969).
80. P. Politzer, *Inorg. Chem.*, **16**, 3350 (1977).
81. J. H. Binks and J. A. Duffy, *J. Chem. Soc., Faraday Trans. 2*, **81**, 473 (1985).
82. F. A. Cotton and G. Wilkinson, *Advanced Inorganic Chemistry*, 4th ed., Wiley–Interscience, New York, 1980, pp. 497–498.
83. F. K. Ross, *Trans. Am. Cryst. Assoc.*, **16**, 79 (1980).
84. P. Politzer and P. H, Reggio, *J. Am. Chem. Soc.*, **94**, 8308 (1972).
85. R. S. Evans and J. E. Huheey, *Chem. Phys. Lett.*, **19**, 114 (1973).
86. N. L. Allinger, M. P. Cava, D. C. DeJongh, C. R. Johnson, N. A. Lebel and C. L. Stevins, *Organic Chemistry*, Worth Publishers, New York, 1971.
87. J. I. Brauman and L. K. Blair, *J. Am. Chem. Soc.*, **92**, 5986 (1970).
88. R. T. Morrison and R. N. Boyd, *Organic Chemistry*, 3rd ed., Allyn and Bacon, 1973, p. 526.
89. A. Streitweiser, Jr. and C. H. Heathcock, *Introduction to Organic Chemistry*, 2nd ed., Macmillan, New York, 1981, pp. 237–240.

90. W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, 1986.
91. A. Hinchliffe, *Computational Quantum Chemistry*, Wiley, Chichester, 1988.
92. J. K. Labanowski and J. W. Andzelm (Eds.), *Density Functional Methods in Chemistry*, Springer-Verlag, New York, 1991.
93. E. S. Kryachko and E. V. Ludeña, *Energy Density Functional Theory of Many-electron Systems*, Kluwer, Dordrecht, 1990.
94. M. Born and J. R. Oppenheimer, *Ann. Phys.*, **84**, 457 (1927).
95. H. A. Bethe and E. E. Salpeter, *Quantum Mechanics of One- and Two-electron Atoms*, Academic Press, New York, 1957.
96. P. Hohenberg and W. Kohn, *Phys. Rev. B*, **136**, 864 (1964).
97. W. Kohn and L. J. Sham, *Phys. Rev. A*, **140**, 113 (1965).
98. E. Clementi and S. J. Chakravorty, *J. Chem. Phys.*, **93**, 2591 (1990).
99. J. M. Seminario, M. C. Concha and P. Politzer, *Int. J. Quantum Chem., Quantum Chem. Symp.*, **25**, 249 (1991).
100. B. Delley, *J. Chem. Phys.*, **92**, 508 (1990).
101. J. M. Seminario, M. C. Concha and P. Politzer, *J. Comput. Chem.*, **13**, 177 (1992).
102. D. A. Clabo and H. F. Schaefer III, *Int. J. Quantum Chem.*, **31**, 429 (1987).
103. J. M. Coffin and P. Pulay, *J. Phys. Chem.*, **95**, 118 (1991).
104. P. Politzer and N. Sukumar, *J. Mol. Struct. (THEOCHEM)*, **179**, 439 (1988).
105. E. Scrocco and J. Tomasi, in *Topics in Current Chemistry*, No. 42, Springer-Verlag, Berlin, 1973, p. 95.
106. E. Scrocco and J. Tomasi, *Adv. Quantum Chem.*, **11**, 115 (1978).
107. P. Politzer and K. C. Daiker, in *The Force Concept in Chemistry* (Ed. B. M. Deb), Chap. 6, Van Nostrand Reinhold Co., 1981.
108. P. Politzer and D. G. Truhlar (Eds.), *Chemical Applications of Atomic and Molecular Electrostatic Potentials*, Plenum Press, New York, 1981.
109. P. Politzer and J. S. Murray, in *Reviews of Computational Chemistry* (Eds. K. B. Lipkowitz and D. B. Boyd), Chap. 7, VCH Publishers, New York, 1991.
110. R. K. Pathak and S. R. Gadre, *J. Chem. Phys.*, **93**, 1770 (1990).
111. P. Sjoberg and P. Politzer, *J. Phys. Chem.*, **94**, 3959 (1990).
112. J. S. Murray and P. Politzer, *J. Org. Chem.*, **56**, 6699 (1991).
113. P. Politzer and P. R. Laurence, *Carcinogenesis*, **5**, 845 (1984).
114. J. S. Murray, B. A. Zilles, K. Jayasuriya and P. Politzer, *J. Am. Chem. Soc.*, **108**, 91 (1986).
115. P. Politzer, R. Bar-Adon and R. S. Miller, *J. Phys. Chem.*, **91**, 3191 (1987).
116. J. S. Murray and P. Politzer, *J. Mol. Struct. (THEOCHEM)*, **163**, 111 (1988).
117. J. S. Murray, S. Ranganathan and P. Politzer, *J. Org. Chem.*, **56**, 3734 (1991).
118. J. S. Murray and P. Politzer, *J. Chem. Res.* (5), 110 (1992).
119. M. J. Kamlet, J.-L. M. Abboud, M. H. Abraham and R. W. Taft, *J. Org. Chem.*, **48**, 2877 (1983).
120. T. Brinck, J. S. Murray and P. Politzer, *Mol. Phys.*, in press.
121. O. Exner, *Correlation Analysis of Chemical Data*, Plenum Press, Publishing Corporation and SNTL Publishers of Technical Literature, Progue Czechoslavakia, 1988.
122. C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, **91**, 165 (1991).
123. J. S. Murray and P. Politzer, *Chem. Phys. Lett.*, **152**, 364 (1988).
124. P. Sjoberg, J. S. Murray, T. Brinck, and P. Politzer, *Can. J. Chem.*, **68**, 1440 (1990).
125. J. S. Murray, T. Brinck, M. E. Grice and P. Politzer, *J. Mol. Struct. (THEOCHEM)*, **256**, 29 (1992).
126. J. S. Murray, T. Brinck and P. Politzer, *J. Mol. Struct. (THEOCHEM)*, **255**, 271 (1992).
127. J. S. Murray, J. M. Seminario, P. Politzer and P. Sjoberg, *Int. J. Quantum Chem., Quantum Chem. Symp.*, **24**, 645 (1990).
128. T. Brinck, J. S. Murray, P. Politzer and R. E. Carter, *J. Org. Chem.*, **56**, 2934 (1991).
129. P. Lane, J. S. Murray and P. Politzer, *J. Mol. Struct. (THEOCHEM)*, **236**, 283 (1991).
130. T. Brinck, J. S. Murray and P. Politzer, *J. Org. Chem.*, **56**, 5012 (1991).
131. D. Swern (Ed.), *Organic Peroxides*, Vol. 1, Wiley–Interscience, New York, 1970.
132. C. Walsh, in *Enzymatic Reaction Mechanisms*, W. H. Freeman and Co., San Francisco, 1979, pp. 406–463.
133. R. D. Bach, J. J. W. McDouall, A. L. Owensby and H. B. Schlegel, *J. Am. Chem. Soc.*, **112**, 7065 (1990).

134. R. D. Bach, A. L. Owensby, C. Gonzalez, H. B. Schlegel and J. J. W. McDouall, *J. Am. Chem. Soc.*, **113**, 6001 (1991).
135. A. Greenberg and J. F. Liebman, *Strained Organic Molecules*, Academic Press, New York, 1978.
136. P. Politzer, L. Abrahmsen, P. Sjoberg and P. R. Laurence, *Chem. Phys. Lett.*, **102**, 74 (1983).
137. R. F. W. Bader, T.-H. Tang, Y. Tal and F. W. Biegler-Konig, *J. Am. Chem. Soc.*, **104**, 940, 946 (1982).
138. R. F. W. Bader and T. T. Nguyen-Dang, *Adv. Quantum Chem.*, **14**, 63 (1981).
139. P. Politzer, K. Jayasuriya and B. A. Zilles, *J. Am. Chem. Soc.*, **107**, 121 (1985).
140. P. Politzer, G. P. Kirschenheuter and J. Alster, *J. Am. Chem. Soc.*, **109**, 1033 (1987).
141. P. Politzer and J. S. Murray, in *Structure and Reactivity (Molecular Structure and Energetics)* (Eds. J. F. Liebman and A. Greenberg), Chap. 1, VCH Publishers, New York, 1988.
142. P. Politzer and J. M. Seminario, *J. Phys. Chem.*, **93**, 588 (1989).
143. W. S. Hehre, R. Ditchfield, L. Radom and J. A. Pople, *J. Am. Chem. Soc.*, **92**, 4796 (1970).
144. J. S. Murray, P. C. Redfern, J. M. Seminario and P. Politzer, *J. Phys. Chem.*, **94**, 2320 (1990).
145. J. S. Murray, J. M. Seminario, P. Lane and P. Politzer *J. Mol. Struct. (THEOCHEM)*, **207**, 193 (1990).
146. M. J. S. Dewar, *J. Am. Chem. Soc.*, **106**, 669 (1984).
147. V. I. Minkin, M. N. Glukhovtsev and B. Y. A. Simkin, *J. Mol. Struct. (THEOCHEM)*, **181**, 93 (1988).
148. M. J. S. Dewar, *Bull. Soc. Chim. Belg.*, **88**, 957 (1979).
149. D. Cremer and E. Kraka, in *Structure and Reactivity (Molecular Structure and Energetics)* Eds. J. F. Liebman and A. Greenberg), Chap. 3, VCH Publishers, New York, 1988.
150. J. G. Pritchard and F. A. Long, *J. Am. Chem. Soc.*, **80**, 4162 (1958).
151. S. Banerjee and B. L. Van Duuren, *Cancer Res.*, **38**, 776 (1977).
152. H. Bartsch, C. Malaveille, A. Barbin and G. Planche, *Arch. Toxicol.*, **41**, 249 (1979).
153. H. M. Bolt, R. J. Laib and J. G. Filser, *Biochem. Pharmacol.*, **31**, 1 (1982).
154. W. S. Tsang and G. W. Griffin, *Metabolic Activation of Polynuclear Aromatic Hydrocarbons*, Pergamon Press, London, 1979.
155. R. G. Harvey, *Acc. Chem. Res.*, **14**, 218 (1981).
156. Y. T. Woo, D. Lai, J. C. Arcos and M. F. Argus (Eds.), *Chemical Induction of Cancer*, Vol. IIIB, Section 5.2.2.1, Academic Press, New York, 1984.
157. A. C. Hopkinson, M. H. Lien, I. G. Csizmadia and K. Yates, *Theor. Chim. Acta*, **47**, 97 (1978).
158. P. Politzer and V. M. Estes, in *Catalysis in Chemistry and Biochemistry. Theory and Experiment* (Ed. B. Pullman), Reidel, Dordrecht, 1979, p. 305.
159. H. Lischka and H. Kohler, *Chem. Phys. Lett.*, **63**, 326 (1979).
160. P. Politzer and P. Trefonas, III, in *Carcinogenesis: Fundamental Mechanism and Environmental Effects* (Eds. B. Pullman, P. O. P. Ts'o and H. V. Gelboin), Reidel, Dordrecht, 1980, p. 67.
161. K. Yamaguchi, S. Yabushita, T. Fueno, S. Kato and K. Morokuma, *Chem. Phys. Lett.*, **70**, 27 (1980).
162. P. Politzer, P. Trefonas, III, I. R. Politzer and B. Elfman, in *Quantum Chemistry in Biomedical Sciences*, Annals of the New York Academy of Sciences, 1981, p. 478.
163. R. H. Nobes, W. R. Rodwell, W. J. Bouma and L. Radom, *J. Am. Chem. Soc.*, **103**, 1913 (1981).
164. A. M. Ross, T. M. Pohl, K. Piazza, M. Thomas, B. Fox and D. L. Whalen, *J. Am. Chem. Soc.*, **104**, 1658 (1982).
165. P. R. Laurence and P. Politzer, *Int. J. Quantum Chem.*, **25**, 493 (1984).
166. P. R. Laurence, T. R. Proctor and P. Politzer, *Int. J. Quantum Chem.*, **26**, 425 (1984).
167. P. Politzer, P. R. Laurence and K. Jayasuriya, in *The Molecular Basis of Cancer: Part A. Macromolecular Structure, Carcinogens and Oncogenes* (Ed. R. Rein), Alan R. Liss, Inc., New York, 1985, p. 227.
168. G. P. Ford and C. T. Smith, *Int. J. Quantum Chem., Quantum Biol. Symp.*, **13**, 107 (1986).
169. G. P. Ford and C. T. Smith, *J. Am. Chem. Soc.*, **109**, 1325 (1987).
170. P. Politzer, *Toxicology Lett.*, **43**, 257 (1988).
171. P. Politzer, in *Chemical Carcinogens* (Eds. P. Politzer and F. J. Martin, Jr.), Chap. 8, Elsevier, Amsterdam, 1988.
172. A. E. Dorigo, K. N. Houk and T. Cohen, *J. Am. Chem. Soc.*, **111**, 8976 (1989).
173. G. P. Ford and C. T. Smith, *J. Comput. Chem.*, **10**, 568 (1989).
174. R. E. Montgomery, *J. Am. Chem. Soc.*, **96**, 7820 (1974).

175. R. W. Murray and V. Ramachandran, *Photochem. Photobiol.*, **30**, 63 (1979).
176. R. Curci, M. Fiorentino, L. Troisi, J. O. Edwards and R. H. Pater, *J. Org. Chem.*, **45**, 4758 (1980).
177. A. R. Gallopo and J. O. Edwards, *J. Org. Chem.*, **46**, 1684 (1981).
178. G. Cicala, R. Curci, M. Fiorentino and O. Lariccinta, *J. Org. Chem.*, **47**, 2670 (1982).
179. R. W. Murray and R. Jeyaraman, *J. Org. Chem.*, **50**, 2847 (1985).
180. W. Adam, R. Curci and J. O. Edwards, *Acc. Chem. Res.*, **22**, 205 (1989).
181. R. W. Murray, *Chem. Rev.*, **89**, 1187 (1989).
182. T.-K. Ha, H. Kühne, S. Vaccani and H. H. Günthard, *Chem. Phys. Lett.*, **24**, 172 (1974).
183. L. B. Harding and W. A. Goddard III, *J. Am. Chem. Soc.*, **100**, 7180 (1978).
184. D. Cremer and M. Shindler, *Chem. Phys. Lett.*, **133**, 293 (1987).
185. R. D. Bach, A. L. Owensby, J. L. Andrés and H. B. Schlegel, *J. Am. Chem. Soc.*, **113**, 7031 (1991).
186. K. R. Kopecky and C. Mumford, *Can. J. Chem.*, **47**, 709 (1969).
187. N. J. Turro, P. Lechtken, N. E. Shore, G. Schuster, H.-C. Steinmetzer and A. Yekta, *Acc. Chem. Res.*, **7**, 97 (1974).
188. G. B. Schuster, N. J. Turro, H.-C. Steinmetzer, A. P. Schaap, G. Faler, W. Adam and J. C. Lui, *J. Am. Chem. Soc.*, **97**, 7110 (1975).
189. C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 7017 (1967).
190. F. Diederich, *Nav. Res. Rev.*, **2**, 2 (1990).
191. S. B. Ferguson, E. M. Seward, F. Diederich, E. M. Sandord, A. Chou, P. Inocencio-Szweda and C. B. Knobler, *J. Org. Chem.*, **53**, 5593 (1988).
192. R. E. Sheridan and H. W. Whitlock, Jr., *J. Am. Chem. Soc.*, **110**, 4071 (1988).
193. K. M. Neder and H. W. Whitlock, Jr., *J. Am. Chem. Soc.*, **112**, 9412 (1990).
194. J. M. Lehn, *Angew. Chem., Int. Ed. Engl.*, **27**, 89 (1988).
195. D. J. Cram, *Angew. Chem., Int. Ed. Engl.*, **27**, 1009 (1988).
196. C. J. Pedersen, *Angew. Chem., Int. Ed. Engl.*, **27**, 1021 (1988).
197. J. March, *Advanced Organic Chemistry*, Wiley, New York, 1985.
198. A. Pullman, C. Giessner-Prettre and Y. V. Kruglyak, *Chem. Phys. Lett.*, **35**, 156 (1975).
199. K. Hori, H. Yamada and T. Yamabe, *Tetrahedron*, **39**, 67 (1983).
200. E. T. Seidl and H. F. Schaefer III, *J. Phys. Chem.*, **95**, 3589 (1991).
201. T. Yamabe, K. Hori, K. Akagi and K. Fukui, *Tetrahedron*, **35**, 1065 (1979).
202. M. J. Bovill, D. J. Chadwick and I. O. Sutherland, *J. Chem. Soc., Perkin Trans. 2*, 1529 (1980).
203. A. E. Howard, U. C. Singh, M. Billeter and P. A. Kollman, *J. Am. Chem. Soc.*, **110**, 6984 (1988).
204. J. R. Danewood, W. P. Anderson and J. J. Urban, *J. Comput. Chem.*, **9**, 111 (1988).

CHAPTER 2

Structural chemistry of selected classes of alcohols, ethers and peroxides

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I. INTRODUCTION

This chapter deals with the structural chemistry of selected classes of alcohols, ethers and peroxides. It relates mainly to data published in the past twelve years (from 1980 through 1991), supplementing the information contained in earlier volumes of this series

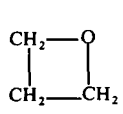
Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

on the corresponding functional groups (*The ether linkage*, 1967; *The hydroxyl group*, 1971; *Supplement E: Ethers, crown ethers, hydroxyl groups and their sulphur analogs*, 1980; *Peroxides*, 1983). New developments in crown ether and polyether chemistry have only recently been reviewed in a special update issue (*Crown ethers and analogs*, 1989), and therefore will not be treated here. A comprehensive discussion of the structural data obtained for oxygen-containing compounds by gas-phase electron-diffraction and microwave spectroscopy has also appeared in 1988[1]. The contents of the current publication refer primarily to crystallographic investigations in the solid state involving X-ray as well as neutron diffraction experimental techniques. Survey of the fundamental geometric information is based on accurate diffraction data measured at low temperatures. In the section on alcohols, special attention is drawn to features of molecular recognition and supramolecular chemistry, to reflect on the upsurging interest in these subjects during the past decade. The discussion which follows is based on experimental data obtained in the author's laboratory as well as on the results of other work retrieved with the aid of the Cambridge Crystallographic Database[2,3].

II. ETHERS

A. Geometry of Small Cyclic Ethers

The cyclic monoether species oxetane (**1**) and tetrahydrofuran (**2**) have recently been studied by low-temperature X-ray diffraction techniques, yielding highly precise structural parameters for these low-molecular-weight compounds in the solid state. The structure of oxetane (m.p. 174 K) was determined at 90 and 140 K, preserving the same crystalline phase within this temperature range[4]. The molecular structure in the crystal is characterized by an exact mirror (C_s) symmetry. The four-membered ring of oxetane



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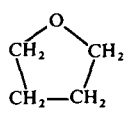

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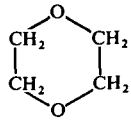


(3)

was found to be non-planar, having puckering angles of 10.7 deg at 90 K and 8.7 deg at 140 K. Previous single-crystal X-ray investigations at room temperature of heavily substituted oxetanes also showed the ring to be non-planar, its puckering angle ranging from about 5 to 23 deg[5–7]. It is interesting to note that in earlier spectroscopic and electron-diffraction investigations in the gas phase the oxetane molecule was found to be planar. One can reasonably assume, however, that the gas-phase results relate to the dynamically averaged conformation of the molecule, while those obtained for the solid state represent an energetically favourable conformation 'frozen out' in the crystal. The observed covalent parameters for oxetane at 90 K and 140 K are shown in Table 1. The apparent differences in bond distances between the two temperatures are most probably due to thermal motion effects, which usually cause an artificial bond shortening at higher temperatures[8]. The results obtained at 90 K should thus be considered as a more accurate representation of the molecular structure. The conformational strain of the four-membered ring is reflected most in the unusually long C—O bond distance of 1.46 Å; significantly shorter C—O bonds are observed in larger O-heterocycles as tetrahydrofuran and 1,4-dioxane (see below).

The structure of tetrahydrofuran (**2**) has also been elucidated by low-temperature X-ray diffraction in order to determine the preferred conformation of this molecule. In the gaseous phase tetrahydrofuran undergoes almost free pseudo-rotation between two

TABLE 1. Covalent parameters of small cyclic ethers, as determined by X-ray diffraction at various temperatures

	Compound						
	oxetane		tetrahydrofuran		1,4-dioxane		
Parameter	140 K	90 K	148 K	103 K	279 K	153 K	100 K[a]
C—O (Å)	1.443	1.460	1.429	1.435	1.425	1.431	1.429
C—C (Å)	1.517	1.534	1.511	1.531	1.478	1.513	1.515
C—H (Å)	0.98	0.97	1.05	1.09	1.00	0.98	1.06
C—O—C (deg)	90.5	90.2	109.8	108.2	109.0	109.9	110.0
O—C—C (deg)	91.9	92.0	106.7	107.4	111.2	110.9	110.8
C—C—C (deg)	85.0	84.8	101.9	102.0	—	—	—
Reference	4	4	9	9	11	11	12

[a]Results from multipole refinement.

or more low-energy conformations, while in the solid state it often appears to be disordered or thermally smeared. The recent low-temperature investigations at 103 and 148 K have established, however, that the tetrahydrofuran molecule possesses an ideal C_2 symmetry in the crystal[9]. The covalent parameters of the molecular structure at 103 K are: C—O 1.435 Å, C—C 1.531 Å, C—O—C 108.2 deg, O—C—C 107.4 deg and C—C—C 102.0 deg (Table 1). The observed data were found to be in good agreement with the values obtained from earlier electron-diffraction study, as well as with those predicted by theoretical *ab initio* calculations; indeed the twist C_2 conformation of tetrahydrofuran was assessed to be more favourable by about 1 kcal mol^{-1} than the alternative envelope conformation of the five-membered ring[10].

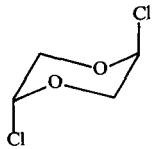
The molecular structure of 1,4-dioxane (**3**) has also been determined at several temperatures. Two crystalline phases of this compound, which melts at 285 K under ordinary pressure, have been detected thus far by differential thermal analysis (DTA)[11]. Phase I exists between 285 and 278 K, while phase II is stable below 278 K. Structure of the latter was analysed at 153 as well as 106 K[11,12]. Examination of the structural results reveals that the molecular structure is close to an ideal chair conformation, the torsion angles along the ring framework ranging from 57.0 to 58.3 deg. The C—O bond distances vary from 1.429 to 1.432 Å, the C—C bond lengths being near 1.515 Å. A rigid-body libration correction, according to the models proposed by Schomaker and Trueblood and by Scheringer to compensate for the bond shortening due to the effects of thermal motion[13,14], produced slightly enlarged values for the C—O and C—C bond lengths (1.44 and 1.52 Å, respectively). The observed C—O—C bond angles were found close to 110.0 deg, while the O—C—C ones were between 110.5 and 111.3 deg.

Table 1 summarizes the covalent parameters of the small cyclic ethers **1–3**, and shows how the observed values are affected by temperature conditions of the experiment.

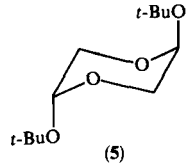
B. Manifestation of the Anomeric Effect

Detailed theoretical and experimental investigations of the *anomeric effect*[15] have been reported in recent literature. A beautiful manifestation of the anomeric effect was provided by the crystal structure analysis of *trans*-2,5-dichloro-1,4-dioxane (**4**) by X-ray and neutron diffraction methods[12,16]. The different techniques used in the crystallographic analysis, combining low-temperature (106 K) X-ray data, neutron data, conventional

least-squares refinement and multipole refinement[17], yielded consistent results. The dihalogenated dioxane compound has two equivalent '*anomeric*' sp^3-carbon atoms attached to two electronegative species O and Cl. The chlorine substituents were found to assume the axial conformation, rather than an equatorial arrangement which would be favoured from steric considerations alone as in *trans*-1,4-dichlorocyclohexane. The anomeric effect is further manifested in the lengthening of the C—Cl and the shortening of the C—O bond. Thus, while the C—O bond length involving the non-anomeric carbon is 1.433 Å, very close to the value found in the unsubstituted 1,4-dioxane, the anomeric C—O bond shows a significant shortening, to 1.382 Å. Correspondingly, the observed C—Cl bond distance of 1.842 Å is significantly longer than, for example, the C—Cl equatorial bond of 1.78 Å found in *cis*-2,3-dichloro-1,4-dioxane. Widening of the C—O—C bond angle in *trans*-2,5-dichloro-1,4-dioxane, 133.2 deg as compared to 109.9 deg in 1,4-dioxane, is also in accord with the anomeric effect. An effort has been made to provide in this case experimental evidence for a suitable interpretation of the anomeric effect on an electronic level by calculating electron deformation density maps. However, the information obtained from the observed charge distributions was inconclusive, and did not allow a rigorous interpretation of the molecular orbital interaction scheme[12].



(4)



(5)

On the other hand, it was shown experimentally that di-*t*-butoxy- and ditrimethylsilyloxy derivatives of 1,4-dioxane exhibit relatively weak anomeric effects[18]. The anomeric effect was probed in a series of such compounds by NMR techniques in solution, molecular mechanics (MM2) and model MO *ab initio* calculations, as well as by a single-crystal X-ray analysis of 2,5-di-*t*-butoxy-1,4-dioxane (**5**; Figure 1). By this combined approach it was possible to isolate and identify steric and electronic contributions. The results of this study indicate that the apparent alleviation of the anomeric effect is caused by electronic factors, which involve mainly an inductive electron donation by the axially positioned substituents; steric factors and π bonding were found to be negligible. It is of interest to examine the relevant structural parameters observed for the di(*t*-butoxy) derivative in comparison with the previously quoted values. Thus, the geometrical parameters involving the anomeric carbon are: C—O *endo* 1.424 Å, C—O *exo* to the axial oxygen 1.400 Å, C—O—C *endo* 111.9 and *exo* 118.4 deg. For the non-anomeric carbon the C—O distance within the dioxane ring was found to be 1.427 Å. The relatively long C—O bond and small C—O—C angle within the anomeric fragment, as compared to previous findings for analogous carbohydrates (e.g. corresponding average values in α-glycosides are C—O 1.437 Å and C—O—C 113.5 deg) and the *trans*-2,5-dichloro-1,4-dioxane, clearly indicate a weaker anomeric effect. Similarly to the diaxial conformation found in the solid structures of the dichloro and di(*t*-butoxy) derivatives, it has been reported that *trans*-2,3- and *trans*-2,5-dimethoxy-1,4-dioxanes, as well as the analogous diphenoxy and diacetoxy derivatives, overwhelmingly prefer the diaxial conformation also in the solution state[19]. This conformational preference is so strong that no significant changes could experimentally be detected by variation of temperature or solvent polarity. On the other hand, the corresponding bis(trimethylsilyloxy) and di(*t*-butoxy) moieties were found to exist in solution as conformational mixtures of diaxial and diequatorial forms, the stabilization of the latter being enhanced

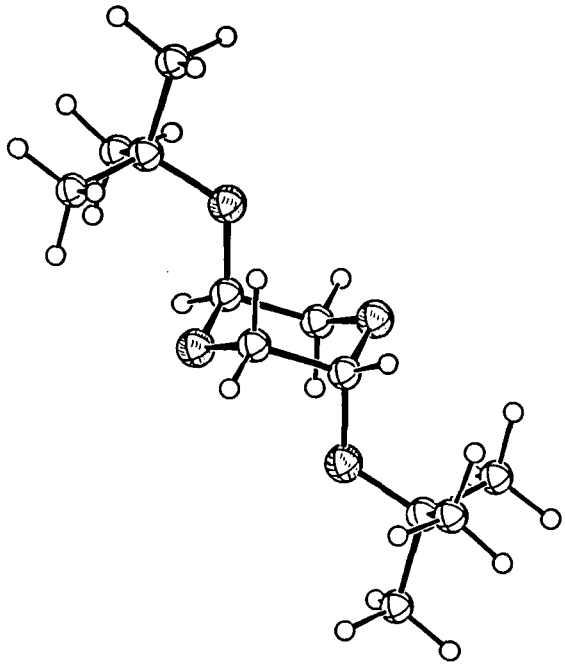


FIGURE 1. The molecular structure of compound 5[18]

by polar solvents. Rationalization of this phenomenon was given in terms of the molecular dipole moments (μ) of the corresponding conformers. When μ of the diequatorial form is larger than that of the diaxial one, the former is stabilized by polar solvents. However, when the $|\mu|$ values of the two structures are similar, the portion of the diaxial conformer increases[19].

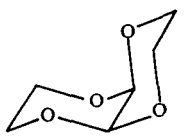
Structural parameters, if critically evaluated, appear to be very reliable probes for both understanding the anomeric effect and using it as a diagnostic tool. In a recent study, a systematic analysis of carbohydrate structures that contain C—O—C—O—R moieties was performed in order to clarify the influence of the anomeric effect on the structural parameters in these compounds[20]. The study was based on over 500 carbohydrate structures retrieved from the Cambridge Structural Database[2,3], scrutinizing with the aid of standard statistical criteria the bond length and bond angle data within the anomeric moiety. The large body of data used in the analysis excluded unreliably refined structures, compounds in which double bonds, triple bonds or carbonyl groups were attached to the C—O—C—O—C moiety, polycyclic species with a bridging oxygen and compounds containing overlapping anomeric groupings. It included, however, geometrically biased systems with constrained conformational features such as cyclodextrins (six-membered axial anomers), furanosides (five-membered quasi-axial anomers) as well as related small ring compounds 1,3-dioxanes and 1,3-dioxolanes. Consequently, the effect of different conformations on the bond lengths and bond angles could also be detected. The resulting structural characteristics are presented in Table 2. They reflect on statistically significant differences between the averaged geometrical parameters of axial and equatorial glycosidic units, bond and angle deformations imposed by the macrocyclic structure of cyclodextrins and by the strained

TABLE 2. Structural manifestation of the anomeric effect in carbohydrate systems, containing the C—O—C—O—C fragment

Compound	No. of examples	With anomeric C			With non-anomeric C			
		O—C (Å)	O—C—O (deg)	C—O (Å)	C—O (Å)	C—O—C (deg)	C—O—C (deg)	O—C (Å)
Eq. glycosides	119	1.425	107.6	1.389	1.436	111.9	114.7	1.439
Ax. glycosides	90	1.416	112.0	1.405	1.437	113.5	113.8	1.430
Cyclodextrins	181	1.416	110.7	1.416	1.447	114.0	118.4	1.435
Furanosides	15	1.423	111.5	1.405	1.439	110.0	113.8	1.431
1,3-Dioxanes	31	1.418	111.0	1.414	1.434	111.3	111.6	1.429
1,3-Dioxolanes	13	1.431	103.9	1.420	1.427	106.2	106.8	1.430

five-membered ring structure of furanosides. Thus, while practically no anomeric effect has been detected in the structure of the geometrically constrained 1,3-dioxolanes, the 1,3-dioxane derivatives tend to exhibit an almost normal anomeric behaviour. It has been concluded in the above study that structural criteria are better suited to monitor the anomeric effect than the energy related features.

The *cis*-1,4,5,8-tetraoxadecalin system with a nearly ideal chair–chair geometry (**6**) is a unique example of two adjacent anomeric moieties incorporated in a bicyclic system with C_2 symmetry. The detailed structure of the parent compound has been known for a long time[21]. More recently, the structure and conformation of 9,10-annelated-1,4,5,8-tetraoxadecalins were investigated in solution using NMR spectroscopy, in the crystal using X-ray diffraction analysis at room as well as at a low temperature, and by computation using a suitably parametrized force field[22]. The study focused on three 2,5,7,10-tetraoxa[*n*.4.4]propellane derivatives (**7–9**; Figure 2), probing variations in the structural



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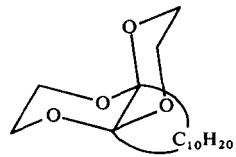

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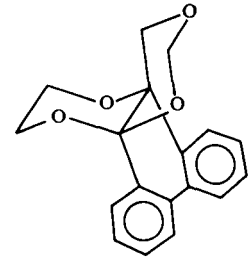

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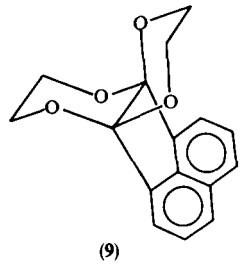

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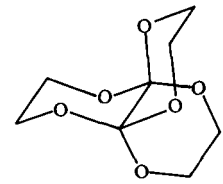


(10)

parameters of the tetraoxadecalin moiety as they are affected by changes in the dihedral angle enforced by the 9,10-annelating system (1,10-decylidene, 2,2′-biphenylene or 1,8-naphthylene). An excellent agreement of the results from the three—NMR, X-ray and computational—probes was achieved with respect to the structure of these compounds. In all of them the chair conformation of the two rings of tetraoxadecaline is preserved, the variation of the 9,10-bridging unit and correspondingly of the torsion angles around the central 9,10-bond distorting only to a minor extent the puckering in the ring periphery. The three structures consistently exhibit long axial and short equatorial C—O bonds and relatively wide C—O—C bond angles, features implicit to the anomeric effect in C—O—C—O—C fragments, as described above. Characteristic structural parameters obtained for **7** from accurate X-ray diffraction measurements at

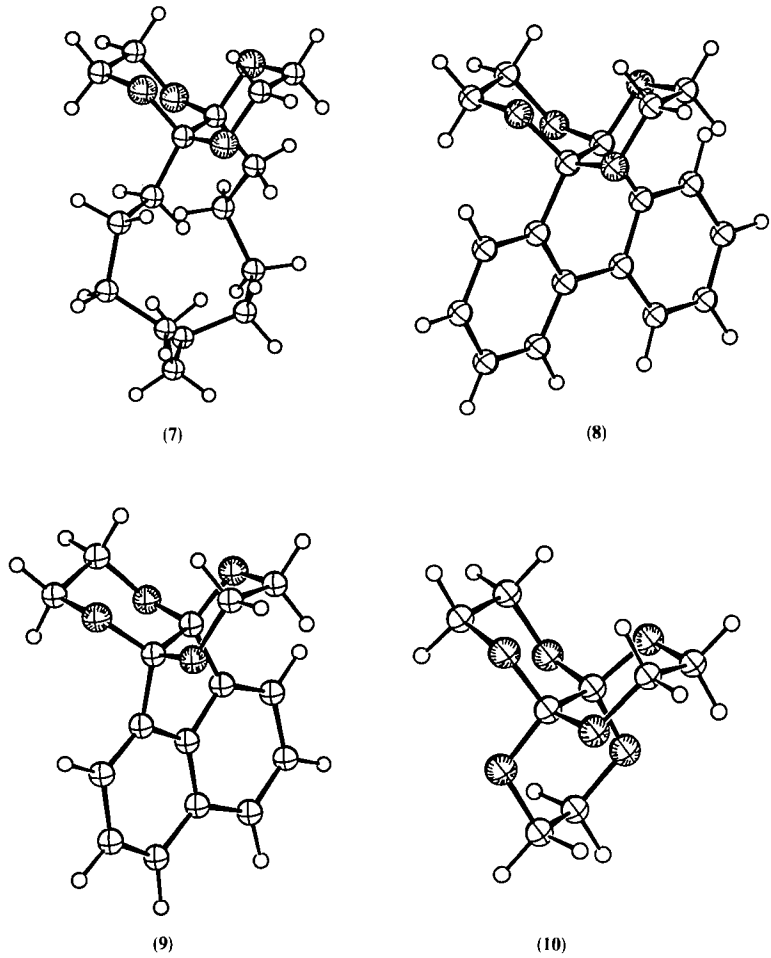


FIGURE 2. Molecular structures of four 2,5,7,10-tetraoxa[*n*.4.4]propellane derivatives **7**–**10**[22,23]

TABLE 3. Structural data for the tetraoxadecaline derivatives **6–9** and the closely related orthooxalate **10**

Compound	**6**	**7**[a]	**8**	**9**	**10**
(a) Bond lengths involving the anomeric carbons (Å)					
O(1)—C(9)	1.420	1.436	1.424	1.414	1.386
O(8)—C(9)	1.410	1.406	1.408	1.409	1.392
O(4)—C(10)	1.393	1.409	1.415	1.410	1.392
O(5)—C(10)	1.420	1.434	1.429	1.406	1.397
C(9)—C(10)	1.522	1.560	1.532	1.567	1.551
(b) Bond lengths involving the non-anomeric carbons (Å)					
O(1)—C(2)	1.439	1.435	1.441	1.434	1.438
C(3)—O(4)	1.441	1.444	1.439	1.432	1.443
O(5)—C(6)	1.430	1.437	1.430	1.438	1.437
C(7)—O(8)	1.432	1.440	1.442	1.432	1.450
C(2)—C(3)	1.503	1.504	1.490	1.492	1.501
C(6)—C(7)	1.509	1.504	1.490	1.491	1.498
(c) The C—O—C bond angles (deg)					
C(2)—O(1)—C(9)	109.2	113.1	113.3	113.2	114.0
C(3)—O(4)—C(10)	113.2	113.7	114.0	113.4	112.7
C(6)—O(5)—C(10)	110.7	113.0	113.4	113.5	113.5
C(7)—O(8)—C(9)	113.2	113.6	113.7	113.4	112.7
(d) The O—C—C—O torsion angles (deg)					
O(1)—C(2)—C(3)—O(4)	58.4	56.1	57.3	62.7	56.4
O(1)—C(9)—C(10)—O(4)	−53.7	−53.3	−49.5	−41.4	−49.4
O(5)—C(6)—C(7)—C(8)	57.9	55.6	57.0	57.0	58.9
O(8)—C(9)—C(10)—O(5)	−51.8	−52.7	−51.4	−41.5	−49.1

[a]Low-temperature data (128 K).

128 K are 1.406–1.409 Å for the axial bonds, 1.434–1.444 Å for the equatorial bonds and within 113.1–113.7 deg for the various angles at oxygen (Table 3).

In addition to the above series of studies further attention was drawn to orthoesters, a group of compounds containing the $C(O—C)_3$ moiety and thus overlapping anomeric C—O—C—O—C units. Structural information on orthoesters is sparse, and a group of only 37 crystallographic structures which include an orthoester moiety could be retrieved from the January 1990 version of the Cambridge Structural Database[2,3]. In this context, the 2,5,7,10,11,14-hexaoxa[4.4.4]propellane (**10**), a unique orthooxalate with a D_3 symmetry, became the object of special scrutiny. The structure of this compound was analysed by NMR spectroscopy, X-ray diffraction as well as the MM2 semi-empirical force field; good agreement was observed between the crystallographic and computational results[23]. Due to the overlap between the anomeric units in this system, the observed inner C—O bond lengths in the C—O—C—O—C units are nearly equal, although still outstandingly short (1.386–1.397 Å). This, together with the long outer C—O bonds (1.437–1.450 Å) and wide C—O—C angles (112.7–114.0 deg) indicate that the anomeric effect is fully operative in this orthoester species as well (Table 3). Very similar structural results had been reported earlier for the 2,10,11-trioxa[4.4.4]propellane, having a virtual D_3 symmetry with all three six-membered rings in the chair form[24] as well as for 3-methyl-2,4,10-trioxa-adamantane[25]. Most of the other orthoester compounds found in the crystallographic database were affected severely by geometric constraints due to

small or condensed ring systems, and showed considerable deviations from the ideal conformations.

C. Bond-shortening in Polyether Compounds

Extensive reference was made in a previous publication of this author to the shortening of covalent C—C and C—O bonds observed in crystal structures of macrocyclic and linear polyethers[26], and numerous additional experimental observations of this phenomenon have since been reported[27–29]. This shortening was explained as either an artifact resulting from an inadequate treatment of thermal motion effects in the crystallographic refinements[30], or as an intrinsic chemical property caused by the difference in electronegativity between oxygen and carbon[31]. Several different theoretical models were applied to the molecule of 18-crown-6, a prototype member of the class of crown ether macrocycles, in order to provide a satisfactory interpretation of this effect. They include several molecular-mechanics studies[32–34], molecular-dynamics study of an isolated 18-crown-6 molecule[35], Monte Carlo simulations of its hydration[36] and molecular mechanics/dynamics representation of its supramolecular interaction with ammonium substrates[37]. Most recently molecular-dynamics simulation of *crystalline* 18-crown-6 has also been performed, the computational box for the simulation consisting of a number of crystallographic unit-cells[38]. Reasonable overall agreement between simulation and experimental results was found for the molecular geometry of the 18-crown-6 entity. For data at 100 K, a shortening of about 0.006 Å was obtained for C—C and C—O bonds due to thermal motion effects, taking into account not only rigid-body libration and rotation, but also the intramolecular motion in the conformationally flexible macrocycles. Simulation calculations at 295 K, the temperature at which most crystal structures are determined, resulted in an estimated shortening of about 0.02 Å of these bonds. For comparison, a C—C bond having two ether O atoms attached to it is expected to be shortened by about 0.015 Å due to polarization effects[31]. These results, which were found to be little dependent on details of the force field and the simulation, should be kept in mind in future evaluations of structural parameters related to polyether molecules.

III. THE PEROXIDE ENTITY

A careful experimental determination of the structural parameters of hydrogen peroxide in the solid state has recently been carried out by various investigators. The crystal structure of pure H_2O_2 was studied by a combination of X-ray and neutron diffraction measurements at 110 K, yielding accurate covalent parameters and a description of the charge-density distribution within the molecule[39]. The relevant distances and angles are summarized in Table 4. The deformation electron density studies revealed that the oxygen

TABLE 4. Accurate crystallographic determinations of the structural parameters of H_2O_2 by X-ray (XR) and neutron diffraction (ND) experiments

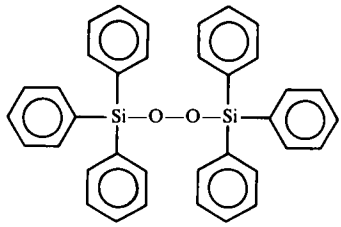
	XR at 81 K	XR at 110 K	ND at 110 K
O—O (Å)	1.457	1.461	1.458
O—H (Å)	1.00	0.77	0.99
O—O—H (deg)	102.5	99.5	101.9
H—O—O—H (deg)	99.0	93.3	90.2
Reference	41	39	39

atom is in a sp^3-hybridization state, with one of the lone pairs involved in intermolecular hydrogen bonding. No significant electron density was found in the oxygen–oxygen bond, in good agreement with independent observations for a nitrogen–nitrogen bond[40]. Very similar structural parameters of hydrogen peroxide were obtained from neutron diffraction analysis of the 1:1 urea:H_2O_2 complex at 81 K (Table 4)[41]. The application of the neutron diffraction technique in these studies allowed one to establish reliably the nuclear positions of the hydrogen atoms. Correspondingly, it was found that the H_2O_2 molecule has a skew conformation, the H—O—O—H torsion angle being within 90–99 deg. Apparently, this conformation is favoured by the interaction between the oxygen lone electron pairs.

The structure of dimethyl peroxide (CH_3OOCH_3) was studied by gas-electron diffraction[42] as well as by *ab initio* theoretical calculations[43]. The experimentally determined geometric parameters of the COOC skeleton are O—O 1.457 Å, O—C 1.420 Å, O—O—C 105 deg and C—O—O—C 119 deg. The relatively large value of the latter parameter, as compared to the torsion angle observed in hydrogen peroxide (see above), was explained by steric repulsion between the side methyl groups. The calculated structure, based on the 4–21 contracted Gaussian basis set, revealed that the *gauche* conformation (with a calculated C—O—O—C torsion angle of 115 deg) represents indeed an energy minimum of an isolated molecule. Similarly, the preferred conformation of the bis(trifluoromethyl) peroxide (CF_3OOCF_3) was found to be *gauche*[43]. In fact, earlier studies had already shown that the peroxide torsion angle may vary from below 90 to 180 deg, due to the fact that the barrier of rotation about the O—O bond is very small. The above observations are further confirmed by results of the structural analysis of bis(*t*-butyl) peroxide [$C(CH_3)_3OOC(CH_3)_3$] by low-temperature X-ray (at 193 K) as well as by electron diffraction[44]. Thus, the experimental data indicate that the peroxide torsion angle in this compound is close to 165 deg both in the solid and in the gas phase, representing a nearly *trans* arrangement of the two alkyl groups. It is evident, therefore, that this structural feature of the peroxide function is strongly affected by intramolecular steric hindrance and, in the condensed solid phase, by intermolecular interactions (packing effects). Another suitable example is provided by the room-temperature crystal structure of bis(triphenylmethyl) peroxide [$(C_6H_5)_3$-$COOC(C_6H_5)_3$], in which the observed conformation around the O—O bond is ideally *trans* (C—O—O—C 180 deg)[45].

The oxygen–oxygen bond length in peroxides correlates with the electronegativity of the substituents. The shortest O—O distance was observed in CF_3OOCF_3 (1.42 Å) and the longest in Si-substituted peroxide derivatives. Crystallographic determination of the structure of bis(triphenylsilyl) peroxide (**11**) revealed a long O—O bond of 1.487 Å; an even longer O—O bond distance of 1.501 Å was observed in a low-temperature (153 K) X-ray diffraction study of bis(dimethylbenzylsilyl) peroxide (**12**)[46]. It should also be noted that the O—C and O—Si bonds in the peroxides are generally longer than the bonds in the analogous ethers. A relatively long O—O bond (1.489 Å) has also been observed in the structure of an ethyl *t*-butyl peroxide derivative of hafnocene (**13**) studied at 97 K[47]. Moreover, the Hf—O—O—C dihedral angle was found to be particularly small (only 70.9 deg), suggesting a substantial π-donation from the oxygen to an empty antibonding orbital of the metal complex moiety. Considerably shorter O—O bond distances (within 1.46–1.47 Å) were observed, however, in crystal structures containing oxoperoxo and oxodiperoxovanadium ions [$VO(O_2)$ and $VO(O_2)_2$][48].

An interesting series of studies has been conducted on diacyl peroxide structures. The structural details relating to the peroxide moiety are quite similar for many of these compounds. Thus, the two acyl groups adopt a skew conformation, and lie in orthogonal planes connected through the peroxide bond. The observed torsion angle about the O—O bond in various peroxides, including the dibenzoyl (**14**), acetyl benzoyl (**15**)[49],



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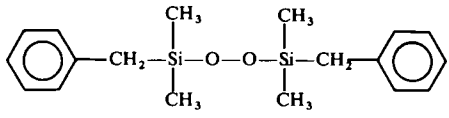

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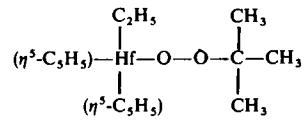

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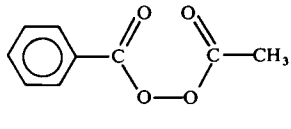
3,3'-dichlorobenzoyl (**16**)[50], *trans*-cinnamoyl (**17**) and α-fluoro-*trans*-cinnamoyl (**18**)[51] derivatives is within the range of 87–91 deg. The O—O bond length is within 1.42–1.45 Å, while the O—O—C bond angle in these compounds varies from 110 to 112 deg. The length of the adjacent carbonyl group was found to be affected by its proximity to the peroxide bond, being significantly shorter (1.19 Å) than is normally observed in unconjugated acyloxy functions.



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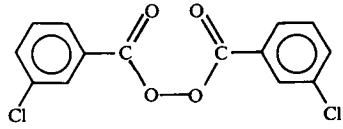

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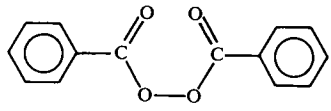

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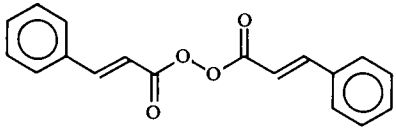

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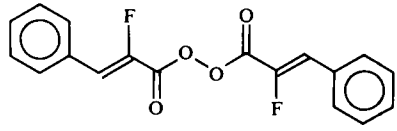

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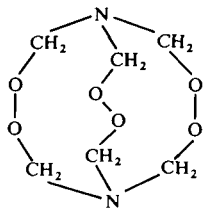
This section is concluded with reference to a series of medium ring bicyclic compounds with peroxide bridges, the structures of which were studied by Schaefer and coworkers: hexamethylene triperoxide diamine (**19**), benzene tetramethylene diperoxide diamine (**20**), cyclohexane tetramethylene diperoxide diamine (**21**) and hexamethylene diperoxide diamine (**22**)[52–54]. These compounds exhibit an unusual geometry, having planar or nearly planar bridgehead N atoms. It seemed clear to the authors that the peroxide

groupings are responsible for the planarity of the nitrogens. The main effect of the O atoms is withdrawal of electron density from the region of the nitrogen atoms, and lowering the energy of the electron pair in the p-orbital of a partially sp^2-hybridized nitrogen. The loss of stabilization at the nitrogens is compensated for by an increase of the bonding density in, and a shortening of, the C—N bonds. The C—O—O—C torsion angles in these compounds are within the range of 115–129 deg, being affected by electrostatic repulsion between the bridging nitrogens and between nitrogen and oxygen atoms, as well as by the ring structure. The observed C—O bond lengths vary from 1.41 to 1.45 Å, while the O—O bond distance in all these compounds is close to 1.46 Å. In the less constrained tricyclotetradecane diperoxide derivative (**23**; it has been claimed that a seven-membered peroxide ring is generally more stable than its six-membered counterpart) the corresponding geometric features are: O—O 1.472 Å, C—O 1.428 and 1.445 Å, C—O—O 106 and 109 deg and C—O—O—C 100 deg[55]. The observed value for the peroxide torsion angle is close to that found in the unsubstituted hydrogen peroxide species.



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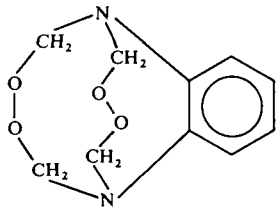

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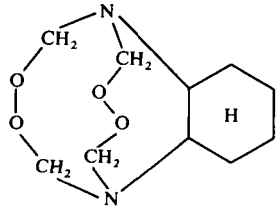

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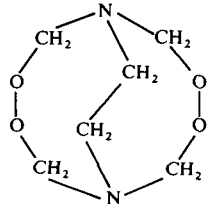

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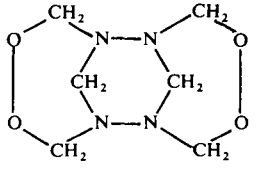

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IV. ALCOHOLS

A. The Covalent Characteristics of the C—O—H Group

The covalent features of the C—O—H group had already been characterized in detail in the past by different methods. The structural parameters obtained from electron-diffraction and microwave-spectroscopy experiments were summarized by this author in a previous publication[26]. To further examine the basic structure of this functional group, as determined by diffraction experiments in the solid state, additional information was extracted from the Cambridge Structural Database[2,3]. The retrieved data were classified and purged in order to maximize accuracy and avoid reference to poorly determined structures. Moreover, the crystallographic determinations considered are based either on low-temperature (usually near 100 K) X-ray measurements or on neutron-diffraction experiments. Only the latter data set, although considerably smaller,

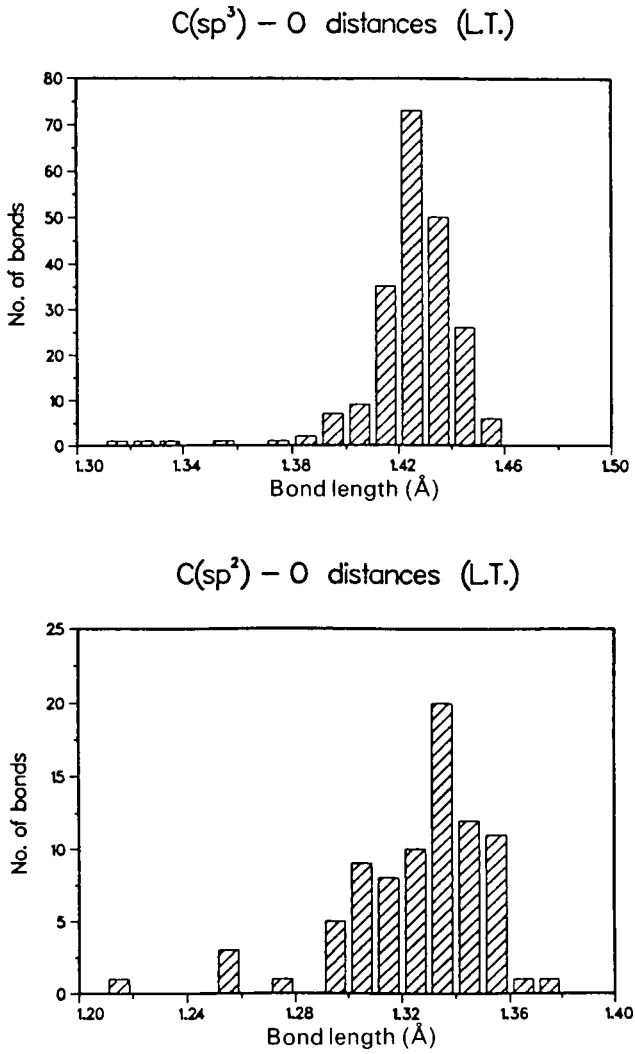


FIGURE 3. Histograms showing distributions of carbon–oxygen distances in alcohols, as determined by X-ray diffraction at low temperature, based on data retrieved from the Cambridge Structural Database[2,3]

was used in characterization of the covalent parameters involving hydrogen. The evaluated distributions of the bonding parameters in alcohols are summarized in a series of histograms (Figures 3–5).

In view of the varying complexity of the molecular and crystal structures included in this survey, and the different experimental conditions applied in the individual determinations, they define ranges of (rather than unique) values for the corresponding bond

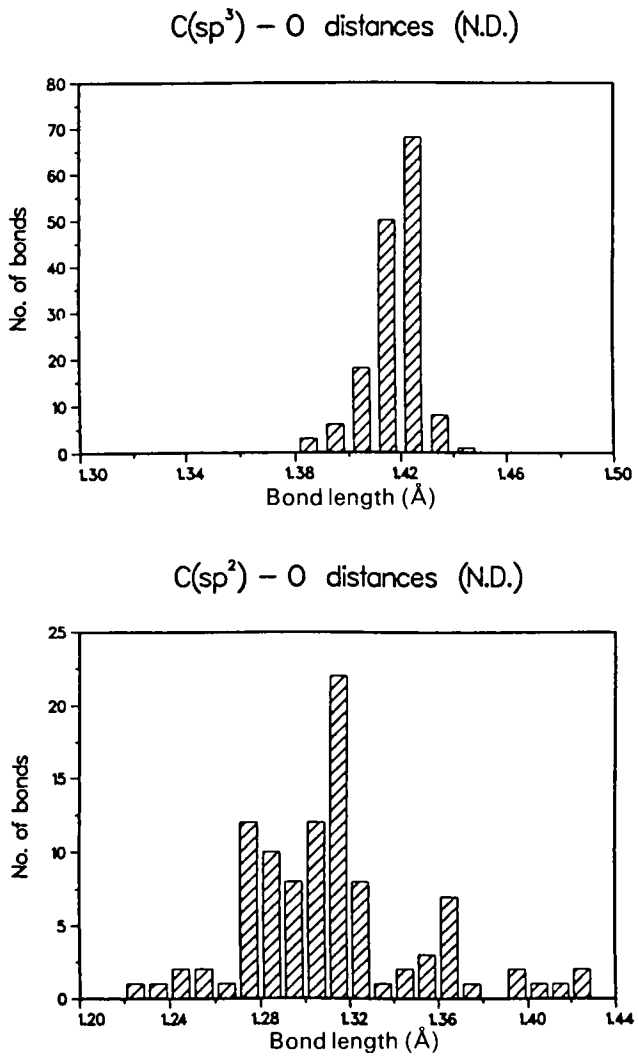


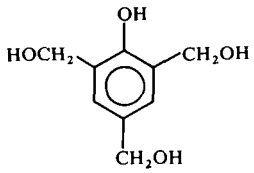
FIGURE 4. Histograms showing distributions of carbon–oxygen distances in alcohols, as determined by neutron diffraction, based on data retrieved from the Cambridge Structural Database[2,3]

lengths and bond angles. One should keep in mind, however, that the presented results, encompassing a large amount of experimental observations, represent a reliable characterization (within known limits)[26] of the structural features. As shown, the C(sp^3)—O bond lengths cluster near 1.42–1.43 Å, the higher value relating to measurements at low temperatures, in perfect agreement with previously quoted observations. The C(sp^2)—O-distances fall within a larger range, 1.27–1.33 Å (neutron diffraction) and 1.29–1.36 Å (low-temperature X-ray diffraction), as they relate to unsaturated systems

with a varying degree of electron delocalization. The values for the O—H bond distance in fully saturated entities fall within a relatively narrow range of 0.94–1.00 Å, while those observed for molecules in which the adjacent C-atom is part of a conjugated fragment lie mostly within 0.96–1.04 Å. The corresponding bond angles involving hydrogen, $C(sp^3)$—O—H and $C(sp^2)$—O—H, have an average value of 109 and 111 deg, repectively. The effects of hydrogen bonding in the crystalline phase on the structural parameters of the O—H group have been discussed elsewhere[56].

B. Phenols

The solid state chemistry features of simple phenols were reviewed comprehensively in a recent publication[57] and only a few comments on this subject are included here. The reader is referred to that report for an excellent overview of the conformations and crystal structure types, solid-state, solid–liquid and solid–gas chemical reactions, as well as industrial applications involving various phenolic derivatives. The detailed molecular structure of phenols depends primarily on the type, number and position of the substituents on the benzene ring. The normal length of the C—O bond of 1.368 Å was found to be shortened for *ortho*-substituted phenols with an intramolecular hydrogen bond, being subjected also to a slight modification by the acidity of the hydroxylic proton[58]. In the condensed crystalline phase, phenol molecules are usually held together by hydrogen bonds, forming either localized aggregates of H-bonded species, or infinite arrays (chains or layers) of linked molecules which extend throughout the crystal. Aromatic molecules substituted with several hydroxy functions are capable of forming three-dimensionally networked arrangements. Representative examples are provided by 2,4,6-trihydroxymethylphenol (**24**) and 3,5,3′,5′-tetrahydroxymethyl-4,4′-dihydroxydiphenylmethane (**25**). In the former structure a bilayered arrangement of the molecular species has been observed, while in the latter an extended three-dimensional network of H-bonded molecules is formed[59]. Heating of the two H-bonded structures above 80 °C causes polycondensation of the molecular entities via elimination of water and formation of ether bonds, and, at higher temperatures, elimination of formaldehyde and formation of methylene bridges[60]. Polymorphism (crystallization of a given compound in several structural forms) of phenolic derivatives has also been referred to, including recent structural studies of the different polymorphs (e.g. of 4-hydroxybiphenyl) as well as calculations of relative stabilities for the different crystalline polymorphic varieties (of 4-chlorophenol and 4-methylphenol)[61,62].



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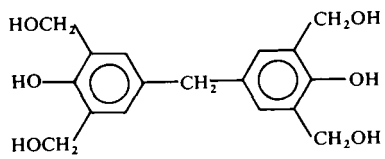

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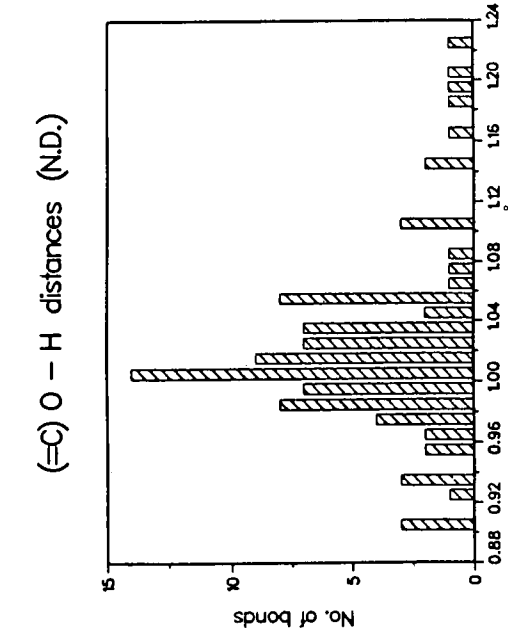
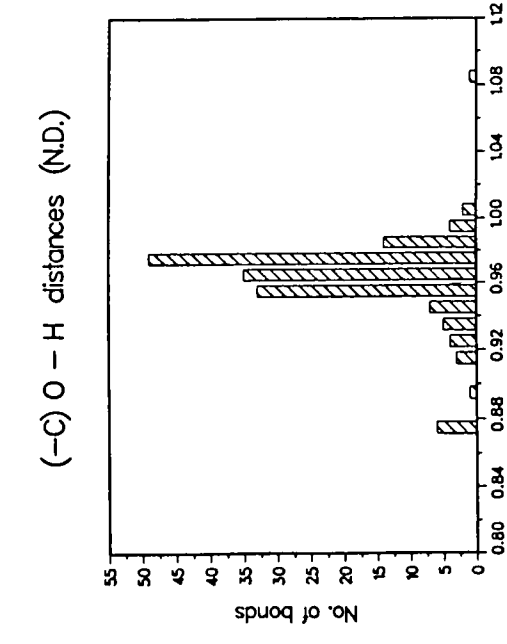
C. Co-crystallization Properties of Alcohols

Compounds containing the hydroxylic function attached to a rigid backbone often tend to form stable co-crystals with other moieties. The OH group provides a very effective multiple binding site for other polar functions, due to its ability to donate as well as accept hydrogen bonds. A large variety of structures of this type has been investigated in recent years. For example, triphenylmethanol (**26**), when crystallized from


(=C) O – H distances (N.D.)
No. of bonds
Bond length (Å)
0
5
10
15
0.88
0.92
0.96
1.00
1.04
1.08
1.12
1.16
1.20
1.24


(–C) O – H distances (N.D.)
No. of bonds
Bond length (Å)
0
5
10
15
20
25
30
35
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0.84
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0.96
1.00
1.04
1.08
1.12

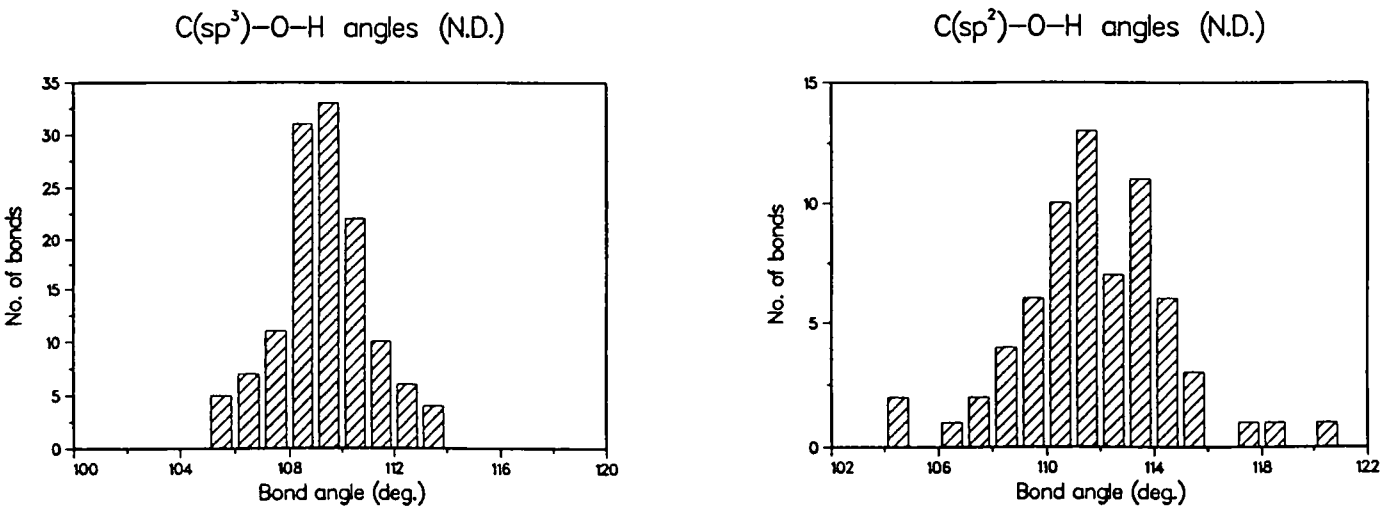


FIGURE 5. Histograms showing distributions of O—H bond lengths and C—O—H bond angles in alcohols, as determined by neutron diffraction, based on data retrieved from the Cambridge Structural Database[2,3]

apolar hydrocarbon solvents, self-associates by forming hydrogen-bonded tetramers[63]. However, when this alcohol is exposed to interaction with polar molecules, it easily forms crystalline complexes with various species such as methanol, acetone, dimethylsulphoxide, dioxane, morpholine, piperidine, *N*-methylpiperazine and others[64]. From the variety of complexing partners, triphenylmethanol co-crystallizes preferentially with methanol and with dimethylsulphoxide, a feature which may be useful for separation and purification of MeOH and DMSO from industrial and environmental solutions and vapours. The intermolecular arrangements in solid **26**, and in the corresponding co-crystals with MeOH, DMSO as well as acetone, are illustrated in Figure 6. The

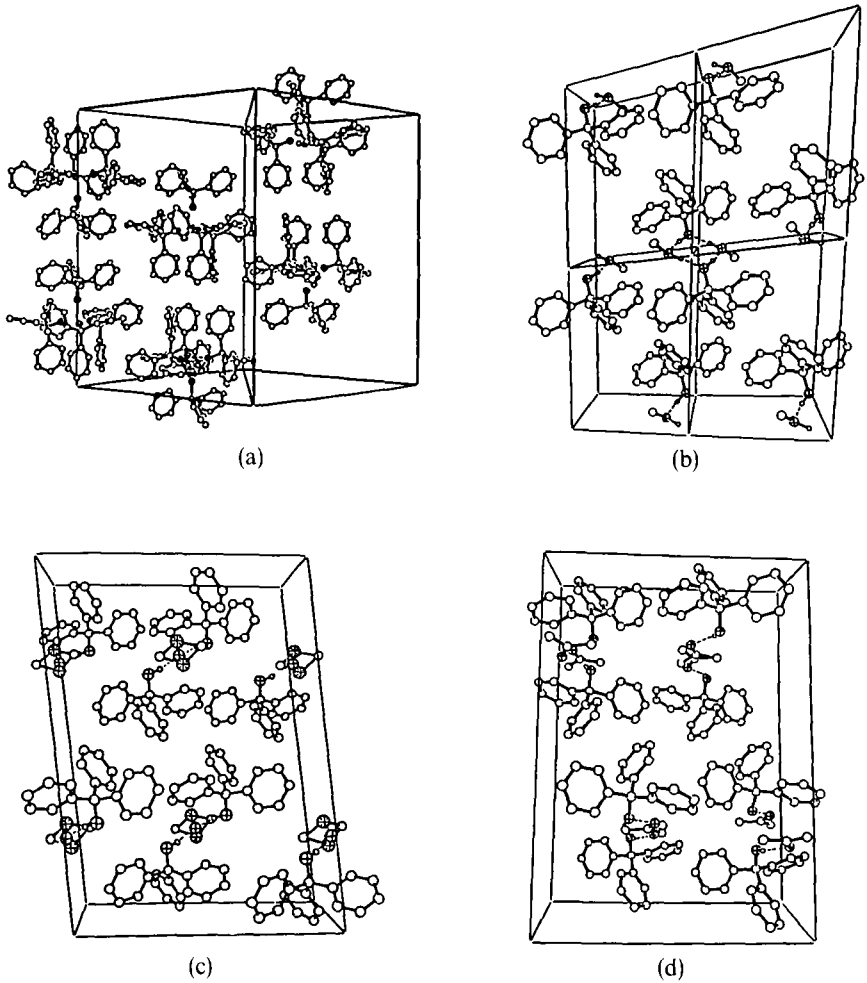
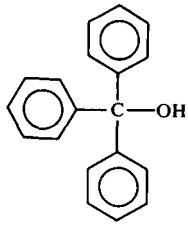


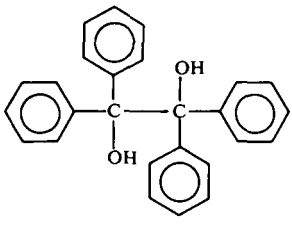
FIGURE 6. Illustration of the crystal structures of (a) uncomplexed **26**, and of the co-crystals of **26** with (b) methanol, (c) dimethylsulfoxide and (d) acetone. Hydrogen-bonding interactions in the complexes are indicated by broken lines. The disordered arrangements of DMSO and acetone in the corresponding crystals are also shown in (c) and (d)[63,64]

preference for complexation of **26** with methanol rather than with DMSO or with acetone can be attributed to the different extent of the hydrogen–bonding interactions (tetrameric, trimeric and dimeric associations, respectively) in the corresponding crystals. The crystal structure of the 1:1 complex of this host with dioxane has also been analysed, showing a weaker association between the two components[65]. The larger analogous alcohol, di(1-naphthyl)phenylmethanol, exhibits similar complexation features towards methanol[66]. The H-bonding nature of intermolecular interactions in the complexes between pentafluorophenol and proton acceptors such as ethers, ketones, and phosphoryl compounds, by which the constituent species are held together in the crystal lattice, have also been elucidated[67].



(26)

Toda and coworkers have reported numerous crystalline complexes of mono- and di-alcohols [such as 1,1,2,2-tetraphenylethane-1,2-diol (**27**), 1,1,6,6-tetraphenylhexa-2,4-dyine-1,6-diol and its octamethyl derivative (**28**), 1,1-bis(2,4-dimethylphenyl)-but-2-yn-1-ol (**29**), 9-hydroxy-9-(1-propynyl)fluorene (**30**), *trans*-9,10-dihydroxy-9,10-diphenyl-9,10-dihydroanthracene (**31**) and 1,4-diphenyl-2,5-dihydroxybenzene (**32**)] with a variety of alcohols[65,68], pyridines and ketones[69] as well as of 1-(*o*-chlorophenyl)-1-phenyl-2-



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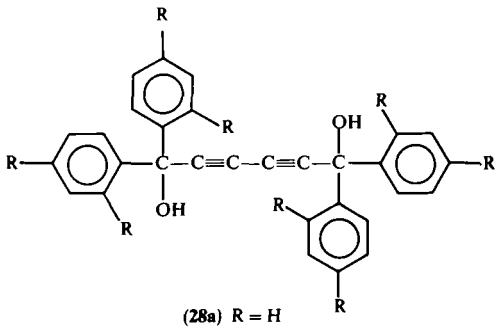
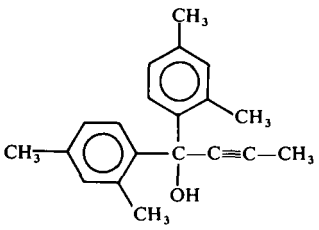


(28a) R = H
(28b) R = CH_3



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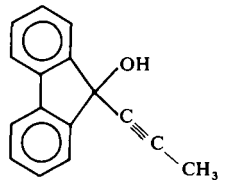

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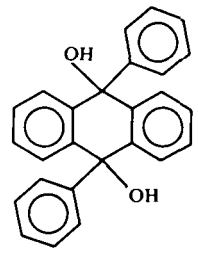

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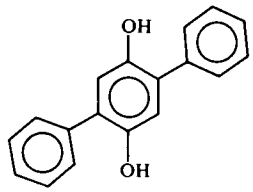

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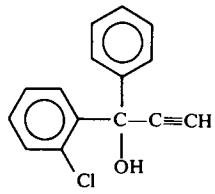

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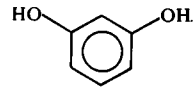


(34)

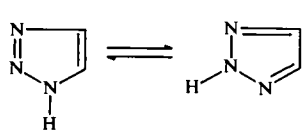
propyn-1-ol (**33**) with cyclic amines[70]. They have also compared the inclusion ability of the different host compounds, and analysed the thermal stability of the co-crystals which form. Simple diphenols such as resorcinol (**34**) also tend to form crystalline complexes with proton-accepting molecules, as is demonstrated by the crystallographic study of the 1:1 adduct between resorcinol and 2,9-dimethyl-1,10-phenanthroline[71]. The hydroxyl groups of the former act as proton donors to the nitrogen sites of the latter, linking together the heteromolecular assembly. Co-crystallization of resorcinol with urea has been reported as well[72].

The tendency of a 'host' molecule to form co-crystals with another species manifests features of mutual molecular recognition, usually through hydrogen-bonding interactions, between the two interacting components in the solid state. One of the current goals in molecular recognition concerns the selective sequestration of isomers, whether they be geometric or enantiomeric, and a major research effort has been directed at this problem in recent years. The chemical and structural properties, as well as the selectivity properties of isomeric separations and chiral recognition of alcohols by crystalline inclusion complexation have been reviewed in a number of earlier publications[73,74]; representative examples will be discussed below.

V. MOLECULAR RECOGNITION BY ALCOHOLS

A. Isomeric Separations

An interesting aspect of molecular recognition has been addressed in the study involving the inclusion complexes of host **29** with 1,2,3-triazole (**35**), 1,2,4-triazole (**36**) and 3(5)-methylpyrazole (**37**). Each of the latter guest compounds exists in solution as an equilibrium mixture of two tautomers of nearly the same stability, and the structure of the individual tautomeric forms could not be studied due to the difficulty in obtaining



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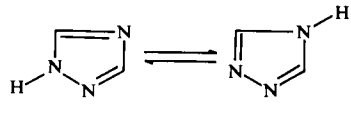

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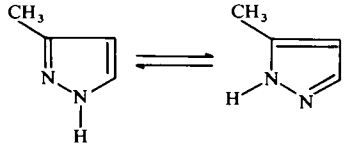

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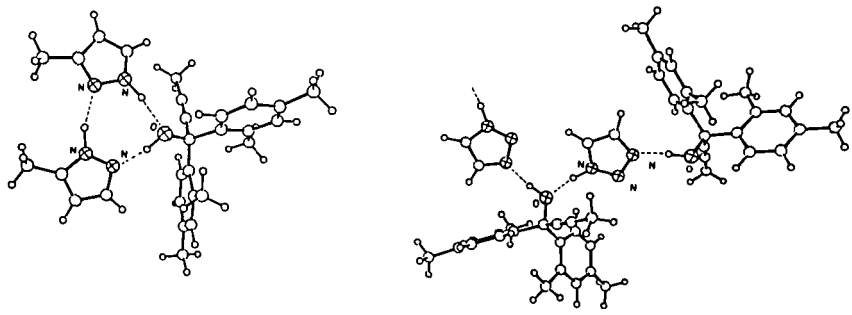
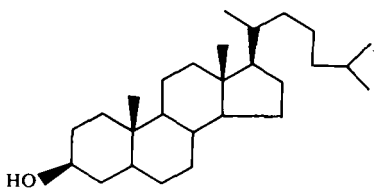


FIGURE 7. Observed structures of the complexes of **29** with (a) **35** and (b) **37**, illustrating resolution of the individual tautomeric forms of **35** and **37** by association with **29** in the solid state[75]

the tautomers in a resolved state. As shown by crystallographic investigations it was possible to isolate one of the tautomers of **35** and **36** (1,2,3-triazacyclopenta-2,4-diene and 1,2,4-triazacyclopenta-3,5-diene, respectively) in the form of their 1:1 complexes with **29**[75,76]. The results indicated that stabilization of one tautomer over the other should be attributed to the formation of an extended H-bonding pattern in the crystal lattice, less likely to form with the counterpart tautomers (Figure 7). The two equilibrating tautomers of **37**, 3-methyltriazole and 5-methyltriazole, were also isolated in a pure state as a 1:1:1 complex with the same host[75]. In the crystal, the three components form a cyclic arrangement of hydrogen bonds, each one of them acting simultaneously as a proton donor to, and as a proton acceptor from, different moieties.

The tendency of cholesterol to form co-crystals has long been known, and the crystal structures of its hydrate and ethanolate were analysed some time ago[77]. More recently, we have observed that hydroxy steroids such as cholestanol (**38**), cholesterol (**39**), sitosterol (**40**), stigmasterol (**41**) and ergosterol (**42**) form co-crystals with a wide variety of guest species (Table 5), often revealing marked selectivity in the crystalline complexation towards guest structural isomers[78]. Of the five steroids tested, cholestanol and cholesterol



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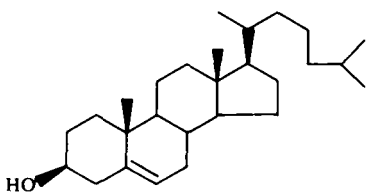

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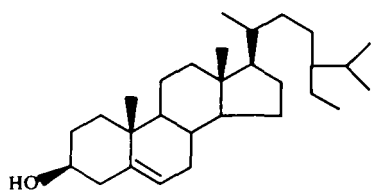

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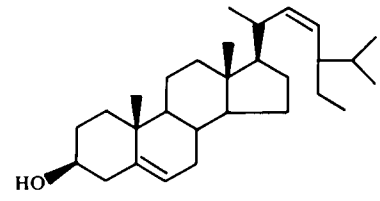

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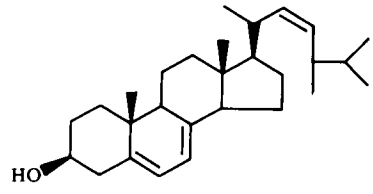

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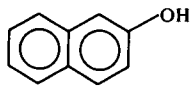

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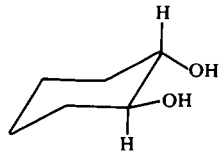

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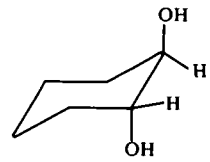

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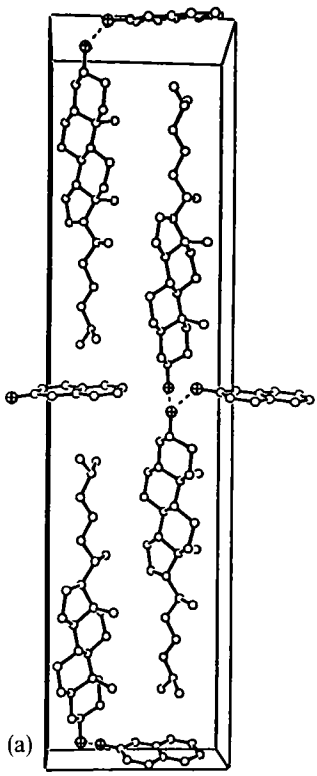


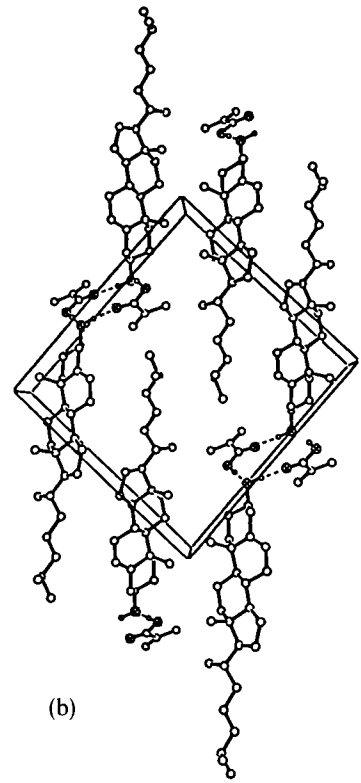


FIGURE 8. The crystal structures of (a) the 2:1 complex between **38** and **43**, and (b) the 1:1 complex between **39** and **44**, showing the intermolecular interaction scheme[78]

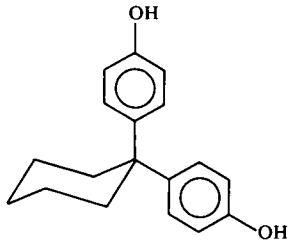
showed a relatively high guest-inclusion ability. Crystal structure analyses of the complexes between **38** and β-naphthol (**43**) (2:1) and between **39** and 2-methylpropenoic acid (1:1) showed either $(-host-host-guest-)_\infty$ or $(-host-guest-)_\infty$ infinite chain arrangements in the lattice (Figure 8). The crystal packing of the H-bonded arrays is dominated primarily by the shape of the large steroid molecules. Molecular recognition

TABLE 5. Composition of the inclusion complexes formed by hosts **38–42** with various guests[78]

Guest	h:g	Guest	h:g
(a) Complexes of ***38***			
MeOH	2:1	*m*-Cresol	2:1
EtOH	2:1	*o*-Cresol	2:1
n-PrOH	2:1	**43**	2:1
Cyclohexanol	1:1	Acetone	4:1
44	1:1	Cyclohexanone	4:1
$CH_2{=}CHCH_2OH$	4:1	*rac*-2-Me-cyclohexanone	4:1
$CH{\equiv}CCH_2OH$	4:1	*rac*-3-Me-cyclohexanone	4:1
cis-$C_2H_5CH{=}CH(CH_2)_2OH$	4:1	4-Me-cyclohexanone	4:1
$CH_2{=}CH(CH_2)_2OH$	2:1	Benzaldehyde	2:1
trans-$CH_3CH{=}CHCH_2OH$	2:1	Acetophenone	2:1
trans-$C_3H_7CH{=}CH(CH_2)_2OH$	2:1	Benzophenone	2:1
trans-$CH_2CH{=}CHCOOH$	2:1	DMF	2:1
$CH_2{=}C(CH_3)CH_2CH_2OH$	2:1	Pyridine	2:1
Phenol	2:1	*rac*-2-(Hydroxymethyl)pyrane	2:1
p-Cresol	2:1		
(b) Complexes of ***39***			
Cyclohexanol	1:1	$HOOC(CH_2)_2COOH$	2:1
44	1:1	$HOOC(CH_2)_4COOH$	2:1
Phenol	2:1	*cis*-$C_2H_5CH{=}CH(CH_2)_2OH$	2:1
p-Cresol	2:1	*rac*-$CH_3CHClCOOH$	2:1
m-Cresol	2:1	*rac*-$CH_3CHBrCOOH$	2:1
o-Cresol	2:1	*rac*-$C_2H_5CHClCOOH$	2:1
43	2:1	*rac*-$C_2H_5CHBrCOOH$	2:1
CH_3COOH	2:1	$CH_3CHClCH_2COOH$	2:1
C_2H_5COOH	2:1	*trans*-$CH_3CH{=}CHCOOH$	2:1
C_3H_7COOH	2:1	$CH_2{=}C(CH_3)COOH$	1:1
(c) Complexes of ***40***			
EtOH	2:1	Cyclohexanone	2:1
n-PrOH	2:1	2-Cyclohexenone	2:1
t-BuOH	2:1	γ-Butyrolactone	2:1
$CH{\equiv}CCH_2OH$	2:1	DMSO	2:1
cis-$C_2H_5CH{=}CH(CH_2)_2OH$	4:1	C_2H_5COOH	2:1
(d) Complexes of ***41***			
MeOH	2:1	$CH{\equiv}CCH_2OH$	2:1
DMF	2:1		
(e) Complexes of ***42***			
p-Cresol	4:1	Acetone	2:1
m-Cresol	4:1	$CH{\equiv}CCH_2OH$	2:1
o-Cresol	4:1		

ability of the steroid hosts associated with spatial complementarity was found to be quite high, and potentially useful for separation of guest isomers. This has been demonstrated by preferential complexation of cholestanol with *p*-cresol from its mixture with *m*-cresol, and of cholesterol with *cis*-1,2-cyclohexanediol (**44**) from its mixture with *trans*-1,2-cyclohexanediol (**45**)[78].

Successful isomeric separations have been achieved in similar host–guest-type crystallization experiments with other organic molecules having two peripherally substituted OH binding sites. The —OH functions in these 'host' compounds may provide attractive sites not only for binding other 'guest' molecules, but also for effective interaction between the phenolic sites of adjacent hosts. The crystalline lattice that forms is characterized by high molecular organization, being dominated by a well-defined and relatively rigid network of H-bonded moieties. Consequently, the co-crystallization process by a given host will exhibit discriminatory features towards guest molecules with non-complementary shapes. Indeed, the host 1,1-di(*p*-hydroxyphenyl)cyclohexane (**46**) and 2,2-di(*p*-hydroxyphenyl)propane (**47**) proved exceptionally useful for separation of close structural isomers by inclusion crystallization. Thus, **46** forms similarly structured complexes with phenol, *o*-cresol, *m*-cresol and *p*-cresol, which contain two-dimensional layers of molecules strongly linked by hydrogen bonds. However, the crystalline complex formation with *m*-cresol is preferential to such an extent that it is possible to isolate an essentially pure fraction of *m*-cresol from a multicomponent cresol mixture[79]. It has been shown that the selection of one guest out of the cresol mixture in the crystallization process correlates well with the degree of steric fit of the given guest within the crystal lattice (Figure 9). Host **47**, having a different topology, exhibits opposing trends in guest inclusion. Thus, in contrast to the previous example, this host was found to co-crystallize preferentially with *p*-cresol than with *m*-cresol from a multi-component guest mixture (Figure 9)[80]. In both cases the observed selectivity is determined by features of spatial complementarity. Similarly, hosts bearing two triphenylcarbinol groups, such as *p*-bis(diphenylhydroxymethyl)benzene (**48**), were also found useful in the separation of close structural isomers, *β*-picoline (**49**) and *γ*-picoline, from their mixture by inclusion



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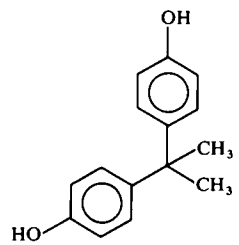

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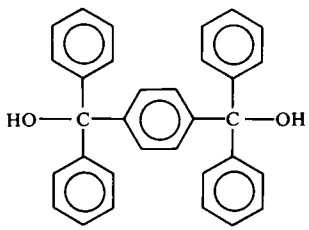

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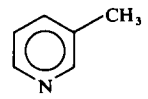

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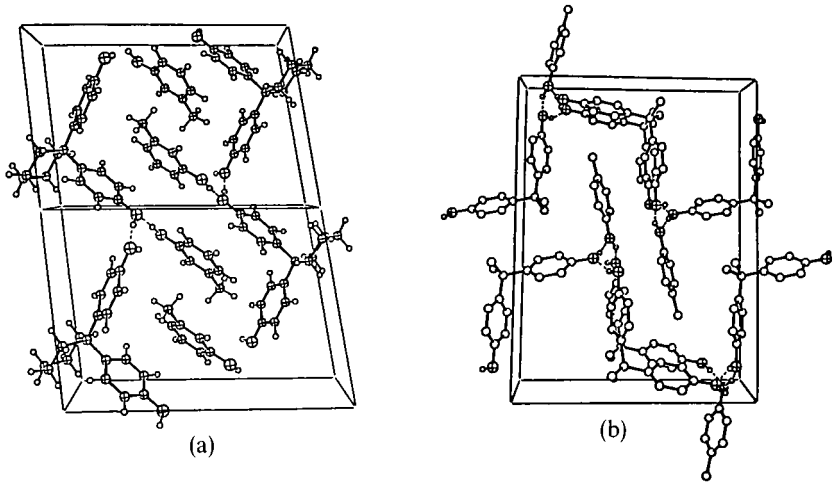


FIGURE 9. Illustration of the different packing modes observed in the favoured crystal structures of the 1:1 complexes (a) between **46** and *m*-cresol and (b) between **47** and *p*-cresol[79,80]

crystallization[81]. Isomeric separations by H-bond-directed co-crystallization is also applicable to aliphatic compounds. The separation of cyclohexanol and cyclohexanone was achieved by selective crystallization with host compounds **27** or **46**, the cyclohexanol forming stabler adducts in both cases[82]. Crystal structure analyses of the corresponding complexes with **46** revealed isomorphous intermolecular arrangements, the discrimination between the two structurally similar guest components being effected primarily by differences in the degree of their functional complementarity (Figure 10).

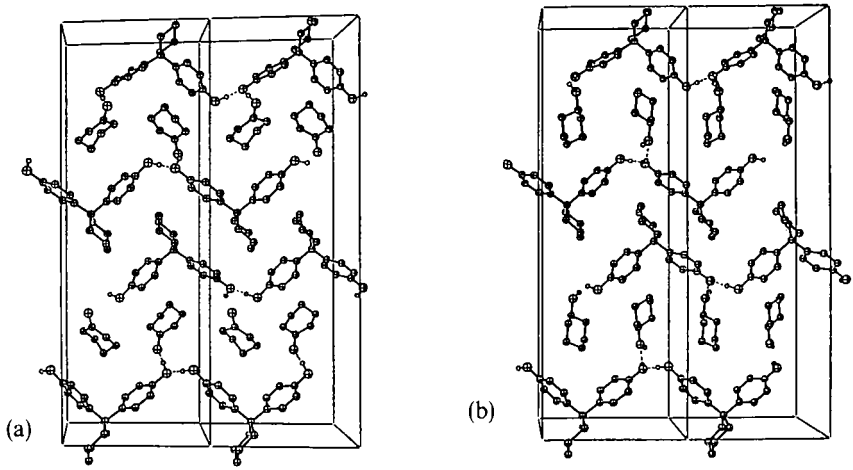
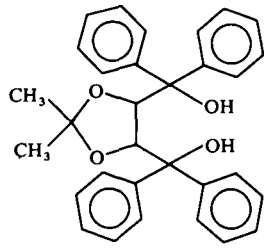
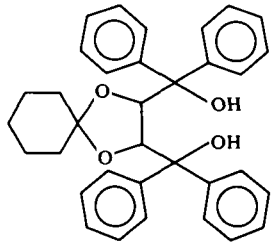


FIGURE 10. Isomorphous crystal packing arrangements of the complexes formed by **46** with (a) cyclohexanone and (b) cyclohexanol[82]

In molecules with two hydroxy functions substituted in the interior segment of the host molecule and partly shielded by the hydrocarbon framework, only localized intermolecular hydrogen bonding may occur. A suitable example is provided by host molecules derived from tartaric acid, 4,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane (**50**) and 2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[5.4]decane (**51**). These compounds can be prepared in the form of racemic, enantiomerically pure or *meso* substances. They have a relatively rigid molecular framework mainly due to the acetal ring closure and an intramolecular hydrogen bond between the two OH groups. Both the racemic and the optically pure stereoisomers of the dioxolane derivative were found to be particularly selective in complexation towards primary and secondary amines[83]. The optically pure *RR*-derivative showed a distinct selectivity towards secondary amines, while the racemic diol was found to interact preferentially with the primary amine analogues. Structural interpretation of the corresponding adducts with mono-, di- and tri-n-propyl amines indicated that the observed selectivity among the amine guests can be attributed to the formation of a cyclic arrangement of H bonds between the interacting moieties in the preferred structures (Figure 11). The corresponding intermolecular binding patterns include insertion of the amine guest species between two hosts into a trimeric or tetrameric H-bonded cluster. The less favoured complexes contain only one direct host-to-guest hydrogen bond. Similarly clustered arrangements of the constituent species have also been observed in the crystalline inclusion complexes of other derivatives of **50** (which contain alkyl, —F or —Cl peripheral substituents on the phenyl rings) with simple alcohol moieties[84].



(50)



(51)

On the other hand, a closely related molecular species with no ring closure in the centre, 1,1,4,4-tetraphenyl-2,3-dimethoxybutane-1,4-diol, forms only intramolecular hydrogen bonds in the crystal, revealing no features of isomeric separation. Rather, this compound tends to form channel-type clathrates in which the included guest molecule is mobile along the channel. A representative structure of a 2:1 complex of this host with limonene is shown in Figure 12; isomorphous arrangements have been observed with a variety of other guests as well.

B. Optical Resolutions

In recent years, several structurally simple optically active synthetic alcohol molecules have become useful agents for resolving chiral organic materials through crystalline complexation. Representative examples studied by Toda and coworkers include chiral diols involving hydroxydiphenylmethyl and other hydroxyaryl fragments, such as: *trans*-**50**, *trans*-**51**, 1,6-bis(*o*-chlorophenyl)-1,6-diphenyl-2,4-dyine-1,6-diol (**52**), 10,10′-dihydroxy-9,9′-biphenanthryl (**53**), 2,2′-dihydroxy-1,1′-binaphthyl (**54**), 4,4′,6,6′-tetrachloro-2,2′-bis(hydroxydiphenylmethyl)biphenyl (**55**) and 2,2′-dihydroxy-9,9′-spirobifluorene

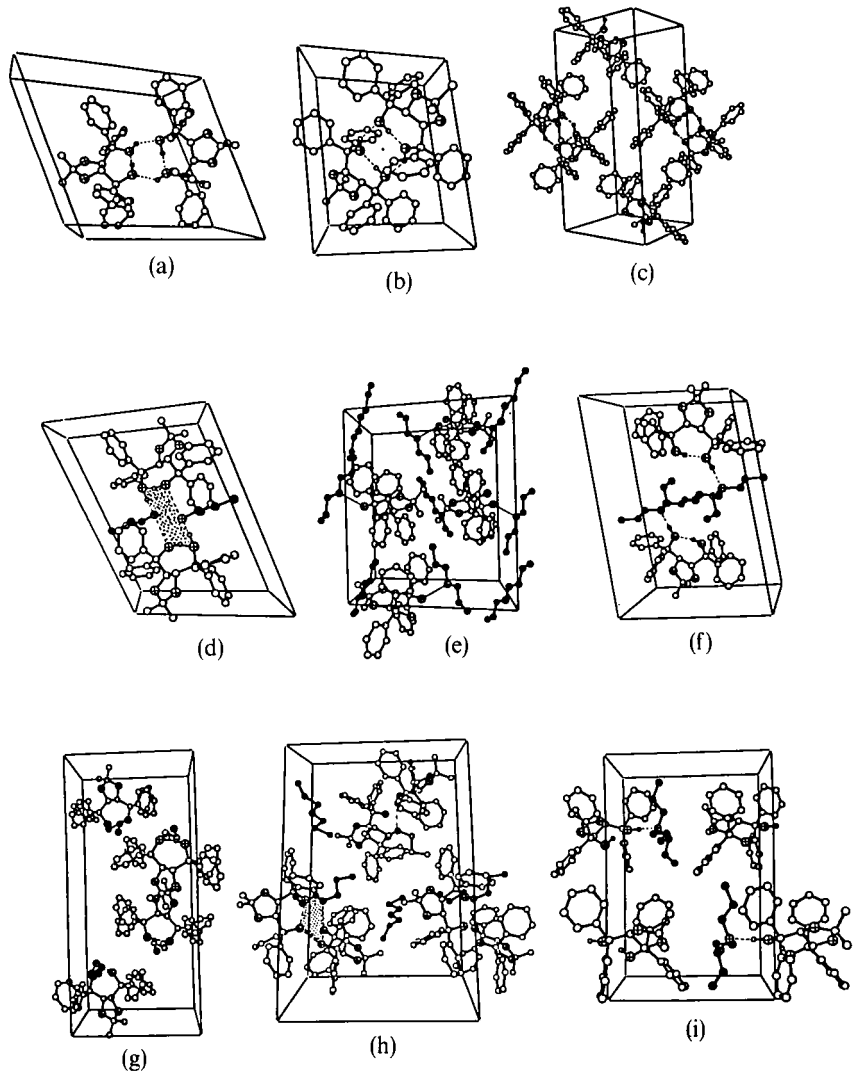


FIGURE 11. Crystal structures of the optically active (a), racemic (b) and *meso* (c) forms of diol **50**; complexes of racemic-**50** with n-$PrNH_2$ (d), $(n\text{-}Pr)_2NH$ (e) and $(n\text{-}Pr)_3N$ (f); complexes of *RR*-**50** with n-$PrNH_2$ (g), $(n\text{-}Pr)_2NH$ (h) and $(n\text{-}Pr)_3N$ (i). Illustrations (d) and (h) show the favoured arrangements in complexes involving the racemic and optically active forms of diol **50**[83]

(**56**). These molecules are configurationally stable and capable of associating strongly with other polar molecules through their hydroxyl groups. Their chiral molecular framework is used to construct an asymmetric environment around the included guest in the condensed crystal lattice, inducing selective co-crystallization with a single enantiomer of the guest moiety. The guest material thus resolved can easily be recovered

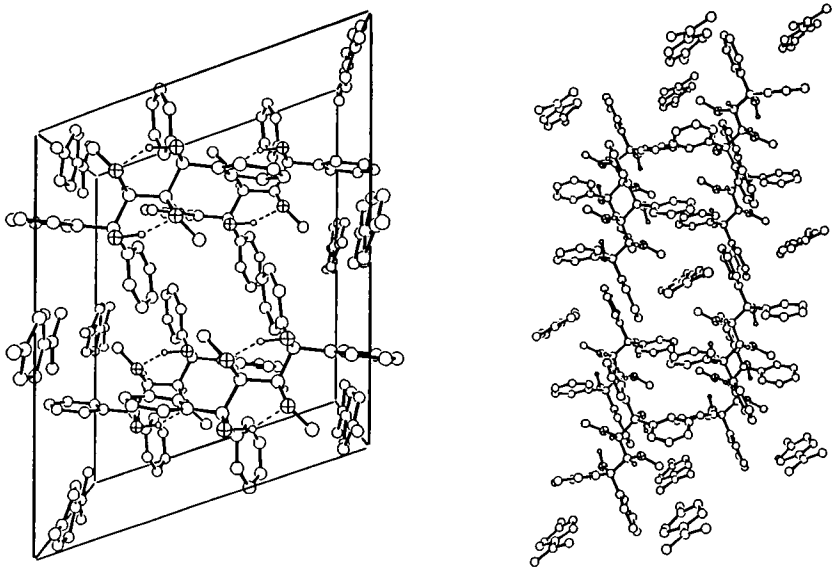
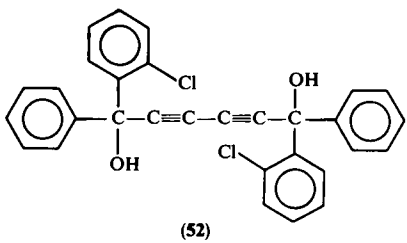


FIGURE 12. Channel-type clathrate formed between 1,1,4,4-tetraphenyl-2,3-dimethoxybutane-1,4-diol and unresolved limonene (two views), which lacks specific interactions between the two constituents of the complex (I. Goldberg, unpublished results)



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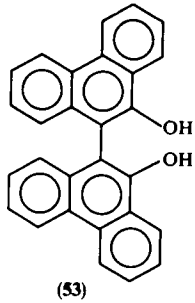

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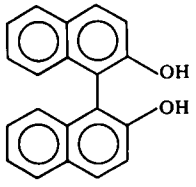

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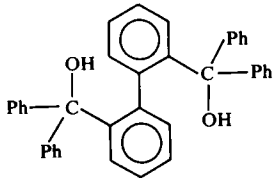

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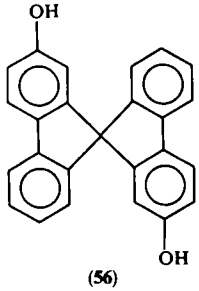
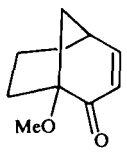


(56)

from the solid complex by standard procedures. The inclusion crystallization method is very simple and often yields 100% optically pure compounds[73,74].

The tartaric acid derived dioxolane host **50**, which can easily be obtained as an optically pure stereoisomer from a natural source, was found useful for optical resolution of bicyclic ketone derivatives[85]. The crystallographic analysis of the resolved complex of this host with 5-methoxybicyclo[3.2.1]oct-2-en-4-one (**57**) showed that the structure consists of locally H-bonded 1:1 host:guest entities (Figure 13). Inspection of the entire crystal structure reveals, however, that the guest species are located one on top of the other in channel-type cavities formed between the hosts. The polar sites of the latter are directed inward while their non-polar lipophilic surface, consisting mainly of C—H bonds, is directed outward. The structural properties of this crystalline complex resemble in some respects those exhibited by adducts of the naturally occurring alkaloids (e.g. brucine and strychnine)[86]. The possible packing arrangements in these compounds are restricted by the particular molecular shape, which makes these hosts effective as resolving agents of optically active guest compounds by crystalline inclusion. Similar structural behaviour characterizes optical resolutions by the dioxaspirodecane derivative **51**, as has been demonstrated in the optical resolution study of pentolactone (**58**)[87]. The resolution of the latter by co-crystallization yielded 99% optically pure compound in 30% yield. As in the previous example, the crystal structure reveals a channel-type arrangement. The chiral host molecules form a helical spiral about the channel axis, each of the guest molecules accommodated in the channel being linked to the channel walls by strong hydrogen bonds.



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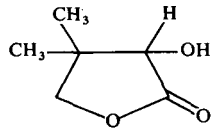
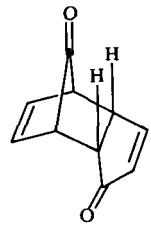


(58)



(59)

From among the above-mentioned synthetic diols, the dyine-diol species **52** is perhaps the most universal resolving agent. It has been successfully applied to a great variety of optically active molecules, some of which could not be resolved effectively by other methods. Specific examples include resolutions of optically active oximes, 2-methylpiperazine and dialkyl sulphoxides[88]. X-ray crystal structure analysis of the 2:1 complex of (−)-**52** with (+)-2-methylpiperazine indicated that the H bonds formed between OH groups of the host and N sites of the guest play an important role in fixing the host and guest molecule close together, and allowing efficient mutual recognition of chirality in the crystal lattice[89]. Resolution and structural behaviour of this host towards bicyclic ketone derivatives has recently been reported as well[85]. A uniquely beautiful crystal structure of the inclusion complex which forms between this host and *endo*-tricyclo[5.2.1.0]deca-3,8-diene-5,10-dione (**59**) is illustrated in Figure 14. It can be best described as consisting of continuous chains of H-bonded species which are aligned in an alternating manner along perpendicularly related directions in the crystal lattice. Along the chain, every guest component is enclosed between, and H-bonded through its carbonyl groups to, two neighbouring host molecules. Enclosure of the guest moiety is completed by two chlorophenyl groups approaching complementarily from opposite directions, as well as by hosts from adjacent chains. A well-defined chiral cage is thus formed around each guest constituent, the chlorophenyl substituents playing an

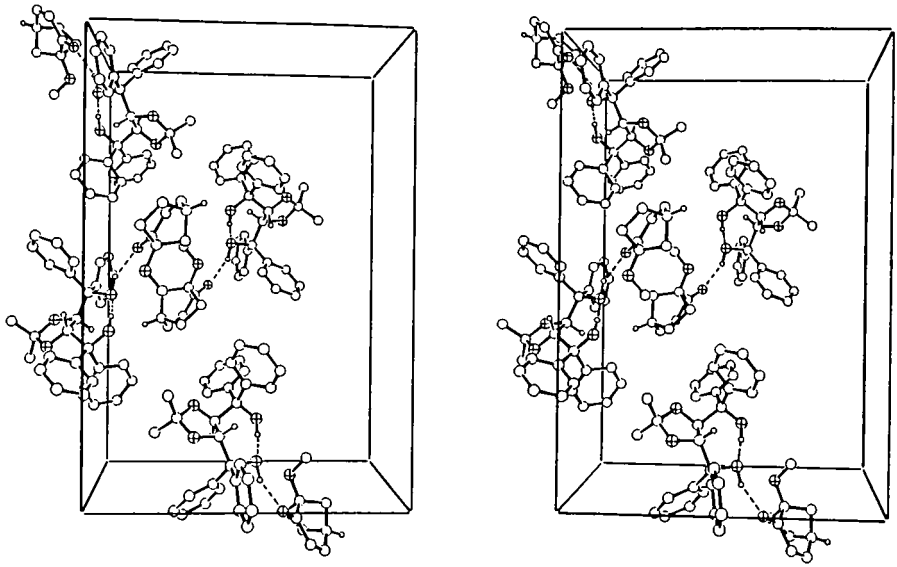


FIGURE 13. The intermolecular interaction scheme in the crystal structure of 1:1 **50**:**57** (stereoview)[85]

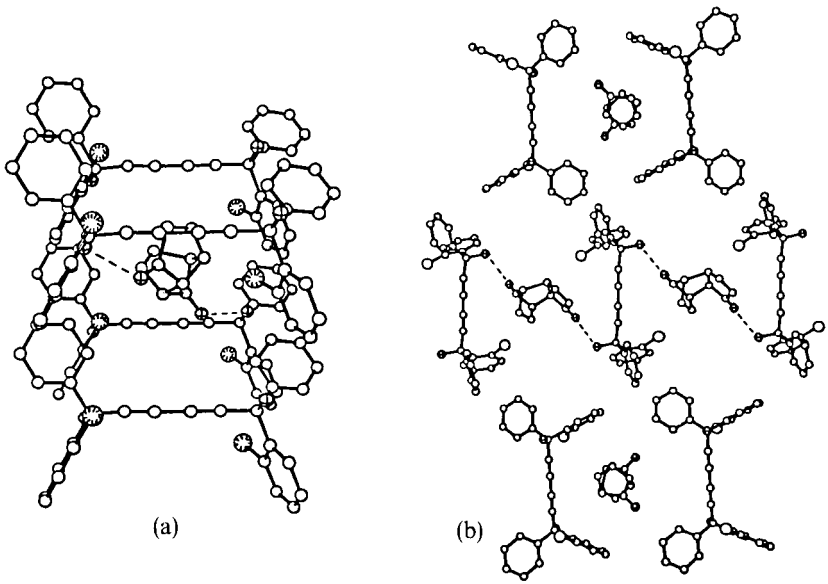
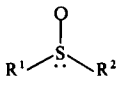


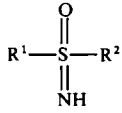
FIGURE 14. Two views of the complex between **52** and **59**, illustrating (a) the asymmetric enclosure around the resolved guest species formed by the chiral host molecules, and (b) the H-bonding association pattern between the two components[85]

important role in asymmetrically shaping the guest cavity. Moreover, it appeared that due to its particular shape and rigidity, this host molecule can also complex selectively guests that contain only one H-bonding function.

The binaphthyl host compound **54** was found to be very effective for the resolution of strongly polar molecules such as sulphoxides (**60**)[90], sulphoximines (**61**)[91], selenoxides (**62**)[92], phosphine oxides (**63**) and phosphonates (**64**)[93], amine *N*-oxides (**65**)[94] and arsine oxides (**66**), by complexation in the solid state[95]. Resolution of the selenoxides and arsine oxides is of particular interest, since their optically active enantiomers tend to racemize rapidly in solution in the presence of a small amount of water; they are stable, however, in a rigid lattice of the crystalline complex. Detailed structural correlations are available for two pairs of diastereoisomeric complexes of the binaphthyl host with an (alkyl-substituted) arene phosphinate (**64**, R^1 = phenyl)[93] and a dialkylarylamine-*N*-oxide (**65**, R^1 = *m*-tolyl and R^2 = ethyl)[94] as well as for adducts with single diastereoisomers of methyl-*m*-tolyl sulphoxide[96] and ethyl-*m*-tolyl selenoxide[97].



(**60**)



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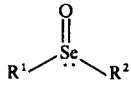
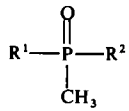
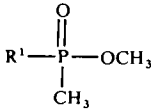


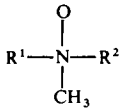
(**62**)



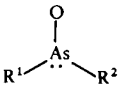
(**63**)



(**64**)



(**65**)



(**66**)

In fact, the six complexes reveal a similar structural pattern in the solid, in which each diol host is bound to two different oxide guests, and each guest bridge between two adjacent hosts, forming continuous chains of ...guest–host–guest–host... hydrogen-bonded moieties in the structure. These chains have lipophilic regions on the outside, consisting of the hydrocarbon frameworks of the two constituents, and an H-bonded polar zone in their central part (see below). They are characterized by a 2_1 screw symmetry in some structures, or by a simple translational symmetry in other compounds. Irrespective of the symmetry features of the individual chains, their crystal packing is effected in a similar manner by van der Waals interactions and steric fit. In all compounds, the aryl guest substituent of one chain is accommodated in the concave sites formed between the naphthyl groups of two adjacent hydrogen-bonded assemblies. In the resulting structures each guest component is thus surrounded asymmetrically by, and is in contact with, four binaphthol hosts. Moreover, it forms also a tight arrangement with neighbouring guest moieties, since the intermolecular distance along the chains is restricted by the particular H-bonding pattern and the limited flexibility of the host species.

Chiral recognition of enantiomeric species in crystalline complexation of the oxide-type guest compounds should be related primarily to the relative stability of the different diastereoisomers. Preferential crystallization usually involves host and guest components which form a sterically more complementary packing arrangement of the hydrogen-bonded chains. Correspondingly, the secondary intermolecular interactions which affect the relative stability of diastereoisomeric crystals with the phosphinate and *N*-oxide guest entities have been identified[93,94]. In the former complexes of **54** with **64** the

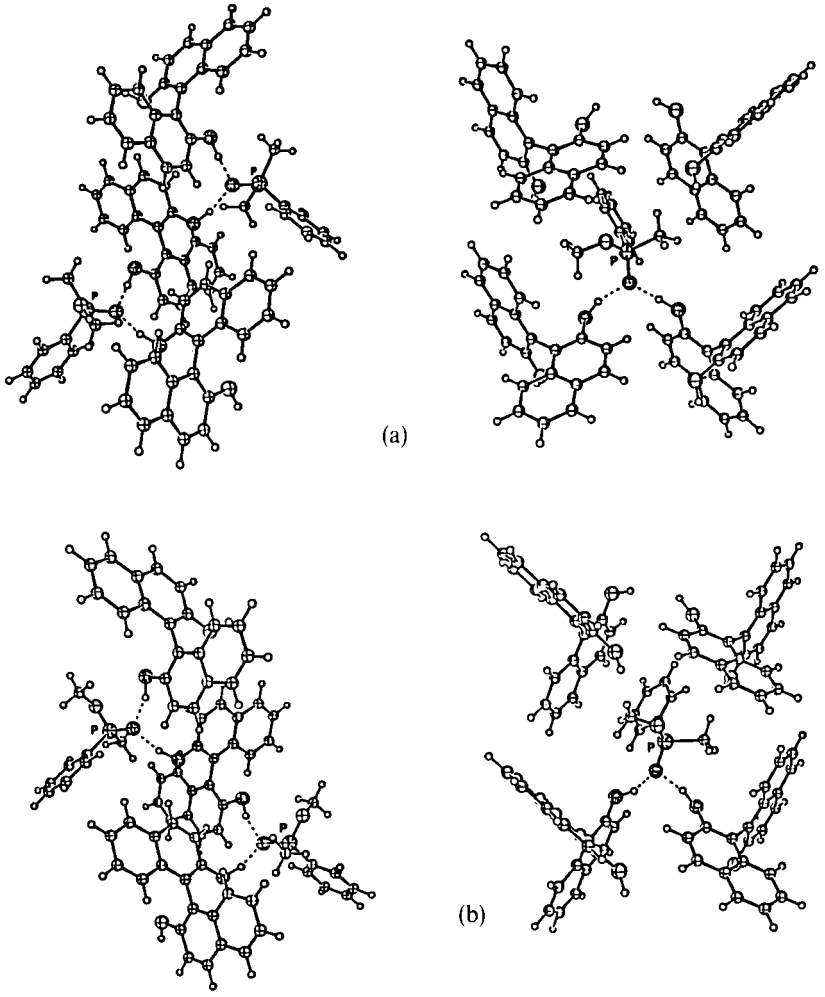


FIGURE 15. Packing arrangements observed in two different crystalline diastereoisomers (both monoclinic, space group $P2_1$) of the 1:1 complex between **54** and **64** (R^1 = phenyl): (a) (−)-**54** with (+)-**64** and (b) (+)-**54** with (+)-**64**[93]

smaller $—CH_3$ and $—OCH_3$ substituents are aligned roughly along the H-bonded chain, while the phenyl group is directed perpendicular to it (Figure 15). As a result, various phosphinates could be efficiently resolved, regardless of the methyl substitution on the phenyl ring, but none when the $—OCH_3$ group is replaced by a larger substituent such as $—OC_2H_5$ or isopropyl. On the other hand, in the *N*-oxide structures (complexes of **54** with **65**), the methyl and *m*-tolyl substituents are oriented along the chain, while the third group extends roughly in a perpendicular direction (Figure 16). Therefore, optical resolution in this system is more sensitive to the methyl position on

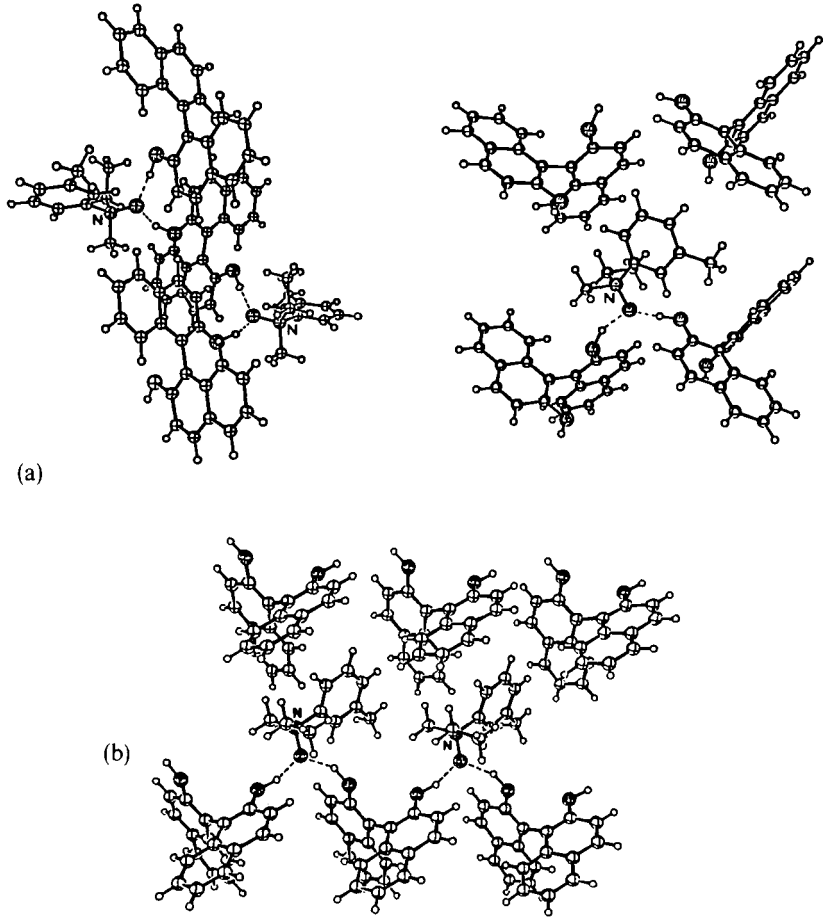
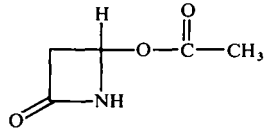


FIGURE 16. Packing arrangements observed in two different crystalline diastereoisomers of the 1:1 complex between **54** and **65** (R^1 = *m*-tolyl, R^2 = ethyl); (a) (+)-**54** with (+)-**65** (monoclinic, space group $P2_1$) and (b) (+)-**54** with (−)-**65** (triclinic, space group P1)[94]

the aryl group and less to the size of the perpendicularly aligned alkyl chain. Correspondingly, the *N*-oxide species which contain either an ethyl or an isopropyl alkyl group could also be resolved successfully as long as the aryl substituent remains *m*-tolyl. Similar trends in the enantiomer selectivity have been found for sulphoxides and sulphoximines, where the efficiency of the resolution is best when the alkyl group is methyl or ethyl and the aryl group is *m*-tolyl.

The successful synthesis of optically active **53** has allowed one to extend the crystallization method of chiral resolution to compounds containing chiral carbon. Indeed, this diol host can be used to resolve efficiently various ester derivatives, as well as other molecules containing alicyclic substituents and two polar sites available for coordinative interactions[98]. The latter are required to optimize hydrogen-bonding interactions (i.e. formation of continuous arrays of host and guest components linked to each other) with

the large biphenanthrol entities. All crystal structures studied thus far, which involve this diol host, reveal similar host–guest interaction schemes. They include 1:1 co-crystals with optically active methyl-2-chloropropionate and methyl 4-chloro-3-hydroxybutyrate[98] as well as with two different β-lactam derivates (**67** and **68**)[99]. These structures contain H-bonded chains of alternately arranged component species, side-packing of the chains being stabilized by van der Waals forces mainly between the aryl groups. Additional interactions between the hydrocarbon framework of the guest and the asymmetric environment of the surrounding phenanthryl substituents are also important, affecting the relative stabilities of the diastereoisomeric crystal structures. In most of the cases studied attempts to prepare single crystals of the less stable diastereoisomers turned out unsuccessful.



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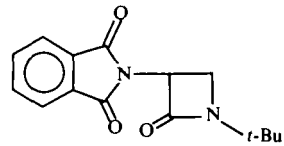


(68)

Crystal structures of the complexes of **53** with the two β-lactam species **67** and **68** are illustrated in Figure 17, showing structural details most important to the resolution process[99]. The structural principles governing the selective crystallizations with the binaphthyl and biphenanthryl diol hosts involve in all cases hydrogen-bonding association between the constituent species of the co-crystals. The formation of continuous chains of strongly coordinated molecules limits considerably the flexibility of the chiral lattice and enhances the significance of secondary steric interactions between the complexing components. Additional examples have been reviewed in other publications[73,74].

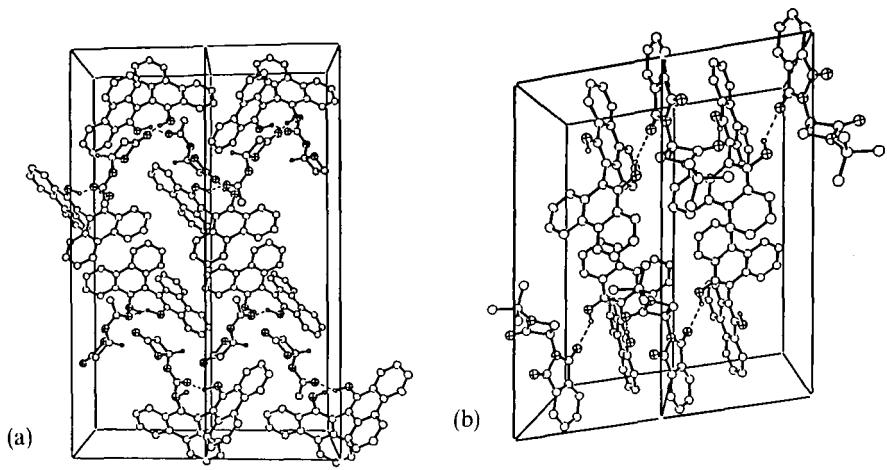
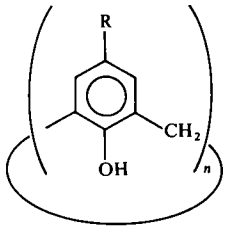


FIGURE 17. Illustration of the characteristic chain-type arrangement in chiral structures involving complexes between optically active host-**53** and guest species with multiple H-binding sites: (a) 1:1 **53**:**67** and (b) 1:1 **53**:**68**[99]

VI. DESIGNING SUPRAMOLECULAR ARCHITECTURES WITH ALCOHOLS

A. Calixarenes—Molecular Containers

Continuously increasing attention has been drawn in recent years to cyclic oligomers of phenolic units isolated from the reaction mixture of based–catalysed condensation of *para*-substituted phenols and formaldehyde. Due to their particular shape resembling a basket ('calyx') these aromatic compounds were coined the name *calix[n]arenes* (**69**, *n* indicating the number of monomeric units included in the cycle) by Gutsche. Similarly interesting are products of acid-catalysed condensation reactions of resorcinol with aldehydes, yielding cyclic tetramers named calix[4]resorcinarenes (**70**). Recently published reviews on the chemistry and structure of calixarenes reflect the extensive activity in this field of research[100,101].



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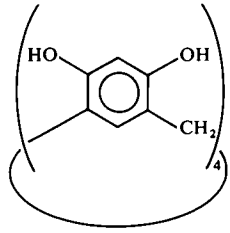
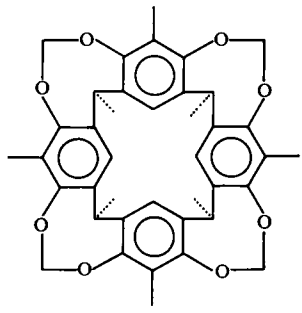


(70)

Several different synthetic procedures have been designed for the production of the oligomeric entities containing either an even or an odd number of phenolic fragments. Among those are one-step syntheses involving a single type of *para*-substituted phenols (being most effective when the substituent is *t*-butyl[102] as well as stepwise reactions[103]. The latter are particularly useful for the introduction of different functional groups into the *para*-positions as an integral part of the synthesis. The parent calixarene compounds (**69**, R = H) can readily be prepared by a reverse Friedel–Crafts reaction from the corresponding *p-t*-butylcalixarene derivatives (**69**, R = *t*-Bu). Subsequently, it can be functionalized at the *para*-positions by a desired group. The feasibility of binding functional groups to the phenolic oxygen atoms of calixarenes has also been demonstrated[104]. More complex molecules, involving a pair of calixarene moieties joined by methylene bridges, are known as well[105]. Introduction of methylene bridges between adjacent OH groups in calix[4]resorcinarenes yields even more strictly organized molecular frameworks, the cavitands (e.g. **71**)[106].



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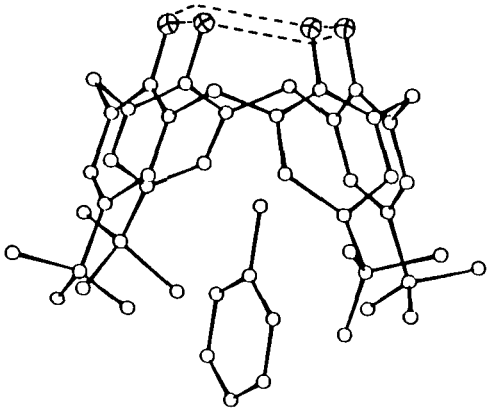
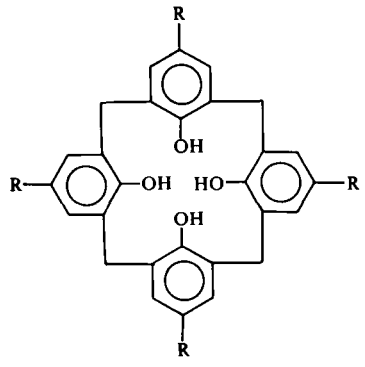


FIGURE 18. The nesting complex of toluene with *p*-*t*-butylcalix[4]arene (**72**, R = *t*-Bu)[107]. Intramolecular hydrogen bonds between the hydroxy groups circularly arranged along the inner rim of the macrocyclic molecule are marked by broken lines

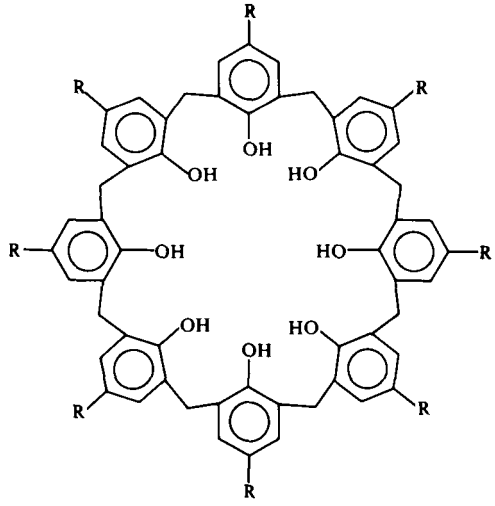
Structural properties of numerous calixarenes in the solid state have been determined by X-ray diffraction. The first examples relate to lower calixarene macrocycles, the structure of which resembles a basket. In fact, the appearance of a cylindrically-shaped intramolecular cavity is common to many of these compounds. Thus, a cone-type conformation of the calixarene framework with a four-fold symmetry was observed in the crystal structures of the *p*-*t*-butylcalix[4]arene (**72**, R = *t*-Bu) complexes with toluene and anisole (Figure 18)[107]. The latter are accommodated within the concave surface of the calixarene macrocycle; in the toluene adduct the guest is aligned with its methyl group along the four-fold axis. Similar features of the calixarene conformation have been observed in the crystal structures of either the free *p*-(1,1,3,3)-tetramethylbutylcalix[4]arene [**72**, R = $C(CH_3)_2CH_2C(CH_3)_3$] or its 1:1 complex with toluene[108]. In this case, however, the intramolecular cavity is filled by two *t*-butyl groups of the octyl chains, the toluene solvent accommodating intermolecular voids. Moreover, the *p*-*t*-butylcalix[4]arene units adopt a regular cone conformation even in their complexes with transition metals [e.g.



(72)

Ti(IV) and Co(II)], in which the metal ions bridge between two macrocycles forming a centrosymmetric dimer[109].

The conformation of the pentameric calix[5]arene in its complex with acetone still preserves the cone characteristics[110]. Recent crystal structure determinations of *p*-(1,1,3,3-tetramethylbutyl)calix[5]arene and its 1:1 inclusion complex with toluene have confirmed this observation, indicating also that this intrinsic property of the molecule is little affected by the length of the alkyl substituent (being the same for the *t*-butyl and the tetramethylbutyl derivatives)[111]. On the other hand, a strong deviation from the cone shape occurs in the structure of the hexamer, *p*-*t*-butylcalix[6]arene[112]. Furthermore, the corresponding octameric calixarene species (**73**) were shown to adopt an essentially planar form, with all —OH groups pointing inward and the alkyl substituents directed outward. The intramolecular cavity thus formed has a van der Waals diameter of approximately 4.0–4.5 Å[113]. In all the above structures the observed molecular conformation is rigidified by intramolecular hydrogen bonds between the hydroxy groups circularly arranged along the 'lower'/inner rim of the macrocyclic molecules. In solution, however, the macrocyclic species tend to be conformationally mobile, the lower members of the series (including the tetrameric species) undergoing ring inversion.



(73)

The calix[*n*]arenes can also be substituted by various functions on the phenolic O-atoms. Due to the apparent rigidity of the molecular framework, many such derivatives of the calix[4]arene moiety were found to maintain the cone structure even in the absence of intramolecular hydrogen bonds along the lower rim. The aryl fragments in these compounds are not restricted, however, to orient in the same direction. For example, varying conformational features have been observed in the crystal structures of the dimethyl-, trimethyl- and tetramethyl-substituted *p*-*t*-butylcalix[4]arenes (**74**, R = *t*-Bu and $X = OCH_3$)[114]. Other examples include the structures of the tetra-acetyl derivatives of this framework (**74**, R = *t*-Bu and $X = OCOCH_3$), which exhibits an irregular conformation[115], the regularly shaped complex of the tetracarbonate derivative (**74**, R = *t*-Bu and $X = OCOOC_2H_5$) with acetonitrile shown in Figure 19[116], and the somewhat different molecular structures of the free crown-bridged *p*-*t*-butylcalixarene and its 1:1 complex with pyridine[117]. The various structures of the methoxy derivatives

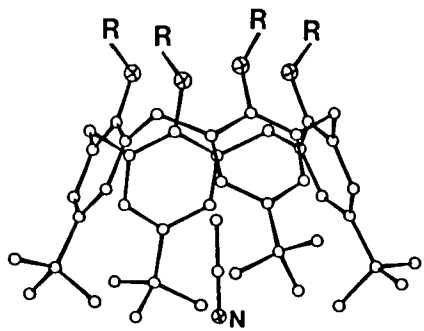
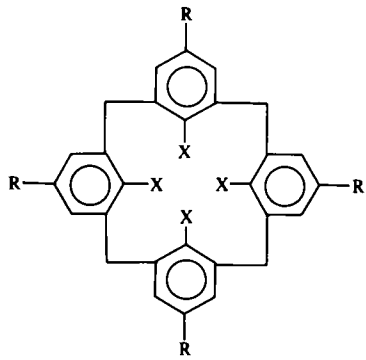


FIGURE 19. Illustration of the nesting complex of acetonitrile with the tetracarbonate derivative of *p-t*-butylcalix[4]-arene (**74**, R = *t*-Bu, X = $OCOOC_2H_5$)[116]

of *p-t*-butylcalix[8]arene are also characterized by different conformations[118]. It is not surprising that calixarenes incorporating polyether chains have been found useful for complexation with metal cations and selective extraction of the latter from solutions. However, the selectivity features of these hosts appear to be considerably less powerful than that of the corresponding crown ether receptors[119].



(74)

In the resorcinol-derived calix[4]arenes the hydroxy groups are located in the 'upper rim' of the macrocycle. The different isomers of the octa-ester derivatives of this compound are characterized by a flattened cone conformation[120]. The parent octa-hydroxy molecule (**70**) represents a tetradentate host, having four independent binding sites which are composed of a pair of hydrogen-bonded OH groups on adjacent benzene rings. It exhibits interesting molecular recognition and stereoselectivity properties, being capable of forming H-bonded complexes in a regio- and stereoselective manner with various cyclohexanol and cyclohexanediol moieties, and selectively extracting sugars from water into CCl_4[121]. Chemical linking of proximate OH groups of the methylcalix-[4]resorcinarene by methylene or dimethylsilyl bridges leads to the formation of rigidly structured cavitands containing enforced hydrophobic cavities which would not collapse in solution (**71**, **75**). The exact geometry of selected complexes has been determined by X-ray diffraction[122]. The intramolecular cavity of the dimethylsilyl host **75** adopts the

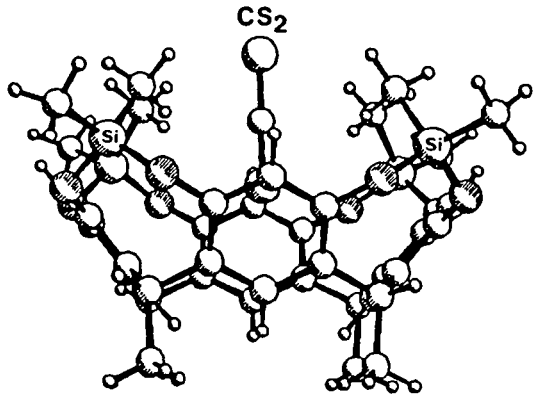
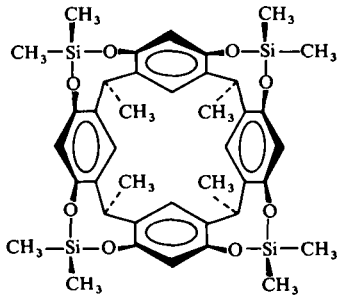


FIGURE 20. The structure of the nesting complex between cavitand **75** and carbon disulphide[122]



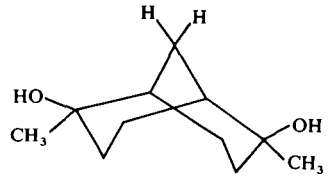
(75)

form of a rectangular well, which can be accommodated by a suitably shaped lipophilic guest species, representing a van der Waals molecular inclusion complex between apolar guest and host constituents. The inclusion complex of this host with carbon disulphide is illustrated in Figure 20.

The various oligomers of condensed phenol and resorcinol species referred to above, forming structure-enforced macrocycles, appear to be excellent building blocks for the construction of molecular containers of various shapes, sizes and functionality. Continuous efforts are being made to design pre-organized compounds with even greater complexity. In view of these special features of the calixarenes, they have become very attractive and widely investigated models of molecular receptors and carriers in the growing research field of *supramolecular chemistry.*

B. Diols Forming Helical Tubular Structures

A series of alicyclic diol molecules based on the 2,6-dihydroxybicyclo[3.3.1]nonane framework (**76**) were found to reveal unusual structural features and inclusion behaviour towards a wide range of small molecules in the solid state[123]. As shown by X-ray analysis, the crystal structures of these compounds are dominated by intermolecular hydrogen



(76)

bonds which tightly link adjacent species in a specific manner throughout the crystal. This leads in some cases to the formation of open network arrangements of the diol hosts suitable for accommodation of guest molecules. Two basic structure types with different modes of the hydrogen bonding have been observed. The first type consists of extended linear H-bonded arrays, resulting in a helical arrangement of the diol entities[124]. In these structures each OH function of the host molecule is involved in three-centre hydrogen bonds as a proton donor as well as a proton acceptor, forming open intermolecular arrangements with tubes/channels (of diameter range within 3.8–4.7 Å), or cages large enough to accommodate small guest molecules. The channel walls provide a lipophilic environment being lined with C—H bonds of the hydrocarbon framework. Figure 21 illustrates a characteristic example of open arrays of H-bonded molecules, as formed in the crystalline state by host **76**. It is noteworthy that some of the diol compounds of this class are able to retain the open helical tubular arrangement even

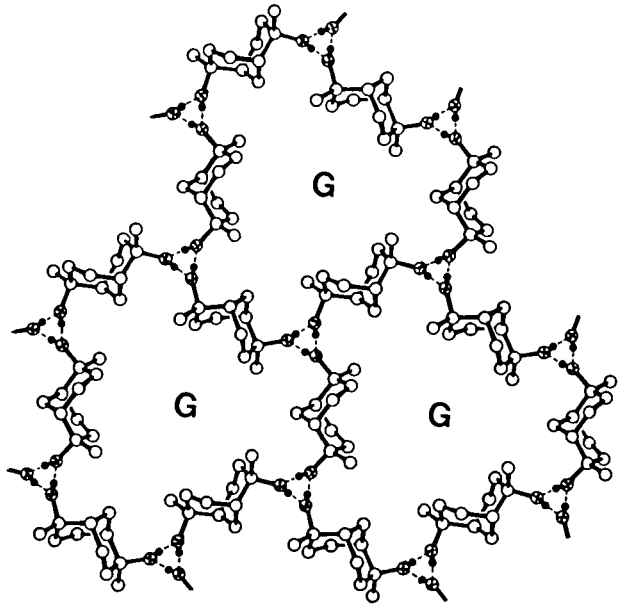


FIGURE 21. Partial representation of the open helical network arrangement of **76** in the crystal structure, showing the three-centred hydrogen bonds between adjacent molecules. 'G' in the cross section of the channels, which run perpendicular to the plane of the projection shown, indicates potential sites for guest occlusion[123]

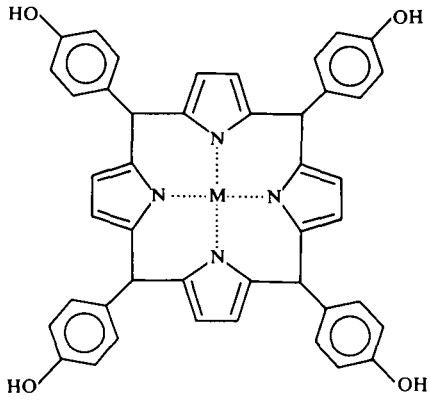
without the presence of guest molecules. Furthermore, although crystallization experiments were carried out from racemic mixtures of the host compound, the crystal structures which formed are often chiral (e.g. with space symmetries $P4_1$ or $P3_221$). The second type is characterized by a considerably denser packing of the diol molecules, mostly circular hydrogen-bond sequences and centrosymmetric intermolecular arrangements; consequently, no occlusion of guest molecules in these lattices has been observed[125].

It appears from the experimental investigations that the following molecular parameters are most significant to the occurrence of the helical and open structures. The corresponding diol molecules must have an approximate C_2 symmetry. Presence of methyl-substituted tertiary alcohol functionalities is also essential. Moreover, the molecular framework has to be rigidified by a methylene bridge located on the same side with the two OH groups (the *syn* face), as in **76**. A similar apex bridge on the opposite side of the hydroxy groups (the *anti* face) is not necessary.

A closely related derivative of 2,6-diol-3,3,7,7-tetramethylbicyclo[3.3.1]nonane, in its resolved form, was also used in the preparation of chiral crown ether ligands exhibiting enantiomer recognition behaviour[126]. The optical resolution of the bicyclononane species was obtained by an enantiomerically selective enzyme-catalysed reaction. The molecular framework of C_2 symmetry thus resolved acts as a chiral support for a crown ether moiety, by binding to it through the hydroxy O-atoms.

C. Microporous Molecular Solids Based on Functionalized Porphyrins

More recently, a large class of clathrates based on the tetraphenylporphyrin molecular building block, and the structural systematics of the host lattice formed by this compound, have been elucidated[127]. It was shown that the porphyrin materials can be tailored for specific applications in many ways. Subsequently, attempts have been undertaken to develop new porous molecular solids with controlled microstructure and cavities with specific geometries, based on a suitably functionalized tetraphenylporphyrin framework[128]. Indeed, investigations with metallated porphyrin species such as Zn(II)-tetra-(4-hydroxyphenyl)porphyrin (**77**) or Zn(II)-tetra(4-carboxyphenyl)porphyrin uncovered a number of new materials in which adjacent porphyrin molecules are joined by hydrogen bonds into a rigid framework, forming crystalline 'polymers' with an extremely high degree of two- and three-dimensional cross-linking. To some extent these compounds



(77)

resemble the structural rigidy of a zeolite. Two major types of intermolecular architecture have been observed with the symmetrically substituted hydroxy derivative **77**, both capable of forming co-crystals with small organic molecules. In one structure type the metalloporphyrin molecules form two-dimensional chains, adjacent (parallely aligned) molecules being linked to each other by hydrogen bonds between two pairs of the peripheral *cis*-related OH substituents. In the second class the tetra-ol metalloporphyrins cross-link in three dimensions, producing large rigid channels in the host lattice which can be accommodated by suitably sized lipophilic species[129]. Representative structures of the corresponding inclusion crystals between **77** and acetophenon or a mixture of toluene and xylenes are illustrated in Figure 22, demonstrating the additional possibilities for tailoring supramolecular structures with the aid of hydrogen-bonding directors between polyol compounds. A related type of polymeric structure containing peripherally linked tetra(hydroxyphenyl)porphyrin building blocks has recently been reported[130].

One of the most interesting features of these host materials involves the transfer of guests to or from the vapour phase. Structural changes that take place upon loss of the guest species have been monitored in several inclusion compounds of various metallotetraphenylporphyrins. These results show that, although in most cases guest desorption produces polycrystalline materials, the inclusion solid can be reconstituted from the desolvated hosts by absorption of the different guest molecules into the lattice. In fact, the metalloporphyrin materials promise to be particularly useful in 'time-release'-type applications because the thermodynamics and kinetics of the release can easily be modified by structural variation of the host species. Since the incorporation of guest molecules into the crystal lattice can increase their stability and decrease vapour pressure, these materials can also be useful in developing new techniques for a controlled delivery of unstable or volatile reagent in various chemical or medical procedures.

The promising results obtained thus far reflect considerable success accomplished in recent years in rationally designing new microporous molecular materials with nanometer-dimension channel and cage-type architectures. Further progress is anticipated in

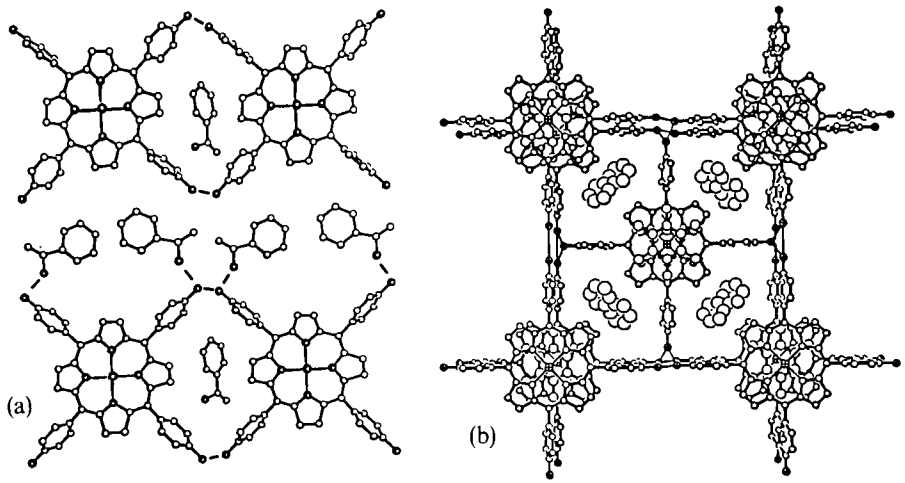


FIGURE 22. Illustration of the characteristic structures observed for complexes of host **77** with organic guest molecules: (a) accommodation of acetophenone in channels and small interporphyrin cavities, and (b) accommodation of toluene/xylene mixture in a three-dimensionally cross-linked host lattice[129]

the construction of elaborate new types of 'polymeric' three-dimensional supramolecular assemblies with prescribed geometries and desired properties of guest recognition.

VII. ACKNOWLEDGEMENTS

The author is grateful to Mrs Z. Stein, Mrs R. Magen and Miss E. Yeger for their assistance with the literature search and with preparation of some of the drawings.

VIII. REFERENCES

1. V. A. Naumov, in *Stereochemical Applications of Gas-Phase Electron Diffraction*, Part B (Eds. I. Hargittai and M. Hargittai), VCH, New York, 1988, pp. 93–146.
2. F. H. Allen, S. Bellard, M. D. Brice, B. A. Cartwright, A. Doubleday, H. Higgs, T. Hummelnik, B. G. Hummelnik-Peters, O, Kennard, W. D. S. Motherwell, J. R. Rodgers and D. G. Watson, *Acta Crystallogr.*, **B35**, 2331 (1979).
3. F. H. Allen, O. Kennard and R. Taylor, *Acc. Chem. Res.*, **16**, 146 (1983); R. Taylor and O. Kennard, *Acta Crystallogr.*, **B39**, 517 (1983).
4. P. Luger and J. Buschmann, *J. Am. Chem. Soc.*, **106**, 7118 (1984).
5. J. H. Noordik and J. M. Cillissen, *Cryst. Struct. Commun.*, **10**, 345 (1981).
6. G. Holan, J. Kowala and J. A. Wunderlich, *J. Chem. Soc., Chem. Commun.*, 34 (1973).
7. M. Hospital, F. Leroy, J. P. Bats and J. Moulines, *Cryst. Struct. Commun.*, **7**, 309 (1978).
8. J. D. Dunitz, M. Dobler, P. Seiler and R. P. Phizackerley, *Acta Crystallogr.*, **B30**, 2733 (1974); E. Maverick, P. Seiler, W. B. Schweizer and J. D. Dunitz, *Acta Crystallogr.*, **B36**, 615 (1980).
9. P. Luger and J. Buschmann, *Angew. Chem., Int. Ed. Engl.*, **22**, 410 (1983).
10. D. Cremer and J. A. Pople, *J. Am. Chem. Soc.*, **97**, 1358 (1975).
11. J. Buschmann, E. Muller and P. Luger, *Acta Crystallogr.*, **C42**, 873 (1986).
12. T. Koritsanszky, M. K. Strumpel, J. Buschmann, P. Luger, N. K. Hansen and V. Pichon-Pesme, *J. Am. Chem. Soc.*, **113**, 9148 (1991).
13. V. Schomaker and K. N. Trueblood, *Acta Crystallogr.*, **B24**, 63 (1968).
14. C. Scheringer, *Acta Crystallogr.*, **A28**, 616 (1972); **A34**, 428 (1978).
15. A. J. Kirkby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, Berlin, 1983; P. Delongchamps, *Stereoelectronic Effects in Organic Chemistry*, Wiley, New York, 1983.
16. G. A. Jeffrey, R. K. MacMullan, J. R. Ruble, J. Buschmann and P. Luger, *Acta Crystallogr.*, **C48** (1992), in press; cited in Reference 12.
17. N. K. Hansen and P. Coppens, *Acta Crystallogr.*, **A34**, 909 (1978).
18. P. Aped, Y. Apeloig, A. Ellencweig, B. Fuchs, I. Goldberg, M. Karni and E. Tartakovsky, *J. Am. Chem. Soc.*, **109**, 1486 (1987).
19. B. Fuchs, A. Ellencweig, E. Tartakovsky and P. Aped, *Angew. Chem., Int. Ed. Engl.*, **25**, 287 (1986); B. Fuchs and A. Ellencweig, *Nouv. J. Chim.*, **3**, 145 (1979).
20. L. Schleifer, H. Senderowitz, P. Aped, E. Tartakovsky and B. Fuchs, *Carbohydr. Res.*, **206**, 21 (1990); B. Fuchs, L. Schleifer and E. Tartakovsky, *Nouv. J. Chim.*, **8**, 275 (1984).
21. B. Fuchs, I. Goldberg and U. Shmueli, *J. Chem. Soc., Perkin Trans. 2*, 357 (1972).
22. P. Aped, B. Fuchs, I. Goldberg, H. Senderowitz, L. Schleifer, E. Tartakovsky, M. Anteunis and F. A. M. Borremans, *Tetrahedron*, **47**, 5781 (1991).
23. P. Aped, B. Fuchs, I. Goldberg, H. Senderowitz, E. Tartakovsky and S. Weinman, *J. Am. Chem. Soc.*, **114**, 5585 (1992).
24. S. H. Banyard and J. D. Dunitz, *Acta Crystallogr.*, **B32**, 318 (1976).
25. J. Lapasset, R. Viani, O. Bouab, G. Lamaty and C. Moreau, *Cryst. Struct. Communn.*, **9**, 1181 (1980).
26. I. Goldberg, in *Crown Ethers and Analogs* (Eds. S. Patai and Z. Rappoport), Wiley, Chichester, 1989, pp. 359–398 and 399–476.
27. G. Shoham, W. N. Lipscomb and U. Olsher, *J. Chem. Soc., Chem. Commun.*, 208 (1983).
28. G. Weber, F. Hirayama, W. Saenger and G. M. Sheldrick, *Acta Crystallogr.*, **C40**, 1570 (1984).
29. Y. Y. Wei, B. Tinant, J.-P. Declercq, M. van Meerssche and J. Dale, *Acta Crystallogr.*, **C43**, 1076, 1080, 1270, 1274, 1279 (1987).

30. J. D. Dunitz, E. F. Maverick and K. N. Trueblood, *Angew. Chem., Int. Ed. Engl.*, **27**, 880 (1988).
31. N. L. Allinger, M. R. Imam, M. R. Frierson, Y. Yuh and L. Schafer, in *Mathematics and Computational Concepts in Chemistry* (Ed. N. Trinajstic), Ellis Horwood, Chichester, 1986, pp. 8–19.
32. G. Wipff, P. Weiner and P. A. Kollman, *J. Am. Chem. Soc.*, **104**, 3249 (1982).
33. R. Perrin, C. Decoret and G. Bertholon, *Nouv. J. Chem.*, **7**, 263 (1983).
34. J. W. H. M. Uiterwijk, S. Harkema and D. Feil, *J. Chem. Soc., Perkin Trans. 2*, 721 (1987).
35. M. Billeter, A. E. Howard, I. D. Kuntz and P. A. Kollman, *J. Am. Chem. Soc.*, **110**, 8385 (1988).
36. G. Ranghino, S. Romano, J.-M. Lehn and G. Wipff, *J. Am. Chem. Soc.*, **107**, 7873 (1985).
37. D. Gehin, P. A. Kollman and G. Wipff, *J. Am. Chem. Soc.*, **111**, 3011 (1989).
38. J. van Eerden, S. Harkema and D. Feil, *Acta Crystallogr.*, **B46**, 222 (1990).
39. J.-M. Savariault and M. S. Lehmann, *J. Am. Chem. Soc.*, **102**, 1298 (1980).
40. I. Goldberg, J. Bernstein and E. M. Kosower, *Acta Crystallogr.*, **B38**, 1990 (1982).
41. C. J. Fritchie Jr. and R. K. McMullan, *Acta Crystallogr.*, **B37**, 1086 (1981).
42. B. Haas and H. Oberhammer, *J. Am. Chem. Soc.*, **106**, 6146 (1984).
43. W. Gase and J. E. Boggs, *J. Mol. Struct.*, **116**, 207 (1984).
44. Yu. L. Slovokhotov, T. V. Timofeeva, M. Yu. Antipin and Yu. T. Struchkov, *J. Mol. Struct.*, **112**, 127 (1984); D. Kaas, H. Oberhammer, D. Brandes and A. Blaschette, *J. Mol. Struct.*, **40**, 65 (1977).
45. C. Glidewell, D. C. Liles and D. J. Walton, *Acta Crystallogr.*, **B35**, 500 (1979).
46. V. E. Shklover, Yu. T. Struchkov and A. V. Ganyushkin, *Zh. Strukt. Khim.*, **26**, 180 (1985); V. E. Shklover, A. V. Ganyushkin, V. A. Yablokov and Yu. T. Struchkov, *Cryst. Struct. Commun.*, **8**, 869 (1979).
47. A. van Asselt, B. D. Santarsiero and J. E. Bercaw, *J. Am. Chem. Soc.*, **108**, 8291 (1986).
48. H. Szentivanyi and R. Stomberg, *Acta Chem. Scand.*, **A38**, 101, 121 (1984); **A37**, 709 (1983).
49. N. J. Karch, E. T. Koh, B. L. Whitsel and J. M. McBride, *J. Am. Chem. Soc.*, **97**, 6729 (1975).
50. A. Syed, P. Umrigar, E. D. Stevens, G. W. Griffin and R. J. Majeste, *Acta Crystallogr.*, **C40**, 1458 (1984).
51. D. Bethell, D. J. Chadwick, M. M. Harding, G. Q. Maling and M. D. Wiley, *Acta Crystallogr.*, **C41**, 470 (1985); D. Bethell, D. J. Chadwick and G. Q. Maling, *Acta Crystallogr.*, **C40**, 1628 (1984).
52. J. T. Fourkas, W. P. Schaefer and R. E. Marsh, *Acta Crystallogr.*, **C43**, 278, 2160 (1987).
53. J. T. Fourkas and W. P. Schaefer, *Acta Crystallogr.*, **C42**, 1395 (1986).
54. W. P. Schaefer, J. T. Fourkas and B. G. Tiemann, *J. Am. Chem. Soc.*, **107**, 2461 (1985).
55. S. N. Whittleton, P. Seiler and J. D. Dunitz, *Helv. Chim. Acta*, **64**, 2614 (1981).
56. R. Taylor and O. Kennard, *Acc. Chem. Res.*, **17**, 320 (1984).
57. R. Perrin, R. Lamartine, M. Perrin and A. Thozet, in *Organic Solid State Chemistry* (Ed. G. R. Desiraju), Elsevier, New York, 1987, pp. 271–329.
58. F. Iwasaki and Y. Kawano, *Acta Crystalogr.*, **B34**, 1286 (1978); T. Kagawa, R. Kawai, S. Kashino and M. Haisa, *Acta Crystallogr.*, **B32**, 3171 (1976).
59. R. Perrin, R. Lamartine, J. Vicens, M. Perrin, A. Thozet, D. Hanton and R. Fugier, *Nouv. J. Chim.*, **10**, 179 (1986).
60. R. Lamartine, R. Perrin, J. Vicens, D. Gemet, M. Perrin, D. Oehler and A. Thozet, *Mol. Cryst. Liq. Cryst.*, **134**, 219 (1986).
61. C. P. Brock and K. L. Haller, *J. Phys. Chem.*, **88**, 3570 (1984).
62. R. Lamartine, C. Decoret, J. Royer and J. Vicens, *Mol. Cryst. Liq. Cryst.*, **134**, 197 (1986).
63. I. Goldberg and E. Weber, unpublished results (1989).
64. E. Weber, K. Skobridis and I. Goldberg, *J. Chem. Soc., Chem. Commun.*, 1195 (1989).
65. S. A. Bourne, L. Johnson, C. Marais, L. Nassimbeni, E. Weber, K. Skobridis and F. Toda, *J. Chem. Soc., Perkin Trans. 2*, 1707 (1991).
66. A. Rahman and D. van der Helm, *Cryst. Struct. Commun.*, **10**, 731 (1981).
67. T. Gramstad, S. Husebye and K. Maartmaan Moe, *Acta Chem. Scand.*, **B40**, 26 (1986).
68. F. Toda, K. Tanaka and T. C. W. Mak, *Bull. Chem. Soc. Jpn.*, **58**, 2221 (1985); F. Toda, K. Tanaka, S. Nagamatsu and T. C. W. Mak, *Isr. J. Chem.*, **25**, 346 (1985); F. Toda, K. Tanaka and T. C. W. Mak, *Tetrahedron Lett.*, **25**, 1359 (1984).
69. D. R. Bond, M. R. Caira, G. A. Harvey, L. R. Nassimbeni and F. Toda, *Acta Crystallogr.*, **B46**, 771 (1990); D. R. Bond, L. R. Nassimbeni and F. Toda, *J. Incl. Phenom.*, **7**, 623 (1989); *J. Crystallogr. Spectrosc. Res.*, **19**, 847 (1989).

70. M. Yasui, T. Yabuki, M. Takama, S. Harada, N. Kasai, K. Tanaka and F. Toda, *Bull. Chem. Soc. Jpn.*, **62**, 1436 (1989); T. Yabuki, M. Yasui, H. Tezuka, S. Harada, N. Kasai, K. Tanaka and F. Toda, *Chem. Lett.*, 749 (1988).
71. W. H. Watson, J. Galloy, F. Vogtle and W. M. Muller, *Acta Crystallogr.*, **C40**, 200 (1984).
72. M. Pickering and R. W. H. Small, *Acta Crystallogr.*, **B38**, 3161 (1982).
73. F. Toda, in *Inclusion Compounds*, Vol. 4 (Eds. J. L. Atwood, J. E. D. Davies and D. D. MacNicol), Oxford University Press, Oxford, 1991, pp. 126–187; F. Toda, *Top. Curr. Chem.*, **140**, 43 (1987).
74. I. Goldberg, in *Inclusion Compounds*, Vol. 4 (Eds. J. L. Atwood, J. E. D. Davies and D. D. MacNicol), Oxford University Press, Oxford, 1991, pp. 406–447; I. Goldberg, *Top. Curr. Chem.*, **149**, 1 (1988).
75. F. Toda, K. Tanaka, J. Elguero, Z. Stein and I. Goldberg, *Chem. Lett.*, 1061 (1988).
76. F. Toda, K. Tanaka, J. Elguero, L. Nassimbeni and M. Niven, *Chem. Lett.*, 2317 (1987).
77. H.-S. Shieh, L. G. Howard and C. E. Nordman, *Acta Crystallogr.*, **B38**, 2411 (1982); B. M. Craven, *Acta Crystallogr.*, **B35**, 1123 (1979).
78. F. Toda, K. Tanaka, H. Krupitsky and I. Goldberg, unpublished results (1991).
79. I. Goldberg, Z. Stein, K. Tanaka and F. Toda, *J. Incl. Phenom.*, **6**, 15 (1988).
80. I. Goldberg, Z. Stein, K. Tanaka and F. Toda, *J. Incl. Phenom.*, **10**, 97 (1991).
81. F. Toda, A. Kai, R. Toyokama, W.-H. Yip and T. C. W. Mak, *Chem. Lett.*, 1921 (1989).
82. I. Goldberg, Z. Stein, A. Kahi and F. Toda, *Chem. Lett.*, 1617 (1987).
83. I. Goldberg, Z. Stein, E. Weber, N. Dorpinghaus and S. Franken, *J. Chem. Soc., Perkin Trans. 2*, 953 (1990); E. Weber, N. Dorpinghaus and I. Goldberg, *J. Chem. Soc., Chem. Commun.*, 1566 (1988).
84. E. Weber, N. Dorpinghaus, C. Wimmer, H. Krupitsky, Z. Stein and I. Goldberg, unpublished results (1990 and 1991).
85. F. Toda, K. Tanaka, D. Marks and I. Goldberg, *J. Org. Chem.*, **56**, 7332 (1991); F. Toda and K. Tanaka, *Tetrahedron Lett.*, **29**, 551 (1988).
86. R. O. Gould and M. D. Walkinshaw, *J. Am. Chem. Soc.*, **106**, 7840 (1984).
87. F. Toda, A. Sato, K. Tanaka and T. C. W. Mak, *Chem. Lett.*, 873 (1989).
88. F. Toda and H. Akai, *J. Org. Chem.*, **55**, 4973 (1990); F. Toda, K. Tanaka and M. Kido, *Chem. Lett.*, 513 (1988); F. Toda, K. Mori, Y. Matsuura and H. Akai, *J. Chem. Soc., Chem. Commun.*, 1591 (1990).
89. F. Toda, K. Tanaka and M. Kido, *Chem. Lett.*, 513 (1988).
90. F. Toda, K. Tanaka and S. Nagamatsu, *Tetrahedron Lett.*, **25**, 4929 (1984); F. Toda and K. Tanaka, *J. Incl. Phenom.*, **2**, 91 (1984).
91. K. Mori and F. Toda, *Chem. Lett.*, 1997 (1988).
92. F. Toda and K. Mori, *J. Chem. Soc., Chem. Commun.*, 1357 (1988).
93. F. Toda, K. Mori, Z. Stein and I. Goldberg, *J. Org. Chem.*, **53**, 308 (1988).
94. F. Toda, K. Mori, Z. Stein and I. Goldberg, *Tetrahedron Lett.*, **30**, 1841 (1989).
95. K. Mori and F. Toda, *Bull. Chem. Soc. Jpn.*, **63**, 2127 (1990).
96. F. Toda, K. Tanaka and T. C. W. Mak, *Chem. Lett.*, 2085 (1984).
97. T. Fujiwara, N. Tanaka, R. Ooshita, R. Hino, K. Mori and F. Toda, *Bull. Chem. Soc. Jpn.*, **63**, 249 (1990).
98. G. H. Lee, Y. Wang, K. Tanaka and F. Toda, *Chem. Lett.*, 781 (1988); F. Toda and K. Tanaka, *Tetrahedron Lett.*, **29**, 1807 (1988).
99. F. Toda, K. Tanaka, M. Yagi, Z. Stein and I. Goldberg, *J. Chem. Soc., Perkin Trans. 1*, 1215 (1990); I. Goldberg and F. Toda, unpublished results (1989).
100. C. D. Gutsche, in *Inclusion Compounds*, Vol. 4 (Eds. J. L. Atwood, J. E. D. Davies and D. D. MacNicol), Oxford University Press, Oxford, 1991, pp. 21–63 and previous references cited therein; G. D. Andreetti, F. Ugozzoli, R. Ungaro and A. Pochini, *ibid*, pp. 64–125.
101. J. Vicens and V. Bohmer (Eds.), *Calixarenes: A Versatile Class of Macrocyclic Compounds*, Kluwer Academic Publishers, Dordrecht, 1990; C. D. Gutsche, *Calixarenes*, Monographs in Supramolecular Chemistry, Royal Society of Chemistry, London, 1989.
102. C. D. Gutsche and M. Iqbal, *Org. Synth.*, **68**, 234 (1989); C. D. Gutsche, B. Dhawan, M. Leonis and D. Stewart, *Org. Synth.*, **68**, 238 (1989); J. H. Munch and C. D. Gutsche, *Org. Synth.*, **68**, 243 (1989).
103. H. Goldmann, W. Vogt, E. Paulus and V. Bohmer, *J. Am. Chem. Soc.*, **110**, 6811 (1988); E.

Paulus, V. Bohmer, H. Goldmann and W. Vogt, *J. Chem. Soc., Perkin Trans. 2*, 1609 (1987); V. Bohmer, F. Marschollek and L. Zetta, *J. Org. Chem.*, **52**, 3200 (1987).
104. S. Shinkai, T. Otsuka, K. Araki and T. Matsuda, *Bull. Chem. Soc. Jpn.*, **62**, 4055 (1989); S. A. McKervey and E. M. Seward, *J. Org. Chem.*, **51**, 3581 (1986); A. Arduini, A. Pochini, S. Reverberi and R. Ungaro, *J. Chem. Soc., Chem. Commun.*, 981 (1984).
105. V. Bohmer, H. Goldmann, W. Vogt, J. Vicens and Z. Asfari, *Tetrahedron Lett.*, **30**, 1391 (1989).
106. D. J. Cram, S. Karbach, H.-E. Kim, C. B. Knobler, E. F. Maverick, J. L. Erickson and R. C. Helgeson, *J. Am. Chem. Soc.*, **110**, 2229 (1988).
107. R. Ungaro, A. Pochini, G. D. Andreetti and P. Domiano, *J. Chem. Soc., Perkin Trans. 2*, 197 (1985); G. D. Andreetti, R. Ungaro and A. Pochini, *J. Chem. Soc., Chem. Commun.*, 1005 (1979).
108. G. D. Andreetti, A. Pochini and R. Ungaro, *J. Chem. Soc., Perkin Trans. 2*, 1773 (1983).
109. M. M. Olmstead, G. Siegel, H. Hope, X. Xu and P. P. Power, *J. Am. Chem. Soc.*, **107**, 8087 (1985).
110. M. Coruzzi, G. D. Andreetti, V. Bocchi, A. Pochini and R. Ungaro, *J. Chem. Soc., Perkin Trans. 2*, 1133 (1982).
111. M. Perrin and S. Lecocq, *J. Incl. Phenom.*, **11**, 171 (1991).
112. M. Halit, D. Oehler, M. Perrin, A. Thozet, R. Perrin, J. Vicens and M. Bourakhoudar, *J. Incl. Phenom.*, **6**, 613 (1988).
113. C. D. Gutsche, A. E. Gutsche and A. I. Karaulov, *J. Incl. Phenom.*, **3**, 447 (1985).
114. P. D. J. Grootenhuis, P. A. Kollman, L. C. Groenen, D. N. Reinhoudt, G. J. van Hummel, F. Ugozzoli and G. D. Andreetti, *J. Am. Chem. Soc.*, **112**, 4165 (1990); S. G. Bott, A. W. Coleman and J. L. Atwood, *J. Incl. Phenom.*, **5**, 747 (1987).
115. C. Rizzoli, G. D. Andreetti, R. Ungaro and A. Pochini, *J. Mol. Struct.*, **82**, 133 (1982).
116. M. A. McKervey, E. M. Seward, G. Ferguson and G. L. Ruhl, *J. Org. Chem.*, **51**, 3581 (1986).
117. G. D. Andreetti, O. Ori, F. Ugozzoli, C. Alfieri, A. Pochini and R. Ungaro, *J. Incl. Phenom.*, **6**, 523 (1988).
118. A. W. Coleman, S. G. Bott and J. L. Atwood, *J. Incl. Phenom.*, **5**, 581 (1987); **4**, 247 (1986).
119. S. R. Izatt, R. T. Hawkins, J. J. Christensen and R. M. Izatt, *J. Am. Chem. Soc.*, **107**, 63 (1985); V. Bocchi, D. Foina, A. Pochini, R. Ungaro and G. D. Andreetti, *Tetrahedron*, **38**, 373 (1982).
120. L. Abis, E. Dalcanale, A. Du Vosel and S. Spera, *J. Org. Chem.*, **53**, 5475 (1988); A. G. S. Hogberg, *J. Org. Chem.*, **45**, 4498 (1980); *J. Am. Chem. Soc.*, **102**, 6046 (1980).
121. Y. Kikushi, Y. Kato, Y. Tanaka, H. Toi and Y. Aoyama, *J. Am. Chem. Soc.*, **113**, 1349 (1991).
122. I. Goldberg, *J. Incl. Phenom.*, **4**, 191 (1986); D. J. Cram, K. D. Stewart, I. Goldberg and K. N. Trueblood, *J. Am. Chem. Soc.*, **107**, 2574 (1985).
123. R. Bishop and I. G. Dance, in *Inclusion Compounds*, Vol. 4 (Eds. J. L. Atwood, J. E. D. Davies and D. D. MacNicol), Oxford University Press, Oxford, 1991, pp. 1–26; *Top. Curr. Chem.*, **149**, 137 (1988).
124. I. G. Dance, R. Bishop, S. C. Hawkins, T. Lipari, M. L. Scudder and D. C. Craig, *J. Chem. Soc., Perkin Trans. 2*, 1299 (1986); R. Bishop, S. Choudhury and I. G. Dance, *J. Chem. Soc., Perkin Trans. 2*, 1159 (1982).
125. S. C. Hawkins, M. L. Scudder, D. C. Craig, A. D. Rae, R. B. Abdul-Raof, R. Bishop and I. G. Dance, *J. Chem. Soc., Perkin Trans. 2*, 855 (1990).
126. K. Naemura, T. Matsumura, M. Komatsu, Y. Hirose and H. Chikamatsu, *J. Chem. Soc., Chem. Commun.*, 239 (1988).
127. M. P. Byrn, C. J. Curtis, S. I. Khan, P. A. Sawin, R. Tsurumi and C. E. Strouse, *J. Am. Chem. Soc.*, **112**, 1865 (1990); W. R. Scheidt and Y. J. Lee, *Struct. Bond. (Berlin)*, **64**, 1 (1987).
128. M. P. Byrn, C. J. Curtis, I. Goldberg, Y. Hsiou, S. I. Khan, P. A. Sawin, S. K. Tendick and C. E. Strouse, *J. Am. Chem. Soc.*, **113**, 6549 (1991).
129. I. Goldberg, H. Krupitsky and C. E. Strouse, unpublished results (1991).
130. A. J. Golder, K. B. Nolan, D. C. Povey and L. R. Milgrom, *Acta Crystallogr.*, **C44**, 1916 (1988).

CHAPTER 3

Chiroptical properties of alcohols, ethers and peroxides

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I. INTRODUCTION

This chapter is an update of the previous review of Gotterelli and Samori[1] published in 1980. It will cover a new chromophore, namely the peroxide moiety, but will not include the thioethers and disulfides which were reviewed in the previous manuscript. This review will be limited to the available literature on the chromophore itself and not on compounds of which the chromophore is one of the substituents responsible for their optical activity. Therefore we will emphasize the alcohol moiety and not sugars or aromatic alcohols where the hydroxyl absorption is mixed or overshadowed by the absorption of the $\pi \rightarrow \pi^*$ bands.

II. CHIROPTICAL PROPERTIES OF ETHERS

A. Oxiranes

Only with the extension of CD measurements to the vacuum-UV did the ether chromophore and its chiroptical properties become amenable to experimental observations[2,3]. While the first reported CD measurements concentrated on aliphatic

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Edited by S. Patai

ethers[2], the last decade has seen the effort shifted towards cyclic ethers, although one study of aliphatic ether was reported. The interest in these compounds arises from the fact that, due to their rigid skeleton, it is much easier for theoreticians to calculate their chiroptical properties.

The first theoretical *ab initio* calculation of an oxirane molecule was reported almost simultaneously with the first published CD spectra of these compounds[4]. Rauk employed *ab initio* SCF-CI methods to study the lower electronic states, the oscillator and optical rotatory strengths of symmetric oxirane and of *S*-3-methyloxirane[4]. The highest occupied molecular orbitals in oxirane were n(O) and W_2, which were calculated by him to be nearly degenerate. These orbitals n(O) and W_2 represent a nonbonding atomic orbital centered on the oxygen atom and a Walsh orbital of cyclopropane, respectively. This energy degeneracy is not in accord with the experimental ionization potential. The first excited state in *S*-2-methyloxirane was calculated[4] as originating to a great extent (72%) at the n(O) orbital and terminating at a combined 3s, σ^*_{CO} orbital. The 3s, σ^*_{CO} orbital is an admixture of an orbital mainly situated on the oxygen atom with the nodal characteristic of an atomic 3s orbital and an antibonding component from the s orbitals on the carbon atoms.

The first transition in *S*-2-methyloxirane whose energy was calculated[4] to be 7.49 eV has a small negative CD signal. This signal is due to the product of a strong magnetic dipole transition moment and a weak electric dipole transition moment. Another reason for the weak CD is due to the fact that the two moments are nearly perpendicular. A much stronger positive CD signal was calculated for the second excited state whose energy transition is 9.12 eV. The experimental results[5] did not agree with Rauk's calculations, exhibiting a positive CD signal for the first excited state of *S*-2-methyloxirane.

In a detailed study of *S*-(−)-2-methyloxirane and (*S*,*S*)-(−)-dimethyloxirane, the CD of these two compounds was measured down to 1450 Å[5,6]. The measurements were accompanied by *ab initio* self-consistent field calculations in which excitation energies, oscillator and rotational strength were determined. All the measurements were carried

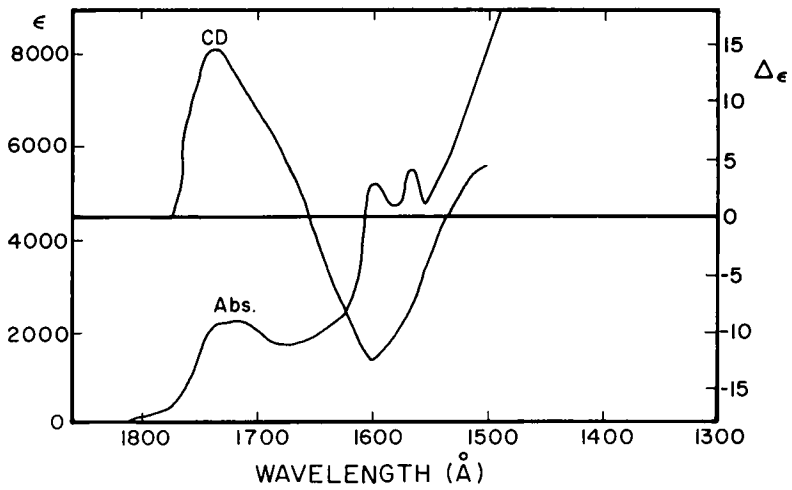


FIGURE 1. Absorption and CD spectra of (*S*)-(−)-2-methyloxirane in the gas phase. The spectral resolution is 16 Å. ε and $\Delta\varepsilon$ are expressed in $l\,mol^{-1}\,cm^{-1}$

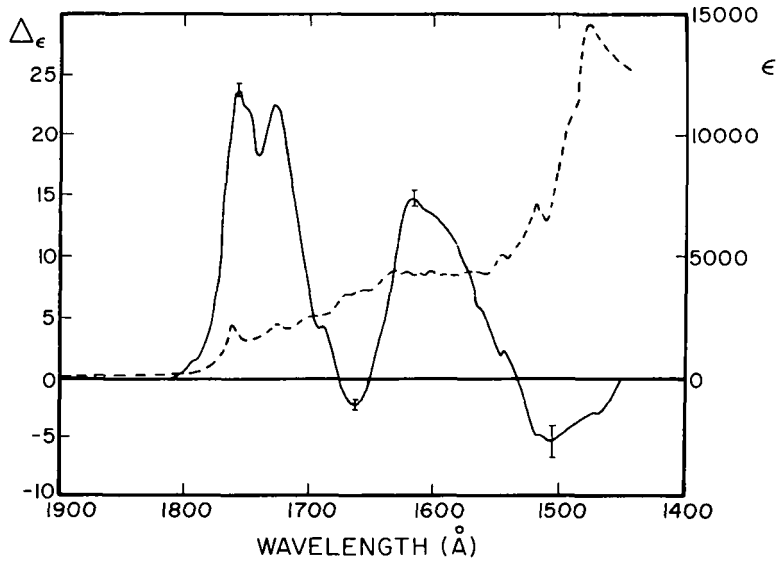


FIGURE 2. Absorption (———) and CD (-----) spectra of (*S,S*)-(−)-2,3-dimethyloxirane in the gas phase. The spectra resolution is 16 Å. ε and Δε are expressed in $l\,mol^{-1}\,cm^{-1}$

out in the gas phase. In Figures 1 and 2 we present the CD and absorption of *S*-(−)-2-methyloxirane (MO) and (*S,S*)-(−)-2,3-dimethyloxirane (DMO). The interpretation of both spectra is based on the detailed study of Basch and coworkes[7] in which the absorption of ethylene oxide was studied in the gas and solid phases, as well as in a VUV transparent solvent such as hexafluoroisopropanol. According to their findings, the absorption bands in ethylene oxides showing vibrational structure are all Rydberg transitions terminating in *ns*, *np* and *nd* ($n = 3$–6) orbitals. These Rydberg transitions are superimposed on valence transitions, which were detected only in the solid phase where the Rydbergs were washed out[7]. Following these guidelines and the *ab initio* results[5] we assigned the peak at 1740 Å in MO as the n(O)→3s Rydberg transition, which shows a positive CD band having $\Delta\varepsilon/\varepsilon$ of *ca* 7×10^{-3}. The same CD sign was observed in DMO for the corresponding 1755 Å band whose $\Delta\varepsilon/\varepsilon$ was found as 1.2×10^{-2}. The CD and absorption of DMO revealed more structure, vibrational and electronic, and was assigned by comparing its spectrum to that of ethylene oxide. The vibrational structure for the n(O)→3s Rydberg revealed a $1100 \pm 50\,cm^{-1}$ spacing, which was attributed to the totally symmetric ring breathing (ν_3) mode. The second CD band is positive and peaks at 1602 Å. It was assigned as an n(O)→3p Rydberg transition based on its $18100\,cm^{-1}$ term value. The third band, a negative CD band at 1510 Å, can be either an n(O)→3d or n(O)→4s, or even a valence transition corresponding to the 1440 Å band in ethylene oxide. The most interesting feature is a negative band at 1655 Å, which does not seem to have any corresponding resolved absorption band in DMO. An early attempt[6] related the transition to the $63000\,cm^{-1}$ shoulder on the absorption of solid ethylene oxide which then leads to an n(O)→σ^* valence transition. However, the *ab initio* calculations[5] suggest that one of the components of the n(O)→3p Rydberg manifold appears in this energy range having a negative CD signal.

TABLE 1. Summary of calculated and experimental quantities for methyloxirane

	Calculated			Experimental		
Transition	ΔE^a	$f(\nabla)$	$RS(\nabla)^b$	ΔE^a	RS^b	f
n(O) → R(3s)	6.4	0.026	+4.92	7.12	11.8	0.025
n(O) → R(3p)	7.16	0.010	−1.30	7.75	−10.8	0.062
n(O) → R(3p)	7.34	0.026	+0.42			
n(O) → R(3p)	7.36	0.006	−0.02			

[a]Excitation energy from the ground state, in eV.
[b]RS ≡ rotational strength, in 10^{-40} cgs units.

TABLE 2. Summary of calculated and experimental quantities for dimethyloxirane

	Calculated			Experimental		
Transition	ΔE^a	$f(\nabla)$	$RS(\nabla)^b$	ΔE^a	RS^b	f
n(O) → R(3s)	6.36	0.0042	+3.44	7.06	+20	0.02
n(O) → R(3p)	6.64	0.0042	−7.34	7.49	−0.4	
n(O) → R(3p)	7.08	0.0024	+1.52	7.74	+14	0.05
n(O) → R(3p)	7.18	0.0002	−0.46			

[a]Excitation energy from the ground state, in eV.
[b]RS ≡ rotational strength, in 10^{-40} cgs units.

In Tables 1 and 2, the results of the *ab initio* calculations are presented and compared to the experimental results. The calculated rotational strength is somewhat lower than the experimental results, but the correct sign is predicted for the n(O) → 3s as well as for n(O) → 3p Rydberg transitions. The calculated energies are always lower than the observed ones. This is a reflection of the lower energies calculated for the first ionization potential. For DMO the reported ionization potential is 9.98 eV[8] while the calculated value is 8.81 eV.

The study of the CD of alkyl-substituted oxiranes was later extended to include other mono-, di- and trisubstituted oxiranes[9,10]. All the observed spectra have a strong CD band centered at 1735 ± 15 Å for monosubstituted oxiranes. This band is assigned as the n(O) → 3s Rydberg transition based on the *ab initio* calculations cited above. The reason for only a slight dependence of the energy of this transition on the nature of the substituent is that, although the ionization potential decreases when a larger substituent is examined, the term value also decreases, leading eventually to this constant energy.

The addition of methyl substituents to the oxirane ring causes a red shift to the n(O) → 3s Rydberg transition, thus for *R*-(+)-2,2,3-trimethyloxirane the first excited state appears at 1810 Å. This is in agreement with the lowering of the ionization potential by 0.27 eV when a methyl group is added to the oxirane moiety[8].

The CD sign of the first excited state for alkyl-substituted oxiranes was found to be correlated with the absolute configuration of the molecule. A simple quadrant rule was formulated based on the observations of signs of the n(O) → 3s transition in 10 alkyl-substituted oxiranes[9,10]. Although at first glance it seems that all *S*-enantiomers exhibit a positive CD signal and *R*-enantiomers a negative sign, we prefer to present the geometrical perspective, which according to the quadrant rule shows a positive CD for substituents with $Y > 0$ and $X > 0$ or with $Y < 0$ and $X < 0$ (Figure 3), and a negative

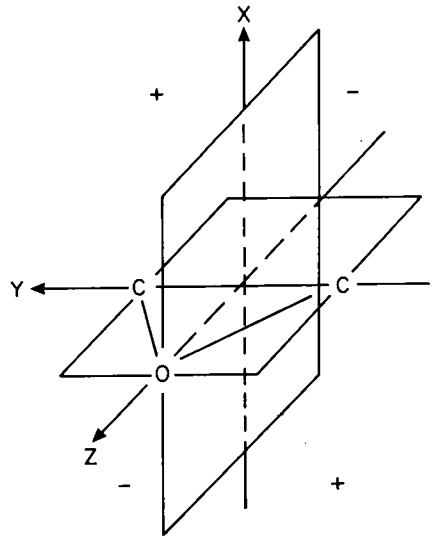


FIGURE 3. The planes of symmetry forming the quadrants of oxirane

CD for the other two quadrants. The reason that such a quadrant rule is demonstrated only for the n(O)→3s is related to its being a low-lying state separated from its neighboring transition, while the n(O)→3p is composed of three electronic transitions which are closer in energy to an underlying valence state which was observed in the thin film absorption spectrum[7].

Of all the alkyl-substituted oxiranes that have been studied, the most interesting is the (2*R*,3*S*)-(−)-*cis*-2-ethyl-3-methyloxirane, whose absorption and CD spectra are presented in Figure 4. This molecule provides a unique opportunity to compare the role of methyl and ethyl groups in inducing optical activity. The subject was addressed previously by Bauman and Lightner in treating the octant rule of the n(O)→π^* transition in carbonyls[11]. According to the oxirane quadrant rule mentioned above, the two groups have opposite contributions to the CD signal of the n(O)→3s transition. Thus one would expect a rather small signal for this state due to this cancellation effect. The observed signal at 1775 Å is indeed small. It is the only case amongst the 10 alkyl-substituted oxiranes in which the intensity of the n(O)→3s is smaller than the higher-energy n(O)→3p band. This attests to the above-mentioned opposite contributions of the methyl and ethyl groups. The positive signal observed for the n(O)→3s transition indicates that the contribution of the methyl group outweighs that of the ethyl group. In some cases correlation of the influence of substituent groups with their polarizability has been made[12]. However, this correlation will not hold in our case because the polarizability of the ethyl group is larger than that of the methyl. These observations were later explained in a comprehensive theoretical study by Rodger[13]. Di- and trisubstituted oxiranes obey the quadrant rule. The energy of the n(O)→3s was found to depend on the number of alkyl groups and a red shift was observed for the di- and trisubstituted oxiranes as compared to the monosubstituted compounds. Thus in *R*-(+)-2,3,3-trimethyloxirane the n(O)→3s transition peaked at 1810 Å. In one case, (2*S*,3*S*)-2-ethyl-3-methyloxirane, a CD at lower energies than the n(O)→3s transition

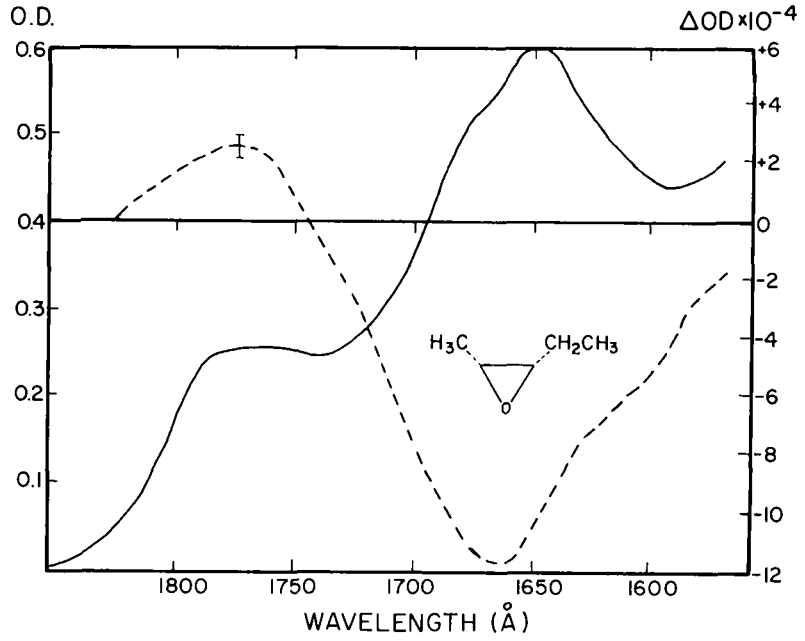


FIGURE 4. Absorption (———) and CD (-----) spectra of (2*R*,3*S*)-(−)-*cis*-2-ethyl-3-methyloxirane in the gas phase. The spectral resolution is 16 Å

was observed[10]. It was assigned as the n(O)→σ^* valence transition. However, this assignment was not substantiated any further by solution studies which would have helped to clarify its nature.

The experimental results reported for oxiranes have been reproduced theoretically in a detailed study by Rodger[13]. This study successfully accounted for the sign of the n(O)→3s as well as the n(O)→3p Rydberg transitions in all alkyl-substituted oxiranes. Since both the n(O)→3s and 3p are essentially localized with the achiral oxirane ring, the CD results from chiral perturbation by the ring substituents. Under these circumstances the most profitable theoretical approach is the independent systems/perturbation approach (ISP). According to this approach perturbation theory is used to express the CD in terms of electrostatic interaction of the achiral ring with the ring substituents. Of the three different terms in the perturbation expansion [static coupling[14], dynamic coupling[15] and coupled oscillator[16] (CO) mechanism], the largest for the electric dipole allowed transitions, n(O)→3s and n(O)→3p, is the coupled oscillation mechanism. The magnitude of the CO CD[13] was found to be proportional to (1) the energy of the transition being studied, (2) the oscillator strength of the transitions, (3) the inverse of the distance between the ring and the perturber, (4) the components of the dynamic polarizability of the substituents and (5) the relative orientation of the ring and its substituents. While the first three elements are always positive, the last two determine the CD sign. According to Rodger[13], since the components of the dynamic polarizabilities vary as a function of the orientation of the transition moment in each perturber, the CD sign is the result of both the position and orientation of the substituents. Thus, two chromophores in the same quadrant, but with different orientations, may have cancelling rather than reinforcing contributions to the CD. The calculations not only accounted

for the sign of the n(O) → 3s transition in all the alkyloxiranes, but also for the magnitude in many cases. For example, the 'competition' of methyl and ethyl substituents was interpreted by calculating the role of adding a second C—C bond. The results show this addition has an opposite effect, thus causing an ethyl-substituted oxirane to have a smaller n(O) → 3s CD than a methyl-substituted oxirane.

For the calculation of the n(O) → 3p manifold, it was assumed that of the three components of the 3p system, only two, the n(O) → $3p_x$ and n(O) → $3p_z$, contribute to the CD, while the magnetic dipole allowed and electric dipole forbidden transition, the n(O) → $3p_y$, has a negligible contribution to the CD. This assumption, which contradicts many arguments in the literature[17], was justified by claiming that the n(O) → $3p_x$ and n(O) → $3p_z$ are dominated by the r^{-2} coupled-oscillator term, whereas the n(O) → $3p_y$ is governed by a r^{-4} coupling term. The results, in spite of the complexity of the n(O) → 3p manifold, have successfully reproduced the sign of many of the alkyl-substituted oxiranes.

The CD study of oxiranes has recently been extended towards nonalkyl substituents when the CD of *R*-(−)- and *S*-(+)-epichlorohydrin were measured in the n(O) → 3s energy region[18]. In the epichlorohydrin (1-chloro-2,3-epoxypropane) molecule, a hydrogen in methyloxirane is replaced by a chlorine atom. In Figure 5 we present the CD and absorption spectra of *R*-(−)-epichlorohydrin. A positive CD band is observed at 1710 Å and although the n(Cl) → σ^* valence transition occurs in the same region of the spectrum, we assign the transition as the n(O) → 3s Rydberg based on the large $\Delta\varepsilon/\varepsilon$ observed for this transition. At first glance it appears that this molecule demonstrates a case in which an *R*-enantiomer exhibits a positive n(O) → 3s CD signal, contrary to all the observations on the alkyl-substituted oxiranes. However, a more careful look reveals that, as far as the quadrant rule is concerned, the *R*-enantiomer of epichlorohydrin

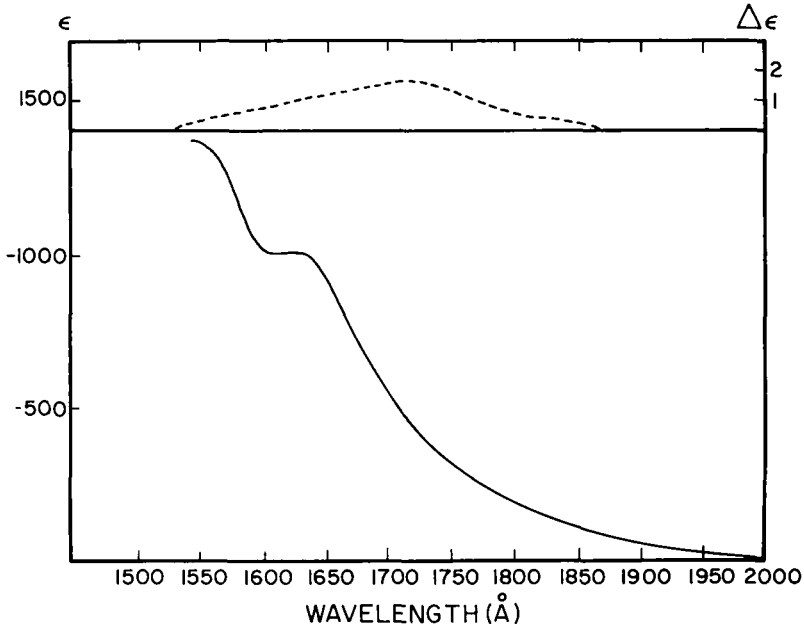


FIGURE 5. Absorption (———) and CD (-----) spectra of (*R*)-(−)-epichlorohydrin. The spectral resolution is 16 Å in the gas phase. ε and $\Delta\varepsilon$ are expressed in l mol^{-1} cm^{-1}

should be compared with the *S*-alkyloxiranes. This is due to the fact that, in both cases, the substituent is placed in a quadrant having $X > 0$ and $Y > 0$ and exhibits a positive signal. This also indicates that care must be taken with the Cahn–Ingold–Prelog (CIP) convention, which uses the atomic mass (or atomic number) of the substituents creating the chiral center rather than the purely electronic factors that determine the CD sign. These results substantiate the importance of the spatial location of the substituents in the oxirane ring.

B. Higher Cyclic Ethers

The CD of optically active 4-, 5- and 6-membered rings containing oxygen have also been measured in the last decade. The first transition in (*S*)-2-methyloxetane appears at 1880 Å[10]. This is almost the same wavelength where the first absorption in the symmetric molecule (trimethylene oxide) occurs. A positive CD band is observed for this transition. If the quadrant rule applies also to the oxetane moiety and quadrants are defined by the intersecting symmetry planes, then the (*S*)-2-methyloxetane obeys the quadrant rule. The positive sign was also predicted by the ISP calculations[13].

The CD measurements of tetrahydro-(+)-*R*-3-methylfuran and of (−)-(*S*)-2-ethyl-tetrahydropyran were initiated by the need to find a correlation between the CD and conformation of sugars[13] and the chiroptical properties of the chromophores composing the sugars. This has led to the study of the other chromophores in the above-mentioned compounds, as well as in acyclic, aliphatic ethers[20] and in polyethers[21]. The CD determinations of the optically active furan and pyran derivatives were carried out in solvents such as pentane, perfluorohexane and hexafluoro-2-propanol[19]. The location of the first excited state was strongly affected by the nature of the solvent. A marked blue shift was observed upon changing from an aprotic to a protic solvent. This was observed in the absorption and the CD spectra. The sensitivity of the CD to the nature of the solvent was also revealed in the CD of the optically active pyrane derivative (Figure 6), where the spectrum shows a band of opposite sign at 1850 Å in perfluoro-hexane. This solvent effect was explained as originating from the transition of the nonbonding electrons of the oxygen atom. The general conclusion of this study was that 'the ether chromophore contributes markedly to the CD of carbohydrates, at least in the long-wavelength portion of the spectrum'. Concerning the quadrant rule, it seems that the sector rule dealing with the first transition in oxiranes would also apply to the optically active furan and pyran if the quadrants are built on the intersecting symmetry planes. This is based on the assumption that the first transition in the furan and pyran chromophores is the $n(O) \rightarrow 3s$ Rydberg transition. The authors relate the transition to an $n(O) \rightarrow 3s\ \sigma^*$ transition which is also observed in unsubstituted saccharides.

The absorption and CD of the cyclic diether, 4-methyl-1,3-dioxolane, was measured in the 1900–1600 Å region[22]. Th absorption spectrum in this region shows only two peaks at 1825 and 1650 Å, while the CD reveals an extra band peaked at 1725 Å. Based on term-value arguments the CD bands were assigned as the $n(O) \rightarrow 3s$, $n(O) \rightarrow 3p$ and $n(O) \rightarrow 3d$. The CD and absorption spectra of another dioxolane, (*S*)-2,2-dimethyl-4-isobutyl-1,3-dioxolane, was reported in different solvents at room temperature[39]. The CD spectrum reveals two bands of opposite sign's, negative at lower energies (at about 190 nm) and positive at higher energies (at about 170 nm). The interpretation of the CD couplet is based on the exciton theory where the two oxygen atoms are the interacting groups. The data will assist in obtaining structural information for the glycosidic linkage in sugars[39].

To summarize the observations concerning the CD of cyclic ethers: the first excited state in cyclic ethers is assigned as the $n(O) \rightarrow 3s$ Rydberg transition and the sign of the CD has been found to correlate with the absolute configuration of the molecule.

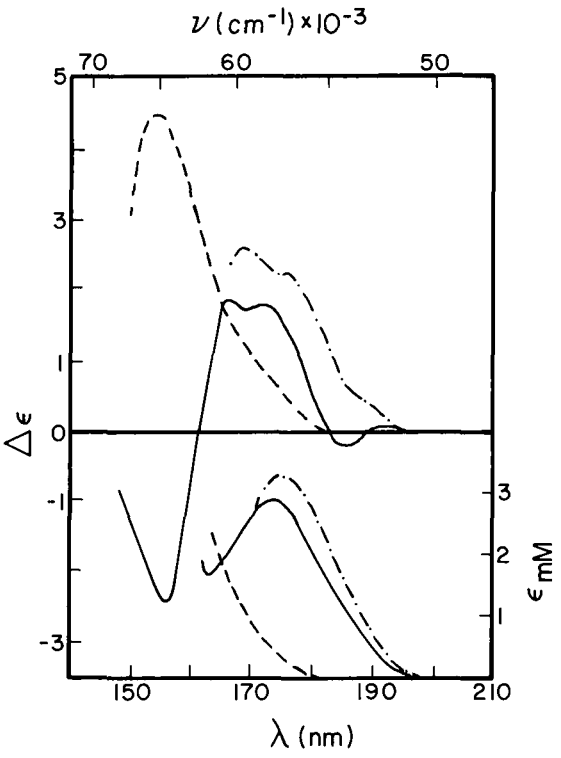


FIGURE 6. Absorption (lower curves) and CD (upper curves) of *S*(−)-2-ethyltetrahydropyran in perfluorohexane (———), pentane (–·–·–) and hexafluoroisopropanol (-----) solution at room temperature

Theoretically, both semiempirical and *ab initio* calculations have accounted successfully for these results. No exceptions to the formulated quadrant rule have been found.

C. Aliphatic Ethers

The CD of (*S*)-1,2,3-trimethylpropyl ethyl ether was measured in the gas phase as well as in various solvents[20]. The results demonstrate strong dependence of the energy and magnitude of the CD of the molecule on the nature of the solvent. The first transition peaked at 1910 Å ($\Delta\varepsilon = -5.6$) in the vapor phase; at 1850 Å ($\Delta\varepsilon = -7.4$) in n-heptane and at 1740 Å ($\Delta\varepsilon = -2.8$) in difluoromethanol. Similar differences were observed for the optical rotation of the molecule in the various solvents. These results were interpreted as being due to solvent interaction with the ether chromophore rather than conformational or structural changes. The Rydberg nature of the first two lower-energy transitions was demonstrated by a temperature dependence study. It showed that a blue shift is observed on lowering the temperature of the ether solution, which is typical for Rydberg transitions.

D. Polyethers

CD spectroscopy has been utilized to determine the conformation of polymers and, in particular, biological polymers[25]. To check the relationship between the conformation in solution and the chiroptical properties, the CD of polyethers was studied in various solutions. The first study[24] reported the CD spectra of poly[(*R*)-oxypropylene] in cyclohexane, acetonitrile, trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) solutions. In the first three solvents only two CD bands were observed, while three CD bands were detected in HFIP (Figure 7). In the energy region in which CD measurements overlap in all four solvents the CD shows similar signs, shape and intensity. This supports an earlier study[26,27] which claimed that the conformation of poly[(*R*)-oxypropylene] is almost the same in all solvents. Despite the similarity in the CD spectra the ORD exhibits a positive sign for the poly[(*R*)-oxypropylene] in cyclohexane and acetonitrile and a negative one in TFE and HFIP (Figure 8). This solvent dependency of the ORD sign was explained using the Kronig–Kramers transformation of the CD spectrum[24]. While for cyclohexane the positive sign was accounted for by the first two CD bands, a third large and negative band at higher energies (below 1600 Å) is needed to account for the negative signal observed for the alcohol solutions.

The fluorine-containing solvents are known to exhibit relatively large blue shifts for Rydberg transitions[23]. Indeed, the first two CD bands in the alcohol solvents demonstrate these shifts when compared to the cyclohexane and acetonitrile solutions. We therefore prefer their assignment as $n \rightarrow 3s$ and $n \rightarrow 3p$ Rydberg transitions, rather than the $n \rightarrow \sigma^*$ valence transitions proposed by Hirano and collaborators[24].

In another study the CD of optically active poly(alkyl vinyl ethers) were studied in the VUV as solutions (in pentane and perfluorohexane) and as a film[21]. The CD and

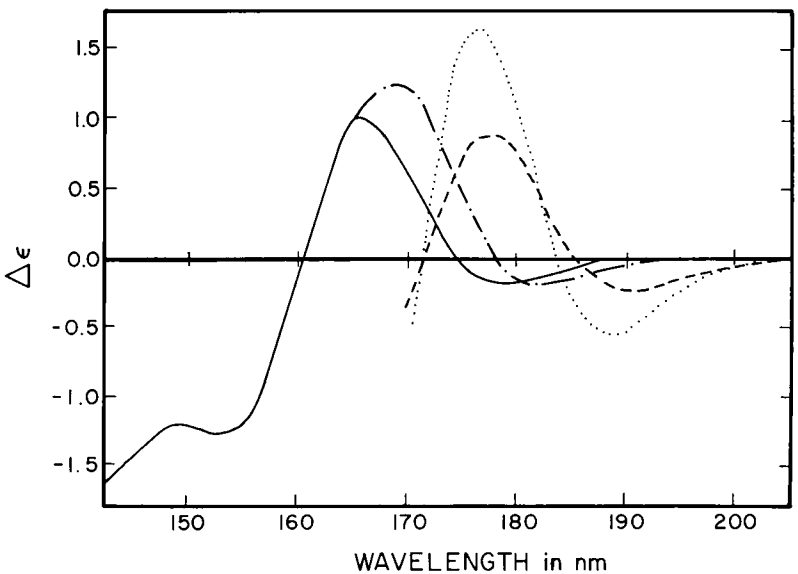


FIGURE 7. Vacuum ultraviolet CD spectra of poly[(*R*)-oxypropylene] solutions at 25 °C in C_6H_{12}(·····), in CH_3CN (-----), in hexafluoroisopropanol (———) and in trifluoroethanol (–·–·–)

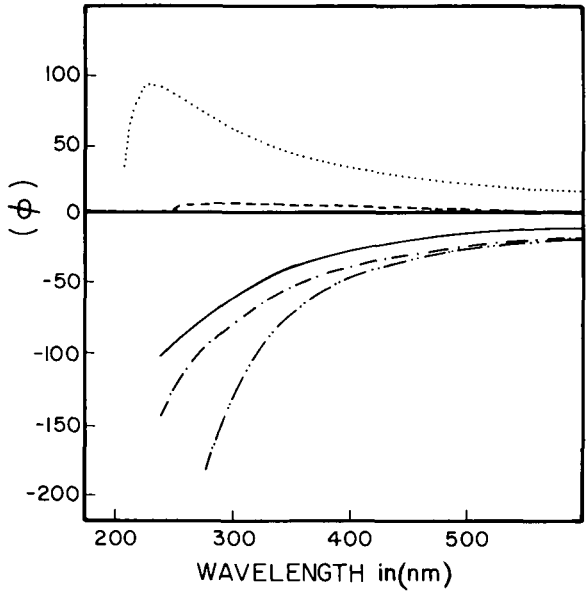


FIGURE 8. Observed ORD spectra of poly[(*R*)-oxypropylene] solutions at 25 °C in C_6H_{12} at 1.06 g dl^{-1} (·····), in CH_3CN at 1.08 g dl^{-1} (-----), in hexafluoroisopropanol (———) at 0.93 g dl^{-1}, in trifluoroethanol at 1.32 g dl^{-1} (–·–·–) and in benzene at 1.98 g dl^{-1} (–···–)

the absorption spectra of the poly(alkyl vinyl ethers) were compared to the corresponding monomer spectra. The absorption spectra of the polymer and monomer showed a steeply rising absorption in the 1800–1500 Å region. The CD spectra of the polymers in the hydrocarbon solutions show bands at the same energies as the solid film. The CD spectra of the polymers also show similarity to their model monomers. In general, the authors summarize these observations by indicating that no significant information can be drawn from the CD on the conformation of the macromolecules. However, the CD was found to be sensitive to even subtle differences in the isotacticity degree of the polymeric samples[21].

III. CHIROPTICAL PROPERTIES OF ALCOHOLS

The work of Texter and Stevens[28] is one of the most comprehensive studies carried out on alcohols or the hydroxyl chromophore. As their work was published at the end of the seventies and was not mentioned in the last survey, it will be reviewed here.

Their investigation includes the measurements of the CD of ten alcohols in hexane solution (except for one compound which was measured in the gas phase). The sign of the CD of these ten alcohols was reported in the energy region of the first excited states. The ten chiral alcohols belonged to three different classes: borneols, decalols and sterols, all chosen for their defined and rigid carbon skeleton. The measurements were followed by semiempirical calculations in the random-phase approximation using a line-dependent Hartree theory.

The nature of the first excited state of alcohols is a matter of controversy[29]. While there is unambiguous agreement that the transition originates from a nonbonding 2p electron on the oxygen atom, there is no such agreement as to its upper orbital.

The two candidates are the antibonding σ^* valence orbital[30,31] and the Rydberg 3s orbital[29,32,33]. The intravalence σ^* itself can be centered along the CO bond or the OH bond. In their calculations, Texter and Stevens[28] adopted a mixed $\sigma^*/3s$ excited orbital despite the fact that it is only the σ^* orbital that contributes to the magnetic moment, and therefore to the CD. The σ^* was built as an in-plane linear combination of the $\sigma_{CO}{}^*$ and $\sigma_{OH}{}^*$ orbitals. The relative contribution of $\sigma_{CO}{}^*$ is introduced by a parameter η. The electric dipole of the first transition of alcohols is perpendicular to the COH plane, while the magnetic moment is in the plane, and when $\eta = 0$ it is perpendicular to the OH bond.

The calculations were carried out by separating the molecules into two groups, the chromophore (COH) and the carbon–hydrogen skeleton. The groups, based on previous calculations by Snyder and Johnson[31], interact electrostatically. The calculations were restricted to the $\mu_e\mu_m$ mechanism. The problem of the rotational freedom of the hydroxyl group was solved by an empirical torsional potential and the thermally averaged $\Delta\varepsilon$ values were calculated. The results show that when $\eta = 0.8$ and the conformations are averaged as mentioned above, very good agreement is obtained between the calculated and experimental $\Delta\varepsilon$ of all the ten alcohols. This correlation suggests that the σ^* orbital has a greater $\sigma_{CO}{}^*$ character than a $\sigma_{OH}{}^*$ character. The results also concur with the sector rule formulated by Kirk and coworkers[34], who claimed that only two sections separated by the nodal plane of the COH group determine the CD sign of alcohols.

Attempts to reproduce theoretically the CD spectrum of (+)-(*S*)-2-butanol have been carried out by Segal and collaborators[33]. They employed *ab initio* configuration interaction calculations on the electronic states of (+)-(*S*)-2-butanol. The calculations involved more than a million distinct spatial configurations at a number of molecular geometries with two basis sets.

The first basis set included only s and p orbitals, while in the second basis 3d Cartesian Gaussian was added to the oxygen atom. In Figure 9 we present the three conformations for the carbon backbone as well as the three conformations of the hydroxyl hydrogen. Conformation I was verified through their calculations to be of the lowest energy, and

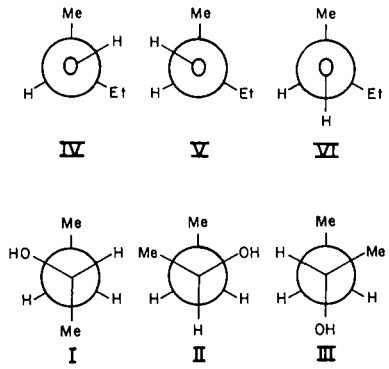


FIGURE 9. Conformations of 2-butanol. I–III: the carbon backbone of 2-butanol; IV–VI: staggered hydroxylic hydrogen in 2-butanol

therefore only this conformation was used in all the calculations. As for the conformation of the hydroxyl hydrogen, the results for the first basis set are reported for all three conformations. According to their calculations, conformation IV has the lowest energy and the results for the second basis set are presented only for this conformation.

The first four unoccupied molecular orbitals of the two basis sets are primarily 3s and 3p Rydberg components centered on the oxygen atom. For the first basis set the result calculated for conformation IV for the first excited state agree well with the experimental results for the energy ($57269\,cm^{-1}$ calculated, $56000\,cm^{-1}$ observed), oscillator and rotational strength ($1.3 \times 10^{-6}\,e^2\,Å^2$ calculated, $1.7 \times 10^{-6}\,e^2\,Å^2$ observed). The other conformations yield either an opposite-sign CD signal (conformation V) or a very large and unreasonable CD sign. Very good agreement was also obtained for the second CD band at $64000\,cm^{-1}$. The calculated energies, oscillator strengths and rotational strengths of conformation V agree well with the measured spectrum of *l*-borneol[35]. This conformation was also used in Snyder and Johnson's calculations of *l*-borneol[35].

The first basis set could not, however, duplicate the strong negative feature at $67000\,cm^{-1}$. The authors hypothesized that a d Rydberg function might provide additional negative rotational strength. This led to the creation of the second basis set. The results which were calculated only for conformer IV are very similar to those obtained with the former basis set and the conclusion is that the third negative CD band is caused by something other than (+)-(*S*)-2-butanol.

In a recent study the CD of (*R*)-(+)-ethanol-1-d was measured in the wavelength region of the first excited state. In Figure 10 we present the spectrum measured in the gas phase. The positive CD signal has a relatively large $\Delta\varepsilon/\varepsilon$ of about 6×10^{-4}. This is considered large for a chiral molecule whose chirality is due to a D/H substitution, especially for a flexible aliphatic system. It is also worth noting that for the first CD band in *S*-(+)-2-butanol a similar value is reported for $\Delta\varepsilon/\varepsilon$[31]. This study does not add relevant information as to the nature of the first excited state in alchols.

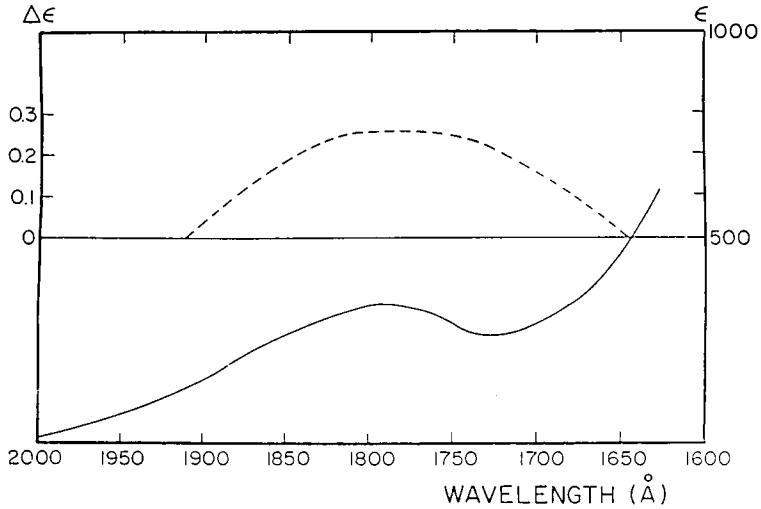


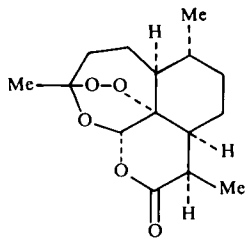
FIGURE 10. Absorption (———) and CD (----) spectra of (*R*)-(+)-ethanol-1-d in the gas phase. The spectral resolution is 16 Å. ε and $\Delta\varepsilon$ are expressed in $1\,mol^{-1}\,cm^{-1}$

In a previous study the ORD of various neopentyl-1-d derivatives were studied[37]. (*R*)-neopentyl-1-d derivatives with X = OH, F, Cl, Br and I gave plain negative ORD at $\lambda > 300$ nm curves. The same sign is observed for *R*-(−)-1-butanol-1-d and *R*-(−)-propanol-1-d. However, these are opposite in sign to the configurationally related *R*-(+)-ethanol-1-d and *R*-(−)-1-propanol-1-d. Clearly, this apparent anomaly requires further investigation. It is noteworthy that the CD signs of the first excited state in (*S*)-(+)-2-butanol[31] and (*R*)-(+)-ethanol-1-d are both positive and Rence these results call for some comparison between the two molecules. At first glance it seems that this comparison is impossible because each molecule has different conformations whose contribution to the CD is unknown. However, for *S*-(+)-2-butanol, in addition to the experimental results which are available[31], the rotatory strength of the important conformers was also calculated, as mentioned above[33]. One conformer (VI in the calculation) has a similar conformation to the anti-(*R*)-ethanol-1-d, the most stable conformer[38], and presumably the one responsible for the positive signal for ethanol-1-d. This comparison would have led to a consignate contribution for the D and ethyl groups. However, despite the large CD calculated for conformer VI, its relative role in the CD is not known and it is clearly not a large one.

IV. CHIROPTICAL PROPERTIES OF PEROXIDES

Unlike ethers and alcohols whose chiroptical properties have been extensively studied, not much work has been carried out on the optical activity of peroxides. Two theoretical calculations on the optical activity of peroxides were reported, the first by Rauk and Barriel[40], who carried out *ab initio* calculations on H_2O_2. Since H_2O_2 is a chiral molecule, the CD was calculated for the geometrical values known for it. The first two excited states originate from an excitation of a nonbonding electron on the oxygen atom to a compact and strongly antibonding combination σ^* orbital built from 3s orbitals of the oxygen atoms. While the low energy state (^1A, 6.24 eV calculated, 4.04 eV observed) is calculated[40] to exhibit a positive CD signal, the second excited state (^1B, 7.51 eV calculated, 5.6 eV observed) is predicted to demonstrate an opposite-sign signal. The energy and rotatory strength of higher excited states were also calculated[40]. Hydrogen peroxide in the gas and liquid state is not resolvable because of the low barrier to interconversion of the enantiomeric conformations[41]. However, H_2O_2 crystallizes in a single enantiomeric form[42].

A second *ab initio* calculation was recently reported by Liang and coworkers[43]. Their model compound was $CH_3—O—O—CH_3$ and the *ab initio* study calculated the CD sign the twist angle of the C—O—O—C group. The results show that for the P form when $90° > \theta \geq 0°$ a positive Cotton effect was obtained, while a negative Cotton effect was calculated for $90° < \theta \leq 180°$. For $\theta = 90°$, a bisignate curve was calculated. This latter calculation followed an earlier study by Liang[44] in which the CD of compounds I–III was measured.



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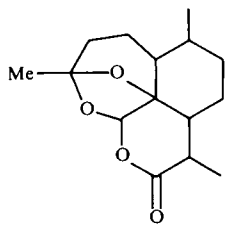

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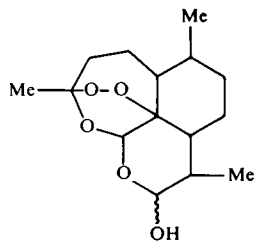

III

Of the three compounds measured in Liang's early study[44], I and III contain the peroxide linkage but II does not. The CD of compound I exhibits a positive peak at 260 nm, changing sign and peaking negatively at 229 nm. The positive peak is associated with the peroxide moiety. In compound II a climbing positive CD curve is observed with no peak above 200 nm. The positive CD curves were attributed to a clockwise twist in the peroxide bond[44]. In a later paper[43] two other peroxides were measured, also showing positive CD curves peaking at *ca* 240 nm. The *ab initio* study[43] substantiated Liang's earlier predictions based on molecular models[44] which related a clockwise twist of the peroxide linkage with a positive CD sign of this bond.

V. REFERENCES

1. G. Gottarelli and B. Samori, in *Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues*, (Ed. S, Patai), Wiley–Interscience, Chichester, 1980, p. 279.
2. E. H. Sherman, O. Schnepp, P. Salvadori, C. Bertucci and L. Lardicci, *J. Chem. Soc., Chem. Commun.*, 1000 (1979).
3. (a) R. G. Nelson and W. C. Johnson, *J. Am. Chem. Soc.*, **94**, 3343 (1972).
   (b) R. G. Nelson and W. C. Johnson, *J. Am. Chem. Soc.*, **98**, 4290 (1976).
   (c) R. G. Nelson and W. C. Johnson, *J. Am. Chem. Soc.*, **98**, 4296 (1976).
4. A. Rauk, *J. Am. Chem. Soc.*, **103**, 1023 (1981).
5. D. Cohen, M. Levi, H. Basch and A. Gedanken, *J. Am. Chem. Soc.*, **105**, 1738 (1983).
6. M. Levi, R. Arad-Yellin, B. S. Green and A. Gedanken, *J. Chem. Soc., Chem. Commun.*, 847 (1980).
7. H. Basch, M. B. Robin, N. A. Kuebler, C. Baker and D. W. Turner, *J. Chem. Phys.*, **51**, 52 (1969).
8. E. J. McAlduff and K. N. Houk, *Can. J. Chem.*, **55**, 318 (1977).
9. A. Gedanken, K. Hintzer and V. Schurig, *J. Chem. Soc., Chem. Commun.*, 1995 (1984).
10. A. Gedanken and V. Schurig, *J. Phys. Chem.*, **91**, 1324 (1987).
11. T. Bauman and D. A. Lightner, *J. Am. Chem. Soc.*, **98**, 3145 (1976).
12. J. H. Brewster, *Top. Stereochem.*, **2**, 31 (1968).
13. A. Rodger, *J. Am. Chem. Soc.*, **110**, 5941 (1988).
14. E. U. Condon, W. Altar and H. J. Eyring, *J. Chem. Phys.*, **5**, 753 (1937).
15. A. E. Weigang, *J. Am. Chem. Soc.*, **101**, 1965 (1979).
16. J. G. Kirkwood, *J. Chem. Phys.*, **5**, 479 (1937).
17. M. G. Mason and O. Schnepp, *J. Chem. Phys.*, **59**, 1092 (1973).
18. A. Basil, S. Ben-Tzur, A. Gedanken and A. Rodger, *Chem. Phys. Lett.*, **180**, 482 (1991).
19. C. Bertucci, R. Lazzaroni and W. C. Johnson, *Carbohydrate Res.*, **133**, 152 (1984).
20. C. Bertucci, R. Lazzaroni, P. Salvadori and W. C. Johnson, *J. Chem. Soc., Chem. Commun.*, 590 (1981).
21. C. Bertucci, E. Chiellini, P. Salvadori and W. C. Johnson, *Macromolecules*, **16**, 507 (1983).
22. A. Gedanken and T. Polonski, *J. Chem. Soc., Perkin Trans. 2*, 355 (1989).
23. A. F. Drake and S. F. Mason, *Tetrahedron*, **33**, 937 (1977).
24. H. Hirano, A. Sato, T. Tsuruta and W. C. Johnson, *J. Polym. Sci., Polym. Phys. Ed.*, **17**, 1601 (1979).
25. W. C. Johnson, *Methods in Biochemical Analysis*, **31**, 61 (1985).
26. T. Hirano, P. H. Khanh and T. Tsuruta, *Makromol. Chem.*, **153**, 331 (1972).
27. N. Oguni, S. Maeda and H. Tani, *Macromolecules*, **6**, 459 (1973).
28. J. Texter and E. S. Stevens, *J. Chem. Phys.*, **70**, 1440 (1979).
29. M. B. Robin, *Higher Excited States of Polyatomic Molecules*, Academic Press, New York, Vol. 1 (1975) and Vol. 3 (1985).
30. D. Salahub and C. Sandorfy, *Chem. Phys. Lett.*, **8**, 71 (1971).
31. P. A. Snyder and W. C. Johnson, *J. Chem. Phys.*, **59**, 2618 (1973).
32. M. B. Robin and N. A. Kuebler, *J. Electron Spectrosc. Relat. Phenom.*, **1**, 13 (1972).
33. G. A. Segal, K. Wolf and J. J. Diamond, *J. Am. Chem. Soc.*, **106**, 3175 (1984).
34. D. W. Kirk, W. P. Mose and P. M. Scopes, *J. Chem. Soc., Chem. Commun.*, 81 (1972).
35. P. A. Snyder and W. C. Johnson, *J. Am. Chem. Soc.*, **100**, 2939 (1978).
36. A. Gedanken, C. W. Mosher and H. S. Mosher, 'The circular dichroism of (*R*)-(+)-ethanol-1-d', *Chem. Commun.*, 430 (1992).

37. P. H. Anderson, B. Stephenson and H. S. Mosher, *J. Am. Chem. Soc.*, **96**, 3171 (1974).
38. R. A. Shaw, H. Wiesen, R. Duther and A. Rauk, *J. Am. Chem. Soc.*, **112**, 5401 (1990).
39. C. Bertucci, P. Salvadori and W. C. Johnson, *CD of Sugars: The Acetal Chromophore*, XIth International Carbohydrate Symposium, Stockholm, Aug. 14–19, 1988, abstracts p. 154.
40. A. Rauk and M. Barriel, *Chem. Phys.*, **25**, 409 (1977).
41. T. H. Dunning Jr. and N. W. Winter, *J. Chem. Phys.*, **63**, 1847 (1975).
42. R. Srinivasan, *Curr. Sci.*, **39**, 130 (1970).
43. J. Liu, G. Duan and X. Liang, *Chin. Chem. Lett.*, **2**, 245 (1991).
44. X. Liang, *Huaxue Xuebao*, **40**, 287 (1982); *Chem. Abstr.*, **97**, 5714y (1982).

CHAPTER 4

Thermochemistry of ethers, alcohols, arenols, enols and peroxides

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Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

I. INTRODUCTION

A. Definition of Thermochemistry

Before commencing with the main body of this chapter, we feel it is desirable to define our chosen title for it. More precisely, some of the words and concepts in the title will be given more narrow meanings than is often the case, while others will be expanded beyond their conventional definition. The word 'Thermochemistry' is taken here to mean 'Heat of Formation', ΔH_f, most generally referring to the numerical value at the thermochemist's idealized conditions of 25 °C (298 K) and 1 atm. Likewise, we use in this paper the thermochemists' choice of unit of kJ mol^{-1} where 4.184 kJ mol^{-1} = 1 kcal mol^{-1}. However, we will avoid consideration of some other key thermochemical quantities such as entropy and heat capacity. We find that compared to heats of formation, there are comparatively insufficient experimental data on these quantities[1], and additionally we also admit we have insufficient intuition either to remediate this or to use optimally the available data.

Although we will endeavor to provide requisite data for all three phases of any organic compound of interest—solid, liquid and gaseous—we acknowledge that most of the key structure/energy concepts such as resonance and strain energy usually refer to isolated, hence gas-phase molecules. To interrelate the various phases, we will need the heats of the various phase changes. While ideally these are derived from experiments, we will nonetheless occasionally derive estimates for these quantities. These are the heat of vaporization, ΔH_v, that thermochemical quantity that definitionally interrelates liquid and gas via equation 1,

$$\Delta H_v \equiv \Delta H_f(g) - \Delta H_f(l) \tag{1}$$

the heat of fusion, ΔH_{fus}, that interrelates the solid and liquid phases via equation 2,

$$\Delta H_{fus} \equiv \Delta H_f(l) - \Delta H_f(s) \tag{2}$$

and the heat of sublimation, ΔH_s, that interrelates solid and gas via equation 3,

$$\Delta H_s \equiv \Delta H_f(g) - \Delta H_f(s) \tag{3}$$

Simple algebra shows that heats of sublimation, vaporization and fusion are definitionally interrelated by equation 4,

$$\Delta H_s \equiv \Delta H_{fus} + \Delta H_v \tag{4}$$

This general omission of the estimation of heats of vaporization, fusion and sublimation

is not due to lack of relevance, interest or experience. Although these estimated numbers are relevant, for the sake of brevity we will consider primarily experimentally derived quantities. The reader will see that our tables are comprehensive and 'cluttered' enough without these extra data. We will make sufficient interrelationships using the data available to present some interesting findings and leave other, perhaps more tenuous or incomplete, patterns to additional publications by us and by other authors. Our interest in these phase-change heats has already been affirmed by papers[2-4] that both document our experience and provide detail and guidance for the reader who wishes to pursue these methods for compounds of greatest personal interest and importance.

Having limited our attention to heats of formation, we now make the disclaimer that we will not present a Benson-like group analysis[5]. This approach has proven powerful in numerous thermochemical chapters in many of the other volumes in the Patai series. However, there are three reasons for this omission in our chapter.

The first is that Benson's group (and ancillary correction term) analysis has generally been applied to gas-phase species[6] and all too many compounds in the current study are too involatile to have much meaning in the gas phase. (For example, consider measurements of the heat of fusion or sublimation of ether/alcohol derivatives that are additionally recognized as sugars or polysaccharides. Simply heating the compound of interest produces caramel and/or charcoal, and thus does not result in a thermochemically meaningful number.)

Secondly, despite the seeming plethora of data as manifest by our extensive tables, some key functionalities and/or correction terms are seemingly absent. For example, consider ethers in which one alkyl group is primary (but not methyl) and the other is secondary. One can imagine needing a correction term to amend the sum of the heats of formation of the general O—$(C)_2$, C—$(C)_2(H)(O)$ and C—$(C)(H)_2(O)$ groups. (One can also imagine that such a correction term is not needed since no special nonbonding interactions are apparent.) The most natural compound from which to derive the desired correction term is ethyl isopropyl ether. But there are no thermochemical data on it. We also find that while there are heat of formation data for both n-propyl and isopropyl ether, no such data seem to be available for the mixed n-propyl isopropyl ether. Indeed, we know of no heat of formation data for any primary/secondary ether group from which a possible correction term could be derived.

Thirdly, it may not be obvious that a group and/or correction term often comes from only one compound and that theory and experiment must necessarily agree. For example, were we to require a term from a di-tertiary alkyl ether, there is but one simple ether with two tertiary alkyl groups for which we have thermochemical data, di-*t*-butyl ether[7].

This does not mean no estimates will be made in this chapter although a disproportionate number of them are to derive necessary ancillary heats of vaporization. Most of our estimates will arise in conjunction with the comparison between suitably 'simple' oxygen compounds and the related hydrocarbons. For example, we will make use of the admittedly 'ancient' comparison[8] of the heats of formation of R—O—R′ and R—CH_2—R′.

B. Definition of Classes of Compounds

We now provide a preliminary definition of the classes of compounds that will be discussed in this chapter. Ethers would appear to be uniquely defined by R—O—R′ wherein R and R′ may be somehow connected to allow for cyclic ethers. There is the obvious proscription against R and/or R′ being an acyl group. After all, do we wish to consider carboxylic acid esters as acyl ethers[9]? But what about furan? Is this compound an ether? We have chosen to consider furan an ether in the same way the aromatic benzene is often discussed in the context of conjugated polyenes. Also, including furan

allows comparisons with its hydrogenated analogs that are unequivocally ethers, namely tetrahydrofuran, and the isomeric triplet 2,3-dihydrofuran, 2,5-dihydrofuran and divinyl ether. Perhaps prompted by recollection of the furanose and pyranose forms of sugars, furan is also naturally included because its simplest 'homologs' are 2*H*- and 4*H*-pyran, and these C_5H_6O species are isomeric with 2- and 3-methylfuran. The pyrans are unequivocally ethers and so all of these furan/pyran comparisons would prove quantitatively instructive—except that there are surprisingly no experimental heat of formation data on either pyran or any simply substituted derivative! (There are also no heat of formation data on either 2- or 3-methylfuran, although there are data on both dibenzofuran and dibenzopyran.)

What about iminoethers? what about oxazoles? We choose to include them here among the substituted ethers because they represent but a small part of our total data collection. It seemed artificial to ignore them rather than to append them to the relevant table in the text.

Next, by 'alcohols' we mean species with an OH group attached to an sp^3 carbon, while arenols correspond to an OH group attached to an sp^2 carbon of an aromatic ring such as benzene or pyridine. In the cases of 2-pyridinol and 4-pyridinol, there is the additional complication of their tautomeric equilibria with 1*H*-2-pyridone and 1*H*-4-pyridone respectively. We include them as well as nitrosophenols, where the alternative description of quinone monooximes has also been given.

A related question applies to the enols of both simple ketones and β-diketones. We have chosen the pragmatic solution of presenting the data for all of these species where it is 'reliably' available. Where there are data for the enol form, *per se*, we obviously cite that data. Where the enol form strongly predominates as in the case of the various β-diketones, we equate the heat of formation of the enolic compound of interest with the value measured for the mixture, rather than trying to derive the value for the pure enol[10]. For example, the heat of formation of (*Z*)-3-penten-2-one-4-ol is taken as the reported heat of formation of 'acetylacetone', and indeed we refer to it in the appropriate table as 'acetylacetone (enol)'.

Both hydroperoxides and peroxides are included in the current study; thus we include species with C—O—H and O—O—H groups but not with N—O—H groups. The energetics of oximes and hydroxylamines appear to us to be more natural in the context of general X—O—H containing species wherein X is some hetero atom, such as in discussions of sulfenic acids[11].

C. Presentation and Sources of Data

Because our chapter is long and the tables of data are both numerous and extensive, we have tried to simplify our presentation. We endeavor to have each table of data autonomous and so there is a 'fine-tuning' of the content of each table. For example, because there are considerable data for the class of compounds, 'ethers'[12], we have generated a subclass called 'monoethers'. Even this subclass is quite extensive, so we have generated tables for various sub-subclasses, which include:

(a) 'unsubstituted acyclic monoethers' (e.g. di-*t*-butyl ether, 6β-methoxy-3,5-cyclocholestane[13]), with the general formula C_aH_bO[14],

(b) 'monoethers with oxygen functional groups' (e.g. tetrahydrofurfuryl alcohol, acetylacetone *O*-methyl ether), with the general formula $C_aH_bO_c$ (where $c > 1$),

(c) 'monoethers with nitrogen (and oxygen) functional groups' (e.g. dipentaerythritol hexanitrate, morphine), with the general formula $C_aH_bO_cN_d$ (where $c \geqslant 1$),

(d) 'monoethers with additional functional groups' [e.g. bis(3,3,3-trifluoropropyl) ether, (chloromethyl)oxirane] with the general formula $C_aH_bO_cN_dHal_e$ (where $c \geqslant 1$, $d \geqslant 0$ and $e \geqslant 1$).

In all tables, each numerical entry will be explicitly accompanied by the appropriate citation to the source of that heat of formation datum. To maximize convenience for both the authors and the readers of this chapter, we have taken much of the data directly from Pedley, Naylor and Kirby[1], from Domalski[15], and from Stull, Westrum and Sinke[8] and have cited those works as the relevant reference. (Where we were aware of more than one value, we used our preference and prejudice based on our other thermochemical knowledge and experience. Where one of us personally has already reviewed a class of compounds and so have gained expertise in understanding their idiosyncracies, our secondary source is cited.) We have also included numerous primary sources of data, most of which are newer than any of the above sources, but some that were missed by the archival sources despite good faith efforts at completeness. Some of the missing data arise from the use of heats of reaction studies, e.g. the hydrolysis of a ketal. Where all of the species involved in that new reaction are found in Pedley's archive, we have cited only the source of the heat of reaction data. Where some ancillary species are needed, both the sources of the heat of reaction data and the additional heat of formation are cited. Sometimes measurement of the heat of formation for a compound of interest has been performed more than once. In the case of such 'conflict', we have made the optimistic, if not artificial, assumption that more recent data are better. We admit to having little sense of how much relevant data we have missed. Sometimes our literature search seemed reminiscent of the form of philately in which the collector wishes to obtain one each of every issue, while simultaneously admitting the futility of realizing that goal[16]. Sometimes our writing of the text and preparation of tables seemed like we were attempting to write the catalog for such a collector. Acknowledging the conscious wordplay, we hope our study has received the reader's stamp of approval.

II. ETHERS

A. Unsubstituted Acyclic Monoethers

This class of organic compound is unequivocally the simplest of those we discuss in this chapter from the standpoint of thermochemical measurement and understanding. Ethers are simpler than alcohols because they lack the relatively strong and orientation-dependent hydrogen bonds of the latter. Thus, for example, steric effects are expected to have a larger effect on the heat of vaporization of alcohols than on ethers. This is documented by the 5.6 kJ mol^{-1} difference of the heats of vaporization of n- and *t*-butyl alcohol, while the difference for their corresponding methyl ethers is but 2.4 kJ mol^{-1}. In addition, the calorimetrically detrimental presence of water impurity in ethers is less likely to be a problem than in alcohols because

(a) there is a decreased miscibility of water with the organic compound (where the water accompanies its synthesis, isolation, or subsequent handling),

(b) the water is more easily detected since ethers lack an O—H group and its consequent spectroscopic signature (e.g. IR, NMR),

(c) they are unreactive towards most of the reagents used to remove any water found [e.g. Na(s)].

Equivalently, for a given level of skill and insight, thermochemical measurements on ethers are more likely to be of higher accuracy, precision and therefore usefulness than are alcohols. Much the same logic applies to arenols. In addition, arenols not uncommonly autooxidize with the concomitant formation of ill-defined polymeric impurities. We also note that comparatively few enols are isolable and so considerable creativity has to be used to measure the heats of formation of an enol of interest.

We have treated monoethers separately from polyethers. Monoethers are simpler than polyethers; clearly they cannot be more complicated. Polyethers often exhibit interesting

structure/energy features such as the 'gauche' and 'anomeric' effects[17] that arise when the two oxygens are two or one carbon apart, respectively. What about the case when two oxygens are no carbons apart? We have just conceptually 'synthesized' peroxides with a unique type of interaction, the O—O bond. That peroxides are generally unstable has seemingly discouraged many thermochemists: spontaneous decomposition before combustion ruins the accuracy of the measurement, and there is also the real possibility of the 'bomb' in bomb calorimetry taking on an alternative, but more conventional meaning.

Unsubstituted monoethers are treated separately from their substituted derivatives[18]. Clearly any substituent complicates our understanding because there is never any guarantee that the formal reaction

$$2\,\text{X—R—Y} \longrightarrow \text{X—R—X} + \text{Y—R—Y} \tag{5}$$

is thermoneutral for any hydrocarbon 'framework' —R— and its affixed groups X and Y. Indeed, for the species with the polar bonds discussed in this chapter, thermoneutrality is almost guaranteed not to be valid because of long-range electrostatic interactions. Relatedly, the formal reaction in equation 6,

$$\text{X—R—Y} + \text{H—R—H} \longrightarrow \text{X—R—H} + \text{H—R—Y} \tag{6}$$

is unlikely to be thermoneutral either, where we explicitly wrote X—R—H and not H—R—X to convey the fact that the two substituted positions need not be equivalent, e.g. in the formal reaction of 2-chloro-1-naphthol with naphthalene, the products are 2-chloronaphthalene and 1-naphthol and not their isomers 1-chloronaphthalene and 2-naphthol.

The conceptual simplicity of unsubstituted monoethers provides us with an opportunity to develop estimation methods and statistically derived equations, and test them without undue complications. Some of our approaches follow although we do not claim completeness. We do make use of heats of vaporization, but here only of data for which the heat of formation of the compound of interest is also known[19].

The heats of formation and of vaporization of structurally similar ethers are linearly related to the total number of carbon atoms, n_c, in the molecule. In particular, we find for the methyl n-alkyl ethers

$$\Delta H_v = 4.93n_c + 8.0 \quad (r^2 = 0.9997, n = 3) \tag{7}$$

$$\Delta H_f(\text{l}) = -25.35n_c - 164.4 \quad (r^2 = 1.000, n = 3) \tag{8}$$

$$\Delta H_f(\text{g}) = -20.42n_c - 156.4 \quad (r^2 = 1.000, n = 3) \tag{9}$$

while for ethers with two (but not necessarily identical) n-alkyl groups, we find[20]

$$\Delta H_v = 4.33n_c + 9.8 \quad (r^2 = 0.9995, n = 4) \tag{10}$$

$$\Delta H_f(\text{l}) = -24.68n_c - 180.5 \quad (r^2 = 1.000, n = 4) \tag{11}$$

$$\Delta H_f(\text{g}) = -20.35n_c - 170.7 \quad (r^2 = 1.000, n = 4) \tag{12}$$

That the slopes and intercepts for equations 7 and 10, 8 and 11, 9 and 12 are not pairwise equal shows that methyl is an atypical alkyl group[21]. But suppose we wished to derive $\Delta H_f(\text{g}, \text{Me}_2\text{O})$. Equations 9 and 12 result in the values -197.2 and $-211.4\,\text{kJ mol}^{-1}$, respectively. Equation 9 that was derived from data for one-methyl (1-Me) species would be expected to be better for the two-methyl (2-Me) species of interest than equation 12 derived from no-methyl (0-Me) species. Furthermore, extrapolating the 1-Me/1-alkyl and 0-Me/2-alkyl cases to the 2-Me/0-alkyl case by assuming linearity of both slope and intercept with the number of alkyl groups results in a value of $-181.6\,\text{kJ mol}^{-1}$. This is close to the literature value, $-183.1\,\text{kJ mol}^{-1}$, and so we are encouraged. However,

despite this success we are surprised that the slopes of equations 7 and 10, and 8 and 11 are so different: for large 'enough' n_c in one alkyl group, we should think that whether the other alkyl group is methyl or not, should be irrelevant.

Let us now compare the heats of vaporization of ethers and the related hydrocarbons, i.e. ROR^1 and RCH_2R^1. We find δ_{13}, the difference quantity derived in equation 13,

$$\delta_{13} \equiv \delta\Delta H_v(RCH_2Me, ROMe) = \Delta H_v(RCH_2Me) - \Delta H_v(ROMe) \quad (13)$$

is between -1 and $-2.5\,kJ\,mol^{-1}$, but for most of the seven cases known to the authors, for general R^1 the related δ_{14},

$$\delta_{14} \equiv \delta\Delta H_v(RCH_2R^1, ROR^1) = \Delta H_v(RCH_2R^1) - \Delta H_v(ROR^1) \quad (14)$$

is greater than or equal to 0. Apparently R^1 = methyl is meaningfully different from other alkyl groups from the standpoints of both heats of vaporization and of formation. However, it appears to be a safe assumption to equate the heat of vaporization of arbitrary ethers ROR^1 and the corresponding hydrocarbon RCH_2R^1 if only a 'few' $kJ\,mol^{-1}$ accuracy is wished[22].

Consider now the general 'ether, methylene exchange' quantity $\delta\Delta H_f(g, RCH_2R^1, ROR^1)$, defined by equation 15:

$$\delta_{15} \equiv \delta\Delta H_f(g, RCH_2R^1, ROR^1) = \Delta H_f(g, RCH_2R^1) - \Delta H_f(g, ROR^1) \quad (15)$$

Based in large part on the awareness of the difference of methyl and n-alkyl, and now wanting to consider also the effects of branching, we have let R and R^1 equal methyl, primary, secondary and tertiary alkyl groups. Table 1 presents the statistically averaged values of $\delta\Delta H_f(g, RCH_2R^1, ROR^1)$ for each possible choice of classes for R and for R^1. [We now rewrite $\delta\Delta H_f(g, RCH_2R^1, ROR^1)$ as $\delta_{15}(R,R^1)$.] As mentioned earlier in the text, there are seemingly no heat of formation data for any primary–secondary ethers and so we cannot fill in the primary/secondary entry, $\delta_{15}(p,s) = \delta_{15}(s,p)$ in this table. Nonetheless, the $120\,kJ\,mol^{-1}$ value of $\delta_{15}(t,t)$ seems sorely out of line and a value of *ca* 150 seems more appropriate. This results in a new value of $\Delta H_f(g, t\text{-}Bu_2O)$ of *ca* $-392\,kJ\,mol^{-1}$, very different from the archival literature value of $-362.0 \pm 1.2\,kJ\,mol^{-1}$.

Consider now another interrelationship involving ethers, the hydrolysis reaction, equation 16, and the accompanying reaction heat δ_{16},

$$H_2O + ROR^1 \longrightarrow ROH + R^1OH \quad (16)$$

When R and R^1 are both n-alkyl groups, $\delta_{16}(l) = 9.4 \pm 0.4$ ($n = 4$) and $\delta_{16}(g) = 23.8 \pm 0.5\,kJ\,mol^{-1}$ ($n = 4$). When R and R^1 are both branched, except for the di-*t*-butyl case, we find $\delta_{16}(l) = 2.1 \pm 1.3\,kJ\,mol^{-1}$ ($n = 6$) and $\delta_{16}(g) = 15.3 \pm 1.1\,kJ\,mol^{-1}$ ($n = 7$). Choosing the $15.3\,kJ\,mol^{-1}$ gaseous 'di-branched' value for di-*t*-butyl we find $\Delta H_f(g, t\text{-}Bu_2O) = -398\,kJ\,mol^{-1}$. Related use of $\delta_{16}(l)$ results in a prediction of $\Delta H_f(l, t\text{-}Bu_2O) = -430\,kJ\,mol^{-1}$.

TABLE 1. Trends in $\delta\Delta H_f(g, RCH_2R^1, ROR^1) \equiv \delta_{15}(R,R^1)$ for dialkyl ethers

	Methyl	Primary	Secondary	Tertiary
Methyl	79	91	98	101
Primary		105	??	114
Secondary			118	134
Tertiary				120

Finally, consider the isomerization reaction, equation 17, and the associated reaction heat δ_{17}.

$$\text{n-BuOR}^1 \longrightarrow t\text{-BuOR}^1 \tag{17}$$

For R^1 = Me, n-Bu and glycidyl, in liquid or in gas, δ_{17} has the rather narrow range of $-25 \pm 3\,\text{kJ mol}^{-1}$. Assuming the same value is found for $R^1 = t$-Bu, the predicted heats of formation of liquid and gaseous di-*t*-butyl ether are -428 and $-394\,\text{kJ mol}^{-1}$. All of our predictions for the heat of formation of liquid and gaseous di-*t*-butyl ether are consonant with each other, and decidedly different from the values of -399.6 ± 1.2 and $-362.0 \pm 1.2\,\text{kJ mol}^{-1}$ found in the literature. Yet, after inspecting molecular models, we conclude that the difference in the measured and predicted heats of formation for di-*t*-butyl ether constitutes the strain energy for two tertiary centers connected by an oxygen atom. While *t*-butyl alcohol is the most stable butyl alcohol, the most stable dibutyl ether is not di-*t*-butyl ether but rather *sec*-butyl *t*-butyl ether. In this branched molecule there is at least one conformation which ameliorates steric crowding; there is no such relief available in di-*t*-butyl ether.

B. Cyclic Monoethers

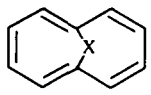
Because of expectations of entirely different strain energies, we are not surprised that the heat of formation of cyclic monoethers fails to show a linear dependence on the number of carbons. Because it is also reasonable to assume that —O— has different electronic and geometric demands than $—CH_2—$, we are not surprised that the earlier value of $\delta\Delta H_f(g, RCH_2R^1, ROR^1)$ for two primary alkyl groups is not equal to that found for the difference of cyclic monoethers and the related cycloalkanes. Nonetheless, the earlier value of $105\,\text{kJ mol}^{-1}$ is consonant with that found here: for 3- through 6-membered rings, we find this difference to be the 'rather constant' 106, 109, 90 and $100\,\text{kJ mol}^{-1}$. Though there is some scatter and no apparent pattern, it appears safe to conclude that cyclic ethers and the related cycloalkanes have comparable strain energies. However, no such constancy is seen for their polycyclic or alkyl derivatives as evidenced by a distressingly wide range of values presented[23] for a collection of three-membered ring species. Even correcting for the two carbons being primary, secondary and/or tertiary, we cannot reconcile the $106\,\text{kJ mol}^{-1}$ for the gaseous parent 'primary/primary' oxirane and the $138\,\text{kJ mol}^{-1}$ for the 'secondary/secondary' *cis*-7-oxabicyclo[4.1.0]-heptane. Completely out of line is the $211\,\text{kJ mol}^{-1}$ for the 'tertiary/tertiary' 8-oxatricyclo[3.2.1.$0^{1,5}$]octane. We should not be discouraged completely—we find the difference of heats of formation for the oxirane/cyclopropane cases is essentially independent of whether the species are in their liquid or gas state. We conclude, again, that the difference in the heats of vaporization of $R—O—R^1$ and $R—CH_2—R^1$ is largely independent of R and R^1. Any data on liquid hydrocarbons and ethers can be immediately used for the quantitative and qualitative understanding of their gas-phase forms. Equivalently, intelligibility and insights for the understanding of molecular phenomena should arise here with less effort than for many other classes of organic compounds.

C. Vinyl Ethers

Recall that the gas-phase replacement of —O— by $—CH_2—$ in di-n-alkyl (i.e. primary/primary) ethers is endothermic by some $105\,\text{kJ mol}^{-1}$, and that the differences in the heats of vaporization for ethers and related hydrocarbons are usually rather small. This value of $105\,\text{kJ mol}^{-1}$ is increased to $120\,\text{kJ mol}^{-1}$ for n-alkyl and hence primary/vinyl ethers; for the conjugated dihydrofuran and dihydropyran, increased endothermicity is seen compared to the saturated cyclic ethers. It is not unreasonable to suggest a

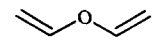
resonance energy of *ca* 15 kJ mol^{-1} for vinyl ethers[24]. Interestingly, the same value of increased endothermicity for n-alkyl vinyl ethers is found for divinyl ether, i.e. the two vinyl groups in divinyl ether contribute negligible additional resonance stabilization beyond that for one vinyl group in monovinyl ethers. Nearly the same increased endothermicity is seemingly found for 1,6-oxido-[10]annulene (**1a**) and 1,6-methano-[10]annulene (**1b**), *ca* 115 kJ mol^{-1} for both the liquid and the gas. However, the uncertainty (defined as the square root of the sum of the squares of the values for the individual compounds) of 6.5 and 11.4 kJ mol^{-1}, respectively obscures understanding and diminishes confidence in our conclusion. As such, nothing can really be said about the comparative aromaticity of these two [10]-annulenes—we still cannot evaluate the effect of the orthogonal geometry of the π orbitals of the [10]-annulene and the oxygen on the thermochemistry.

Furan shows a numerically unambiguous and considerably enhanced endothermicity, 169.2 kJ mol^{-1} for the gas and 168.2 kJ mol^{-1} for the liquid. This difference upon replacement of —O— by —CH_2— between divinyl ether and furan is clearly related to the classical 6 π Hückel aromaticity of the latter[25]. However, the near equality of the heats of vaporization for furan, cyclopentadiene, divinyl ether and 1,4-pentadiene (27.4, 28.4, 27.4 and 26.4 kJ mol^{-1}[26]) is hard to reconcile with the textbook ionic resonance structures generally suggested for both divinyl ether and furan. The orientation of the two double bonds with the oxygen in an arbitrary bis-vinylic ether (i.e. 'U', 'W' or 'sickle', **2a–3c**) may well be an important factor and so we regret the absence of thermochemical data on both the 2*H*- and 4*H*-isomers of pyran, or, for that matter, any of their substituted derivatives. (For example, we believe it would be highly instructive to determine the heats of formation of the isomeric species **3a–3d**.)

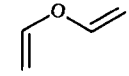


(**1a**) (X = O)
(**1b**) (X = CH_2)

(**2a**)



(**2b**)



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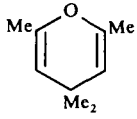
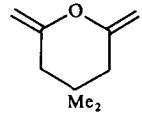


(**3a**)



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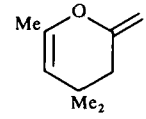
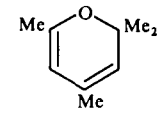


(**3c**)



(**3d**)

We conclude our discussion of the thermochemistry of vinyl ethers by turning to a relatively simple species, liquid isobutyl vinyl ether, *i*-BuOVi. In particular, we will now document that the reported heat of formation of −268 kJ mol^{-1} is highly suspect. Recall that the ether, methylene exchange for vinyl ethers, δ_{15}(Vi, R^1), was endothermic by 120 kJ mol^{-1}. From the literature value of ΔH_f(g, '*i*-BuCH_2Vi') (i.e. of 5-methyl-1-hexene) of −66 kJ mol^{-1}, we derive ΔH_f(g, *i*-BuOVi) = −186 kJ mol^{-1}. To obtain the desired heat of formation of the liquid ether, we need the heat of liquefaction (also called condensation), ΔH_{liqn}, of the gaseous compound. By definition, equation 18 is true for all substances. From any of our earlier enunciated methods of estimating the heat of vaporization of ethers, we obtain ΔH_v(*i*-BuOVi) ≈ 36 kJ mol^{-1} and so ΔH_f(l, *i*-BuOVi) = −222 kJ mol^{-1}.

$$\Delta H_{cond} = \Delta H_{liqn} \equiv -\Delta H_v \tag{18}$$

Alternatively, we may use the earlier interrelationship, equation 16, that relates to the hydrolysis of an ether. It is not obvious what class of ether we should consider isobutyl vinyl ether to be. This problem is seemingly exacerbated by the realization that we lack data for the heat of formation of liquid vinyl alcohol[27]. However, both problems are remediated when we recognize that all aliphatic, alkyl and hence acyclic ethers (save di-*t*-butyl ether) seemingly hydrolyze with a heat of $6 \pm 5\,\mathrm{kJ\,mol^{-1}}$ in the liquid phase and $19 \pm 5\,\mathrm{kJ\,mol^{-1}}$ for the gas. As such, we may safely assume that for any three such groups, R, R^1 and R^2, and for all species either gas or liquid, reaction 19 is nearly thermoneutral.

$$ROR^1 + R^2OH \longrightarrow ROR^2 + R^1OH \qquad (19)$$

It seems logical we can generalize this conclusion to include R = Vi, if R^1 and R^2 are limited to alkyl groups. Assuming that this be valid and choosing R^1 to be *i*-Bu and R^2 to be its isomer n-Bu, we deduce ΔH_f(l, *i*-BuOVi) and ΔH_f(g, *i*-BuOVi) equal -223 ± 5 and $-194 \pm 5\,\mathrm{kJ\,mol^{-1}}$, respectively. The near equality of our two sets of predicted values for the heat of formation of isobutyl vinyl ether suggests that the literature value is wrong. We believe that the discrepancy of *ca* $40\,\mathrm{kJ\,mol^{-1}}$ between theory and experiment is too large to explain by any steric or electronic factor. Rather, we should not be surprised if the experimental value does correspond to a sample that has either partially polymerized and/or hydrolyzed. A new measurement is strongly suggested.

D. Aryl Ethers

There are two comparisons we wish to make. The first again makes use of the —O— and $-CH_2-$ exchange. Table 2 presents the desired heat of formation difference, δ_{15}(Ph, R), where R = Me, Et, Vi and Ph. Data for both liquid and gaseous species are presented, where we additionally included the heats of formation of solid diphenyl ether and of diphenylmethane. Since the heat of formation difference is nearly the same as found for di-n-alkyl ethers, it seems the apparent resonance energy for phenyl ethers can be ignored. However, this is hard to understand for two reasons. The first is that δ_{15}(Ph, R) is meaningfully larger for liquids than for gases suggesting the importance of ionic resonance structures, a contribution that we just said was seemingly negligible. Secondly, recall that we just asserted that vinyl ethers had some $15\,\mathrm{kJ\,mol^{-1}}$ of resonance energy stabilization. How is this difference to be reconciled with the assertion of the general thermochemical similarity of phenyl and vinyl groups[28]? That is, δ_{20}(PhX, ViX), the difference of the heats of formation of gas-phase PhX and ViX for arbitrary X, has

TABLE 2. $\delta\Delta H_f(\mathrm{PhCH_2R, PhOR}) \equiv \delta_{15}$(Ph, R) for phenyl ethers

R	$\delta\Delta H_f$(lq, $PhCH_2R$, PhOR)	$\delta\Delta H_f$(g, $PhCH_2R$, PhOR)	δ(lq, g)
Me	102.5	97.8	4.7
Et	114.3	109.5	4.8
Vi	115.2	110[a]	5.2
Ph	104.6[b]	102.9[c]	1.7

[a]The heat of formation of gaseous allylbenzene was obtained using the archival heat of formation of the liquid and the two-term estimation approach of Refererence 2a for the requisite heat of vaporization.

[b]For completeness, the difference of heats of formation of solid diphenylmethane and diphenylether is $103.6\,\mathrm{kJ\,mol^{-1}}$.

[c]The heat of formation of gaseous diphenylmethane was obtained by using the archival heat of formation of the solid and the more recent heat of sublimation reported in Reference 4.

been shown to be quite constant.

$$\delta_{20}(\text{g, PhX, ViX}) = \Delta H_f(\text{g, PhX}) - \Delta H_f(\text{g, ViX}) \approx 30\,\text{kJ mol}^{-1} \quad (20)$$

E. Aliphatic Acetals

From a thermochemical perspective we find aliphatic acetals may logically and conveniently be divided into three categories: (a) di-n-alkoxymethanes, (b) 1,1-dimethoxy-n-alkanes and (c) 2,2-dimethoxy-n-alkanes. (The simplest aliphatic acetal, dimethoxymethane, logically belongs in all of these cateogories. It also belongs in none—recall our assertion that methyl is an atypical alkyl group and therefore it seems logical that methane is an atypical alkane[29].) As with the monoethers, the heat of formation of these species (as liquid) parallels the total number of carbons, n_c:

$$\text{category (a) } \Delta H_f = -24.8n_c - 325.0, \quad r^2 = 0.9968 \quad (n = 3) \quad (21)$$

$$\text{category (b) } \Delta H_f = -24.3n_c - 322.8, \quad r^2 = 1.0000 \quad (n = 4) \quad (22)$$

$$\text{category (c) } \Delta H_f = -24.9n_c - 335.5, \quad r^2 = 1.0000 \quad (n = 3) \quad (23)$$

Were we to apply these equations indiscriminately to dimethoxymethane, we would predict heats of formation of -399.4, -394.5 and $-410.2\,\text{kJ mol}^{-1}$ while the experimentally measured value is $-377.7 \pm 0.9\,\text{kJ mol}^{-1}$: dimethoxymethane fulfills our expectation that it is thermochemically anomalous.

The reader may well be expecting our next analysis to be the energetics of —O— and —CH_2— exchange, i.e. the direct comparison of aliphatic acetals with monoethers. This exchange and the accompanying δ_{15} has been a motif for much of our discussion of the heats of formation of monoethers. However, we find that heat of formation data are lacking for many of the monoethers that are directly related to the diethers of current interest. Because there are extensive data on the energetics of saturated hydrocarbons, a double exchange energy can readily be studied. That is, we define a new quantity $\delta_{24}(\text{R, R}^1\text{, R}^2)$ by equation 24:

$$\delta_{24}(\text{R, R}^1\text{, R}^2) \equiv \Delta H_f(\text{l, RR}^1\text{C(CH}_2\text{R}^2)_2) - \Delta H_f(\text{l, RR}^1\text{C(OR}^2)_2) \quad (24)$$

for which we find for our three categories: (a) 222.9 ± 3.0 ($n = 3$), (b) 218.1 ± 0.4 ($n = 4$) and (c) 229.0 ± 3.84 ($n = 3$). (For completeness, we find 230.2 ± 1.3 for dimethoxymethane and its analog, pentane.) We note that the 'intermediate' monoethers are respectively 'primary/primary', 'methyl/secondary' and 'tertiary/methyl' (and 'primary/methyl'). However, none of our earlier gleaned awarenesses of the thermochemical differences of these types of monoethers helps us in understanding the differences of the δ_{24} for the various types of aliphatic acetals[30].

F. Alicyclic Acetals: The 1,3-Dioxacycloalkanes

There are experimentally measured heats of formation of four of these species, namely with 5-, 6-, 7- and 8-membered rings. Since there are no values known to the authors for the one-oxygen derivatives of cycloheptane and cyclooctane, we are again thwarted from investigating the energetics of single —O—, —CH_2— δ_{15} exchange. Defining n_r as the total ring size, Table 3 presents the energy for the two-oxygen/methylene exchange process, i.e.

$$\delta_{25}(n_r) \equiv \Delta H_f((\text{CH}_2)_{n_r}) - \Delta H_f((\text{CH}_2)_{n_r-3}\text{OCH}_2\text{O}) \quad (25)$$

The 7-membered ring species seems sorely out of line relative to 5, 6 and 8. It is reasonable to presume that for 'large enough' rings, $\delta_{25}(n_r)$ will equal the value for 'large enough'

TABLE 3. $\delta_{25}(n_r)$: The heat of the two-oxygen/methylene exchange process in cycloalkanes and their 1,3-dioxa analogs

n_r	$\delta_{25}(n_r, l)$	$\delta_{25}(n_r, g)$
5	228.1	221.6
6	223.3	218.9
7	231.0	228.5
8	211.0	212.5
∞^a	222.2	230.4

[a]We define this '$n = \infty$' case to correspond to the heat of formation difference of the 'largest' acyclic mimic of cyclic acetals for which we have any thermochemical data, di(n-butoxy)methane and n-undecane.

acyclic di(n-alkoxy)methanes and their corresponding hydrocarbons. Indeed, the entry cavalierly marked $n_r = \infty$ corresponds to the values obtained for the heat of formation differences of liquid and gaseous di-(n-butoxy)methane and n-undecane. We are nowhere near the 'large enough' limit—consider the individual values of $\delta_{25}(n_r, l)$ and $\delta_{25}(n_r, g)$, and, even simpler, the dependence of the quantity of interest on the phases of the compounds, i.e. $[\delta_{25}(n_r, l) - \delta_{25}(n_r, g)]$.

Furthermore, it is quite clear, at least *a posteriori*, there is no sense in which an 8-membered ring could have been considered to be 'large enough'—a quick appraisal of strain energies of the carbocyclic cycloalkanes attests to that[31]. We should not have expected the values of $\delta_{25}(n_r)$ to be constant: after all, the 'anomeric' effect[17] shows profound dependence of the stability of acetals as a function of the two distinct dihedral angles in the C—O—C—O—C unit as befits the customary resonance structures/energy description of acetals (equation 26).

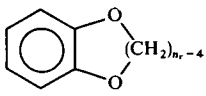
$$R—O—CH_2—O—R^1 \longleftrightarrow R—O^+{=}CH_2\ {}^-O—R^1 \longleftrightarrow R—O^-\ CH_2{=}O^+—R^1 \tag{26}$$

This angle and conformation dependence is entirely reminiscent of other strong ring-size conjugation dependencies such as hydrogenation and hydration enthalpies of 1,3-cycloalkadienes, and the solution-phase acidity of benzocycloalkenones[32]. We suspect that understanding of the energetics of the cyclic acetals will await measurements of the heat of formation of oxacycloheptane and oxacyclooctane, species recognized as being useful for the understanding of the simpler class of compounds, the cyclic monoethers. In addition, a new determination of the heat of formation of 1,3-dioxacycloheptane is also suggested.

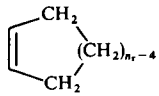
G. Cyclic Diethers with Oxygens in a 1,4-Relation

We have just seen that compounds with two oxygens situated 1,3-relative to each other show interesting structure/energy features. Likewise interesting phenomena arise for compounds with two oxygens situated 1,4 to each other. The aforementioned 'gauche-effect'[17] directly relates to that. There are few data directly comparing 1,3- and 1,4-interactions, although it is generally suggested that the former is stabilizing and the latter is destabilizing. It is certainly unequivocal that 1,3-dioxane is more stable than its 1,4-isomer by *ca* 27 kJ mol^{-1} whether we consider their liquid or gaseous phases[33].

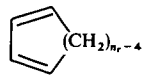
No other 1,4-dioxacycloalkanes are thermochemically characterized to allow us any additional comparison such as with the above cyclic acetals. However, there are data for the benzoanalogs of the 1,4-dioxacycloalk-2-enes for the 5-, 6- and 7-membered ring cases (**4a–4c**). What thermochemical comparisons should we make? Single ether/methylene exchange can only be quantitated for the 6-membered ring case and double ether/methylene for the 5- and 6-membered ring cases. Recall that benzoannelation results[34] in a nearly constant increase of heat of formation for relatively strainless cyclic olefins. We may thus derive a heat of formation for benzocycloheptene. Alternatively, we may compare the benzo-1,4-dioxacycloalk-2-enes (**4a–4c**) with the cycloalkenes (**5a–5c**) using equation 27 and so define $\delta_{27}(n_r)$. (Recall that n_r is the ring size.) We decide to do the latter because we can also compare the diethers with the conjugated 1,3-cycloalkadienes (**6a–6c**) by the related quantity $\delta_{28}(n_r)$ defined by equation 28. After all, both dienes and



(**4a**) $n_r = 5$
(**4b**) $n_r = 6$
(**4c**) $n_r = 7$



(**5a**) $n_r = 5$
(**5b**) $n_r = 6$
(**5c**) $n_r = 7$



(**6a**) $n_r = 5$
(**6a**) $n_r = 6$
(**6c**) $n_r = 7$

diethers have four contiguous atoms with formally conjugated p orbitals. Table 4 presents the requisite numbers for these comparisons.

$$\delta_{27}(n_r) \equiv \Delta H_f(\text{g}, \mathbf{4}) - \Delta H_f(\text{g}, \mathbf{5}) \tag{27}$$

$$\delta_{28}(n_r) \equiv \Delta H_f(\text{g}, \mathbf{4}) - \Delta H_f(\text{g}, \mathbf{6}) \tag{28}$$

As has been so often noted in this chapter, trends are often hard to discern. In particular, there is no obvious reason why the benzo-1,4-dioxacyclohexene with $n_r = 6$

TABLE 4. $\delta_{27}(n_r, \text{g})$ and $\delta_{28}(n_r, \text{g})$: The differences of the heat of the formation of gas-phase benzo-1,4-dioxacycloalk-2-enes and their monocyclic hydrocarbon analogs, the cycloalkenes and 1,3-cycloalkadienes, respectively

n_r	$\delta_{27}(n_r, \text{g})$	$\delta_{28}(n_r, \text{g})$
5	176.6	276.0
6	199.1	310.3
7	176.3	279.8
∞	168.9[a]	267.5[b]
∞'	191[c]	289[d]

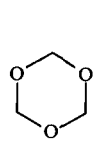
[a]We define this '$n = \infty$' case to be the difference in the heats of formation of *o*-dimethoxybenzene and (*E*)-3-hexene.
[b]We define this '$n = \infty$' case to be the difference in the heats of formation of *o*-dimethoxybenzene and of (*E,E*)-2,4-hexadiene. (This latter number was obtained from W. Fang and D. W. Rogers, *J. Org. Chem.*, 57, 2294 (1992).)
[c]Acknowledging the aforementioned thermochemical anomalies of methyl groups and so possible idiosyncracies of *o*-dimethoxybenzene, we defined this '$n = \infty$'' case by definition '*a*' and corrected it by twice $\{[\Delta H_f(\text{g, PhOEt}) - \Delta H_f(\text{g, PhOMe})] - [\Delta H_f(\text{g, PhCH}_2\text{Et}) - \Delta H_f(\text{g, PhCH}_2\text{Me})]\}$.
[d]Acknowledging the aforementioned thermochemical anomalies of methyl groups and so possible idiosyncracies of *o*-dimethoxybenzene, we define this '$n = \infty$'' case by definition '*b*' and corrected it by twice $\{[\Delta H_f(\text{g, PhOEt}) - \Delta H_f(\text{g, PhOMe})] - [\Delta H_f(\text{g, PhCH}_2\text{Et}) - \Delta H_f(\text{g, PhCH}_2\text{Me})]\}$.

species should be so stable compared to benzo-1,3-dioxacyclopentene with $n_r = 5$; after all, we recognize that the former contains a destabilizing 1,4-dioxygen arrangement while the latter contains a stabilizing 1,3-dioxygen arrangement. We now offer excuses rather than explanations. By a judicious use of *ab initio* quantum-chemical calculations and photoelectron spectroscopy[35], it has been deduced that 1,2-dimethoxybenzene prefers nonplanarity because of electronic interactions of the two oxygens. Yet we find that reaction 29 is strangely exothermic by some $12\,kJ\,mol^{-1}$ for the liquid phase, and 5 kJ in the gas phase. It is also interesting that numerous enzyme-catalyzed 1,2-proton transfer reactions proceed through neutral and anionic *Z*-enediol intermediates[36].

$$2\,PhOMe \longrightarrow 1,2\text{-}C_6H_4(OMe)_2 + C_6H_6 \qquad (29)$$

H. A Brief Discussion of Cyclic Polyethers

There are two types of cyclic polyethers we will discuss: the 1,3,5,...,(2*n* + 1)-polyoxacycloalkanes (**7a–7d**) and the 1,4,7,...,(3*n* + 1)-polyoxacycloalkanes (**8a–8e**). Both of these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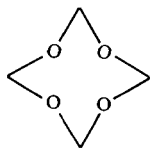
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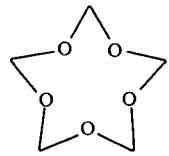
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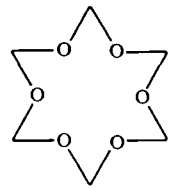
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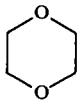
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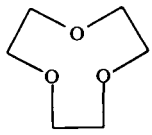
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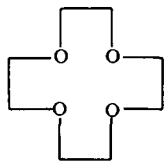
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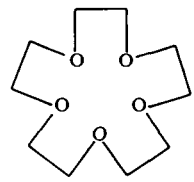
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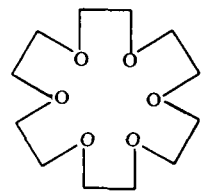

(8e)

classes of species are 'quasi-atom diagonal' or 'group diagonal'[37], i.e. they are composed of but one type of group. The former are recognized as oligomers of formaldehyde and so are composed solely of the $—CH_2—O—$ group. The latter are oligomers of ethylene oxide, and so are composed solely of the $—CH_2—CH_2—O—$ group. (Or should we say 'solely of the $—CH_2—O—CH_2—$ group'[38]?). Table 5 presents the heats of formation

TABLE 5. The heats of formation of gas-phase 1,3,5,..., (2*n* + 1)- and the 1,4,7,...,(3*n* + 1)-polyoxacycloalkanes per monomeric group

n	$\Delta H_f(g, (CH_2O)_n)/n$	$\Delta H_f(g, (CH_2CH_2O)_n)/n$
2		−157.9
3	−155.3	
4	−155.1	−157.3
5	−156.0	−159.9

of both classes of compound, as gases, *per* monomeric group. All of the values in this table are surprisingly close—the average value for the heat of formation of a $—CH_2O—$ unit is $-155.4\,kJ\,mol^{-1}$, and for $—CH_2CH_2O—$ is $-158.5\,kJ\,mol^{-1}$. From this we may deduce sequentially the following:

(a) Unlike the cycloalkanes there is seemingly little strain energy in the 1,3,5,..., $(2n+1)$-polyoxacycloalkanes. However, we also note that medium-size rings are often highly strained and so measurements on $(CH_2O)_6$ (**7d**) are suggested. To argue that transannular CH_2/CH_2 repulsions are minimized in the ethers belies the possibility of transannular oxygen–oxygen repulsions.

(b) Unlike the cycloalkanes there is seemingly little strain energy in the 1,4,7,...,$(3n+1)$-polyoxacycloalkanes. However, we note that for all of the studies of 'crown ethers', there are apparently no heat of formation data for $(CH_2CH_2O)_6$ (**8e**, 18-crown-6) which is generally understood as the species of greatest interest and importance.

(c) The 1,4,7,...,$(3n+1)$-polyoxacycloalkanes have one additional $—CH_2—$ per group compared to the 1,3,5,...,$(2n+1)$-polyoxacycloalkanes. To say that these two classes of compounds have comparable heats of formation per group means that the former is less stable than the latter by the heat of formation of a $—CH_2—$ group, *ca* $20\,kJ\,mol^{-1}$.

(d) This stabilization is consonant with resonance stabilization suggested for species with two 1,3-oxygens relative to each other, cf equation 26. This suggests greater intermolecular interactions for such compounds since the bonds are more polar—a plausible deduction given that all of the $(CH_2O)_n$ species discussed in Table 5 are normally solids at STP while all of the $(CH_2CH_2O)_n$ species are liquids.

(e) From our earlier analysis on diethers we recall that both 1,3- and 1,4-oxygen,oxygen interactions have considerable geometry dependence. So why are heats of formation of both 1,3,5,...,$(2n+1)$-polyoxacycloalkanes and 1,4,7,...,$(2n+1)$-polyoxacycloalkanes so independent of n?

(f) Or are they? One may construct 'mixed' oligomers and derive their heats of formation. The two species that thermochemically qualify are 1,3-dioxolane and 1,3,6-trioxacyclooctane. If we formally synthesize them from our $—CH_2O—$ and $—CH_2CH_2O—$ units[39], we would predict respective heats of formation of -313.9 and $-467.1\,kJ\,mol^{-1}$, while the experimental values are found to be -298.0 and $-472.4\,kJ\,mol^{-1}$.

III. ALCOHOLS

A. The Methyl/Alcohol Exchange Energy of Monoalcohols

Following Wiberg and his coworkers[40] and Stull, Westrum and Sinke[41] before them, we describe the energetics of alcohols in terms of their isoelectronic and isosteric analog. More precisely, we define a quantity $\delta_{30}(*, **)$ by

$$\delta_{30}(*, **) \equiv \Delta H_f(*, \mathrm{RMe}) - \Delta H_f(*, \mathrm{ROH}) \tag{30}$$

where * defines the phase and ** defines the type of alcohol. For the 1-alkanols, we find the following results for this methyl/alcohol exchange energy:

$$\delta_{30}(\mathrm{g}, \text{1-alkanols}) = 127.8 \pm 1.6 \quad (C_2—C_{10}, C_{12}) \tag{31}$$

$$\delta_{30}(\mathrm{l}, \text{1-alkanols}) = 153.1 \pm 1.8 \quad (C_2—C_{12}, C_{14}) \tag{32}$$

The former result is close to that reported by Wiberg and his coworkers, $128.9 \pm 1.1\,kJ\,mol^{-1}$ for a smaller but more general set of primary alcohols, i.e. these authors also included both isobutyl and isopentyl alcohol. It is thus safe to conclude

δ_{30}(g, pri) $\approx$ 128 kJ mol^{-1} and δ_{30}(l, pri) $\approx$ 153 kJ mol^{-1}. Relatedly, we have found

$$\delta_{30}(\text{g, 2-alkanols}) = 138.6 \pm 0.7 \quad (C_3—C_5) \tag{33}$$

$$\delta_{30}(\text{l, 2-alkanols}) = 162.7 \pm 1.6 \quad (C_3—C_7) \tag{34}$$

The former result is close to that reported by Wiberg and his coworkers, 137.2 $\pm$ 1.3 kJ mol^{-1}, for a more general set of secondary alcohols, i.e. these authors also included data on 3-methyl-2-butanol, cyclopentanol and cyclohexanol. Linear extrapolation of the heats of formation of 2-PrOH, 2-BuOH and 2-PeOH to their 6- and 7-carbon analogs differ from experiment by a few kJ mol^{-1} while profound linearity is seen for the 1-alkanols,

$$\Delta H_f(\text{g, 1-alkanols}) = -20.14n_c - 194.7 \; (r^2 = 0.99997, C_4—C_{10}, C_{12}, C_{16}) \tag{35}$$

From their insights and ours, we suggest δ_{30}(g, sec) $\approx$ 138 kJ mol^{-1} and δ_{30}(l, sec) $\approx$ 164 kJ mol^{-1}. Finally, for the admittedly small set of tertiary alcohols, we derive the following: δ_{30}(g, tert) $\approx$ 148 kJ mol^{-1} and δ_{30}(l, tert) $\approx$ 170 kJ mol^{-1}. Perhaps because a greater structural variety has been used, the standard deviations are considerably larger than before, namely 4.6 and 3.6 kJ mol^{-1} for the gaseous and liquid values. Nonetheless, it is safe to assert a natural order for the various δ_{30}(g, **) quantities: tertiary (148) > secondary (138) > primary (128). Following Wiberg and his associates, we note that this order follows the stability of carbonium ions, attesting to the greater relative importance of the ionic $R^+ OH^-$ resonance structure for alcohols than $R^+ CH_3^-$ for the related alkane. Indeed, δ_{30}(g, pri) > δ_{30}(g, Me)(= 117.7 kJ mol^{-1}) is in accord with this reasoning. This logic is quite compelling[42]. Recalling that bridgehead carbonium ions are comparatively unstable, we therefore suggest heat of formation measurements on the 1-, 2-(*endo*), 2-(*exo*) and 7-norbornanols and the corresponding methylnorbornanes as a test of this understanding.

B. Is the Heat of Formation of Alcohols Linear with the Number of Carbons?

There are two classes of alcohols we will quantitatively discuss in this section, the 1- and 2-alkanols. Equation 35 documents an emphatic affirmative answer to this question. Nonetheless, the result is disconcerting in that the slope, −20.14, is meaningfully different from the n-alkanes, −20.63, derived using heat of formation data for the n-alkanes from n-butane to n-eicosane. This −20.63 is but a difference of 0.49 kJ mol^{-1} and so would not normally distress us. However, since it is multiplied by the number of carbons, it can result in a major discrepancy. Indeed, some two decades ago, Cox and Pilcher[43] labelled this a seeming deviation from a 'universal' constant—the heat of formation of *the* strainless methylene increment [ΔH_f(g, —CH_2—) = −20.63 kJ mol^{-1})]. Indeed, the situation is more troublesome than when it was first so-enunciated—there are new entries in the alcohol data set which were not available to these authors. One cannot invoke the anomalous properties of methyl relative to the higher alkyl groups[21] because the smallest alkane and alcohol included by both Cox and Pilcher and ourselves are n-butane and n-butyl alcohol. An explanation of this discrepancy is still evasive.

For the 2-alkanols (equation 36)

$$\Delta H_f(\text{g, 2-alkanols}) = -20.03n_c - 212.7 \quad (r^2 = 1.0000, C_3—C_5) \tag{36}$$

the slope differs only 0.22 kJ mol^{-1} from that of the 2-methylalkanes. We additionally note that the heat of formation of secondary alcohols formed from n-alkanes is largely independent of the site of substitution, e.g. the heats of formation of liquid 2- and

3-hexanol are encouragingly close. This is not particularly surprising, but there are insufficient, adequately reliable data to define this conclusion more strongly.

C. Cyclic Alcohols

A simple examination of the data for cycloalkanols shows that the heat of formation of these species, either as liquid or as gas, is not linear with the number of carbons. This is not surprising—recall the concept of strain energy (SE) and the simple 'diagonal' definition[37] for cycloalkanes (equation 37), wherein n_r is the ring size. This is based on the assumption that cyclohexane is unstrained and thus, by definition, that the heat of formation of the strainless methylene increment is $\frac{1}{6}[(\Delta H_f(g,(CH_2)_6]$. This is numerically equal to $-20.6\,kJ\,mol^{-1}$, and in reasonable agreement with our earlier numbers. Distressingly, we have no understanding to explain why $\delta_{30}(*,$ cycloalkanol) has no simple dependence on the number of carbons (ring size) or strain of the parent hydrocarbon or nature of the —OH substituent[44]. Table 6 presents the relevant available values, namely $n_c = 4, 5, 6$, where to our surprise inclusion of additional entries are more limited by paucity of thermochemical data for the methylcycloalkanes than for the cycloalkanols.

$$SE(g,(CH_2)n_r)) = \Delta H_f(g,(CH_2)n_r)) - n_r/6[(\Delta H_f(g,(CH_2)_6] \tag{37}$$

D. Polyalcohols

There are two types of polyalcohols we will discuss in this section. The first are the 1,ω-alkanediols, $HO(CH_2)_nOH$, for which thermochemical data exist for $n = 2$–10. Because these compounds are so hygroscopic, obtaining the desired heat of formation data is fraught with complications. We find that the exchange of both OH groups with CH_3, $\sigma_{30}(*,**)$, generally decreases with increasing n but in a rather erratic and nonmonotonic way. (For liquids, δ_{30} 'dribbles' from 313 to 299 kJ mol^{-1} with increasing n, while for gases, δ_{30} 'drifts' from 269 to 233 kJ mol^{-1}.) Remembering that $\delta_{30}(*,$ n-alkanol) is rather well-defined, we are not surprised that the single Me/OH exchange for these diols is also erratic and nonmonotonic, although there is the general liquid-phase dribble and gas-phase drift from 157 to 148 kJ mol^{-1} and 139 to 104 kJ mol^{-1}, respectively. We will not endeavor to try to reconcile this in terms of the conformational demands of the polymethylene chain and the desired linearity of intramolecular hydrogen bonding. Nor will we adopt the attitude that the heat of formation of these species is derived by estimation and extrapolation using a constant methylene increment, as was done in a recent study of the thermochemistry of lactones[45]. Rather, we believe it would prove interesting and informative to do the last study 'in reverse' i.e. measure directly the heats of formation of the lactones and derive the heats of formation of the desired

TABLE 6. The methyl/alcohol exchange energy for liquid and gaseous cycloalkanols

n_r	$\delta_{30}(l, n_r)$	$\delta_{30}(g, n_r)$
4	154.6	123.7
5	162.2	136.4
6	153.1	131.1

diols. (Consistency has already been demonstrated in the one case of γ-butyrolactone, i.e. by reproducing the literature heat of formation -420.7 ± 0.8 vs -422.4 ± 1.1 kJ mol^{-1}.)

The second class of compounds is the cycloalkane and n-alkane derivatives in which each carbon has an appended OH group. In that some of these species are liquids and others solids, it is most instructive only to consider these species in their gaseous states. Following our earlier 'diagonal' reasoning for CH_2 groups, we now define the strainless —CHOH— group as $\frac{1}{6}\Delta H_f(g,(CHOH)_6)$ without particular concern of which stereoisomer of inositol was in fact employed. The desired number is -186.0 kJ mol^{-1}. A linear fit of the seven available heats of formation of the relevant gaseous polyhydroxyalkanes[46] with the number of CHOH (hydroxymethylene) groups, n_{hm}, resulted in equation 38. Encouragingly, the slope is nearly the same as the above diagonally derived quantity. It would appear that the idiosyncracies of individual carbon stereochemistry and hydrogen bonding are less relevant than one might have otherwise thought.

$$\Delta H_f(g, HOCH_2(CHOH)_{hm}CH_2OH) = -187.2n_{hm} - 395.0 \quad (r^2 = 0.9999) \qquad (38)$$

IV. ARENOLS

A. Isomer Stability Patterns

In the textbook resonance structure description of phenol, the oxygen becomes partially positive while the 2-, 4- and 6- carbons become somewhat negative. This suggests that electron-donating groups will be relatively destabilized in any of these positions as opposed to the 3- and 5-carbons. In addition, to minimize charge separation, it is reasonable to assume that $C_{(2)}$ and $C_{(6)}$ are somewhat more negative than $C_{(4)}$. Destabilization at the 2- and 6-positions should be greater than at the 4-position. To maximize resonance stabilization, all of the atoms in phenol should be in the same plane. No steric repulsion is expected for substitution in the 3-, 4- or 5-positions. In the 2- and 6-positions, there is the possibility of some repulsion of the hydrogen with the substituent. However, if only one of these positions is substituted, then simple rotation around the C—O bond alleviates any steric effects. Both the electronic and the steric arguments suggest that gas-phase monoalkyl-subsituted phenols will increase in stability in the order 2- < 4- < 3-. Yet the experimental data show for the isomeric methylphenols that the thermodynamic stability increases in the order 4- < 2- < 3- and, for the ethylphenols, all three isomers have the same heat of formation within ± 1 kJ mol^{-1}. The isopropylphenols have the order of increasing stability 2- < 3- < 4-. However, we are dismayed at the individual error bars of ± 13 kJ mol^{-1} and astonished at the *ca* 14 kJ mol^{-1} difference between the 2- and 3-, and the 3- and 4-isomers.

What about naphthols? The introduction of the second ring provides new steric and electronic features. 1-Naphthol has peri- (1,8-) repulsions between the —OH and an H—, a feature not shared by its isomer 2-naphthol. On the other hand, one can draw two ionic resonance structures for 1-naphthol that do not 'sabotage' the benzenoid sextet in both aromatic rings while there is but one for the 2-isomer. Since the heats of formation of the two isomers differ by *ca* 1 kJ mol^{-1}, it would appear that these two effects essentially cancel. We look forward to a thermochemical study of alkylated naphthols that can help disentangle these phenomena.

The analysis of arenediols is instructive. If alkylation of a phenol is destabilizing in the 2-, 4- and 6-positions, effects of hydroxylation should be even stronger. It is found for both benzene and naphthalenediols that stability increases in the order 1,4- < 1,2- < 1,3-. It is not obvious how much the relative stability of the 1,4- and 1,2-isomers arises from a weak intramolecular hydrogen bond in the latter. One can also invoke the (earlier enunciated[36]) stabilization of enediols to be (*Z*)- and not (*E*)-.

Naphthalene offers the opportunity of having the two —OH groups on different rings. However, gas-phase data for any relevant species seem to be absent. There are thermochemical data for appropriate, albeit solid-phase, naphthalenediols. We suggest heat of sublimation measurements on these compounds.

B. Methyl/Arenol Exchange Energy

The difference for the exchange of methyl and hydroxy groups proceeds much as it did for alcohols. More precisely, we define δ_{39}(*, aryl) for arenols (equation 39) much as δ_{30}(*, alkyl) was earlier defined for alcohols. We find δ_{39}(g, Ph) = 146.8 ± 1.1 kJ mol^{-1}, which is nearly the same as for a tertiary alcohol. This should not be taken to mean Ph^+ has nearly the same stability as t-Bu^+ but rather that stabilization is due to differing types of resonance in the hydroxy compounds. We additionally find δ_{39}(l, Ph) = 166.0 kJ mol^{-1}, again very similar to the t-butyl case[47]. For the methylphenols, the values of δ_{39}(g, Tol) and δ_{39}(l, Tol) are within a few kJ mol^{-1} of the phenol case. Where the data exist, the values for the related δ_{39}(*, EtC_6H_4) and δ_{39}(g, $Me_2C_6H_3$) are generally consonant with the earlier results, although the discrepancies and error bars are getting uncomfortably large. No such agreement exists for δ_{39}(*, i-$PrC_6H_4^-$) but, as mentioned before, we do not trust the data for these phenols. The δ_{39} values found for gaseous phenyl derivatives are about the same as those found for the naphthalene derivatives: for the 1- and 2- species, the differences are 144.3 and 139.5 kJ mol^{-1}. Summarizing these results, δ_{39}(g, Ar) = 145 ± 5 kJ mol^{-1} and δ_{39}(l, Ar) = 245 ± 5 kJ mol^{-1} appear to be generally useful numbers.

$$\delta_{39}(*, \text{aryl}) \equiv \Delta H_f(*, \text{ArMe}) - \Delta H_f(*, \text{ArOH}) \tag{39}$$

C. Arenediols and Polyols

Even though the three benzenediols have significantly different heats of formation, nonetheless their methyl/arenol exchange energies for *one* —OH group are surprisingly constant, 140.4 ± 1.8 kJ mol^{-1}. This is also seen in the energetics of replacing both, 287.3 ± 4.4 kJ mol^{-1}, or 143.7 ± 3.1 kJ mol^{-1} on an 'average' or 'normalized' —OH basis. The comparable result of 142.8 ± 4.9 kJ mol^{-1} is found for the naphthalene case, although the lack of thermochemical data for any methylated naphthols forces us to consider only the 'average' or 'normalized' basis. Again, naphthalene derivatives seem to offer us no real surprises. Not unexpectedly, the exchange reaction of benzenetriols and dimethylphenols shows some positional dependence, with an average exchange energy of 141.6 ± 3.7 kJ mol^{-1}. Nonetheless, the average value found for replacing all three groups results in the comparative normal value of 143.6 ± 2.1 kJ mol^{-1}.

V. ENOLS

A. Unsubstituted, Acyclic Enols

Not too many years ago, enols were generally viewed as transient intermediates for which one could derive some information about their energetics via enol/carbonyl equilibration or kinetics experiments in the condensed phase. It is now clear that considerable knowledge has been amassed about enols, both quantitative and qualitative. This understanding has been gained using a variety of experimental and theoretical techniques[48]. Even a tentative set of Benson group increments has been generated[49]. While Reference 48 is recent and therein are several chapters that deal directly with the energetics of enols, nonetheless we believe there are some additional thermochemical insights to express here. In particular, Table 7 presents the energetics consequences of

TABLE 7. Energetics of methyl/enol exchanges, $\delta_{40}(g, R) \equiv \delta_{30}(g, \text{'enyl'})$

R	$\delta_{40}(g, R)$
CH_2=CH—	148
CH_2=C(Me)—	159
(Z)-MeCH=CH—	167
(E)-MeCH=CH—	158
CH_2 = C(Vi)—	153
(Z)-ViCH=CH—	171
(E)-ViCH=CH—	164
CH_2=C(C≡CH)—	176[a]
(Z)-HOCH=CH—	142
$\frac{1}{2}$((Z)-—CH=CH—)	155

[a]The heat of formation for the requisite hydrocarbon was found in N. D. Lebedeva, V. L. Ryadnenko, N. N. Kiseleva and L. F. Nazarova, *Vses. Konf. Kalorim.* [*Rasshir Tezisy Dokl.*] 7th **1**, 91 (1977) [*Chem. Abstr.*, **92**, 75617 (1980)].

methyl/enol exchange reactions, $\delta_{40}(g, \text{'enyl'})$, where for the one example of an ene-diol both single and 'averaged' energies are given.

$$\delta_{40}(g, \text{'enyl'}) \equiv = \Delta H_f(g, \text{'enyl-Me'}) - \Delta H_f(g, \text{enol}) \quad (40)$$

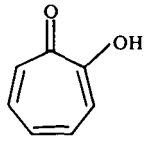
It is seen that the $\delta_{40}(g, \text{'enol'})$ has a rather wide spread of values, a not altogether surprising result since all 'types' of enols are lumped together. Had we done so for alcohols we would have found an analogous spread of values, but the paucity of thermochemical data for enols convinced us not to divide this class of molecules into subclasses. Nonetheless, we recognize that there are some thermochemical patterns. For hydrocarbon (nonenolic) acyclic olefins, (E)-RCH=CHR′ is more stable than its (Z)-isomer. However, for the few enols we have data for, the (E)-RCH=CHOH is less stable than (Z)- (R = Me- and Vi—). This is no doubt formally related to our earlier assertion about enediolates and difluoroethylene[36]; indeed, equilibration experiments[50] have shown that the (Z)-isomers of MeCH=CHX (X = F, Cl, Br) are all more stable than their (E)-isomers by a nearly constant *ca* 3 kJ mol^{-1}. It would be interesting to contrast the heats of formation for RCH=CHX and RCH=CHOH with other and hence larger R groups to find out when these olefins prefer to be (E)-; we await and encourage these measurements. We also note that the 2-enol of 1,3-butadiene is substantially less stable than either the (Z)- or (E)-1-enol as shown by the 18 kJ mol^{-1} spread of values of $\delta_{40}(g, \text{'enyl'})$. This is compatible with classical resonance structure reasoning—indeed the partially positive oxygen and partially negative $C_{(4)}$ provides additional stabilization of the (Z)-1-enol. Nonetheless, we hesitate to draw any immediate conclusion about polyenols and note that quantitative study of the energetics of the all-hydrocarbon polyenes is still surprisingly embryonic[51].

B. Tropolone and Acetylacetone

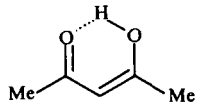
Tropolone (**9**) is an intriguing species. If we designate it as 2-hydroxytropone we may discuss this species both as an arenol, thereby assuming that tropone is aromatic, and as an enol, thereby assuming that tropone is not. The latter is tantamount to describing tropolone as the enol of a 'ξ'-diketone. In that the enols of β-diketones are thermo-

chemically quite well-described (see Reference 10), a comparison would seem in order. Ideally, a thermochemical comparison of tropolone with its isomer 3-hydroxytropone would prove the most instructive since differences in σ-effects would presumably be minimized. Indeed, a natural extension of both the conjugation and our 'wish list' would include 4-hydroxytropone, the enol of a δ-diketone. However, thermochemical data are lacking for both isomers.

We will thus make our comparisons with the best understood β-diketone enol, namely that of acetylacetone (**10**). This species has an intramolecular hydrogen bond and has



(**9**)



(**10**)

accompanying synergistic 'push–pull' resonance (equation 41). Taken together, considerable stabilization is suggested. What is the relative stabilization energy of tropolone and acetylacetone (enol)? For our initial effort at discussing this, we first determine the stabilization energy of each species separately and then take the difference of these quantities. The energetics of the methyl/enol exchange reaction for tropolone cannot be directly determined because we lack the necessary heat of formation of the gaseous 2-methyltropone. We may derive it using the experimentally measured heat of formation of tropone and the 'methylation' energies (equation 42), where we should use appropriate conjugated, electron-withdrawing groups 'R'. For R = PhCO—, (*E*)-NCCH=CH— and *p*-$O_2NC_6H_4$—, we find decreasing differences of 50.0, 39.9 and 36.5 kJ mol^{-1}, but all are significantly larger than those for the 'comparable' but non-electron-withdrawing R = PhCH(Me)—, (*E*)-MeCH=CH— and *p*-MeC_6H_4—, namely 29.9, 31.4 and 32.4 kJ mol^{-1}. It is most unobvious how to decide which of the first, stabilizing, set of three R groups is the best simulation for our tropone/tropolone story. Choosing an average δ_{42}(H, Me) of 42 kJ mol^{-1} results in a predicted heat of formation of gaseous 2-methyltropone of 2 kJ mol^{-1}. Combining this approximate number with the experimentally measured heat of formation of tropolone results in a methyl/enol exchange of *ca.* 157 mol^{-1}.

$$HO—C(Me)=CH—C(Me)=O \longleftrightarrow HO^+=C(Me)—CH=C(Me)—O^- \quad (41)$$

$$\delta_{42}(H, Me) \equiv \Delta H_f(g, RH) - \Delta H_f(g, RCH_3) \quad (42)$$

Neither can the energetics of the methyl/enol exchange reaction, δ_{40}, for acetylacetone enol be directly determined because we lack the necessary heat of formation of the gaseous 4-methyl-3-penten-2-one. However, it may be derived by combining the value for the liquid, -248 kJ mol^{-1}, and an estimated[52] heat of vaporization of 42 kJ mol^{-1} resulting in the desired value of -206 kJ mol^{-1}. Alternatively, it has been recently noted[53] that the formal gas-phase reactions of two 1-olefins to form the conjugated diene, and of two aldehydes to form an α-diketone (equations 43 and 44) are essentially thermoneutral. By comparison, the reaction of an alkene and an aldehyde is exothermic by 12 kJ mol^{-1}, at least for the one case which we take to be the most reliable, i.e. unambiguous, data. This is reaction 45 for crotonaldehyde. Accepting the generality of this result[54], we may formally combine isobutene and acetaldehyde to 'synthesize' the desired species for which a value of -195 kJ mol^{-1} is found. This value is different enough from our earlier one to be troublesome. Nonetheless, the resultant value of ΔH_f(g, 4-methyl-3-penten-2-one) of *ca* -200 kJ mol^{-1} is no doubt plausible, resulting in a methyl/enol exchange energy for acetylacetone (enol) of *ca* 186 kJ mol^{-1}. Combining

this with our earlier exchange energy of *ca* 157 kJ mol^{-1} for tropolone suggests an additional stabilization for acetylacetone (enol) of some 30 kJ mol^{-1}.

$$RCH{=}CH_2 + R'CH{=}CH_2 \longrightarrow RCH{=}CH{-}CH{=}CHR' + H_2 \quad (43)$$

$$RCHO + R'CHO \longrightarrow R{-}C(O){-}C(O){-}R' + H_2 \quad (44)$$

$$CH_3CH{=}CH_2 + CH_2O \longrightarrow CH_3CH{=}CHCHO + H_2 \quad (45)$$

An alternative approach notes that reaction 46 would be thermoneutral in the absence of any additional stabilizing or destabilizing features.

$$\text{tropolone} + (E)\text{-2-pentene} \longrightarrow \text{tropilidene} + \text{acetylacetone (enol)} \quad (46)$$

In fact, this reaction is exothermic by 12.4 kJ mol^{-1}. That it is exothermic is compatible with our previous finding. But why is the seeming stabilization of acetylacetone (enol) reduced from the 30 kJ mol^{-1} of our previous analysis to but 12 in the present analysis? It is tempting to invoke the 18 kJ mol^{-1} discrepancy by ascribing it to homoaromaticity for the tropilidene in reasonable agreement with some recent analyses[55] based on molecular mechanics, measurements of heats of hydrogenation and yet other conceptual reactions.

VI. PEROXIDES AND HYDROPEROXIDES

A. The Quantity and Quality of the Data

The defining O—O bond in peroxides and hydroperoxides is weak and, upon either thermally-, photochemically- or impurity-induced cleavage, the resulting oxyradicals assist the decomposition of other molecules. Spontaneous decomposition is always accompanied by low sample purity and so seriously aggravates thermochemical investigation. Furthermore, compounds with O—O bonds are often explosive which discourages 'large-scale' synthesis and purification as well as measurements of heats of vaporization and sublimation. As such, the study of peroxides and hydroperoxides is notable for the paucity of reliable data. We are thus generally thwarted in deriving meaningful thermochemical trends. Nonetheless, we will recount some seemingly logical relations and describe our findings if for no other reason than to prod otherwise reluctant experimentalists.

B. Unsubstituted Alkyl and Cycloalkyl Hydroperoxides

We commence with the observation that the heats of formation of ethyl and propyl hydroperoxide are accompanied by error bars of *ca* 60 kJ mol^{-1}. Clearly these data are conceptually without value except to pose the cynical question of how many error bars for other hydroperoxides and peroxides are unrealistically low. (For example, have enough measurements on a given species been made to guarantee appropriate statistical analysis of the data?) We will proceed optimistically with the admission that we have often asked the same question about more stable species, even when we have not explicitly singled out their heats of formation as we had earlier for di-*t*-butyl ether and isobutyl vinyl ether.

Based on our earlier experience gained from the ether/methylene and alcohol/methyl exchanges, it is logical to define the two quantities $\delta_{47}(\text{l}, \text{ROOH}, \text{RCH}_2\text{OH})$ and $\delta_{48}(\text{l}, \text{ROOH}, \text{ROMe})$:

$$\delta_{47}(\text{l}, \text{ROOH}, \text{RCH}_2\text{OH}) = \Delta H_f(\text{l}, \text{ROOH}) - \Delta H_f(\text{l}, \text{RCH}_2\text{OH}) \quad (47)$$

$$\delta_{48}(\text{l}, \text{ROOH}, \text{ROMe}) = \Delta H_f(\text{l}, \text{ROOH}) - \Delta H_f(\text{l}, \text{ROMe}) \quad (48)$$

Disappointingly, we find that there is almost no thermochemical information to derive trends using the derived data δ_{47}. Surprisingly, this is not the 'fault' of the hydroperoxide literature. Rather, there are almost no data at all for the necessary primary alcohols and, where there are, they are generally of poor quality. More precisely, while we trust the data for *t*-butyl hydroperoxide, we find that the heat of formation for the formally related neopentyl alcohol is accompanied by an experimental uncertainty of 16.7 kJ mol^{-1}. This may appear a legitimization of our earlier conclusion that ethers are more thermochemically reliable than alcohols. However, we find that δ_{48} is less useful than we should think. While the heat of formation data on *t*-butyl methyl ether are seemingly of impeccable quality (with its error bar of only 1.1 kJ mol^{-1}), we find no data of any accuracy for other needed methyl ethers. After all, prior to starting our analysis we would have thought that a thermochemical investigation of the now desired species 1-methylcyclohexyl methyl ether and 2-hexyl methyl ether to be relatively routine and the results without particular interest and/or relevance. Besides now encouraging some new experimental measurements, what can be said or done?

It may be suggested that these heats of formation be estimated by using the various methods earlier mentioned for alcohols and ethers. Since these have been successfully related to hydrocarbons—after all, this is what legitimized suggesting equations 47 and 48—why not replace both oxygens with methylenes and so compare hydroperoxy and ethyl derivatives via the single interrelation equation 49. In fact, this too is rather disappointing. For *t*-butyl and 1-methylcyclohexyl, the differences are *ca* 80 and 90 kJ mol^{-1}, with error bars large enough to claim equality as 85 kJ mol^{-1}. Primary and secondary R groups both result in differences of between 50 and 70 kJ mol^{-1}. It seems unequivocal that there are errors in the experimental measurements for the hydroperoxides—e.g. from the earlier results on the energetics of the homologous n-alkyl derivatives (cf. Reference 21), we are convinced that the over 40 kJ mol^{-1} difference for the values for n-hexyl and n-heptyl hydroperoxide cannot be correct, even though we have presented neither an experimental nor a calculational handle to help us decide which result is more likely to be correct[57].

$$\delta_{49}(\mathrm{l, ROOH, REt}) = \Delta H_f(\mathrm{l, ROOH}) - \Delta H_f(\mathrm{l, REt}) \tag{49}$$

The final interrelationship we will make is between liquid hydroperoxides and the corresponding alcohols. Equation 50 defines the relational quantity δ_{50}.

$$\delta_{50}(\mathrm{l, ROOH,ROH}) = \Delta H_f(\mathrm{l, ROOH}) - \Delta H_f(\mathrm{l, ROH}) \tag{50}$$

If we ignore the thermochemically useless data for $R = \mathrm{Et}$ and Pr, we find that $\delta_{50}(\mathrm{l, ROOH, ROH}) = 75.1 \pm 9.3$ kJ mol^{-1}, comparable to the value of 79 ± 3 suggested in Reference 56. The uncertainty is larger than we would wish but equation 50 nonetheless suggests a useful trend. However, compound-by-compound examination shows that this difference increases in the anomalous average alkyl group order primary < tertiary < secondary, although we admit that the uncertainty within each small group allows for the three averages to be the same. None of this prepares us for the 98.1 ± 0.1 kJ mol^{-1} difference in the indisputably accurate R = H case. As such, we are reticent to use the current finding to help decide the relative validity of the measurements of n-hexyl and n-heptyl hydroperoxides.

C. Unsubstituted Dialkyl Peroxides

We find that there are heats of formation data for only three compounds in the gas-phase and liquid-phase results for only two compounds. In particular, we have data only for heats of formation of gaseous ROOR with R = Me, Et and *t*-Bu, and of liquid with R = Et and *t*-Bu. In principle we can estimate $\Delta H_{\mathrm{liqn}}(\mathrm{MeOOMe})$ using the 'tentative'

heat of vaporization peroxide parameter offered in Reference 2b, although the same few carbon caveat expressed in Reference 27 most assuredly applies. We have thus decided to discuss interrelationships only involving experimentally measured quantities, although we admit that a sample space of two compounds for liquids and three for gases is much smaller than we would have liked to use.

The first interrelationship to be discussed is the formal hydrogenolysis of a peroxide (equation 51) and the associated reaction heat, $\delta_{51}(R)$:

$$ROOR + H_2 \longrightarrow 2\,ROH \tag{51a}$$

$$\delta_{51}(R) \equiv \Delta H_f(ROOR) - 2\Delta H_f(ROH) \tag{51b}$$

For the liquid peroxides we find $\delta_{51}(R)$ equals $334.7 \pm 4.0\,kJ\,mol^{-1}$, while for the gaseous species the value is reduced[58] to $276.9 \pm 0.8\,kJ\,mol^{-1}$. We know of no thermochemical data for mixed, but otherwise unfunctionalized, dialkyl peroxides, and so deviation of the heat of the 'disproportionation' reaction 52, δ_{52}, from the expected (idealized) value of $0\,kJ\,mol^{-1}$ cannot be determined. For the same reason, the hydrogenolysis reaction 53 and the new 'natural' quantity $\delta_{53}(R, R')$ cannot be evaluated. Letting $R' = H$ returns us briefly to the energetics of hydroperoxides and we recognize the identity in equation 54.

$$2\,ROOR' \longrightarrow ROOR + R'OOR' \tag{52}$$

$$ROOR' + H_2 \longrightarrow ROH + R'OH \tag{53a}$$

$$\delta_{53}(R, R') \equiv \Delta H_f(ROOR') - [\Delta H_f(ROH) + \Delta H_f(R'OH)] \tag{53b}$$

$$\delta_{53}(R, H) = \delta_{51}(R) - \Delta H_f(H_2O) \tag{54}$$

From our admittedly tentative value of *ca* $75\,kJ\,mol^{-1}$ for $\delta_{51}(R)$, and the highly accurate value for the heat of formation of liquid water, $-285.830 \pm 0.040\,kJ\,mol^{-1}$, we find $\delta_{53}(R, H)$ equals *ca* $360\,kJ\,mol^{-1}$. This is highly discrepant compared to the value of $\delta_{53}(R, R) = \delta_{51}(R) = 334.7\,kJ\,mol^{-1}$. However, should we let $R = H$ and so consider the dialkyl peroxide and alkyl hydroperoxide with no carbons at all, we find the value of $383.9\,kJ\,mol^{-1}$. The series $\delta_{53}(R, R)$, $\delta_{53}(R, H)$ and $\delta_{53}(H, H)$ increases smoothly and, at least for the case where $R' = H$, we find disproportionation reaction 52 to be nearly thermoneutral as we had anticipated. Indeed, since we would expect greater discrepancies in the liquid than in the gas phase because of differences in hydrogen bonding, we may safely assume that the gas-phase reaction 55 is also nearly thermoneutral.

$$ROOR + H_2O_2 \longrightarrow 2\,ROOH \tag{55}$$

Summarizing and making use of the archival value[59] of $\Delta H_f(g, H_2O_2) = -136.31\,kJ\,mol^{-1}$, we now present the simple procedures for estimating the heat of formation of liquid and gaseous hydroperoxides (equations 56):

$$\Delta H_f(l, ROOH) = \tfrac{1}{2}\Delta H_f(l, ROOR) - 93.9 \tag{56a}$$

$$\Delta H_f(g, ROOH) = \tfrac{1}{2}\Delta H_f(g, ROOR) - 68.2 \tag{56b}$$

For the one case where this can be tested, R = *t*-Bu, we find that our predictions are seen to be in error by nearly $10\,kJ\,mol^{-1}$ for the liquid and are almost exact for the gas. Considering the typical experimental error bars for most hydroperoxides (note *t*-BuOOH has an ascribed uncertainty of $\pm 5 kJ\,mol^{-1}$), we are highly encouraged.

Finally, let us consider the formal decomposition reaction 57. The heats of this reaction, $\delta_{57}(g, R)$ and $\delta_{57}(l, R)$, necessarily parallel those of the formal deoxygenation reaction 58 for all X and so it suffices to present results only from the former. $\delta_{57}(g, R)$ and $\delta_{57}(l, R)$ are given in Table 8, where we include our findings using both the literature values and those we had earlier suggested (see Section II.A) for the heat of formation of hypothetical

TABLE 8. The heats of the formal decomposition reaction equation 57, δ_{57}(g, R) and δ_{57}(l, R) using both the literature ('lit.') and our hypothetical ('strainless') values for the heats of formation of di-*t*-butyl ether

R	δ_{57}(g, R)	δ_{57}(l, R)
Me	58.4	
Et	59.3	50.0
t-Bu (lit.)	12.7	18.7
t-Bu (strainless)	~53	~50

strainless di-*t*-butyl ether. Again it is seen that these values, suggesting that the peroxide is unstrained, result in better general agreement than does the literature value. Indeed, in that the thermochemistry of ethers is generally sound, we find that the combined use of interrelationships of ethers and peroxides (equation 57) and of peroxides and hydroperoxides (equation 55) gives us a comfortably reliable method for estimating the desired data for hydroperoxides.

$$\cdot \mathrm{ROOR} \longrightarrow \mathrm{ROR} + \tfrac{1}{2}\mathrm{O}_2 \tag{57}$$

$$\mathrm{ROOR} + \mathrm{X} \longrightarrow \mathrm{ROR} + \mathrm{XO} \tag{58}$$

VII. ACKNOWLEDGMENTS

We wish to thank Virginia A. Hurst for assistance in the preparation of this manuscript. JFL also thanks the Center for Chemical Technology, National Institute of Standards and Technology, for partial support of his research.

VIII. REFERENCES AND COMMENTARY

1. For the reader who is interested in these entropy and heat capacity data, we cite the compendia:
(a) E. S. Domalski, W. H. Evans and E. D. Hearing, 'Heat Capacities and Entropies of Organic Compounds in the Condensed Phase', *J. Phys. Chem. Ref. Data*, **13** (1984), Suppl. 1;
(b) supplement by E. S. Domalski and E. D. Hearing, *J. Phys. Chem. Ref. Data*, **19**, 881 (1990).
While we defer to a later section discussion in detail of the sources of heats of data for the current chapter, we note now that there is one compendium we will most often use rather than return to the original primary reference. This is
(c) J. B. Pedley, R. D. Naylor and S. P. Kirby, *Thermochemical Data on Organic Compounds*, 2nd edn., Chapman and Hall, London and New York, 1986,
and indeed, the plurality of numbers in our chapter is taken from the extensive compendium by Pedley, Naylor and Kirby. In fact, compared to the number of organic compounds, heat of formation data remain disappointingly sparse even if one makes the observation that, for whatever reasons, Pedley and his coworkers have seemingly not cited an estimated 50% of the results from the primary literature (Stephen E. Stein and Jeol F. Liebman, unpublished and unrigorously documented conclusion as part of planning for the preparation for a new thermochemical archive). The aphorism about scientific data of any type, 'There is more than you think, but less than you need', is painfully valid for thermochemical studies.
2. Estimation of heats of vaporization:
(a) J. S. Chickos, A. S. Hyman, L. H. Ladon and J. F. Liebman, *J. Org. Chem.*, **46**, 4294 (1981) (for hydrocarbons);
(b) J. S. Chickos, D. G. Hesse, J. F. Liebman and S. Y. Panshin, *J. Org. Chem.*, **53**, 3424 (1988) (for 'simple hydrocarbon derivatives');
(c) J. S. Chickos, D. G. Hesse and J. F. Liebman, *J. Org. Chem.*, **54**, 5250 (1989) (for 'organic compounds with ··· multiple substitution').

It should be noted that the only parameters used for hydrocarbons and the carbon 'backbone' of the substituted derivatives are the number of quanternary and nonquanternary carbons.

3. Estimation of heats of fusion: J. S. Chickos, C. M. Braton, D. G. Hesse and J. F. Liebman, *J. Org. Chem.*, **56**, 927 (1991). Actually this paper estimated total entropies of fusion and so the experimentally measured melting point is needed.
4. Estimation of heats of sublimation:
   (a) J. S. Chickos, R. Annunziata, L. H. Ladon, A. S. Hyman and J. F. Liebman, *J. Org. Chem.*, **51**, 4311 (1986) (for hydrocarbons).
   This paper used the estimation approach in Reference 2a along with experimental heats of fusion. We note, of course, that equation 4 can be used to obtain reliable heats of sublimation for most organic compounds with no need for experimental data save the experimental melting point, a method used recently by us in
   (b) J. S. Chickos, D. G. Hesse, S. Y. Panshin, D. W. Rogers, M. Saunders, P. M. Uffer and J. F. Liebman, *J. Org. Chem.*, **57**, 1897 (1992).
   to understand the strain energy of cyclotetradecane.
5. S. W. Benson, *Thermochemical Kinetics*, 2nd edn., Wiley, New York, 1976.
6. For an application to both the gaseous and condensed phase of hydrocarbons, see E. S. Domalski and E. D. Hearing, *J. Phys. Chem. Ref. Data*, **17**, 1637 (1988). This will also be our general source of information on hydrocarbons not found in the archive by Pedley, Naylor and Kirby (Reference 1c).
7. To make this more concrete, albeit not with an oxygen-bearing functionality, consider the heat of formation of gaseous diphenylmethane from which the $C-(C_B)_2(H)_2$ increment is naturally taken. Domalski and Hearing (Reference 6) use the selected value given in Pedley's archive[1c]. However, there is reason to believe that the heat of formation, and so derived increment, is incorrect: a new heat of sublimation of solid diphenylmethane has been recently reported[4] that differs from that chosen in the above by *ca* $10\,kJ\,mol^{-1}$. The new heat of formation results are also in accord with the simple predictions made in this paper, but we remind the reader that we used an experimental measurement of heat of fusion and an estimated heat of vaporization that used nothing more than a count of the number of carbon atoms.
8. The word 'simple' will be defined explicitly at the time these estimates are first used. For reference, the earliest citation that we know to these ether/hydrocarbon comparisons is the thermochemical archive D. R. Stull, E. F. Westrum, Jr. and G. C. Sinke, *The Chemical Thermodynamics of Organic Compounds*, Wiley, New York, 1969, pp. 406–407. It is to be noted that they discussed a very restricted set of ethers and alcohols and so these simple comparisons deserve the current scrutiny we are giving them. We should not be surprised if we are told that there are even earlier references to this approximation. Proper attribution of concepts, as opposed to those of facts, is generally perilous—we know of more recent studies of these interrelations that have completely ignored the source we have cited in this chapter.
9. We do note, however, that carboxylic acid esters are essentially equivalent to acyl ethers from the vantage point of heats of vaporization [J. F. Liebman and J. S. Chickos, *Struct. Chem.*, **1**, 501 (1990)] but manifestly different from the vantage point of heats of formation [cf. the discussion of the resonance energy of esters and amides in J. F. Liebman and A. Greenberg, *Biophys. Chem.*, **1**, 222 (1974)]. Certainly, the reactions of ethers and esters are generally distinct. Relatedly, the reaction chemistry of esters is distinct from that of diacyl ethers, i.e. carboxylic acid anhydrides.
10. This was done with impunity by
    (a) J. F. Liebman and R. M. Pollack for the thermochemistry chapter in *The Chemistry of the Enones* (Eds. S. Patai and Z. Rappoport), Wiley, Chichester, 1989,
    wherein these same enolic β-diketones were identified as enones. By contrast
    (b) J. P. Guthrie, in his thermochemistry chapter in *The Chemistry of Enols* (Ed. Z. Rappoport), Wiley, Chichester, 1990, took a more conservative approach and cited almost no β-diketones in his chapter on the heats of formation of enols. We leave it to the reader to decide for him/herself about the desirability of our decision. We additionally note the chapters by Y. Apeloig and J. Toullec in the latter volume for additional data and insights on general ketone/enol energy discussions.
11. Indeed, we will be making such comparisons in our thermochemical chapter in the forthcoming Supplement S on sulfur-containing species in the present series, wherein we recognize that

sulfenic acids with X = S are a thermochemically interesting but comparatively ignored class of compounds.

12. To simultaneously say that the data are sparse and that the data are extensive may appear to be contradictory. It is not so, because our reading has shown there are no thermochemical data for numerous 'simple' compounds, nor even for some entire groups of related compounds. Yet, if an important goal of presenting a large number of numbers is to encourage both prediction and explanation, it has been our experience that an individual table should not be too large.
13. This brings up the question of nomenclature: how systematic should our names be? We admit to not always following the dictates of either Chemical Abstracts or IUPAC, or being particularly systematic, but have generally accepted the name given by the originator of the data.
14. We are using a modification of the Hill (or Chemical Abstracts) method of writing formulas in which our order of the elements is C, H, O, N and then everything else given alphabetically. This sorting scheme seems highly natural in a volume devoted to oxygen-containing organic compounds wherein nitrogen is a much more common 'hetero-atom' than are the halogens.
15. E. S. Domalski, *J. Phys. Chem. Ref. Data*, **1**, 221 (1972). This is a highly useful archive for the thermochemistry of natural compounds and their semi-synthetic derivatives.
16. For a not unrelated discussion of philately and chemistry, see Z. Rappoport, *Acc. Chem. Res.*, **25**, 24 (1992).
17. (a) S. Wolfe, *Acc. Chem. Res.*, **5**, 102 (1972).
    (b) A. J. Kirby, *The Anomeric Effect and Related Stereochemical Effects at Oxygen*, Springer-Verlag, Berlin, 1983.
    (c) Also see K. Pihlaja, in *Molecular Structure and Energtics: Physical Measurements*, Vol. 2 (Eds. J. F. Liebman and A. Greenberg), VCH, New York, 1987.
18. When we speak of a compound being unsubstituted, we mean that the rest of the compound is some hydrocarbon. This obviates the question of whether methyl 4-methylphenyl ether is substituted—we argue it is no more substituted than is methyl 4-methylpentyl ether. However, both methyl 4-chlorophenyl ether and methyl 4-pyridinyl ether are considered substituted in this chapter.
19. Equivalently, we have not made use of the extensive literature on heats of vaporization that is independent of that on heats of formation. This is because our greatest interest for this chapter is the energetics of molecules, not intermolecular interactions.
20. Our equations were derived by standard linear regression techniques on the available data using weighting factors inversely proportional to the squares of the experimental uncertainty intervals. That the difference of the slopes for the two equations for ΔH_f(l) and for ΔH_f(g) is *not* that for ΔH_v is due to the somewhat different data sets used for the three equations. In that we derived the value of ΔH_v as the difference of the heats of formation of the liquid and gas, we were occasionally thwarted in one equation or another by the absence of thermochemical data in one or another phase. As such, we should not be surprised if the results here differ from some other sources, e.g. from our findings on heats of vaporization in Reference 2.
21. While this has long been known in the thermochemical literature, we recommend the following references: R. L. Montgomery and F. D. Rossini, *J. Chem. Thermodyn.*, **10**, 471 (1977) and P. Sellers, G. Stridh and S. Sunner, *J. Chem. Eng. Data*, **23**, 250 (1978).
22. This conclusion is related to, but not identical to, the observation that the '*b*' value or substituent term for heats of vaporization found for —O— is nearly the same as an additional carbon in Reference 2b. It differs, because in the latter approach no difference of heats of vaporization would have been predicted for the isomeric 4-carbon ethers n-PrOMe, *i*-PrOMe and Et_2O. (For reference, the literature values are 27.8, 26.7 and 27.2 kJ mol^{-1}.)
23. See the text and discussion in J. F. Liebman and A. Greenberg, *Chem. Rev.*, **89**, 1225 (1989).
24. For a thorough experimental and theoretical study of the energetics of vinyl ethers, see N. L. Allinger, J. A. Glaser, H. E. Davis and D. W. Rogers, *J. Org. Chem.*, **46**, 638 (1981). In this paper, the authors report the results from heats of hydrogenation measurements for a collection of vinyl ethers. In that the heat of formation of vinyl isopropyl ether has been reported elsewhere, a measurement of the heat of hydrogenation of this species would give us the desired heat of formation of ethyl isopropyl ether, the archetype of the missing primary/secondary ethers.
25. We remind the reader of another interrelation of divinyl ether and furan that was used to estimate the aromaticity of the latter: J. F. Liebman and R. S. Hosmane, *Tetrahedron Lett.*, **32**, 3049 (1991).

26. The heats of vaporization for both oxygen compounds and cyclopentadiene are from experiment; that for 1,4-pentadiene is derived by use of the two-term estimation approach of Reference 2a. We use this approach because it is conceptually independent of our analysis of ethers and so is less 'prejudiced' than any of our findings presented in this chapter.
27. We are thwarted from obtaining a meaningful value for the heat of formation of liquid vinyl alcohol for various disjoint, but unavoidable, reasons. Although stable in the gas phase, vinyl alcohol immediately tautomerizes in the condensed phase and so it cannot be obtained as the pure liquid. Relatedly, a measured value for the heat of the keto–enol isomerization doesn't particularly help us, since it refers to a highly dilute solution of the enol in acetaldehyde solution. In principle, one can estimate the heat of liquefaction of vinyl alcohol using the estimation approach of Reference 2b, remembering $\Delta H_v \equiv -\Delta H_{liqn}$, but experience has shown that all of the estimation approaches in References 2–4 are least reliable when applied to compounds with few carbon atoms.
28. (a) J. F. Liebman, in *Molecular Structure and Energetics: Studies of Organic Molecules*, Vol. 3 (Eds. J. F. Liebman and A. Greenberg), VCH, Deerfield Beach, 1986.
(b) P. George, C. W. Bock and M. Trachtman, in *Molecular Structure and Energetics: Biophysical Aspects*, Vol. 4 (Eds. J. F. Liebman and A. Greenberg) VCH, New York, 1987.
29. This may be understood simultaneously in terms of the various n-alkanes being alternatively understood as n-alkyl hydrides, in which case the 'new' assertion follows from the old. Alternatively, one may do a Perturbation Molecular Orbital (PMO) analysis of saturated hydrocarbons in which it may be shown that methane logically—and thermochemically consistently—may be considered a 2-methylalkane [M. J. S. Dewar, in *Modern Models of Bonding and Delocalization* (Eds. J. F. Liebman and A. Greenberg), VCH, New York, 1988].
30. K. B. Wiberg and R. R. Squires, *J. Am. Chem. Soc.*, **101**, 5512 (1979), concluded that most chemical intuition on acetals ultimately relates less to heats of formation than to their Gibbs energies, i.e. entropy considerations cannot be ignored either quantitatively or qualitatively.
31. How large is large enough? This requires more thermochemical data than are available. We do note, however, that Reference 4 showed that cyclotetradecane is nearly strainless and so mimics cyclohexane and the acyclic n-alkanes as opposed to earlier literature studies that suggested a value of *ca* 40 kJ mol^{-1}.
32. (a) Diene hydrogenation, J. L. Jensen, *Prog. Phys. Org. Chem.*, **12**, 189 (1977).
(b) Diene hydration, J. L. Jensen and V. Uaprasert, *J. Org. Chem.*, **41**, 649 (1976).
(c) Benzocycloalkenone acidity, S. Eldin, R. M. Pollack and D. L. Whalen, *J. Am. Chem. Soc.*, **113**, 1344 (1991).
33. We now inquire how much the apparent lack of obvious pattern in the results of Table 3 is exacerbated because the $n_r = 5$ case is conceptually ambiguous—i.e., simultaneously, there is stabilization of 1,3-dioxolane because the two oxygens are in a 1,3-relation and destabilization because these oxygens are also 1,4-relative to each other.
34. See J. F. Liebman, in *The Cyclophanes* (Eds. P. M. Keehn and S. M. Rosenfeld), Academic Press, New York, 1983. We recognize both this benzo-annelation relation and the phenyl-vinyl thermochemical equivalence (Reference 28) as examples of a 'constant' heat of formation difference of *o*-C_6H_4XY and (*Z*)-XCH=CHY; the former relation applies wherein X and Y are joined together to form a ring and the latter where Y = H. We should expect this new comparison of *o*-phenylene and vinylene derivatives to be least valid when X and Y are 'too close' because the ring is small or X and Y are too large. (Remember the relevant, read unstrained, carbon–carbon bond distance is *ca* 1.33 Å in olefins and *ca* 1.40 Å in substituted benzenes.)
35. G. M. Anderson III, P. A. Kollman, L. N. Domelsmith and K. N. Houk, *J. Am. Chem. Soc.*, **101**, 2344 (1979).
36. See the extensive discussion by D. J. Creighton and N. S. R. K. Murthy in *The Enzymes*, **19**, 323 (1990). We concur with these authors that the formation of (*Z*)-enediolates is no doubt assisted by metallic cation stabilization. However, the predilection of enediols in any charge state to have the (*Z*)-structure is precedented by the relative, and likewise surprising, stabilities of the isoelectronic 1,2-difluoroethylenes. See the discussion by B. E. Smart, in *Molecular Structure and Energetics: Studies of Organic Molecules*, Vol. 3 (Eds. J. F. Liebman and A. Greenberg), VCH, Deerfield Beach, 1986.
37. See J. F. Liebman and D. Van Vechten, in *Molecular Structure and Energetics: Physical Measurements*, Vol. 2 (Eds. J. F. Liebman and A. Greenberg), VCH, New York, 1987.

38. Clearly from the vantage point of the $1,4,7,\ldots,3n+1$ polyoxacycloalkane, the two groups $-CH_2-CH_2-O-$ and $-CH_2-O-CH_2-$ are indistinguishable. Yet asking for preference in an admittedly not very random poll, we obtained the following replies:
(a) From a physical organic chemist, '$-CH_2-CH_2-O-$ because it looks more like $-CH_2-O-$'.
(b) From a physicist/materials scientist, '$-CH_2-O-CH_2-$ because it looks more symmetric'.
(c) From a synthetic organic chemist, '$-CH_2-O-CH_2-$ because it shows crown ethers can bind cations'.
(d) From a theoretical chemist, '$-CH_2-CH_2-O-$ because oxiranes usually open by C—O and not C—C bond cleavage'.
39. The heat of formation of each group was obtained by averaging the heats of formation, per group, of the species composed solely of that group. Had we taken weighted averages determined by the number of groups in each compound, the discrepancy would have been larger for 1,3-dioxolane and smaller for 1,3,6-trioxocane.
40. (a) K. B. Wiberg and D. J. Wasserman, *J. Am. Chem. Soc.*, **103**, 6563 (1981).
(b) K. B. Wiberg, D. J. Wasserman and E. Martin, *J. Phys. Chem.*, **88**, 3684 (1984).
(c) K. B. Wiberg, D. J. Wasserman, E. J. Martin and M. M. Murchko, *J. Am. Chem. Soc.*, **107**, 6019 (1985).
(d) K. B. Wiberg, in *Molecular Structure and Energetics: Physical Measurements*, Vol. 2 (Eds. J. F. Liebman and A. Greenberg), VCH, New York, 1987.
(e) K. B. Wiberg and S. Hao, *J. Org. Chem.*, **56**, 5108 (1991).
41. See Reference 8, pp. 407–408.
42. For an electronegativity parameterized equation unifying these findings and those of other alkyl derivatives, see Y.-R. Luo and P. D. Pacey, *J. Phys. Chem.*, **93**, 9470 (1991).
43. J. D. Cox and G. Pilcher, *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, London and New York, 1970, pp. 518 ff.
44. A. Greenberg and T. A. Stevenson, in *Molecular Structure and Energetics: Studies of Organic Molecules*, Vol. 3 (Eds. J. F. Liebman and A. Greenberg), VCH, Deerfield Beach, 1986.
45. K. B. Wiberg and R. F. Waldron, *J. Am. Chem. Soc.*, **113**, 7697 (1991).
46. To prevent biasing the calculation for the longer chains, we took the heats of formation of the pentane–pentaol and hexane–hexaol to be the average of the two polyols in each case. This should not result in a particularly egregious error, because in the former case the heats of formation differed by 6 kJ mol^{-1} while in the latter case they differed by 7 kJ mol^{-1}. Nonetheless, we recognize that using but two polyols apiece for these two cases involves a rather small subset of the total number of stereoisomers of each type.
47. We cannot, however, resist noting that phenols may also be considered tertiary alcohols because both classes of compounds have the hydroxy-bearing carbon bonded to no hydrogens and by three bonds to other carbons. Perhaps the near equality of methyl/—OH stabilization energies is not completely fortuitous.
48. The recent volume *The Chemistry of Enols* (Ed. Z. Rappoport), Wiley, Chicester, 1990 documents the seeming maturity of the experimental and theoretical study of enols.
49. F. Turecek and Z. Havlas, *J. Org. Chem.*, **51**, 4066 (1986).
50. P. I. Abell and P. K. Adolf, *J. Chem. Thermodyn.*, **1**, 333 (1969).
51. (a) W. v. E. Doering and T. Kitagawa, *J. Am. Chem. Soc.*, **113**, 4288 (1991).
(b) W. v. E. Doering, L. Birladeanu, X.-h. Cheng, T. Kitagawa and K. Sarma, *J. Am. Chem. Soc.*, **113**, 4558 (1991).
(c) W. Fang and D. W. Rogers, *Org. Chem.*, in press.
52. The heat of vaporization, obtained using the estimation approach in Reference 2b, may well be an underestimate by a few kJ mol^{-1} by analogy to the analogous α,β-unsaturated carbonyl compound. (*E*)-2-Butenal has a heat of vaporization some 3 kJ mol^{-1} higher than its saturated analog, n-butanal. On the other hand, it may well be an overestimate by a few kJ mol^{-1} by analogy to the difference of the saturated unbranched and branched isomers 2-hexanone and 2-methyl-3-pentanone.
53. J. F. Liebman, *Struct. Chem.*, in press.
54. For the following we implicitly make use of the earlier enunciated thermochemical similarities of PhX and ViX (Reference 28). In particular, we considered the reactions PhH + RCHO →

PhC(O)R + H_2 for R = H, Me, Et and Pr. These reactions are exothermic by 10.7, 3.2, 5.7 and 6.0 kJ mol^{-1}. This is a reasonably large spread of values, and thus suggests further investigation into the energetics of all of these coupling reactions since no explanation for the results of Reference 53 was offered in the original paper.

55. J. F. Liebman and D. W. Rogers, Rogers, unpublished results.
56. Y. Y. Van-Chin-Cyan and N. S. Kachurina, *Russ J. Phys. Chem.*, **59**, 227 (1985).
57. Occasionally one can 'decide' relative reliabilities of results by comparing the usual accuracy of the various experimental techniques or even of the various experimentalists. We are thwarted in doing so here because the hexyl and heptyl results are from the same paper, namely W. Pritzkow and K. A. Muller, *Chem. Ber.*, **89**, 2318 (1956).
58. We naturally expect that δ_{51} will be larger for liquids because the alcohol product of the hydrogenolysis strongly hydrogen-bonds while the peroxide reactant does not. The difference of the two phases, 29 kJ (mol-ROH)$^{-1}$, seems high when calibrated against the customarily-believed hydrogen bond strength of *ca* 20 kJ mol^{-1} such as found in water.
59. The heat of formation of gaseous H_2O_2 is not found in any of the thermochemical archives we have so far cited in this chapter. We obtained this desired value from the classic inorganic thermochemistry archive by D. D. Wagman, W. H. Evans, V. B. Parker, R. H. Schumm, I. Halow, S. M. Bailey, K. L. Churney and R. L. Nuttall, 'The NBS Tables of Chemical Thermodynamic Properties: Selected Values for Inorganic and C_1 and C_2 Organic Substances in SI Units', *J. Phys. Chem. Ref. Data*, **11** (1982), Suppl. 2.

IX. APPENDIX: ORGANIZATION OF THE DATA

The tables of heats of formation for ethers, alcohols, arenols, enols and peroxides are presented here in the same order in which they are discussed in the text. A 'List of Appendices' is included below as a guide.

The compounds are generally listed by increasing numbers of C, H, O, N and the halogens. Each compound has been named in accord with the author(s) nomenclature preferences rather than with truly consistent, systematic (CA or IUPAC) names, although we often give synonyms. In those cases where we consider the compound name ambiguous, we adopt uncritically the original name.

Each heat of formation is referenced to a literature source, either an archival secondary source or its primary citation, or to a brief discription of how we derived the data from other literature sources and a suitable heat of reaction and/or phase change.

Finally, we follow the official thermochemical convention of presenting all energies in kJ mol^{-1} where 4.184 kJ mol^{-1} = 1 kcal mol^{-1}. When the literature heat of formation values were given in kcal mol^{-1} with no accompanying error bars, we converted them to integral values of kJ mol^{-1}.

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APPENDIX A1. Heats of formation of unsubstituted acyclic monoethers (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
C_2H_6O	Dimethyl ether							−184.1	0.5	*a*
C_3H_8O	Methyl ethyl ether							−216.4	0.7	*a*
$C_4H_{10}O$	Diethyl ether				−279.3	0.8	*a*	−252.1	0.8	*a*
$C_4H_{10}O$	Methyl isopropyl ether				−278.7	1.0	*a*	−252.0	1.0	*a*
$C_4H_{10}O$	Methyl propyl ether				−266.0	0.7	*a*	−238.2	0.7	*a*
$C_5H_{12}O$	Ethyl propyl ether				−303.6	1.1	*a*	−272.2	1.1	*a*
$C_5H_{12}O$	Methyl n-butyl ether				−290.6	1.2	*a*	−258.1	1.2	*a*
$C_5H_{12}O$	Methyl *t*-butyl ether				−313.6	1.1	*a*	−283.5	1.1	*a*
$C_6H_{14}O$	Di-n-propyl ether				−328.8	0.9	*a*	−292.9	1.1	*a*
$C_6H_{14}O$	Diisopropyl ether				−351.5	1.4	*a*	−319.2	1.6	*a*
$C_6H_{14}O$	Methyl *t*-amyl ether (2-ethyl-2-methoxypropane)				−340.1	0.8	*b*	−305.4	1.8	*b*
$C_7H_{16}O$	Isopropyl *t*-butyl ether				−392.8	3.0	*a*	−357.6	5.1	*a*
$C_8H_{18}O$	Di-n-butyl ether				−377.9	1.3	*a*	−333.4	1.4	*a*
$C_8H_{18}O$	Di-*sec*-butyl ether				−401.5	1.1	*a*	−360.9	1.7	*a*
$C_8H_{18}O$	Di-*t*-butyl ether				−399.6	1.2	*a*	−362.0	1.2	*a*
$C_8H_{18}O$	Isobutyl *t*-butyl ether				−409.1	1.6	*c*	−369.0	1.6	*c*
$C_8H_{18}O$	n-Butyl *t*-butyl ether				−403.3	1.9	*c*	−361.0	1.9	*c*
$C_8H_{18}O$	*sec*-Butyl *t*-butyl ether				−420.3	1.8	*c*	−380.0	1.8	*c*
$C_{11}H_{24}O$	Methyl decyl ether				−443.4	1.5	*a*	−381.1	1.6	*a*
$C_{28}H_{48}O$	6β-Methoxy-3,5-cyclocholestane	−628.0	5.5	*a*						

[a]Reference 1c.
[b]A. M. Rozhnov, V. V. Safronov, S. P. Verevkin, K. G. Sharonov and V. I. Alevin, *J. Chem. Thermodyn.*, **23**, 629 (1991).
[c]K. G. Sharonov, Y. B. Mishentsiva, A. M. Rozhnov, E. A. Miroshnichenko and L. I. Korchatova, *J. Chem. Thermodyn.*, **23**, 637 (1991).

APPENDIX A2. Heats of formation of unsubstituted aryl, vinyl and other unsaturated monoethers (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
C_4H_4O	Divinyl ether (2)				−39.8	1.3	*a*	−13.6	1.0	*a*
C_4H_4O	Furan [5-oxa-1,3-cyclopentadiene]				−62.3	0.7	*a*	−34.9	0.7	*a*
C_4H_6O	2,3-Dihydrofuran [3-oxacyclopentene]				−109.1	2.7	*b*	−77.1	2.7	*b*
C_4H_6O	2,5-Dihydrofuran [4-oxacyclopentene]				−99.0	2.6	*b*	−67.0	2.6	*b*
C_4H_6O	Methyl 1-propynyl ether [methyl propargyl ether]				45.4	1.3	*c*	78.2	1.3	*c*
C_4H_6O	Methyl 2-propynyl ether							82.0		*d*
C_4H_8O	Ethyl vinyl ether				−167.4	1.5	*a*	−140.8	0.9	*a*
C_4H_8O	Methyl 2-propenyl ether				−177.3	0.9	*a*			
C_5H_8O	2-Methyl-4,5-dihydrofuran [2-methyl-3-oxacyclopentene]				−165.0	2.3	*e*	−130.2	3.5	*e*
C_5H_8O	Dihydro-2*H*-pyran [3-oxacyclohexene]				−157.4	1.3	*a*	−125.1	1.5	*a*
C_5H_8O	Ethyl 1-propynyl ether [ethyl propargyl ether]				10.1	1.3	*c*	46.3	1.3	*c*
$C_5H_{10}O$	Isopropyl vinyl ether				−205.1	0.9	*a*	−173.8	2.3	*a*
$C_5H_{10}O$	n-Propyl vinyl ether				−190.9	0.9	*a*	−161.6	2.3	*a*
C_6H_6O	2-Vinyl furan				−10.3	3.3	*a*	27.8	3.6	*a*
$C_6H_{10}O$	1-Methoxycyclopentene				−167.8	2.0	*a*			
$C_6H_{10}O$	Diallyl ether [4-oxa-1,6-heptadiene]							3.0		*d*
$C_6H_{12}O$	Isobutyl vinyl ether				−268		*d*			
$C_6H_{12}O$	n-Butyl vinyl ether				−218.8	0.9	*a*	−184.5	2.7	*a*
C_7H_8O	Methyl phenyl ether [anisole]				−114.8	0.8	*a*	−67.9	0.9	*a*
$C_7H_{14}O$	Isopentyl vinyl ether				−277		*d*			

(*continued*)

APPENDIX A2. *(continued)*

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
C_8H_8O	Phenyl vinyl ether				−26.2	0.9	*a*	22.7	1.9	*a*
$C_8H_{10}O$	Ethyl phenyl ether [phenetol]				−152.6	0.6	*a*	−101.6	0.6	*a*
$C_8H_{10}O$	Methyl 3-methylphenyl ether [*m*-tolyl methyl ether]				−155.6	4.6	*a*	−104.1	4.9	*a*
C_9H_8O	Indene oxide [6,6*a*-dihydro1*A*-oxireno(*A*)indene]				−8.0		*f*			
$C_9H_{10}O$	2,3-Benzodihydropyran [chroman]				−139.1	1.2	*g*	−82.4	1.2	*g*
$C_9H_{10}O$	3,4-Benzodihydropyran [isochroman]				−120.2	1.1	*g*	−43.1	1.0	*g*
$C_9H_{12}O$	Ethyl 4-methylphenyl ether [*p*-tolyl ethyl ether]				−178		*d*			
$C_9H_{12}O$	*m*-Xylenol methyl ether				−173		*d*			
$C_9H_{12}O$	Propyl phenyl ether				−177		*d*			
$C_{10}H_8O$	1,4-Dihydro-1,4-epoxynaphthalene	62.1	5.7	*a*						
$C_{10}H_8O$	1,6-Oxido[10]annulene (**1a**)	110.5	5.1	*a*	139.1	5.1	*a*	199.9	9.8	*a*
$C_{10}H_{12}O$	Ethyl 1-phenylvinyl ether				−139		*d*			
$C_{10}H_{12}O$	Methyl 4-(1-propenyl)phenyl ether	−104		*d*						
$C_{10}H_{12}O$	Methyl 4-(2-propenyl)phenyl ether [*p*-allyl anisole]				−61		*d*			
$C_{10}H_{14}O$	*p*-Xylenol ethyl ether				−205		*d*			
$C_{11}H_{10}O$	Methyl 2-naphthyl ether	−97.9	1.2	*a*						
$C_{11}H_{14}O$	1,1-Dimethyl-4-pentene-2-yn-1-yl butyl ether				−62.4	1.7	*h*	−6.7	1.4	*h*

$C_{11}H_{16}O$	Methyl 2-isopropyl-5-methylphenyl ether				−232		*d*			
$C_{12}H_8O$	Dibenzofuran	−5.3	4.2	*a*				83.4	4.7	*a*
$C_{12}H_{10}O$	Diphenyl ether	−32.1	1.5	*a*	−14.9	1.5	*a*	52.0	1.5	*a*
$C_{12}H_{12}O$	Ethyl 2-naphthyl ether	−134.0	1.3	*a*						
$C_{12}H_{18}O$	Ethyl 1-isopropyl-5-methylphenyl ether				−259		*d*			
$C_{13}H_{10}O$	Dibenzopyran	−63.8	3.8	*a*				48.4	4.4	*a*
$C_{15}H_{14}O$	2,3,4-Trimethylindene[2,1-*b*]pyran	−137.5	7.9	*a*				2.2	8.3	*a*
$C_{16}H_{10}O$	Benz[*b*]indeno[1,2-*e*]pyran	70.3	7.9	*a*				199.7	8.1	*a*
$C_{18}H_{12}O$	6-Phenyl-2,3-benzoxalene	128.0	8.8	*a*				270.5	8.9	*a*
$C_{22}H_{18}O$	Methyl 1,1,3-triphenyl-2-propynyl ether	235		*d*						
$C_{23}H_{20}O$	Ethyl 1,1,3-triphenyl-2-propynyl ether	192		*d*						
$C_{24}H_{22}O$	Propyl 1,1,3-triphenyl-2-propynyl ether	166		*d*						
$C_{28}H_{48}O$	3β-Methoxycholest-5-ene	−652.8	5.1	*a*						

[a]Reference 1c.
[b]Reference 24. We combined their heat of hydrogenation with the heat of formation of the hydrogenated product to derive these numbers.
[c]Ph.D. thesis of John H. Hallman, May 1986, with Richard Fuchs, University of Houston, obtained by heats of hydrogenation with corrections of heats of solution, dilution, adsorption and vaporization explicitly considered (personal communication, Richard Fuchs).
[d]Reference 8.
[e]K. Pihlaja and J. Heikkila, *Suomen Kemishlekh*, **B42**, 338 (1969).
[f]Reference 23.
[g]R. D. Chirico, D. G. Archer, I. A. Hossenlopp, A. Nguyen, W. V. Steele and B. E. Gammon, *J. Chem. Thermodyn.*, **22**, 665 (1990).
[h]Y. Y. Van-Chin-Syan, T. N. Dolbneva, V. P. Vasil'ev, S. K. Chuchmarev and V. A. Prichin, *Russ. J. Phys. Chem.*, **56**, 1736 (1982).

APPENDIX A3. Heats of formation of unsubstituted cyclic monoethers (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
C_2H_4O	Oxirane [oxacyclopropane] [ethylene oxide]				−77.6	0.6	*a*	−52.6	0.6	*a*
C_3H_6O	Methyloxirane				−122.6	0.6	*a*	−94.7	0.6	*a*
C_3H_6O	Oxetane [oxacyclobutane]							−80.5	0.6	*b*
C_4H_4O	Furan [5-oxa-1,3-cyclopentadiene]				−62.3	0.7	*b*	−34.9	0.7	*b*
C_4H_6O	2,3-Dihydrofuran [3-oxacyclopentene]				−109.1	2.7	*c*	−77.1	2.7	*c*
C_4H_6O	2,5-Dihydrofuran [4-oxacyclopentene]				−99.0	2.6	*c*	−67.0	2.6	*c*
C_4H_8O	Ethyloxirane				−168.9	2.6	*a*			
C_4H_8O	Tetrahydrofuran [oxacyclopentane]				−216.2	0.8	*b*	−184.2	0.8	*b*
C_5H_8O	2-Methyl-4,5-dihydrofuran [2-methyl-3-oxacyclopentene]				−165.0	2.3	*d*	−130.2	3.5	*d*
C_5H_8O	6-Oxabicyclo[3.1.0]hexane				−130.8	6.4	*a*	−97.1	7.0	*a*
C_5H_8O	Dihydro-2*H*-pyran [3-oxacyclohexene]				−157.4	1.3	*b*	−125.1	1.5	*b*
$C_5H_{10}O$	2,2,3-Trimethyloxirane				−257.0		*a*			
$C_5H_{10}O$	3,3-Dimethyloxetane				−182.2	1.6	*b*	−148.2	1.7	*b*
$C_5H_{10}O$	Tetrahydropyran [oxacyclohexane]				−258.3	1.3	*b*	−223.4	1.0	*b*
C_6H_6O	2-Vinyl furan				−10.3	3.3	*b*	27.8	3.6	*b*
$C_6H_{10}O$	7-Oxabicyclo[2.2.1]heptane				−223.9	1.6	*b*			
$C_6H_{10}O$	7-Oxabicyclo[4.1.0]heptane, *cis*				−166.0	1.1	*a*	−125.5	1.1	*a*
$C_6H_{12}O$	2,2-Diethyloxirane				−249		*e*			
$C_6H_{12}O$	2,3-Diethyloxirane				−249		*e*			
$C_6H_{12}O$	2-Butyloxirane				−258		*e*			
$C_7H_{10}O$	3-Oxatricyclo[3.2.1.0(2,4)]octane [*exo*-norbornene oxide]	−98.0	2.5	*f*				−53.9	2.6	*f*

$C_7H_{10}O$	8-Oxatricyclo[3.2.1.0(1,5)]octane				−9.5	1.0	*b*	26.9	1.6	*b*
$C_7H_{12}O$	2-Methyl-7-oxabicyclo[2.2.1]-heptane, *endo*				−250.3	1.6	*b*			
$C_7H_{12}O$	2-Methyl-7-oxabicyclo[2.2.1]-heptane, *exo*				−253.8	1.7	*b*			
$C_7H_{12}O$	8-Oxabicyclo[5.1.0]octane, *cis*				−197.5	3.1	*a*	−152.3	3.1	*a*
$C_7H_{14}O$	2,2-Diethyloxetane				−320		*e*			
$C_7H_{14}O$	2,2-Dimethyl-3-propyloxirane				−297		*e*			
$C_8H_{14}O$	3-Oxabicyclo[3.2.2]nonane	−275.6	0.9	*b*				−222.5	1.1	*b*
$C_8H_{14}O$	9-Oxabicyclo[6.1.0]nonane, *cis*	−212.5	2.1	*a*				−165.1	2.4	*a*
C_9H_8O	Indene oxide [6,6α-Dihydro-1*A*-oxireno(*A*)indene]				−8.0		*a*			
$C_9H_{10}O$	2,3-Benzodihydropyran [chroman]				−139.1	1.2	*g*	−82.4	1.2	*g*
$C_9H_{10}O$	3,4-Benzodihydropyran [isochroman]				−120.2	1.1	*g*	−43.1	1.1	*g*
$C_{10}H_8O$	1,4-Dihydro-1,4-epoxynaphthalene	62.1	5.7	*b*						
$C_{10}H_8O$	1,6-Oxido[10]annulene (**1a**)	110.5	5.1	*b*	139.1	5.1	*b*	199.9	9.8	*b*
$C_{10}H_{16}O$	1,4,4-Trimethyl-*anti*-8-oxatricyclo-[5.1.0.0(3,5)]octane				−156.5	1.5	*a*	−106.9		*a*
$C_{10}H_{16}O$	1,4,4-Trimethyl-*syn*-8-oxatricyclo-[5.1.0.0(3,5)]octane				−148.0	1.6	*a*	−97.8		*a*
$C_{12}H_8O$	Dibenzofuran	−5.3	4.2	*b*				83.4	4.7	*b*
$C_{13}H_{10}O$	Dibenzopyran	−63.8	3.8	*b*				48.4	4.4	*b*
$C_{15}H_{14}O$	2,3,4-Trimethylindeno[2,1-*b*]pyran	−137.5	7.9	*b*				2.2	8.3	*b*
$C_{16}H_{10}O$	Benz[*b*]indeno[1,2-*e*]pyran	70.3	7.9	*b*				199.7	8.1	*b*
$C_{18}H_{12}O$	6-Phenyl-2,3-benzoxalene	128.0	8.8	*b*				270.5	8.9	*b*

[a]Reference 23.
[b]Reference 1c.
[c]Reference 24. We combined their heat of hydrogenation with the heat of formation of the hydrogenated product to derive these so-cited numbers.
[d]K. Pihlaja and J. Heikkila, *Suomen Kemishlekh*, **B42**, 338 (1969).
[e]Reference 8.
[f]M. P. Kozina, I. P. Timofeeva, V. A. Luk'yanova, S. M. Pimenova and L. I. Kas'yan, *Russ. J. Phys. Chem.*, **62**, 609 (1988).
[g]R. D. Chirico, D. G. Archer, I. A. Hossenlopp, A. Nguyen, W. V. Steele and B. E. Gammon, *J. Chem. Thermodyn.*, **22**, 665 (1990).

APPENDIX A4. Heats of formation of monoethers with oxygen functional groups (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_3H_6O_2$	2,3-Epoxy-1-propanol [oxiranyl methanol; glycidyl alcohol]				−298.2	0.9	*a*			
$C_3H_8O_2$	2-Methoxyethanol				−422.0	7.6	*b*	−376.9	8.1	*b*
$C_4H_8O_3$	Ethoxyacetic acid				−648.4	0.5	*c*			
$C_4H_{10}O_3$	2,2′-Dihydroxy diethyl ether [diethylene glycol]				−628.5	2.4	*a*	−572.3	6.3	*a*
$C_5H_4O_2$	Furfural				−201.6	4.6	*a*	−151.0	4.6	*a*
$C_5H_4O_3$	2-Furancarboxylic acid	−498.4	1.1	*a*				−389.9	2.3	*a*
$C_5H_6O_2$	2-Furyl methanol [furfuryl alcohol]				−276.2	1.3	*a*	−211.8	2.1	*a*
$C_5H_{10}O_2$	2-Tetrahydrofuryl methanol [tetrahydrofurfuryl alcohol]				−435.7	5.9	*a*	−369.2	6.2	*a*
$C_5H_{12}O_4$	2-(2-Hydroxyethoxy)-1,2-propanediol				−865		*d*			
$C_5H_{12}O_4$	3-(2-Hydroxyethoxy)-1,2-propanediol				−863.4	5.0	*a*			
$C_6H_6O_3$	Methyl α-furoate				−450.0	0.5	*a*	−404.8	1.0	*a*
$C_6H_{10}O_2$	Acetylacetone *O*-methyl ether				−366		*d*			
$C_6H_{10}O_5$	1,2-Anhydro-3,4,5,6-cyclohexanetetraol [cyclohexene oxide 3,4,5,6-tetraol]	−906.2	1.7	*a*						
$C_6H_{12}O_2$	1-Ethoxy-2-butanone				−410.0	0.7	*c*			
$C_6H_{12}O_3$	Ethoxymethyl propionate				−667.2	0.8	*a*	−627.3	0.8	*a*
$C_6H_{12}O_3$	Ethyl ethoxyacetate				−639.5	0.6	*c*			
$C_7H_6O_2$	3-(2-Furyl)propenal [3-(2-furyl)acrolein]	−182.0	0.9	*a*				−105.9	2.3	*a*
$C_7H_6O_3$	3-(2-Furyl)propenoic acid [3-(2-furyl)acrylic acid]	−459.0	6.3	*a*						

$C_7H_8O_3$	3-Methoxybenzene-1,2-diol [3-methoxycatechol]	−510.2	1.2	*e*				−418.5	1.4	*e*
$C_7H_{10}O_2$	1-(2-Furyl)propan-1-ol				−447.0	7.1	*a*			
$C_7H_{10}O_3$	1-(2,3-Epoxy)propyl methylpropenoate (glycidyl *methacrylate*)				−454.4	2.6	*f*	−394.2	2.7	*f*
$C_7H_{12}O_2$	acetylacetone *O*-ethyl ether				−416		*d*			
$C_7H_{12}O_3$	1-(2,3-Epoxy)propyl butanoate [glycidyl butyrate]				−560.4	2.7	*f*	−501.7	2.6	*f*
$C_7H_{12}O_3$	Ethyl 2-ethoxypropenoate [ethyl 2-ethoxyacrylate]	−592		*d*						
$C_7H_{12}O_3$	Ethyl 3-ethoxypropenoate [ethyl 3-ethoxyacrylate]				−603		*d*			
$C_8H_8O_2$	2-Methoxybenzaldehyde	−266.4	7.5	*a*						
$C_8H_8O_2$	3-Methoxybenzaldehyde				−276.0	7.5	*a*			
$C_8H_8O_2$	4-(2-Furyl)-3-buten-2-one	−240.2	1.6	*a*						
$C_8H_8O_2$	4-Methoxybenzaldehyde				−267.2	5.0	*a*	−202.7	5.4	*a*
$C_8H_8O_3$	2-Methoxybenzoic acid	−538.5	0.7	*a*				−433.8	0.8	*a*
$C_8H_8O_3$	3-Methoxybenzoic acid	−553.5	0.7	*a*				−446.1	0.8	*a*
$C_8H_8O_3$	4-Methoxybenzoic acid	−561.7	0.8	*a*				−451.9	1.0	*a*
$C_8H_8O_3$	Phenoxyacetic acid	−514		*g*						
$C_8H_{14}O_3$	Ethyl 3-ethoxy-2-butenoate				−647.0	2.1	*a*			
$C_8H_{18}O_4$	1-(*t*-Butylperoxy)-3-methoxy-2-propanol				−666.3	2.6	*a*			
$C_9H_6O_2$	2,3-Benzo-4-pyrone [*chromone*]	−229.8	2.9	*h*				−148.5	2.9	*h*
$C_9H_{10}O_5$	2-(Diacetoxymethyl)furan	−882.1	0.6	*a*				−772.5	2.6	*a*
$C_9H_{18}O_6$	4-Hydroxy-tetrahydropyran-3,3,5,5-tetramethanol	−1267.7	5.0	*a*						

(*continued*)

APPENDIX A4. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_9H_{20}O_4$	1-(*t*-Butylperoxy)-3-ethoxy-2-propanol				−706.7	3.0	*a*			
$C_{10}H_{10}O_3$	3-(4-Methoxyphenyl)propenoic acid, *cis*, allo [methoxycinnamic acid]	−451		*d*						
$C_{10}H_{10}O_3$	Methoxycinnamic acid, *cis*, *ortho*	−472		*d*						
$C_{10}H_{10}O_3$	Methoxycinnamic acid, *trans*, *ortho*	−498		*d*						
$C_{10}H_{10}O_3$	Methoxycinnamic acid, *trans*, *para*	−490		*d*						
$C_{10}H_{12}O_2$	2-Methoxy-4-(1-propenyl)phenol				−300		*d*			
$C_{10}H_{12}O_2$	2-Methoxy-4-(2-propenyl)phenol				−263		*d*			
$C_{10}H_{16}O_3$	Octahydronaphthalene ozonide	−594		*d*						
$C_{10}H_{22}O_4$	1-(*t*-Butylperoxy)-3-propoxy-2-propanol				−725.0	3.0	*a*			
$C_{10}H_{22}O_7$	2,2′-(Oxybismethylene)-bis-(hydroxymethyl)-1,3-propanediol [dipentaerythritol]	−1572.3	7.8	*a*						
$C_{11}H_{12}O_3$	Ethoxycinnamic acid, *cis*, *ortho*				−499		*d*			
$C_{11}H_{12}O_3$	Ethoxycinnamic acid, *trans*, *ortho*				−529		*d*			
$C_{11}H_{24}O_4$	1-Butoxy-3-(*t*-butylperoxy)-2-propanol				−747.0	3.0	*a*			
$C_{12}H_{14}O_3$	2-Methoxy-4-(2-propenyl)phenyl acetate	−451		*d*						
$C_{12}H_{14}O_3$	2-Methoxy-4-propenylphenyl acetate	−491		*d*						
$C_{12}H_{14}O_3$	Propoxycinnamic acid, *cis*, *ortho*				−457		*d*			
$C_{12}H_{14}O_3$	Propoxycinnamic acid, *trans*, *ortho*				−477		*d*			
$C_{12}H_{20}O_3$	2,5-Dimethyl-5-*t*-butylperoxy-3-hexyn-2-ol				−636.0	3.3	*i*	−561.8	3.8	*i*

$C_{12}H_{26}O_4$	1-(*t*-Butylperoxy)-3-pentoxy-2-propanol				−771.2	4.6	*a*			
$C_{13}H_8O_2$	Dibenzo-4-pyrone [xanthone]	−196.8	3.6	*h*				−98.2	3.6	*h*
$C_{13}H_{16}O_3$	Butoxycinnamic acid, *cis, ortho*	−541		*d*						
$C_{13}H_{16}O_3$	Butoxycinnamic acid, *trans, ortho*	−568		*d*						
$C_{14}H_{12}O_3$	3,5-Diphenyl-1,2,4-trioxolane	−123.8	12.6	*a*						
$C_{14}H_{12}O_4$	Methoxyphenyl salicylate, *ortho*	−567		*d*						
$C_{14}H_{18}O_3$	Isopentyloxycinnamic acid, *cis, ortho*	−574		*d*						
$C_{14}H_{18}O_3$	Isopentyloxycinnamic acid, *trans, ortho*	−580		*d*						
$C_{16}H_{20}O_3$	Desmotroposantonin methyl ether, (−) α-	−655.8	2.3	*a*						
$C_{16}H_{20}O_3$	Desmotroposantonin methyl ether, (+) β-	−668.2	2.2	*a*						
$C_{17}H_{16}O_2$	1,3-Diphenyl-3-ethoxy-2-propen-1-one, *trans* [β-ethoxychalcone]	−190.4	1.8	*a*						
$C_{17}H_{16}O_3$	2-Methoxy-4-propenylphenyl benzoate	−371		*d*						
$C_{17}H_{16}O_3$	4-Allyl-2-methoxyphenyl benzoate	−333		*d*						
$C_{17}H_{16}O_3$	β-Tolylmethoxycinnamic acid, labile	−429		*d*						
$C_{17}H_{16}O_3$	β-Tolylmethoxycinnamic acid, stable	−446		*d*						

[a]Reference 1c.
[b]J. P. Guthrie, *Can. J. Chem.*, **55**, 3562 (1977).
[c]N. M. Gutner, N. D. Lebedeva, S. L. Dobychin and N. N. Prikeleva, *J. Appl. Chem. USSR*, **53**, 1523 (1980).
[d]Reference 8.
[e]M. D. M. C. Ribeiro da Silva, M. A. V. Ribeiro da Silva and G. Pilcher, *J. Chem. Thermodyn.*, **18**, 295 (1986).
[f]Y. Y. Van-Chin-Syan and N. S. Kachurina, *Russ. J. Phys. Chem.*, **61**, 622 (1987).
[g]Reference 15.
[h]R. Sabbah and L. El Watik, *Bull. Soc. Chim. Fr.*, 626 (1988). These authors also presented the heats of fusion of chromone and xanthone at their triple points—17.3 ± 0.2 (330.3 K) and 26.1 ± 0.2 (449.6 K), respectively.
[i]Y. Y. Van-Chin-Syan, V. F. Korotyuk and Yu. U. Panchenko, *Russ. J. Phys. Chem.*, **57**, 1727 (1983).

APPENDIX A5. Heats of formation of monoethers with nitrogen (and oxygen) functional groups ($kJ\,mol^{-1}$)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_2H_4ON_4$	5-Methoxytetrazole	69.1	1.4	*a*						
C_3H_3ON	Oxazole				−48.0	0.5	*a*	−15.5	0.5	*a*
C_4ON_4	3,4-Dicyano-1,2,4-oxadiazole	−1372.8	5.4	*a*						
$C_4H_3O_3N$	2-Nitrofuran	−104.1	0.5	*a*				−28.8	2.1	*a*
C_4H_7ON	Ethoxyacetonitrile				−111.7	0.6	*b*			
C_4H_7ON	2-Methyl-2-oxazoline				−169.0	0.9	*a*	−130.5	0.9	*a*
C_4H_9ON	*N*-Methyl *O*-Methylacetimidate				−207.2	6.5	*c*	−164.1	6.8	*c*
C_4H_9ON	Morpholine				−185.7	2.7	*d*	−142.8	3.3	*d*
C_4H_9ON	Tetrahydro-1,3-oxazine				−198.9	1.9	*d*	−157.2	2.7	*d*
$C_4H_9O_2N$	Ethoxyacetamide	−491.0	0.4	*b*						
$C_4H_{11}ON$	β-Ethoxypropionitrile				−116.9	0.9	*b*			
$C_5H_3O_4N$	5-Nitrofurfural	−226.9	0.5	*a*				−147.4	2.6	*a*
$C_5H_3O_5N$	5-Nitrofuran-2-carboxylic acid	−516.8	0.9	*a*						
$C_5H_4O_4N_2$	5-Nitro-2-furamide	−322.9	0.5	*a*						
C_5H_9ON	2-Ethyl-2-oxazoline				−193.2	1.1	*a*	−148.9	1.2	*a*
$C_5H_9O_7N_3$	2-Ethoxy-1,1,1-trinitropropane	−276.8	0.8	*b*						
$C_5H_9O_{10}N_3$	3-(2-Hydroxyethoxy)1,2-propanediol trinitrate				−536.3	2.7	*a*			
$C_5H_{11}ON$	2-Methyltetrahydro-1,3-oxazine				−246.2	1.6	*d*	−206.9	2.5	*d*
$C_5H_{11}ON$	3-Methyltetrahydro-1,3-oxazine				−204.8	3.1	*d*	−164.0	3.7	*d*
$C_5H_{11}ON$	4-Methylmorpholine				−196.2	2.9	*d*	−155.5	3.6	*d*
$C_6H_5O_5N$	5-Nitrofuran-2-carboxylic acid methyl ester	−471.1	0.5	*a*				−366.9	2.2	*a*
$C_6H_6O_{13}N_4$	Cyclohexene oxide 3,4,5,6-tetranitrate	−444.1	2.5	*e*						
$C_6H_{13}ON$	3,6-Dimethyltetrahydro-1,3-oxazine				−240.3	3.5	*d*	−196.4	4.0	*d*

$C_7H_5O_4N$	3-(5-Nitro-2-furyl)-2-propenal	−162.5	1.3	*a*			−64.7	2.5	*a*
$C_7H_5O_7N_3$	2-Methoxy-1,3,5-trinitrobenzene	−157.4	3.3	*a*			−24.4	3.9	*a*
$C_7H_6O_5N_2$	2,4-Dinitro-1-ethoxybenzene	−226.4	4.1	*a*					
$C_7H_6O_5N_2$	2,4-Dinitro-1-methoxybenzene	−186.6	3.4	*a*					
$C_7H_6O_5N_2$	2,6-Dinitro-1-methoxybenzene	−189.3	3.4	*a*					
$C_7H_{10}O_{15}N_8$	*N*-Nitro(2,2,2-trinitroethyl)-(((2,2,2-trinitroethyl)-amino)methyl)ether	−303.7	7.1	*a*					
$C_8H_6O_{10}N_4$	2-(2,4,6-Trinitrophenoxy)ethanol nitrate	−292.8	5.3	*a*					
$C_8H_7O_7N_3$	2-Ethoxy-1,3,5-trinitrobenzene	−204.6	3.9	*a*			−84.1	4.4	*a*
$C_8H_7O_8N_3$	2-(2,4-Dinitrophenoxy)ethanol nitrate	−292.8	6.0	*a*					
$C_8H_8O_6N_2$	2-(2,4-Dinitrophenoxy)ethanol	−398.7	1.0	*a*					
$C_8H_9O_3N$	2-Nitro-1-ethoxybenzene				−209	*f*			
$C_8H_9O_3N$	3-Nitro-1-ethoxybenzene				−162	*f*			
$C_8H_9O_3N$	4-Nitro-1-ethoxybenzene				−222	*f*			
$C_8H_9O_7N$	5-Nitro-2-acetoxy-2,5-dihydro-2-furancarboxylic acid methyl ester	−919.4	0.9	*a*			−830.2	2.3	*a*
$C_9H_8ON_2$	3-Methyl-5-phenyl-1,2,4-oxadiazole	103.3	5.4	*a*					
$C_9H_8ON_2$	5-Methyl-3-phenyl-1,2,4-oxadiazole	97.4	5.4	*a*					
$C_9H_9O_7N$	2-(Diacetoxymethyl)-5-nitrofuran	−897.8	0.9	*a*			−771.4	2.7	*a*
$C_9H_{11}O_2N$	2-Methoxyacetophenone oxime	−365		*f*					
$C_9H_{11}O_3N$	2-Hydroxy-4-methoxyacetophenone oxime	−594		*f*					
$C_9H_{11}O_3N$	2-Hydroxy-5-methoxyacetophenone oxime	−584		*f*					

(*continued*)

APPENDIX A5. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_9H_{12}O_2N_2$	3-Amino-4-methoxyacetanilide	−554.0	6.0	*g*						
$C_9H_{12}O_2N_2$	*N*-(4-Ethoxyphenyl)urea	−468.8	3.4	*a*				−385.1	9.0	*a*
$C_9H_{12}O_3N_2$	*N*-(3-Ethoxyphenyl)urea	−429.5	4.2	*a*				−354.2	9.4	*a*
$C_9H_{13}O_{16}N_5$	2-Hydroxy-tetrahydropyran-3,3,5,5-tetramethanol pentanitrate	−792.9	9.2	*a*						
$C_{10}H_8O_2N_2$	Methylbenzoylfurazan	127		*f*						
$C_{10}H_{10}O_2N_2$	Methyl *p*-methoxyphenylfurazan	90		*f*						
$C_{10}H_{10}O_3N_2$	4-(*p*-Methoxyphenyl)-5-methyl-1,2,3,6-dioxadiazine	28		*f*						
$C_{10}H_{10}O_3N_2$	Methyl *p*-methoxyphenylfuroxan	−8		*f*						
$C_{10}H_{11}O_4N$	Anisoylglycine, *para*	−757.0		*h*						
$C_{10}H_{13}O_2N$	4'-methoxy-2'-methylacetophenone oxime	−398		*f*						
$C_{10}H_{13}O_2N$	4'-Methoxy-3'-methylacetophenone oxime	−418		*f*						
$C_{10}H_{13}O_2N$	*N*-(4-Ethoxyphenyl)acetamide [phenacetin]	−423		*h*				−307		*i*
$C_{10}H_{16}O_{19}N_6$	Bis-(2,2,2-tri(nitromethyl)ethyl) ether[dipentaerythritol hexanitrate]	−979.6	5.4	*a*						
$C_{11}H_{11}O_7N$	2-(3,3-Diacetoxy-2-propenyl)-5-nitrofuran	−872.3	1.3	*a*						
$C_{11}H_{13}O_9N$	5-Nitro-2-acetoxy-2,5-dihydro-furfural diacetate	−1374.1	1.7	*a*						

$C_{11}H_{15}O_2N_3$	3-(*N*-(β-Cyanoethyl)amino-4-methoxyacetanilide	−265.9	1.7	*g*						
$C_{12}H_9ON$	2-Methylnaphth[1,2-*d*]oxazole	−87.6	11.7	*a*						
$C_{12}H_9ON$	2-Methylnaphth[2,1-*d*]oxazole				−50.3	2.4	*a*			
$C_{12}H_9ON$	2-Methylnaphth[2,3-*d*]oxazole				−42.9	7.1	*a*			
$C_{14}H_{10}ON_2$	2,5-Diphenyl-1,3,4-oxadiazole	165.3	8.4	*a*						
$C_{14}H_{10}ON_2$	3,5-Diphenyl-1,2,4-oxadiazole	207.1	11.3	*a*						
$C_{14}H_{13}O_2N$	*N*-4-Methoxyphenylmethylene-benzenammine *N*-oxide	−20.9	2.2	*j*				109.7	2.5	*j*
$C_{16}H_{10}O_3N_2$	3,4-Dibenzoyl-1,2,5-oxadiazole	104.2	9.2	*a*						
$C_{17}H_{18}O_2N_2$	*N,N*-Diphenyl-4-morpholine carboxamide	−217.6	5.9	*a*						
$C_{18}H_{14}O_3N_2$	3,4-Bis(4-methylbenzoyl)-1,2,5-oxadiazole	20.4	13.0	*a*						
$C_{18}H_{14}O_3N_2$	3,4-Bis(4-methylbenzoyl)-1,2,4-oxadiazole	20.4	13.0	*a*						
$C_{18}H_{22}O_4N$	Codeine monohydrate	−712		*h*						
$C_{20}H_{24}O_4N_2$	Quinidine	−160		*h*						
$C_{20}H_{24}O_4N_2$	Quinine	−155		*h*						
$C_{21}H_{22}O_2N_2$	Strychnine	−172		*h*						

[a]Reference 1c.
[b]N. M. Gutner, N. D. Lebedeva, S., L. Dobychin and N. N. Prikeleva, *J. Appl. Chem. USSR*, **53**, 1523 (1980).
[c]The heats of formation of liquid *N*-methyl *O*-methylacetimidate were obtained from the heat of formation of liquid *N,N*-dimethylacetamide from Reference 1c and the heat of isomerization to form the desired species from P. Beak, J.-K. Lee and J. M. Ziegler, *J. Org. Chem.*, **43**, 1536 (1978). The heat of formation of gaseous *N*-methyl *O*-methylacetimidate was obtained using this new value and the heat of vaporization reported by Beak, Lee and Ziegler in the same reference.
[d]K. Pihlaja, W. V. Steele and P. Vainiotalo, unpublished results, cited in Reference 17c.
[e]Reference 23.
[f]Reference 8.
[g]I. Contineanu, D. Bretcanu and D. I. Marchidan, *Rev. Roum. Chim.*, **27**, 55 (1982).
[h]Reference 15.
[i]To obtain the heat of formation of the gas, we used the heat of formation of the solid from the source cited and the heat of sublimation from J. S. Chickos, in Reference 17c.
[j]J. J. Kirchner, W. E. Acree, G. Pilcher and L. Shaofeng, *J. Chem. Thermodyn.*, **18**, 793 (1986).

APPENDIX A6. Heats of formation of monoethers with additional functional groups ($kJ\,mol^{-1}$)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_3OCl_3F_5$	1,4,4-trichloro-1,1,3,3,4-pentafluoro-2-oxabutane							−1325.6	7.3	*a*
$C_3OCl_3F_5$	2,2-Dichloro-1,1,2-trifluoroethyl-chlorodifluoromethyl ether				−1361.1	7.1	*b*	−1329.3	7.1	*b*
$C_3H_4OClF_3$	4-Chloro-3,3,4-trifluoro-2-oxabutane							−882.3	2.1	*a*
C_3H_5OCl	Chloromethyloxacyclopropane [(chloromethyl)oxirane]				−148.4	0.5	*c*	−107.8	4.2	*c*
$C_4OCl_4F_5$	1,1,1,4-Tetrachloro-3,3,4,5,5,5-hexafluoro-2-oxapentane							−1524.1	4.9	*a*
$C_4OCl_5F_5$	1,1,1,5-Pentachloro-3,3,4,4,5-pentafluoro-2-oxapentane							−901.2	2.9	*a*
$C_4H_4O_9N_4F_2$	Bis(2-fluoro-2,2-dinitroethyl)-ether				−670.2	2.6	*d*			
C_4H_7OCl	2-Chloroethyl vinyl ether				−208.2	3.3	*d*	−170.1	3.6	*d*
$C_4H_8ON^{\cdot}$	Morpholino radical							−7.1	9.2	*e*
C_4H_9OCl	1-Chloro-2-ethoxyethane				−335.6	2.3	*d*	−301.3	2.3	*d*
$C_5OCl_5F_7$	1,1,4,4,6-Pentachloro-1,2,2,5,5,6,6-heptafluoro-3-oxahexane							−1752.5	6.5	*a*
$C_5OCl_3F_5$	2,2-Dichloro-1,1,2-trifluoroethyl-1,1,3-trichloro-2,2,3,3-tetrafluoropropyl ether				−1804.6	4.6	*b*	−1753.9	4.6	*b*
$C_5H_3O_3F_7$	2,2,3,3-Tetrafluoro-3-trifluoromethoxypropanoic acid methyl ester				−2074.2	2.2	*d*			
$C_5H_4OClF_7$	1-Chloro-1,2,2,5,5,6,6-heptafluoro-3-oxahexane							−1720.7	5.0	*a*

$C_5H_6O_{11}N_6F_2$	1,7-Difluoro-1,1,3,7,7-pentanitro-3-aza-5-oxaheptane	−663.3	4.6	*d*						
$C_5H_6O_{13}N_7F$	1-Fluoro-1,1,3,7,7,7-hexanitro-3-aza-5-oxaheptane	−436.5	3.7	*d*						
$C_5H_8OCl_2$	3,3-Bis(chloromethyl)oxacyclobutane				−259.8	1.8	*d*	−203.8	1.9	*d*
C_6OF_{14}	Bis(perfluoro-n-propyl)ether				−3179.4	9.5	*f*	−3148.2	9.5	*a*
$C_6H_5OF_9$	1,1,2,2′,3,3,3,3′,3′-Nonafluoro n-propyl ether							−2359.5	8.0	*a*
$C_6H_6O_2F_8$	2,2,3,3-Tetrafluoro-3-trifluoromethoxypropanoic acid methyl ester				−2211.6	2.3	*d*			
$C_6H_8OF_6$	Bis(3,3,3-trifluoropropyl)ether				−1645.3	0.3	*d*	−1604.3	2.5	*a*
$C_6H_8O_{11}N_6F_2$	1,8-Difluoro-1,1,4,8,8-pentanitro-4-aza-6-oxanonane	−726.4	1.5	*d*						
$C_6H_8O_{13}N_8F_2$	1,1′-Oxybis(2,4,4-trinitro-4-fluoro-2-azabutane	−663.6	3.4	*d*						
$C_6H_{11}OCl$	3-Ethyl-3-(chloromethyl) oxacyclobutane				−243.0	1.6	*d*	−193.3	1.6	*d*
$C_7OCl_5F_{11}$	1,1,4,4,8-Pentachloro-1,2,2,5,5-6,6,7,7,8,8-hendecafluoro-3-oxaoctane							−2560.6	8.3	*a*
$C_7OCl_5F_{11}$	2,2-Dichloro-1,1,2-trifluoroethyl-1,1,5-trichloro-2,2,3,3,4,4,5,5-octafluoropentyl ether				−2623.4	4.2	*b*	−2564.4	4.2	*b*
$C_7H_4OClF_{11}$	1-Chloro-1,2,2,5,5,6,6,7,7,8,8-hendecafluoro-3-oxanonane							−2555.6	7.3	*a*
$C_7H_5O_4N$	3-(5-Nitro-2-furyl)-2-propenal							−64.6	2.5	*d*
$C_7H_6O_5F_6$	2,2,3,3-Tetrafluoro(difluoro (methoxycarbonyl)-methoxy) propanoic acidmethyl ester				−2211.6	2.3	*d*			

(*continued*)

APPENDIX A6. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_7H_{10}O_{11}N_6F_2$	1,9-Difluoro-1,1,4,9,9-pentanitro-4-aza-6-oxanonane	−775.6	2.7	*d*						
C_8OF_{18}	Bis(perfluorodi-n-butyl) ether				−4019.2	3.3	*d*	−3978.6	3.4	*d*
$C_8H_4OF_{14}$	1,1,1,2,3,3,6,6,7,7,8,8,9,9-Tetradecafluoro-4-oxanonane							−3162.4	12.4	*a*
C_8H_9OF	3-Fluorophenyl ethyl ether (*m*-fluorophenetole)				−333		*g*			
C_8H_9OF	4-Fluorophenyl ethyl ether (*p*-fluorophenetole)				−346		*g*			
$C_8H_{11}O_5Cl$	2,4,6-Trimethylpyrylium perchlorate	−172.3	3.1	*d*						
$C_8H_{12}O_{16}N_{10}F_2$	1,1′-Oxybis(2,5,5-trinitro-5-fluoro-2-azapentane)	−763.7	3.1	*d*						
$C_9H_4OClF_{15}$	1-Chloro-1,2,2,5,5,6,6,7,7,8,8,9,9-10,10-pentadecafluoro-3-oxadecane							−3391.9	11.0	*a*
$C_{10}OF_{22}$	Bis(perfluoro-di-n-pentyl)ether				−4855.9	20.7	*f*	−4806.4	20.7	*a*

[a]V.P. Kolesov and M. P. Kozina, *Russ. Chem. Rev.*, **55**, 912 (1986).
[b]V. P. Kolesov, P. A. Erastov and K. Boudarenko, *Russ. J. Phys. Chem.*, **55**, 803 (1981).
[c]Reference 23.
[d]Reference 1c.
[e]O. F. Golanova, G. V. Sitiviina, V. I. Pepekin, B. L. Korshunskii and F. I. Dubovitskii, *Bull. Acad. Sci. USSR. Chem. Ser.*, 881 (1988).
[f]R. M. Varushenko and L. L. Pushchenko, *Russ. J. Phys. Chem.*, **63**, 664 (1989). This paper provided calorimetrically measured heats of vaporization data.
[g]Reference 8.

APPENDIX A7. Heats of formation of unsubstituted diethers (acetals) ($kJ\,mol^{-1}$)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_3H_6O_2$	1,3-Dioxolane				−333.5	1.3	*a*	−298.0	1.4	*a*
$C_3H_8O_2$	Dimethoxymethane				−377.7	0.9	*a*	−348.4	0.8	*a*
$C_4H_8O_2$	1,3-Dioxane				−379.7	4.2	*a*	−342.3	4.3	*a*
$C_4H_8O_2$	2-Methyl-1,3-dioxolane				−386.9	1.8	*a*	−352.0	2.3	*a*
$C_4H_{10}O_2$	1,1-Dimethoxyethane				−420.2	0.8	*a*	−389.7	0.8	*a*
$C_5H_8O_2$	2,4-Dimethyl-1,3-dioxole				−458.0	5.3	*b*	−423.0	5.3	*b*
$C_5H_8O_2$	2-Methyl-4-methylene-1,3-dioxolane				−420.2	5.3	*b*	−383.0	6.5	*b*
$C_{15}H_{10}O_2$	1,3-Dioxepane				−387.8	0.9	*a*	−346.6	1.5	*a*
$C_5H_{10}O_2$	2,2,-Dimethyl-1,3-dioxolane				−423.1	2.0	*a*			
$C_5H_{10}O_2$	2,4-Dimethyl-1,3-dioxolane, *cis*				−421.3	2.3	*a*	−382.6	2.7	*a*
$C_5H_{10}O_2$	2,4-Dimethyl-1,3-dioxolane, *trans*				−419.8	2.4	*a*	−380.5	2.7	*a*
$C_5H_{10}O_2$	2-Methyl-1,3-dioxane				−436.4	2.6	*a*	−397.8	3.1	*a*
$C_5H_{10}O_2$	4-Methyl-1,3-dioxane				−416.1	2.9	*a*	−376.9	3.1	*a*
$C_5H_{12}O_2$	1,1-Dimethoxypropane				−443.3	1.1	*a*			
$C_5H_{12}O_2$	2,2-Dimethoxypropane				−459.0	1.9	*a*	−429.6	2.3	*a*
$C_5H_{12}O_2$	Diethoxymethane				−450.0	0.8	*a*	−414.8	0.8	*a*
$C_6H_{12}O_2$	1,3-Dioxocane				−378.7	1.3	*a*	−336.8	1.8	*a*
$C_6H_{12}O_2$	2,2-Dimethyl-1,3-dioxane				−468.9	2.1	*a*			
$C_6H_{12}O_2$	2,4-Dimethyl-1,3-dioxane, *cis*				−465.2	4.2	*a*	−425.3	4.4	*a*
$C_6H_{12}O_2$	2-Methoxy-2,3-dihydropyran				−333.6	2.4	*c*	−291.2	2.7	*c*
$C_6H_{12}O_2$	2-Methoxytetrahydropyran				−442.2	1.3	*a*	−399.6	1.8	*a*
$C_6H_{12}O_2$	4,5-Dimethyl-1,3-dioxane				−451.6	2.1	*a*	−409.1	2.4	*a*
$C_6H_{12}O_2$	4,6-Dimethyl-1,3-dioxane, *cis*				−474.8	2.4	*a*			
$C_6H_{12}O_2$	4,6-Dimethyl-1,3-dioxane, *trans*				−462.6	1.8	*a*			
$C_6H_{12}O_2$	5,5-Dimethyl-1,3-dioxane				−461.3	2.3	*a*	−420.1	2.6	*a*
$C_{16}H_{14}O_2$	1,1-Diethoxyethane				−491.4	2.3	*a*	−453.5	2.5	*a*
$C_6H_{14}O_2$	1,1-Dimethoxy-2-methylpropane				−476.3	1.7	*a*			
$C_6H_{14}O_2$	1,1-Dimethoxybutane				−468.1	1.5	*a*			
$C_6H_{14}O_2$	2,2-Dimethoxybutane				−485.1	1.0	*a*			
$C_7H_6O_2$	1,3-Benzodioxole (**4a**)				−184.1	2.1	*a*	−142.7	3.0	*a*
$C_7H_{14}O_2$	(2α, 4α, 6α)2,4,6-Trimethyl-1,3-dioxane				−488.3	2.9	*a*	−445.1	3.1	*a*

(*continued*)

APPENDIX A7. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_7H_{14}O_2$	2,2,4-Trimethyl-1,3-dioxane				−500.8	2.6	*a*			
$C_7H_{14}O_2$	4,4,6-Trimethyl-1,3-dioxane				−500.5	3.5	*a*			
$C_7H_{16}O_2$	1,1-Dimethoxypentane				−494.6	2.4	*a*			
$C_7H_{16}O_2$	2,2-Diethoxypropane				−538.5	1.0	*a*	−506.6	1.3	*a*
$C_7H_{16}O_2$	2,2-Dimethoxy-3-methylbutane				−512.2	1.0	*a*			
$C_7H_{16}O_2$	2,2-Dimethoxypentane				−509.2	1.2	*a*			
$C_7H_{16}O_2$	Dipropoxymethane				−495		*d*			
$C_8H_{16}O_2$	2,2,4,6-Tetramethyl-1,3-dioxane, *cis*				−539.4	3.5	*a*			
$C_8H_{16}O_2$	2,2,4,6-tetramethyl-1,3-dioxane, *trans*				−526.3	4.7	*a*	−482.7	3.3	*e*
$C_8H_{16}O_2$	4,4,6,6-Tetramethyl-1,3-dioxane				−518.0	2.6	*e*	−470.6	3.3	*e*
$C_8H_{16}O_2$	2,2-Dimethoxy-3,3-dimethylbutane				−524.4	1.0	*a*			
$C_8H_{18}O_2$	Acetaldehyde diisopropyl acetal				−569.2	3.6	*a*	−526.1	5.5	*a*
$C_8H_{18}O_2$	2,2,4,6,6-Pentamethyl-1,3-dioxane				−567.1	3.6	*e*	−520.9	3.8	*e*
$C_9H_{18}O_2$	2,4,4,6,6-Pentamethyl-1,3-dioxane				−559.6	3.1	*e*	−512.8	3.7	*e*
$C_9H_{20}O_2$	Dibutoxymethane				−549.4	1.7	*a*	−501.3	3.1	*a*
$C_9H_{20}O_2$	Diisobutoxymethane				−557		*d*			
$C_{10}H_{10}O_2$	5-Allylbenzo-1,3-dioxole				−197		*d*			
$C_{11}H_{24}O_2$	1,1-Dibutoxypropane				−608.6	3.3	*a*	−552.7	5.4	*a*
$C_{12}H_{22}O_2$	1,1-Diethoxy-2-octyne [pentylpropiolic diacetal]				−368		*d*			
$C_{13}H_{24}O_2$	1,1-Diethoxy-2-nonyne [hexylpropiolic diacetal]				−395		*d*			
$C_{14}H_{12}O_3$	3,5-Diphenyl-1,2,4-trioxolane	−123.8	12.6	*a*						
$C_{21}H_{16}O_2$	β-Dioxydinaphthylmethane	−190		*d*						
$C_{21}H_{16}O_2$	β-Naphthol formal	−86		*d*						

[a]Reference 1c.
[b]K. Pihlaja and J. Heikkila, *Suomen Kemishlekh*, **B42**, 338 (1969).
[c]Reference 24. We combined their heat of hydrogenation with the heat of formation of the hydrogenated product to derive these numbers.
[d]Reference 8.
[e]K. Pihlaja, W. V. Steele and P. Vainiotalo, unpublished results, cited by Pihlaja Reference 17c.

APPENDIX A8. Heats of formation of unsubstituted diethers (nonacetals) (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_4H_8O_2$	1,4-Dioxane (**8a**)				−353.9	0.8	*a*	−315.8	0.8	*a*
$C_5H_{10}O_2$	(Ethoxymethyl)oxirane [glycidyl ethyl ether]				−295.3	2.2	*a*			
$C_6H_{10}O_2$	Bis(vinyloxy)ethane				−277		*b*			
$C_6H_{12}O_2$	(Methylethoxy)methyloxirane [glycidyl isopropyl ether]				−342.9	2.2	*c*	−298.8	2.7	*c*
$C_6H_{12}O_2$	(Propoxymethyl)oxirane [glycidyl propyl ether]				−321.2	2.2	*c*	−272.6	2.3	*c*
$C_6H_{14}O_2$	1,2-Diethoxyethane				−451.4	1.0	*a*	−408.2	1.0	*a*
$C_7H_{14}O_2$	((1,1-Dimethylethoxy)methyl)oxirane [glycidyl *t*-butyl ether]				−370.1	3.0	*a*	−319.7		*c*
$C_7H_{14}O_2$	((2-Methylpropoxy)methyl)oxirane [glycidyl isobutyl ether]				−357.7	2.5	*c*	−306.8	2.6	*c*
$C_7H_{14}O_2$	(n-Butoxymethyl)oxirane [glycidyl butyl ether]				−345.2	2.6	*c*	−291.9	2.7	*c*
$C_7H_{16}O_2$	1,3-Diethoxypropane				−482.1	1.4	*a*	−436.2	1.4	*a*
$C_8H_8O_2$	2,3-Dihydro-1,4-benzodioxin				−254.7	1.3	*a*	−204.1	2.8	*a*
$C_8H_{10}O_2$	1,2-Dimethoxybenzene				−290.2	2.1	*a*	−223.3	3.0	*a*
$C_8H_{10}O_2$	1,4-Dimethoxybenzene	−328		*b*	−295		*b*			
$C_8H_{16}O_2$	((Pentyloxy)methyl)oxirane [glycidyl pentyl ether]				−368.6	2.9	*d*			

(*continued*)

APPENDIX A8. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_9H_{10}O_2$	(Phenoxymethyl)oxirane [glycidyl phenyl ether]				−182.0	2.1	*d*	−116.4	2.1	*d*
$C_9H_{10}O_2$	3,4-Dihydro-2*H*-1,5-benzodioxepin (**4c**)				−241.1	0.9	*a*	−185.5	2.7	*a*
$C_{10}H_{12}O_2$	((Phenylmethoxy)methyl)oxirane [glycidyl benzyl ether]				−209.0	3.5	*c*	−138.0	3.6	*c*
$C_{10}H_{20}O_2$	((1,1-Dimethylpentyl)oxy)methyl oxirane [glycidyl *t*-heptyl ether]				−442.2	3.7	*d*			
$C_{11}H_{14}O_2$	Methyl (2-methoxy-4-propenylphenyl) ether [methyl isoeugenol]				−287		*b*			
$C_{11}H_{14}O_2$	Methyl (5-allyl-2-methoxyphenyl) ether [methyl eugenol]				−222		*b*			
$C_{12}H_{26}O_2$	1,1,2,2-Tetraethylethyleneglycol dimethyl ether				−572.0	2.5	*e*	−512.1	2.9	*e*
$C_{16}H_{16}O_2$	4,4′-Dimethoxystilbene	−144		*b*						
$C_{20}H_{26}O_2$	1,2-Dimethyl-1,2-diphenyl-ethyleneglycol diethyl ether, *dl*-	−297.5	5.9	*e*				−183.3	6.3	*e*

[a]Reference 1c.
[b]Reference 8.
[c]Y. Y. Van-Chin-Syan and N. S. Kachurina, *Russ. J. Phys. Chem.*, **61**, 622 (1987).
[d]Reference 23.
[e]B. Dogan, H.-D. Beckhaus, H. Birkhofer and C. Ruchardt, *Chem. Ber.*, **123**, 1365 (1990).

APPENDIX A9. Heats of formation of diethers with oxygen functional groups (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_5H_{12}O_3$	2-(2-Methoxyethoxy)ethanol				−673		*a*			
$C_6H_{10}O_3$	2,2-Dimethyl-1,3-dioxolane-4-carboxaldehyde [acetone glyceraldehyde]				−753		*a*			
$C_6H_{10}O_5$	Levoglucosan	−959		*b*						
$C_6H_{12}O_3$	2,2-Dimethyl-4-methanol-dioxolane [acetone glycerol]				−682		*b*			
$C_6H_{14}O_4$	Triethylene glycol				−804.2	3.6	*c*	−725.0	8.7	*c*
$C_7H_{14}O_6$	Methylglucofuranoside, α-				−1202.7	0.9	*c*			
$C_7H_{14}O_6$	Methylglucopyranoside, α-, D-	−1233.3	0.9	*c*						
$C_7H_{14}O_6$	Methylglucopyranoside, β-, D-	−1237.5	0.5	*c*						
$C_8H_6O_3$	1,3-Benzodioxole-5-carboxaldehyde [piperonylaldehyde]	−359		*a*				−268		*d*
$C_8H_6O_4$	3,4-Methylenedioxybenzoic acid [piperonylic acid]	−641		*a*						
$C_8H_{10}O_4$	3,4-Diethoxycyclobutenedione [diethyl squarate]				−552.1	1.4	*c*	−478.5	4.1	*c*
$C_8H_{14}O_6$	Dimethyl dimethoxysuccinate, *dl*-	−1110		*a*						
$C_8H_{14}O_6$	Dimethyl dimethoxysuccinate, *meso*	−1153		*a*						
$C_9H_{10}O_2$	2,3-Dimethoxybenzoic acid	−687.0	1.4	*e*						
$C_9H_{10}O_4$	2,4-Dimethoxybenzoic acid	−717.2	1.4	*e*						
$C_9H_{10}O_4$	2,6-Dimethoxybenzoic acid	−693.8	1.4	*e*						

(*continued*)

APPENDIX A9. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_9H_{10}O_4$	3,4-Dimethoxybenzoic acid	−714.0	1.4	*e*						
$C_9H_{10}O_4$	3,5-Dimethoxybenzoic acid	−725.0	1.5	*e*						
$C_9H_{20}O_3$	1-*t*-Butoxy-3-ethoxy-2-propanol				−750.7	2.6	*c*			
$C_{10}H_6O_4$	Bis(2-furyl)ethanedione [furil]	−336		*a*						
$C_{10}H_8O_4$	1,2-Bis(2-furyl)2-keto-ethanol [furoin]	−414		*a*						
$C_{10}H_8O_4$	3,4-Methylenedioxycinnamic acid, *cis*	−567		*a*						
$C_{10}H_8O_4$	3,4-Methylenedioxycinnamic acid, *trans*	−605		*a*						
$C_{10}H_{10}O_4$	5,6-Dimethoxyphthalide	−608		*a*						
$C_{10}H_{10}O_5$	5,6-Dimethoxy-2-formylbenzoic acid [opianic acid]	−805		*a*						
$C_{10}H_{10}O_6$	4,5-Dimethoxyphthalic acid	−1076		*a*						
$C_{10}H_{22}O_3$	1-*t*-butoxy-3-ethoxy-2-propanol				−774.0	3.0	*c*			
$C_{11}H_{24}O_3$	1-Butoxy-3-*t*-butoxy-2-propanol				−794.3	4.2	*c*			
$C_{12}H_{16}O_8$	Levoglucosan triacetate	−1554		*b*						
$C_{12}H_{26}O_3$	1-*t*-butoxy-3-pentoxy-2-propanol				−818.0	4.6	*c*			
$C_{13}H_{10}O_3$	Bis(2-furyl)-1,4-pentadiene-3-one [difurfurylidene acetone]	−201.1	26.0	*c*						

[a]Reference 8.
[b]Reference 15.
[c]Reference 1c.
[d]To obtain the heat of formation of the gas, we used the heat of formation of the solid from the source cited and the heat of sublimation from J. S. Chickos, in Reference 37.
[e]M. Colomina, M. V. Roux and C. Turrion, *J. Chem. Thermodyn.*, **13**, 1169 (1981).

APPENDIX A10. Heats of formation of diethers with additional functional groups (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_5H_6ON_6$	Bis-(2,2,2-trinitroethoxy)-methane	−402.1	3.3	*a*	−300.8	4.7	*a*			
$C_5H_6O_{10}N_4F_2$	1,7-Difluoro-1,1,7,7-tetranitro-3,5-dioxaheptane				−849.0	1.8	*b*			
$C_5H_6O_{14}N_6$	1,1,1,7,7,7-Hexanitro-3,5-dioxaheptane	−402.0	2.1	*b*						
$C_5H_7O_6N_2F$	((2-Fluoro-2,2-dinitroethoxy)-methyl)oxacyclopropane				−510.8	1.8	*b*			
$C_5H_{13}O_2N$	1,1-Dimethoxy-*N*,*N*-dimethyl-methylamine				−395.7	1.8	*b*			
$C_6H_8O_{12}N_6F_2$	1,9-Difluoro-1,1,5,9,9-penta-nitro-3,7-dioxa-5-azaheptane	−851.9	1.9	*b*						
$C_6H_8O_{16}N_8$	*N*-Nitro(bis(2,2,2-trinitro-ethoxy)methyl)amine	−387.7	3.8	*b*						
$C_6H_{11}O_6N$	(2-Carbamoylmethoxy)ethoxy) acetic acid				−1306		*c*			
$C_6H_{11}O_2N$	β-Cyanopropionaldehyde dimethylacetal				−310.8		*d*			
$C_6H_{15}O_2N$	1,1-Dimethoxy-*N*,*N*-dimethyl-ethylamine				−427.3	3.8	*b*			
$C_7H_{10}O_{14}N_4$	Methyl-glucopyranoside 2,3,4,6-tetranitrate, α-, D-	−825.8	3.3	*b*						
$C_8H_{12}O_{29}N_{12}$	*N*,*N*,*N*-Trinitrobis(((2-nitro-ethoxy)methyl)amino methyl) amine	−340.2	3.3	*b*						
$C_8H_{14}O_2N_2$	*N*-Formylimidazole diethylacetal				−329.3	2.8	*e*	−255.3	3.0	*e*

(*continued*)

APPENDIX A10. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_9H_{13}O_{16}N_9F_2$	1,13-Difluoro-1,1,5,7,9,13,13-heptanitro-3,11-dioxa-5,9-diazatridecane	−796.7	3.1	*b*						
$C_9H_{16}O_2N_2$	*N*-Acetylimidazolediethylacetal				−368.9	2.0	*e*	−296.7	2.3	*e*
$C_{10}H_8O_2N_2$	Lin-dimethyl-2,2′-benzo-4,5,4′,5′-bisoxazole	−207		*c*						
$C_{10}H_8O_3N_2$	Ang-dimethyl-2,2′-benzo-4,5,4′,5′-bisoxazole	−201		*c*						
$C_{10}H_9O_4N$	3,4-Dimethoxyphthalimide	−632		*c*						
$C_{12}H_{14}O_2N_2$	*N*-Benzoylimidazole dimethylacetal				−162.1	3.6	*e*	−77.5	3.7	*e*
$C_{14}H_{14}O_2N_2$	4,4′-Azodianisole				12		*c*			
$C_{16}H_{18}O_2N_2$	4,4′-Azodiphenetole	−75		*c*						
$C_{16}H_{18}O_3N_2$	2,2′-Azoxydiphenetole	−133		*c*						
$C_{16}H_{18}O_3N_2$	4,4′-Azoxydiphenetole	−82		*c*						
$C_{18}H_{22}O_4N_1$	Codeine monohydrate	−712		*f*						
$C_{22}H_{20}O_4N_2$	*N*,*N*′-Bis(2-methoxyphenyl)-1,4-benzenedicarboxamide	−507.9	3.5	*b*				−310.4	5.4	*b*
$C_{22}H_{20}O_4N_2$	*N*,*N*′-Bis(3-methoxyphenyl)-1,4-benzenedicarboxamide	−549.2	3.2	*b*				−340.0	9.0	*b*
$C_{22}H_{20}O_4N_2$	*N*,*N*′-Bis(4-methoxyphenyl)-1,4-benzenedicarboxamide	−548.4	3.2	*b*				−320.7	9.0	*b*

[a]N. B. Lebedeva, V. L. Ryadnenko, N. N. Gutner, L. F. Nazarova, N. N. Kisleva, I. N. Aizenshtadt and I. V. Kirilenko, *J. Appl. Chem. USSR*, **50**, 726 (1977).
[b]Reference 1c.
[c]Reference 8.
[d]G. G. Nurullaev and K. A. Karasharii, *Azerb. Khim. Zh.*, 140 (1981); *Chem. Abstr.*, **96**, 142102 (1982).
[e]J. P. Guthrie and D. C. Pike, *Can. J. Chem.*, **65**, 2951 (1987).
[f]Reference 15.

APPENDIX A11. Heats of formation of unsubstituted polyethers (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_3H_6O_3$	1,3,5-Trioxacyclohexane [1,3,5-trioxane] (**7a**)	−522.5	0.4	*a*				−465.9	0.5	*a*
$C_4H_8O_3$	2-Methoxy-1,3-dioxolane				−523.3	3.3	*b*	−481.6	5.3	*b*
$C_4H_{10}O_3$	Trimethoxymethane [trimethyl orthoformate]				−570.0	2.4	*a*	−531.9	2.8	*a*
$C_5H_{10}O_3$	1,3,6-Trioxacyclooctane [1,3,6-trioxocane]				−515.9	1.0	*a*	−467.1	1.0	*a*
$C_5H_{10}O_3$	2-Methoxy-2-methyl-1,3-dioxolane				−572.8	2.5	*b*	−530.8	4.9	*b*
$C_5H_{12}O_3$	1,1,1-Trimethoxyethane [trimethyl orthoacetate]				−612.0	1.1	*a*	−572.7	2.3	*a*
$C_6H_{12}O_3$	2,4,6-Trimethyl-1,3,5-trioxane				−673.2	2.5	*a*	−631.8	2.4	*a*
$C_6H_{14}O_3$	1,1,1-Trimethoxypropane [trimethyl orthopropionate]				−634.2	1.1	*c*	−591.7	4.4	*c*
$C_6H_{14}O_3$	2,5,8-Trioxanonane [bis(2-methoxyethyl)ether]				−556.4	0.9	*d*			
$C_6H_{14}O_3$	3,5,7-Trioxanonane [bis(ethoxymethyl) ether]				−625.8	1.0	*a*	−581.1	1.0	*a*
$C_7H_{10}O_3$	2,4,10-Trioxaadamantane	−573.6	1.9	*a*				−499.2	2.0	*a*
$C_7H_{16}O_3$	Triethoxymethane [triethyl orthoformate]				−678.4	1.5	*e*	−630.6	1.5	*e*
$C_8H_{16}O_3$	2-(2-Methoxyethoxy)tetrahydropyran				−623.3	4.2	*a*	−563.0	4.7	*a*
$C_9H_{12}O_3$	Metacrolein	−363		*f*						
$C_9H_{18}O_3$	2-Ethoxy-3,3,4,4-tetramethyl-1,3-dioxolane				−727.5	8.8	*b*	−679.6	9.7	*b*
$C_{10}H_{14}O_3$	Trimethoxyphenylmethane [trimethyl orthobenzoate]				−485.8	3.1	*c*	−429.3	5.4	*c*
$C_{12}H_{16}O_3$	1,2,4-Trimethoxy-5-propenylbenzene				−409		*f*			
$C_{14}H_{12}O_3$	3,5-Diphenyl-1,2,4-trioxolane	−123.8	12.6	*a*						
$C_4H_8O_4$	1,3,5,7-Tetraoxacyclooctane [1,3,5,7-tetroxane] (**7b**)	−699.9	0.5	*a*				−620.2	0.6	*a*
$C_6H_{10}O_4$	4,4′-Bis(1,3-dioxolanyl) [erythritol diformal]	−677		*g*						

(*continued*)

APPENDIX A11. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_7H_{12}O_4$	2,4,8,10-Tetraoxaspiro[5.5]undecane	−702.3	5.4	*a*				−629.5	5.7	*a*
$C_7H_{16}O_4$	3,5,7,9-Tetraoxaundecane				−794.6	1.2	*a*	−741.0	1.3	*a*
$C_8H_{14}O_4$	4,4′-Bis(2-methyl-1,3-dioxolanyl) [erythritol diacetal]	−761		*g*						
$C_8H_{16}O_4$	1,4,7,10-Tetraoxacyclododecane [12-crown-4] (**8c**)				−696.6	1.8	*a*	−631.0	1.8	*a*
$C_9H_{20}O_4$	Tetraethoxymethane [tetraethyl orthocarbonate]				−914.6	2.1	*e*	−861.7	2.1	*e*
$C_{12}H_{14}O_4$	1,4-Dimethoxy-2,3-(methylenedioxy)-5-propenylbenzene	−492		*f*						
$C_{12}H_{14}O_4$	1-Allyl-2,5-dimethoxy-3,4-(methylenedioxy)benzene	−447		*f*						
$C_{12}H_{22}O_4$	1,1,4,4-Diethoxy-2-butyne [acetylene dicarboxaldehyde bis(diethylacetal)]	−644		*f*						
$C_5H_{10}O_5$	1,3,5,7,9-Pentaoxacyclodecane (**7c**)	−867.7	1.0	*a*				−779.8	1.2	*a*
$C_8H_{19}O_5$	3,5,7,9,11-Pentaoxatridecane				−968.4	1.4	*a*	−905.9	1.9	*a*
$C_{10}H_{20}O_5$	1,4,7,10,13-Pentaoxacyclopentadecane [15-crown-5] (**8d**)				−879.2	1.5	*a*	−799.5	1.5	*a*
$C_9H_{14}O_6$	4,5-Bis(1,3-dioxolan-2-yl)-1,3-dioxolane [mannitol triformal]	−1013		*g*						
$C_{12}H_{20}O_6$	2-Methyl-4,5-bis(2-methyl-1,3-dioxolanyl)-1,3-dioxolane [mannitol triacetal]	−1151		*g*						
$C_xH_{2x}O_x$	Paraformaldehyde [poly-(oxymethylene)]	−174.5	0.5	*a*						

[a]Reference 1c.
[b]J. P. Guthrie, *Can. J. Chem.*, **55**, 3562 (1977).
[c]J. P. Guthrie and P. A. Cullimore, *Can. J. Chem.*, **58**, 1281 (1980).
[d]N. M. Gutner, N. D. Lebedeva, S. L. Dobychin and N. N. Prikeleva, *J. Appl. Chem. USSR*, **53**, 1523 (1980).
[e]K. Marsh and M. Mansson, *J. Chem. Thermodyn.*, **17**, 995 (1985).
[f]Reference 8.
[g]Reference 15.

APPENDIX A12. Heats of formation of polyethers with oxygen functional groups (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_8H_{18}O_5$	Tetraethylene glycol				−981.7	4.6	*a*	−883.0	11	*a*
$C_{11}H_{12}O_5$	Methyl 5,6-dimethoxyphthaldehyate	−759		*b*						
$C_{12}H_{22}O_{11}$	Cellobiose	−2228		*c*						
$C_{12}H_{22}O_{11}$	Lactose, β-	−2236.7	0.7	*a*						
$C_{12}H_{22}O_{11}$	Maltose	−2221		*c*						
$C_{12}H_{22}O_{11}$	Sucrose, D-	−2226.1	3.0	*a*						
$C_{12}H_{22}O_{11}$	Trehalose	−2223		*c*						
$C_{12}H_{24}O_{12}$	Lactose monohydrate, α-	−2484.1	1.1	*a*						
$C_{12}H_{24}O_{12}$	Maltose monohydrate, β-	−2459.6	0.7	*a*						
$C_{12}H_{26}O_{13}$	Trehalose dihydrate	−2829		*c*						
$C_{18}H_{32}O_6$	Melezitose	−3410		*c*						
$C_{18}H_{32}O_{16}$	Raffinose	−3184		*c*						
$C_{18}H_{42}O_{21}$	Raffinose pentahydrate	−4694		*c*						
$C_{24}H_{40}O_{20}$	Diamylose	−3556		*c*						
$C_{24}H_{42}O_{21}$	Stachyose	−4130		*c*						
$C_{28}H_{38}O_{19}$	Cellobiose octaacetate	−3776		*c*						
$C_{28}H_{38}O_{19}$	Lactose octaacetate	−3791		*c*						
$C_{28}H_{38}O_{19}$	Maltose octaacetate	−3785		*c*						
$C_{28}H_{38}O_{19}$	Sucrose octaacetate	−3774		*c*						
$C_{36}H_{60}O_{30}$	α-Tetramylose (α-cyclodextrin)	−5690		*c*						
$C_{48}H_{60}O_{40}$	β-Hexamylose (γ-cyclodextrin)	−7753		*c*						

[a]Reference 1c.
[b]Reference 8.
[c]Reference 15.

APPENDIX A13. Heats of formation of polyethers with additional functional groups (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_5H_9O_3F_3$	Trimethyltrifluoroorthoacetate				−1230		*a*	−1192		*a*
$C_6H_8O_{11}N_4F_2$	1,9-Difluoro-1,1,9,9-tetranitro-3,5,7-trioxanonane				−1031.4	1.9	*b*			
$C_6H_{18}O_{15}N_6$	(Bis(3,3,3-trinitroethoxy)ethyl) ether	−596.9	1.3	*b*						
$C_7H_9O_2N_9$	Tris(2,2,2-trinitroethyl)-orthoformate	−582.8	3.3	*c*	−433.0	5.4	*c*			
$C_9H_8O_2N_2$	Tetrakis-(2,2,2-trinitroethyl) orthocarbonate	−767.0	4.2	*c*						
$C_{10}H_9O_4N$	5,6-Dimethoxyphthaldehydic acid anhydride oxime	−400		*d*						
$C_{12}H_{14}O_{27}N_8$	Saccharose octanitrate	−1364.0	10.9	*b*						
$C_{19}H_{21}O_3N$	Thebaine	−264		*e*						
$C_{20}H_{21}O_4N$	Papaverine	−503		*e*						
$C_{20}H_{27}O_{11}N$	Amygdalin	−1904		*e*						
$C_{22}H_{23}O_7N$	Narcotine	−882		*e*						
$C_{23}H_{21}O_{10}N$	Narceine dihydrate	−1762		*e*						
$C_{23}H_{26}O_4N_2$	Brucine	−496		*e*						
$C_{24}H_{24}O_3N_2$	Anisine	−213		*e*						

[a] J. P. Guthrie, *Can. J. Chem.*, **54**, 212 (1976).
[b] Reference 1c.
[c] N. B. Lebedeva, V. L. Ryadnenko, N. N. Gutner, L. F. Nazarova, N. N. Kisleva, I. N. Aizenshtadt and I. V. Kirilenko, *J. Appl. Chem. USSR*, **50**, 726 (1977).
[d] Reference 8.
[e] Reference 15.

APPENDIX A14. Heats of formation of unsubstituted monoalcohols (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
CH_4O	Methanol				−239.1	0.3	*a*	−201.5	0.3	*a*
C_2H_6O	Ethanol				−277.6	0.2	*a*	−235.2	0.4	*a*
C_3H_4O	2-Propyn-1-ol				−22		*b*	42		*b*
C_3H_5O	2-Propen-1-ol [allyl alcohol]				−171.8	2.2	*a*	−124.5	1.8	*a*
C_3H_8O	1-Propanol				−302.6	0.5	*a*	−255.1	0.5	*a*
C_3H_8O	2-Propanol [isopropyl alcohol]				−318.1	0.5	*a*	−272.8	0.5	*a*
C_4H_8O	Cyclobutanol				−207.4	1.4	*c*	−154.6	1.6	*c*
$C_4H_{10}O$	1-Butanol				−327.3	0.4	*a*	−275.8	0.5	*a*
$C_4H_{10}O$	2-Butanol [*sec*-butyl alcohol]				−342.6	0.7	*a*	−292.9	0.7	*a*
$C_4H_{10}O$	2-Methyl-1-propanol [isobutyl alcohol]				−334.7	0.9	*a*	−283.9	0.9	*a*
$C_4H_{10}O$	2-Methyl-2-propanol [*t*-butyl alcohol]				−359.2	0.8	*a*	−312.5	0.8	*a*
$C_5H_{10}O$	1-Penten-3-ol				−246		*b*			
$C_5H_{10}O$	Cyclobutanemethanol				−268		*b*			
$C_5H_{10}O$	Cyclopentanol				−300.1	1.6	*a*	−242.6	1.7	*a*
$C_5H_{12}O$	1-Pentanol				−351.6	0.4	*a*	−294.7	0.5	*a*
$C_5H_{12}O$	2,2-Dimethyl-1-propanol [neopentyl alcohol]				−399.4	16.7	*a*			
$C_5H_{12}O$	2-Methyl-1-butanol				−356.6	0.6	*a*	−302.0	1.4	*a*
$C_5H_{12}O$	2-Methyl-2-butanol [*t*-amyl alcohol]				−379.5	0.5	*d*	−330.8	1.4	*a*
$C_5H_{12}O$	2-Pentanol				−365.2	1.1	*a*	−312.7	1.7	*a*
$C_5H_{12}O$	3-Methyl-1-butanol				−356.4	0.6	*a*	−301.3	1.4	*a*
$C_5H_{12}O$	3-Methyl-2-butanol				−366.6	0.7	*a*	−315.2	1.4	*a*
$C_5H_{12}O$	3-Pentanol				−368.9	0.6	*a*	−317.2	1.4	*a*
$C_6H_{10}O$	2-Methylenecyclopentanol				46.9	3.8	*a*			
$C_6H_{10}O$	Cyclopentene-1-methanol				34.4	3.3	*a*			
$C_6H_{12}O$	1-Methylcyclopentanol				−343.5	0.8	*e*	−352.0	0.8	*e*
$C_6H_{12}O$	2-Methylcyclopentanol, *cis*				−345.5	1.6	*a*			
$C_6H_{12}O$	Cyclohexanol				−348.2	2.1	*a*	−286.1	1.0	*a*
$C_6H_{14}O$	1-Hexanol				−377.5	0.5	*a*	−315.8	0.6	*a*

(continued)

APPENDIX A14. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_6H_{14}O$	2,3-Dimethyl-2-butanol				−411.0	1.5	*d*	−357.0	1.7	*d*
$C_6H_{14}O$	2-Hexanol				−392.0	3.6	*a,f,i*			
$C_6H_{14}O$	2-Methyl-3-pentanol				−396.4	1.0	*a*			
$C_6H_{14}O$	3,3-Dimethyl-2-butanol				−434		*b*			
$C_6H_{14}O$	3-Hexanol				−391.0	0.9	*f*			
$C_6H_{14}O$	3-Methyl-3-pentanol				−404.9	0.9	*d*	−348.3	1.2	*d*
$C_6H_{14}O$	4-Methyl-2-pentanol				−394.7	0.8	*a*			
C_7H_8O	Phenylmethanol [benzyl alcohol]				−160.7	1.2	*a*	−100.4	1.3	*a*
$C_7H_{10}O$	1,1-Dimethyl-4-penten-2-yn-1-yl alcohol				−14.6	0.7	*g*	46.2	0.7	*g*
$C_7H_{12}O$	1,6-Heptadien-4-ol				−167		*b*			
$C_7H_{12}O$	2-Methylenecyclohexanol				−277.6	3.3	*a*			
$C_7H_{12}O$	Bicyclo[2.2.1]heptan-2-ol [norbornan-2-ol]	−281.3	2.1	*e*	−278.7	2.1	*e*			
$C_7H_{12}O$	Bicyclo[2.2.1]heptan-7-ol [norbornan-7-ol]							−218.0	8.0	*h*
$C_7H_{12}O$	Cyclohexene-1-methanol				−382.6	2.1	*a*			
$C_7H_{14}O$	1,3-Dimethylcyclopentanol				−429		*b*			
$C_7H_{14}O$	1-Methylcyclohexanol	−391.9	0.8	*e*	−381.0	0.8	*e*			
$C_7H_{14}O$	2,5-Dimethylcyclopentanol				−443		*b*			
$C_7H_{14}O$	2-Ethylcyclopentanol				−408		*b*			
$C_7H_{14}O$	2-Methylcyclohexanol, *cis*				−390.2	5.0	*a*	−327.0	5.4	*a*
$C_7H_{14}O$	2-Methylcyclohexanol, *trans*				−415.7	8.8	*a*	−352.5	9.0	*a*
$C_7H_{14}O$	3-Methyl-5-hexen-3-ol				−384		*b*			
$C_7H_{14}O$	3-Methylcyclohexanol, *cis*				−416.1	8.8	*a*	−350.9	9.0	*a*
$C_7H_{14}O$	3-Methylcyclohexanol, *trans*				−394.4	8.8	*a*	−329.1	9.0	*a*
$C_7H_{14}O$	4-Methylcyclohexanol, *cis*				−413.2	5.0	*a*	−347.5	5.4	*a*
$C_7H_{14}O$	4-Methylcyclohexanol, *trans*				−433.3	10.5	*a*	−367.2	10.7	*a*
$C_7H_{14}O$	Cycloheptanol				−360.1	1.2	*c*	−239.9	1.8	*c*
$C_7H_{14}O$	Cyclohexanemethanol				−378.1	8.4	*a*			

$C_7H_{16}O$	1-Heptanol				−403.3	0.7	*a*	−336.4	1.0	*a*
$C_7H_{16}O$	2-Heptanol				−416.9	0.7	*i*			
$C_7H_{16}O$	3-Ethyl-3-pentanol				−522		*b*			
$C_7H_{16}O$	3-Heptanol				−416.8	0.7	*i*			
$C_7H_{16}O$	4-Heptanol				−416.3	0.7	*i*			
$C_8H_{14}O$	2-Octyn-1-ol				−162		*b*			
$C_8H_{14}O$	4-Methyl-1,6-heptadien-4-ol				−208		*b*			
$C_8H_{14}O$	Bicyclo[2.2.2]octan-2-ol							−285.0	8.0	*h*
$C_8H_{16}O$	(1α,3α,5α)-3,5-Dimethylcyclohexanol				−424.4	11.3	*a*			
$C_8H_{16}O$	(1α,3α,5β)-3,5-Dimethylcyclohexanol				−509.7	11.3	*a*			
$C_8H_{16}O$	(1β,3α,5α)-3,5-Dimethylcyclohexanol				−485.1	11.3	*a*			
$C_8H_{16}O$	1,2-Dimethylcyclohexanol				−420		*b*			
$C_8H_{16}O$	1,3-Dimethylcyclohexanol				−448		*b*			
$C_8H_{16}O$	2,6-Dimethylcyclohexanol				−430		*b*			
$C_8H_{16}O$	4-Methyl-1-hepten-4-ol				−405		*b*			
$C_8H_{16}O$	Cyclooctanol				−376.4	1.7	*c*	−311.2	2.2	*c*
$C_8H_{18}O$	1-Octanol				−426.5	0.7	*a*	−355.5	0.8	*a*
$C_8H_{18}O$	2-Ethyl-1-hexanol				−432.8	1.6	*a*	−365.3	2.3	*a*
$C_8H_{18}O$	4-Methyl-4-heptanol				−562		*b*			
C_9H_8O	3-Phenyl-2-propyn-1-ol				76		*b*			
$C_9H_{12}O$	2-Phenyl-2-propanol				−250.4		*j*			
$C_9H_{16}O$	2-Nonyn-1-ol				−219		*b*			
$C_9H_{18}O$	1-Cycloheptylethanol [cycloheptylmethyl carbinol]				−497		*b*			
$C_9H_{18}O$	1-Ethyl-3-methylcyclohexanol				−580		*b*			
$C_9H_{18}O$	4-Methyl-1-octen-4-ol				−403		*b*			
$C_9H_{20}O$	1-Nonanol				−453.4	0.9	*a*	−376.3	1.4	*a*
$C_9H_{20}O$	3,5,5-Trimethyl-1-hexanol				−456.5	3.0	*a*			
$C_9H_{20}O$	4-Ethyl-4-heptanol				−598		*b*			
$C_{10}H_{12}O$	1,2,3,4-Tetrahydro-1-naphthol [1-tetralol]	−241.4	25.1	*a*						
$C_{10}H_{16}O$	Adamantan-1-ol	−397.6	2.6	*a*				−311.0	3.6	*a*
$C_{10}H_{16}O$	Adamantan-2-ol	−388.0	3.8	*a*				−299.3	4.6	*a*

(*continued*)

APPENDIX A14. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_{10}H_{16}O$	Isopinocampheol							−182.0	8.0	*h*
$C_{10}H_{16}O$	Neoisopinocampheol							−180.0	8.0	*h*
$C_{10}H_{16}O$	Neopinocampheol							−184.0	8.0	*h*
$C_{10}H_{16}O$	Pinocampheol							−188.0	8.0	*h*
$C_{10}H_{18}O$	3-Thujanol				−313		*b*			
$C_{10}H_{18}O$	4-Propyl-1,6-heptadien-4-ol				−347		*b*			
$C_{10}H_{18}O$	Borneol, *d*-	−372		*b*						
$C_{10}H_{18}O$	Caran-2-ol, *cis*				−307.5	2.3	*k*	−230.3		*k*
$C_{10}H_{18}O$	Caran-3-ol, *cis*	−329.0	3.0	*k*				−249.7	3.3	*k*
$C_{10}H_{18}O$	Caran-3-ol, *trans*	−343.5	2.4	*k*				−259.2	2.5	*k*
$C_{10}H_{18}O$	Caran-4-ol, *cis*				−312.1	2.8	*k*	−234.1	4.3	*k*
$C_{10}H_{18}O$	Decahydro-1-naphthol, *cis*	−426		*b*						
$C_{10}H_{18}O$	Decahydro-1-naphthol, *trans*	−443		*b*						
$C_{10}H_{18}O$	Decahydro-2-naphthol, *cis*	−438		*b*						
$C_{10}H_{18}O$	Decahydro-2-naphthol, *trans*	−444		*b*						
$C_{10}H_{18}O$	Decahydro-9-naphthol, *trans*	−444		*b*						
$C_{10}H_{18}O$	Isoborneol	−347		*b*						
$C_{10}H_{18}O$	Terpineol	−358		*b*						
$C_{10}H_{20}O$	Menthol	−480		*b*						
$C_{10}H_{22}O$	1-Decanol				−478.2	1.2	*a*	−396.4	1.6	*a*
$C_{11}H_{14}O$	1-Methyl-1,2,3,4-tetrahydro-1-naphthol [α-methyltetralol]	−244.2	18.4	*a*						
$C_{11}H_{22}O$	4-Methyl-1-decen-4-ol				−598		*b*			
$C_{11}H_{24}O$	1-Undecanol				−504.8	0.9	*a*			
$C_{12}H_{18}O$	2-(4-Isopropylphenyl)-2-propanol	−343.7		*l*						
$C_{12}H_{18}O$	*exo*-4-Hydroxy-*endo*-*endo*-tetracyclo-[6.2.1(3,6).0(2,7)]decane	−264.2	3.6	*a*				−185.2	4.4	*a*
$C_{12}H_{18}O$	*exo*-4-Hydroxy-*exo*-*endo*-tetracyclo-[6.2.1(3,6).0(2,7)]decane	−294.3	4.6	*a*				−218.0	5.1	*a*
$C_{12}H_{18}O$	*exo*-4-Hydroxy-*exo*-*exo*-tetracyclo-[6.2.1(3,6).0(2,7)]decane	−284.9	3.9	*a*				−209.0	4.5	*a*

$C_{12}H_{26}O$	1-Dodecanol				−528.5	0.9	*a*	−436.6	1.1	*a*
$C_{13}H_{12}O$	Diphenylmethanol [benzhydrol]	−104.8	2.0	*m*						
$C_{13}H_{28}O$	1-Tridecanol	−599.4	1.0	*a*						
$C_{13}H_{28}O$	Tri-*t*-butylmethanol	−473.3	3.8	*n*	−464.5		*n*	−410.1	4.0	*n*
$C_{14}H_{18}O$	1-Phenyl-2-octyn-1-ol				−161		*b*			
$C_{14}H_{20}O$	Diamantan-1-ol	−428.8	1.1	*a*				−310.8	1.3	*a*
$C_{14}H_{20}O$	Diamantan-3-ol	−413.8	1.5	*a*				−297.6	4.6	*a*
$C_{14}H_{20}O$	Diamantan-4-ol	−434.9	1.7	*a*				−317.1	1.7	*a*
$C_{14}H_{30}O$	1-Tetradecanol	−629.6	0.8	*a*	−580.6	1.2	*a*			
$C_{15}H_{32}O$	1-Pentadecanol	−658.2	0.8	*a*						
$C_{16}H_{34}O$	1-Hexadecanol	−696.5	1.2	*a*				−517.0	2.4	*a*
$C_{19}H_{16}O$	Triphenylmethanol	−2.5	2.3	*a*						
$C_{21}H_{16}O$	1,1,3-Triphenyl-2-propyn-ol	−215		*b*						
$C_{22}H_{22}O$	Tri-(4-methylphenyl)methanol	−67.4	23.8	*a*						
$C_{22}H_{28}O$	3′,5′-Diisopropyl-4,4-dimethyl-3-phenyl-1,2-benzocyclobuten-3-ol	−218.8	1.7	*a*				−101.8	9.2	*a*
$C_{27}H_{46}O$	Cholesterol	−674.8		*o*						
$C_{28}H_{44}O$	Ergosterol	−789.8	24.7	*a*				−670.9	25.5	*a*

[a]Reference 1c.
[b]Reference 8.
[c]The heat of formation of cycloalkanones from G. Wolf, *Helv. Chim. Acta*, **55**,1446 (1972) was combined with the heat of reduction from K. B. Wiberg, L. S. Crocker and K. M. Morgan, *J. Am. Chem. Soc.*, **113**, 3447 (1991).
[d]Reference 40e.
[e]Reference 40c.
[f]Reference 40a.
[g]Y. Y. Van-Chin-Syan, T. N. Dolbneva, V. P. Vasil'ev, S. K. Chuchmarev and V. A. Prichin, *Russ. J. Phys. Chem.*, **56**, 1736 (1982).
[h]Unpublished results of William V. Steele and Paul Muller, personal communication to the authors from Prof. Muller.
[i]Reference 40b.
[j]T. N. Dolbneva, M. A. Dikii and C. H. Wang, Deposited document, 1982, SPSTL, 295Khp-D82; *Chem. Abstr.*, **101**, 22822a (1984).
[k]V. P. Kolesov and M. P. Kozina, *Russ. Chem. Rev.*, **55**, 912 (1986).
[l]T. N. Dolbneva, M. A. Dikii and C. H. Wang, Deposited document, 1982, SPSTL, 293Khp-D82; *Chem. Abstr.*, **101**, 22824c (1984).
[m]G. S. Parks, K. R. Manchester and L. M. Vaughn, *J. Chem. Phys.*, **22**, 2089 (1954).
[n]H. Maskill and W. V. Steele, *J. Chem. Thermodyn.*, **15**, 481 (1983).
[o]W. H. Johnson, *J. Res. Natl. Bur. Stand.*, **79A**, 492 (1975).

APPENDIX A15. Heats of formation of monoalcohols with oxygen functional groups ($kJ\,mol^{-1}$)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_2H_4O_2$	Hydroxyacetaldehyde							−318.0		*a*
$C_2H_4O_3$	Hydroxyacetic acid [glycolic acid]				−664		*b*			
$C_3H_4O_5$	Hydroxypropanedioic acid [tartronic acid]	−1060		*c*						
$C_3H_6O_2$	2,3-Epoxy-1-propanol [oxirane methanol; glycidyl alcohol]				−298.2	0.9	*d*			
$C_3H_6O_2$	2-Hydroxypropanal [lactaldehyde]	−439		*c*						
$C_3H_6O_3$	2-Hydroxypropanoic acid, *d*- [lactic acid]	−694		*b*						
$C_3H_6O_3$	2-Hydroxypropanoic acid, *l*- [lactic acid]	−694.0	1.0	*d*						
$C_3H_6O_3$	2-Hyroxypropanoic acid, *dl*- [lactic acid]				−671		*b*			
$C_3H_8O_2$	2-Methoxyethanol				−480		*c*			
$C_4H_6O_5$	2-Hydroxybutanedioic acid, (*R*-) [malic acid]	−1105.7	0.6	*d*						
$C_4H_6O_5$	2-Hydroxybutanedioic acid, (*S*-) [malic acid]	−1103.6	4.2	*d*						
$C_4H_6O_5$	2-Hydroxybutanedioic acid, *dl*- [malic acid]	−1106		*b*						
$C_4H_8O_2$	3-Hydroxybutanal				−431		*c*			
$C_4H_8O_3$	2-Hydroxy-2-methylpropanoic acid [2-hydroxyisobutyric acid]	−744.0		*b*						
$C_4H_8O_3$	2-Hydroxybutanoic acid	−677.0		*c*						
$C_4H_8O_3$	3-Hydroxybutanoic acid, *dl*- [hydroxybutyric acid]				−679		*b*			
$C_4H_8O_3$	Methyl 2-hydroxypropanoate [methyl lactate]				−637		*c*			
$C_5H_6O_2$	2-Furyl methanol [furfuryl alcohol]				−276.2	1.3	*d*	−211.8	2.1	*d*
$C_5H_{10}O_2$	2-Tetrahydrofuryl methanol [tetrahydrofurfuryl alcohol]				−435.7	5.9	*d*	−369.2	6.2	*d*

$C_5H_{10}O_2$	5-Hydroxy-1-pentanal				−450		*b*			
$C_5H_{10}O_3$	Ethyl 2-hydroxypropanoate [ethyl lactate]				−664		*c*			
$C_5H_{12}O_3$	2-(2-Methoxyethoxy)ethanol				−673		*c*			
$C_6H_8O_7$	2-Hydroxy-1,2,3-propanetricarboxylic acid [citric acid]	−1543.8	4.6	*d*						
$C_6H_{10}O_8$	Citric acid monohydrate	−1837.5	0.5	*d*						
$C_6H_{12}O_2$	2-Methyl-4-oxo-2-pentanol				−592.7	7.7	*e*			
$C_6H_{12}O_2$	4-Hydroxy-4-methyl-2-pentanone [diacetone alcohol]				−531		*e*			
$C_6H_{12}O_3$	2,2-Dimethyl-4-methanol-dioxolane [acetone glycerol]				−682		*b*			
$C_6H_{12}O_3$	2,3-Butanediol monoacetate [(3-hydroxy)-2-butyl acetate]				−729.6	39.0	*d*			
$C_6H_{14}O_3$	2-(*t*-Butylperoxy)ethanol				−511.7	2.3	*f*	−465.2	3.0	*f*
$C_7H_8O_2$	Hydroxybenzyl alcohol, *ortho*	−361		*c*						
$C_7H_{10}O_2$	1-(2-Furyl)propan-1-ol				−447.0	7.1	*d*			
$C_7H_{12}O_5$	1,2,3-Propanetriol 1,3-diacetate [glycerol-1,3-diacetate]				−1120.7	6.7	*d*			
$C_7H_{16}O_3$	2-(*t*-Pentylperoxy)ethanol				−534.2	1.6	*f*	−464.3	3.0	*f*
$C_7H_{16}O_3$	3-(*t*-Butylperoxy)-1-propanol				−511.7		*g*			
$C_8H_8O_3$	4-Hydroxy-3-methoxybenzaldehyde							−375.0		*h*
$C_8H_8O_3$	Hydroxy(phenyl)acetic acid *dl*- [mandelic acid]	−579.4	0.9	*d*						
$C_8H_8O_3$	Hydroxy(phenyl)acetic acid, (*S*-) [mandelic acid]	−580.6	0.9	*d*						
$C_8H_8O_3$	Hydroxymethylbenzoic acid, *ortho*	−576		*c*						
$C_8H_{14}O_2$	1-(2-Hydroxycyclopentyl)-2-propanone				−472.0	4.6	*d*			
$C_8H_{18}O_3$	3-(*t*-Pentylperoxy)-1-propanol				−534.2		*g*			
$C_8H_{18}O_4$	1-(*t*-Butylperoxy)-3-methoxy-2-propanol				−666.3	2.6	*d*			

(*continued*)

APPENDIX A15. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_9H_{10}O_4$	Phenyl-2,3-dihydroxypropanoic acid, *dl*- [phenylglyceric acid]	−747		*b*						
$C_9H_{20}O_4$	1-(*t*-Butylperoxy)-3-ethoxy-2-propanol				−706.7	3.0	*d*			
$C_{10}H_8O_4$	Furoin	−414		*c*						
$C_{10}H_{10}O_3$	Hydroxy-methylcinnamic acid, *cis*	−472		*c*						
$C_{10}H_{10}O_3$	Hydroxy-methylcinnamic acid, *trans*	−498		*c*						
$C_{10}H_{12}O_2$	2-Methoxy-4-(1-propenyl)phenol				−300		*c*			
$C_{10}H_{12}O_2$	2-Methoxy-4-(2-propenyl)phenol				−263		*c*			
$C_{10}H_{20}O_3$	1-(*t*-Butylperoxy)cyclohexanol				−589.1	5.7	*i*			
$C_{10}H_{22}O_3$	1-*t*-Butoxy-3-ethoxy-2-propanol				−750.7	2.6	*d*			
$C_{10}H_{22}O_3$	1-*t*-Butoxy-3-propoxy-2-propanol				−774.0	3.0	*d*			
$C_{10}H_{22}O_4$	1-(*t*-Butylperoxy)-3-propoxy-2-propanol				−725.0	3.0	*d*			
$C_{11}H_{24}O_3$	1-Butoxy-3-*t*-butoxy-2-propanol				−794.3	4.2	*d*			
$C_{11}H_{24}O_4$	1-Butoxy-3-(*t*-butylperoxy)-2-propanol				−747.0	3.0	*d*			
$C_{12}H_{20}O_2$	2-(1-Hydroxycyclohexyl)-cyclohexanone				−590.2		*j*			
$C_{12}H_{20}O_3$	2,5-Dimethyl-5-(*t*-butylperoxy)-3-hexyn-2-ol				−696.9	2.2	*k*	−624.6	2.8	*k*
$C_{12}H_{20}O_7$	Triethyl citrate	−1476		*c*						
$C_{12}H_{26}O_3$	1-*t*-Butoxy-3-pentoxy-2-propanol				−818.0	4.6	*d*			
$C_{12}H_{26}O_4$	1-(*t*-Butylperoxy)-3-pentyloxy-2-propanol				−771.2	4.6	*d*			
$C_{13}H_{20}O_3$	2-(4-*t*-Butylperoxyphenyl)-2-propanol	−564.2		*l*						
$C_{14}H_{12}O_2$	Benzoin [benzoyl phenyl methanol]	−248		*c*						

$C_{14}H_{12}O_3$	Diphenyl (hydroxy)acetic acid [benzilic acid]	−448	*c*		
$C_{14}H_{20}O_9$	Rhamnose triacetate	−1905	*b*		
$C_{16}H_{26}O_3$	(2-(4-(2-Hydroxyisopropyl)phenyl)-2-propyl)-*t*-butyl peroxide	−564.2	*m*		
$C_{18}H_{16}O_2$	Cinnamoin			−129	*c*
$C_{19}H_{28}O_2$	5α-Androstane-3-one-17β-ol	−502	*b*		
$C_{19}H_{28}O_2$	Androsterone	−679	*b*		
$C_{19}H_{28}O_2$	Dehydroandrosterone, *trans*	−448	*b*		
$C_{19}H_{28}O_3$	Epiandrosterone	−636	*b*		
$C_{19}H_{28}O_2$	Testosterone	−393	*b*		
$C_{21}H_{18}O_2$	1-Hydroxy-3,3-diphenylpropiophenone			−215	*c*
$C_{21}H_{30}O_3$	Cortexone	−519	*b*		
$C_{47}H_{88}O_5$	Glyceryl dibrassidate	−1975	*b*		
$C_{47}H_{88}O_5$	Glyceryl dierucate	−1870	*b*		

[a]F. Turecek and Z. Havlas, *J. Org. Chem.*, **51**, 4061 (1986).
[b]Reference 15.
[c]Reference 8.
[d]Reference 1c.
[e]R. Vilen and S. Perisanu, *Rev. Roum. Chim.*, **24**, 237 (1979).
[f]Y. Y. Van-Chin-Syan, N. S. Kachurina, G. A. Petrovkaya and S. K. Chuchmarev, *Russ. J. Phys. Chem.*, **57**, 1751 (1983).
[g]N. S. Kachurina, C. N. Wang and G. A. Petrovkaya, Deposited, document, 1981, SPSTL, 950Khp-D81; *Chem. Abstr.*, **98**, 142797a (1983).
[h]To obtain the heat of formation of the gas, we used the heat of formation of the solid from the source cited and the heat of sublimation from J. S. Chickos, in Reference 37.
[i]The value is from the liquid-phase heat of reaction of cyclohexanone and *t*-butyl hydroperoxide from V. L. Antonovskii. E. V. Federova, N. E. Shtivel and V. D. Emelin, *Kinet. Katal.*, **30**, 1235 (1989).
[j]The value is from the liquid-phase equilibration of cyclohexanone and the compound of interest, its aldol condensation product: data from G. A. Efimova, I. V. Shustova, Y. E. Shapirov, V. A. Efimov, B. S. Turov and V. M. Makarov, *Zh. Org. Khim.*, **25**, 1201 (1989) using heat of formation of liquid cyclohexanone from Reference 1c.
[k]Y. Y. Van-Chin-Syan, V. F. Korotyuk and Yu. U. Panchenko, *Russ. J. Phys. Chem.*, **57**, 1727 (1983).
[l]T. N. Dolbneva, M. A Dikii and C. H. Wang, Deposited document, 1982, SPSTL, 295Khp-D82; *Chem. Abstr.*, **101**, 22822a (1984).
[m]T. N. Dolbneva, M. A. Dikii and C. H. Wang, Deposited document, 1982, SPSTL, 293Khp-D82; *Chem. Abstr.*, **101**, 22824c (1984).

APPENDIX A16. Heats of formation of monoalcohols with nitrogen (and oxygen) functional groups (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
C_2H_3ON	Cyanomethanol [glycolonitrile]				−143		*a*			
$C_2H_3O_7N_3$	2,2,2-Trinitroethanol	−262.0	2.5	*b*	−249.7	2.8	*b*			
$C_2H_5ON_3$	2-Azidoethanol				94.4	1.9	*b*			
$C_2H_5O_3N$	2-Nitroethanol				−350.7	2.3	*b*			
C_2H_7ON	2-Aminoethanol [ethanolamine]				−274		*a*			
$C_2H_8O_4N_2$	2-Aminoethanol, nitrate salt	−576		*a*						
C_3H_5ON	1-Cyanoethanol [lactonitrile]				−132		*a*			
$C_3H_6O_5N_6$	Glycerin-1,3-dinitrate				−477.7	3.3	*c*			
$C_3H_6O_5N_2$	Glycerin-1,2-dinitrate				−472.2	2.9	*c*			
$C_3H_7O_2N$	2-Amino-3-hydroxypropanoic acid D,L- [serine]	−739.0	1.9	*d*						
$C_3H_7O_3N$	2-Amino-3-hydroxypropanoic acid, L- [serine]	−732.7	0.3	*b*				−647		*e*
$C_3H_7O_3N$	3-Amino-2-hydroxypropanoic acid, L- [isoserine]	−744.0		*b*						
$C_3H_7O_3N_3$	2-(Methylnitroamino)ethanol	−186.1	2.0	*b*						
C_3H_9ON	*N*,*N*-Dimethylaminomethanol				−253.6	1.2	*b*	−203.3	4.4	*b*
$C_4H_4O_4N_2$	2,4,6(1*H*,3*H*)-Pyrimidine trione-5-ol [dialuric acid]	−1315		*f*						
$C_4H_9O_3N$	2-Methyl-2-nitro-1-propanol	−410.1	1.7	*b*						
$C_4H_9O_3N$	3-Nitro-2-butanol				−390.0	5.0	*b*			
$C_4H_9O_3N$	2-Amino-2-hydroxybutyric acid L- [threonine]	−807.2	0.9	*b*				−709		*e*
$C_4H_9O_3N$	2-Amino-2-hydroxybutyric acid *dl*- [threonine]	−758.8	0.5	*b*						

$C_5H_9O_3N$	4-Hydroxyproline, L-	−661.1	1.8	*b*						
$C_5H_{11}O_2$	2-Keto-5-(2-hydroxyethyl)-tetrahydro-1,3,5-triazine	−465.8	3.8	*g*						
$C_6H_{11}O_5N$	Ethanolamine *N,N*-diacetic acid	−1134.0	2.3	*h*						
$C_6H_{15}ON$	2-(Diethylamino)ethanol				−309.5	0.6	*b*			
$C_8H_8O_6N_2$	2-(2,4-Dinitrophenoxy)ethanol	−398.7	1.0	*b*						
$C_9H_{18}O_2N$	4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxyl	−392.6	7.6	*b*				−291.1	9.2	*b*
$C_9H_{19}O_2N$	1-Hydroxy-2,2,6,6-tetramethyl-4-piperidinol	−445.5	1.4	*b*				−345.1	1.5	*b*
$C_{10}H_9O_4N$	5,6-Dimethoxyphthaldehydic acid anhydride oxime	−400		*a*						
$C_{10}H_{13}O_3N$	2-Methyl-2-nitro-1-phenyl-1-propanol	−317.0	5.9	*b*						
$C_{10}H_{13}O_3N$	2-Methyl-2-nitro-3-phenyl-1-propanol	−347.5	4.6	*b*						
$C_{12}H_{17}O_5N$	5-(Hydroxymethyl)-3-methyl-pyrrole-2,4-dicarboxylic acid, diethyl ester	−1057.7	6.3	*b*						
$C_{13}H_{19}O_5N$	3-Methyl-5-(1-hydroxyethyl)-pyrrole-2,4-dicarboxylic acid, diethyl ester	−1135.8	6.7	*b*						
$C_{14}H_{21}O_5N$	3-Methyl-5-(1-hydroxypropyl)-pyrrole-2,4-dicarboxylic acid, diethyl ester	−1084.6	7.5	*b*						
$C_{15}H_{16}O_2N_2$	3-(2-Hydroxyethyl)-1,1-diphenylurea	−319.2	7.5	*b*						
$C_{16}H_{11}O_5N$	Nitroacetylbenzoin, *para*	−62		*a*						
$C_{17}H_{21}O_4N$	Morphine monohydrate	−711		*f*						
$C_{18}H_{23}O_4N$	Codeine monohydrate [morphine 3-methyl ether]	−633		*f*						

APPENDIX A16. (*continued*)

Name		Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_{19}H_{13}O_7N_3$	Tri(*p*-nitrophenyl)carbinol	−60		*a*						
$C_{19}H_{22}ON_2$	Cinchonidine [α-quinidine]	31		*f*						
$C_{19}H_{22}ON_2$	Cinchonine	30		*f*						
$C_{19}H_{24}ON_2$	Cinchonamine	−44		*f*						
$C_{19}H_{25}ON_3$	Tri(*p*-aminotriphenyl)carbinol	205		*a*						
$C_{19}H_{25}O_4N_3$	Cinchonamine nitrate	−334		*f*						
$C_{20}H_{24}O_2N_2$	Quinidine	−160		*f*						
$C_{20}H_{24}O_2N_2$	Quinine	−155		*f*						
$C_{21}H_{13}O_5N$	Nitrobenzoylbenzoin, *para*	−110		*a*						

[a]Reference 8.

[b]Reference 1c.

[c]The heat of formation was determined by A. I. Kazakov, G. V. Lagolzinskaya, E. P. Kirpichev, L. P. Andrienko, N. G. Yunda, A. M. Korolev, Yu. I. Rubisov, G. V. Manelis and L. T. Eremenko, *Doklady Phys. Chem.*, **305**, 287 (1989), via nitration reactions of glycerin. We have used the results of Kazakov and coworkers, regardless of the method, and have averaged their values when more than one method was used. However, we have used the new heat of formation of glycerin from M. Bastos, S. O. Nilsson, M. D. M. C. Ribeiro da Silva, M. A. V. Ribero da Silva and I. Wadso, *J. Chem. Thermodyn.*, **20**, 1353 (1988), thereby decreasing the heats of formation by 1.1 kJ mol^{-1} but maintaining the original error bars. For completeness, the heat of formation of liquid glycerin trinitrate is -371.1 ± 2.1 kJ mol^{-1}.

[d]V. A. Vasil'ev, V. A. Borodin and S. B. Kopnyshev, *Russ. J. Phys. Chem.*, **65**, 29 (1991).

[e]These data are considered unreliable. To obtain the heat of formation of the gas, we used the heat of formation of the solid from the source cited and the heat of sublimation from J. S. Chickos, in Reference 37.

[f]Reference 15.

[g]N. A. Karpenko, N. M. Gutriev, V. L. Ryadnenko and V. I. Timofe'eva, *Russ. J. Appl. Chem.*, **63**, 204 (1990).

[h]V. P. Vasil'ev, V. A. Borodin and S. B. Kopnyshev, *Russ. J. Phys. Chem.*, **63**, 1566 (1989).

APPENDIX A17. Heats of formation of monoalcohols with additional functional groups (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_2H_3OF_3$	2,2,2-Trifluoroethanol				−932.4	0.9	*a*	−888.4	1.0	*a*
$C_2H_3O_5N_2F$	2-Fluoro-2,2-dinitroethanol	−480.3	2.6	*a*				−181.8	2.9	*a*
$C_2H_4OF_2$	2,2-Difluoroethanol				−687		*b*			
C_2H_5OCl	2-Chloroethanol				−294		*b*			
C_2H_5OF	2-Fluoroethanol				−465		*b*			
$C_3H_3OF_5$	2,2,3,3,3-Pentafluoro-1-propanol				−1354.7	2.9	*a*	−1310.3	2.9	*a*
$C_3H_4OF_4$	2,2,3,3-Tetrafluoro-1-propanol				−1114.9	0.8	*c*	−1064.8	2.7	*c*
$C_3H_5OF_3$	3,3,3-Trifluoro-1-propanol				−969.6	1.6	*c*	−921.0	2.5	*c*
$C_3H_6OCl_2$	2,3-Dichloro-1-propanol				−381.5	2.1	*a*	−316.3	4.7	*a*
$C_4H_3OF_7$	2,2,3,3,4,4,4-Heptafluoro-1-butanol				−1782.9	6.3	*c*	−1739.7	7.9	*c*
$C_4H_4O_2F_6$	1,1,1,3,3,3-Hexafluoro-2-methoxy-2-propanol				−1577.0		*d*	−1506.0		*d*
$C_4H_4O_2F_6$	1,1,1,3,3,3-Hexafluoro-2-methoxy-2-propanol				−1578.6		*d*	−1505.8		*d*

[a]Reference 1c.
[b]Reference 8.
[c]V. P. Kolesov and M. P. Kozina, *Russ. Chem. Rev.*, **55**, 912 (1986).
[d]F. E. Rogers and R. J. Rapiejko, *J. Am. Chem. Soc.*, **93**, 4596 (1971).

APPENDIX A18. Heats of formation of unsubstituted dialcohols (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_2H_6O_2$	1,2-Ethanediol				−460.0	2.8	*a*	−394.4	2.8	*a*
$C_3H_8O_2$	1,2-Propanediol				−501.0	4.1	*b*	−429.8	4.1	*b*
$C_3H_8O_2$	1,3-Propanediol				−480.8	5.1	*a*	−408.4	5.1	*a*
$C_4H_6O_2$	2-Butyn-1,4-diol	−227		*c*						
$C_4H_8O_2$	2-Buten-1,4-diol				−390		*c*			
$C_4H_{10}O_2$	1,2-Butanediol				−546.7	7.5	*b*	−565.1	7.5	*b*
$C_4H_{10}O_2$	1,3-Butanediol				−501.0	2.1	*d*	−433.2	3.0	*d*
$C_4H_{10}O_2$	1,4-Butanediol				−505.3	5.7	*a*	−426.0	5.7	*a*
$C_4H_{10}O_2$	2,3-Butanediol				−541.5	2.5	*d*	−482.3	3.2	*d*
$C_4H_{10}O_2$	2-Methyl-1,2-propanediol				−539.7	2.5	*d*			
$C_5H_{10}O_2$	1,1-Cyclopropanedimethanol				−436		*c*			
$C_5H_{10}O_2$	1,2-Cyclopentanediol, *cis*	−485.1	4.2	*d*						
$C_5H_{10}O_2$	1,2-Cyclopentanediol, *trans*	−490.1	2.9	*d*						
$C_5H_{12}O_2$	1,5-Pentanediol				−528.8	5.7	*a*	−442.0	5.7	*a*
$C_5H_{12}O_2$	2,2-Dimethyl-1,3-propanediol	−551.2	4.3	*d*						
$C_6H_{12}O_2$	1,2-Cyclohexanediol, *cis*	−555		*c*						
$C_6H_{12}O_2$	1,2,-Cyclohexanediol, *trans*	−551		*c*						
$C_6H_{12}O_2$	1-Methylcyclopentan-1,2-diol, *cis*	−530		*c*						
$C_6H_{12}O_2$	1-Methylcyclopentan-1,2-diol, *trans*	−539		*c*						
$C_6H_{14}O_2$	1,2-Hexanediol, D,L-				−577.1	7.1	*b*	−590.1		*b*
$C_6H_{14}O_2$	1,6-Hexanediol	−574.1	4.4	*e*	−544.4	4.8	*d*	−466.0	4.4	*e*
$C_6H_{14}O_2$	2,3-Dimethyl-2,3-butanediol [pinacol]	−606.3	8.5	*f*				−540.4	9.4	*f*
$C_7H_8O_2$	Hydroxybenzyl alcohol, *ortho*	−361		*c*						
$C_7H_{14}O_2$	1-Methylcyclohexan-1,2,diol, *cis*	−603		*c*						
$C_7H_{14}O_2$	1-Methylcyclohexan-1,2-diol, *trans*	−593		*c*						
$C_7H_{16}O_2$	1,7-Heptanediol				−574.2	9.3	*e*	−477.6	9.3	*e*
$C_8H_{10}O_2$	1,4-Bis(hydroxymethyl)benzene	−393.9	1.7	*d*						
$C_8H_{14}O_2$	2,5-Dimethyl-3-hexyn-2,5-diol	−386.0	3.3	*g*				−279.3	3.4	*g*
$C_8H_{16}O_2$	2,5-Dimethyl-3-hexen-2,5-diol, (*E*)	−512		*c*						
$C_8H_{16}O_2$	2,5-Dimethyl-3-hexen-2,5-diol, (*Z*)	−526		*c*						

$C_8H_{18}O_2$	1,8-Octanediol	−626.2	4.8	*e*				−487.3	4.9	*e*
$C_8H_{18}O_2$	2,5-Dimethylhexane-2,5-diol	−682.7	1.7	*d*						
$C_8H_{18}O_2$	2,5-Dimethylhexane-2,5-diol	−681.6	1.6	*g*				−580.9	1.8	*g*
$C_9H_{10}O_2$	Hydrindene-1,2-diol, *cis*	−373		*c*						
$C_9H_{10}O_2$	Hydrindene-1,2-diol, *trans*	−381		*c*						
$C_9H_{20}O_2$	1,9-Nonanediol				−657.6	7.0	*e*	−508.9	7.5	*e*
$C_{10}H_{12}O_2$	1,2,3,4-Tetrahydronaphthalene-2,3-diol, *trans*	−421		*c*						
$C_{10}H_{12}O_2$	1,2,3,4-Tetrahydronaphthalene-1,2-diol, *cis*	−415		*c*						
$C_{10}H_{12}O_2$	1,2,3,4-Tetrahydronaphthalene-1,2-diol, *trans*	−421		*c*						
$C_{10}H_{12}O_2$	1,2,3,4-Tetrahydronaphthalene-2,3-diol, *cis*	−415		*c*						
$C_{10}H_{22}O_2$	1,10-Decanediol	−678.0	2.3	*e*				−523.1	2.4	*e*
$C_{10}H_{22}O_2$	2,7-Dimethyl-2,7-octanediol	−730.0	2.1	*d*						
$C_{12}H_{16}O_2$	1-Phenyl-1,2-cyclohexanediol, *cis*	−468		*c*						
$C_{12}H_{16}O_2$	1-Phenyl-1,2-cyclohexanediol, *trans*	−464		*c*						
$C_{12}H_{22}O_2$	3,6-Diethylocta-4-yn-3,6-diol	−481.5	2.6	*d*						
$C_{12}H_{26}O_2$	2,9-Dimethyl-2,9-decanediol	−789.6	4.6	*d*						
$C_{14}H_{14}O_2$	1,2-Diphenylethane-1,2-diol, *dl* -[isohydrobenzoin]	−275		*c*						
$C_{14}H_{14}O_2$	1,2-Diphenylethane-1,2-diol, *meso* [hydrobenzoin]	−295		*c*						
$C_{14}H_{30}O_2$	2,11-Dimethyl-2,11-dodecanediol	−846.2	3.8	*d*						
$C_{18}H_{20}O_2$	Hydrocinnamoin				−187		*c*			

[a]P. Knauth and R. Sabbah, *Struct. Chem.*, **1**, 43 (1990).
[b]P. Knauth and R. Sabbah, *Thermochim. Acta*, **164**, 145 (1990).
[c]Reference 8.
[d]Reference 1c.
[e]P. Knauth and R. Sabbah, *Can. J. Chem.*, **68**, 731 (1990).
[f]J. P. Guthrie, *Can. J. Chem.*, **55**, 3562 (1977).
[g]Y. Y. Van-Chin-Syan, V. F. Korotyuk and Yu. U. Panchenko, *Russ. J. Phys. Chem.*, **57**, 1727 (1983).

APPENDIX A19. Heats of formation of dialcohols with any functional groups ($kJ\,mol^{-1}$)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_2H_3O_2Br_3$	Tribromoethanal hydrate [2,2,2-tribromoethanediol]	−473		*a*						
$C_2H_3O_2Cl_3$	Trichlorethanal hydrate [chloral hydrate]	−553		*a*				−502.0		*b*
$C_2H_6O_4$	Bis(hydroxymethyl)peroxide	−665.8	5.1	*c*				−571.7	6.7	*c*
$C_3H_2O_2F_6$	Hexafluoroacetone hydrate	−1628.0		*d*						
$C_3H_4O_6$	2,2-Dihydroxy-1,2-propandioic acid [dihydroxymalonic acid]	−1216		*e*						
$C_3H_6O_2$	2,3-Epoxy-1-propanol [oxirane methanol; glycidyl alcohol]				−298.2	0.9	*c*			
$C_3H_6O_3$	2,3-Dihydroxypropanal, *dl*- [glyceraldehyde]	−623		*a*	−598		*e*			
$C_3H_7O_2Cl$	2-Chloro-1,3-propanediol				−517.5	1.1	*c*			
$C_3H_7O_2Cl$	3-Chloro-1,2-propanediol				−525.3	0.9	*c*			
$C_3H_7O_5N$	Glycerin-1-nitrate				−574.3	3.3	*f*			
$C_3H_7O_5N$	Glycerin-2-nitrate				−568.5	5.0	*f*			
$C_3H_8O_2$	2-Methoxyethanol				−422.0	7.6	*g*	−376.9	8.1	*g*
$C_3H_8O_3N_2$	*N,N'*-Bis(hydroxymethyl)urea	−715		*a*						
$C_3H_8O_3N_2$	*Bis*(hydroxymethyl)urea	−727.0	0.7	*c*						
$C_4H_4O_5N_2$	Alloxan monohydrate	−1000.7	0.5	*c*						
$C_4H_6O_6$	2,3-Dihydroxy-1,4-butanedioic acid, D- [tartaric acid]	−1257		*a*						
$C_4H_6O_6$	2,3-Dihydroxy-1,4-butanedioic acid, *dl*-	−1291		*e*						
$C_4H_6O_6$	2,3-Dihydroxy-1,4-butanedioic acid, L-	−1282		*e*						
$C_4H_6O_6$	2,3-Dihydroxy-1,4-butanedioic acid, *meso*	−1280								

$C_4H_8O_4N_2$	Tartaramide, D-	−930		*a*						
$C_4H_8O_4N_2$	Tartaramide, L-	−932		*e*						
$C_4H_8O_4N_2$	Tartaramide, *meso*	−935		*e*						
$C_4H_8O_4N_2$	Tartramide	−1193.5	5.9	*c*						
$C_4H_8O_7$	2,3-Dihydroxy-1,4-butanedioic acid monohydrate, *dl*-	−1552		*e*						
$C_4H_9O_4N$	2-Nitro-2-methyl-1,3-propanediol	−574.4	4.7	*c*						
$C_4H_9O_6N$	Monoammonium D-tartrate	−1430		*a*						
$C_4H_9O_6N$	Monoammonium *meso*-tartrate	−1433		*a*						
$C_4H_9O_6N$	Monoammonium tartrate	−1436		*a*						
$C_4H_{10}O_3$	2,2′-Dihydroxydiethyl ether [diethylene glycol]				−628.5	2.4	*c*	−571.2	6.3	*c*
$C_4H_{11}O_2N$	2,2′-Dihydroxydiethyl amine [ethanol amine]				−493.8	2.6	*h*	−397.1	2.9	*h*
$C_5H_6O_2$	2-Furyl methanol [furfuryl alcohol]				−276.2	1.3	*c*	−211.8	2.1	*c*
$C_5H_6O_4F_6$	1,1,1,5,5,5-hexafluoroacetyl-acetone dihydrate	−2286.7	7.1	*i*						
$C_5H_7O_4N$	*N*-Methyl-2,3-dihydroxy-1,4-butanimide, *dl*- [*N*-methyl tartrimide]	−806		*a*						
$C_5H_{10}O_4$	1,2,3-Propanetriol l-acetate				−909.2	3.7	*c*			
$C_5H_{11}O_4N$	2-Nitro-2-ethyl-1,3-propanediol	−606.4	2.6	*c*						
$C_6H_4O_2F_8$	2,2,3,3,4,4,5,5-Octafluoro-1,6-hexanediol	−2173.4	4.7	*j*				−2084.2	12.0	*j*
$C_6H_6O_6$	Mannonic-1,4-3,6-dilactone, D-	−1065		*e*						
$C_6H_8O_6$	Ascorbic acid, L-	−1164.6	1.0	*c*						

(*continued*)

APPENDIX A19. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_6H_9O_4N$	*N*-Ethyltartrimide, D-	−838		*a*						
$C_6H_9O_4N$	*N*-Ethyltartrimide, *dl*-	−837		*a*						
$C_6H_9O_4N$	*N*-Ethyltartrimide, *meso*	−834		*a*						
$C_6H_{10}O_4N_2$	3,6-Bis(hydroxymethyl)-2,3-piperazinedione	−875.6	0.9	*c*						
$C_6H_{12}O_5N_2$	*N*-Serylserine	−1177.7	0.5	*c*						
$C_6H_{13}O_4N$	2-Nitro-2-isopropyl-1,3-propanediol	−623.0	4.2	*c*						
$C_6H_{13}O_4N$	2-Nitro-2-propyl-1,3-propanediol	−625.2	2.9	*c*						
$C_6H_{14}O_4$	Triethylene glycol				−804.2	3.6	*c*	−725.0	8.7	*c*
$C_7H_{16}O_4$	3-(*t*-Butyldioxy)-1,2-propanediol				−719.2		*k*			
$C_8H_{10}O_{10}N_4$	Alloxantin dihydrate	−2135		*e*						
$C_8H_{14}O_6$	Diethyl 2,3-dihydroxy-1,4-butandioate, D- [diethyl tartrate]				−1253		*a*			
$C_8H_{14}O_6$	Diethyl 2,3-dihydroxy-1,4-butanedioate, *meso*				−1251		*a*			
$C_8H_{14}O_6$	Dimethyl dihydroxyadipic acid	−1154		*a*						
$C_8H_{16}O_4N_2$	Tartaric diethylamide, D-	−980		*a*						
$C_8H_{16}O_4N_2$	Tartaric diethylamide, *dl*-	−980		*a*						
$C_8H_{16}O_4N_2$	Tartaric diethylamide, *meso*	−975		*a*						
$C_8H_{18}O_5$	Tetraethylene glycol				−981.7	4.6	*c*	−883.0	11.0	*c*
$C_{10}H_9O_4N$	*N*-Phenyltartrimide, D-				−676		*a*			
$C_{10}H_9O_4N$	*N*-Phenyltartrimide, *dl*-				−675		*a*			
$C_{10}H_{12}O_4$	1,2,3-Propanetriol 1-benzoate	−777.3	1.2	*c*						
$C_{10}H_{12}O_4$	1,2,3-Propanetriol 2-benzoate	−772.8	1.2	*c*						
$C_{11}H_{11}O_4N$	*N*-Benzyltartrimide, D-	−718		*a*						
$C_{11}H_{11}O_4N$	*N*-Benzyltartrimide, *dl*-	−718		*a*						
$C_{11}H_{11}O_4N$	*N*-Benzyltartrimide, *meso*	−706		*a*						
$C_{12}H_{14}O_8N_4$	Amalic acid [tetramethyl alloxantin]	−1535		*e*						
$C_{12}H_{22}O_6$	1,2,5,6-Diacetonemannitol	−1464		*e*						

$C_{13}H_{26}O_4$	1,2,3-Propanetriol-1-decanoate	−1109.0	1.3	*c*
$C_{13}H_{26}O_4$	1,2,3-Propanetriol 2-decanoate	−1095.7	2.0	*c*
$C_{14}H_{10}O_3$	Disalicylic aldehyde	−289		*a*
$C_{15}H_{30}O_4$	1,2,3-Propanetriol-1-dodecanoate	−1160.9	1.7	*c*
$C_{15}H_{30}O_4$	1,2,3-Propanetriol 2-dodecanoate	−1152.6	1.7	*c*
$C_{16}H_{12}O_4N_2$	Isatidè	−582		*e*
$C_{17}H_{34}O_4$	1,2,3-Propanetriol 1-tetradecanoate	−1222.6	1.9	*c*
$C_{17}H_{34}O_4$	1,2,3-Propanetriol 2-tetradecanoate	−1212.9	1.9	*c*
$C_{19}H_{38}O_4$	1,2,3-Propanetriol 1-hexadecanoate	−1281.5	2.2	*c*
$C_{19}H_{38}O_4$	1,2,3-Propanetriol 2-hexadecanoate	−1268.7	1.9	*c*
$C_{21}H_{28}O_5$	Cortisone	−1067.0		*c*
$C_{21}H_{42}O_4$	1,2,3-Propanetriol 1-octadecanoate	−1337.4	1.9	*c*
$C_{21}H_{42}O_4$	1,2,3-Propanetriol 2-octadecanoate	−1321.3	2.4	*c*
$C_{22}H_{44}O_4$	13,14-Dihydroxybehenic acid [13,14-dihydroxydocosanoic acid]	−1410		*e*

[a]Reference 8.
[b]To obtain the heat of formation of the gas, we used the heat of formation of the solid from the source cited and the heat of sublimation from J. S. Chickos, in Reference 37.
[c]Reference 1c.
[d]F. E. Rogers and R. J. Rapiejko, *J. Am. Chem. Soc.*, **93**, 4596 (1971).
[e]Reference 15.
[f]The heat of formation was determined by A. I. Kazakov, G. V. Lagolzinskaya, E. P. Kirpichev, L. P. Andrienko, N. G. Yunda, A. M. Korolev, Yu, I. Rubisov, G. V. Manelis and L. T. Eremenko, *Doklady Phys. Chem.*, **305**, 287 (1989), via nitration reactions of glycerin. We have used the results of Kazakov and coworkers, regardless of the method, and have averaged their values when more than one method was used. However, we have used the new heat of formation of glycerin from M. Bastos, S. O. Nilsson, M.D.M.C. Ribeiro da Silva, M. A. V. Ribeiro da Silva and I. Wadso, *J. Chem. Thermodyn.*, **20**, 1353 (1988), thereby decreasing the heats of formation by 1.1 kJ mol^{-1}, but we maintained the original error bars. For completeness, the heat of formation of liquid glycerin trinitrate is -371.1 ± 2.1 kJ mol^{-1}.
[g]J. P. Guthrie, *Can. J. Chem.*, **55**, 3562 (1977).
[h]C. Mindakis and R. Sabbah, *Thermochim. Acta*, **55**, 147 (1984).
[i]P. A. Erastov, V. P. Kolesov and I. K. Igumenov, *Russ. J. Phys. Chem.*, **58**, 1311 (1984).
[j]V. P. Kolesov and M. P. Kozina, *Russ. Chem. Rev.*, **55**, 912 (1986).
[k]N. S. Kachurina, C. N. Wang and G. A. Petrovkaya, Deposited document, 1981, SPSTL, 95aKhp-D81; *Chem. Abstr.*, **98**, 142797a (1983).

APPENDIX A20. Heats of formation of polyols with and without any functional groups (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_3H_8O_3$	1,2,3-Propanetriol [glycerin]	−687.9		*a*	−669.6	0.6	*b*	−577.9	1.1	*b*
$C_4H_9O_5N$	2-(Hydroxymethyl)-2-nitro-1,3-propanediol	−735.5	6.4	*b*						
$C_4H_{10}O_4$	2*R*,3*S*-1,2,3,4-butanetetraol [*meso*-erythritol]	−910.4	1.3	*c*	−887.0	1.3	*c*	−775.2	2.5	*c*
$C_4H_{11}O_3N$	2-Amino-2-(hydroxymethyl-1,3-propanediol	−717.8	0.8	*c*						
$C_4H_{12}O_3NBr$	2-Amino-2-(hydroxymethyl)-1,3-propanediol hydrochloride	−936.8	2.0	*c*						
$C_5H_6O_4F_6$	1,1,1,5,5,5-hexafluroacetylacetone dihydrate	−2286.7	7.1	*d*						
$C_5H_8O_5$	Arabonic acid-γ-lactone, D-	−997		*f*						
$C_5H_8O_7$	Trihydroxyglutaric acid, *dl*-	−1490		*f*						
$C_5H_{10}O_5$	Arabinose, D-	−1057.9	1.6	*d*						
$C_5H_{10}O_5$	Arabinsoe, β-	−1057.0	0.4	*g*						
$C_5H_{10}O_5$	Levoglucosan	−959		*f*						
$C_5H_{10}O_5$	Ribose, D-	−1047.0	0.2	*f*						
$C_5H_{10}O_5$	Xylose, α-, D-	−1057.8	1.4	*f*						
$C_5H_{12}O_3$	2-(Hydroxymethyl)-2-methyl-1,3-propanediol	−744.6	2.9	*c*						
$C_5H_{12}O_4$	3-(2-Hydroxyethoxy)-1,2-propanediol				−863.4	5.0	*c*			
$C_5H_{12}O_4$	Pentaerythritol	−920.6	2.8	*c*				−776.7	2.9	*c*
$C_5H_{12}O_5$	Arabitol, L-	−1124.0		*e*				−964.0		*g*
$C_5H_{12}O_5$	Xylitol	−1118.5	0.7	*c*				−958.0		*g*
$C_5H_{12}O_4$	2-(2-Hydroxyethoxy)-1,2-propanediol				−865.0		*h*			

$C_5H_{12}O_4$	3-(2-Hydroxyethoxy)-1,2-propanediol				−863.4	5.0	*c*	
$C_6H_7O_{11}N_3$	Trinitrocellulose	−652.3	0.8	*i*				
$C_6H_8O_7$	Glucaric acid 1,4-lactone, D-	−1435.8	4.2	*c*				
$C_6H_8O_7$	Glucaric acid 3,6-lactone, D-	−1437.5	2.9	*c*				
$C_6H_8O_9N_2$	Dinitrocellulose	−753.3	1.5	*i*				
$C_6H_{10}O_5$	Cellulose (per unit)	−962.5	1.5	*j*				
$C_6H_{10}O_5$	Cyclohexene oxide 3,4,5,6-tetraol [1,2-anhydro-3,4,5-alloinositol]	−906.2	1.7	*c*				
$C_6H_{10}O_5$	Saccharinic acid lactone	−1004		*e*				
$C_6H_{10}O_6$	Galactonic acid-γ-lactone, D-	−1248		*e*				
$C_6H_{10}O_6$	Gluconic acid-δ-lactone, D-	−1256		*e*				
$C_6H_{10}O_6$	Gluconolactone, L-	−1219		*h*				
$C_6H_{10}O_6$	Gulonic acid-γ-lactone, L-	−1220		*e*				
$C_6H_{10}O_6$	Mannolactone, D-	−1202		*h*				
$C_6H_{10}O_6$	Mannolactone, L-	−1212		*h*				
$C_6H_{10}O_6$	Mannonic acid-γ-lactone, D-	−1239		*e*				
$C_6H_{10}O_8$	Allogalactaric acid	−1722		*h*				
$C_6H_{10}O_8$	Allomucic acid	−1724		*e*				
$C_6H_{10}O_8$	Galactaric acid	−1766		*h*				
$C_6H_{10}O_8$	Mucic acid	−1770		*e*				
$C_6H_{12}O_5$	1,2,3,4,5-Pentahydroxycyclohexane [quercitol]	−1128		*h*				
$C_6H_{12}O_5$	Fucose	−1096		*h*				
$C_6H_{12}O_5$	Rhamnose	−1069		*h*				
$C_6H_{12}O_6$	Fructose, β-	−1269.5	1.1	*f*				
$C_6H_{12}O_6$	Galactose, α-	−1272.3	1.1	*f*				
$C_6H_{12}O_6$	Glucose, α-	−1273.0	0.9	*f*				
$C_6H_{12}O_6$	Glucose, β-	−1266.8	0.9	*f*				
$C_6H_{12}O_6$	Inositol	−1304		*h*			−1116.0	*g*

(*continued*)

APPENDIX A20. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_6H_{12}O_6$	Mannose	−1266.5	1.8	*f*						
$C_6H_{12}O_6$	Sorbose, L-	−1270.2	3.8	*f*						
$C_6H_{12}O_7$	Galactonic acid, D-	−1610		*e*						
$C_6H_{12}O_7$	Gluconic acid, D-	−1587		*e*						
$C_6H_{14}O_3$	2-Ethyl-2-(hydroxymethyl)-1,3-propanediol	−750.9	3.6	*c*						
$C_6H_{14}O_6$	Galactitol [dulcitol]	−1346.7	1.8	*c*	−1317.0	1.8	*c*			
$C_6H_{14}O_6$	Mannitol, D-	−1337.1	1.0	*c*	−1314.5	1.8	*c*	−1135.0		*g*
$C_6H_{14}O_6$	Rhamnose monohydrate, α-, L-	−1055		*e*						
$C_6H_{14}O_7$	Glucose hydrate, α-, D-	−1987		*e*						
$C_6H_{15}O_3N$	Triethanolamine	−667		*h*	−664.2	1.5	*k*	−558.3	2.7	*k*
$C_7H_{12}O_7$	D-Gluco-D-gluo-heptonic acid-γ-lactone	−1488		*e*						
$C_7H_{12}O_7$	Gluco-α-heptose, D-	−1479		*e*						
$C_7H_{14}O_6$	Methyl-D-glucofuranoside, β-	−1203		*e*						
$C_7H_{14}O_6$	Methyl-D-glucopyranoside, α-	−1233.3	0.9	*c*						
$C_7H_{14}O_6$	Methyl-D-glucopyranoside, β-	−1237.5	0.5	*c*						
$C_7H_{14}O_6$	Methylglucofuranoside, α-	−1202.7	0.9	*c*						
$C_7H_{16}O_7$	D-Glucero-D-galactoheptitol	−1542		*h*						
$C_7H_{16}O_7$	D-Gluco-α-heptite	−1525		*e*						
$C_7H_{16}O_7$	Perseitol, D-	−1545		*e*						
$C_8H_{14}O_8$	D-Gluco-α,α-octonic acid-γ-lactone	−1649		*e*						
$C_9H_{18}O_6$	4-Hydroxy-tetrahydropyran-3,3,5,5-tetramethanol	−1267.7	5.0	*c*						
$C_{10}H_{22}O_7$	2,2′-(Oxybis(methylene))-bis-(hydroxymethyl)-1,3-propanediol [dipentaerythritol]	−1572.3	7.8	*c*						
$C_{12}H_{22}O_{11}$	Cellobiose	−2228		*e*						
$C_{12}H_{22}O_{11}$	Lactose, β-	−2236.7	0.7	*c*						
$C_{12}H_{22}O_{11}$	Maltose	−2221		*e*						

$C_{12}H_{22}O_{11}$	Sucrose, D-	−2226.1	3.0	*c*
$C_{12}H_{22}O_{11}$	Trehalose	−2223		*e*
$C_{12}H_{24}O_{12}$	Lactose monohydrate, α-	−2484.1	1.1	*c*
$C_{12}H_{24}O_{12}$	Maltose monohydrate, β-	−2459.6	0.7	*c*
$C_{12}H_{26}O_{13}$	Trehalose dihydrate	−2829		*e*
$C_{14}H_{20}O_9$	Rhamnose triacetate	−1905		*e*
$C_{16}H_{22}O_{11}$	Galactose pentaacetate	−2229		*e*
$C_{16}H_{22}O_{11}$	Glucose pentaacetate, α-, D-	−2249.4	1.7	*c*
$C_{16}H_{22}O_{11}$	Glucose pentaacetate, β-, D-	−2232.6	2.0	*c*
$C_{18}H_{32}O_{16}$	Melezitose	−3405		*e*
$C_{18}H_{32}O_{16}$	Raffinose	−3184		*e*
$C_{21}H_{30}O_5$	Cortisol	−1071		*e*
$C_{24}H_{40}O_{20}$	Diamylose	−3556		*e*
$C_{24}H_{42}O_5$	3α,7α,12α-Trihydroxy-5β-cholan-24-oic acid monohydrate	−1205		*e*
$C_{24}H_{42}O_{21}$	Stachyose	−4140		*e*
$C_{28}H_{38}O_{19}$	Cellobiose octaacetate	−3776		*e*
$C_{28}H_{38}O_{19}$	Lactose octaacetate	−3791		*e*
$C_{28}H_{38}O_{19}$	Maltose octaacetate	−3785		*e*
$C_{28}H_{38}O_{19}$	Sucrose octaacetate	−3774		*e*
$C_{36}H_{60}O_{30}$	Tetraamylose, α-	−5690		*e*
$C_{48}H_{80}O_{40}$	Hexamylose, β-	−7753		*e*

[a]Reference 1a and 1b, where we made the assumption $\Delta H_s = \Delta H_{fus(T_m)} + \Delta H_v$ where T_m is the melting point.
[b]M. Bastos, S. O. Nilsson, M. D. M. C. Ribeiro da Silva, M. A. V. Ribeiro da Silva and I. Wadso, *J. Chem. Thermodyn.*, **20**, 1353 (1988).
[c]Reference 1c.
[d]F. E. Rogers and R. J. Rapiejko, *J. Am. Chem. Soc.*, **93**, 4596 (1971).
[e]Reference 15.
[f]R. N. Goldberg and Y. B. Tewari, *J. Phys. Chem. Ref. Data*, **8**, 809 (1989).
[g]To obtain the heat of formation of the gas, we used the heat of formation of the solid from the source cited and the heat of sublimation from G. Barone, G. Della Gatta, D. Ferro and V. Piacente, *J. Chem. Soc., Faraday Trans.*, **86**, 75 (1990).
[h]Reference 8.
[i]R. S. Jessup and E. J. Prosen, *J. Res. Natl. Bur. Stand.*, **44**, 387 (1950).
[j]R. S. Jessup and E. J Prosen, *J. Res. Natl. Bur. Stand.*, **44**, 387 (1950). The value given is the heat of formation per monomeric unit, where we have taken the average value of the two sources of the material, namely 'cotton liners' and 'wood pulp'. The error bar is half of the difference of the two values.
[k]C. Mindakis, R. Sabbah, *Thermochim. Acta*, **55**, 147 (1984).

APPENDIX A21. Heats of formation of all unsubstituted arenols (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
C_6H_6O	Phenol	−165.1	0.8	*a*	−153.6		*b*	−96.4	0.9	*a*
C_7H_8O	2-Methylphenol [*o*-cresol]	−204.6	1.0	*a*				−128.6	1.3	*a*
C_7H_8O	3-Methylphenol [*m*-cresol]				−194.0	0.7	*a*	−132.3	1.3	*a*
C_7H_8O	4-Methylphenol [*p*-cresol]	−199.3	0.8	*a*				−125.4	1.6	*a*
$C_8H_{10}O$	2,3-Dimethylphenol	−241.2	1.0	*a*				−157.2	1.4	*a*
$C_8H_{10}O$	2,4-Dimethylphenol				−228.7	1.0	*a*	−162.9	1.0	*a*
$C_8H_{10}O$	2,5-Dimethylphenol	−246.6	0.9	*a*				−161.6	1.2	*a*
$C_8H_{10}O$	2-Ethylphenol				−208.8	1.8	*a*	−145.2	2.1	*a*
$C_8H_{10}O$	3,4-Dimethylphenol	−242.3	1.0	*a*				−156.6	1.2	*a*
$C_8H_{10}O$	3,5-Dimethylphenol	−244.4	1.0	*a*				−161.5	1.2	*a*
$C_8H_{10}O$	3-Ethylphenol				−214.3	1.6	*a*	−146.1	1.7	*a*
$C_8H_{10}O$	4-Ethylphenol				−224.4	1.0	*a*	−144.1	1.1	*a*
$C_9H_{12}O$	2,4,5-Trimethylphenol	−268		*c*						
$C_9H_{12}O$	2-Isopropylphenol	−246.6	12.6	*a*	−233.7	12.6	*a*	−182.2	12.7	*a*
$C_9H_{12}O$	3-Isopropylphenol	−263.0	12.6	*a*	−252.5	12.6	*a*	−196.0	12.8	*a*
$C_9H_{12}O$	4-Isopropylphenol	−279.7	12.6	*a*	−265.9	12.6	*a*	−209.4	12.8	*a*
$C_{10}H_8O$	1-Naphthol	−122.0	1.5	*d*	−98.7		*b*	−30.8	1.6	*d*
$C_{10}H_8O$	2-Naphthol	−124.1	1.6	*d*	−105.3		*b*	−29.9	1.7	*d*
$C_{10}H_{12}O$	5,6,7,8-Tetrahydro-1-naphthol	−285.3	5.4	*a*						
$C_{10}H_{14}O$	2-Isopropyl-5-methylphenol [thymol]	−309.7	9.6	*a*				−218.5	10.5	*a*
$C_{10}H_{14}O$	2-Isopropyl-6-methylphenol				−287.5	12.6	*a*	−235.6	12.8	*a*
$C_{10}H_{14}O$	2-*t*-Butylphenol							−168.0		*e*
$C_{10}H_{14}O$	3-Isopropyl-2-methylphenol				−295.9	10.5	*a*	−241.5	12.8	*a*
$C_{10}H_{14}O$	3-*t*-Butylphenol							−185.0		*e*
$C_{10}H_{14}O$	4-Isopropyl-2-methylphenol				−300.1	12.6	*a*	−242.3	12.8	*a*
$C_{10}H_{14}O$	4-*t*-Butylphenol	−310.5	1.2	*f*				−186.2		*g*
$C_{10}H_{14}O$	5-Isopropyl-2-methylphenol				−287.5	12.6	*a*	−228.5	12.8	*a*
$C_{12}H_{10}O$	2-Phenylphenol	39		*c*						
$C_{14}H_{22}O$	2,4-Di-*t*-butylphenol							−257.0		*e*
$C_{14}H_{22}O$	2,6-Di-*t*-butylphenol							−226.0		*e*
$C_{14}H_{22}O$	3,5-Di-*t*-butylphenol							−275.0		*e*
$C_{18}H_{30}O$	2,4,6-Tri-*t*-butylphenol							−315.0		*e*
$C_6H_6O_2$	Benzene-1,2-diol [catechol]	−354.1	1.1	*h*				−267.5	1.9	*h*
$C_6H_6O_2$	Benzene-1,3-diol [resorcinol]	−368.0	0.5	*a*				−274.7	2.2	*a*

$C_6H_6O_2$	Benzene-1,4-diol [hydroquinone]	−364.5	1.6	*a*	−265.3	2.3	*a*
$C_7H_8O_2$	2-Methylbenzene-1,4-diol	−401		*c*			
$C_7H_8O_2$	3-Methylbenzene-1,2-diol	−392.5	1.1	*h*	−299.3	1.6	*h*
$C_7H_8O_2$	4-Methylbenzene-1,2-diol	−393.3	1.2	*h*	−298.4	1.6	*h*
$C_7H_8O_2$	5-Methylbenzene-1,3-diol	−446		*c*			
$C_9H_{12}O_2$	3-Isopropylbenzene-1,2-diol	−447.8	1.6	*h*	−350.0	2.3	*h*
$C_{10}H_8O_2$	Naphthalene-1,2-diol	−309.8	1.6	*i*	−200.5	1.8	*i*
$C_{10}H_8O_2$	Naphthalene-1,3-diol	−327.2	1.5	*i*	−211.2	1.9	*i*
$C_{10}H_8O_2$	Naphthalene-1,4-diol	−317.4	1.5	*i*	−197.0	1.8	*i*
$C_{10}H_8O_2$	Naphthalene-2,3-diol	−302.4	1.7	*i*	−192.8	2.0	*i*
$C_{10}H_8O_2$	Naphthalene-2,7-diol	−326.1	1.1	*a*			
$C_{10}H_{14}O_2$	1-Isopropyl-4-methylbenzene-2,3-diol	−475.7	1.6	*h*	−379.1	1.8	*h*
$C_{10}H_{14}O_2$	1-Isopropyl-4-methylbenzene-2,5-diol	−463		*c*			
$C_{10}H_{14}O_2$	4-*t*-Butylbenzene-1,2-diol	−474.0	1.6	*h*	−374.7	2.1	*h*
$C_{11}H_{10}O_2$	2-Methylnaphthalene-1,4-diol	−229		*c*			
$C_{14}H_{10}O_2$	Phenanthrene-2,5-diol	−238		*c*			
$C_{14}H_{20}O_2$	3,5-Bis(*t*-butyl)-benzene-1,2-diol	−570.6	2.6	*h*	−470.4	2.7	*h*
$C_{15}H_{16}O_2$	2,2,-Bis-(4-hydroxyphenyl)propane [bisphenol A]	−349.4	1.7	*i*			
$C_6H_6O_3$	Benzene-1,2,3-triol [pyrogallol]	−551.1	0.9	*k*	−434.2	1.1	*k*
$C_6H_6O_3$	Benzene-1,2,4-triol [hydroxyhydroquinone]	−563.8	1.1	*k*	−444.0	1.6	*k*
$C_6H_6O_3$	Benzene-1,3,5-triol [phloroglucinol]	−584.6	1.1	*k*	−452.9	1.5	*k*

[a] Reference 1c.

[b] From Reference 1a and 1b, where we made the assumption $\Delta H_s = \Delta H_{fus(T_m)} + \Delta H_v$, where T_m is the melting point.

[c] Reference 8.

[d] M. A. V. Ribeiro da Silva, M. D. M. C. Ribeiro da Silva and G. Pilcher, *J. Chem. Thermodyn.*, **20**, 969 (1988).

[e] We combined the heat of formation of gaseous phenol from Reference 1c, the heat of formation of gaseous *t*-butylphenol from S. P. Verevkin, *Termodin. Org. Soedin*, 67 (1982); *Chem. Abstr.*, **99**, 157649 (1983) and the heats of rearrangement and other *trans*-*t*-butylation reactions from F. A. Pil'shchnikov, T. N. Vesterova and A. M. Rozhnov, *J. Appl. Chem. USSR*, **54**, 1768 (1981). It is not obvious what phase of the species of interest this analysis refers to. We chose gaseous because these are high-temperature reactions.

[f] M. M. Ammar, N. El Sayed, S. E. Morsi and A. El Azmirly, *Egypt J. Phys.*, **8**, 111 (1977).

[g] S. P. Verevkin, *Termodin. Org. Soedin.*, 67 (1982); *Chem. Abstr.*, **99**, 157649 (1983).

[h] M. D. M. C. Ribeiro da Silva, M. A. V. Ribeiro da Silva and G. Pilcher, *J. Chem. Thermodyn.*, **16**, 1149 (1984).

[i] M. A. V. Ribeiro da Silva, M. D. M. C. Ribeiro da Silva and G. Pilcher, *J. Chem. Thermodyn.*, **20**, 969 (1988).

[j] V. N. Lavina and N. V. Novoselova, *Termodin. Org. Soedin*, 110 (1982); *Chem. Abstr.*, **99**, 159287q (1983).

[k] M. D. M. C. Ribeiro da Silva, M. A. V. Ribeiro da Silva and G. Pilcher, *J. Chem. Thermodyn.*, **18**, 295 (1986).

APPENDIX A22. Heats of formation of arenols with other functional groups (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
C_5H_5ON	2-Hydroxypyridine [2-pyridone]	−166.3	0.8	*a*				−79.7	1.5	*a*
C_5H_5ON	3-Hydroxypyridine	−132.0	1.1	*a*				−43.7	1.7	*a*
C_5H_5ON	4-Hydroxypyridine [4-pyridone]	−148.9	0.8	*b*				−30.3	5.3	*b*
C_6HOCl_5	Pentachlorophenol	−292.5	3.0	*c*				−225.1	3.6	*c*
C_6HOF_5	Pentafluorophenol	−1024.0	2.1	*c*	−1007.7	2.1	*c*	−956.8	2.7	*c*
$C_6H_2O_2Cl_4$	2,3,5,6-tetrachloro-1, 4-benzenediol	−453.6	8.4	*c*				−365.0		*d*
$C_6H_3OBr_3$	2,4,6-Tribromophenol	−98.5	2.3	*e*				−0.9	2.5	*e*
$C_6H_3O_2Cl_3$	2,3,5-Trichloro-1,4-benzenediol	−440.7	8.4	*c*				−339.4	11.8	*c*
$C_6H_3O_7N_3$	2,4,6-Trinitrophenol [picric acid]	−217.0	2.0	*f*	−249.7	2.8	*c*	−106.0		*d*
$C_6H_3O_{10}N_3$	2,4,6-Trinitro-1,3-benzenediol	−435		*g*				−321.0		*d*
$C_6H_4O_2Cl_2$	2,3-Dichloro-1,4-benzenediol	−416.0	8.4	*c*						
$C_6H_4O_2Cl_2$	2,5-Dichloro-1,4-benzenediol	−427.3	8.4	*c*						
$C_6H_4O_2Cl_2$	2,6-Dichloro-1,4-benzenediol	−423.5	8.4	*c*				−331.5	11.8	*c*
$C_6H_4O_5N_2$	2,4-Dinitrophenol	−238.5	3.1	*h*				−128.1	5.2	*c*
$C_6H_4O_5N_2$	2,6-Dinitrophenol	−209.6	3.3	*h*				−97.8	5.0	*c*
$C_6H_4O_6N_2$	2,4-Dinitro-1,3-benzenediol	−415.6	2.5	*c*						
$C_6H_4O_6N_2$	4,6-Dinitro-1,3-benzenediol	−439.6	2.5	*c*						
C_6H_5OF	2-Fluorophenol				−302		*g*			
C_6H_5OI	2-Iodophenol	−95.8	4.2	*c*						
C_6H_5OCl	3-Chlorophenol	−206.4	8.4	*c*	−189.3	8.4	*c*	−153.3	8.7	*c*
C_6H_5OF	3-Fluorophenol				−340		*g*			
C_6H_5OI	3-Iodophenol	−94.5	4.2	*c*						
C_6H_5OCl	4-Chlorophenol	−197.7	8.4	*c*	−181.3	8.4	*c*	−145.8	8.7	*c*
C_6H_5OF	4-Fluorophenol	−334		*g*						
C_6H_5OI	4-Iodophenol	−95.4	4.2	*c*						
$C_6H_5O_2Cl$	2-Chloro-1,4-benzenediol	−383.0	9.4	*c*				−314.0	11.8	*c*
$C_6H_5O_2N$	4-Nitrosophenol [benzoquinone oxime, *para*]				−88		*g*			

$C_6H_5O_3N$	2-Nitrophenol	−202.8	1.0	*i*				−128.8	1.0	*i*
$C_6H_5O_3N$	3-Nitrophenol	−210		*g*				−118		*d*
$C_6H_5O_3N$	4-Nitrophenol	−212.4	1.0	*i*				−117.7	3.0	*i*
$C_6H_5O_4N$	4-Nitro-1,2-benzenediol	−411.1	1.1	*j*				−290.0	1.8	*j*
$C_6H_5O_5N_3$	2-Amino-4,6-dinitrophenol [picramic acid]	−249		*k*						
C_6H_7ON	2-Aminophenol	−191.0	0.9	*l*				−87.2	1.3	*l*
C_6H_7ON	2-Methyl-3-hydroxypyridine	−173.6	1.2	*a*				−84.5	1.8	*a*
C_6H_7ON	2-Methyl-4-hydroxypyridine	−184.7	1.1	*a*				−71.7	1.7	*a*
C_6H_7ON	2-Methyl-5-hydroxypyridine	−166.0	1.5	*a*				−69.8	2.6	*a*
C_6H_7ON	2-Methyl-6-hydroxypyridine	−212.3	2.1					−120.3	2.5	
C_6H_7ON	3-Aminophenol	−194.1	0.9	*l*				−89.4	1.6	*l*
C_6H_7ON	4-Aminophenol	−190.6	0.9	*l*				−81.5	1.7	*l*
$C_7H_5OF_3$	2-(Trifluoromethyl)phenol				−8.14	*g*				
$C_7H_5O_2Cl$	Chlorosalicylaldehyde	−371		*g*						
$C_7H_5O_3I$	Iodosalicylic acid	−513		*g*						
$C_7H_5O_7N_3$	3-Methyl-2,4,6-trinitrophenol	−255.9	3.2	*c*						
$C_7H_6O_2$	2-Hydroxybenzaldehyde [salicylaldehyde]				−280	*k*				
$C_7H_6O_2$	3-Hydroxybenzaldehyde	−306	*g*							
$C_7H_6O_2$	4-Hydroxybenzaldehyde	−295		*g*						
$C_7H_6O_3$	2-Hydroxybenzoic acid [salicylic acid]	−589.1	1.1	*m*				−494.0	1.4	*m*
$C_7H_6O_3$	3-Hydroxybenzoic acid	−590.5	1.0	*m*						
$C_7H_6O_3$	4-Hydroxybenzoic acid	−594.5	1.0	*m*				−467.0		*d*
$C_7H_6O_4$	2,4-Dihydroxybenzoic acid	−779		*g*						
$C_7H_6O_5N_2$	2,6-Dinitro-4-methylphenol [*p*-2,6-dinitrocresol]	−241		*g*						
$C_7H_6O_5$	3,4,5-Trihydroxybenzoic acid [gallic acid]	−959		*g*				−883.0		*d*
$C_7H_6O_5N_2$	4,6-Dinitro-2-methylphenol [*o*-4,6-dinitrocresol]	−281		*g*						
$C_7H_7O_2N$	2-Hydroxybenzaldoxime	−183.7	0.8	*c*						
$C_7H_8O_2$	Hydroxybenzyl alcohol, *ortho*	−361		*g*						
$C_7H_8O_3$	3-Methoxybenzene-1,2-diol [3-methoxycatechol]	−510.2	1.2	*j*				−418.5	1.4	*j*

(*continued*)

APPENDIX A22. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_7H_{14}O_3I_2$	Diiodosalicylic acid	−397		*g*						
$C_8H_8O_2$	2-Hydroxyacetophenone	−357.6	3.8	*c*						
$C_8H_8O_2$	3-Hydroxyacetophenone	−370.6	4.2	*c*						
$C_8H_8O_2$	4-Hydroxyacetophenone	−364.3	4.2	*c*						
$C_8H_8O_3$	2-Hydroxy-3-methylbenzoic acid	−612		*g*						
$C_8H_8O_3$	2-Hydroxy-4-methylbenzoic acid	−616		*g*						
$C_8H_8O_3$	2-Hydroxy-5-methylbenzoic acid	−608		*g*						
$C_8H_8O_3$	2-Hydroxy-6-methylbenzoic acid	−595		*g*						
$C_8H_8O_3$	3-Hydroxy-4-methoxybenz-aldehyde	−453.4	5.9	*c*						
$C_8H_8O_3$	4-Acetyl-1,3-benzenediol	−573.5	3.8	*c*						
$C_8H_8O_3$	4-Hydroxy-3-methoxy-benzaldehyde [vanillin]	−464		*g*				−375		*d*
$C_8H_8O_3$	Methyl 2-hydroxybenzoate				−532		*k*			
$C_8H_8O_3$	Methyl 4-hydroxybenzoate	−542		*g*						
$C_8H_8O_5$	Methyl gallate	−936		*g*						
$C_8H_9O_2N$	2-Hydroxyacetophenone oxime	−221		*g*						
$C_8H_9O_2N$	4-Hydroxyacetophenone oxime	−213		*g*						
C_9H_7ON	8-Hydroxyquinoline							6.5	1.7	*n*
$C_9H_8O_3$	Hydroxycinnamic acid, *cis, para*	−508		*g*						
$C_9H_8O_3$	Hydroxycinnamic acid, *trans, para*	−529		*g*						
$C_9H_{10}O_2$	2-Hydroxy-3-methylaceto-phenone				−399		*g*			
$C_9H_{10}O_3$	2-Hydroxy-4-methoxyaceto-phenone	−544		*g*						
$C_9H_{10}O_3$	Ethyl 2-hydroxybenzoate				−569		*g*			
$C_9H_{10}O_3$	Ethyl 4-hydroxybenzoate	−605		*g*						
$C_9H_{11}O_2N$	2-Hydroxy-2-methylaceto-phenone oxime	−455		*g*						
$C_9H_{11}O_2N$	2-Hydroxy-3-methylaceto-phenone oxime	−483		*g*						

$C_9H_{11}O_3N$	2-Hydroxy-4-methoxyaceto-phenone oxime	−594		*g*						
$C_9H_{11}O_3N$	2-Hydroxy-5-methoxyaceto-phenone oxime	−584		*g*						
$C_9H_{11}O_3N$	Tyrosine, L-	−685.1	1.6	*c*				−581.0		*d*
$C_{10}H_6O_4$	5,8-Dihydroxy-1,4-naphthoquinone	−595.8	1.4	*o*				−499.2	3.2	*o*
$C_{10}H_6O_5N_2$	2,4-Dinitro-1-naphthol	−181.4	4.6	*c*						
$C_{10}H_7O_2N$	1-Nitroso-2-naphthol [1,2-naphthoquinone-1-oxime]	−50.5	2.2	*c*				36.1	4.7	*c*
$C_{10}H_7O_2N$	2-Nitroso-1-naphthol [1,2-naphthoquinone-2-oxime]	−61.8	4.5	*c*				−5.4	6.2	*c*
$C_{10}H_7O_2N$	4-Nitroso-1-naphthol [1,2-naphthoquinone-4-oxime]	−107.8	2.5	*c*				−20.3	4.9	*c*
$C_{10}H_9ON$	2-Methyl-4-hydroxyquinoline	−162.3	2.7	*n*				−23.3	2.9	*n*
$C_{10}H_9ON$	2-Methyl-8-hydroxyquinoline							−39.4	2.2	*n*
$C_{10}H_9ON$	4-Methyl-2-hydroxyquinoline	−189.1	2.8	*n*				−61.0	3.2	*n*
$C_{10}H_{10}O_4$	2,4-Diacetyl-1,3-benzenediol	−753.5	6.3	*c*						
$C_{10}H_{10}O_4$	4,6-Diacetyl-1,3-benzenediol	−776.5	6.7	*c*						
$C_{10}H_{12}O_2$	2-Methoxy-4-propenylphenol				−300	*g*				
$C_{10}H_{12}O_2$	4-Allyl-2-methoxyphenol				−263	*g*				
$C_{10}H_{12}O_3$	Propyl 2-hydroxybenzoate				−595	*g*				
$C_{10}H_{12}O_3$	Propyl 4-hydroxybenzoate	−623		*g*						
$C_{10}H_{13}O_2N$	2-Isopropyl-5-methyl-4-nitrosophenol	−216		*g*						
$C_{11}H_8O_3$	3-Hydroxy-2-naphthoic acid	−547.8	1.0	*c*						
$C_{11}H_{12}O_3N_2$	Alanyltyrosyl anhydride	−512.3	0.6	*c*						
$C_{12}H_{10}O_4$	Quinhydrone	−564		*g*						
$C_{12}H_{12}ON_2$	4-Phenylazophenol	138		*g*						
$C_{13}H_{10}O_3$	2,4-Dihydroxybenzophenone	−492.8	1.9	*p*						
$C_{13}H_{10}O_3$	Phenyl 2-hydroxybenzoate [phenyl salicylate]	−436.6		*c*				−344.5	6.2	*c*
$C_{13}H_{11}O_2N$	*N*-2-Hydroxyphenylmethyl-enebenzenamine *N*-oxide	−62.6	2.0	*q*				−53.9	2.4	*q*
$C_{14}H_8O_3$	Hydroxyanthraquinone	−448		*g*						

(*continued*)

APPENDIX A22. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_{14}H_8O_4$	1,2-Dihydroxy-9,10-anthraquinone [alizarin]	−585		*g*				−461		*d*
$C_{14}H_8O_4$	1,4-Dihydroxy-9,10-anthraquinone	−595.1	2.1	*o*				−471.7	2.3	*o*
$C_{14}H_8O_5$	1,2,4-Trihydroxy-9,10-anthraquinone [purpurin]				−781.0		*g*			
$C_{14}H_8O_8$	1,2,3,5,6,7-Hexahydroxy-9,10-anthraquinone	−1423		*g*						
$C_{14}H_{10}O_5$	Salicylosalicylic acid	−1045		*g*						
$C_{14}H_{12}O_4$	Methoxyphenyl 2-hydroxybenzoate	−567		*g*						
$C_{14}H_{14}O_3$	Isobutyl 2-hydroxybenzoate	−612		*g*						
$C_{17}H_{16}O_3$	Allyl 3,4-guaiacol benzoate	−332		*g*						
$C_{17}H_{21}O_4N$	Morphine monohydrate	−711		*k*						

[a]S. Suradi, N. El. Saiad, G. Pilcher and H. A. Skinner, *J. Chem. Thermodyn.*, **14**, 45 (1982).
[b]M. A. V. Ribeiro da Silva, M. A. R. Matos, Y. Meng-Yan and G. Pilcher, *J. Chem.* Thermodyn., **24**, 107 (1992).
[c]Reference 1c.
[d]To obtain the heat of formation of the gas, we used the heat of formation of the solid from the source cited and the heat of sublimation from J. S. Chickos, in Reference 37.
[e]P. H. Aliot, A. Finch, G. Pilcher, L. Nunez and L. Barral, *J. Chem. Thermodyn.*, **19**, 771 (1987).
[f]A. Finch and A. E. Smith, *Thermochim. Acta*, **52**, 317 (1982).
[g]Reference 8.
[h]A. Finch and A. E. Smith, *Thermochim. Acta*, **69**, 375 (1983).
[i]A. Finch, P. J. Gardner and D. Wu, *Thermochim. Acta*, **66**, 333 (1983).
[j]M. D. M. C. Ribeiro da Silva, M. A. V. Ribeiro da Silva and G. Pilcher, *J. Chem. Thermodyn.*, **18**, 295 (1986).
[k]Reference 15.
[l]L. Nunez, L. Barral, S. Gavilanes Largo and G. Pilcher. *J. Chem. Thermodyn.*, **18**, 575 (1986).
[m]M. Colomina, P. Jimenez, M. V. Roux and C. Turrion, *An. Quim, Ser. A*, **77**, 114 (1981).
[n]M. A. V. Ribeiro da Silva, M. R. Matos, and M. J. S. Monte, *J. Chem. Thermodyn.*, **22**, 609 (1990).
[o]The results were obtained from the heats of formation and evaluated heat of sublimation of M. A. V. Ribeiro da Silva, M. D. M. C. Ribeiro da Silva, J. A. S. Teixeira, J. M. Bruce, P. M. Guyan and G. Pilcher, *J. Chem. Thermodyn.*, **21**, 265 (1989).
[p]I. Contineanu and D. I. Marchidan, *Rev. Chim.*, **30.**, 1096 (1979).
[q]J. J. Kirchner, W. E. Acree, G. Pilcher and L. Shaofeng, *J. Chem. Thermodyn.*, **18**, 793 (1986).

APPENDIX A23. Heats of formation of enols ($kJ\,mol^{-1}$)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
C_2H_4O	Ethenol [vinyl alcohol]							−128.0		*a*
$C_2H_4O_2$	Ethen-1,2-diol (*Z*)							−316.0		*b*
$C_3H_4O_3$	Hydroxymalonaldehyde (enol)				−505.0		*c*			
C_3H_6O	1-Propenol (*E*)							−169.0		*a*
C_3H_6O	1-Propenol (*Z*)							−174.0		*a*
C_3H_6O	2-Propenol							−176.0		*a*
$C_4H_2O_4$	3,4-Dihydroxycyclobutenedione [squaric acid]	−598.3	0.4	*c*				−443.9		*c*
C_4H_4O	1-Buten-3-yn-2-ol							83.0		*b*
$C_4H_4O_2$	Cyclobutan-1,3-dione (enol)	−259.8	2.1	*c*				−185.8	2.9	*c*
C_4H_6O	1,3-Butadien-1-ol (*E*)							−88.0		*a*
C_4H_6O	1,3-Butadien-1-ol (*Z*)							−90.0		*a*
C_4H_6O	1,3-Butadien-2-ol							−77.0		*a*
C_4H_8O	2-Buten-2-ol (*E*)							−212		*d*
C_4H_8O	2-Buten-2-ol (*Z*)							−214		*d*
C_4H_8O	2-Methyl-1-propen-1-ol							−207		*d*
C_5H_5ON	2-Hydroxypyridine [2-pyridone]	−166.3	0.8	*e*				−79.7	1.5	*e*
C_5H_5ON	3-Hydroxypyridine	−132.0	1.1	*e*				−43.7	1.7	*e*
C_5H_5ON	4-Hydroxypyridine [4-pyridone]	−144.6	1.3	*e*				−40.8	2.1	*e*
$C_5H_5O_2F_3$	Trifluoroacetylacetone (enol)				−1040.1	3.3	*c*	−1003.3	3.3	*c*
$C_5H_8O_2$	Acetylacetone (enol) (**10**)				−427.6	1.3	*c*	−384.5	1.3	*c*
$C_5H_{10}O$	3-Methyl-2-buten-2-ol							−241		*d*
$C_6H_2O_4Cl_2$	2,5-Dichloro-3,6-dihydroxy-*p*-benzoquinone [chloranilic acid]	−659.4		*c*						
$C_6H_{10}O_2$	3-Methylpentane-2,4-dione (enol)							−439.7		*c*
$C_6H_{10}O_2$	Hexane-2,4-dione (enol)							−428.9		*c*

(*continued*)

APPENDIX A23. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_7H_4O_7$	3-Hydroxy-4-pyrone-2,6-dicarboxylic acid trihydrate [meconic acid trihydrate]	−1273.2		*c*						
$C_7H_6O_2$	2-Hydroxycycloheptatrienone [tropolone] (**9**)	−239.3	1.3	*c*				−155.2	1.7	*c*
$C_7H_{12}O_2$	3-Ethylpentane-2,4-dione (enol)							−439.7		*c*
$C_7H_{12}O_2$	5-Methylhexane-2,4-dione (enol)							−439.7		*c*
$C_7H_{12}O_2$	Heptane-3,5-dione (enol)							−456.9		*c*
C_8H_8O	1-Phenylethenol							−46.0	6.0	*f*
$C_8H_{14}O_2$	3,5-Dimethylhexane-2,4-dione (enol)				−460.7		*c*			
$C_8H_{14}O_2$	3-Isopropylpentane-2,4-dione (enol)				−448.9		*c*			
$C_8H_{14}O_2$	3-Propylpentane-2,4-dione (enol)				−453.1		*c*			
$C_8H_{14}O_2$	6-Methylheptane-2,4-dione (enol)				−456.9		*c*			
$C_8H_{14}O_2$	Octane-2,4-dione (enol)				−452.7		*c*			
$C_9H_6O_3N_2$	3-Benzoyl-5-hydroxy-1,2,4-oxadiazole	−269.9	7.9	*c*						
$C_9H_6O_3N_2$	5-Benzoyl-3-hydroxy-1,2,4-oxadiazole	−42.7	8.4	*c*						
$C_9H_{16}O_2$	2,2-Dimethyl-3,5-heptane dione (enol)				−527.6	2.5	*c*	−470.7	2.5	*c*
$C_9H_{16}O_2$	2,6-Dimethyl-3,5-heptane dione (enol)				−527.2	2.1	*c*	−470.3	2.5	*c*

$C_9H_{16}O_2$	3-Butylpentane-2,4-dione (enol)							−461.1		*c*
$C_{10}H_7O_2F_3$	Benzoyltrifluoroacetone (enol)				−952.7	4.2	*c*	−875.3		*c*
$C_{10}H_{10}O_2$	Benzoylacetone (enol)	−335.1	2.9	*c*				−251.5	2.9	*c*
$C_{10}H_{12}O_2$	4-Isopropyltropolone	−340.6	3.8	*c*						
$C_{10}H_{18}O_2$	2,2,6-Trimethyl-3,5-heptanedione (enol)				−568.6	2.1	*c*	−510.9	2.1	*c*
$C_{11}H_{20}O_2$	2,2,6,6-Tetramethyl-3,5-heptanedione (enol)				−587.9	3.8	*c*	−528.0	3.8	*c*
$C_{15}H_{12}O_2$	Dibenzoylmethane (enol)	−224.7	1.7	*c*				−149.4		*c*

[a]F. Turecek and Z. Havlas, *J. Org. Chem.*, **51**, 4061 (1986).
[b]Reference 49.
[c]Reference 10a.
[d]F. Turecek, L. Brabec and J. Korvola, *J. Am. Chem. Soc.*, **110**, 7984 (1988).
[e]S. Suradi, N. El Saiad, G. Pilcher and H. A. Skinner, *J. Chem. Thermodyn.*, **14**, 45 (1982).
[f]F. Turecek, *Tetrahedron Lett.*, **27**, 4219 (1986).

APPENDIX A24. Heats of formation of hydroperoxides and peroxides with and without functional groups (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_2H_6O_2$	Dimethyl peroxide							−125.7	1.3	*a*
$C_2H_6O_2$	Ethyl hydroperoxide				−242.0	58.6	*a*	−198.9	58.7	*a*
$C_2H_6O_4$	Bis(hydroxymethyl) peroxide	−665.0	5.1	*a*				−571.7	6.7	*a*
$C_3H_8O_2$	Propyl hydroperoxide				−318.0	62.8	*a*			
$C_4H_{10}O_2$	Diethyl peroxide				−223.3	1.3	*a*	−192.8	2.5	*a*
$C_4H_{10}O_2$	*t*-Butyl hydroperoxide				−293.6	5.0	*a*	−245.9	5.0	*a*
$C_5H_{12}O_3$	*t*-Butylperoxymethanol				−480.6	2.8	*b*	−421.0	4.0	*b*
$C_6H_{12}O_2$	3,3,4,4-Tetramethyl-1,2-dioxetane				−285.0	42.0	*c*			
$C_6H_{12}O_2$	Cyclohexyl hydroperoxide				−273.2	2.9	*a*			
$C_6H_{14}O_2$	1-Hexyl hydroperoxide				−299.6	5.0	*a*			
$C_6H_{14}O_2$	2-Hexyl hydroperoxide				−310.1	2.9	*a*			
$C_6H_{14}O_2$	3-Hexyl hydroperoxide				−305.1	7.5	*a*			
$C_6H_{14}O_3$	2-(*t*-Butylperoxy)ethanol				−511.7	2.3	*b*	−465.2	3.0	*b*
$C_7H_{14}O_2$	1-Methylcyclohexanehydroperoxide				−330.4	6.3	*a*			
$C_7H_{14}O_3$	((1,1-Dimethylethylperoxy)methyl) oxirane [glycidyl *t*-butyl peroxide]				−321.3	2.7	*d*	−267.5	2.8	*d*
$C_7H_{16}O_2$	1-Heptyl hydroperoxide				−343.0	5.0	*a*			
$C_7H_{16}O_2$	2-Heptyl hydroperoxide				−346.4	2.1	*a*			
$C_7H_{16}O_2$	4-Heptyl hydroperoxide				−333.8	2.1	*a*			
$C_7H_{16}O_3$	2-(*t*-Pentylperoxy)ethanol				−534.2	1.6	*b*	−464.3	3.0	*b*
$C_7H_{16}O_3$	3-(*t*-Butylperoxy)-1-propanol				−511.7		*e*			
$C_7H_{16}O_4$	3-(*t*-Butylperoxy)-1,2-propanediol				−719.2	1.6	*b*	−631.2	3.1	*b*
$C_7H_{10}O_2$	1,1-Dimethyl-4-penten-2-yn-1-yl hydroperoxide				63.3	1.9	*f*	127.1	1.9	*f*
$C_8H_{14}O_4$	2,5-Dimethyl-3-hexyne-2,5-bis-hydroperoxide	−257.6	2.8	*g,h*				−130.2	3.3	*g,h*
$C_8H_{18}O_2$	*t*-Butyl peroxide				−380.9	0.9	*a*	−349.1	3.1	*a*
$C_8H_{18}O_4$	1-(*t*-Butylperoxy)-3-methoxy-2-propanol				−666.3	2.6	*a*			
$C_8H_{18}O_4$	2,5-Dimethylhexane-2,5-bis-(hydroperoxide)	−567.2	3.5	*g,h*				−428.7	3.7	*g,h*

$C_9H_{12}O_2$	(2-Hydroperoxy-2-propyl)benzene [cumyl hydroperoxide]				−148.3	6.7	*a*	−78.4	6.7	*a*
$C_9H_{14}O_5$	*E*-4-*t*-Butoxy-4-oxo-2-butenperoxoic acid methyl ester				−746.7	1.7	*a*			
$C_9H_{20}O_4$	1-*t*-Butylperoxy-3-ethoxy-2-propanol				−706.7	3.0	*a*			
$C_{10}H_{12}O_2$	1,2,3,4-Tetrahydro-1-hydroperoxynaphthalene	−185.7	6.5	*a*						
$C_{10}H_{18}O_2$	4α-Hydroperoxydecahydronaphthalene	−340.2	6.3	*a*						
$C_{10}H_{20}O_3$	1-(*t*-Butylperoxy)cyclohexanol				−589.1	5.7	*i*			
$C_{10}H_{22}O_4$	1-(*t*-Butylperoxy)-3-propoxy-2-propanol				−725.0	3.0	*a*			
$C_{11}H_{14}O_2$	1,2,3,4-Tetrahydro-1-methyl-1-hydroperoxynaphthalene	−157.2	18.4	*a*						
$C_{11}H_{18}O_2$	5-Methyl-5-*t*-butylperoxy-hex-3-yn-1-ene				−28.9	3.5	*f*	22.7	3.5	*f*
$C_{11}H_{24}O_4$	1-butoxy-3-(*t*-Butylperoxy)-2-propanol				−747.0	3.0	*a*			
$C_{12}H_{18}O_2$	*t*-butyl-(2-Phenyl-2-propyl)-peroxide	−263.0		*j*						
$C_{12}H_{20}O_3$	2,5-Dimethyl-5-*t*-butylperoxy-3-hexyne-2-ol				−696.9	2.2	*h*	−624.6	2.8	*h*
$C_{12}H_{20}O_4$	2,5-Dimethyl-5-*t*-butylperoxy-3-hexyn-2-hydroperoxide				−636.0	3.3	*h*	−561.8	3.8	*h*
$C_{12}H_{26}O_4$	1-(*t*-Butylperoxy)-3-pentoxy-2-propanol				−771.2	4.6	*a*			
$C_{12}H_{26}O_4$	*sec*-Butylidene bis(*t*-butylperoxide)				−619		*k*			
$C_{13}H_{18}O_2$	*t*-Butyl 1,1-dimethyl-4-penten-2-yn-1-yl peroxide				−28.9	3.5	*f*	−22.7	3.5	*f*
$C_{13}H_{20}O_3$	2-(4-*t*-Butylperoxyphenyl)-2-propanol	−564.2		*j*						
$C_{14}H_{10}O_2$	9,10-Epidioxyanthracene [anthracene peroxide]	92.9	3.4	*a*						
$C_{14}H_{12}O_3$	3,5-Diphenyl-1,2,4-trioxolane	−123.8	12.6	*a*						
$C_{16}H_{24}O_2$	(2-(4-Isopropenylphenyl)-2-phenyl)-*t*-butyl peroxide	−144.2		*l*						
$C_{16}H_{26}O_2$	(2-(4-Isopropylphenyl)-2-propyl)-*t*-butyl peroxide	−352.1		*l*						
$C_{16}H_{26}O_3$	(2-(4-(2-Hydroxyisopropyl)phenyl)-2-propyl)-*t*-butyl peroxide	−564.2		*l*						

(*continued*)

APPENDIX A24. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_{38}H_{30}O_2$	Bis-(triphenylmethyl)peroxide	321.4	4.3	*a*						
$C_{42}H_{28}O_2$	4β-9-Dihydro-4β,9,10-triphenylindeno-[1,2,*fg*]	607.7	21.3	*a*						
$C_{42}H_{28}O_2$	5,12-Dihydro-5,6,11,12-tetraphenyl-5,12-epidioxynaphthacene	516.5	20.9	*a*						
$C_{42}H_{28}O_4$	5,12,6,11-Bisepidioxy-5,6,11,12-tetra-hydro-5,6,11,12-tetraphenylnaphthacene	278.4	20.9	*a*						

[a]Reference 1c.
[b]Y. Y. Van-Chin-Syan, N. S. Kachurina, G. A. Petrovkaya and S. K. Chuchmarev, *Russ. J. Phys. Chem.*, **57**, 1751 (1983).
[c]P. Lechtken and G. Holne, *Angew. Chem., Int. Ed. Engl.*, **16**, 73 (1973). This is the result of measurements of both the heat of thermal decomposition to form acetone as well as the heat of combustion.
[d]Y. Y. Van-Chin-Syan and N. S. Kachurina, *Russ. J. Phys. Chem.*, **61**, 622 (1987).
[e]N. S. Kachurina, C. N. Wang and G. A. Petrovkaya, Deposited document, 1981, SPSTL, 950Khp-D81; *Chem. Abstr.*, **98**, 142797a (1983).
[f]Y. Y. Van-Chin-Syan, T. N. Dolbneva, V. P. Vasil'ev, S. K. Chuchmarev and V. A. Prichin, *Russ. J. Phys. Chem.*, **56**, 1736 (1982).
[g]E. T. Denisov and T. G. Denisova, *Russ. J. Phys. Chem.*, **62**, 131 (1988). These authors presented numerous heats of formation of gaseous hydroperoxides obtained by combining the heat of formation of the liquid species via group additivity. Using these numbers, Denisov and Denisova also derived the difference of the heats of formation of gaseous ROOH and RH to be $93.6 \pm 12.7\,kJ\,mol^{-1}$ and of ROOH and ROH to be $-80.3 \pm 11.0\,kJ\,mol^{-1}$.
[h]Y. Y. Van-Chin-Syan, V. F. Korotyuk and Yu. U. Panchenko, *Russ. J. Phys. Chem.*, **57**, 1727 (1983).
[i]The value is from the liquid-phase heat of reaction of cyclohexanone and *t*-butyl hydroperoxide from V. L. Antonovskii. E. V. Federova, N. E. Shtivel and V. D. Emelin, *Kinet. Katal.*, **30**, 1235 (1989).
[j]T. N. Dolbneva, M. A. Dikii and C. H. Wang Deposited document, 1982, SPSTL, 295Khp-D82; *Chem. Abstr.*, **101**, 22822a (1984).
[k]Reference 8.
[l]T. N. Dolbneva, M. A. Dikii and C. H. Wang, Deposited document, 1982, SPSTL, 293Khp-D82; *Chem. Abstr.*, **101**, 22824c (1984).

APPENDIX A25. Heats of formation of alcohols, arenols, ethers and peroxides (Additional entries) (kJ mol^{-1})

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
C_2H_5OI	Methyl iodomethyl ether							−122.6		*a*
$C_3H_3OCl_2F_2$	Methyl 1,1,-dichloro-2,2-difluoroethyl ether							−696.0		*b*
C_3H_7OCl	Methyl 1-chloroethyl ether							−272.7	5.0	*a*
$C_4H_8O_2N_2$	*N*-Nitrosomorpholine				−138.1	2.2	*c*	87.9	2.5	*c*
$C_4H_8O_3N_2$	*N*-Nitromorpholine	−212.5	1.3	*c*				−131.0	1.7	*c*
$C_4H_8O_4$	2-Methoxyethyl formate				−565.3	7.9	*d*	−521.7		*d*
$C_4H_{11}O_2N$	Bis(2-hydroxyethyl)amine	−493.8	2.6	*e*				−397.1	2.9	*e*
$C_5H_6O_7N_2$	Tetrahydrofuran-3,4-dinitrate, *cis*				−406.0	2.5	*f*			
$C_5H_6O_7N_2$	Tetrahydrofuran-3,4-dinitrate, *trans*				−386.0	1.7	*f*			
$C_5H_{10}O_3$	2-Methoxyethyl acetate				−622.8	8.6	*d*	−572.6	8.6	*d*
$C_6H_4ON_2$	Benzofurazan	235.8	1.4	*g*				300.2	2.1	*g*
$C_6H_4O_2N_2$	Benzofuroxan	218.9	1.4	*g*				298.5	2.2	*g*
$C_6H_8O_2N_2$	2,4-Dimethoxypyrimidine	−226.4	15.8	*h*				154.6	19.7	*h*
$C_6H_8O_2N_2$	4-Methoxy-*N*-methyl-2-pyridinone	−306.7	5.5	*h*				−200.6	17.2	*h*
$C_6H_9O_3N_3$	Trimethyl cyanurate	−478.3	1.2	*i*				−387.9	1.3	*i*
$C_6H_{14}O_6$	Sorbitol, D-	−1353.7	1.4	*j*				−1168.0		*k*
$C_6H_{15}O_3N$	Tris(2-hydroxyethyl)amine				−664.2	1.5	*e*	−558.3	2.7	*e*
$C_7H_{14}O_4$	2,3-Dimethylbutane-2,3-diol monoformate				−733.3	8.9	*d*	−674.3	9.8	*d*
$C_8H_{12}O_2N_2$	3-Amino-4-methoxy-*N*-acetylaniline	−554.1	1.7	*l*						
$C_9H_{12}O_5$	Tetrahydrofuran-3,4-diacetate, *cis*				−978.0	3.7	*f*			
$C_9H_{12}O_5$	Tetrahydrofuran-3,4-diacetate, *trans*				−980.6	3.7	*f*			
$C_{10}H_{15}O_2N_3$	3-(2-Cyanoethylamino)-4-methoxy-*N*-acetylaniline	265.9	1.7	*l*						
$C_{10}H_{20}O_6$	1,3,6,9,11,14-Hexaoxacyclohexadecane				−1061.0		*m*			

(*continued*)

APPENDIX A25. (*continued*)

	Name	Solid	Error	Ref.	Liquid	Error	Ref.	Gas	Error	Ref.
$C_{11}H_{12}O$	2-Phenyl-bicyclo[1.1.1]pentan-2-ol	48.7	3.0	*n*				135.8	3.3	*n*
$C_{11}H_{16}O$	3-Methyl-2-phenyl-2-butanol				−278.7	3.1	*n*	−211.3	3.5	*n*
$C_{12}H_{20}O_2N_4$	4,4′-Azo-bis(4-cyanopentan-1-ol)	−222.3	6.8	*o*						
$C_{13}H_{10}O_2$	Benzophenone-*O*-oxide							157.3	1.7	*p*
$C_{26}H_{20}ON_6$	Bis(2-(*o*-aminophenyl)-benzimidazol-5-yl) ether	101.7	10.0	*q*						
$C_{31}H_{52}O_3$	α-Tocopherol acetate				−1094.8		*r*			

[a]F. R. Cruickshank and S. W. Benson, *J. Am. Chem. Soc.*, **91**, 2487 (1969).
[b]This number was derived by combining the heat of formation of 1,1-dichloro-2,2-difluoroethylene from V. P. Kolesov and T. S. Papina, *Russ. Chem. Rev.*, **52**, 754 (1983) with the gas-phase heat of reaction of this olefin with methanol from J. Hine and F. E. Rogers, *J. Am. Chem. Soc.*, **90**, 6701 (1968).
[c]O. F. Golanova, G. V. Sitiviina, V. I. Pepekin, B. L. Korshunskii and F. I. Dubovitskii, *Bull. Acad. Sci. USSR, Chem. Ser.*, 881 (1988).
[d]J. P. Guthrie, *Can. J. Chem.*, **55**, 3562 (1977).
[e]C. Mindakis and R. Sabbah, *Thermochim. Acta*, **55**, 147 (1982).
[f]L. T. Eremenko, A. M. Korolev, L. I. Berezina, E. P. Kirichev, Y. I. Rubstov and T. V. Sorokina, *Bull. Acad. Sci. USSR, Chem. Ser.*, 795 (1985).
[g]M. L. P. Leitao, G. Pilcher, W. I. Acree, A. I. Zraigzne, S. A. Tucker and M. D. M. C. Riberiro da Silva, *J. Chem. Thermodyn.*, **22**, 923 (1990).
[h]Used heat of formation of condensed-phase and gaseous *N,N′*-dimethyluracil from A. Imamura, K. Takhashi, S. Murata and M. Sakiyama, *J. Chem. Thermodyn.*, **21**, 237 (1989), and heats of isomerization and of vaporization from P. Beak and J. M. White, *J. Am. Chem. Soc.*, **104**, 7073 (1982).
[i]A. Imamura, K. Takahashi, S. Murata and M. Sakiyama, *J. Chem. Thermodyn.*, **21**, 237 (1989).
[j]A. I. Gubareva, P. A. Gerasimov and E. L. Blokh, *J. Appl. Chem. USSR*, **59**, 797 (1986).
[k]To obtain the heat of formation of the gas, we used the heat of formation of the solid from the source cited and the heat of sublimation from G. Barone, G. Della Gatta, D. Ferro and V. Piacente, *J. Chem. Soc., Faraday Trans.*, **86**, 75 (1990).
[l]I. Contineanu, D. Bretcanu and D. I. Marchidan, *Rev. Roum. Chim.*, **27**, 55 (1982).
[m]We derived this number from the data in W. K. Busfield, in *Polymer Handbook*, 3rd ed. (Eds. J. Brandrup and E. H. Immergut), Wiley, New York, 1989. We find that the difference of the CH_2Cl_2 solution-phase (at 0 °C) heat of polymerization of (twice) 1,3,6-trioxocane and the desired compound is 28.8 kJ mol^{-1}. If it is assumed that the heat of solution of the latter ether is twice that of the former, and temperature effects can be neglected, then the heat of formation of 1,3,6,9,11,14-hexaoxacyclohexadecane is 28.8 kJ mol^{-1} more negative than twice that of 1,3,6-trioxocane which was obtained from Reference 1c.
[n]M. P. Kozina, S. M. Pimenova, V. A. Lukyanova and L. S. Surmina, *Doklady Physical Chemistry*, **283**, 713 (1985).
[o]N. S. Kachurina, C. H. Wang, A. V. Bednarskaya and A. V. Kolesnikova, *Visn. L'viv. Politekh. Inst.*, **181**, 30 (1984).
[p]We used the analysis of F. W. Harstock, J. M. Kanabus-Kaminska and D. Griller, *Int. J. Chem. Kinet.*, **21**, 157 (1989), but rather than using their estimate of the heat of formation of gaseous $(C_6H_5)_2CHOC_2H_5^-$ from the heat of formation of $(C_6H_5)_2CH_2$, we used the condensed-phase heat of formation of diphenylmethane from Reference 1c with new phase-change enthalpy information from Reference 4a.
[q]N. V. Karyakin, N. G. Shvetsova, G. P. Kamelova, A. L. Rusanov, V. V. Korshak and L. K. Plieva *Polymer Sci. USSR, Ser. A.*, **25**, 40 (1984).
[r]P. A. Gerasimov, A. L. Gubereva, E. L. Blokh and T. G. Cherkasova, *Khim. Farm. Zh.*, **19**, 1274 (1985), *Chem. Abstr.*, **104**, 149186 (1986).

CHAPTER 5

Analytical methods for alcohols, phenols, ethers and peroxides

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Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

ABBREVIATIONS*

AAP	4-aminoantipyrine	MID	multiple ion detection
AY	acridine yellow	MTBE	methyl *t*-butyl ether
BHA	butylated hydroxyanisole	PCP	pentachlorophenol
CIMS	chemical ionization mass spectroscopy	PTV	programmed temperature vaporization
EC	electron capture	SEC	size exclusion chromatography
FID	flame-ionization detection	SFC	supercritical fluid chromatograpy
FTIR	Fourier transform infrared	SGFET	suspended gate field effect transistor
HODS	higher-order derivative spectroscopy	TLC	thin layer chromatography

*See also general list of abbreviations after the table of Contents at the beginning of this volume.

HPLC	high performance liquid chromatography	TRIS	tris(hydroxymethyl)-methylamine
ITDS	ion-trap detection system	WCOT	wall-coated open-tube

The development and availability of gas chromatography and high performance liquid chromatography has revolutionized the practice of organic analysis. The present chapter is a good illustration of this point. Many of the methods described in the corresponding chapter in the earlier edition are generally valid methods, but the more recent developments have brought us to a state of the science in which gas chromatography is usually the first choice for determination of any organic compound or for the analysis of any organic mixture. In those cases where the sample under consideration is not amenable to gas chromatography, some combination of solvents will almost certainly make it possible to use high performance liquid chromatography. These are, of course, other methods which are important and useful. Thus, this chapter includes methods using spectroscopy of various types, thin layer chromatography, electrochemistry as well as methods best described as chemical methods. However, in its broadest and truest sense, chemistry is involved in all of the methods discussed.

In general, only the more modern methods have been selected for discussion, but at the same time older methods have been included when it appears that these methods are sound and still useful.

The widespread availability and use of infrared spectroscopy has reduced greatly the need and use of specific color tests for detecting the presence of many of the common functional groups.

Mass spectroscopy and nuclear magnetic resonance spectroscopy are outside the scope of this chapter. However, in a few cases methods which incorporate these techniques have been included to give a more nearly complete picture.

I. ALCOHOLS

A. Gas Chromatography

1. Without derivatization

The majority of gas chromatographic determinations of alcohols or alcohol derivatives make use of wall-coated open-tube (WCOT) capillary columns coated with a number of proprietory materials, temperature programming and flame-ionization detection (FID).

In a series of papers, Korhonen investigated the relative merits of WCOT capillary columns coated with either nonpolar SE-30 or highly-polar OV-351 for the separation of alcohols and several derivatives. Alcohols analyzed in these studies include: primary straight-chain C_1–C_{12}, C_{14}, C_{16} and C_{18} alcohols and their propanoyl, 2-chloro- and 3-chloropropanoyl derivatives[1]; primary straight-chain C_8–C_{12}, C_{14}, C_{16} and C_{18} alcohols and their acetate, mono-, di- and trichloroacetate derivatives[2]; C_1–C_{12} straight-chain alcohols and their mono-, di- and tribroomoacetate derivatives[3]; secondary and branched-chain C_3–C_5 alcohols and their propanoyl, 2- and 3-chloropropanoyl derivatives and their 2-, 3- and 4-chlorobutanoyl derivatives[4]; seven unsaturated alcohols and their acetate, mono-, di- and trichloroacetate derivatives and their mono-, di- and tribromoacetate derivatives[5].

For most of these alcohols and their derivatives, columns coated with SE-30 gave better separations than those coated with OV-351. Relative retention data and retention indices were given.

Other coatings which have been found to be useful in the analysis of alcohols alone or in mixtures with hydrocarbons, esters and in some cases with carboxylic acids and some volatile neutral compounds include Durabond-5 (DB-5)[6], or SP-1000[6,7], and DB-1[8].

In the analysis of alcohol, alkane and ester mixtures it was found that cold programmed-temperature vaporization (PTV) injection in the splitless mode gave better accuracy and precision. Tenax was used as the packing in the vaporizer[6].

Volatile alcohols and ethanediol in serum samples can be determined without interference from tris(hydroxymethyl)methylamine (TRIS) by using WCOT columns coated with SPB-1[9]. It had been observed that TRIS interferes with the determination of volatile alcohols using Porapak-packed columns.

Ethanol in breath samples can be determined with a detection limit of 5 pg using a porous-layer open-tubular column coated with Poraplot Q and ion-trap detection[10].

A direct determination of C_9–C_{14} fatty alcohols in oxyethylated alcohol mixtures makes use of a packed column filled with 5% PFMS silicone oil on Khromaton N-AW-HMDS[11].

Atypical WCOT coatings have been investigated in an attempt to achieve improved separations of alcohols. The liquid-phase 3-pentadecylbenzo-15-crown-5 was used to separate aliphatic and aromatic alcohols[12] and ethylpyridinium bromide was used to separate C_1–C_5 and C_7–C_{14} n-alcohol mixtures[13]. Columns utilizing the quaternary salt liquid phase were stable only when the capillary column contained a highly roughened whiskered surface.

Special WCOT columns containing chiral phases have been developed for the separation of enantiomeric mixtures of alcohols. One such phase utilized was octakis-(3-*O*-butyl-2,6-di-*O*-pentyl)-γ-cyclodextrin[14] and another was Ni(II) bis-(3-heptafluoro-butyryl-(*R*)-camphorate) mixed with SE-54[15].

Numerous chromatographic methods have been developed for the determination of alcohols and other oxygenates in gasoline. Most procedures involve the use of WCOT capillary columns coupled with various detection systems and either a direct injection of the gasoline sample or a prior separation of the oxygenates from the alkanes.

Typical direct injection methods involve the detection of analytes by use of an ion-trap detection system (ITDS)[16] or by use of a FTIR spectrometer coupled with a quadrupole mass spectrometer[17].

In the former method, by arranging the ITDS to collect data in the multiple ion detection (MID) mode, the complex chromatogram usually associated with gasoline is eliminated and the instrument collects only those chromatographic peaks that exhibit specific mass-to-charge ratios. For the determination of these lower molecular weight alcohols only the peaks at *m/e* 31 and 45, commonly encountered in alcohols, were used.

A recently developed technique for the detection of alcohols and other organic compounds in gas chromatographic eluent involves matrix-isolation at 10 K coupled with FTIR. Because identifications are based on absorption frequencies in comparison with published spectra, the effect of the matrix on the positioning of absorption bands has been investigated. Generally, absorption frequencies were lower with a xenon matrix than with an argon matrix, while those obtained from deposition on a bare gold disk were lowest. These results suggest that comparisons of matrix-obtained frequencies with published spectra should take these frequency shifts into account[18].

Typical indirect methods involve an initial extraction of the alcohols with ethanediol followed by gas chromatographic analysis of the extract[19] or a tandem column system in which the oxygenates are separated from the hydrocarbons (DB-W column) and then the oxygenates transferred by a valve to a second column (DB-1) for their analysis[20]. A similar approach involves the simultaneous injection of the gasoline sample into parallel columns—one polar (DW-1) and the other nonpolar (DB-5). Methanol, ethanol,

1- and 2-propanol, 2-methyl-2-propanol, 1- and 2-butanol and 2-methoxy-2-methylpropane can be determined over the concentration range of 0.1 to 10% with coefficients of variation between 0.7 and 3.6%[21].

A packed column containing a 1:1 mixture of Porapak Q and Porapak N coupled with infrared detection gave recoveries of low molecular weight alcohols and other oxygenates ranging from 99–102%[22].

Steam-carrier chromatography, often referred to as gas–solid chromatography, usually employs packed columns containing a highly porous silica gel, a mobile phase of either steam or a composite of steam and nitrogen or helium and FID detection. The chief advantages of this technique are that aqueous samples often may be directly injected and that trace detection at the ppb to ppm level may be attained[23,24]. Porasil F was found to give good separation of alcohols[24].

The surface area of the porous packing has a large influence on elution times[23,25] and represents an additional parameter which can be adjusted to achieve the desired separation.

The steam-carrier method has been found to be useful in the determination of C_1 to C_3 alcohols, glycols, alkoxy alcohols and alkanolamines in liquid detergents. A Porapak Q or Tenax GC column was used[26].

A recent modification for the determination of alcohols by steam-carrier chromatography involved the use of inorganic salt coatings (LiCl, NaCl, $NaNO_2$, $LiNO_3$ and others) on the solid phase (Celite C-22). The selectivity of the column was related to the ability of the salt coating to absorb water. In an analysis of C_1 to C_9 alcohols, the C_2 to C_9 alcohols eluted before methanol[27].

A development which may prove valuable for the detection of alcohols is a suspended gate field effect transistor (SGFET) electrochemically coated with a polypyrrole layer. This device responds to the lower alcohols at room temperature and has potential as a useful detector for alcohols in gas chromatography[28].

2. *With derivatization*

a. Precolumn derivatization. Trimethylsilyl derivatives are often used in the gas chromatographic determination of a wide range of alcohols. Some representative examples involve the determination of alcohols and other organic compounds in airborne particulate matter[29] and the determination of polyhydric alcohols in urine and serum[30]. In each of the above methods, derivatization is accomplished, after suitable extraction procedures, by reaction with bis(trimethylsilyl)trifluoroacetamide and analyses were carried out on WCOT capillary columns coated with DB-1 or OV-101, respectively.

A packed column containing 3% OV-17 on Chromosorb G-AW-DMCS was effective in separating trimethylsilyl derivatives of oxyethylated derivatives of hexylamines[31].

It has been found that an improved resolution of underivatized aliphatic alcohols can be achieved through the use of WCOT fused-silica capillary columns deactivated with polysiloxane and coated with OV-1. When positive and/or negative ion detection is utilized, mass spectral sensitivities can be improved by converting the alcohols into their heptafluorobutyryl derivatives[32].

Low molecular weight alcohols can be determined via headspace gas chromatography by converting the alcohols into alkyl nitrities.

In one method, the nitrites are produced by reaction of the alcohol with nitrogen dioxide in the presence of borosilicate glass. The resulting gas is analyzed on a 10% tritolyl phosphate on Chromosorb W AW DCMS column with electron-capture detection. The detection limits for methanol and ethanol are 3 and 0.6 ppb, respectively[33].

Aqueous solutions of alcohols could also be determined as nitrites by treating the

alcohol solution with sodium nitrite and oxalic acid and then analyzing the headspace gas on a column containing a mixture of Carbowax 200 and Carbowax 600 on Celite C-22[34].

When electron-capture (EC) detection is used in the analysis of primary and secondary alcohols, conversion of the alcohols to their pentafluorobenzoyl derivatives improves sensitivity[35].

Similarly, the EC detection sensitivity and volatility of dihydric alcohols (1,2-, 1,3- and 1,4-diols) can be enhanced by reaction with one of the following reagents: 3,5-bis-(trifluoromethyl)-, 2,4-dichloro- and 4-bromobenzeneboronic acids and 4-iodobutane-boronic acid[36].

The various boronic acid derivatization reagents used in the selective determination of bifunctional alcohols have been reviewed[37].

Chiral alcohols undergo reaction with bifunctional achiral alkyl- or arylthiophosphonic dichlorides to form a mixture of two *meso* and two D,L-pair diastereomers which can be separated by WCOT capillary gas chromatography (methylsilicone stationary phase). If it is assumed that no diastereoselection occurs in the coupling phase, it is possible to calculate the enantiomeric excess of a chiral alcohol mixture[38].

b. On-column derivatization. An on-column derivatization procedure which involves the reaction of alcohols with boric acid present as the stationary phase (5% H_3BO_3 on Chromosorb W) was utilized for the analysis of C_{12} to C_{15} alcohols in mixtures also containing C_{11} to C_{14} alkenes. Alcohols in the concentration range of 20–90% could be determined with a relative standard deviation of 0.03[39].

c. Postcolumn derivatization. A report of postcolumn derivatization reactions suitable for use with mass spectroscopic detection is worth consulting for methods of derivatization which might be useful for other techniques. Of considerable interest is the use of 2-chloro-1,3,2-benzodioxaphosphole for the derivatization of alcohols[40].

B. Supercritical Fluid Chromatography

Alcohols, as well as several other types of organic compounds, have been separated by a unified gas chromatography and supercritical fluid chromatography apparatus. The method combines both high-pressure gas chromatography and supercritical fluid chromatography. During the sample run the mobile phase is switched from high-pressure helium to supercritical carbon dioxide[41].

C. High Performance Liquid Chromatography

High performance liquid chromatography (HPLC) has become an important technique for the determination of alcohols because of the development of various precolumn derivatization procedures that allow detection of UV transparent alcohols while using the commonly available UV detector. In addition, improvements in sensitivity can be achieved through the use of fluorescent derivatizing agents and fluorescence detectors. More recently a number of indirect photometric methods have been described which make use of the UV detector in HPLC analyses. New detection systems have also been developed which have increased the usefulness of HPLC in the analysis of organic substances.

1. Detection methods other than photometric

Differential refractive index detection, while relatively insensitive, has been used to advantage in a few cases. In a typical example, alcohols in gasoline have been determined with a detection limit of 100 ppm using Merck C18 column packing[42].

A high-frequency permittivity detector, which appears to be most useful for the detection of simpler alcohols, has been developed[43].

FTIR detection has the potential of being a universal detector when deuterated solvents are employed as the mobile phase[44].

Alcohols and other substances which undergo photooxidation with oxygen can be determined in the HPLC effluent by the use of a postcolumn reactor–detector system. The analyte is oxidized in the photoreactor resulting in the production of hydrogen peroxide, which is then determined by the chemiluminescence produced in the oxidation of luminol. The photooxidation is sensitized by anthraquinonedisulfonate and the luminol oxidation catalyzed by Co(II). Both the sensitizer and the catalyst are present in the mobile phase[45].

An indirect conductometric detection method involving ligand exchange has been developed for the analysis of alcohol mixtures. The mobile phase contains an ionized sorbitol–boric acid complex whose conductance is monitored with a conductometric detector. In the presence of the alcohol analyte, the conductance decreases due to the formation of unionized alcohol borate complex. Methanol and ethanol in mixtures with ethylene glycol, glycerol, raffinose and sucrose could be determined with a detection limit of 0.01 *M*. The detection limits of the other alcohol species[46] ranged from 1×10^{-3} *M* to 5×10^{-3} *M*.

2. *Indirect photometric detection methods*

Indirect photometric detection methods have been usually applied to reversed-phase HPLC determinations of ultraviolet (UV) transparent analytes using a UV-photometric detector. A neutral UV-absorbing species, added to the mobile phase, becomes distributed between the mobile and stationary phases thus providing a background signal. The analyte interferes with or disturbs the equilibrium of absorbing species between the two phases and as a result produces a change in the background signal of the eluant.

The mechanisms by which the analyte affects the partitioning of the UV-absorbing species have been the subject of several papers to which the reader is referred. In one report, evidence is presented which supports complex formation between the analyte (alcohol) and the UV-absorber (methylene blue)[47] while in another solubility enhancement by the analyte of the UV-absorber appears to be involved[48]. In most of the reports on indirect detection methods, the analyte appears to facilitate the transfer (to or from) of the UV-absorbing species between the mobile and stationary phases[49,50].

In this latter type of indirect detection, the chromatogram contains peaks attributed to the analytes and a 'system' peak that has the same retention time as the UV-absorbing species (visualization agent). Because signal intensity increases the nearer the analyte elutes to the system peak and because signal intensity depends on composition of the mobile phase, it is possible to attain considerable signal enhancement by the appropriate selection of visualizing agent and by altering mobile phase composition[49,50].

Detection limits in the subnanogram range are readily attainable through the use of micro HPLC columns and indirect photometric detection[49,51].

The use of the following visualizing agents has been described for alcohol analysis: methylene blue[47]; benzamide, propyl *p*-aminobenzoate, uracil, theobromine[52]; methyl ethyl ketone[53]; anthracene, naphthalene[49]; theophylline[51]; and 4-nitro-4-chlorophenol[54].

The technique of indirect photometric detection has been extended to a laser-induced indirect fluorometric method using a microbore column and anthracene as the visualizing agent[55].

3. *Precolumn derivatization with photometric and fluorometric detection*

Numerous derivatizing agents have been developed which allow the determination of the UV-transparent alcohols. These are summarized in Tables 1 and 2.

TABLE 1. Precolumn derivatization reagents with photometric detection

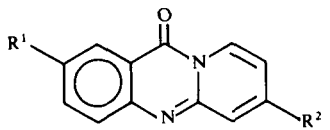
Reagent or derivative	Substrate	Comment	Ref.
3,5-Dinitrobenzoates	Mono- and diols C_{1-12} alcohols		56
4-Methylthiobenzoates	Longer-chain alcohols	Detection limit 200 pmole. Derivatives useful for mass spectral detection	57
Benzoyl chloride/pyridine	—	—	58
Benzoates, 2-naphthoates	C_{5-20} isoprenoid alcohols	—	59
4'-Dimethylaminoazobenzene-4-sulfonate 4-Naphthalene-1-azo-(4'-dimethylaminobenzene)sulfonate 4-(4'-Dimethylamino-phenylazo)naphthalene-1-sulfonate	C_{1-7} n-alcohols	—	60
Trityl chloride/pyridine	C_{1-14} aliphatic alcohols	Trityl ether derivative	61
1-Naphthyl isocyanate	C_{8-16} aliphatic alcohols	Best detection sensitivity at 290 nm. (Also used with fluorometric detection)	62

TABLE 2. Precolumn derivatization reagents with fluorometric detection

Reagent or derivative	Substrate	Comment	Ref.
4-(2-Phthalimidyl)benzoates 3-(2-Phthalimidyl)benzoates 3-(2-Phthalimidyl)-*p*-anisoates	Alcohols	—	63
3,4-Dihydro-6,7-dimethoxy-4-methyl-3-oxoquinoxaline-2-carboxylates	Prim or *s*-alcohols. *t*-alcohols, hydroxy-carboxylic acids, phenols do not form fluorescent derivatives	Detection limit 2–3 fmol/10 μL	64
2,2-Diphenyl-1-oxa-3-oxonia-2-boratanaphthalene	Amino alcohols	Detection limit, 0.84–1.7 μM	65
2-Dansylethyl chloroformate/pyridine	Cholesterol, cholestanol	Detection limit (cholesterol) 50 pg.	66
1-Anthroyl cyanide	Ethoxylated alcohols	Detection limit 0.05 ppm	67
1-Anthracenecarboxylazide/4-(dimethylamino)pyridine	C_{2-27} prim and *s*-alcohols. *t*-Alcohols and phenols do not produce derivatives	Detction for cholestanol, 250 fmol/10 μL	68
7-Methoxycoumarin-3- or -4-carbonylazide	prim and *s*-alcohols	Detection limits for cholesterol: 3 deriv, 50 fg; 4 deriv, 10 ng	69

(*continued*)

TABLE 2. (*continued*)

Reagent or derivative	Substrate	Comment	Ref.
4-Diazomethyl-7-methoxycoumarin	Me, Et, Bu, *i*-Pr, *t*-Bu benzyl, cyclohexyl, cholestanyl, cholesteryl alcohols	Room temp reaction with alcohols catalyzed by HBF_4	70
 I $R^1 = CH_3$, $R^2 = CH_2Br$ II $R^1 = CH_2Br$, $R^2 = CH_3$	Alcohols		71
Anthracene isocyanate	Prim, *s*- and *t*-alcohols	Also used in TLC analyses	72
4-(6-Methylbenzothiazol-2-yl)phenyl isocyanate	Prim, *s*- and *t*-alcohols	Detection limit 500 pg/80 μL injection volume	73
1-Naphthyl isocyanate	Prim, *s*- and *t*-alcohols	Triethylenediamine catayst used. Detection limit for 1-butanol 10 pmol/100 μL injection volume. Also used in TLC analyses[74]	74, 75

4. Precolumn derivatization with electrochemical detection

Alcohols are converted into electroactive urethanes by reaction with ferrocenecarbonyl azide or with 3-ferrocenylpropionyl azide which are detected with an electrochemical detector. At the maximum detection sensitivity of 0.4 V (vs Ag–AgCl), phenols, guaiacols and aromatic amines did not interfere. When applied to the determination of sterols, the detection limit was 0.5 pmol[76].

D. Size Exclusion Chromatography (SEC)

Two size exclusion column systems were investigated for the separation of isoprene oligomers from dimethyloctadienols. With a Bio Bead SX-8/CH_2Cl_2 system the octadienols eluted prior to the oligomers, while with a Sephadex LH-20/CH_2Cl_2 system the octadienols eluted after the oligomers. It was concluded that hydrogen bonding is involved in substrate absorption on Sephadex and as a result selective separations can be achieved with this column[77].

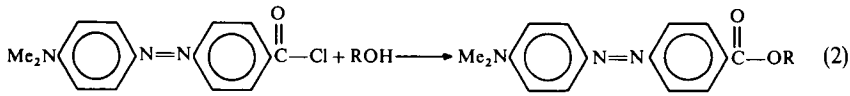
In an investigation of the separation of C_{1-7} alcohols on a Cellulofine GC-100-m (Chesso) SEC column using a micellar mobile phase, better separation occurred with the micellar solution than with the usual SEC mobile phases. It was concluded as a result of this study that this technique is probably not practical for analytic determination[78].

E. Thin Layer Chromatography (TLC)

For the normal alkanols containing up to five carbons, an effective separation is based on conversion of the alcohols to potassium xanthates. The xanthates are separated on a microcrystalline cellulose with fluorescent indicator (Polygran CEL 400, Machery, Nagel and Co.). By using this high performance TLC it is possible to get a satisfactory separation in only 25 minutes and avoid some of the earlier difficulties, which were apparently due to instability of the xanthates. The xanthates appear as dark brown spots under ultraviolet light[79]. It is necessary to prepare the xanthates in a prior reaction. The alcohol (1 mL) is mixed with 0.2 g powdered potassium hydroxide, cooled and mixed with 3 mL carbon disulfide (equation 1). The precipitate of xanthate is dissolved in acetone, the solution is filtered to remove excess potassium hydroxide and the filtrate is evaporated under reduced pressure. The residual xanthate (10 mg) is dissolved in 2–3 mL of water just before application to the chromatographic plate.

$$ROH + CS_2 + KOH \longrightarrow ROC(=S)SK \qquad (1)$$

A method for the TLC of the n-alkanols containing 6–18 carbons converts the alcohols to esters of 4-(dimethylamino)benzene-4′-azobenzoic acid by heating the sample with 4-(dimethylamino)benzene-4′-azobenzoyl chloride and pyridine in a sealed ampule in a water-bath for 90 minutes[80] (equation 2). The red derivatives are then separated on silical gel (Silufol) plates which have been impregnated with '10% paraffin oil in light petroleum ether'. Suitable solvent systems are either DMF–methanol (9:1) or DMF–water (9:1). This method has been used for the detection of these alcohols in the presence of their acrylate and methacrylate esters.



(2)

The higher alcohols decanol, dodecanol, tetradecanol and hexadecanol have also been separated on Adsorbosil RP plates using aqueous 98% acetonitrile containing the fluorophore 2-(4-biphenylyl)-5-phenyl-1,3,4-oxadiazole as the eluting solvent[81]. Detection at the nanomole level is achieved.

A variety of primary, secondary and tertiary alcohols can be determined by conversion to their fluorescent 1-naphthylurethanes by treatment with 1-naphthyl isocyanate (equation 3). The urethanes are subjected to thin layer chromatography and the fluorescence is measured[74]. Enhancement of the sensitivity is reported to be obtained by dipping the chromatogram into a methanol solution of polyethylene glycol, thus permitting detection limits in the lower picomole range. The sensitivity can be increased by a factor of ten if anthryl isocyanate is used in place of the naphthyl isocyanate[72]. The anthracene reagent reacts a little more slowly than the naphthalene reagent but gives good reproducibility along with the increased sensitivity. Primary and secondary alcohols react in 30 minutes at 95 °C (xylene or toluene) and tertiary alcohols require 2 hours at 140 °C (xylene). Other reagents which give fluorescent derivatives of alcohols include 4-(6-methylbenzothiazol-2-yl)phenyl isocyanate[73] and a bromomethylpyridoquinazolinone[71]. This latter compound, unlike the isocyanates mentioned above, reacts through its reactive bromomethyl group to form an ether derivative of the alcohol.

$$1\text{-}C_{10}H_7NCO + ROH \longrightarrow 1\text{-}C_{10}H_7NHCOOR \qquad (3)$$

F. Spectroscopic Methods

1. *Infrared methods*

The strong absorbance of alcohols due to OH stretching in the infrared is commonly used to determine alcohols, often in the presence of other substances that do not absorb in this region. Such a method for determining long-chain primary alcohols in high molecular weight alcohol–vegetable oil mixtures is based on measurement of the absorbance at 3660 cm^{-1} in a solution of the alcohol at less than 0.05 M concentration. The method is reported to give accurate quantification in concentrations greater than 5 mM. The sample must be dried over phosphorus pentoxide in vacuum for over twenty-four hours and is then dissolved in trichlorotrifluoroethane for the absorbance measurement[82].

The conversion of several types of compounds including alcohols, phenols and thiols to their *N*-butylcarbamate derivatives (equation 4) is reported to provide improved IR spectra. The frequency shift of the carbonyl band of the various derivatives permits distinguishing between the various compounds[83].

$$BuN{=}C{=}O + ROH \longrightarrow BuNHCOOR \qquad (4)$$

The coupling of microprocessors to IR spectrophotometers offers advantages for routine analyses of alcohols. The concentration of oleyl alcohol in wax samples was monitored using this combination[84].

It appears that pattern recognition techniques applied to FTIR spectra can be a useful way to identify the classes of compounds (including alcohols) in complex mixtures[85].

2. *Ultraviolet and visible methods*

An indirect kinetic method for the determination of alcohols and their binary mixtures is based on their oxidation by silver(II) and is monitored spectrophotometrically by a stopped flow technique in which the decrease in the absorbance of the silver(II) at 470 nm is observed. In determination of binary mixtures by this method the ratio of rate constants must be three or greater[86].

A spectrophotometric method for some of the longer primary alkanols (C_6–C_{10}) is

based on an oxidation of these alcohols catalyzed by an NAD(P)-independent alcohol dehydrogenase isolated from an alkane-oxidizing strain of *Pseudomonas putida*. An iodonitrotetrazolium chloride is reduced to its formazan derivative to provide for the measured color change. A unique property of the method is that 3 nmol of a higher alcohol could be determined in the presence of a 1000-fold excess of ethanol. An unsaturated alcohol, 2,4-hexadienol, was also determined by this method. A possible drawback to the wide use of the method is that the investigators had to isolate the enzyme from the microorganism. Perhaps the enzyme will become more readily available in the future[87].

3. *Luminescence methods*

Ethanol can be determined with a detection limit of 30 pmol using a flow injection system containing immobilized bacterial luciferase and oxidoreductase (downstream), both on a cyanogen bromide activated Sepharose 4B column. The bioluminescence produced is related to the concentration of the ethanol[88].

G. Chemical Methods

1. *Electrochemical methods*

The PVC-membrane xanthate-selective electrode based on tetraheptylammonium ethylxanthate has been used for the determination of some lower alcohols[89]. The alcohols are first converted to the corresponding sodium xanthates by mixing the sample with carbon disulfide and sodium hydroxide for 2–3 hours in the presence of tetrabutylammonium hydrogen sulfate as a phase-transfer catalyst. An aliquot of the sample is treated to decompose any trithiocarbonate formed and after pH adjustment and dilution the potential is measured. For ethanol, the response is rectilinear over the range from 40 μM to 10 mM. Detection limits for ethanol, propanol, 2-propanol and 2-butanol are 40 μM, 46 μM, 120 μM and 47 μM, respectively[90].

An electrode consisting of alcohol dehydrogenase and catalase immobilized on a commercial Clark-type oxygen electrode is useful for the determination of lower primary alcohols in aqueous solution. The electrode response is rectilinear for 1–25 ppm of ethanol. The electrode can be prepared in about one hour and remains stable during 400 determinations over two weeks[91]. A related method uses alcohol dehydrogenase and NAD immobilized by adsorption on an electrode of oxidized spectral grade graphite[92]. Another electrode and also a thermistor probe both use a commercially available alcohol oxidase isolated from *Candida boidinii* to determine methanol, ethanol, butanol and propanol. The alcohols are listed above in the order of their decreasing response to the electrode. The determination of propanol by these methods is not very practical. The enzyme electrode is best used in the rate mode. The thermistor probe is used with a column of the bound enzyme and a continuous flow approach is used[93]. These methods are limited to lower alcohols. An amperometric method for the determination of alcohols in the C_6–C_{10} range uses an enzyme electrode based on an NAD-independent alcohol dehydrogenase[94]. The electrode, in the presence of phenazine methosulfate, gives a rectilinear calibration graph over the 20–400 micromole range. Precision with hexanol was about 3%. For a related spectrometric method, see Reference 87 discussed in the Spectroscopic Methods (I.F.2) section above.

2. *Titration methods*

Alcohols can be titrated with the strong base lithium bis(trimethylsilyl)amide in THF solvent. A solution of an excess of the reagent is actually titrated with a solution of the

unknown. The endpoint can be determined potentiometrically and also by the red–yellow color change of *N*-phenyl-*p*-aminoazobenzene. The method has been demonstrated with propanol, pentanol, butanol, heptadecanol and hexanediol. The lithium reagent is prepared from butyllithium and hexamethyldisilazane (equation 5) and is standardized against benzoic acid[95].

$$(Me_3Si)_2NH + BuLi \longrightarrow (Me_3Si)_2NLi + BuH \quad (5)$$

H. Qualitative Tests

Aqueous solutions of lower alcohols can be detected with a color reagent prepared from a pyrrolidine salt of a vanadium complex of 8-hydroxyquinoline. A wine-red color is obtained in aqueous solution, in benzene solution or in melts. Phenols and other oxygen compounds do not react. However, reducing compounds interfere. The reagent has the structure $MH(VO_2L_2)$ where M is pyrrolidine and HL is 8-hydroxyquinoline[96].

Another reagent based on vanadium consists of a chloroform solution of the *N*-phenylbenzohydroxamic acid complex of vanadium(V). When an alcohol is added to this reagent the violet color of the reagent is changed to pale yellow, usually within one minute, although heating to 50 °C is required in some cases. A number of compounds such as phenols, dioxane and ketones interfere[97].

I. Enols

The classic method for measuring enol content was first described by Meyer[98] in 1911 and depends on the addition of bromine to the enol (but not to the keto form), followed by addition of potassium iodide and the liberation of iodine which is ultimately titrated with thiosulfate. The method is satisfactory for compounds such as β-dicarbonyl compounds where the enol content is relatively high, but is not satisfactory for simple carbonyl compounds such as cyclohexanone where the enol content is low. Thus, three variations on the Meyer method have given widely different results for this latter compound[99–102]. For simple aldehydes and ketones, the recommended method[103,104] is based on determination of the rate of enolization (k_E) and the rate of ketonization (k_K). From this information the equilibrium constant (K_E) is obtained from the simple relationship

$$K_E = k_E/k_K$$

These workers obtain the rate of enolization from the halogen scavenging of the enol as it forms in the rate-determining step of the halogenation reaction. To obtain the rate of ketonization they generate the enol form by one of several methods they have developed and then measure its rate of disappearance by ultraviolet spectroscopy based on the absorbance of the enol and keto forms. For additional information and leading references the excellent summary of their work should be consulted[105].

II. PHENOLS

A. Gas Chromatography

1. Without derivatization

Several types of columns appear to be suitable for the separation and determination of phenols. As seen from the following examples, carrier gases can be hydrogen, nitrogen or steam. A method for phenol and alkylphenols uses a fused-silica column with a 1.0 μ

bonded layer of DB-1701 together with a temperature program starting at 150 °C (8 min) and going to 200 °C at 10 °C min^{-1}, using hydrogen as the carrier gas and flame ionization detection[106].

Phenol and salicylic acid have been determined using steam as the carrier gas and a column (3 m × 212 mm) packed with Chromosorb P AW (60–80 mesh) modified with 4% H_3PO_4 and temperature-programmed from 130 to 240 °C at 10 °C min^{-1}. The water feed rate is 10 μL min^{-1} and flame ionization detection is used[107].

Dichlorophenol isomers have been separated on a stainless steel column packed with 20% of the stationary phase on acid-washed firebrick C22 (60–80 mesh) at 140 °C. Again, flame ionization detection was used but the carrier gas was nitrogen. Several stationary phases were studied but dibenzo-18-crown-6 was recommended[108]. The porous polymer Chromosorb 101 is also a satisfactory chromatographic adsorbent for phenol[109].

Direct gas chromatographic methods applied specifically to pentachlorphenol utilize in one case a fused silica capillary column with electron-capture detection[110]. The column was coated with either SE-54 or DB-5 and was programmed from 90 to 300 °C at 5 °C min^{-1}. The method has been applied to samples of urine, water, serum and fish. Hydrolysis converts salts and biological conjugates of the pentchlorophenol (and also of 2,3,4,6-tetrachlorophenol) into the free phenols which are then extracted with toluene. The detection limit is 0.5 ppb. In another method, which was designed for the determination of pentachlorophenol in gelatin, the procedure, after hydrolysis, partitioning, clean up and extraction into hexane, is a good example of direct gas chromatographic determination of this compound. A column with a 1% AP-124DA liquid phase and a ^{63}Ni electron capture detector is used. Recoveries of added sample averaged 106% and the limit of detection is 4–6 ppb[111].

2. *With derivatization*

In addition to the determination of phenols by direct chromatography of the underivatized phenols, a few methods use a derivatized form of the phenol. This may be done for various reasons. Thus, in one procedure, nitrophenols and 1-naphthol are first acetylated and then analyzed as the acetyl derivatives. The purpose here is to facilitate the extraction of the phenol from a very dilute solution (in this case river water). For the acetylation reaction a 750-mL sample of water is treated with 30 g of sodium bicarbonate and 2 mL of acetic anhydride. After completion of the acetylation reaction, the acetylated phenols are extracted with three portions of dichloromethane (50, 25, 25 mL). The extract is concentrated and a 1-μL sample is used for gas chromatography on a glass column (1.26 m × 4 mm) packed with 5% OV-101 on Chromosorb W (80–100 mesh). The column was programmed at 8 °C min^{-1} from 100–200 °C and used flame-ionization detection[112]. A related procedure uses acetic anhydride or butyric anhydride for the acylation of the phenols, followed by extraction with ethyl acetate[113]. The same article also reports that extraction of the underivatized phenol with toluene followed by acylation with perfluorobutyric anhydride was also efficient. Detection limits for several phenols were in the subnanogram range.

In another acylation procedure, 4-alkyl-2,6-di-*t*-butylphenols are acylated with pentafluorobenzoyl chloride in toluene with dry sodium hydroxide and with benzyltriethylammonium chloride as catalyst. The acylation reaction requires just fifteen minutes at 25–35 °C. The resulting pentafluorobenzoates are taken up in hexane for analysis by gas chromatography. The advantage of these perfluoro acylating agents is the sensitivity to electron-capture detection which they confer[114].

Triethylsulfonium hydroxide is a useful reagent for the preparation of ethyl ethers of phenols. The reagent, which can be prepared from triethylsulfonium iodide and an

equivalent amount of silver oxide, can be added to the sample prior to injection on the chromatograph and the pyrolytic ethylation takes place in the chromatograph[115,116].

$$Et_3S^+OH^- + ArOH \xrightarrow[\Delta]{} ArOEt + Et_2S + H_2O \quad (6)$$

The examples cited were designed for the determination of pentachlorphenol in widely varying samples. Ethylation can also be accomplished by the use of ethyl sulfate[117]. The yields are greatly improved if the ethylation reaction is carried out in the presence of the crown ether 18-crown-6.

Other reagents found to be satisfactory for the derivatization of pentachlorophenol include an acetic anhydride–pyridine mixture or diazomethane[118].

A rather simple way to enhance the sensitivity of phenol for electron-capture detection is to brominate the sample to form 2,4,6-tribromophenol[119].

$$C_6H_5OH + 3Br_2 \longrightarrow 2,4,6\text{-}Br_3C_6H_2OH \quad (7)$$

A study of postcolumn derivatization reactions suitable for use with mass spectroscopic detection[40] is worth consulting for methods of derivatization.

B. Supercritical Fluid Chromatography

Supercritical fluid chromatography can be successfully applied to the separation of phenols. It does appear that modifiers are necessary to prevent tailing and that a very polar modifier such as trifluoroacetic acid improves peak shapes[120].

C. High Performance Liquid Chromatography

1. Without derivatization

For the separation of certain monosubstituted phenols, such as the cresols, the ethylphenols, the nitrophenols and the aminophenols, the use of packings containing covalently bonded cyclodextrins has some advantages. The preparation of packings having cyclodextrins bound to polyacrylamide gels has been described[121]. This is a good leading reference for directions for attaching cyclodextrins to polyacrylamide gels. In this case the spacers used in the attachment are either ethylenediamine or diethylenetriamine. While the packings described in this reference will separate the *ortho, meta* and *para* isomers of cresol, ethylphenol and nitrophenol, the time required for the separation may be several hours. The use of a commercially available column has been described which permits the separation of the *ortho, meta* and *para* isomers of cresol, aminophenol, nitrophenol and chlorophenol in less than thirty minutes[122]. The column used in this work is described as based on 5-μm silica material covalently bonded via a non-nitrogen-containing spacer to β-cyclodextrin units.

It should be pointed out that the separations of monosubstituted phenols discussed above are not related to the fact that the compounds are phenols but that they are disubstituted benzenes. The separations are based on the way in which these disubstituted benzenes fit into the cavity of the cyclodextrin unit. Various disubstituted benzenes such as the dinitrobenzenes are also separated by such a technique.

HPLC separation followed by fluorescence detection has been used for the determination of phenol and alkylphenols[123] and also for the determination of 4-aminophenol[124].

In order to prevent oxidation of 1,2,4-benzenetriol, hydroquinone, catechol and phenol during HPLC determination, Greenlee and colleagues[125] added ascorbic acid to the

aqueous solution to be analyzed and the eluting solvents were equilibrated with nitrogen, degassed and maintained under a nitrogen atmosphere during the analysis.

A straightforward procedure for the determination of pentachlorophenol (PCP) in waste water uses HPLC with a commercial microparticulate silica gel column and detection at 254 nm. A suitable solvent system is cyclohexane-acetic acid (98:2, v/v). This system separates PCP from 2,3,4,6-tetrachlorophenol, 2,4,6-trichlorophenol and the various benzodioxins and other impurities found in technical PCP[126].

Other HPLC methods for pentachlorophenol include the following. A method designed for determination of PCP in mushrooms, but apparently suitable for other sample materials, extracts the sample with 3% sodium bicarbonate. The acidified extract is then extracted with dichloromethane, concentrated and then chromatographed on a LiChrosorb RP-8 column using 85% methanol–15% phosphoric acid (1:10) as the mobile phase. The method has the same detection limit (0.5 μg/kg) as a gas chromatographic procedure which uses the acetylated phenol prepared by acetic anhydride treatment of an aqueous extract[127]. Another method uses a correlation HPLC instrument operating under on-line microprocessor control to separate PCP and eleven other polychlorinated phenols on a reverse-phase column. The detection limit for PCP is about 0.6 μg/L. Correlation chromatography is essentially a statistical procedure and only a change in the injection system is required to make a conventional chromatograph suitable for the method. It is reported that the method is a powerful way to decrease the detection limit. The work of Smit and colleagues[128] and references cited therein should be consulted for additional information on this potentially important method. A review on the subject is also available[129].

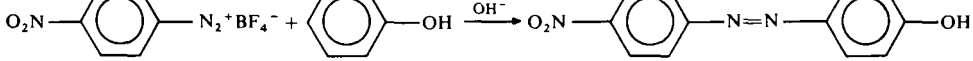
In other HPLC methods for chlorinated phenols, electrochemical detection with a vitreous carbon electrode has also been used with a column of Spherisorb ODS and a mobile phase of 0.1 M $NH_4H_2PO_4$ (pH 4.0)–acetonitrile (3:1)[130].

PCP and less highly chlorinated phenols have been satisfactorily separated by reverse-phase chromatography using a nonpolar bonded phase containing octadecyl groups. This C_{18} column provided a separation of nineteen different phenols with a 30-minute gradient of 56–80% methanol and 44–20% of 0.02 M KH_2PO_4 (pH 4.0)[131].

Other workers[132] have successfully used amperometric and electron capture detection as well as ultraviolet detection at 220, 230 and 254 nm for the determination of PCP by high performance liquid chromatography.

2. *With derivatization*

Phenol has been derivatized for determination by reversed-phase HPLC by converting the phenol to *p*-nitrobenzeneazophenol[133]. Derivatization is accomplished by treating an alkaline solution (pH 11.5) of the sample with a 3:1 to 4:1 excess of *p*-nitrobenzenediazonium tetrafluoroborate. The column used is a Polygosil 60-5 C_{18} column and the ultraviolet detector was set at 365 nm.



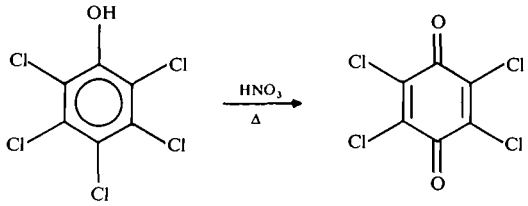
(8)

D. Thin Layer Chromatography

Separations of many combinations of phenols can be accomplished on plates prepared in the laboratory[134] or on commercially available plates[135]. In this last reference is described the behavior of many of the chlorophenols, bromophenols and alkylphenols

on RP-18 (Merck), Sil C_{18-50} (Machery, Nagel & Co.) and OPTI-UP C_{12} plates. Pentachlorophenol is not included. The plates are impregnated with the ionic detergents dodecylbenzenesulfonic acid or the triethanolamine salt of dodecylbenzenesulfonic acid. However, the OPTI-UP plates cannot be used with the anionic detergents because of the formation of a double solvent front. These plates can be eluted with 0.1 M ammonia and 0.1 M ammonium chloride in 20% methanol. The elution is quite rapid in this case (10 minutes for a migration distance of 7 cm), but with the RP-18 plates the time is appreciably longer and depends on which of the detergents is used. Thus, with an eluting solvent of acetic acid–methanol–water (5.7:40:54.3) the elution time is about 6 hours with plates impregnated with the triethanolamine salt but only 50 minutes with plates impregnated with dodecylbenzenesulfonic acid. Not all mixtures can be readily separated by these techniques but the monochlorophenols can be separated from each other and many of the dichlorophenols can be separated. For detection of the phenol spots the Boute reaction[136] was used. This involves exposure of the plates to nitrogen dioxide followed by ammonia vapor.

A simple method for the detection of pentachlorophenol first coverts the pentachlorophenol to chloranil by brief boiling with concentrated nitric acid[137]. The resulting chloranil is spotted on silica gel G plates and eluted with dichloromethane. The spots of chloranil are detected by spraying with a citric acid solution of *N,N,N',N'*-tetramethyl-*p*-diaminodiphenylmethane. It can be seen from equation 9 that not only pentachlorophenol but also 2,3,5,6-tetrachlorophenol will be converted to chloranil by this reaction. Since these are usually found associated with each other, no problem is presented. The other less-chlorinated phenols give other oxidation products which are separated during the chromatography.

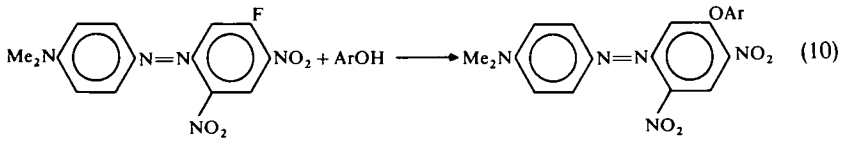


(9)

For the separation of eleven antioxidants commonly found in food and pharmaceutical preparations on RP-18 plates, a mixture of acetic acid–methanol–water (2:82:16) was used[138]. In another study of antioxidants including butylated hydroxyanisole, butylated hydroxytoluene, gallate esters and nordihydroguaiaretic acid, silica gel plates were used with benzene–petroleum ether–acetic acid (40:40:20) or chloroform–methanol–acetic acid as the solvents[139].

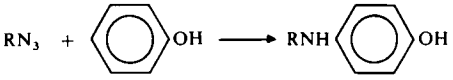
In a thin-layer chromatographic method for the determination of phenol, the phenol was derivatized by treating a solution of it in acetonitrile with an 8% solution of 2,4-dinitrobenzenesulfonyl chloride in 9:1 acetonitrile: 2-propanol containing 5% triethylamine. After two minutes the mixture was chromatographed on silica gel F-254 using 7:1 chloroform:carbon tetrachloride. The plate was dried at 20 °C, sprayed with 50% butylamine in acetone and the phenol was determined planimetrically[140]. The method was applied to the determination of phenol in phenol–formaldehyde resins which are extracted with acetonitrile, but might be useful for the estimation of phenol in other types of samples.

p-(5-Fluoro-2,4-dinitro-1-phenylazo)-*N,N*-dimethylaniline has been suggested for the preparation of colored derivatives of phenols for TLC[141], as shown in equation 10.



(10)

Derivatization directly on silica gel 60 F-254 plates with Fast Blue B Salt (Naphthanil diazo blue B) has been reported to be useful for the separation of *o*-, *m*- and *p*-ethylphenols although the chemistry of this kind of derivatization remains obscure[142]. For the separation of isomeric methylphenols and dimethylphenols, silical gel impregnated with 4,4′-diazido-2,2′-disulfostilbene has been used[143]. The apparent ultraviolet-catalyzed reaction in this case is shown in equation 11, were RN_3 represents the azidostilbene.



(11)

In at least one case, the phenols separated on silica gel are quantitated by extraction of the spots and potentiometric microtitration of the phenolic extracts with tetrabutylammonium hydroxide using an automatic titrator with a one-milliliter buret[144]. Phenols for which this technique has been demonstrated include phenol, 1-naphthol, 3-nitro-, 4-nitro- and 4-chlorophenol.

E. Spectroscopic Methods

1. Ultraviolet–visible methods

Since the phenol group, by definition, contains a good ultraviolet chromophore, the use of ultraviolet spectroscopy is a logical and straightforward method for this group.

A procedure for the determination of pentachlorophenol in water illustrates the simplicity inherent in the method[145].The water sample is acidified with concentrated hydrochloric acid and extracted with chloroform. The chloroform layer is extracted with sodium hydroxide and the aqueous sodium hydroxide solution is examined at 320 nm.

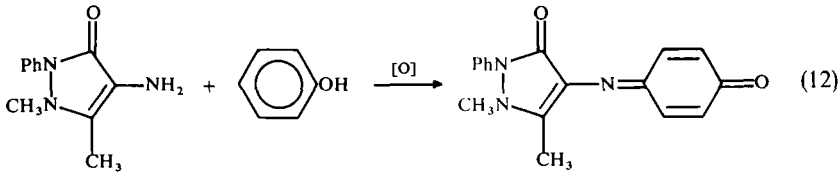
While phenol could be analyzed in a manner similar to that above, but using the appropriate wavelength, the ultraviolet determination of phenol can be made more sensitive by first converting the phenol to its iodo derivative by treatment with iodine monobromide. The product is extracted into hexane for the spectral measurement. The high absorptivity of the substituted phenol allows for the determination of as little as 10 ppb of phenol[146].

Higher-order derivative spectroscopy (HODS) is useful in the ultraviolet-visible range for the determination of pollutants such as phenol in water, air and soil. The method provides for the separation of overlapping curves so that quantitative measurements can be made. Fourth and fifth derivative measurements allow the simultaneous determination of phenol and aniline, giving a rectilinear calibration graph over the range 2 to 10 ppm. A fourth derivative spectrum of pentachlorophenol gave a similar calibration over the range 0.5 to 5 ppm[147].

A novel method for determination of as little as 200 picomoles of butylated hydroxytoluene and butylated hydroxyanisole (both are used as antioxidants in food) is based on their reaction with tris(*p*-bromophenyl)ammonium hexachloroantimonate. This reagent is a colored stable cation radical which reacts with the above phenols. The decrease in absorbance at 730 nm is a linear measure of the concentration of the substituted phenol[148].

2. Ultraviolet–visible methods with chromophore development

A widely used colorimetric method for phenols is commonly known as the 4-aminoantipyrine method. It depends on the chromophore formed from the oxidative coupling of a phenol with 4-aminoantipyrine (4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one), (4-AAP), usually with potassium hexacyanatoferrate(III) as the oxidizing agent. The reaction (equation 12) was first reported in 1943[149] but it was not until 1957 that it was adapted for analytical purposes[150]. It would appear from equation 12 that *p*-substituted phenols cannot undergo the coupling reaction. While it is true that some *p*-substituents do block the reaction, a chlorine in the *para*-position is lost in the oxidative coupling process. Thus, *p*-chlorophenol and phenol both give the same derivative. As will be seen below, PCP can also be satisfactorily determined by this method. Other *para* substituents which can be eliminated in the oxidative coupling process are carboxylic, sulfonic, hydroxyl and methoxyl groups. A nitro group in the *ortho* position of phenol prevents the reaction and a nitro group in the *meta* position hinders the reaction[149].



(12)

A suitable procedure is described by Norwitz and Keliher[151]. For samples containing more than 0.05 mg phenol/100 mL, the direct version is used. If the sample contains less than 0.05 mg phenol/100 mL the extraction process is used. In this latter procedure the colored product is concentrated by extraction with chloroform. This procedure avoids interferences from aromatic amines and formaldehyde. In those cases where substantial amounts of sulfite are present in the sample, a modified procedure must be used[152]. It is not clear how the sensitivity is reduced by the sulfite but presumably the sulfite reacts with the colored product resulting from the reaction of the phenol with 4-AAP. The interference is best eliminated by adding sodium sulfide. The sulfide converts the sulfite to a mixture of thiosulfate and polythionates. The excess sulfide can be precipitated with copper(II).

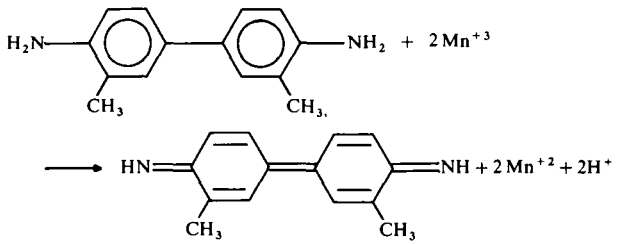
An interesting study based on thin layer and paper chromatographic work[153] shows that phenols having an alkyl group in the *para* position do react with the reagent but give a yellow color rather than a red color. These yellow products are apparently not stable in the presence of air and light and give rise to several other unknown products. The yellow products are formed only from those *para*-substituted phenols that have an unsubstituted *ortho* position. However, if one of the two blocked *ortho* positions is occupied by a halogen, the halogen is displaced. Thus, the product obtained from reaction with 2-bromo-4,6-dimethylphenol has the same RF value as that derived from 2,4-dimethylphenol. It is interesting to note that in the case of unsymmetrically substituted phenols with both *ortho* positions free (e.g. 3,4-dimethylphenol), two yellow products are formed, one apparently from reaction at the 2-position and the other from reaction at the 6-position. 2-Chloro-4,5-dimethylphenol was also observed to give two products, one resulting from loss of chlorine and the other from attack at the open *ortho* position. It should be noted that the sensitivity of the reaction with *p*-alkylphenols is much less than that for phenols unsubstituted in the *para* position and that the results discussed in this paragraph were obtained with a modified reagent.

The 4-aminoantipyrine procedure can also be adapted for flow injection methods and applied to the determination of pentachlorophenol[154]. The sample solution is injected into the carrier solution of 4-aminoantipyrine and the oxidant is hexacyanatoferrate(III).

There are several methods for determining phenol or certain substituted phenols which depend on the oxidation of the phenol by metaperiodate. The chemistry of these methods is not clear cut, but they appear to provide useful procedures. In what is perhaps the simplest of these[155], phenol itself is oxidized to what is described as quinones and quinols which absorb at about 340 nm. Since the reaction is not clear cut and stoichiometric, a kinetic method, using the fixed time technique for the oxidation, is applied.

In other methods based on periodate oxidation, the oxidation products are coupled with such reagents as *m*-aminophenol[156], *p*-*N*,*N*-dimethylphenylenediamine[157] and *m*-phenylenediamine[158] to give colored products whose absorbance can be measured. These colorimetric methods are applicable only to such compounds as catechol, resorcinol, guaiacol, thymol, butylated hydroxyanisole (BHA), 1-naphthol, *o*-aminophenol, *p*-aminophenol and *p*-(*N*-methylamino)phenol. Phenol and many monosubstituted phenols do not give a color. Catechol and its monoalkyl ethers do give a color.

It will be noted that the above oxidative methods can be applied only to easily oxidized phenols which can give rise to quinone-type structures. A micro method with somewhat similar limitations uses the fluoride complex of trivalent manganese as the oxidizing agent. In this method, which has been applied to hydroquinone, *p*-aminophenol and *p*-(*N*-methylamino)phenol, the compound to be analyzed is oxidized with trivalent manganese and the excess manganese is determined colorimetrically with *o*-tolidine. To do this, a known amount of *o*-tolidine is added after the phenol oxidation is complete, and the excess manganese oxidizes the *o*-tolidine (equation 13). The colored product of the tolidine oxidation can be measured at 437 nm. Since the molar absorptivity for this oxidation product is quite large, the method is capable of high sensitivity. Samples of hydroquinone in the 10–50 microgram range can be determined with an error of less than 2%[159]. A related method uses hypochlorite as the oxidant[160].



(13)

3. *Infrared methods*

Free phenol in aqueous solutions of phenol–formaldehyde condensates has been determined by IR spectra. The sample is first diluted with acetone and then dried over 5 Å molecular sieves. The determination is based on the IR absorption at 694 cm^{-1} due to the O—H out-of-plane bending[161]. An IR method for determining *p*-nonylphenol in mixtures with the *ortho* isomer uses the absorption of the *para* isomer at 830 cm^{-1} and the absorption of the *ortho* isomer at 750 cm^{-1}. A calibration is made by using essentially pure *para* isomer and a 50:50 mixture of the two isomers. The ratio of the intensities of the two absorptions is determined and a correction factor must be used to calculate the composition. It appears that the method could be slightly modified for use with other mixtures of alkylphenols[162].

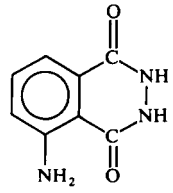
4. *Raman methods*

A method using Raman spectroscopy requires derivatization of the phenol by coupling with diazotized *p*-nitroaniline followed by Raman measurements on the resulting azo

dye[163]. (See Section II.C.2, equation 8.) The method may be of limited value, but demonstrates the potential of Raman spectroscopy in this area.

5. *Luminescence methods*

A sensitive method for certain phenols uses the luminescence-producing reaction between luminol (**1**) and hexacyanatoferrate(III). Thus, the oxidation of 0.1 μM luminol by 0.1 mM $K_3Fe(CN)_6$ in 10 mM KOH containing 0.1 mM EDTA gives a luminescence which is enhanced by the presence of trace amounts of phenol, 4-bromophenol, 4-iodophenol, resorcinol and pyrogallol. The luminescence is linearly related to the concentration of the phenolic compound. The limits of detection for the above compounds are respectively 0.1 μM, 0.2 μM, 0.2 μM, 0.2 nM and 0.3 μM. The method can also be used for determining hydrazine, hydroxylamine, ascorbic acid and cysteine. Catechol and quinol interfere by inhibiting the luminescence. This inhibition can be partially masked by using 10 μM luminol and 0.1 μM osmium tetroxide (toxicity)[164].



(1)

6. *Fluorescence methods*

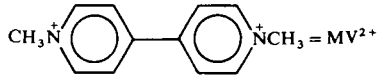
Far-ultraviolet laser-induced fluorescence can be used for the remote detection of such groundwater contaminants as phenol, *o*-cresol, 2-chlorophenol, 2-nitrophenol and 2,4-dinitrophenol, as well as for toluene, xylenes and humic acid[165].

F. Chemical Methods

An unusual and sensitive technique for phenol and *p*-acetaminophenol (acetaminophen) is based on the inhibitory properties of either of these compounds on a reaction whose rate can be easily measured spectrophotometrically. The reaction used is a photochemical reaction between methylviologen cation (represented as MV^{+2}) and ethylenediaminetetraacetic acid (EDTA) in the presence of acridine yellow (AY). The latter compound serves as a photosensitizer in the reaction (equation 14). The methylviologen radical cation (MV^{+}) formed has absorption maxima at 396 and 606 nm and these peaks can be readily measured as the reaction proceeds. The developers of this method[166] elected to measure the time taken to reach a certain absorbance value (*ca* 0.8) as a measure of the rate of reaction. A plot of time to reach this maximum versus concentration of phenol or acetaminophenol is rectilinear. The reaction must be run under anaerobic conditions and the authors have worked out conditions which need to be controlled. Thus, to a solution made up to 2 mL of 2 M acetate buffer (pH 5), 5 mL of 0.2 M EDTA, 2 mL of 1 mM AY and 3 mL of 5 mM methylviologen is added sufficient sample to give a final concentration of 2.8–37 μg/mL in the case of phenol or 7.5–40 μg/mL in the case of *p*-acetaminophenol. The solution is diluted to a total volume of 25 mL with water and oxygen is removed by passing nitrogen through the solution for 10 minutes. A halogen lamp is used and the intensity of illumination should be such

that the time required for reaching the prefixed value of absorbance in the absence of inhibiting phenolic sample should be 150 seconds.

$$MV^{2+} + EDTA + H_2O \xrightarrow[h\nu]{AY} MV^{+\cdot} + ED\,triacetic\,acid + CH_2O + 2H^+ + CO_2 \quad (14)$$



The method has been demonstrated with only the two phenols mentioned above, but presumably other phenols which inhibit the photochemical reaction could also be determined with suitable modifications of the procedure.

Substances which interfere no more than slightly include caffeine, saccharin, acetylsalicylic acid, acetate, chloride, sulfate, nitrate, bromide, phosphate and ions of magnesium, zinc, calcium, lead(II), manganese(II), cadmium and nickel. Extra EDTA must be added if metal ions which form stable complexes with these substances are present. Vanadium(IV) and iodide each provide strong interference, apparently because they are deactivators of the triplet state of acridine yellow.

Phenol itself is oxidized by oxygen in the presence of a suitable enzyme such as mushroom polyphenol oxidase. Based on this, a flow-through system using a membrane-covered Clark oxygen cell permits the determination of phenol, whose concentration is related to the oxygen consumption[167]. The enzyme is immobilized on the membrane. The method is rapid; 15–30 samples can be analyzed in one hour.

In other methods[168] involving enzymes, phenol 2-hydroxylase and catechol 1,2-oxygenase have each been immobilized on Sepharose and used with an oxygen electrode to determine phenol in the one case and catechol in the other. An electrode with immobilized *Trichosporon cutaneum* cells instead of the purified phenol 2-hydroxylase was equally effective for the determination of phenol.

Aminophenols are oxidized by iodate or periodate, as discussed in Section II.E.2. A micro method based on this oxidation determines the excess iodate by potentiometric titration with iodide[169].

Other oxidative methods use manganese(III) or cobalt(III). The spectral method (see Section II.E.2) of Barek, Berka and Skokanova can also be used as a titrimetric method in which the excess of Mn(III) can be determined indirectly by titration with 1 mM iron(II) sulfate or the analyte can be determined directly by potentiometric titration with the Mn(III) reagent[170]. *p*-Aminophenol, *p*-phenylenediamine, *p*-(methylamino)phenol and hydroquinone can be directly titrated with Co(III) in the form of hexamminecobalt(III) tricarbonatocobaltate(III) $[(NH_3)_6Co][Co(CO_3)_3]$ using a ferroin indicator. Hydroquinone, but not the other phenols mentioned, can also be determined by potentiometric titration[171].

Direct titration of weak acids normally requires the use of a nonaqueous solvent, but it has been found[172] that if the data obtained from a potentiometric titration are plotted as pH vs logarithm of the titrant volume, the plot consists of two linear portions with an inflection between the two parts. The center of the inflection can be obtained graphically and corresponds to the equivalence point. The only phenol used in the study was phenol itself, but presumably the method could be applied to other phenols.

Methods developed for determination of pentachlorophenol include differential pulse cathodic-stripping voltammetry[173] and a voltammetric method using glassy carbon electrodes[174].

III. ETHERS

The methods discussed under the chromatographic headings are considered to be primarily chromatographic, although the methods of detection used in some cases may be of a chemical nature or may use techniques such as mass spectroscopy which are outside the scope of this chapter. It is evident from the examples cited below that a variety of column packings are suitable for the separation or analysis of ethers.

A. Gas Chromatography

1. Without derivatization

A method designed for many types of aliphatic compounds, including ethers and other polar substances which might be found in water, uses steam as the carrier gas[175]. The column packing is Chromosorb P with 3.5% phosphoric acid and hydrogen flame ionization detection is used.

A method for methyl ether uses flame ionization detection with a packing of Porapak T if the ether concentration is higher than 0.1% or a packing of 3.8% Halcomid M18 and 0.5% PEG 600 on Teflon if the concentration is lower than 0.1%[176]. A mixture of Porapak N and Porapak Q in a 4:1 ratio is also useful for determination of methyl ether[177].

For determination of ethyl ether, a column of 3% polyoxyethylene glycol 1000 or 10% Carbowax 20 M on Chromosorb W is satisfactory[178]. In a head space method for a variety of compounds including ethyl ether, 3% SP-1500 on Carbopack B is useful[179].

Oxygen compounds in gasoline have been determined on a fused silica WCOT column coated with 5% phenylmethylsilicone. In this case detection was by FTIR and quadrupole MS[17].

A Tenax GC column coated with polymetaphenoxylene and using flame ionization detection has been used for analysis of mixtures of phenyl ether and biphenyl purged from oils[180].

There are several methods available for the gas chromatographic determination of methyl *t*-butyl ether (MTBE). These include use of an OV-1701 capillary column[181], a DB-1 WCOT capillary column with flame ionization detection[20] and a 50-m chemically bonded, nonpolar fused silica BP-1 WCOT column[182].

For other determinations of methyl *t*-butyl ether suitable columns include 20% LAC-1R-296 on Chromosorb W AW DMCS modified with 3% phosphoric acid[183] and dual WCOT columns of Durawax 1 and Durabond 5[21]. The first of these two methods is used for the determination of MTBE (and methanol) in air and the second method is for determination in gasoline.

Infrared detection has been used following separation on a mixed Porapak Q-Porapak N column[22].

Bis(chloromethyl) ether has been determined on a capillary column coated with CP wax 57, using MS–MS detection with ion monitoring at *m/e* 79 ($ClCH_2O$)[184].

Bis(pentabromophenyl) ether and 1,2-bis-(pentabromophenoxy)ethane have been separated from structurally similar compounds on a fused silica column coated with DB-1, with electron-capture detection[185].

A rather novel method for determination of methyl *t*-butyl ether, as well as other ethers and also alcohols in gasoline starts rather simply with a straightforward chromatographic separation on Carbopack 1500[186]. The novelty and potential wide use of the method lies in the chemical ionization mass spectroscopy (CIMS) detection system. This system uses tetramethylsilane as the CI reagent gas. Tetramethylsilane, or rather its major ion, $(CH_3)_3Si^+$, is virtually unreactive toward the hydrocarbon components of

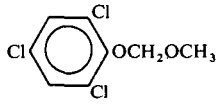
the gasoline but has a high reactivity with compounds containing a nucleophilic center, such as ethers and alcohols. Thus, the detector can, in effect, ignore the gasoline components and detect only the ethers and alcohols. In fact, it is not necessary for the ethers and alcohols to be separated from the gasoline hydrocarbons for the analysis. Equations 15 and 16 illustrate the reactions involved. The trimethylsilyl cation has a *m/e* 73. The tetramethylsilane CI spectrum of methanol contains ions only at *m/e* 105 resulting from the $(CH_3)_3Si + CH_3OH)^+$ adduct ion. Simple dialkyl ethers containing at least two carbons in one of the alkyl groups give a spectrum which contains peaks for adduct ions (M + 73), ions arising from the loss of alkene from these ions, i.e. $(M + 73 - C_xH_{2x})^+$ and alkyl ions for ethers having C_4 and higher alkyl groups. A graph of the sum of ion currents for $m/e = 91$, $m/e = 105$ and $m/e = (M + 73)$ provides an indication of the amount of alcohols and ethers in the sample. In the case of methyl *t*-butyl ether, the dominant peak is at $m/e = 105$ $(M + 73 - C_4H_8)^+$.

$$(CH_3)_3Si^+ + C_nH_{2n+1}OH \longrightarrow (CH_3)_3SiOH_2^+ + C_nH_{2n} \quad (15)$$

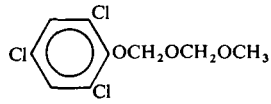
$$(CH_3)_3SiOH_2^+ + ROH \longrightarrow (ROH + 73)^+ + H_2O \quad (16)$$

2. With precolumn derivatization

In view of the generally unreactive nature of ethers, there is almost no derivatization for chromatography. An exception exists for bis(chloromethyl) ether, since this compound has a highly reactive chlorine whose reactivity is related to the adjacent ether function. Derivatization stabilizes the ether and reduces the necessity for working with the carcinogenic ether. In the case in which the derivatization is done with 2,4,6-trichlorophenol, an additional advantage is that the derivative is well-suited for electron-capture detection[187]. This method is useful at the parts per billion range for both chloromethyl methyl ether and for bis(chloromethyl) ether. The air to be sampled is scrubbed through impingers loaded with equimolar amounts of 2,4,6-trichlorophenol and sodium methoxide. The derivatization reaction appears to give **2** and **3** as the derivatives of chloromethyl methyl ether and bis(chloromethyl) ether, respectively. These are probably not the only products formed from the reaction of the two ethers with the two nucleophiles. In a related derivatization, chloromethyl methyl ether is trapped and derivatized by passing contaminated air through an air sampling tube containing 1.5% potassium 2,4,6-trichlorophenoxide on GLC-110 as the adsorbent. In this case only the first of the above compounds is formed[188].

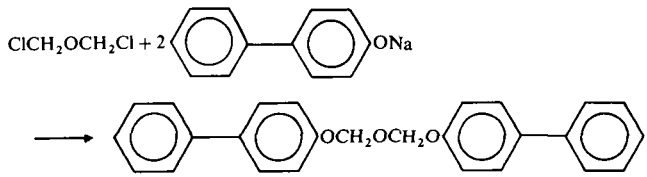


(2)



(3)

In another derivatization procedure, bis(chloromethyl) ether is trapped from air by a Tenax trap and then derivatized in a DMF solution of sodium *p*-phenylphenoxide (equation 17). The resulting bis(*p*-phenylphenoxymethyl) ether is then highly suitable for



(17)

detection with a flame ionization detector after passage through a glass capillary column deactivated with benzyltriphenyphosphonium chloride and coated with SE 54. As little as 0.1 ppb can be detected in industrial atmospheres[189].

B. High Performance Liquid Chromatographic (HPLC) Methods

Simple straightforward methods for ethers differ from each other primarily in the type of column packing and detection. Graphitic carbon appears to be a suitable packing for a variety of ethers[190]. When the ethers contain aromatic groups, the detection can be done by UV at 254 nm. The solvent in this latter case can be methanol–water mixtures containing up to 30% water.

The presence of an alkoxy group on an aromatic ring activates the ring toward aromatic substitution reactions such as bromination. A bromination procedure in which the bromine is generated electrochemically takes advantage of this reactivity and provides the basis for detection of phenolic ethers after separation by HPLC. The method has been applied to such ethers as morphine, codeine, noscapine and papaverine[191].

In the case where the ether contains only aliphatic groups detection at 254 nm is not possible, but in at least one case, separation of polyethylene glycol oligomers, UV detection was possible at 185 nm[192]. A reverse-phase column with acetonitrile solvent was used. Presumably this method of detection should be useful for a variety of aliphatic ethers.

Refractometric detection has been used for the determination of diisopropyl ether in water[193].

An aliphatic ether which has attracted much attention in recent years is methyl *t*-butyl ether (MTBE) and the methods described are for its determination in gasoline. The method of Pauls[194] uses refractometric detection after separation on Spherisorb ODS-II with 60% acetonitrile–water. Related compounds such as alcohols are also determined. Similar mixtures of MTBE with other ethers and alcohols in gasoline have been separated on C18-treated silica with a mobile phase of water–methanol (83:17)[195].

C. Chemical Methods

The traditional (Zeisel) method for determination of methoxy and ethoxy groups consists of the cleavage of the ether with hydrogen iodide, followed by the determination of the resulting methyl or ethyl iodide by either volumetric or gravimetric means.

$$PhOCH_3 + HI \longrightarrow PhOH + CH_3I \tag{18}$$

$$CH_3OCH_3 + 2\,HI \longrightarrow 2\,CH_3I + H_2O \tag{19}$$

$$ROCH_3 + 2\,HI \longrightarrow RI + CH_3I + H_2O \tag{20}$$

The method, which requires special apparatus, has been applied to procedures using samples of several milligrams[196], 0.1 mg[197] and 50 μg[198]. Alternatively, the methyl iodide can be determined by gas chromatography[199] or by HPLC[200]. Reviews of the older literature on determination of *O*-alkyl groups, ethers and oxiranes may also be consulted[201–203]. In a modification designed to permit determination of higher alkoxy groups, the alkyl iodides are determined by ultraviolet spectroscopy[204].

IV. PEROXIDES

The methods and their limitations used for the determination of organic peroxides prior to 1979 have been published[205,206]. It should be emphasized again, as was pointed out by the authors in the preceding references, that because peroxides exhibit a wide range

of reactivities, the conditions used for the analysis of an individual peroxide should be carefully evaluated.

Chromatography is widely employed for the determination of peroxides and, with the use of appropriate detectors, the technique becomes an excellent quantitative procedure.

A. Gas Chromatography

Sufficiently volatile and stable peroxides are determined directly using ordinary gas chromatographic techniques. Capillary columns coated with SP2250 (50:50 polymethylphenylsiloxane)[207] or SE-30[208] appear to give good results. In the latter reference, dicumyl peroxide is determined in mixtures containing cumene oxidation products with relative errors of $<8\%$ over the concentration range 0.05 to 40%.

For nonvolatile or unstable peroxides indirect methods are used. The peroxide is converted into a stable volatile substance by reaction or by pyrolysis and the products are determined by gas chromatography.

The di-*t*-butyl peroxide groups in polymers derived from substances such as (**4**) are determined by a reductive transformation to acetone and *t*-butyl alcohol with transition metal salts (Cu naphthenate in the presence of benzoin). The reduction products are determined by gas chromatography[209].

$$CH_2{=}CHC{\equiv}CCMe_2OOCMe_3$$

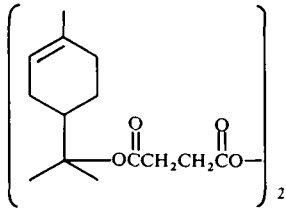
(**4**)

Pyrolysis chromatography can be utilized in a similar fashion. The gas chromatographic determination of the volatile thermal decomposition products of organometallic peroxides, such as dimethyl(methylperoxy)gallium and dimethyl(*t*-butylperoxy)gallium, was used to analyze these substances with a standard deviation of 0.05 over the concentration range of 0.01–0.17 mol/L[210].

If fragmentation patterns are sufficiently reproducible, the nature of the pyrolysis products allows a structure determination of the analyte. Pyrolysis chromatography has been used in this way to identify hydroperoxy cyclic peroxides[211].

B. Supercritical Fluid Chromatography

Because capillary supercritical fluid chromatography (SFC) is potentially a useful technique for the analysis of heat-sensitive and nonvolatile analytes, its use was investigated for the analysis of peroxides. By using an SB-Methyl 100 coated silica column, a carbon dioxide mobile phase and MS detection, it was found that the on-column decomposition of benzoyl peroxide was minimal and the benzoyl peroxide could be determined. However, a second peroxide studied, terpineol succinate peroxide (**5**), undergoes significant decomposition[212].



(**5**)

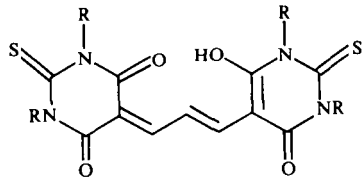
C. High Performance Liquid Chromatography

HPLC represents a relatively recent and highly powerful technique for the determination of peroxides. Because HPLC is carried out at room temperature or below, nonvolatile and thermally sensitive peroxides can be detected. The method lends itself also to a variety of highly sensitive detectors which allows analysis in some instances in the nanogram range.

Some typical conditions for the determination of representative peroxides appear in Table 3.

It has been found that a mixture of the following peroxides: di-*t*-butylperoxy dicarbonate, *t*-butyl peroctanoate, *t*-butyl perbenzoate, cumene hydroperoxide and *t*-butyl hydroperoxide, can be separated qualitatively on a μ Porasil column using a gradient 2-propanol-hexane mobile phase. The individual peroxides can be determined quantitatively using the same system but with isocratic elution[219].

The detection of lipid peroxides has attracted considerable interest, because of the correlation of peroxide concentrations with various pathological conditions and because of the possible relationship of peroxides in foods to toxicity and rancidity. Although lipid peroxides have been also determined by iodometric methods[220] and by an iodometric-colorimetric procedure[221] derived from the method described by Swoboda and Lea[222], a colorimetric assay, based on the red coloration produced when lipid hydroperoxides in acidic media are treated with thiobarbituric acid, has been used more extensively, probably because of its convenience and simplicity. The method, which measures precursors of malonaldehyde, is useful primarily in determining relative peroxide levels in a number of similar samples, since it has been found that the color intensity developed parallels the peroxide content[223]. The procedure is carried out generally by heating the sample in acidic media containing thiobarbituric acid, during which time malonaldehyde is produced by the thermal and/or acid-catalyzed decomposition of peroxides (and other substances), which then reacts with the thiobarbituric acid to generate the red species **6**. Since the adduct absorbs at 523 nm and emits at 553 nm on excitation at 515 nm, visual, spectrophotometric or fluorescence detection can be used.



or tautomer

(6) R = H
(7) R = C_6H_5

In addition to endoperoxides[224] and hydroperoxides[225], it has been found that unsaturated aldehydes such as 2-hexenal and 2,4-hexadienal[225] also produce the colored species which absorbs at 532 nm. When the method is applied to biological systems, bilirubin, sugars and sialic acid interfere[226] with the colorimetric detection.

Recently, techniques using HPLC have been developed to improve the reproducibility and sensitivity of the method and to separate the malonaldehyde–thiobarbituric adduct (**6**) from interfering substances.

In a typical procedure[227] the lipid peroxides in plasma are hydrolyzed by heating (100 °C) in dilute phosphoric acid containing thiobarbituric acid and, after precipitation of protein material, the sample is chromatographed on a μ bondapak C_{18} column. The

TABLE 3. Typical conditions for determination of selected peroxides by HPLC

Analyte	Column	Mobile phase	Detection	Detection limit	Ref.
Cumene hydroperoxide *t*-Butyl hydroperoxide, 13-Hydroperoxy-9(*Z*)-11-octadecadienoic acid	C_8 or ODS	Acetonitrile–acetic acid containing $Na_2B_2O_7$	Polarographic and amperometric	1–2.5 ng	213
Benzoyl peroxide	Portisil 10/25 ODS-3	Acetonitrile–H_2O containing $NaClO_4$	Electrochemical (Ag/AgCl)	0.5 ng	214
Benzoyl peroxide	Zorbax BP ODS	MeOH–H_2O	Amperometric	10 ng	215
Dicumyl peroxide		MeOH–H_2O		100 ppm	216
Benzoyl peroxide	Polygosil 60-10 C18	Acetonitrile–H_2O	UV at 254 nm	—	217
Benzyoyl peroxide	Bondapak	MeOH–H_2O	UV at 238 nm	—	218

detection limit of malonaldehyde was 0.7 μmol/liter of plasma when using a fluorescence detector and 0.15 μmol/liter of plasma using a spectrophotometric detector.

A considerable enhancement in the sensitivity of the lipid peroxide (malonaldehyde) determination has been achieved by the use of 1,3-diphenyl-2-thiobarbituric acid in place of thiobarbituric acid and separation of the adduct (7) from interfering substances by HPLC. Fluorometric detection results in a 192-fold greater sensitivity over the thiobarbituric acid method[228].

A diphenylthiobarbituric acid–HPLC method that uses spectrophotometric detection of the colored adduct had been developed for the assay of lipid peroxides in serum[226]. The method is reported to be rapid because it eliminates extraction and protein removal. This method has been applied to the determination of lipid peroxides in blood serum and it was found that glucose, bilirubin and sialic acid do not interfere[229].

D. Thin Layer Chromatography

The separation and detection of organic peroxides by TLC most often utilizes a silica gel adsorbent with either specific or nonspecific visualization of the spots.

Mixtures of alkyl aryl peroxides, aryl peroxides, benzoyl peroxides and their decomposition products were analyzed on silica gel using xylene as the mobile phase. Detection utilized the ammonium thiocyanate–ferrous sulfate pair. Recoveries ranged from 82–98% and the detection limits were 0.5–5.0 μg[230].

Dicumyl peroxide, *t*-butyl perbenzoate and 1,3-bis(*t*-butyldioxyisopropyl)benzene were separated using a silica gel adsorbent with detection by spraying the plates with *N*,*N*-dimethyl-*p*-phenylenediamine or potassium iodide–starch solutions. The separated spots were extracted and determined by HPLC using a Zorbax C8 column and an acetonitrile–water mobile phase. The separated components were identified by mass spectroscopy[231].

A reversed-phase system composed of a C-18 adsorbent and an acetonitrile–water mobile phase was used to analyze benzoyl peroxide–benzoic acid mixtures. The spots were detected by ultraviolet light (fluorescent indicator plates) and identified by their RF values[232].

E. Spectroscopic Methods

1. Ultraviolet–visible methods

Several spectrophotometric methods have been examined and evaluated for their use in the determination of peroxides (hydrogen peroxide, cumene and *t*-butyl hydroperoxides, peracetic acid and *m*-chloroperbenzoic acid) in aqueous media at the 1–10 μM concentration level[233].

Of the methods studied, the procedure involving a coupled oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) was regarded as the most widely applicable. In this procedure, the peroxide analyte oxidizes glutathione (GSH) in the presence of glutathione reductase to give the oxidized form of glutathione (GSSG), which is then reduced by NADPH (equations 21 and 22). The peroxide concentration is related to the decrease in the absorbance of NADPH at 340 nm. All of the peroxides above reacted within 20–30 min and gave linear calibration curves.

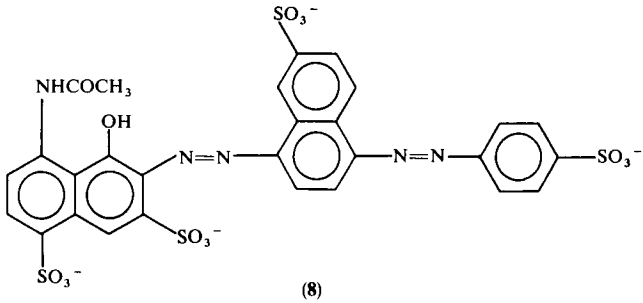
$$2\,GSH + ROOH \xrightarrow[\text{reductase}]{\text{glutathione}} GSSG + ROH + H_2O \tag{21}$$

$$GSSG + NADPH + H^+ \xrightarrow[\text{reductase}]{\text{glutathione}} 2\,GSH + NADP^+ \tag{22}$$

An iodide method based on the procedure developed by Allen and coworkers[234] was also investigated to determine low concentrations of peroxides. Peroxide oxidizes iodide to triiodide under ammonium molybdate catalysis. The triiodide is then determined spectrophotometrically at 352 nm. The procedure was useful for the analysis of peracids and hydrogen peroxide, but the hydroperoxides reacted too slowly under the conditions developed to give useful results.

The low reactivity of hydroperoxides was also a problem with a procedure[235] in which peroxides convert the colorless phenolphthalin by a Cu(II)-catalyzed oxidation into its colored derivative, phenolphthalein. Results of the study suggest that while the procedure might not be useful for the determination of total active oxygen, it could be employed for the analysis of individual peroxides.

In this same study, a catalytic-dye-bleaching procedure was found to be a rapid and convenient way to determine hydrogen peroxides and hydroperoxides. An iron–porphyrin complex (deutroferrihaem) interacts with peroxides to produce a complexed oxidized iron species, which then reacts with Black PN dye (**8**)[236]. The decrease in absorbance at 576 nm is a measure of the peroxide concentration. The analysis is carried out in an inert atmosphere, since oxygen interferes.



(**8**)

A procedure that takes advantage of the fact that acyl peroxides and peresters react with hydroxylamine to form hydroxamic acids has been developed for the selective determination of these compounds. The hydroxamic acid concentration is determined spectrophotometrically after conversion to the colored iron(III) complexes. Both the peresters and acyl peroxides can be determined together if the reaction is carried out at pH 14, while acyl peroxides alone react at pH 7. Other peroxides and hydrogen peroxide do not interfere. Acyl peroxides can be determined at a concentration of $\geqslant 2.5 \times 10^{-6}$ M with a relative standard deviation of $\leqslant 0.1$[237].

Cumene and *t*-butyl hydroperoxides can be selectively determined in the presence of dialkyl and diacyl peroxides because the hydroperoxides form a colored 1:1:1 complex with cobalt(II) and EDTA (at pH 13) which absorbs at 590 nm. Beer's law is followed over the concentration range of 0.5–2 μM. Although ketone peroxides interfere with the hydroperoxide assay, this method can also be used to determine the ketone peroxides in the absence of hydroperoxides[238].

Applications of other well-known methods for the spectrophotometric determination of peroxides have been reported.

Peroxide levels in various organic solvents were estimated using ammonium metavanadate and nitric acid. The absorbance of the developed color was measured at 450 nm. A blank and calibration curve were required[239].

The iodine produced from the reaction of peroxides in polysorbate 60, sorbitan monostearate and sorbitol monooleate with iodide was used to determine the peroxide content in these materials[240].

The active oxygen in mixtures of bis(1-hydroxycyclohexyl)peroxide, 1,1'-dioxybis-(cyclohexyl hydroperoxide) and 1-(1-hydroxycyclohexyldioxy)cyclohexyl hydroperoxide in aqueous solution was determined by the oxidation of *N,N*-dimethyl-*p*-phenylene-diamine in acetic acid followed by measurement of the color developed at 490 nm[241].

It has been found that methanolic ferrous thiocyanate produces a red-brown color when peroxides are present in intact plant tissues[242].

2. *Fluorescence methods*

Kinetic fluorescence methods have been extensively applied to the determination of peroxides in a variety of substrates.

A procedure which involves the MnO_2-catalyzed oxidation of 2-hydroxynaphthaldehyde thiosemicarbazone by hydroperoxide to produce a blue fluorescence has been used to determine cumene and *t*-butyl hydroperoxides and lipohydroperoxides at the nanomole level. By using an initial rate method, *t*-butyl and cumene hydroperoxides could be detected with a relative standard deviation of 2.3–2.5%[243].

t-Butyl hydroperoxide was determined by measuring the rate of change of fluorescence in the reaction of the hydroperoxide with 4-hydroxy-3-methoxyphenylacetic acid. Fluorescent dimer formation is catalyzed by iron(III)[244].

In a similar method, the peroxide oxidation of 4-hydroxyphenylacetic acid is catalyzed by horseradish peroxidase. The fluorescence developed is measured either by a batch method or in a flow system. In an application of this procedure in which peroxides in rain were measured, it was found that quantitative results at the 10^{-5} *M* level could be obtained from methyl and n-propyl hydroperoxides and peracetic acid but not from *t*-butyl hydroperoxide[245].

The luminescence which results from the reaction of peroxides with secondary or tertiary amines is the basis of an analytical method for peroxides.

Benzoyl peroxide, extracted from pharmaceutical preparations, has been determined through the luminescence produced on reaction with triethylamine. The detection limit of the benzoyl peroxide was 0.07 μg/mL with a relative standard deviation of 4% at the 1 μg/mL level. The results agreed closely with those obtained by gas chromatography[246].

Aromatic peroxides obtained by extracting airborne particulate matter with toluene were determined by the luminescence produced on reaction with piperidine in DMSO[247].

It was found that a variety of organic peroxides including hydroperoxides, peroxyesters, diacylperoxides, peroxyketals, endoperoxides and cyclic peroxides could be determined readily at the nmol to pmol level by a chemiluminescent procedure using a *cypyridina* luciferin–cerium(III) acetoxylacetone reagent. The luminescent intensities depended on the structures of both the *cypyridina* luciferin derivative and the hydroperoxide[248].

Amino acid peroxides, after separation by HPLC, were determined by the use of the chemiluminescence reagent cytochrome *c*-luminol and a chemiluminescence detector[249].

3. *Nuclear magnetic resonance methods*

While nuclear magnetic resonance is not strictly within the province of this chapter, the following method is included to illustrate that NMR does have some utility and potential in the analysis of peroxides.

A carbon-13 NMR technique has been developed for the determination of *t*-butyl hydroperoxide and *t*-butyl peroxide in *t*-butyl alcohol. The ^{13}C pulse width and acquision delay times were selected so that all ^{13}C nuclei were completely relaxed between pulses, and thus the resonance integrals corresponded to relative numbers of nuclei at a particular carbon. Mol% of components were calculated from the methyl resonances. A limit of detection of 0.5 mol% could be achieved by acquiring 600 free-electron decays[250].

F. Volumetric Methods

1. Titration methods

Of the titrimetric methods described recently, the iodometric method is the most commonly used and the majority of reports deal with the evaluation of the analysis of specific peroxides or mixtures. The method is based on the oxidation of iodide by peroxides, usually in acidic media, to produce iodine which is titrated with thiosulfate. The oxidation

$$ROOR' + 2I^- + 2H^+ \longrightarrow ROH + R'OH + I_2 \qquad (23)$$

is carried out in an inert atmosphere since oxygen interferes with the oxidation.

Peroxides in propylene trimers are determined by potentiometric titration (using Ag and Pt wire electrodes) of the iodine released with $Na_2S_2O_3$. Interference from oxygen is avoided by bubbling Ar through the reaction medium[251].

Carbon dioxide, generated by the reaction of $NaHCO_3$ with acid in the reaction medium, is also used to eliminate the deleterious effects of oxygen. In a determination of di-*t*-butyl peroxide, recoveries of *ca* 95% were obtained in acetic acid–$NaHCO_3$ at 80–85 °C[252] while in a second method for the analysis of 8:1 to 1:1 mixtures of *t*-butyl 2-chloroethyl peroxide (**9**) and 2,2-bis(*t*-butylperoxy)-1,1-diethoxyethane (**10**), CO_2 is generated by reaction of $NaHCO_3$ with HCl in the acetic acid solvent at 100 °C[253]. In the first analysis, recoveries of *ca* 95% and coefficients of variation of 0.2% are obtained. In the latter experiments, the combined **9** and **10** are determined, then **9** is selectively reacted with ammonia and the remaining **10** analyzed iodometrically.

Peroxide and double-bond content in analytes are determined by an initial iodometric peroxide analysis followed by reaction of an aliquot with bromine (KBr–$KBrO_3$–H_2SO_4) and titration of the excess to give total double-bond and peroxide equivalents. The coefficient of variation for the determination of 2-(1-peroxyallyloxy)ethanol is 1.9%[254].

The analysis of milligram amounts of acyl peroxide and peroxy ester mixtures ranging in concentration ratios of 1:9 to 9:1 is accomplished by an initial alkaline hydrolysis followed by an iodometric determination of total peroxide on an aliquot. The peroxy carboxylic acid, in a separate aliquot, is subjected to a selective diphenyl sulfide reduction and the remaining alkyl hydroperoxide determined iodometrically[255].

An indirect method for the determination of methyl ethyl ketone peroxide, dibenzoyl peroxide, cyclohexanone peroxide and methylcyclohexanone peroxide involves the use of $SnCl_2$ in alkaline media complexed with glycerol or sorbitol as reductant. The excess Sn(II) is titrated with $K_2Cr_2O_7$ with potentiometric, bipotentiometric or biamperometric detection. Best results for the determination of *m*-chloroperbenzoic acid are obtained by using the $SnCl_2$–sorbitol reducing system[256].

2. Flow-injection methods

A flow-injection system containing nested loops has been developed and applied to the analysis of aqueous solutions containing hydrogen peroxide and methyl hydroperoxide. One of the loops in the system contains MnO_2, which selectively decomposes hydrogen peroxide under the conditions used. Detection of the analytes is based on the method of Guilbault and workers[257] in which peroxides in the presence of peroxidase convert *p*-hydroxyphenylacetic acid into a fluorescent dimer. The dimer concentration is then measured by spectrofluorimetry. In this procedure, total peroxides are determined by excluding the loop containing the MnO_2 from the system, followed by switching in the MnO_2 loop. The hydrogen peroxide is effectively removed and the remaining methyl hydroperoxide determined fluorometrically. The reproducibility of

duplicate runs is reported to be excellent and the relative standard deviations between peaks are less than 1%. The low and erratic results observed with benzoyl peroxide in this system are attributed to its low solubility in water[258].

V. REFERENCES

1. I. O. O. Korhonen, *J. Chromatogr.*, **268**, 229 (1983); J. K. Haken and I. O. O. Korhonen, *J. Chromatogr.*, **319**, 131 (1985).
2. I. O. O. Korhonen, *J. Chromatogr.*, **258**, 443 (1984).
3. I. O. O. Korhonen, *J. Chromatogr.*, **287**, 399 (1984).
4. I. O. O. Korhonen, *J. Chromatogr.*, **270**, 171 (1983).
5. I. O. O. Korhonen, *J. Chromatogr.*, **288**, 329 (1984).
6. G. Reglero, M. Herraiz, T. Herraiz and E. Loyola, *J. Chromatogr.*, **438**, 243 (1988).
7. D. B. Drucker, *J. Chromatogr.*, **208**, 279 (1981).
8. R. E. Osborn and A. H. Ullman, *J. Am. Oil Chem. Soc.*, **63**, 95 (1986).
9. N. B. Smith and N. Rawal, *Clin. Chem.*, **33**, 2324 (1987).
10. Y. Ghoos, M. Hiele, P. Rutgeerts and G. Vantrappen, *Biomed. Environ. Mass Spectrom.*, **18**, 613 (1989).
11. P. R. Nichikova, N. S. Kiseleva, G. A. Tember, Z. I. Getmanskaya and V. N. Ivanov, *Neftepererab. Neftekhim.*, 37 (1978); *Chem. Abstr.*, **90**, 106076c (1979).
12. Y. Jin, R. Fu and Z. Huang, *J. Chromatogr.*, **469**, 153 (1989).
13. S. C. Dhanesar, M. E. Coddens and C. F. Poole, *J. Chromatogr.*, **324**, 415 (1985).
14. W. A. Koenig, R. Krebber and P. Mischnick, *J. High Resolut. Chromatogr.*, **12**, 732 (1989).
15. V. Schurig, U. Leyrer and R. Weber, *J. High Resolut. Chromatogr., Chromatogr. Commun.*, **8**, 459 (1985).
16. J. H. Shofstahl and J. K. Hardy, *Anal. Chem.*, **58**, 2412 (1986).
17. J. Schulz, *Fresenius' Z. Anal. Chem.*, **333**, 759 (1989).
18. W. M. Coleman, III and B. M. Gordan, *Appl. Spectrosc.*, **43**, 1008 (1989).
19. V. K. Agarwal, *Analyst (London)*, **113**, 907 (1988).
20. N. G. Johansen, *J. High Resolut. Chromatogr., Chromatogr. Commun.*, **7**, 487 (1984).
21. J. M. Levy and J. A. Yancey, *J. High Resolut. Chromatogr., Chromatogr. Commun.*, **9**, 383 (1986).
22. R. A. Cochrane and D. E. Hillman, *J. Chromatogr.*, **287**, 197 (1984).
23. C. L. Guillemin, F. Martinez and S. Thiault, *J. Chromatogr. Sci.*, **17**, 677 (1979).
24. J. Teply and M. Dressler, *J. Chromatogr.*, **191**, 221 (1980).
25. M. Koel, M. Kaljurand and E. Kullik, *Anal. Chim. Acta*, **199**, 197 (1987).
26. T. Tanaka, *Yukagaku*, **30**, 51 (1981); *Chem. Abstr.*, **94**, 123508v (1981).
27. V. G. Berezkin, E. N. Viktorova and V. S. Gavichev, *J. Chromatogr.*, **456**, 351 (1988).
28. M. Josowicz and J. Janata, *Anal. Chem.*, **58**, 514 (1986).
29. A. R. Gholson, Jr., R. H. St. Louis and H. H. Hill, Jr., *J. Assoc. Off. Anal. Chem.*, **70**, 897 (1987).
30. T. Niva, N. Yamamoto, K. Maeda, K. Yamada, T. Ohki and M. Mori, *J. Chromatogr., Biomed. Appl.*, **28**, 378 (1983).
31. J. Szymanowski and H. Szewczyk, *Chem. Anal. (Warsaw)*, **26**, 469 (1981).
32. L. R. Hogge and D. J. H. Olson, *J. Chromatogr. Sci.*, **20**, 109 (1982).
33. Y. Maeda, Y. Fujio, T. Suetaka and M. Munemori, *Analyst (London)*, **113**, 189 (1988).
34. B. V. Stolyarov, S. Talantov and L. A. Kartsova, *Zh. Anal. Khim.*, **43**, 894 (1988); *Chem. Abstr.*, **109**, 103886s (1988).
35. D. V. Crabtree, A. J. Adler and G. J. Handelman, *J. Chromatogr.*, **466**, 251 (1989).
36. C. F. Poole, S. Singhawangcha and A. Zlatkis, *J. Chromatogr.*, **186**, 307 (1979).
37. C. F. Poole and A. Zlatkis, *J. Chromatogr.*, **184**, 99 (1980).
38. A. Blink, M. L. Suijkerbuijk, T. Ishiwata and B. L. Feringa, *J. Chromatogr.*, **467**, 285 (1989).
39. N. A. Prokopenko, N. A. Dubrova and T. P. Kirsh, *Zh. Anal. Khim.*, **35**, 805 (1980); *Chem. Abstr.*, **93**, 106515g (1980).
40. W. V. Ligon, Jr. and H. Grade, *Anal. Chem.*, **63**, 255 (1991).
41. Y. Liu and F. J. Yang, *Anal. Chem.*, **63**, 926 (1991).
42. N. Petroff and G. Codet, *Rev. Inst. Fr. Pet.*, **38**, 545 (1983); *Chem. Abstr.*, **99**, 90660m (1983).
43. J. F. Alder, P. K. P. Drew and P. R. Fielden, *J. Chromatogr.*, **212**, 167 (1981).
44. C. Fujimoto, G. Uematsu and K. Jinno, *Chromatographia*, **20**, 112 (1985).

45. M. S. Gandelman and J. W. Birks, *J. Chromatogr.*, **242**, 21 (1982).
46. T. Okada, *Anal. Chem.*, **60**, 1336 (1988); **53**, 909 (1981); **54**, 1282 (1982).
47. T. Gnanasambandan and H. Freiser, *Anal. Chem.*, **54**, 1282 (1982).
48. S. Banerjee, *Anal. Chem.*, **57**, 2590 (1985).
49. T. Takeuchi and D. Ishii, *J. Chromatogr.*, **393**, 419 (1987).
50. T. Takeuchi and D. Ishii, *J. Chromatogr.*, **396**, 149 (1987).
51. T. Takeuchi, K. Murase and D. Ishii, *J. Chromatogr.*, **445**, 139 (1988).
52. J. E. Parkin, *J. Chromatogr.*, **287**, 457 (1984); J. E. Parkin and H. T. Lau, *J. Chromatogr.*, **314**, (1984).
53. P. K. Gupta and J. G. Nikelly, *J. High Resolut. Chromatogr., Chromatogr. Commun.*, **9**, 572 (1986).
54. S. W. Kang and J. T. Kang, *Taehan Hwahakhoe Chi*, **33**, 406 (1989); *Chem. Abstr.*, **114**, 16868x (1991).
55. T. Takeuchi and E. S. Yeung, *J. Chromatogr.*, **366**, 145 (1986).
56. Y. Suzuki and N. Tsuchiya, *Bunseki Kagaku*, **30**, 240 (1981); *Chem. Abstr.*, **95**, 34894w (1981).
57. J. D. Willett, E. P. Brody and M. M. Knight, *J. Am. Oil Chem. Soc.*, **59**, 273 (1982).
58. R. Galensa, *Z. Lebensm.-Unters.-Forsch.*, **178**, 475 (1984); *Chem. Abstr.*, **101**, 109073f (1984).
59. T.-H. Yang, T. M. Zabriskie and C. D. Poulter, *J. Chromatogr.*, **312**, 121 (1984).
60. T. Wolski, W. Golkiewicz and G. Bartuzi, *J. Chromatogr.*, **362**, 217 (1986).
61. Y. Suzuki and K. Tani, *Bunseki Kagaku*, **28**, 610 (1979); *Chem. Abstr.*, **92**, 14889h (1980).
62. G. Czichocki, H. Much and D. Vollhardt, *J. Chromatogr.*, **280**, 109 (1983).
63. Y. Tsuruta and K. Kohashi, *Anal. Chim. Acta*, **192**, 309 (1987).
64. T. Iwata, M. Yamaguchi, S. Hara, M. Nakamura and Y. Ohkura, *J. Chromatogr.*, **362**, 209 (1986).
65. K. E. Claas and E. Hohaus, *Fresenius' Z. Anal. Chem.*, **322**, 343 (1985).
66. A. Takadate, M. Iwai, H. Fukino, K. Tahara and S. Goya, *Yakugaku Zasshi*, **103**, 962 (1983); *Chem. Abstr.*, **100**, 114276h (1984).
67. M. Kudoh, H. Ozawa, S. Fudano and K. Tsuji, *J. Chromatogr.*, **287**, 337 (1984).
68. H. Fujino, M. Hidaka and S. Goya, *Yakugaku Zasshi*, **109**, 606 (1989); *Chem. Abstr.*, **112**, 178253d (1990).
69. A. Takadate, M. Irikura, T. Suehiro, H. Fujino and S. Goya, *Chem. Pharm. Bull.*, **33**, 1164 (1985).
70. A. Takadate, T. Tahara, H. Fujino and S. Goya, *Chem. Pharm. Bull.*, **30**, 420 (1982).
71. R. Wintersteiger and O. S. Wolfbeis, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.*, **38B**, 248 (1983); *Chem. Abstr.*, **98**, 179325h (1983).
72. R. Wintersteiger, *J. Liq. Chromatogr.*, **5**, 897 (1982).
73. R. Wintersteiger, G. Gamse and W. Pacha, *Fresenius' Z. Anal. Chem.*, **312**, 455 (1982).
74. R. Wintersteiger and G. Wenniger-Weinzierl, *Fresenius' Z. Anal. Chem.*, **309**, 201 (1981).
75. R. Wintersteiger, G. Wenniger-Weinzierl and W. Pacha, *J. Chromatogr.*, **237**, 399 (1982).
76. K. Shimada, S. Orii, M. Tanaka and T. Nambara, *J. Chromatogr.*, **352**, 329 (1986).
77. C. Troeltzsch, *J. Liq. Chromatogr.*, **9**, 1367 (1986).
78. S. Terabe, H. Tanaka, K. Otsuka and T. Ando, *J. Chromatogr. Sci.*, **27**, 653 (1989).
79. A. Messina and D. Corradini, *J. Chromatogr.*, **207**, 152 (1981).
80. A. Horna, H. Pechova and J. Churacek, *J. Chromatogr.*, **330**, 439 (1985).
81. Y. Ma and E. S. Yeung, *J. Chromatogr.*, **455**, 382 (1988).
82. P. J. Davies and R. F. A. Ginman, *Analyst (London)*, **109**, 727 (1984).
83. I. Muntean, J. M. Herdan and G. Valeanu, *Rev. Roum. Chim.*, **33**, 467 (1988); *Chem. Abstr.*, **110**, 50471q (1989).
84. H. Bober, *Labor Praxis*, **6**, 794 (1982); *Chem. Abstr.*, **97**, 192503p (1982).
85. D. S. Frankel, *Anal. Chem.*, **56**, 1011 (1984).
86. E. Mentasti and C. Baiocchi, *Anal. Chim. Acta*, **119**, 91 (1980).
87. S. Vorberg, W. Schoepp and H. Tauchert, *Monatsch. Chem.*, **114**, 563 (1983).
88. A. Nabi and P. J. Worsfold, *Analyst (London)*, **112**, 531 (1987).
89. W. H. Chan, A. W. M. Lee and K. T. Fund, *Talanta*, **35**, 807 (1988).
90. W. H. Chan, A. W. M. Lee, K. S. Lam and C. L. Tse, *Analyst (London)*, **114**, 233 (1989).
91. C. Verduyn, J. P. Van Dijken and W. A. Scheffers, *Biotechnol. Bioeng.*, **25**, 1049 (1983).
92. P. P. Gladyshev, V. P. Gladyshev, V. S. Mamleev and S. Kovalyova, *Mikrochim. Acta*, **2**, 289 (1981).
93. G. G. Guilbault, B. Danielsson, C. F. Mendenius and K. Mosbach, *Anal. Chem.*, **55**, 1582 (1983).

94. S. Vorberg and W. Schoepp, *Fresenius' Z. Anal. Chem.*, **320**, 48 (1985).
95. D. D. Clyde, *Anal. Chem.*, **52**, 1308 (1980).
96. M. Paraia, *Afinidad*, **39**, 551 (1982); *Chem. Abstr.*, **99**, 15845 (1983).
97. B. R. Sahu and U. Tandon, *J. Indian Chem. Soc.*, **60**, 615 (1983).
98. K. H. Meyer, *Justus Liebigs Ann. Chem.*, **380**, 212 (1911).
99. G. Schwarzenbach and C. Witwer, *Helv. Chim. Acta*, **30**, 669 (1947).
100. A. Gero, *J. Org. Chem.*, **19**, 469 (1954).
101. A. Gero, *J. Org. Chem.*, **19**, 1960 (1954).
102. R. P. Bell and P. W. Smith, *J. Chem. Soc. B*, 241 (1966).
103. Y. Chiang, A. J. Kresge and P. A. Walsh, *J. Am. Chem. Soc.*, **104**, 6122 (1982).
104. Y. Chiang, A. J. Kresge and P. A. Walsh, *J. Am. Chem. Soc.*, **108**, 6314 (1986).
105. Y. Chiang and A. J. Kresge, *Science*, **253**, 395 (1991).
106. U. Knecht and H.-J. Nitsch, *Fresenius' Z. Anal. Chem.*, **324**, 142 (1986).
107. M. Morishita, H. Iizuka, M. Katayanagi and T. Yajima, *Bunseki Kagaku*, **35**, 193 (1986); *Chem. Abstr.*, **104**, 230573j (1986).
108. A. Ono, *Analyst (London)*, **108**, 1265 (1983).
109. P. D. Handson and P. D. Hanrahan, *J. Agric. Food Chem.*, **31**, 447 (1983).
110. D. A. Kalman, *J. Chromatogr. Sci.*, **22**, 452 (1984).
111. A. P. Borsetti and L. S. Thurston, *J. Assoc. Off. Anal. Chem.*, **67**, 275 (1984).
112. R. T. Coutts, E. E. Hargesheimer and F. M. Pasutto, *J. Chromatogr.*, **195**, 105 (1980).
113. G. Bengtsson, *J. Chromatogr. Sci.*, **23**, 397 (1985).
114. K. I. Pashkevich, I. A. Peterskikh and V. E. Kirichenko, *Zh. Anal. Khim.*, **43**, 1840 (1988); *Chem. Abstr.*, **111**, 108294y (1989).
115. W. Butte, M. Kirsch and J. Denker, *Int. J. Environ. Anal. Chem.*, **13**, 141 (1983); *Chem. Abstr.*, **98**, 27094u (1983).
116. W. Butte, *Fresenius' Z. Anal. Chem.*, **326**, 449 (1987).
117. M. Tanaka, K. Funazo, T. Hirashima and T. Shono, *J. Chromatogr.*, **234**, 373 (1982).
118. K. Grob, Jr. and H. P. Neukom, *J. Chromatogr.*, **295**, 49 (1984).
119. P. J. Rennie, *Analyst (London)*, **107**, 327 (1982).
120. T. A. Berger and J. F. Deye, *J. Chromatogr. Sci.*, **29**, 54 (1991).
121. M. Tanaka, Y. Kawaguchi, M. Nakae, Y. Mizobuchi and T. Shono, *J. Chromatogr.*, **246**, 207 (1982).
122. C. A. Chang, Q. Wu and D. W. Armstrong, *J. Chromatogr.*, **354**, 454 (1986).
123. K. Ogan and E. Katz, *Anal. Chem.*, **53**, 160 (1981).
124. B. Schultz, *J. Chromatogr.*, **299**, 484 (1984).
125. W. F. Greenlee, J. P. Chism and D. E. Rickert, *Anal. Biochem.*, **112**, 367 (1981).
126. H. E. Ervin and G. D. McGinnis, *J. Chromatogr.*, **190**, 203 (1980).
127. R. Schoenhaber, A. Schwarz and D. Kranl, *Dtsch. Lebensm.-Rundsch.*, **78**, 254 (1982); *Chem. Abstr.*, **97**, 143211h (1982).
128. H. C. Smit, T. T. Lub and W. J. Vloon, *Anal. Chim. Acta*, **122**, 267 (1980).
129. H. C. Smit, *Trends Anal. Chem. (Pers. Ed.)*, **2**, 1 (1983).
130. K. D. McMurtrey, A. E. Holcomb, A. U. Ekwenchi and N. C. Fawcett, *J. Liq. Chromatogr.*, **7**, 953 (1984).
131. K. Ugland, E. Lundanes, T. Greibrokk and A. Bjørseth, *J. Chromatogr.*, **213**, 83 (1981).
132. C. E. Goewie, R. J. Berkhof, F. A. Maris, M. Treskes and U. A. T. Brinkman, *Int. J. Environ. Anal. Chem.*, **26**, 305 (1986).
133. K. Kuwata, M. Uebori and Y. Yamazaki, *Anal. Chem.*, **52**, 857 (1980).
134. L. Lepri, P. G. Desideri and D. Heimler, *J. Chromatogr.*, **195**, 339 (1980).
135. L. Lepri, P. G. Desideri and D. Heimler, *J. Chromatogr.*, **248**, 308 (1982).
136. J. Boute, *Ann. Endocrinol.*, **14**, 518 (1953); *Chem. Abstr.*, **48**, 8299f (1954).
137. H.-H. Ting and M. Quick, *J. Chromatogr.*, **195**, 441 (1980).
138. J. Alary, C. Groset and A. Coeur, *Ann. Pharm. Fr.*, **40**, 301 (1982); *Chem. Abstr.*, **98**, 105794p (1983).
139. M. Guldborg, *Fresenius' Z. Anal. Chem.*, **309**, 117 (1981).
140. J. Urbanski and S. Banaszkiewicz, *Chem. Anal. (Warsaw)*, **30**, 451 (1985); *Chem. Abstr.*, **104**, 89599p (1986).
141. H. Berbalk and K. Eichinger, *Monatsch. Chem.*, **111**, 529 (1980).
142. I. M. Jakovljevic and R. H. Bishara, *J. Chromatogr.*, **192**, 425 (1980).

143. H. Thielemann, *Z. Chem.*, **19**, 225 (1979); *Chem. Abstr.*, **91**, 134910j (1979).
144. W. Haumesser, W. Berlach, U. Drewes and C.-H. Roeder, *Fresenius' Z. Anal. Chem.*, **305**, 262 (1981).
145. R. S. Carr, P. Thomas and J. M. Neff, *Bull. Environ. Contam. Toxicol.*, **28**, 477 (1982); *Chem. Abstr.*, **97**, 51115b (1982).
146. F. Bosch Serrat and G. Font Perez, *Afinidad*, **41**, 80 (1984); *Chem. Abstr.*, **100**, 202838 (1984).
147. G. Talsky, *Int. J. Environ. Anal. Chem.*, **14**, 81–91 (1983).
148. N. R. Clement and J. M. Gould, *Anal. Biochem.*, **101**, 299 (1980).
149. E. Emerson, H. H. Beacham and L. C. Beegle, *J. Org. Chem.*, **8**, 417 (1943).
150. B. Drabek, *Chem. Tech. (Berlin)*, **9**, 77 (1957); *Chem. Abstr.*, **51**, 8586h (1957).
151. G. Norwitz and P. N. Keliher, *Anal. Chim. Acta*, **119**, 99 (1980).
152. G. Norwitz, A. H. Bardsley and P. N. Keliher, *Anal. Chim. Acta*, **128**, 251 (1981).
153. J. Gasparic, D. Svobodova and A. Matysova, *J. Chromatogr.*, **88**, 364 (1974).
154. M. Rodriguez-Alcala, P. Yanez-Sedeno and L. M. Polo Diez, *Talanta*, **35**, 601 (1988).
155. L. R. Sherman, V. L. Trust and H. Hoang, *Talanta*, **28**, 408 (1981).
156. K. E. Rao and C. S. Sastry, *Mikrochim. Acta*, **I**, 313 (1984).
157. K. E. Rao and C. S. Sastry, *J. Inst. Chem. (India)*, **55**, 161 (1983); *Chem. Abstr.*, **99**, 224456k (1983).
158. C. S. P. Sastry, K. E. Rao and U. V. Prasad, *Talanta*, **29**, 917 (1982).
159. J. Barek, A. Berka and H. Skokankova, *Microchem. J.*, **31**, 227 (1985).
160. T. T. Ngo and C. F. Yam, *Anal. Lett.*, **17**, 1771 (1984).
161. M. Panetti, A. Cangelosi and F. Ferrero, *Ann. Chim. (Rome)*, **71**, 743 (1981).
162. M. E. Garcia-Figueroa, *Rev. Inst. Mex. Pet.*, **11**, 86 (1979), *Chem. Abstr.*, **91**, 222042h (1979).
163. L. Van Haverbeke and M. A. Herman, *Anal. Chem.*, **51**, 932 (1979).
164. I. E. Kalinichenko, T. M. Tkachuk and A. T. Pilipenko., *Zh. Anal. Khim.*, **43**, 2074 (1988), *Chem. Abstr.*, **111**, 208486f (1989).
165. W. A. Chudyk, M. M. Carrabba and J. E. Kenny, *Anal. Chem.*, **57**, 1237 (1985).
166. C. Martinez-Lozano, T. Perez-Ruiz, V. Tomas and E. Yague, *Microchem. J.*, **39**, 204 (1989).
167. L. Macholan, P. Londyn and J. Fischer, *Collect. Czech. Chem. Commun.*, **46**, 2871 (1981), *Chem. Abstr.*, **96**, 96813 (1982).
168. H. Y. Neujahr, *Appl. Biochem. Biotechnol.*, **7**, 107 (1982).
169. M. A. Zayed, H. Khalifa and F. A. Nour El-Dien, *Microchem. J.*, **34**, 204 (1986).
170. J. Barek, A. Berka and H. Skokanova, *Microchem. J.*, **28**, 308 (1983).
171. M. F. M. El Ghandour and A. A. El Razek, *Microchem. J.*, **30**, 201 (1984).
172. K. Kamakura, *Bull. Chem. Soc. Jpn.*, **53**, 658 (1980).
173. R. Bin Othman, J. O. Hill and R. J. Magee, *Mikrochim. Acta*, **I**, 171 (1986).
174. E. C. Guijarro, P. Yanez-Sedeno, J. M. Pingarron Carrazon and L. M. Polo Diez, *Analyst (London)*, **113**, 625 (1988).
175. K. Urano, K. Ogura and H. Wada, *Water Res.*, **15**, 225 (1981); *Chem. Abstr.*, **94**, 162499n (1981).
176. R. Schneider, *Aerosol Rep.*, **21**, 431 (1982); *Chem. Abstr.*, **98**, 100539z (1983).
177. J. K. Lin, R. L. Hendrickson and M. R. Ladisch, *J. Chromatogr.*, **367**, 195 (1986).
178. M. Vrabel, *Farm. Obz.*, **55**, 269 (1986); *Chem. Abstr.*, **105**, 66549d (1986).
179. M. Deveaux and J.-P. Huvenne, *Chromatographia*, **23**, 626 (1987).
180. D. B. Min and J. Wen, *J. Am. Oil Chem. Soc.*, **59**, 278 (1982).
181. J. A. Price and K. J. Saunders, *Analyst (London)*, **109**, 829 (1984).
182. A. Bianchi and M. S. Varney, *J. High Resolut. Chromatogr.*, **12**, 184 (1989).
183. K. Nowicka and J. Gromiec, *Chem. Anal. (Warsaw)*, **31**, 635 (1986).
184. T. G. Blease, J. H. Scrivens and W. E. Morden, *Biomed. Environ. Mass Spectrom.*, **18**, 775 (1989); *Chem. Abstr.*, **111**, 200772a (1989).
185. L. J. Anthony, S. A. Kozlowski and R. A. Holland, *J. High Resolut. Chromatogr., Chromatogr. Commun.*, **10**, 117 (1987).
186. R. Orlando and B. Munson, *Anal. Chem.*, **58**, 2788 (1986).
187. R. A. Solomon and G. J. Kallos, *Anal. Chem.*, **47**, 955 (1975).
188. M. L. Langhorst, R. G. Melcher and G. J. Kallos, *Am. Ind. Hyg. Assoc. J.*, **42**, 47 (1981); *Chem. Abstr.*, **94**, 161976d (1981).
189. L. G. J. v. D. Ven and A. Venema, *Anal. Chem.*, **51**, 1016 (1979).
190. F. Y. K. Ghauri and C. F. Simpson, *Anal. Proc. (London)*, **26**, 69 (1989).
191. W. T. Kok, U. A. T. Brinkman and R. W. Frei, *Anal. Chem. Acta*, **162**, 19 (1984).

192. S. Van der Wal and L. R. Snyder, *J. Chromatogr.*, **255**, 463 (1983).
193. P. L. Desbene and N. Jehanno, *Analusis*, **10**, 292 (1982).
194. R. E. Pauls, *J. Chromatogr. Sci.*, **23**, 437 (1985).
195. N. Petroff and G. Codet, *Rev. Inst. Fr. Pet.*, **38**, 545 (1983); *Chem. Abstr.*, **99**, 90660m (1983).
196. A. Steyermark, *Quantitative Organic Microanalysis*, Chap. 16, Academic Press, New York, 1961, pp. 422–443.
197. M. G. Kovalycsik and A. Steyermark, *Microchem. J.*, **25**, 196 (1980).
198. R. Belcher, M. Bhatty and T. S. West, *J. Chem. Soc.*, 4480 (1987).
199. A. M. T. Magalhaes and P. M. Chalk, *Analyst (London)*, **111**, 77 (1986).
200. E. Dumont, *Fresenius' Z. Anal. Chem.*, **295**, 21 (1979).
201. J. S. Fritz, in *Chemistry of the Ether Linkage* (Ed., S. Patai), Wiley–Interscience, London, 1967, pp. 669–680.
202. A. S. Inglis, *Treatise Anal. Chem.*, **14**, 23–160 (1971).
203. R. T. Hall and R. D. Mair, *Treatise Anal. Chem.*, **14**, 259–93 (1971).
204. Y. Zuo, C. Yue, L. Li and F. Wei, *Fenxi Huaxue*, **13**, 811 (1985); *Chem. Abstr.*, **104**, 199244b (1986).
205. S. Siggia and J. G. Hanna, *Quantitative Organic Analysis via Functional Groups*, 4th ed., Wiley, New York, 1979, pp. 325–372.
206. R. M. Johnson and I. W. Siddiqi, *The Determination of Organic Peroxides*, Pergamon Press, London, 1970.
207. V. I. Bogomolov, A. G. Etinger, R. V. Poponova and M. S. Chupakhin, *Vysokochist. Veshchestva*, 203 (1987); *Chem. Abstr.*, **107**, 228119j (1987).
208. L. G. Tsypysheva, E. A. Kruglov, Yu. N. Popov and A. S. Ziganshin, *Zh. Anal. Khim.*, **39**, 174 (1984); *Chem. Abstr.*, **100**, 95869k (1984).
209. S. S. Min'ko, S. V. Shevchuk, S. P. Gubar, S. A. Voronov and R. V. Kucher, *Zavod. Lab.*, **53**, 20 (1987); *Chem. Abstr.*, **106**, 177191w (1987).
210. A. F. Shushunova, G. I. Makin, N. V. Chikinova, A. N. Bryukhanov and Yu. A. Aleksandrov, *Zh. Anal. Khim.*, **34**, 1614 (1979); *Chem. Abstr.*, **92**, 69062p (1980).
211. E. N. Frankel, W. E. Neff and E. Selke, *Lipids*, **18**, 353 (1983).
212. J. D. Pinkston, D. J. Bowling and T. E. Delaney, *J. Chromatogr.*, **474**, 97 (1989).
213. M. O. Funk, Jr. and W. J. Baker, *J. Liq. Chromatogr.*, **8**, 663 (1985).
214. C.-K. Chou and D. C. Locke, *J. Assoc. Off. Anal. Chem.*, **67**, 913 (1984).
215. M. O. Funk, Jr., M. B. Keller and B. Levison, *Anal. Chem.*, **52**, 771 (1980).
216. M. Duval and Y. Giguere, *J. Liq. Chromatogr.*, **5**, 1847 (1982).
217. H. J. Doorenbos, J. W. Van Duijn, J. Nienhuis and H. M. Smits, *Pharm. Weekbl.*, **119**, 573 (1984); *Chem. Abstr.*, **101**, 97761p (1984).
218. N. Gaddipati, F. Volpe and G. Anthony, *J. Pharm. Sci.*, **72**, 1398 (1983).
219. L. A. Cornish, R. Ferrie and J. E. Paterson, *J. Chromatogr. Sci.*, **19**, 85 (1981).
220. T. Asakawa and S. Matsushita, *Lipids*, **15**, 137 (1980).
221. H. Khkawa, N. Ohishi and K. Yagi, *J. Lipid Res.*, **19**, 1053 (1978).
222. P. A. T. Swoboda and C. H. Lea, *Chem. Ind.*, 1090 (1958).
223. R. S. Kim and F. S. LaBella, *J. Lipid Res.*, **28**, 1110 (1987).
224. W. A. Pryor, J. P. Stanley and E. Blair, *Lipids*, **11**, 370 (1976).
225. T. Bigwood and G. Read, *Free Radical Res. Commun.*, **6**, 387 (1989).
226. K. Nakashima, T. Ando, T. Nakamizo and S. Akiyama, *Chem. Pharm. Bull.*, **33**, 5380 (1985).
227. S. H. Y. Wong, J. A. Knight, S. M. Hopper, O. Zahara, C. N. Leach, Jr. and F. W. Sunderman, Jr., *Clin. Chem.*, **33**, 214 (1987).
228. K. Ohsawa, Y. Yoshimura, H. Tanaka, F. Okajima, K. Tamura and K. Imaeda, *Anal. Sci.*, **1**, 473 (1985).
229. T. Hirano, M. Hatta, K. Oka and K. Wakasugi, *J. Chromatogr., Biomed. Appl.*, **61**, 371 (1987).
230. L. P. Novitskaya, *Zh. Anal. Khim*, **44**, 1138 (1989); *Chem. Abstr.*, **111**, 12484t (1989).
231. H. Read, *Anal. Proc. (London)*, **21**, 197 (1984).
232. T. A. Perenich and M. Avakian, *Text. Chem. Color.*, **19**, 27 (1987); *Chem. Abstr.*, **107**, 98047w (1987).
233. J. E. Frew, P. Jones and G. Scholes, *Anal. Chim. Acta*, **155**, 139 (1983).
234. A. O. Allen, C. J. Hochanadel, J. A. Ghormley and T. W. Davis, *J. Phys. Chem.*, **56**, 575 (1952).
235. E. K. Dukes and M. L. Hyder, *Anal. Chem.*, **36**, 1689 (1964) and references cited therein.

236. P. Jones and I. Wilson, in *Metal Ions in Biological Systems* (Ed. H. Sigel), M. Dekker, New York, 1978, p. 185.
237. N. A. Kozhikhova, M. M. Buzlanova, Z. S. Smirnova, A. M. Koukova and V. L. Antonovskii, *Zh. Anal. Khim.*, **34**, 1217 (1979); *Chem. Abstr.*, **91**, 222040f (1979).
238. V. F. Toropova, S. G. Selyanina and L. A. Anisimova, *Zh. Anal. Khim.*, **38**, 1066 (1983); *Chem. Abstr.*, **99**, 133065r (1983).
239. M. Benatsky and B. Tomik, *Chem. Listy*, **82**, 759 (1988); *Chem. Abstr.*, **109**, 221642g (1988).
240. A. Magill and A. R. Becker, *J. Pharm. Sci.*, **73**, 1663 (1984).
241. E. M. Sevast'yanova and Z. S. Smirnova, *Gig. Sanit.*, 48 (1987); *Chem. Abstr.*, **106**, 143701x (1987).
242. R. Caniato, R. Filippini, E. M. Cappelletti and G. Appendino, *Filoterapia*, **60**, 549 (1989); *Chem. Abstr.*, **114**, 224765p (1991).
243. J. Peinado, F. Toribio and D. Perez-Bendito, *Talanta*, **33**, 914 (1986).
244. R. Ebermann and A. Couperus, *Anal. Biochem.*, **165**, 414 (1987).
245. G. L. Kok, K. Thompson, A. L. Lazrus and S. E. McLaren, *Anal. Chem.*, **58**, 1192 (1986).
246. J. R. Bowyer and S. R. Spurlin, *Anal. Chim. Acta*, **192**, 289 (1987).
247. G. Staerk and J. Stauff, *Staub-Reinhalt. Luft*, **46**, 289 (1986); *Chem. Abstr.*, **105**, 65535j (1986).
248. H. Sawada, K. Masuyama, M. Mitani and M. Nakayama, *Bunseki Kagaku*, **39**, 573 (1991); *Chem. Abstr.*, **114**, 55055z (1991).
249. R. Saeki, H. Miyazawa and F. Inaba, *Jpn. Kokai Tokkyo Koho JP 02,128,146 [90,128,146] (cl. G01N21/76), 16 May 1990, Appl. 88/281,681, 8 Nov. 1988, 7 pp; Chem. Abstr.*, **114**, 38804a (1991).
250. W. W. Fleming and S. A. MacDonald, *Anal. Chem.*, **55**, 1625 (1983).
251. V. G. Abashin, V. M. Mamedova and O. A. Kurdova, *Azerb. Khim. Zh.*, 143 (1981); *Chem. Abstr.*, **96**, 210120x (1982).
252. Z. Wang and M. Guo, *Hauxue Shiji*, **10**, 365 (1988); *Chem. Abstr.*, **111**, 146083 (1989).
253. T. P. Aleinikova, A. A. Brailovskaya, L. V. Kargina, V. A. Navrotskii and A. P. Khardin, *Zh. Anal. Khim.*, **39**, 1120 (1984); *Chem. Abstr.*, **101**, 183176h (1984).
254. A. N. Gvozdetskii, L. I. Mizrath and O. F. Smirnova, *Zh. Anal. Khim.*, **43**, 2268 (1988); *Chem. Abstr.*, **111**, 186648f (1989).
255. S. S. Ivanchev, L. R. Uvarova, M. S. Matveentseva and I. Zyat'kov, *Zh. Anal. Khim.*, **39**, 95 (1984); *Chem. Abstr.*, **110**, 114314u (1984).
256. J. Dolezal, M. Rousal and J. Zima, *Microchem. J.*, **27**, 168 (1982).
257. G. G. Guilbault, P. Brignac and M. Juneau, *Anal. Chem.*, **40**, 1256 (1968).
258. P. K. Dasqupta and H. Hwang, *Anal. Chem.*, **57**, 1009 (1985).

CHAPTER 6

ESR and NMR spectroscopy

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Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

I. ELECTRON SPIN RESONANCE STUDIES

A. Introduction

Oxygen-centred radicals have provided a fruitful source for ESR studies. Neutral alkoxyl ($RO^{\bullet}$), aryloxyl ($ArO^{\bullet}$) and peroxyl ($ROO^{\bullet}$) radicals have all been investigated, as have the radical cations of phenols ($ArOH^{+\bullet}$), ethers ($R^1OR^{2+\bullet}$) and dialkyl peroxides ($R^1OOR^{2+\bullet}$). The only radical anions to have been subjected to study thus far are those of aryl ethers ($ArOR^{-\bullet}$). Interest in oxygen-centred radicals derives largely from their role in biological and environmental processes. For example, oxidative degradation of lipids, both autocatalytic and enzyme catalysed, proceeds via the formation of peroxyl and alkoxyl radicals. Likewise, polymer decomposition, induced by γ-irradiation, air oxidation or oxidative pyrolysis, involves alkoxyl and peroxyl radicals. Moreover, peroxyl radicals are considered to be the main chain-carrying species in these autoxidation processes, generating new, carbon-centred, radicals through hydrogen-atom abstraction reactions at C—H bonds. Consequently, phenol-derived anti-oxidants, such as vitamins E and K, which provide alternative sites for hydrogen-atom abstraction, and which form aryloxyl radicals, have also been the subject of investigation. Alongside these studies, interest in alkoxyl radicals also derives from their formation during the γ-irradiation of nucleic acids. Therefore, the present chapter sets out to provide a review of the ESR spectral characteristics of each type of radical in turn. Following a brief introduction outlining the methods used to generate the radicals, the features of the spectra that allow an understanding of the structure of the radical, and the motional processes they undergo, are described.

B. Alkoxyl and Aryloxyl Radicals, $RO^{\bullet}$ and $ArO^{\bullet}$

For alkoxyl radicals, the unpaired electron resides in a degenerate p_π orbital. The consequence of this is that the ESR detection of such a radical requires it to reside in an asymmetric environment so that the orbital degeneracy is lifted[1]. Thus, despite reports to the contrary[2], alkoxyl radicals have yet to be detected in solution, the medium being unable to provide the appropriate asymmetry[3]. However, studies using crystalline[4-6] and polycrystalline[7] solids have resulted in the detection of ESR spectra of alkoxyl radicals derived from alcohols or alcohol-containing molecules, e.g. deoxyadenosine and serine. For the nucleosides at least, hydrogen bonding contributes to the observation of the spectra[4]. In contrast, reports detailing the ESR spectra of aryloxyl radicals are relatively extensive, since the unpaired spin density is delocalized. Current interest in the aryloxyl radical stems from the biological roles played by vitamin E (α-tocopherol) and vitamin K.

1. Formation

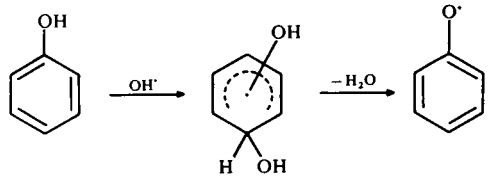
All alkoxyl radicals studied to date have been generated by subjecting a crystal of the material under investigation to ionizing radiation, e.g. X-rays (equation 1)[4-7]. Presumably, the formation of the alkoxyl radical proceeds by way of the very acidic alcohol radical cation.

$$R{-}OH \xrightarrow[\text{radiation}]{\text{ionizing}} R{-}\overset{+\bullet}{O}H \longrightarrow R{-}O \qquad (1)$$

Aryloxyl radicals are formed under milder conditions (equation 2). One of the more common methods involves the reaction of the parent phenol with an oxidizing agent such as PbO_2[8-12], Ce^{IV}[13-15], or Ti^{III}/H_2O_2[16]. Alternatively, the use of a hydrogen-atom

abstracting agent, such as the *t*-butoxyl radical[17,18], superoxide ion[19] or the diphenylpicrylhydrazyl radical[20], is equally effective. Pulse radiolysis to generate the hydroxyl radical has also been successfully employed for aqueous solutions[21,22]. Neta and Fessenden have proposed that, under these conditions, the aryloxyl radical is formed by a process that first involves addition of the hydroxyl radical to the ring followed by the elimination of water (equation 3)[22].

$$\mathrm{Ar{-}OH} \xrightarrow[\text{or } \mathrm{Bu^tO^{\bullet}}]{\mathrm{PbO_2}} \mathrm{Ar{-}O^{\bullet}} \tag{2}$$

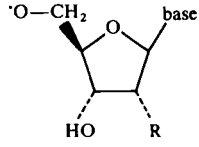


(3)

The α-tocopheroxyl radical has been generated on a silica surface by incorporating α-tocopherol into a monolayer of methyl linoleate and allowing the methyl linoleate to partially oxidize[23]. The peroxyl radical so formed then abstracts the phenolic hydrogen atom from α-tocopherol.

2. *g-Values and hyperfine coupling constants*

ESR spectral data for alkoxyl radicals trapped in a crystal lattice are shown in Table 1. The majority of the radicals studied are those of nucleotides which have the general structure **1**, in which the unpaired electron is located on the 5′-oxygen atom of the sugar unit.



(1)

TABLE 1. ESR spectral parameters for alkoxyl radicals, RO·

RO·	*g*-Value[a,b,c]	Hyperfine coupling (G) *a*(H)	Ref.
$CH_3O^{\bullet}$	2.088[a], 1.999[c]	52 (3H)	7
$^{-}O_2C(H_3\overset{+}{N})CH_2O^{\bullet}$	2.079[a], 2.005[b], 1.998[c]	113.8 (1H), 19.8 (1H)	6
1 (R = H, base = thymine)	2.0831[a], 2.0052[b], 1.9999[c]	80.4 (1H), 71.3 (1H)	5
1 (R = OH, base = adenine)	2.0798[a], 2.0055[b], 2.0005[c]	93.5 (1H), 48.0 (1H)	4
1 (R = H, base = adenine)	2.054[a], 2.033[d]	103 (1H), 53 (1H)	4
1 (R = H, base = 5-chlorocytosine)	2.0929[a], 2.0048[b], 1.9975[c]	83.3 (1H), 58.5 (1H)	4
1 (R = H, base = 5-bromocytosine)	2.0922[a], 2.0090, 1.0059	85.6 (1H), 57.3 (1H)	4

[a] g_{max}.
[b] g_{int}.
[c] g_{min}.
[d] Average of g_{min} and g_{int}.

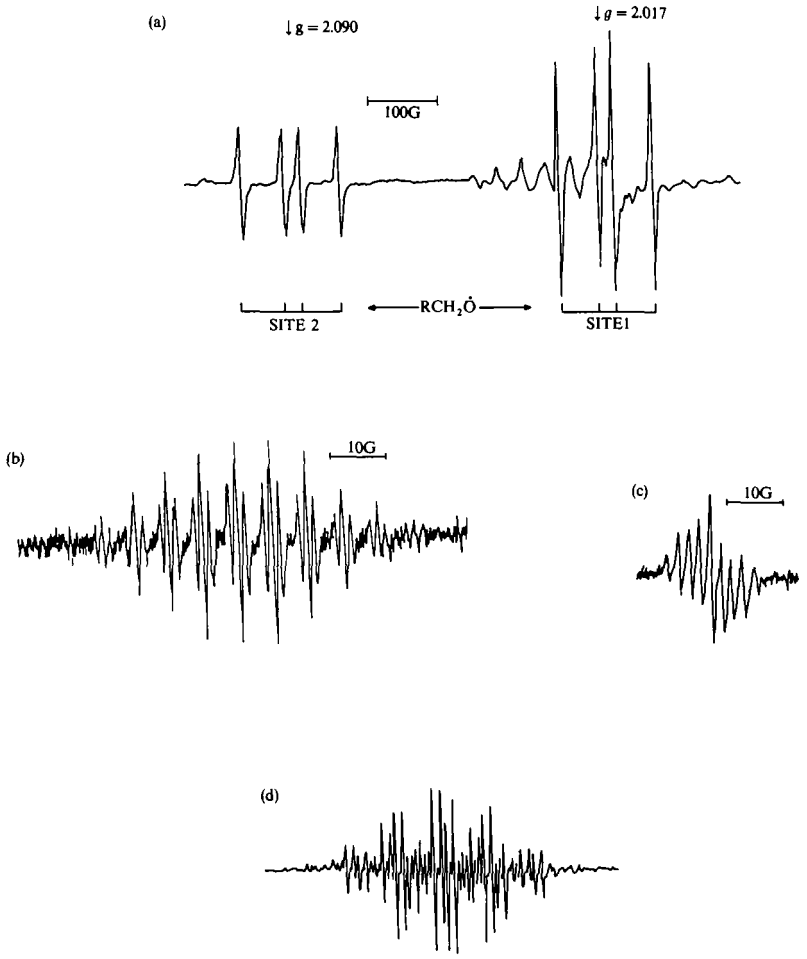


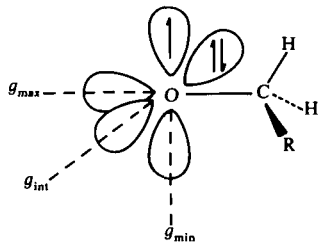
FIGURE 1. Representative spectra of some aryloxyl radicals. Reproduced from References 4 and 14 by permission of the American Institute of Physics and the Royal Society of Chemistry.

The spectrum of **1** (R = H, base = 5-bromouracil) is shown in Figure 1a, and it can be seen that there are two magnetically distinct sites which have similar hyperfine splittings. The g-tensor is highly anisotropic, as would be expected if the unpaired electron occupied a p_π orbital on the oxygen atom, as in structure **2**. The principal axis corresponding to the maximum g-value is expected to be parallel to the direction of the C—O bond. Table 2 contains the direction cosines for several of the radicals and it is evident that g_{max} does largely coincide with the C—O bond direction. Discrepancies, such as those found for the 5-chlorocytosine and 5-bromocytosine derivatives, can be ascribed to differences in the temperatures used to acquire the ESR and crystal data and the likely phase changes that take place in the respective crystals between these temperatures. The unpaired electron can be thought of as occupying an oxygen p_z orbital which is parallel

TABLE 2. Direction cosines of g_{max} and of the C—O bond direction for alkoxyl radicals

Radical	Direction cosines						Angle between g_{max} and C—O
	g_{max}			C—O bond direction			
1 (R = H, base = thymine)	0.084	0.996	−0.018	0.17	0.983	0.050	6°
1 (R = OH, base = adenine)	−0.597	0.130	0.792				3°
1 (R = H, base = 5-chlorouracil)	0.075	0.541	0.838				23°
1 (R = H, base = 5-bromouracil)	0.130	0.511	0.850				28°

to the principal axis of g_{min}; the pair of non-bonding electrons occupy the p_y orbital, which is the direction of g_{int}.



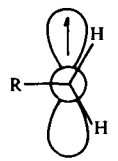
(2)

All of the alkoxyl radicals exhibit coupling to the hydrogen atoms attached to the α-carbon. For the methoxyl radical these hydrogen atoms appear equivalent, but for the radicals **1**, and for that derived from serine, the two hydrogen atoms display two different hyperfine coupling constants. This can be rationalized by assuming that the radical is frozen in a preferred conformation in which the two C—H bonds subtend different angles with the p_z orbital. The angular dependence of the proton hyperfine coupling can be expressed by either of two equations, equation 4 in which $B = 101(\pm 13)$ G or equation 5 in which $B_0 = 5$ G and $B_2 = 94$ G[4]. These predict that for methoxyl, which has a freely rotating methyl group and therefore $\langle\cos^2\theta\rangle = 1/2$, the hyperfine coupling should be *ca* 50–52 G, precisely the value determined experimentally[7].

$$a(\mathrm{H}) = B\cos^2\theta \tag{4}$$

$$a(\mathrm{H}) = B_0 + B_2\cos^2\theta \tag{5}$$

Using equation 5 and the data in Table 1, it is possible to deduce that the most probable conformation of the alkoxyl radical is one that resembles structure **3**.

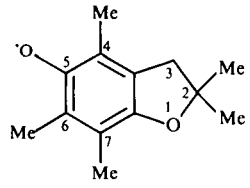


(3)

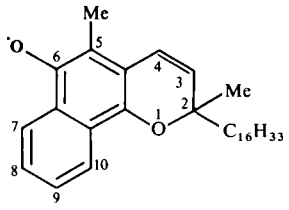
TABLE 3. ESR spectral data for some aryloxyl radicals

Radical	g-Value	Hyperfine coupling constant (G)		References
		a(H)	a(X)	
$C_6H_5O^{\cdot}$	2.00461	6.65(2H, *ortho*), 1.8(2H, *meta*), 10.2(1H, *para*)		14–16, 22
2-$MeC_6H_4O^{\cdot}$		6.0(4H, *ortho*-H and CH_3), 1.9(2H, *meta*), 11.5(1H, *para*),		13
		7.5(3H, CH_3), 2.0(1H, *H*-3), 9.7(1H, *H*-4), 1.5(1H, *H*-5), 6.0(1H, *H*-6)		15
3-$MeC_6H_4O^{\cdot}$		5.9(1H, *H*-2), 1.5(3H, CH_3), 10.5(1H, *H*-4), 1.9(1H, *H*-5), 7.1(1H, *H*-6)		15
4-$MeC_6H_4O^{\cdot}$		6.1(2H, *ortho*), 1.4(2H, *meta*), 12.3(3H, *para*)		15, 16
2-$MeCOC_6H_4O^{\cdot}$		1.5(1H, *H*-3), 10.25(1H, *H*-4), 2.0(1H, *H*-5), 7.0(1H, *H*-6)		15
3-$MeCOC_6H_4O^{\cdot}$		7.1(1H, *H*-2), 9.9(1H, *H*-4), 1.9(1H, *H*-5), 6.5(1H, *H*-6)		15
4-$MeCOC_6H_4O^{\cdot}$		6.75(2H, *ortho*), 2.1(2H, *meta*)		13, 15
2-$FC_6H_4O^{\cdot}$		2.1(1H, *H*-3), 10.0(1H, *H*-4), 1.4(1H, *H*-5), 5.5(1H, *H*-6)	16.8(F)	14, 15
3-$FC_6H_4O^{\cdot}$		5(1H, *H*-2), 10.75(1H, *H*-4), 2.25(1H, *H*-5), 8(1H, *H*-6)	5.8(F)	15
4-$FC_6H_4O^{\cdot}$		6.25(2H, *ortho*), 1.45(2H, *meta*)	27.5(F)	14, 15
2-$H_2NC_6H_4O^{\cdot}$	2.00372	0.9(1H, *H*-3), 6.62(1H, *H*-4), 1.15(1H, *H*-5), 2.6(1H, *H*-6)	6.62(N)	15, 22
		8.13(2H, NH_2)		
3-$H_2NC_6H_4O^{\cdot}$		3.1(1H, *H*-2), 10.9(1H, *H*-4), 2.0(1H, *H*-5), 8.6(1H, *H*-6)	6.9	15
		8.1(2H, NH_2)		
4-$H_2NC_6H_4O^{\cdot}$		4.0(2H, *ortho*), 0.5(2H, *meta*), 8.0(2*H*, NH_2)	6.6(N)	15
	2.0377	2.76(2H, *ortho*), 1.77(2H, *meta*), 5.53(2H, NH_2)	5.21(N)	22
2-$O_2NC_6H_4O^{\cdot}$		1.2(1H, *H*-3), 10.25(1H, *H*-4), 2.4(1H, *H*-5), 7.25(1H, *H*-6)	2.1(N)	15
3-$O_2NC_6H_4O^{\cdot}$		7.35(1H, *H*-2), 9.8(1H, *H*-4), 2.1(1H, *H*-5), 6.75(1H, *H*-6)	0.5(N)	15
4-$O_2NC_6H_4O^{\cdot}$		7.0(2H, *ortho*), 2.4(2H, *meta*)	2.4(N)	14, 15
2-$MeOC_6H_4O^{\cdot}$		1.9(1H, *H*-3), 8.5(1H, *H*-4), 4.3(1H, *H*-6), 1.8(3H, CH_3)		15
3-$MeOC_6H_4O^{\cdot}$		3.5(1H, *H*-2), 11.4(1H, *H*-4), 2.3(1H, *H*-5), 9.0(1H, *H*-6)		15
		0.6(3H, CH_3)		
4-$MeOC_6H_4O^{\cdot}$		4.9(2H, *ortho*), 2.1(3H, CH_3)		14, 15
	2.005	5.75(2H, *ortho*), 0.85(2H, *meta*), 1.75(3H, CH_3)		17
2-$^{-}OC_6H_4O^{\cdot}$	2.00455	0.75(2H, *H*-3 and *H*-6), 3.75(2H, *H*-4 and *H*-5)		15, 22
3-$^{-}OC_6H_4O^{\cdot}$		0.7(1H, *H*-2), 11.2(2H, *H*-4 and *H*-6), 2.8(1H, *H*-5)		15
4-$^{-}OC_6H_4O^{\cdot}$	2.00455	2.37(4H)		15, 22
2,4,6-$Me_3C_6H_2O^{\cdot}$		1.4(2H, *meta*), 6.0(6H, *ortho* CH_3), 11.95(3H, *para* CH_3)		14
2,6-Me_2-4-$MeOC_6H_2O^{\cdot}$	2.00482	5.43(6H, *ortho* CH_3), 0.95(2H, *meta*), 1.50(3H, OCH_3)		17
2,3,5,6-Me_4-4-$MeOC_6O^{\cdot}$	2.00479	6.18(6H, *ortho* CH_3), 1.56(6H, *meta* CH_3)		17

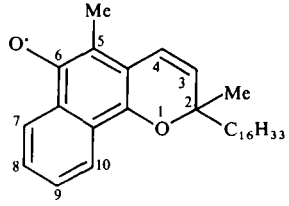
2,5,6-Me_3-4-($MeOCOCH_2CH_2S$)$C_6HO^{\cdot}$	2.0055	1.42(1H, *H*-3), 1.65(2H, SCH_2), 5.75(3H, 2-CH_3), 4.95(3H, 6-CH_3), 1.42(3H, 5-CH_3)		18
2,6-Bu^t_2-4-$MeC_6H_2O^{\cdot}$		1.63(2H, *meta*), 11.22(3H, *para* CH_3)		8–10
2,4,6-$Bu^tC_6H_2O^{\cdot}$		1.8(2H, *meta*)		8
4a	2.00475	6.02(3H, 5-Me), 4.64(3H, 7-Me), 1.0(3H, 8-Me), 1.41(2H) 3.30(1H, OCH)		17
4b	2.0046	6.07(3H, 5-Me), 4.55(3H, 7-Me), 0.98(3H, 8-Me), 1.52(2H)		19
4c		6.06(3H, 5-Me), 0.74(3D, 7-CD_3), 0.74(3H, 8-Me), 1.50(2H)		19
4d		6.07(3H, 5-Me), 4.55(3H, 7-Me), 0.15(3D, 8-CD_3), 1.52(2H)		19
4e		0.93(3D, 5-CD_3), 4.52(3H, 7-Me), 0.93(3H, 8-Me), 1.47(2H)		19
4f		6.08(3H), 4.56(3H), 1.40(2H), 0.9(3H, 8-Me)		21
4g(α-tocopheroxyl)	2.0046	6.07(3H, 5-Me), 4.55(3H, 7-Me), 0.98(3H, 8-Me), 1.52(2H)		19, 20
4h		6.25(3H, 5-Me), 4.66(1H, *H*-7), 0.85(3H, 8-Me), 1.68(2H)		20
4i		5.92(1H, *H*-5), 4.60(1H, *H*-7), 1.11(3H, 8-Me), 1.11(2H)		20
4j		5.95(1H, *H*-5), 4.77(3H, 7-Me), 1.16(3H, 8-Me), 1.16(2H)		20
4k	2.0056	5.80(3H, 5-Me), 4.60(3H, 7-Me), 1.50(3H, 8-Me), 1.50(2H)		18
4l	2.0056	5.71(3H, 5-Me), 4.67(3H, 7-Me), 1.35(3H, 8-Me), 1.75(2H)		18
4m	2.00431	4.45(6H, 5-Me and 7-Me), 0.7(5H, 8-Me and CH_2) 6.5(1H, NCH)	4.4(N)	17
5	2.00471	5.78(3H, 4-Me), 4.78(3H, 6-Me), 1.03(3H, 7-Me)		17
6	2.00427	8.06(3H, 5-Me), 1.68(4H, 4-CH_2, *H*-8 and *H*-10), 0.42(2H, *H*-7 and *H*-9)		12
7	2.00421	7.21(3H, 5-Me), 1.88(2H, *H*-8 and *H*-10), 0.43(4H, *H*-3, *H*-4, *H*-7, *H*-9)		12



(5)



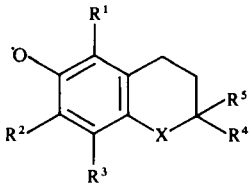
(6)



(7)

Attempts to calculate the hyperfine coupling constants using MO methods have so far met with little success[4,24]. INDO calculations for the ethoxyl radical result in a value for a(H) of 37.3 G, much smaller than those observed for $RCH_2O^{\cdot}$ radicals[4]. *Ab initio* calculations for the methoxyl radical yield a value for a(H) of 36.6 G, again much smaller than the experimentally determined hyperfine coupling constant[24].

Some representative spectra of aryloxyl radicals are shown in Figure 1, and these clearly demonstrate coupling between the unpaired electron and the protons of the aryl ring. A more detailed analysis of some aryloxyl radicals, especially the radicals **4–7** which are of relevance to the chemistry of vitamins E and K, is contained in Table 3.



(4)

	R^1	R^2	R^3	R^4	R^5	X
(a)	Me	Me	Me	H	H	O
(b)	Me	Me	Me	Me	Me	O
(c)	Me	CD_3	Me	Me	Me	O
(d)	Me	Me	CD_3	Me	Me	O
(e)	CD_3	Me	Me	Me	Me	O
(f)	Me	Me	Me	Me	CO_2H	O
(g)	Me	Me	Me	Me	$C_{16}H_{33}$	O
(h)	Me	H	Me	Me	$C_{16}H_{33}$	O
(i)	H	H	Me	Me	$C_{16}H_{33}$	O
(j)	H	Me	Me	Me	$C_{16}H_{33}$	O
(k)	Me	Me	Me	Me	Me	S
(l)	Me	Me	Me	Me	$C_{16}H_{33}$	S
(m)	Me	Me	Me	H	H	NEt

Several observations are of interest. First, the g-value of aryloxyl radicals (*ca* 2.005) is much smaller than that of alkoxyl radicals (*ca* 2.03). Since oxygen has a large spin–orbit coupling constant, this would be expected if the unpaired spin density is delocalized onto the aryl ring and consequently lowered at the oxygen atom. Within the aryloxyl series, radicals containing a *para* sulphur substituent have somewhat larger g-values, whereas those with a *para* nitrogen substituent have somewhat lower g-values.

This is entirely consistent with the relative magnitudes of the spin–orbit coupling constants for these atoms, and implies that the unpaired spin density is indeed delocalized. As previously mentioned, coupling to the ring protons is evident, and the magnitude of the coupling follows the order *para* > *ortho* > *meta*. This is the order expected for a π-radical.

The sign of the coupling is positive for the *ortho* and *para* protons, but generally negative for the *meta* protons[15]. Substituents in the aryl ring can affect both the size and sign of the observed hyperfine coupling constants. Thus, for *para*-substituted aryloxyl radicals, the size of the coupling constant to the *ortho* proton diminishes as the electron-donating power of the substituent increases. Coupling to the *meta* protons, in contrast, gets more positive on going from *p*-nitro [$a(H) = -2.4$ G] to *p*-amino [$a(H) = +0.5$ G]. This has led to the empirical observation that, for *para*-substituted aryloxyl radicals, $a(H)_{ortho} + a(H)_{meta} = 4.7(\pm 0.2)$G[14,15]. Interestingly, the *para*-semiquinone radical anion is entirely symmetric, displaying only one hyperfine coupling constant (2.37 G) that also fits this relationship. This is further evidence for the delocalization of spin density onto the aryl ring and its substituents. Coupling also can be observed to other ring substituents, such as *N* and *F*.

The magnitude of the proton hyperfine coupling constant has been used to estimate the spin densities at the aryl ring carbon atoms by application of the McConnell equation (equation 6) with $Q = -24$ G[14,15] (though values of -27 G[12] and -30 G[15] have also been proposed in some cases). A similar equation, with $Q = 27$ G, is also applicable to the hyperfine coupling of the protons in the methyl groups of methyl-substituted phenols[11,12,14].

$$a(H) = \rho_C^{\pi} Q_C \tag{6}$$

The results of such calculations are shown in Table 4, and these demonstrate that significant unpaired spin density resides at the ring *ortho* and *para* carbon atoms. Overall, only 20–25% of the unpaired spin density is associated with the aryloxyl oxygen atom and the *ipso* carbon atom. Interestingly, for the radicals **4b**, **4g**, **6** and **7**, the spin density at the ring carbon atom '*ortho*' to the oxygen atom, i.e. C-5 and C-7, is much the same as found for the simple phenoxyls, as is the spin density at the *meta* position, C-8 in **4b**, **g**. There appears to be little spin density in the benzo-fused ring of radicals **6** and **7**.

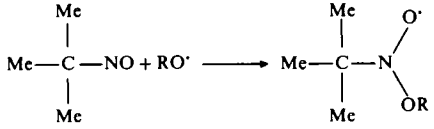
TABLE 4. Spin densities of some aryloxyl radicals

Radical	Spin density[a]
$C_6H_5O^{\bullet}$	0.28(*ortho*), −0.075(*meta*), 0.42(*para*)
4-$MeC_6H_4O^{\bullet}$	0.25(*ortho*), −0.06(*meta*), 0.44(*para*)
2,4,6-$Me_3C_6H_2O^{\bullet}$	0.22(*ortho*), −0.06(*meta*), 0.44(*para*)
4b	0.23(C-5), 0.17(C-7), 0.04(C-8), 0.04(C-10)
4g	0.23(C-5), 0.17(C-7), −0.4(C-8), −0.04(C-10)
	(0.22) (0.21) (−0.03) (−0.04)
6	0.30(C-5), 0.016(C-7), 0.06(C-8), −0.016(C-9), 0.06(C-10)
	(0.27) (0.005) (0.06) (−0.002) (0.07)
7	0.27(C-5), 0.016(C-7), 0.07(C-8), −0.016(C-9), 0.07(C-10)
	(0.26) (0.007) (0.05) (0.00) (0.06)

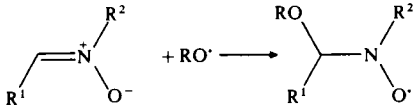
[a]Values in parentheses are calculated using the McLachlan MO method [A.D. McLachlan, *Mol. Phys.*, 3, 233 (1960)].

3. Spin trapping

Since alkoxyl radicals cannot be observed directly by ESR spectroscopy, there has been a significant amount of effort expended in detecting them using the spin trapping method. Many of the common spin traps have been employed, including both nitrosoalkanes (equation 7) and imine *N*-oxides (nitrones) (equation 8).



(7)



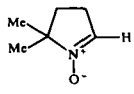
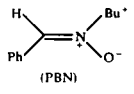
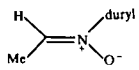
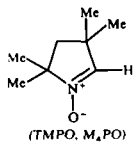
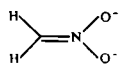
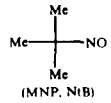
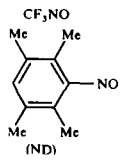
(8)

Reaction of alkoxyl radicals with either type of spin trap is rapid. For example, second-order rate constants for the reaction of Bu^{t}O$^\bullet$ with a variety of spin traps lie in the range 1×10^6 (for 2-methyl-2-nitrosopropane) to $5 \times 10^8\,dm^3\,mol^{-1}\,s^{-1}$ (for 5,5-dimethyl-1-pyrroline-*N*-oxide)[33]. It has generally been found that the nitroxyl radicals derived from the nitroso compounds are less stable than those from the *N*-oxides. This is unfortunate, since the nitroxyls formed from nitroso compounds can potentially display more information about the trapped radical. This can be seen quite nicely in Table 5, which contains representative data for a series of trapped alkoxyl radicals (a more extensive collection can be found in Reference 25). The radicals formed from 2-methyl-2-nitrosopropane (MNP) and MeO$^\bullet$ and EtO$^\bullet$ both display coupling to the β-protons of the alkoxyl group, whereas no such coupling is observed for any of the trapped radicals derived from the *N*-oxide spin traps.

A major impetus for the spin trapping of alkoxyl radicals arises from the desire to identify the types of radical involved in peroxide degradation. This is of considerable biological and environmental importance, and the need to distinguish between alkyl, alkoxyl and alkylperoxyl radicals is a significant goal. To this end, several *N*-oxides have been examined as suitable spin traps (Table 5). No one radical is ideal, though the cyclic compounds 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) and 3,3,5,5-tetramethyl-1-pyrroline-*N*-oxide (TMPO, M_4PO) are able to distinguish between the R$^\bullet$, RO$^\bullet$, and ROO$^\bullet$ radicals. Trapping of carbon-centred radicals by DMPO gives rise to a nitroxyl that has a characteristic hyperfine coupling constant of > 20 G, due to coupling to the β-proton of the heterocyclic ring. In contrast, both alkoxyl and peroxyl radicals form nitroxyl radicals with DMPO that have much smaller β-proton hyperfine coupling constants. Differentiation between alkoxyl and peroxyl radicals by spin trapping with DMPO is less clear cut, but it has been found that TMPO will trap alkoxyl radicals but not peroxyls[34]. This is thought to be a consequence of steric hindrance.

The spectral characteristics of the nitroxyl radicals formed upon spin trapping are solvent dependent. Thus, the radical formed from Bu^{t}O$^\bullet$ and DMPO has a(N) 12.84 G and a(H) 6.19 (β-H) and 2.15 G (γ-H) in cyclohexane, but a(N) 14.84 G and a(H) 16.03 G (β-H) in water[35]. Indeed, for this radical it has been observed that there is a general increase of both a(N) and a(β-H) with solvent polarity, whereas a(γ-H) decreases with solvent polarity[35]. A solvent-dependent change in the ring conformation, which affects the dihedral angles of the β- and γ-hydrogen atoms in opposite senses, is thought to account for the variation in the hyperfine coupling. Conversely, the radical formed from Bu^{t}O$^\bullet$ and MNP has a(N) 27.34 G in cyclohexane, but 26.92 G in 0.1 M aqueous sodium

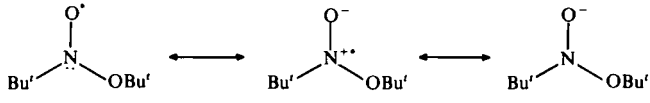
TABLE 5. ESR spectral parameters for spin-trapped alkoxyl (and related) radicals

Spin trap	Alkoxyl radical trapped	g-Value	Hyperfine coupling constants (G) a_N	a_H	a_X	References
 (DMPO)	MeO·		13.58	7.61, 1.85		25
	EtO·		13.22	6.96, 1.89		25
	Bu^{t}O·		13.19	8.16, 1.82		25
	Me·		14.3	20.50		26
	$PhMe_2CO$·		13.08	8.88, 1.68		26
	$PhMe_2COO$·		13.92	11.2		26
 (PBN)	MeO·		14.5	2.8	4.55(^{13}C)[a]	25, 27
	EtO·		14.4	2.6		25
	Bu^{t}O·		14.48	1.86	4.91(^{13}C)[a]	25, 27
		2.0064	13.62	1.72	5.05(^{17}O)[b]	28
	Bu^{t}OO·	2.0064	13.42	0.95	2.9(^{17}O)[b]	28
	$(CN)Me_2C$·	2.00599	14.3	3.22	5.78(^{13}C)[a]	29
	$(CN)Me_2CO$·	2.00610	13.87	2.06	4.70(^{13}C)[a]	29
	$(CN)Me_2COO$·		12.94	1.25	5.05(^{13}C)[a]	29
	Bu^{t}O·	2.0059	13.13	7.91		25
 (TMPO, M_4PO)	Bu^{t}O·		13.28	5.42		25
	MeO·		23.8	8.5(2H)		30
	EtO·		23.8	8.6(2H)		30
 (MNP, NtB)	MeO·		29.6	1.4(OMe)		31
	EtO·		29.1	1.1(OCH_2)		31
	Bu^{t}O·	2.0057	26.8		1.03(^{17}O)[b]	25, 28
 (ND)	Bu^{t}O·	2.0059	22.76		5.80(3F) 0.93(^{17}O)[b]	32
	Bu^{t}O·		25.18			25

[a] α-^{13}C of nitrone.
[b] Coupling to ^{17}O in RO adduct, not ^{17}O of nitroxyl.

hydroxide solution[36]. The nitrogen hyperfine coupling of this radical generally decreases with increasing solvent polarity. This may be due to an increase in the planarity of the radical centre in the more polar solvents, or alternatively to a greater contribution to the overall structure of the radical in polar solvents of the resonance form **8C**.

The dependence of the spectra upon the solvent can make radical identification difficult. For example, it has been found that the spectra displayed by the radicals, formed from



(8A) (8B) (8C)

either HO$^{\bullet}$ or RO$^{\bullet}$ are quite different in ethyl acetate or acetonitrile but identical in water[37].

C. Phenol Radical Cations, ArOH$^{+\bullet}$

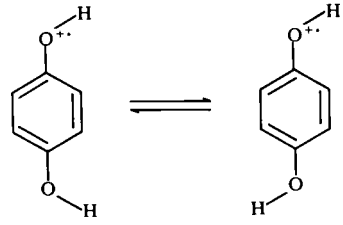
1. Formation

Alcohol radical cations have yet to be observed by ESR spectroscopy. Phenol radical cations have been reported, however, and they are commonly generated by the reaction of the parent phenol with $AlCl_3$ in nitromethane (equation 9). Phenol radical cations have pK_a values *ca* -2 (or p*A* values, i.e. the h_0 value at half protonation, of *ca* -5) and have therefore been generated by oxidation using Ce^{IV} in concentrated sulphuric acid.

$$\mathrm{Ar{-}OH} \xrightarrow[Ce^{IV}/H_2SO_4]{AlCl_3} \mathrm{Ar{-}\overset{+\cdot}{O}H} \qquad (9)$$

2. g-Values and hyperfine coupling constants

Table 6 contains spectral data for some representative phenol radical cations. *g*-Values are somewhat smaller, by *ca* 0.0014, than those of the corresponding aryloxyl radicals, presumably because there is less spin density associated with the oxygen atom. Hyperfine coupling to the phenolic proton is observable, especially if a non-protic solvent is used, and the *a*(H) value of such coupling is *ca* 3 G. Interestingly, for the sterically hindered radical 2,6-Bu^t-4-Me-$C_6H_2OH^{+\bullet}$ coupling to only *one* of the *meta* protons is observable[41]. The non-equivalence of the *meta* protons is attributed to the restricted internal rotation of the hydroxyl group, the dihedral angle between the O—H bond and the ring plane being about 15°. Similar restricted rotation has been observed in 1,4-dihydroxybenzene radical cations, giving rise to *cis*, **9**, and *trans*, **10**, isomers[39,42,43].



(9) (10)

The energy barrier to rotation for 1,4-dihydroxybenzene radical cation is *ca* 40 kJ mol^{-1}. The equivalent barrier for the 2,3,5,6-tetramethyl-1,4-dihydroxybenzene radical cation, *ca* 17 kJ mol^{-1}, is much smaller presumably because the energy of the co-planar conformation is destabilized because of steric hindrance. The dihedral angle between the O—H bond and the plane of the aryl ring is thought to be *ca* 15° in this case too[43]. In contrast, the 2,3-dimethyl-1,4-dihydroxy- and 2,5-dimethyl-1,4-dihydroxy-

TABLE 6. ESR spectra data for phenol radical cations

Radical	g-Value	Hyperfine coupling constant (G)		References
		a(H)	a(X)	
$C_6H_5OH^{+\cdot}$	2.0091	10.7(2H, *para*), 5.3(2H, *ortho*), 0.8(2H, *meta*)		38
$4\text{-}MeC_6H_4OH^{+\cdot}$	2.00317	15.1(3H, 4-Me), 4.5(2H, *ortho*), 0.05(2H, *meta*)		38
$4\text{-}MeOC_6H_4OH^{+\cdot}$	2.00358	3.2(3H, 4-OMe), 1.9(2H, *H*-2 and *H*-6), 2.2(*H*-3), 3.0(*H*-5)		38
$4\text{-}HOC_6H_4OH^{+\cdot}$		3.29(2H, O*H*)[a], 2.45(2H)[a], 2.05(2H)[a] 3.29(2H, O*H*)[b], 2.35(2H)[b], 2.14(2H)[b]		39
	2.0035		7.83(^{17}O) 4.23(^{13}C-1) 1.2(^{13}C-2) 1.65(^{13}C-2)	40
$2,6\text{-}Bu^t_2\text{-}4\text{-}MeC_6H_2OH^{+\cdot}$		3.72(1H, O*H*), 0.89(1H, *meta*) 14.19(3H, 4-Me)		41
$2,3\text{-}Me_2\text{-}4\text{-}HOC_6H_2OH^{+\cdot}$	2.00343	3.13(2H, O*H*), 2.58(2H), 1.83(6H)		42
$2,5\text{-}Me_2\text{-}4\text{-}HOC_6H_2OH^{+\cdot}$	2.00338	3.11(2H, O*H*), 0.95(2H), 3.81(6H)		42
$2,6\text{-}Me_2\text{-}4\text{-}HOC_6H_2OH^{+\cdot}$	2.00337	2.99(1H, 1-O*H*)[a], 3.11(1H, 4-O*H*)[a], 2.11(3H, 2-Me)[a] 2.26(3H, 6-Me)[a], 1.87(1H, 3-*H*)[a], 2.12(1H, 5-*H*)[a] 2.99(1H, 1-O*H*)[b], 3.11(1H, 4-O*H*)[b], 2.55(3H, 2-Me)[b] 1.82(3H, 6-Me)[b], 1.70(1H, 3-*H*)[b], 2.29(1H, 5-*H*)[b]		42
$2,3,5,6\text{-}Me_4\text{-}4\text{-}HOC_6OH^{+\cdot}$		2.15(6H)[a], 1.90(6H)[a], 2.73(2H, O*H*)[a] 2.48(6H)[b], 1.57(6H)[b], 2.73(2H, O*H*)[b]		43

[a] *cis* isomer.
[b] *trans* isomer.

TABLE 7. Spin densities in phenol radical cations

Radical	O	C-1	C-2	C-3	C-4	C-5	C-6
$C_6H_5OH^{+\cdot}$			0.196	0.03	0.396	0.03	0.196
2,6-Bu^t_2-4-$MeC_6H_2OH^{+\cdot}$	0.108			0.033	0.526		
4-OH-$C_6H_4OH^{+\cdot}$	0.101	0.233	0.083	0.083	0.233	0.083	0.083
2,3-Me_2-4-$HOC_6H_2OH^{+\cdot}$	0.096		0.073	0.073		0.105	0.105
2,5-Me_2-4-$HOC_6H_2OH^{+\cdot}$	0.094		0.127	0.035		0.127	0.035

benzene radical cations both appear to exist as one major isomer, the former in the *cis* conformation and the latter in the *trans*.

The ^1H, ^{13}C and ^{17}O hyperfine coupling constants have been used to calculate the unpaired spin density distribution in the phenol radical cations[39,40,42,43]. The spin density at the ring C-2, C-3, and C-4 carbon atoms may be evaluated using equation 6 with a value for Q_C of -27 G. The spin density at the oxygen atom can be calculated from equation 10 using a value for Q_O of -34.4 G[43]. Calculated spin densities are contained in Table 7, and these show that approximately 10% of the unpaired spin is associated with each oxygen atom. Unfortunately, the lack of equivalent data for aryloxyl radicals does not allow a comparison of the oxygen spin density between the two radicals to be made. However, there appears to be a significant reduction in the spin density at the *ortho* carbon atom in the phenol radical cation.

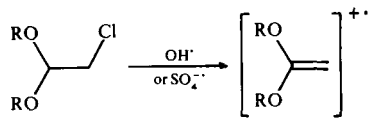
$$a(H) = Q_O \rho^{\pi}_O \tag{10}$$

D. Ether Radical Cations, $R^1OR^{2+\cdot}$

1. Formation

γ-Radiolysis of an ether in $CFCl_3$ solution gives rise to the corresponding ether radical cation (equation 11). Radical cations of dialkyl[44,45], alkyl alkenyl[46] and alkyl aryl[47] ethers have been studied in this way. Additionally, alkyl alkenyl ethers have been generated by the $OH^{\cdot}$ or $SO_4^{-\cdot}$ promoted oxidative elimination of HCl from β-chloroethyl ethers (equation 12)[48], or the addition of $Bu^tOH^{+\cdot}$ to alkynes (equation 13)[49]. Alkyl aryl ethers have also been generated by a variety of methods involving one-electron oxidation (equation 14), such as Tl^{2+} or Ag^{2+} [50], Ce^{IV}/H_2SO_4[51], $AlCl_3$/nitromethane[52], H_2SO_4[53] and electrolysis[53].

$$R^1OR^2 \xrightarrow[CFCl_3]{\gamma\text{-irradiation}} R^1OR^{2+\cdot} \tag{11}$$



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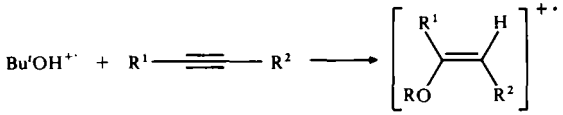
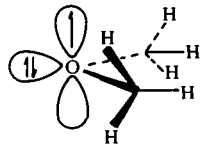


(13)

$$ArOR \xrightarrow{-e^{\cdot}} ArOR^{+\cdot} \tag{14}$$

2. g-Values and hyperfine coupling constants

ESR spectral data for some representative ether radical cations are presented in Table 8. The spectrum for dimethyl ether at 77 K comprises seven lines as expected for coupling to six equivalent hydrogen nuclei, implying that at this temperature the methyl groups are rapidly rotating and the hyperfine coupling is averaged. The ^1H hyperfine coupling is largely anisotropic, characteristic of β-hyperfine coupling. Taken together with the anisotropic nature of the g-tensor (g_1 2.0138, g_2 2.0072, g_3 2.0045) these data suggest that the ether radical cation is an oxygen-centred π-radical[44]. Both INDO and *ab initio* molecular orbital calculations correctly predict the magnitude of the proton hyperfine coupling constant assuming that the radical has a structure similar to **11**; 38.1 G (INDO)[44] and 39.4 G (*ab initio*)[24]. The INDO calculations have the hydrogen atoms in the nodal plane as *anti*, whereas the *ab initio* results place them both *syn*, as shown in **11**. The unpaired spin density at the oxygen atom is calculated to be 0.71, the remainder associated with the hydrogen 1*s* orbitals. At low temperatures, *ca* 25 K, the spectrum of the radical cation of dimethyl ether displays extra lines due to the restricted rotation of the methyl groups[57]. Spectral simulation identifies an activation energy to rotation of 0.4 kJ mol^{-1} above 25 K. Below 25 K tunnelling rotation is evident.

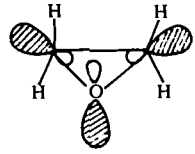


(11)

The large hyperfine coupling constant observed for the radical cation of diethyl ether implies that, for this radical, rotation is restricted. Using equation 4, and a value of $B = 86$ *G* [obtained from the a(H) value for the methyl group], the dihedral angle between the plane of the orbital containing the unpaired spin and the C—H bond is *ca* 30°. The structure is therefore similar to **11**, except that the in-plane hydrogen atoms are replaced by methyl groups. Presumably these in-plane groups are oriented *anti* in this case.

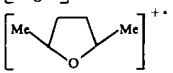
At temperatures below 100 K, the radical cation of the cyclic ether THF displays two different hyperfine coupling constants which can be assigned to the axial and equatorial hydrogen atoms of a fixed ring conformation. The large coupling to the axial hydrogen places it close to the plane of the orbital containing the unpaired electron. The axial and equatorial protons become equivalent on warming to 150 K, with an average hyperfine coupling of 65 G. This is consistent with a rapid puckering of the ring system, for which an energy barrier of 7 kJ mol^{-1} is calculated[55]. The 2,5-dimethyl substituted THF radical cation exhibits one hyperfine coupling that is unchanged on warming. Thus, the ring is conformationally rigid with the methyl groups equatorial and the hydrogen atoms axial[55].

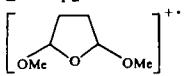
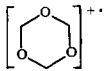
Of all the cyclic ethers, oxirane appears anomalous. The coupling of only 16 G is remarkably low if the radical cation were to adopt the normal π-structure. This has led



(12)

TABLE 8. ESR spectral data for ether radical cations

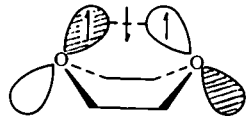
Radical	g-Value	Hyperfine coupling constant (G) a(H)	References
$MeOMe^{+\cdot}$	2.0085	43(6H)	44, 45
$EtOEt^{+\cdot}$		68.7(4H)	46
$Pr^iOPr^{i+\cdot}$	2.0065–2.007	45(2H)	54
		16(4H)	46
		64(4H), 11(2H)	46
		89(2H), 40(2H)	46, 55
		97(2H)	46
		34.5(2H), 14(2H)	46
$EtOH{=}CH_2^{+\cdot}$		19.3(2H), 3.5(2H, OCH_2)	46
$Bu^tOCH{=}CH_2^{+\cdot}$	2.0034	18.44(2H)	49
$(MeO)_2C{=}CH_2^{+\cdot}$	2.00305	20.55(2H), 3.1(3H), 0.66(3H)	46, 48
$(MeO)_2C{=}CHMe^{+\cdot}$	2.00311	19.1(1H), 24(3H, C—Me), 1.5(3H, OMe)	46, 48

$Bu^tO(Me)C{=}CHMe^{+\cdot}$		23.91 (3H), 16.44(1H), 4.98(3H)	49
$Bu^tO(Et)C = CHEt^{+\cdot}$		28.68(2H), 16.71(1H), 8.98(2H)	49
$MeOC{\equiv}CH^{+\cdot}$		22(1H), 11(3H)	46
$MeOCH_2OMe^{+\cdot}$	2.0072	136.1(2H, OCH_2O), 31.3(2H), 6.0(4H)	56
	2.0070	153(2H), 11.2(4H)	46, 56
	2.0066	135(2H), 32(2H)	56
	2.0065	160.2(2H)	56
		11(4H), 8(4H)	46
$C_6H_5OMe^{+\cdot}$	2.00351	4.83(3H) 4.52(1H, *ortho*) 5.51(1H, *ortho*) 0.21(1H, *meta*), 1.00(1H, *meta*), 9.97(1H, *para*)	50
$4\text{-}MeOC_6H_4OMe^{+\cdot}$	2.00388	3.41(6H)[a], 1.59(2H, *H*-2 and *H*-5)[a], 2.92(2H, *H*-3 and *H*-6)[a]	50
	2.00388	3.24(6H)[b], 2.61(2H, *H*-2 and *H*-3)[b], 1.88(2H, *H*-5 and *H*-6)[b]	50
$4\text{-}MeC_6H_4OMe^{+\cdot}$	2.0032	4.3(3H, OMe), 3.5(1H, *ortho*), 4.3(1H, *ortho*), 0.2(1H, *meta*), 0.8(1H, *meta*), 15.25(3H, *para* Me)	51

[a] *trans* isomer.
[b] *cis* isomer.

Symons to propose that the unpaired electron occupies a non-bonding σ-orbital on oxygen, as in **12**[46].

1,4-Dioxane also gives rise to small hypderfine coupling constants, but in this case this has been interpreted as evidence for intramolecular O$\therefore$O σ^* bonding (**13**). Hyperfine coupling is expected to be about a factor of three lower for such cation radicals compared with that for the normal ether radical cations[46].



(13)

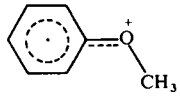
Radical cations of alkyl alkenyl ethers display large coupling, a(H) *ca* 20 G, to the γ-hydrogens of the alkenyl group, but only small coupling to the protons of the alkyl group. Assuming a hyperfine coupling of 22 G for interaction with the γ-protons corresponds to unit spin density; then the spin density at the β-vinyl carbon atom is approximately 0.9. Thus, such radicals resemble structure **14B**, where the spin density has been largely delocalized onto the carbon atom, and the positive charge is associated with the oxygen atom.

$$\underset{\textbf{(14A)}}{R\dot{\overset{+}{O}}-CH=CH_2} \longleftrightarrow \underset{\textbf{(14B)}}{R\overset{+}{O}=CH-\dot{C}H_2}$$

The somewhat larger coupling to the methyl group in the radical cation of methyl ethynyl ether (11 G) suggests for this radical that about 20% of the spin density resides on the oxygen atom. Again, most of the spin density has been delocalized onto the β-carbon (**15B**).

$$\underset{\textbf{(15A)}}{R\dot{\overset{+}{O}}-C\equiv CH} \longleftrightarrow \underset{\textbf{(15B)}}{R\overset{+}{O}=C=\dot{C}H}$$

Consistent with delocalization of the spin density onto the carbon atoms of the radical cations of these unsaturated ethers, the g-values are much smaller by 0.003–0.005 than those of the corresponding dialkyl ethers. This reflects the smaller spin–orbit coupling of carbon versus oxygen. A similar situation pertains to alkyl aryl cations, where g-values very similar to those for alkyl alkenyl ethers are observed. The implication is that, in cation radicals of alkyl aryl ethers, a significant amount of the unpaired spin density is delocalized onto the carbon atoms of the aryl ring. This is clearly demonstrated by the observed hyperfine coupling to the aryl ring protons (Table 8). Significantly, for anisole and its 4-methyl derivative, both the two *ortho* protons and the two *meta* protons are non-equivalent. This is readily explained by a structure such as **16**, in which the unpaired spin density is delocalized over the aryl ring as well as the ether oxygen atom. The C—O bond between the oxygen atom and the ring carbon atom thus has considerable double-bond character, and this restricts rotation of the methyl group about this bond.



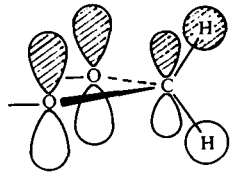
(16)

Using the hyperfine coupling data in Table 8, and the McConnell equation 6 with a Q-value of 24 G, it is possible to calculate the π-spin density of the ring carbon atoms.

For anisole, 88% of the unpaired spin density resides in the ring, of which 42% resides at the *para* carbon atom and 42% shared between the two *ortho* carbon atoms. This implies that about 12% of the unpaired spin density resides at the oxygen atom and, using the value of the hyperfine coupling constant for the methyl groups in the radical cation of dimethyl ether as representing coupling to unit spin density on an oxygen atom, from the coupling to protons of the anisole methyl group a value of 11% is obtained.

The radical cations of 1,4-dialkoxybenzenes exhibit, like the analogous dihydroxybenzenes (*vide supra*), *cis–trans* isomerism[52,58]. The energy differences between the two isomers vary from 0–1 kJ mol^{-1}. As the size of the alkyl group increases so does the percentage of the *trans* isomer[52]. Again this is a consequence of restricted rotation about the C—O bond due to delocalization of the unpaired spin density into the aryl ring.

Acetals are a unique type of ether. The cation radicals derived from them exhibit a remarkably large hyperfine coupling (*ca* 150 G) that can be assigned to the bridging methylene protons of the OCH_2O group (Table 8). To accommodate such a large coupling, the unpaired electron is believed to reside in a π–σ–π delocalized orbital which involves the p-orbitals on the two oxygen atoms and a CH_2 group orbital, as depicted in structure **17**.



(17)

The radical cation of 1,3-dioxacyclopentane demonstrates that the four non-acetal protons are all equivalent, suggesting a planar structure for the radical. The radical cation of 1,3-dioxacyclohexane, however, exhibits hyperfine coupling to two sets of two non-equivalent protons, a(H) 26 and 12.5 G, indicative of a fixed non-planar ring conformation. Interestingly, the acyclic acetal dimethoxymethane also clearly demonstrates a preferred conformation. Thus, coupling to both methyl groups is apparent, as would be expected for a delocalized radical, but two of the six protons exhibit a distinctly different hyperfine coupling (Table 8). The spectrum of *s*-trioxane (1,3,5-trioxacyclohexane) demonstrates that the orbital containing the unpaired electron is confined to a single acetal functional group rather than delocalized around the ring, and this would imply that the cation radical retains a non-planar ring conformation. However, when the conformational restriction is lifted, as it is in 2,5-dimethoxytetrahydrofuran, delocalization of the unpaired spin over more than one acetal group, in this case the O—C—O—C—O unit, is evident[56].

E. Ether Radical Anions, $R^1OR^{2-\cdot}$

1. Formation

Radical anions of dialkyl ethers have not been studied by ESR spectroscopy. The most common method employed for generating radical anions of alkyl aryl ethers is reduction by an alkali metal (Li, Na, K and Cs have all been employed) in THF or dimethoxyethane (DME) solvents (equation 15)[59–62]. Alternatively, for aryl or alkyl groups that contain nitro substituents, reduction using the potassium salt of 2,4,6-tri-*t*-butylnitrobenzene has also been used[63]. Reduction by electrolysis has been reported to fail[64].

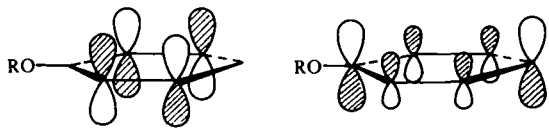
$$Ar—OR \xrightarrow{K/THF} [Ar—OR]^{-\cdot} \qquad (15)$$

The ether radical anions are generally unstable, decomposing by fragmentation and dimerisation processes[63,65-68].

2. *g-Values and hyperfine coupling constants*

The range of ether radical anions for which ESR spectral data have been reported is much smaller than that for ether radical cations. Table 9 contains data for most, though not all, of the radical anions so far studied. The following features are worthy of note.

The proton hyperfine coupling constants are large for the *ortho* and *meta* positions but small for the *para* position. This is in marked contrast to both phenoxyl radicals and aryl ether radical cations, where the *para* position displays the largest hyperfine coupling. Thus, in aryl ether radical anions the unpaired spin density mainly resides at the ring *ortho* and *meta* carbon atoms. Indeed, using equation 6 and a value of $Q_C = 23\,G$[62], it is evident that essentially all of the spin density is associated with the aryl ring rather than the oxygen atom (Table 10). The unpaired electron occupies the antisymmetric e_{2u} orbital **18** but, as this would predict a zero spin density at the *para* carbon atom, there is potentially some admixture ($< 10\%$) with the symmetric e_{2u} orbital **19** as well.



(18) **(19)**

However, molecular orbital calculations using the unrestricted Hartree–Fock spin annihilation method have shown that the computed spin densities for the antisymmetric orbital **18** can account for the observed hyperfine couplings[60]. Such MO calculations predict an unpaired spin density of 0.002 at the oxygen atom of these radical anions. Now, *if* we can assume that the value of *B* for the dimethyl ether radical *cation* (86 G) can be applied to the radical anions also, and that there is unit spin density at the oxygen atom in the dimethyl ether radical cation, then a hyperfine coupling of 0.086 G to the methyl protons in aryl methyl ether radical anions can be calculated. Remarkably, the coupling to the methyl protons in the radical anion of 2-methoxynaphthalene is reported to be 0.09 G. The only other alkyl aryl ether radical anions for which coupling to the alkyl protons has been reported both contain a nitro substituent in the aryl ring. The hyperfine coupling to the alkyl protons in these compounds is *ca* 0.3 G. Clearly, the presence of the nitro group perturbs the radical anion. That this is so can be seen by comparing the radical anions of 4-$NO_2C_6H_4CH_2OC_6H_5$ and 4-$NO_2C_6H_4OCH_2C_6H_5$. In both radicals the unpaired electron is associated only with the ring containing the nitro group, as is evident from the lack of any hyperfine coupling to the protons of the other ring. However, in the former radical the electron resides in the alkyl moiety, whereas in the latter it resides in the aryl moiety.

Upon reduction by the alkali metal caesium, both anisole and 4-dimethoxybenzene display coupling to the caesium counterion[60]. It is most probable that the cation is associated with the ether oxygen atom[62] and that it resides in the plane of the aromatic ring. For 9-methoxyanthracene, however, the caesium ion is thought to be situated over the central ring due to steric repulsions with the 1,8-hydrogen atoms[62].

TABLE 9. ESR spectral data for ether radical anions

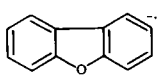
Radical	Hyperfine coupling constant (G)		References
	a(H)	*a*(X)	
$C_6H_5OMe^{-\cdot}$	5.36(2H, *ortho*), 6.18(2H, *meta*), 0.61(1H, *para*)	7.4(^{13}C) 2.6(^{133}Cs)	59, 60
$C_6H_5OEt^{-\cdot}$	5.36(2H, *ortho*), 6.18(2H, *meta*), 0.61(1H, *para*)	7.4(^{13}C)	60
4-$MeC_6H_4OEt^{-\cdot}$	5.41(2H, *ortho*), 5.93(2H, *meta*), 0.82(3H)	7.58(^{13}C)	60
4-$MeOC_6H_4OMe^{-\cdot}$	5.63(4H)	8.0(^{13}C) 2.8(^{133}Cs)	60
2-$NO_2C_6H_4OMe^{-\cdot}$	3.56(1H, *H*-3), 0.89(1H, *H*-4), 4.02(1H, *H*-5), 1.14(1H, *H*-6)	10.18(N)	64
3-$NO_2C_6H_4OMe^{-\cdot}$	3.85(1H, *H*-2), 3.29(1H, *H*-4), 1.01(1H, *H*-5), 3.29(1H, *H*-6)	9.49(N)	64
4-$NO_2C_6H_4OMe$	1.10(2H, *ortho*), 3.43(2H, *meta*), 0.37(3H, OMe)	10.60(N)	64
3-$MeC_6H_4OMe^{-\cdot}$	3.43(1H, *H*-2), 3.15(1H, *H*-4), 6.01(1H, *H*-5), 4.28(1H, *H*-6), 5.2(3H, 3-Me)		62
4-$Bu^tC_6H_4OMe^{-\cdot}$	5.22(2H, *ortho*), 6.02(2H, *meta*)		62
4-$NO_2C_6H_4CH_2OC_6H_5^{-\cdot}$	3.3(2H, *ortho*), 1.0(2H, *meta*), 2.6(2H, CH_2)	9.4(N)	63
4-$NO_2C_6H_4OCH_2C_6H_5$	1.1(2H, *ortho*), 3.4(2H, *meta*), 0.3(2H, OCH_2)	10.7(N)	63
2-$MeOC_{10}H_7^{-\cdot}$	4.22(1H, *H*-1), 3.42(1H, *H*-3), 4.98(1H, *H*-4),5.45(1H, *H*-5), 0.55(1H, *H*-6), 3.21(1H, *H*-7), 4.22(1H, *H*-8), 0.09(3H, OMe)		62
	4.81(4H, *H*-1 and *H*-4), 0.98(2H, *H*-2), 1.96(2H, *H*-3)		61

TABLE 10. π spin densities of some aryl ether radical anions

Radical	Spin density	Total ring spin density
$C_6H_5OMe^{-\bullet}$	0.23(*ortho*) 0.27(*meta*) 0.03(*para*)	1.03
$3\text{-}MeC_6H_4OMe^{-\bullet}$	0.15(C-2), 0.23(C-3), 0.14(C-4), 0.26(C-5). 0.19(C-6)	0.97
$4\text{-}MeC_6H_4OMe^{-\bullet}$	0.24(*ortho*) 0.26(*meta*) 0.04(*para*)	1.04
$4\text{-}MeOC_6H_4OMe^{-\bullet}$	0.24(*ortho*)	0.98

F. Peroxide Radical Cations, $R^1OOR^{2+\bullet}$

1. Formation

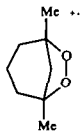
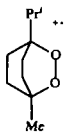
There have been remarkably few studies of peroxide radical cations. Of those that have been undertaken, two methods of generating such radicals have been employed, viz. γ-radiolysis in a $CFCl_3$ matrix[69,70] and electrolysis in $CH_2Cl_2/CF_3CO_2H/(CF_3CO)_2O$ (equation 16)[71].

$$R^1O—OR^2 \xrightarrow{-e^-} [R^1O—OR^2]^{+\bullet} \tag{16}$$

2. g-Values and hyperfine coupling constants

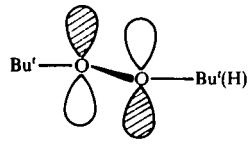
Table 11 contains the ESR spectral data of the known peroxide radical cations. The smallest **g** tensor for both $Bu^tOOBu^{t+\bullet}$ and $Bu^tOOH^{+\bullet}$ is close to the free spin value, and indicates that these radical cations are planar like the analogous disulphide cation radicals[72]. Indeed, the shifts of the g_x and g_y components from the free spin value are

TABLE 11. ESR spectral data for peroxide radical cations

Radical	g-Value	Hyperfine coupling (G) a(H)	References
$Bu^tOOH^{+\bullet}$	2.0087[a]	2.3[b](1H)	69
$Bu^tOOBu^{t+\bullet}$	2.0084[c]		69, 70
	2.0084	4.81(2H), 0.71(2H), 1.61(1H), 0.49(1H) 0.25(1H), 0.15(1H)	71
	2.0091	4.7(4H)	71

[a] g_{iso}; $g_x = 2.0152$, $g_y = 2.0083$, $g_z = 2.0025$.
[b] a_{iso}; $a_x = 0.2$ G, $a_y = 2.0$ G, $a_z = 4.8$ G.
[c] g_{iso}; $g_x = 2.015$, $g_y = 2.0082$, $g_z = 2.0020$.

directly proportional to those of the corresponding sulphur radicals through the spin–orbit coupling constants of oxygen and sulphur[69,70]. *Ab initio* MO calculations identify the *trans* coplanar arrangement **20** as the most likely[69].



(20)

These calculations also reveal that the spin density at each oxygen atom is 0.56 for the radical cation of the symmetrical dimethyl peroxide, whereas for the radical cations of methyl hydroperoxide or *t*-butyl hydroperoxide the spin density on the O—C oxygen atom is 0.91 and on the O—H oxygen atom 0.15. Thus, the structure of the symmetrical radical cations can be thought of as a hybrid of structures **21A** and **21B** in which each canonical form contributes equally, and the unsymmetrical radical cations as a hybrid in which **21A** ($R^2 = H$) is a closer representation of the true structure.

$$R^1—\overset{+\cdot}{O}—O—R^2 \longleftrightarrow R^1—O—\overset{+\cdot}{O}—R^2$$

(21A) **(21B)**

The most likely reason for the asymmetric spin and charge density is the differing electron-donating properties of the two groups R^1 and R^2; the charge and unpaired spin density reside on the oxygen atom bonded to the group with the greater electron-donating power. The small spin density on the O—H oxygen atom of the radical cations of the hydroperoxide thus explains the small hyperfine coupling observed to the O—H proton.

The cyclic radicals of course are constrained to a *cis* conformation. Unlike the radical cation from di-*t*-butylperoxide, coupling to the axial γ-hydrogen atoms (i.e. those attached to the β-carbon atom) is observed in such radicals. Coupling to the equatorial γ-hydrogen atoms can also be observed, though this is much smaller than to the axial γ-hydrogen atoms. Interestingly, coupling to the γ-hydrogen atoms of the methyl groups in these radicals is not observed (Table 11).

G. Peroxyl Radicals, ROO·

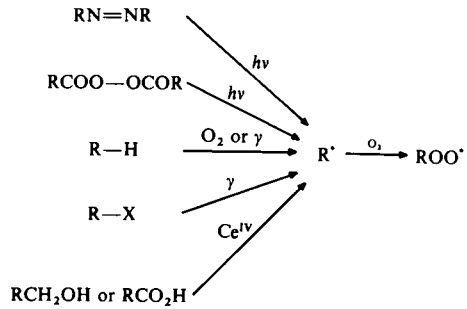
1. Formation

Peroxyl radicals are generated by the direct photolysis of the corresponding hydroperoxide (equation 17), a reaction that involves hydrogen-atom abstraction from the hydroperoxide by intermediate alkoxyl or hydroxyl radicals[73–76]. Alternatively,

$$RO—OH \xrightarrow{h\nu} RO^{\cdot} + OH^{\cdot} \xrightarrow{ROOH} ROO^{\cdot} \qquad (17)$$

oxidation of a hydroperoxide using a metal oxide catalyst, e.g. PbO_2[77], MnO_2[78] or CoO[78], or by a metal-derived enzyme system such as haematin[79] also gives rise to a peroxyl radical. However, by far the most common method of generating peroxyl radicals for study by ESR spectroscopy is the reaction of a carbon-centred radical with dioxygen. Rate constants for the formation of a peroxyl radical from the corresponding alkyl radical and oxygen lie in the region of 10^9 dm^3 mol^{-1} s^{-1}; thus, ROO· formation is complete within *ca* 20 μs[80]. Many methods for generating the parent carbon-centred radical have been employed, ranging from the photolysis of azoalkanes[81] and diacylperoxides[73], through the autoxidation of hydrocarbons either at room temperature[82] or in a pyrolysis

chamber[83], as well as the oxidative cleavage of primary alcohols or their corresponding carboxylic acids using Ce^{IV}[84], to the γ-radiolysis of hydrocarbons or haloalkanes (equation 18)[85–89].



(18)

For polymers derived from alkenes (e.g. polyethene) or haloalkenes (e.g. polytetrafluoroethene) γ-irradiation has proved to be the preferred method for generating peroxyl radicals[90–92], whereas for lipids both γ-irradiation and UV photolysis, either of the lipid itself or of the lipid containing *t*-butylhydroperoxide, have been used[93–95].

2. *g-Values and hyperfine coupling constants*

Table 12 contains repesentative ESR spectral data for a variety of peroxyl radicals. In general, peroxyl radicals give rise to a broad ESR signal with a line width in the range 2–20 G at *g ca* 2.015[73,74]. The signal is not saturatable, in contrast to that from the alkyl radicals from which they are commonly formed[89]. The line width is dependent on several factors, viz. temperature, oxygen concentration and the radical structure[73]. Line widths are broad at *ca* 190 K due to an increase in the spin–rotation interaction. Below *ca* 130 K line widths are also broad due to the increased viscosity of the solvent which prevents rotational averaging of the signal. Moreover, the intensity of the signal decreases at lower temperatures as a result of the dimerisation reaction (equation 19) favouring the tetroxide. Line broadening increases with the amount of oxygen present, and results from the interaction of the unpaired electron in the peroxyl radical with those of the dioxygen molecule. Line widths are also larger the smaller the radical[73].

$$2ROO^{\bullet} \longrightarrow ROOOOR \tag{19}$$

Not surprisingly, tertiary alkyl peroxyl radicals exhibit a single line, but coupling to the protons bonded to the carbon atom adjacent to the peroxy group can be observed for primary and secondary alkyl peroxyls. The magnitude of the proton hyperfine coupling lies in the range 2–7.5 G, and is dependent on both the structure of the radical and the polarity of the solvent in which the spectrum is recorded. The greater the solvent polarity the greater the proton hyperfine coupling. Both of these effects will be discussed later, when the structure of the radical is more apparent.

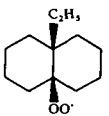
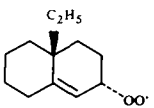
Exposure of an alkyl radical to oxygen-17 labelled O_2 results in the formation of three isotopically labelled peroxyl radicals, viz. $RO^{17}O^{\bullet}$, $R^{17}OO^{\bullet}$ and $R^{17}O^{17}O^{\bullet}$. Coupling to the ^{17}O nucleus in all three species can be detected, though the intensity of the doubly labelled radical is low due to the isotopic content of the O_2 used[88]. However, the presence of coupling to two oxygen atoms within the same radical confirms its identity as a peroxyl. In glassy matrices at 77–108 K, the parallel components of the two ^{17}O hyperfine couplings can be detected; that for the terminal oxygen atom lies in the range 95–105 G, whereas that for the inner oxygen atom lies in the range 45–60 G[88]. Clearly there is more

TABLE 12. ESR spectral parameters for selected peroxyl radicals

Radical	Matrix/solvent	g-Value	Hyperfine coupling constant (G)		References
			a(H)	a(^{17}O)	
$CH_3OO^{\cdot}$		2.013–2.015			84
$C_2H_5OO^{\cdot}$		2.0154			73, 84
$C_3H_7OO^{\cdot}$		2.0154	4.9 (2H)		73
$(CH_3)_2CHOO^{\cdot}$		2.0154	5.2 (1H)		73
$(CH_3CH_2)CHOO^{\cdot}$		2.0154	2.2 (1H)		73
$C_5H_{11}OO^{\cdot}$		2.0149	5.3 (2H)		84
$(CH_3)_3COO^{\cdot}$		2.014		21.8[a,c], 16.4[b,c] (94[a,d], 59[b,d])	74, 81, 88
$\overbrace{CH_2(CH_2)_2}CHOO^{\cdot}$		2.0154	3.2 (1H)		73
$\overbrace{CH_2(CH_2)_3}CHOO^{\cdot}$		2.0154	7.4 (1H)		73
$HOCH_2OO^{\cdot}$	CH_3OH/CCl_3Br (90 K)	2.035, 2.008, 2.003		94.8[a,d], 56.8[b,d]	88
$Me_3\overset{+}{N}CH_2OO^{\cdot}$	D_2O (90 K)	2.035, 2.008, 2.003		102.8[a,d], 51.3[b,d]	88
$HO_2CCH_2OO^{\cdot}$	D_2O (77 K)	2.035, 2.008, 2.003		98[a,d], 58.4[b,d]	88
$NCCH_2OO^{\cdot}$	D_2O (77 K)	2.035, 2.008, 2.003		98.4[a,d], 57.2[b,d]	88
$CH_2ClOO^{\cdot}$	D_2O (100 K)	2.035, 2.008, 2.003		97.5[a,d], 55.5[b,d]	88
$CHCl_2OO^{\cdot}$	D_2O (105 K)	2.035, 2.008, 2.003		100.8[a,d], 51.3[b,d]	88
$CCl_3OO^{\cdot}$	methanol (93 K)	2.035, 2.008, 2.003		102.6[a,d], 49.2[b,d]	88
$C_6H_5CH_2OO^{\cdot}$	methanol (77 K)	2.035, 2.008, 2.003		95.4[a,d], 56.6[b,d]	88
$C_6H_5C(CH_3)_2OO^{\cdot}$		2.0148		21.8[a,c], 16.4[b,c] (95[a,d], 60.3[b,d])	77, 78, 81
$(C_6H_5)_3COO^{\cdot}$		2.014		91[a,c], 61[a,d]	89, 97
$CH_2{=}CHCH_2OO^{\cdot}$		2.016		96[a,c], 60[a,d]	83, 96

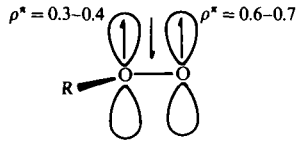
(continued)

TABLE 12. (*continued*)

Radical	Matrix/solvent	*g*-Value	Hyperfine coupling constant (G)		References
			a(H)	*a*(^{17}O)	
$CH_3CHCHCH(CH_3)OO^{\cdot}$		2.0154	5.0 (1H)		73
$CH_2{=}CH(CH_2)_2C(CH_3)_2OO^{\cdot}$		2.0151			75
$CH_2{=}CH(CH_2)_2CH_2OO^{\cdot}$		2.0137	5.97 (2H)		75
		2.0149			76
		2.0147	5.1 (1H)		76

[a] Due to terminal oxygen atom.
[b] Due to inner oxygen atom.
[c] Isotropic.
[d] Anisotropic parallel component.

spin density associated with the terminal oxygen atom. Interestingly, the parallel components of the ^{17}O hyperfine couplings in the superoxide radical, $O_2^{\cdot-}$, are both 77.3 G. The sum of the ^{17}O hyperfine couplings, corresponding to unit spin density, is thus *ca* 155 G. Inspection of Table 12 reveals that, remarkably, the sum of the parallel couplings for a variety of alkyl peroxyl radjcals lies between 152–156 G. Thus, there is negligible delocalization of the unpaired spin into the alkyl group. Moreover, using the values of the isotropic ^{17}O hyperfine couplings (Table 12), and the relationship $a_{\parallel} = (a + 2B)\rho^{\pi}$ where a and B are, respectively, the isotropic and anisotropic components of the couplings, it is possible to calculate a value for B of 57.4 G and an average value for a of 39.5 G. Since unit spin in an oxygen 2*s* orbital is associated with a coupling of 1660 G[98], the unpaired electron resides in an orbital on oxygen that has 2.5% *s*-character. Thus, the peroxyl radical is one in which the electron resides in a π molecular orbital that originates from the oxygen p-orbitals, as in structure **22**[88]. An estimate of the spin



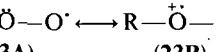
(22)

density at each oxygen atom is obtained by dividing the observed value of $a_{\parallel}$ by 155 G; approximately 60–70% of the spin density resides on the terminal oxygen, the remainder on the inner oxygen. The observation that, in the doubly substituted species $R^{17}O^{17}O^{\cdot}$, the principal axes of the parallel components of both oxygen atoms are aligned demonstrates that the oxygen p-orbitals are parallel and further corroborates the radical structure. The structure of peroxyl radicals bears considerable similarities to the corresponding perthiyl radicals, $RSS^{\cdot}$[72].

For a series of substituted alkyl peroxyl radicals, the data in Table 12 demonstrate that, as the electron-withdrawing ability of the alkyl group increases, the ^{17}O hyperfine coupling to the terminal oxygen increases whereas that to the inner oxygen atom decreases proportionately. Indeed, there is a correlation between the size of the hyperfine coupling to the terminal oxygen and the Taft σ^* parameter (equation 20).

$$a_{\parallel}(^{17}O_{term}) = 94.1 + 3.3\sigma^* \; (r^2 = 0.91) \tag{20}$$

The effect of the nature of the alkyl group on the ^{17}O hyperfine coupling may be explained by considering the two contributing resonance structures **23A** and **23B**. For strongly electron-withdrawing alkyl groups structure **23B** is disfavoured due to the proximity of the positive charge on the inner oxygen atom and the electron-withdrawing



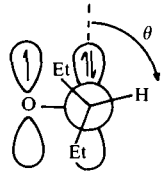
(23A) **(23B)**

group. Thus, for these radicals **23A** is the major contributing form and unpaired spin density at the terminal oxygen is greatest. As the alkyl group is more able to accommodate the positive charge on the inner oxygen atom, **23B** makes a greater contribution to the overall structure and the spin density at the terminal oxygen decreases while the spin density at the inner oxygen increases. Interestingly, there appears to be a strong correlation between the reactivity of peroxyl radicals, as measured by their rate of electron transfer, and the ^{17}O hyperfine coupling to the terminal oxygen. The more reactive radicals have the larger coupling constant, which would imply that reactivity is associated with a greater unpaired spin density at this oxygen atom[88].

The trends observed earlier for the proton hyperfine coupling can also be accounted for by the π-structure of peroxyl radicals. As all of the spin density is associated with the oxygen atoms, coupling to the protons bonded to the carbon atom adjacent to the peroxyl group arises through a hyperconjugative mechanism. In such a situation, the proton hyperfine coupling is governed by equation 21 (which is identical to equation 4 except that it takes account of the spin density at the adjacent oxygen atom).

$$a(\mathrm{H}) = B\rho_{\mathrm{O}}^{\pi}\cos^2\theta \tag{21}$$

From the values of the ^{17}O hyperfine couplings for simple alkylperoxyl radicals $\rho_{\mathrm{O}}^{\pi} = 0.38$ and $B = 57.4$ G (see Table 12 and the above discussion). Thus, for a freely rotating alkyl group the proton hyperfine coupling can be calculated to be *ca* 11 G. Most of the hyperfine couplings reported in Table 12 are much smaller than this value, almost certainly because the radicals adopt a preferred orientation. For the sterically hindered 3-pentylperoxyl radical the dihedral angle subtended between the C—H bond and the orbital containing the unpaired electron is *ca* 72°, putting the proton almost in the nodal plane of the π-orbital (**24**).



(**24**)

Ab initio molecular orbital calculations at the UHF/6-31G(d) level tend to confirm this structure[99]. For $CH_3OO^{\bullet}$ two conformational minima are observed. In both one proton is co-planar with the C—O—O fragment, oriented either *trans*, as in **24**, or *cis*. For $CH_3OO^{\bullet}$ the *trans* conformer is favoured by 1.6 kJ mol^{-1}, and for $(CH_3)_2CHOO^{\bullet}$ the energy difference is 2.7 kJ mol^{-1}. For the more sterically demanding radical $(C_2H_5)_2CHOO^{\bullet}$, which is a model for the peroxyl site in polyethene and lipids (*vide infra*), the *trans* conformer is favoured by only 0.5 kJ mol^{-1}.

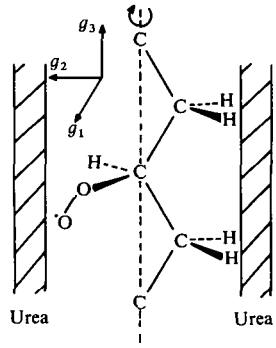
The increase in the proton hyperfine coupling brought about by an increase in the solvent polarity can be accounted for by the polar solvent enabling a greater contribution of the charge separated resonance form **23B** to the overall structure of the radical. In turn, this increases the spin density, ρ_{O}^{π}, on the inner oxygen atom and hence the hyperconjugative coupling to the protons.

Despite the fact that peroxyl radicals give rise to broad, often featureless, signals, the changes observed in the temperature-dependent g anisotropy can be used to probe both the environment of the radical centre and the types of molecular motion the peroxyl radical is undergoing. Averaging of the g anisotropy extends over a range of *ca* 200 MHz at 9 GHz, and *ca* 800 MHz at 35 GHz, making peroxyl radicals much more sensitive to faster motions than the often used nitroxyls. For this reason, and also because they are formed directly in polymer and lipid degradation, peroxyl radicals have been well studied as probes of molecular environment.

The triphenylmethylperoxyl radical, $(C_6H_5)_3COO^{\bullet}$, provides the simplest example for which changes in g anisotropy identify molecular motion. In a rigid lattice at 80 K this radical displays three g-values that are consistent with rhombic symmetry, viz. 2.0320, 2.0092 and 2.0035, and characteristic of peroxyl radicals in general (see Table 12). The **g** tensor is thus a property of the peroxyl group rather than the rest of the molecule. The direction of the largest g-value coincides with the O—O bond, while the direction of the minimum g-value lies along the direction of the orbital containing the unpaired

electron. On warming to 282 K the spectrum undergoes a series of complex changes, but results in a spectrum that is consistent with an axially symmetric **g** tensor with g values $g_{\parallel} = 2.0175$ and $g_{\perp} = 2.0128$. At the higher temperature $g_{\parallel}$ lies along the direction of the C—O bond. The spectral changes could be simulated only by using a model which involves a 120° three-jump rotation of the peroxyl group about the C—O bond. Using this model, an activation energy for the rotational process of 9.2 kJ mol^{-1} can be calculated[100,101]. An *ab initio* calculation of this energy barrier for $(C_2H_5)_2CHOO^{\cdot}$, using a rigid rotor model, is reportedly 164 kJ mol^{-1}[99]. One possible explanation for such a large discrepancy could lie in the relative extents of the equilibria of the peroxyl radicals with the corresponding alkyl radicals and dioxygen. For triphenylmethylperoxyl there is a greater extent of dissociation. Alternative rotational modes, such as 90° and 180° jumps about the C—O bond or chain axis rotation involving 60°, 90° or 180° jumps of the peroxyl group about the C—C—C chain, all fail to simulate satisfactorily the observed spectra. Changes in the anisotropy of the ^{17}O hyperfine coupling with temperature have likewise been interpreted in terms of rotation of the peroxyl group about the C—O bond[97].

Alkanes form complexes with urea by occupying the hexagonal channels in the urea lattice. Irradiation of such complexes followed by exposure to oxygen generates peroxyl radicals trapped in a polycrystalline environment. Below *ca* 120 K the radicals display the usual anisotropy associated with peroxyls, viz $g_1 = 2.037$, $g_2 = 2.008$ and $g_3 = 2.002$[86]. Above 120 K the spectra reveal features that are characteristic of the motional effects of the peroxyl radical. However, g_3, which lies along the direction of the orbital containing the unpaired electron and also parallel to the main chain axis (because the plane containing the peroxyl group is perpendicular to this axis), remains unaltered. In contrast, the g_1 and g_2 values are averaged. This indicates that the alkane chain is free to rotate in the urea cavity (see **25**).



(25)

Indeed, simulation of the experimental spectra is best achieved using a model involving 120° rotational jumps of the peroxyl group about the molecular chain axis[86]. The activation energy for this process increases from 6.8 kJ mol^{-1} for the peroxyl radical formed from dodecane (C_{12}) to 10.4 kJ mol^{-1} for that from eicosane (C_{20}). For longer-chain radicals the activation energy is similar to that for eicosane. For a peroxyl radical formed from the branched chain alkane, 2-methyloctadecane, the chain axis rotation is best described by a model involving 90° jumps with an activation energy of 11.3 kJ mol^{-1}[87].

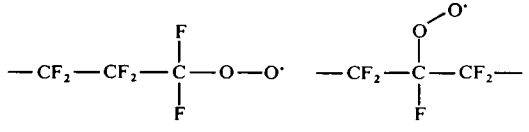
Lipids trapped in urea matrices behave similarly[102]. Both methyl stearate ($C_{17}H_{35}CO_2CH_3$) and methyl tetracosanoate ($C_{23}H_{47}CO_2CH_3$) form peroxyl radicals α to the carbonyl group, and stearyl oleate ($C_{17}H_{33}CO_2C_{18}H_{37}$) forms an allylic peroxyl

radical. At *ca* 100 K all three radicals display the usual g anisotropy, viz. $g_1 = 2.035$, $g_2 = 2.008$ and $g_3 = 2.0025$, while at ambient temperatures averaging of g_1 and g_2 occurs to give a single line at 2.021 and g_3 remains largely unchanged. Such averaging of the **g** tensor may be explained in tems of the chain axis rotation previously described. Spectral simulation is achieved for a 120° rotational jump model, though for methyl tetracosanoate a 90° jump model gives a better fit above 160 K. Activation energies are comparable to those for pure alkanes, ranging from 8.7 kJ mol^{-1} for methyl stearate, to 10 kJ mol^{-1} for methyl tetracosanoate and 13 kJ mol^{-1} for stearyl oleate. However, for the lipids the activation energy corresponds to *ca* 0.4 kJ mol^{-1} per unit chain length, whereas for the alkanes the corresponding value is 0.55 kJ mol^{-1}. ^{17}O Isotopically labelled lipid peroxyl radicals trapped in a urea clathrate give rise to ^{17}O hyperfine couplings at low temperature of 95 G and 59 G for the terminal and inner oxygen atoms respectively[102]. These are entirely consistent with those expected for simple alkyl peroxyls (Table 12). At higher temperatures these diminish somewhat to 87 G and 55 G. Nonetheless, the observation that neither g_3 nor the ^{17}O hyperfine couplings are significantly averaged implies that in the urea clathrate the barrier to rotation about the C—O bond must be relatively large.

The peroxyl radical formed from triarachidin, the triglyceride of eicosanoic acid, behaves in a fashion consistent with those of alkylperoxyls trapped in urea matrices. Thus, at *ca* 100 K the peroxyl g anisotropy of peroxyl radicals, $g_1 = 2.0338$, $g_2 = 2.0080$ and $g_3 = 2.0032$, is observed[94,95]. Upon warming, g_3 remains unaltered but g_1 and g_2 are averaged. The spectral changes are consistent with 90° rotational jumps about the chain axis, for which the energy barrier is 13.9 kJ mol^{-1}.

Similar observations have been made on the peroxyl radical formed from linoleic acid. However, for this radical either of two types of motion may pertain. Either the plane containing the peroxyl group is tilted from the perpendicular to the main chain axis by 42° (which is not inconsistent with the larger values of the proton hyperfine couplings observed for simple secondary peroxyl radicals, *vide supra*) and 180° rotational jumps about the chain axis take place, or rotation occurs about the C—O bond. Whichever occurs, the calculated energy barrier, 3.4 kJ mol^{-1}, is low[95].

Peroxyl radicals derived from polymers have been observed upon irradiation[90–92] and upon oxidative pyrolysis[103]. For example, poly(tetrafluoroethene) (PTFE) produces two types of peroxyl radical, one designated as end-chain (**26**) and the other as mid-chain (**27**). Exclusive formation of **26** may be achieved by subjecting the precursor alkyl radicals to UV irradiation prior to exposure to oxygen[92].



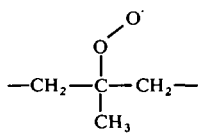
(26) (27)

The isotropic g-value of **26** is 2.0168 and that for **27** is 2.0165[92]. However, whereas the end-chain radical has an isotropic spectrum at 298 K, the mid-chain radical is axially symmetric at that temperature. At 77 K both radicals give rise to anisotropic spectra that are characterized by $g_1 = 2.0394$, $g_2 = 2.0070$ and $g_3 = 2.0016$[92,104,105]. The ^{17}O hyperfine couplings observed at 77 K for both types of isotopically labelled radicals are 107 G for the terminal, and 46 G for the inner, oxygen atoms[104–106]. These values are precisely those expected for peroxyl radicals in which the alkyl group is strongly electron-withdrawing (*vide supra*), and reflect the differing spin densities on the two oxygen atoms. At 300 K, the ^{17}O hyperfine couplings for the mid-chain radical are 89 G and 40 G, still well above the isotropic values, whereas the corresponding values for the end-chain radical, 26.5 G and 13 G, are isotropic[105]. The temperature dependence of the

g and **a** tensors demonstrate that rotational averaging of the end-chain radical **26** starts at *ca* 150 K whereas for the mid-chain radical **27** such averaging occurs at *ca* 250 K[92,104]. Spectral simulations identify the motional process involved for the end-chain radical as a cubic jump model, i.e. one in which the peroxyl group rotates about an axis that is equally inclined to each of the three principal directions of the **g** tensor. The process can be visualized as a helical twisting of the polymer chain, and is associated with an energy barrier of 11.2 kJ mol^{-1}. The motion of the mid-chain radical involves chain axis rotation in 90° jumps, a process that has an activation energy of 18.4 kJ mol^{-1} [92,101].

Poly(ethene) forms a mid-chain peroxyl radical analogous to **27**[107,108]. The temperature-dependent averaging of the *g*-values, $g_\perp = 2.0224 = g_1 + g_2/2$ and $g_\parallel = 2.0022 = g_3$, is consistent with a radical that has structure **25**, that is undergoing either a 90° jump rotation about the polymer chain axis or a 180° rotational jump of the O—O group about the C—O bond, the energy barrier for the process being 16.6 kJ mol^{-1} [107]. Although the latter type of motion was originally favoured[107], it would appear that chain axis rotation is the more likely[101] bearing in mind the types of motion observed for the peroxyl radicals derived from long-chain alkanes, lipids and PTFE.

The peroxyl radical formed from poly(propene) has the mid-chain tertiary structure **28**. However, in contrast to the peroxyl radicals derived from unbranched polymers in which the plane containing the O—O bond lies at right angles to the main chain axis, the helical structure of isotactic poly(propene) results in the peroxyl group lying in a plane that is inclined by 55.5° to the main chain axis. Moreover, the O—O bond has a *gauche* relationship with the two adjacent C—C bonds of the polymer chain. Thus, the radical adopts a conformation in which the peroxyl group lies *trans* to the pendant methyl group, as in structure **29**[109,110]. This is entirely consistent with the *ab initio* results for the $(C_2H_5)_2CHOO^\cdot$ radical described earlier. The motional processes observed for the peroxyl radical of poly(propene) are the subject of some debate.



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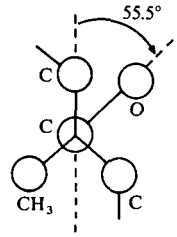
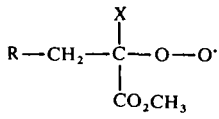


(29)

The presence of the methyl substituent is thought to provide enough steric hindrance to preclude rotation about the polymer chain axis[101,111]. Rather, rotation of the O—O group about the C—O bond in 180° jumps is proposed as the dominant mode of motion[111]. A similar situation appears to hold for the sterically hindered peroxy radicals **30**, derived from poly(methacrylates). However, for poly(propene) this interpretation has been challenged, and a chain axis rotation proposed[112]. Clearly, this is an area that requires clarification.



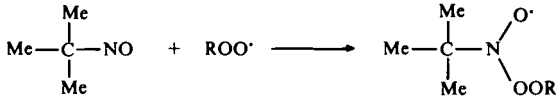
X = CH_3, F, CN

(30)

3. Spin trapping

Although peroxyl radicals can be detected directly, even during enzyme catalysed reactions[79,113], there is a well documented body of literature on the spin trapping of these radicals. In part, this stems from the need to distinguish between the carbon-centred precursor radicals, the peroxyl radicals themselves and the alkoxyl radicals that are formed from the decomposition of the peroxyl radicals, and also from the short lifetimes the peroxyl radicals have in biological milieu. For example, in the presence of haematin tertiary alkyl peroxides give rise to a peroxyl radical that can be observed directly, whereas a corresponding primary alkyl peroxide is too reactive to detect except by the spin trapping method[79]. Moreover, even though alkyl and alkyl peroxyl radicals can be easily distinguished from each other, the presence of an alkoxyl radical can go undetected unless spin trapping is used (Section I.B), and then, as we shall see, it can be quite difficult to distinguish between peroxyl and alkoxyl radicals.

Both nitroso and nitrone spin-trapping agents have been successfully employed for peroxyl radicals (equations 22 and 23), the most commonly employed being the nitrone spin traps.



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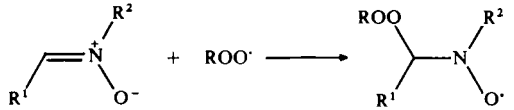
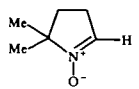
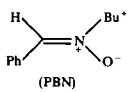


(23)

Table 13 contains ESR spectral parameters for representative spin-trapped peroxyl radicals (Reference 25 contains a more extensive list). The spin-trap α-phenyl-*N*-*t*-butylnitrone (PBN) has been the subject of most study. A comparison of the data in Table 13 with that in Table 5 shows that the a(N), a(^{17}O) and a(β-H) hyperfine coupling constants for the spin-trapped peroxyl radical are somewhat smaller than those for the corresponding trapped alkoxyl radical while the a(α-^{13}C) values are roughly the same. Unfortunately, these differences are unable to distinguish definitively between spin-trapped peroxyl and alkoxyl radicals. Thus, spin trapping using PBN of the smoke derived from the oxidative pyrolysis of perfluoro polymers gives rise to a radical that has a(N) = 13.3 G and a(H) = 1.5 G and could be assigned to either a spin-trapped alkoxyl or peroxyl radical[123]. Peroxyl radicals spin trapped by PBN are not stable above 270 K, decomposing above this temperature to the corresponding spin-trapped alkoxyl. Light appears to catalyse this decomposition[121].

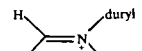
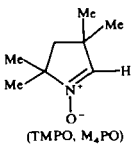
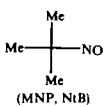
As an attempt to distinguish between spin-trapped alkoxyl and peroxyl radicals, and to increase the stability of the trapped peroxyl radical, the cyclic nitrones 5,5-dimethylpyrroline-*N*-oxide (DMPO) and 3,3,5,5-tetramethylpyrroline-*N*-oxide (TMPO) have been employed as spin-trapping agents[114]. The rationale behind this approach lies in the magnitude of the observed proton hyperfine coupling constants to the β-H of the pyrroline ring. For the acyclic spin traps like PBN the similar magnitudes of the hyperfine couplings probably arise from the lack of any conformational rigidity in the spin-trapped radicals. For the cyclic analogues, however, it has been established that the a(H) value of the β-proton is dependent on the size and nature of the radical trapped[124]. DMPO most clearly distinguishes between alkyl radicals on the one hand,

TABLE 13. ESR spectral parameters for spin-trapped peroxyl (and related) radicals

Spin trap	Peroxyl radical trapped	Solvent	g-Value	Hyperfine coupling constants (G)			References
				a_N	a_H	a_X	
 (DMPO)	EtOO$^{\bullet}$	water		14.6	11.0(β-H) 1.25(γ-H)		79
	Bu^{t}OO$^{\bullet}$	toluene		12.72	9.36(β-H) 1.44(γ-H)		114
		water		14.48	10.88(β-H) 1.30(γ-H)		115
	$PhMe_2COO^{\bullet}$	toluene		13.92	11.20		114
		water		14.5	10.75(β-H) 1.75(γ-H)		116
 (PBN)	Bu^{t}OO$^{\bullet}$	benzene		13.25	1.15	4.65(α-^{13}C)[a]	27
		toluene	2.0064	13.42	0.95	2.9(^{17}O)[b]	28
	$C_5H_{11}OO^{\bullet}$	CH_2Cl_2	2.0062	13.44	1.39		117
	$PhMe_2COO^{\bullet}$	CH_2Cl_2	2.0062	13.46	1.47		17
	$PhMeCHOO^{\bullet}$	benzene		13.57	1.74		118
	$C_{18}H_{37}OO^{\bullet}$	CH_2Cl_2	2.0062	13.50	1.61		117
	$(CN)Me_2COO^{\bullet}$	toluene		12.94	1.25	5.05(α-^{13}C)[a]	119
	$Cl_3COO^{\bullet}$	CCl_4		13.5	1.6		119
	LOO$^{\bullet}$[c]	benzene		13.44	1.63		120

(*continued*)

TABLE 13. (*continued*)

Spin trap	Peroxyl radical trapped	Solvent	*g*-Value	Hyperfine coupling constants (G)			References
				a_N	a_H	a_X	
 (MDN)	$Bu^tOO^{\cdot}$	benzene	2.0059	12.8	4.61		121, 122
	$LOO^{\cdot}$[c]	benzene		12.45	4.69		120
	($LO^{\cdot}$[c]	benzene		13.35	6.25)		120
 (TMPO, M_4PO)	does not trap peroxyl radicals						114
 (MNP, NtB)	$Cl_3COO^{\cdot}$			27.0			119
	$Bu^tOO^{\cdot}$		2.0056	28.7		4.6(^{17}O)[b]	28

[a] α-^{13}C of nitrone.
[b] Coupling to α-^{17}O in RO adduct.
[c] Radical from methyl 13-hydroperoxylinoleate.

and alkoxyl/peroxyl radicals on the other. Thus, the $a(\beta$-H) value for a spin-trapped alkyl radical is *ca* 20 G, whereas that for the spin-trapped alkoxyls and peroxyls is *ca* 10 G. The ability to differentiate between alkoxyls and peroxyls is less clear cut; the nitrogen hyperfine couplings are about the same for both types of spin-trapped radical (though that for the peroxyl is slightly the larger), and the β-proton hyperfine coupling for the spin-trapped peroxyl lies in the range 9–11 G whereas that for the equivalent alkoxyls lies in the range 7–8 G[114]. Nevertheless, these differences have enabled peroxyl radicals to be detected during the oxidation of a variety of lipids[125]. However, definitive assignments require careful observations of the spectral changes with experimental conditions such as substrate concentration[114,115]. In contrast, TMPO is able to trap alkoxyl but not peroxyl radicals[114].

The best trap currently in use that can distinguish between alkoxyl and peroxyl radicals is methyl *N*-duryl nitrone (MDN). For alkoxyls, the nitrogen hyperfine coupling is > 13 G while for peroxyls it is < 13 G but, more importantly, the β-proton hyperfine coupling for alkoxyls lies in the range 6–8 G whereas for peroxyls it is much smaller than this, *ca* 4.5 G (Table 13)[121,122]. Thus, in the decomposition of the hydroperoxide of methyl linoleate carbon-centred radicals, alkoxyls and peroxyls can all be detected and assigned unambiguously[120]. Unfortunately, the stability of the spin-trapped peroxyl radicals of MDN is slightly less than those of PBN[121].

II. THE NMR SPECTRA OF ALCOHOLS, ETHERS AND PEROXIDES

A. Proton and Carbon-13 Chemical Shifts and Coupling Constants

1. *Chemical shifts—general*

Alcohols, ethers and peroxides, $-O-X$ (X = H, R, OH, OR) are modestly electron-withdrawing by the inductive effect and thus have a deshielding effect on adjacent alkyl groups. Table 14 gives the substituent constants for these groups and Table 15 gives the range of proton and carbon-13 chemical shifts for adjacent CH_2 groups. As expected the deshielding effect falls off with distance. Proton chemical shifts for protons on the α carbon of alcohols are around 3.5–3.7 ppm and shift upfield by about 0.2–0.3 ppm on methylation. Protons on the β carbon shift to a varied extent but mainly downfield. Obviously the chemical shift of protons on the α carbon depends upon the overall structure, the chemical shifts of the CH_3 protons in a group of substituted anisoles are related linearly to the σ parameter with a ρ of 0.24 ppm[100]. The proton NMR of CH_2 and CH_3 groups β to a peroxy function shows similar chemical shift behaviour to those groups β to an alcohol[135].

An empirical increment system[136] allows the calculation of the carbon-13 shift for alcohols, as shown in Table 16. With ethers the α carbon is deshielded by about 10–12 ppm with respect to the corresponding alcohol, whilst the β carbon experiences a shielding of about 3 ppm. This latter figure depends upon the configuration of any substituents[137]. Numerous computer programmes are available which allow the

TABLE 14. Some substituent constants for OX groups

OX	σ_m	σ_p	Ref.	σ_I	σ_R°	Ref.	σ_p^+	Ref.
O—H	0.13	−0.38	126	0.25	−0.43	128	−0.92	130
O—CH_3	0.10	−0.12	127	0.25	−0.43	128	−0.78	131
O—OR	—	—	—	0.32	—	129	—	—

TABLE 15. Proton and carbon-13 chemical shifts of CH_2 adjacent to OX groups

		^{1}H chemical shift				^{13}C chemical shift			
O—X	Compound	1	2	3	Ref.	1	2	3	Ref.
OH	$CH_3CH_2\overset{3}{C}H_2—\overset{2}{C}H_2—\overset{1}{C}H_2—OH$	3.6	1.4	—	132	62	33	28	133
OCH_3	$CH_3CH_2—\overset{3}{C}H_2—\overset{2}{C}H_2—\overset{1}{C}H_2—OCH_3$	3.4	1.5	—	132	72	30	26	133
O—OH	$CH_3—\overset{2}{C}H_2—\overset{1}{C}(CH_3)_2—OOH$	—	1.52	—	135				134
O—OR	$(\overset{2}{C}H_3)_3\overset{1}{C}—O—O—C(CH_3)_3$	—	1.17	—	135	78.2	27	—	134
CH_3	$CH_3—CH_2—CH_2—\overset{3}{C}H_2—\overset{2}{C}H_2—\overset{1}{C}H_3$					14	23	32	133
OCH_3	$CH_3—\overset{2}{C}H_2—\overset{2}{C}H{=}\overset{1}{C}H—OCH_3$					147	104	26	133
CH_3	$\overset{3}{C}H_3—\overset{2}{C}H_2—\overset{1}{C}H{=}CH—CH_2—CH_3$					130.1	33	—	133

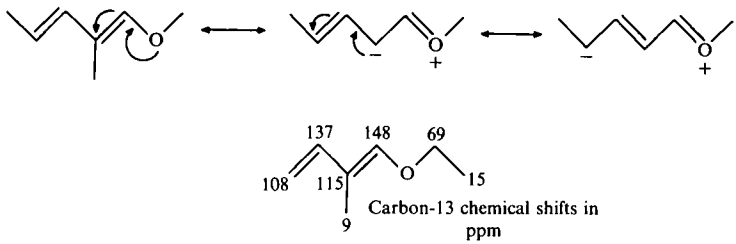
TABLE 16. Increment set for the prediction of alcohol carbon-13 shifts according to $\delta_c(R—CH_2—OH) = b_k + a_k\delta_c(R—CH_2—CH_3)$

Alcohol	Carbon position relative OH group	b_k	a_k
Primary	α	46.45	0.709
	β	1.81	0.963
	γ	−2.28	0.963
	δ	0	1.0
Secondary	α	45.65	0.786
	β	2.07	0.958
	γ	−0.48	0.982
	δ	0	1.0
Tertiary	α	48.37	0.755
	β	−0.06	1.029
	γ	−1.03	1.137
	δ	0.07	0.995

calculation of such carbon-13 chemical shifts using empirical data[138]. As yet not enough data exist for calculation of the carbon-13 chemical shifts of peroxides. However, the α carbon of peroxides are about 10 ppm downfield of the corresponding alcohols.

Whilst O—X groups are withdrawing by the inductive effect, they are usually electron-donating by the resonance effect, as shown in Table 14. This means that if the O—X is adjacent to a multiple bond, a shift to high field on the β carbon can often be observed, as shown in Table 15. The effect of the adjacent oxygen on the α carbon is mainly inductive leading to a downfield shift of the carbon-13 chemical shift. The upfield shift on the β carbon arises from electron donation into the π system by the non-bonded pair on oxygen.

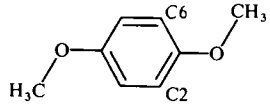
In fact, the carbon-13 chemical shift of the β olefinic carbon in enol ethers is also susceptible to the conformation of the OR group with respect to the double bond[139]. The α carbon shows no such effect. With 1-OX substituted butadienes transmission of the electron releasing and withdrawing effect alternates along the conjugated system.



Proton and carbon-13 chemical shift data are used extensively in structural analysis and such discussion is beyond the scope of this chapter. However, we will highlight a

few examples where the NMR chemical shift of alcohols and ethers has been employed to provide other information.

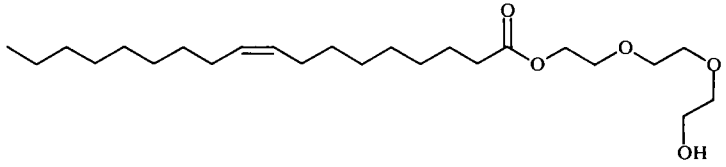
Solid state proton and carbon-13 NMR can be used to reveal structural effects within the crystalline state, such as molecular packing and packing-induced conformational changes. One such example, involving ethers, leads to chemically non-equivalent resonances appearing for carbons in the solid state, which are magnetically equivalent in solution NMR.



(31)

1,4-Dimethoxybenzene, **31**, and related diethers, have different chemical shifts in the solid state carbon-13 NMR for the C2 and C6 carbons, because in the crystal the ether dihedral angle C2—C1—O—CH_3 is not 90°[140]. Calculations indicate that for small dihedral angles the chemical shift difference is dominated by the linear electric field effect, but for angles approaching 90° both steric hindrance and ring current mechanisms need to be taken into account.

Ethers and alcohols are important functional groups in polymers and surfactants. NMR studies in solution and in the solid state give information on the structure and mobility of such materials. For example, polymerization of vinyl ethers gives polymers where the stereoregularity can be determined by NMR[141]. The presence of multiplets in the carbon-13 NMR spectrum reflect the different environments of the carbons which in turn reflect the tacticity and regularity of the polymer. Carbon-13 NMR studies of some high molecular weight derivatized cellulose ethers in solution gave information on the degree of substitution and line broadening gave information on gross structure[142]. Magic angle spinning gave better defined resonances which enabled the degree of substitution to be determined.



(32)

Carbon-13 relaxation time measurements of the surfactant **32** in the reversed micellar state showed that the ester group is anchored, leading to small correlation times. The hydrophilic ether groups were hydrogen bonded, leading to reduced internal mobility and, again, low correlation times[143]. The lipophilic part of the molecule had large segmental motion, although there was restricted motion in the vicinity of the double bond.

A good correlation has been obtained between the carbon-13 and the proton chemical shifts of alcohols and rate constants for their photodegredation by hydroxyl radicals[144].

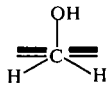
2. *Chemical shifts and hydrogen bonding*

The proton chemical shifts of the hydroxy proton is both solvent and concentration dependent due to intermolecular hydrogen bonding. Concentration effects can be overcome by recording the proton NMR at various known concentrations of solute and

TABLE 17. Proton chemical shifts (δ) in substituted benzyl alcohols

Substituent	DMSO[a]		CCl_4[b]		
	$\delta(CH_2)$	δ(OH)	$\delta(CH_2)$	δ(OH)	σ^c
p-OMe	4.410	5.037	4.502	0.98	−0.268
p-Me	4.472	5.091	4.538	0.97	−0.170
m-Me	4.452	5.115	4.539	1.00	−0.069
H	4.457	5.143	4.598	1.09	0.000
m-OMe	4.464	5.164	4.567	1.05	0.115
p-Cl	4.479	5.269	4.603	1.15	0.227
p-Br	4.460	5.269	4.590	1.18	0.232
m-Cl	4.498	5.321	4.629	1.20	0.373
m-Br	4.497	5.318	4.618	1.26	0.391
m-NO_2	4.639	5.539	4.780	1.43	0.710
p-NO_2	4.636	5.532	4.780	1.48	0.778

using a linear extrapolation to infinite dilution. For example, Table 17 shows the proton chemical shifts of the CH_2 and OH groups for a series of benzyl alcohols extrapolated to infinite dilution[145]. After correction, both $\delta(CH_2)$ and δ(OH) change consistently with substituent giving good Hammett correlations with a correlation coefficient of 0.98 or better for δ(OH). The large difference (up to 4 ppm) between the data in DMSO and in CCl_4 reflects hydrogen bonding between the OH and DMSO leading to deshielding of the nucleus. The greater sensitivity of the hydroxyl proton compared with the nearer CH protons was interpreted in terms of the field effect of the substituent having a greater effect on the larger bond dipole moment of the OH versus the CH bond. A similar study of the effect of substituents on the proton chemical shift of benzylic protons for a range of benzyl compounds, showed that benzyl alcohols and ethers had large ρ values compared to larger functional groups[146]. This was interpreted in terms of **33** being the predominant conformation .



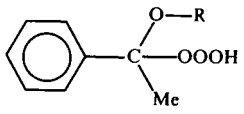
Plane of benzene ring

(33)

In comparison with alcohols the OOH group is not extensively hydrogen bonded. Large downfield shifts of the signal of the OOH proton (8 ppm) are observed compared with the OH in analogous compounds (2 ppm)[135]. This demonstrates the large deshielding effect of the peroxy group on the adjacent proton.

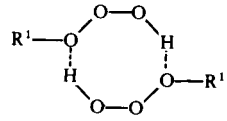
NMR chemical shift and relaxation time measurements of the OH proton have been used to provide information about the nature and degree of hydrogen bonding in alcohols[147], which can be correlated with thermodynamic factors[148]. Solid state proton NMR enables hydrogen bonding to be examined in the solid state[149]. Subsequent theoretical analysis of these data[150] shows that the chemical shift tensor is a sensitive measure of hydrogen bonding and can yield more information than the isotropic shift alone. A relationship between the O···O separation and the isotropic chemical shift is observed which was explained in terms of a strong dependence of the perpendicular shielding component and the O···O separation. No correlation was observed between the O···O separation and the chemical shift anisotropy, implying a lack of correlation with the parallel component of the shielding tensor.

The proton NMR of the trioxide compound **34** shows two peaks arising from the O—H proton. This has been explained in terms of two intramolecular hydrogen-bonded forms, involving either of the non-bonded pairs on oxygen[151]. Alternatively, two conformational forms of the intramolecularly hydrogen-bonded six-membered ring form have been proposed with the O—R groups axial or equatorial[151]. A more compelling explanation is that dimers of the type **35** are formed and the presence of a chiral centre leads to distinct *R–R* and *S–S* or *R–S* and *S–R* diastereoisomers that have different chemical shifts for the O—H proton[152].



R = Me or H

(34)



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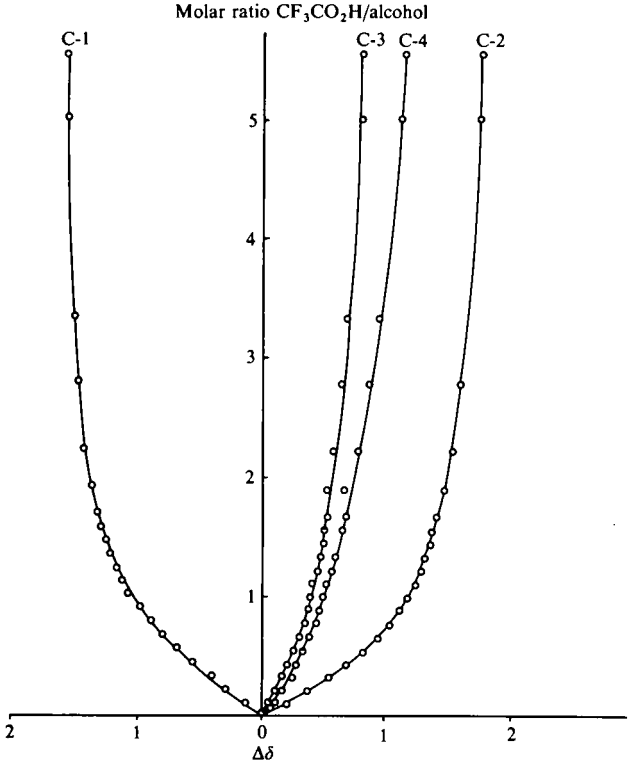


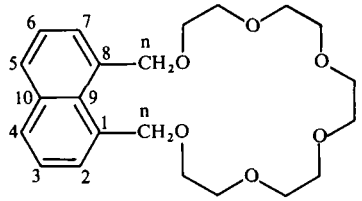
FIGURE 2. ^{13}CNMR shift changes of a 1 M solution of butan-1-ol in CCl_4 containing trifluoroacetic acid, as a function of the molar ratio acid/alcohol. Reproduced from Reference 153 by permission of the Royal Society of Chemistry.

Protonation of the oxygen of alcohols[153] or ethers[154] using trifluoroacetic acid in carbon tetrachloride leads to a downfield shift of the carbon-13 chemical shift for the C-1 position but an upfield shift for all other carbons, as shown in Figure 2. Primary, secondary and tertiary alcohols and ethers exhibit slightly different behaviour and thus allow structural determination. An empirical increment system is described which allows the calculation of the carbon-13 shift for protonated alcohols and ethers. The shift displacements also reveal stereochemical characteristics allowing distinction between *endo* and *exo* or between axial and equatorial groups.

Relationships have been discovered between the change in OH stretching frequency and the change in carbon-13 chemical shift on association of alcohols with acids or bases. A linear correlation has been observed between the change in O—H stretching frequency ($\Delta\nu_{O-H}$) of alcohols complexed with bases and the carbon-13 chemical shift of the α carbon. Increasing hydrogen bond strength (as evidenced by $\Delta\nu_{O-H}$ values) is accompanied by progressive downfield shifts in the carbon-13 peaks of the C-1 of phenol[155]. A similar linear relationship was found between the acid induced carbon-13 chemical shift change of the α carbon and the O—H stretching frequency of the hydroxy group in a range of aliphatic alcohols[156]. As $\Delta\delta^{13}C$ became more negative so ν_{O-H} became smaller.

3. *Chemical shifts and complexation*

Complexation at the oxygen of O—H and O—R also leads to dramatic changes in the proton and carbon-13 chemical shifts. Crown ethers provide the exemplar here. Proton NMR can yield useful conformational information. Complexes of benzo-18-crown-6, dibenzo-18-crown-6 and dibenzo-30-crown-10 (except Na^+) were shown to have the same conformation in solution as in the crystalline state[157]. Multinuclear NMR (^{23}Na, ^{133}Cs and ^{13}C) has been applied to dibenzo-30-crown-10 complexes in a range of solvents, giving information on the conformation, stoichiometry and thermodynamic parameters of the complexes[158]. The carbon-13 NMR spectra of six naphthalene-based crown ethers, for example **36**, were measured over a range of concentrations of alkali metal cations in CD_3OD[159]. Non-linear least-squares analysis gave the binding constants and the limiting chemical shifts of the complexes. Conformational processes were shown to be fast on the NMR timescale and thus the chemical shift value of any given carbon reflects contributions from all conformations. Figure 3 shows a typical set of results for compound **36**. Despite variations in behaviour, trends in the series of compounds could



(36)

be identified. For all the crown ethers studied, the naphthylic carbons (n in **36**) of the Na^+ complexes are shifted the furthest downfield, those of the Cs^+ complexes are shifted furthest upfield and the K^+ and Rb^+ species provide a smooth transition between the extremes. Similar trends can be observed for the other carbons. These trends are explained in terms of a regular cation-dependent trend, arising from the location of the cation in the ring, field effects of the cation and localized solvent effects. Deviations from these

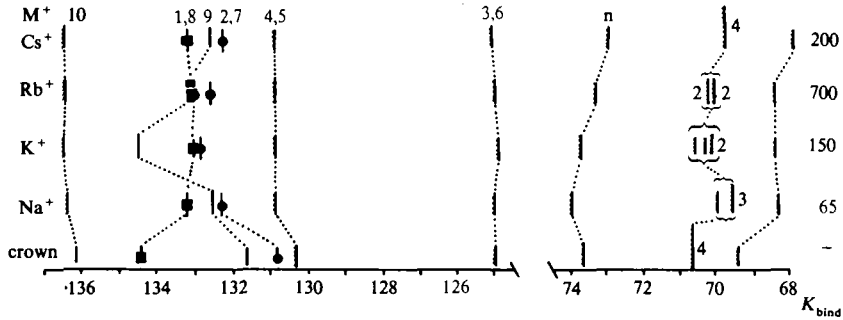


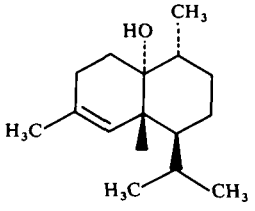
FIGURE 3. Limiting ^{13}C NMR chemical shifts (ppm) for 1,8-naphtho-21-crown-6 and alkali metal ion complexes. Reproduced by permission from Reference 159.

trends were interpreted in terms of specific conformational differences. If this occurs near the naphthalene, its chemical shifts showed a great deviation; if the conformational difference occurred at a distance from the naphthalene, the naphthalene chemical shifts only changed a little. In general the Na^+ ion provided the largest conformational differences.

Information about the structure and motion of crown ether complexes can also be obtained from NMR relaxation-time measurements. A study of the relaxation times for a series of cryptands and cryptates[160] revealed that, within a molecule, the T_1 values were essentially identical, indicating that all molecular motion is isotropic. NOE factors show the relaxation mechanism to be predominantly dipolar. In those cases where the cation does not fit the ligand precisely, the anion and solvent remain in contact with the cation leading to an increase in correlation time and shorter T_1. Where the cation fits the ligand, the T_1 values remain unaltered or increase because of ligand compression and desolvation.

Dynamic NOE experiments on the potassium complex of 18-crown-6 again demonstrate the dominance of the dipole–dipole mechanism for carbon-13 relaxation[37]. The carbon-13 relaxation times of a range of crown ether complexes were shown to be shorter in the complexes than in the free ethers and decrease as the size of the complex and cation increases[161]. This arises from the slowing of the overall reorientation and the loss of segmental motion in the ring.

Europium shift reagents complex to alcohols and ethers enabling extra structural information to be obtained. Plotting the proton chemical shifts against $Eu(dpm)_3$ concentration gives the relative shift effect, known as DEu values, which reflects how far the nucleus in question is from the shift reagent. Calculations of DEu values for potential candidates enables a likely structure to be proposed. Many structures have been determined in this way such as that of cubenol, **37**, and epicubenol, **38**, two sesequiterpene alcohols from the wood of *Athrotaxis selaginoides* Don[162].



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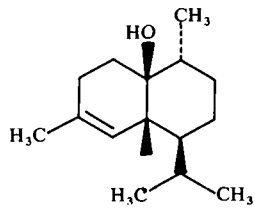

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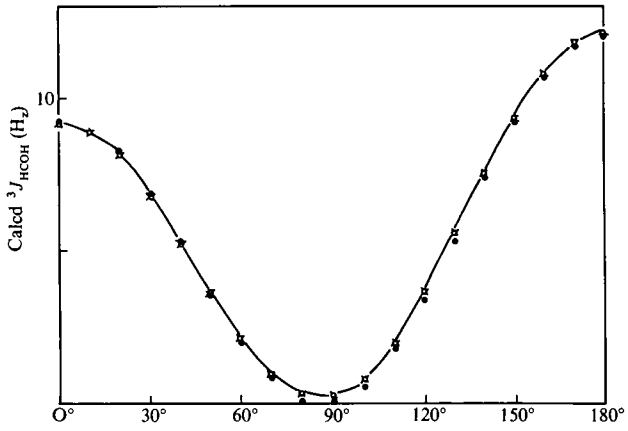
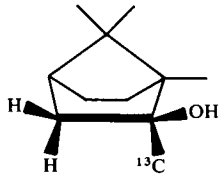


FIGURE 4. Dependence upon the dihedral angle θ of the values of $^3J_{HCOH}$. Reproduced from Reference 163 by permission of Elsevier Science Publishers BV.

4. Coupling constants

In this section we shall limit the discussion of coupling constants to those solely associated with the OX group, for example, H—O—C—H. Fast exchange of the proton in OH groups often leads to a loss of coupling constant information. However, when present, important structural and conformational information can be obtained. Empirical Karplus-type relationships between $^3J_{HCOH}$ and the dihedral angle θ have been presented, using both an empirical and a calculated approach (Figure 4)[163].

Vicinal ^{13}C—H coupling constants also provide conformational information. Karplus-type relationships have been determined for $^3J^{13}$C—C—C—H in alcohols



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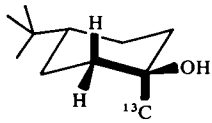


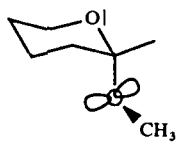
(40)

such as **39** and **40**. The best fit equation is:

$$^3J(\text{C—H}) = 3.09 - 0.38\cos(\phi - 5.53) + 2.57\cos 2(\phi - 5.53)$$

The phase shift of 5.53 is a result of the orientation of the hydroxyl group with respect to the C—H bond[164].

Such coupling constant data have been used to determine the conformational preference in solution of 2-methoxytetrahydropyrans[165]. The axial (**41**) and equatorial (**42**) conformations of such compounds can each assume three staggered rotamers with respect to rotation about the exocyclic C_2—O bond. $^3J_{CH}$ (CH_3—O—C2—H), $^3J_{CC}$(CH_3—O—C2—C3) and $^4J_{CH}$(CH_3—O—C—C—H) coupling constants have been measured and show that **41b** and **42b** are the preferred rotamers. With four-bond coupling, two dihedral angles are involved and the Karplus-like analysis shows the



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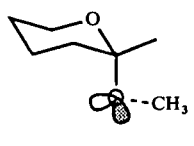
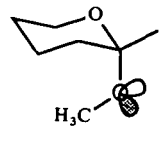
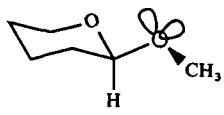


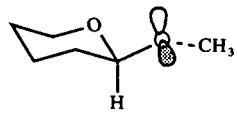
(41b)



(41c)



(42a)



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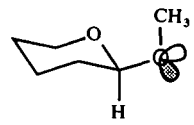


(42c)

maximum values occurring for a 'W' geometry in which both dihedral angles are about 180°. Nuclear Overhauser enhancement experiments were used to back up the conclusions.

B. Oxygen-17 NMR of Alcohols, Ethers and Peroxides

A review covering the oxygen-17 NMR of alcohols, ethers and their derivatives has recently appeared[166]. Table 18 shows some of the nuclear magnetic resonance parameters of the oxygen-17 nucleus[167]. Although oxygen sensitivity is good, the poor receptivity arises from the very low natural abundance of this isotope. Nevertheless, recent developments in hardware and techniques have allowed oxygen-17 NMR to be carried out in a more routine manner. Oxygen-17 has an appreciable electric quadrupole moment; this leads to very short relaxation times. Thus it is possible to employ acquisition times of 5–30 ms, allowing the accumulation of 10^4–10^6 scans in times not much longer than those used for recording carbon-13 NMR spectra. In cases where oxygen-17 enriched samples can be synthesized, the signal-to-noise ratio can be extensively improved, as shown in Figure 5[168]. The oxygen-17 chemical shift ranges for different X—O bonds is

TABLE 18. ^{17}O magnetic properties and nuclear magnetic resonance parameters

Property		Units
Spin number	5/2	
Nuclear magnetic moment	−1.893997	nuclear magneton
Magnetogyric ratio	−3.628	radian sec^{-1} $tessla^{-1}$
Resonance frequency (at 2.114 tessla)	12.2	MHz
Chemical shift range	>1500	ppm
Quadrupole moment	-0.0263×10^{-24}	electron cm^2
Nuclear quadrupole coupling		Mhz
Constant range	−10 to +14	
Relaxation times	<0.2	sec
Natural abundance	0.037	%
Relative sensitivity per nucleus ($H = 1$)	22.9×10^{-2}	
Relative sensitivity at natural abundance ($H = 1$) (Receptivity)	1.1×10^{-5}	

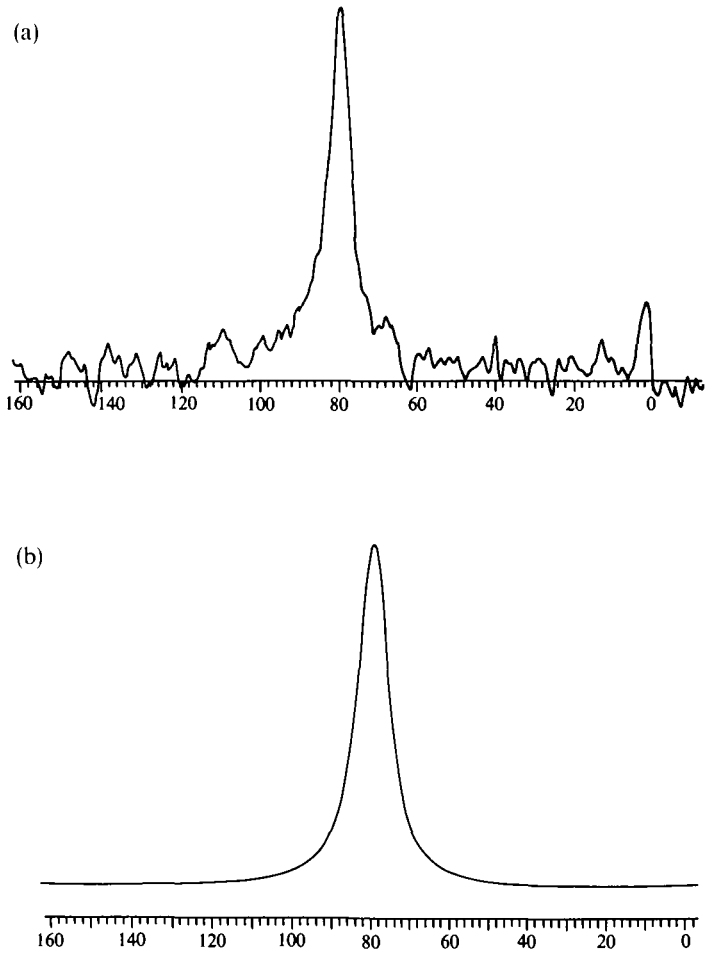


FIGURE 5. ^{17}O NMR spectra for phenols at 40.660 MHz. There were 29,000 transients and 300 Hz line broadening was applied: (a) natural abundance; (b) ^{17}O enriched phenol. Reproduced by permission from Reference 168.

shown in Figure 6. Here the oxygen in water is given a chemical shift of zero and the chemical shift of a compound in ppm calculated in the usual way. Oxygen-17 enriched water is readily available as are acetone and nitromethane, which can be used as reference and the chemical shift determined using the formulae:

$$\delta_{(H_2O)} = \delta_{(CH_3NO_2)} + 605 \text{ ppm}$$

$$\delta_{(H_2O)} = \delta_{((CH_3)_2CO)} + 569 \text{ ppm}$$

As Figure 6 shows, the chemical shift range is quite large with ethers and alcohols having a range of -50 to 200 ppm; peroxides come at a lower field, about 180 to 320 ppm. The wide range of chemical shift values available for oxygen-17 suggests it can provide a great deal of structural information; however, we must also take line width into account.

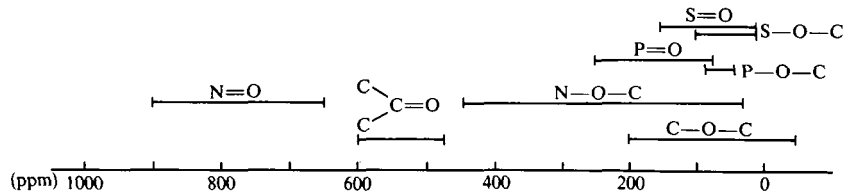


FIGURE 6. ^{17}O chemical shift ranges for different X—O bonds. Note the considerable shift of C=O or N=O with respect to C—O— and N—O—. Reproduced from Reference 167 by permission of Springer-Verlag.

Oxygen-17 has substantial line broadening because it has an appreciable electric quadrupole moment. The amount of information available from chemical shift data is given approximately by the chemical shift range divided by the spectral line width. The typical ranges of chemical shifts for proton, carbon-13 and oxygen-17 can be taken as 0.8, 4 and 8 kHz and the line widths are approximately 1, 1 and 100 Hz, respectively. The capacity of information from chemical shift data are thus 800, 4000 and 80, respectively.

As with carbon, oxygen chemical shifts can be calculated using an empirical increment system. A good linear correlation exists between the oxygen-17 chemical shifts for ROH and the carbon-13 chemical shifts for RCH_3[169]. An equation of the form:

$$\delta(^{17}OH) = 3.83 \times \delta(^{13}CH_3) - 49.3\,\text{ppm}$$

can be used to predict the chemical shift to within about 3 ppm. This type of correlation suggests that the structural aspects that are important in determining the carbon-13 chemical shift of RCH_3 are also critical for the oxygen-17 chemical shifts of ROH. However, the OH group is almost four times as sensitive to these effects. A similar correlation exists for ethers[170]. In this case the equation for the correlation is:

$$\delta(^{17}ROR') = 2.96 \times \delta(^{13}RCH_2R') - 93.6\,\text{ppm}$$

In general, methyl substitution on oxygen leads to an upfield shift as seen in the series water, 0 ppm, methanol, − 38 ppm and dimethyl ether, − 52.5 ppm. In fact this is true irrespective of the nature of the alcohol. This effect is in the opposite direction to that observed in carbon-13 NMR. This has been rationalized in terms of the overriding electrostatic effect of the $C^{\delta+}—O^{\delta-}$ bond dipole which leads to an upfield shift for the oxygen. No such dipole is seen in C—C bonds, so other factors lead to the downfield shift[171].

Methanol has a chemical shift of − 38. Ethanol has a chemical shift of 5.9, which is well within the range of primary alcohols (− 2 to 10 ppm). Propan-2-ol has a chemical shift of 39.8 (secondary alcohols have a range of 30 to 40 ppm) whereas *t*-butyl alcohol has a chemical shift of 62.3 (tertiary alcohols fall within 55–70 ppm). This shows the effect of methyl substitution at the α carbon. Each methyl group has a deshielding effect which is attenuated on successive substitution, as seen in carbon-13 NMR. This is also mirrored in the ether and ester series. The effect of substitution on the β carbon is shown in Scheme 1.

$$\underset{}{CH_3CH_2OH} \xrightarrow[-6\,\text{ppm}]{} \underset{}{CH_3CH_2CH_2OH} \xrightarrow[-2\,\text{ppm}]{} \underset{}{(CH_3)_2CHCH_2OH} \xrightarrow[-5\,\text{ppm}]{} \underset{}{(CH_3)_3CCH_2OH}$$

SCHEME 1. Change in chemical shift on β substitution

Successive substitution causes an upfield shift with the first and third prompting a

larger change than the second. This is analogous to the well-known γ effect in carbon-13 NMR, which is traditionally rationalized in terms of 1,4-*gauche* interactions.

Studies of the factors affecting the oxygen-17 chemical shift have revealed a number of interesting facets. Taft σ^* values suggest that the electron density at the oxygen atom increases as we go from methanol via ethanol and 2-propanol to *t*-butyl alcohol, yet the oxygen-17 chemical shifts show that the screening decreases in this series. This is not compatible with the diamagnetic term dominating the oxygen-17 chemical shifts and so the paramagnetic term must be the dominant factor. However, Kintzinger points out that the diamagnetic contribution is not always as constant as is often claimed[167]. As we saw earlier, the shielding sequence water > methanol > dimethyl ether arises mainly from an increase in the diamagnetic contribution from the C—O dipole. Nevertheless, most discussions of the origin of shielding in oxygen-17 NMR focus on the paramagnetic contribution. Pople's theory on paramagnetic screening suggests the nuclear shielding is given by:

$$\sigma_p = K(\Delta E)^{-1} \langle r^{-3} \rangle_{2p} \Sigma_{B \neq A} Q_{AB} \tag{24}$$

where ΔE is the mean or effective excitation energy, which is often taken from electronic spectra, $\langle r^{-3} \rangle_{2p}$ is the inverse cube of the $2p$ electron radius on oxygen and can be calculated, Q_{AB} is an orbital term defined in terms of the elements of the charge density and bond order matrix and, again, can be calculated using MO techniques such as INDO.

Correlations between $(\Delta E)^{-1}$ and chemical shift have been observed. A reasonably good relationship is found between the oxygen-17 chemical shifts and the ionization potentials of a series of alcohols[172]. It was also pointed out that since the HOMO levels of the oxygen non-bonding electrons are more sensitive to structural change than the terminating MO levels, in this case the HOMO energy levels will mainly determine the chemical shift. A similar argument was used to explain the good correlation between the oxygen-17 chemical shift and the O—H stretching frequency in a range of alcohols[173]. The least-squares correlation equation is:

$$\delta(^{17}\text{ROH}) = -2.7316 \times \nu(\text{ROH}) + 9939.1$$

with a correlation coefficient of 0.992. CNDO calculations show that in the model compounds chosen the increase in the instability of the highest occupied orbital, which is mainly occupied by the non-bonding pair of the oxygen atom and which determines the paramagnetic shielding, is proportional to the increase in the non-bonding interaction to the oxygen atom. The non-bonding interaction between the OH group and other parts of the molecule is more important than the inductive effect in determining the value of ν(ROH). A similar correlation exists between ν(ROH) and the oxygen-17 chemical shift of the corresponding ether; however, here the aliphatic and phenol series lie on different lines. This was attributed to the fact that, because of conjugation between the benzene ring and the $2p$ non-bonding electrons of the oxygen atom in the methoxy group, its oxygen atom is subjected to less α-methyl effect than the oxygen atom of $ROCH_3$ which have no conjugation.

The corelation between the carbon-13 chemical shifts and the oxygen-17 chemical shifts discussed earlier can also be explained using equation 24, since the chemical shifts of both nuclei are governed by the paramagnetic screening. The larger response of oxygen-17, and thus the constant of proportionality, can be related to the difference between the orbital expansion term $\langle r^{-3} \rangle_{2p}$ for the two nuclei.

Figure 7 shows a plot of oxygen-17 chemical shift versus electronegativity of substituents[174]. Changes in the chemical shift appear to be caused primarily by alterations in the electron density at oxygen. However, the paramagnetic screening is still dominant here, since increasing the electronegativity effects the mean inverse cube of the $2p$ electron radius $\langle r^{-3} \rangle_{2p}$ and the orbital term Q_{AB}.

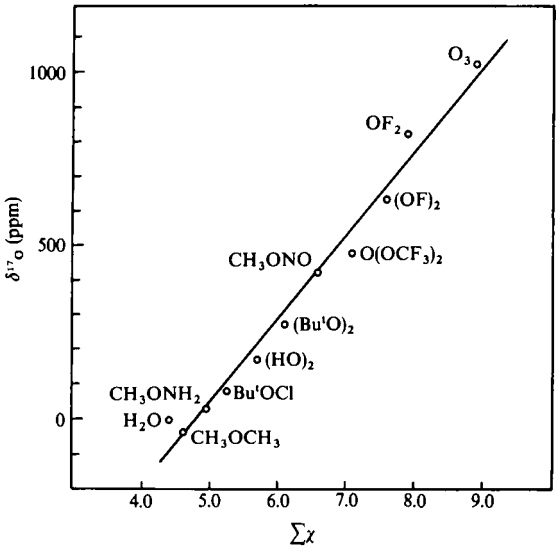
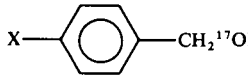


FIGURE 7. Plots of ^{17}O NMR shifts vs. the sum of the electronegativities for dicoordinated oxygen compounds. Reproduced by permission of the Chemical Society of Japan from Reference 174.

The calculation of the charge density on oxygen for a series of aliphatic ethers shows that any gain in electronic charge at the oxygen atom is accompanied by a downfield oxygen-17 shift, largely because of a more negative paramagnetic contribution[175]. This trend is illustrated by the oxygen-17 chemical shifts of a series of benzyl alcohols, **43**[176].



$X = p\text{-}NO_2, p\text{-}CN, p\text{-}CF_3, p\text{-}Cl, H, p\text{-}F, p\text{-}CH_3, p\text{-}OCH_3, p\text{-}N(CH_3)_2$

(43)

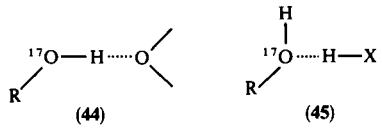
A dual substituent parameter correlation of the chemical shifts gives the equation:

$$\text{(Substituent chemical shift) } \Delta\delta(^{17}OH) = -6.71\sigma_I - 8.56\sigma_R$$

Electron-donating substituents increase the charge density on the oxygen leading to a downfield shift (deshielding) whereas electron-withdrawing substituents decrease the charge on oxygen so there is an upfield shift. An oxygen-17 study of polyfluorinated alcohols and ethers suggests substitution of fluorine at the γ position has no effect on chemical shift, whereas substitution at the β position changes the chemical shift by -10 ppm per fluorine and substitution at the α position changes the chemical shift by 36 ppm per fluorine[177]. This reflects the trends observed in the carbon-13 of polyfluorinated alkanes. However, the effect of α substitution is much larger than expected and an explanation may require a consideration of all three terms in the Pople approximation (equation 24).

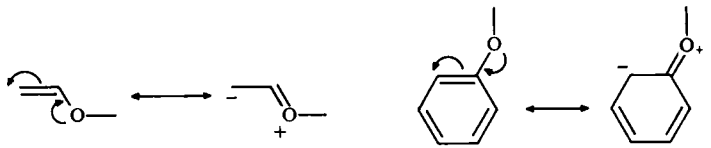
Oxygen-17 NMR studies of hydrogen bonding in water and alcohols suggest that breaking a R—O—H$\cdots$O bond, **44**, leads to an upfield shift of 12 ppm, whereas breaking a R—O$\cdots$H—X bond, **45**, leads to an upfield shift of 6 ppm[178].Complexation of crown ethers and cryptands with metal ions leads to an upfield shift of around

10 ppm[179]. These shifts are mainly electrostatic in origin and are created by the electric field generated by the cations. Changes in line widths were shown to arise from overall reorientation of the ligand and from local motions.



(44) (45)

Interactions between the p orbital on the oxygen and a π system, as in aryl or vinyl ethers, leads to substantial changes in the oxygen-17 chemical shift.



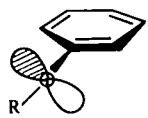
It is proposed that such conjugation leads to an increase in the $(\Delta E)^{-1}$ term and a decrease in the electron density on oxygen. Both of these lead to a downfield shift, as is observed[180].

An alternative explanation has been put forward[181]. Calculation of ΔE in equation 24, from ionization potentials of a range of vinyl and aryl ethers, show they do not seem to vary significantly, even when compared to alkyl ethers. So it was suggested that this factor does not play a significant role in determining the oxygen-17 chemical shift. The $\langle r^{-3}\rangle_{2p}$ term depends upon the charge on the oxygen which in turn depends on the extent of p,π conjugation. Calculations of the charges on oxygen q_π for a series of vinyl and aryl ethers show the following correlation;

$$\delta(^{17}\text{OR}) = 12 + 1229q_\pi$$

The slope suggests that the chemical shift increases by about 1200 ppm per unit of charge.

Typical values of the oxygen-17 chemical shift in aryl and vinyl ethers are given in Table 19, which confirms that p,π overlap leads to an increase in the oxygen-17 chemical shift by between 50–220 ppm compared to the corresponding saturated ether. In a series of alkyl vinyl ethers, progressive substitution of the alkyl group, from methyl to *t*-butyl, follows the trends observed with dialkyl ethers. The same trend is observed for alkyl phenyl ethers from methyl to *iso*-propyl. However, on going to *t*-butylphenyl ether, the

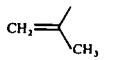


change in chemical shift is less than expected. This is attributed to steric hindrance to p,π interactions in the PhO fragment. Calculations based on a comparison of the observed and expected chemical shift changes suggest that in the *t*-butyl phenyl ether, the p orbital on oxygen is approximately 45° to the aromatic π system.

Oxygen-17 chemical shifts of polyfluoroethers suggest that the RCF_2 ether reduces the availability of the oxygen non-bonding pair for p,π conjugation. Thus the corresponding vinyl and aryl ethers do not show such a large increase in chemical shift compared to the saturated ether.

Studies of substituent effects in methyl aryl ethers show that the oxygen-17 chemical

TABLE 19. Oxygen-17 chemical shifts of some aryl and vinyl ethers $R^1O\,R^2$

R^1	R^2	$\delta^{17}O$	Reference
Ph	CH_3	49	181
Ph	CH_2CH_3	78	181
Ph	$CH_2CH_2CH_3$	75	181
Ph	$CH(CH_3)_2$	103	181
Ph	$C(CH_3)_3$	103	181
p-An	CH_3	38	182
p-Tol	CH_3	44	182
p-BrC_6H_4	CH_3	51	182
p-$NO_2C_6H_4$	CH_3	67	182
Ph	Ph	109	181
CH_2=CH	CH_3	59	181
CH_2—CH	CH_2CH_3	88	181
CH_2=CH	$CH_2CH_2CH_3$	84	181
CH_2=CH	$CH_2CH_2CH_2CH_3$	83	181
CH_2=CH	$CH(CH_3)_2$	107	181
CH_2=CH	$C(CH_3)_3$	117	181
CH_2=CH	Ph	125	181
CH_2=CH	*p*-An	120	181
CH_2=CH	*p*-$NO_2C_6H_4$	139	181
CHCl=CH	Ph	113	181
CCl_2=CH	Ph	119	181
CH_2=CH	CH=CH_2	129	181
CH_3CH=CH	CH_2CH_3	70	181
	CH_2CH_3	98	181
	—	59	181
	—	241	181

shift correlates well with substituent parameters:

$$\delta(^{17}OR) = 47.6 + 17.1\sigma_I + 30.4\sigma_R$$

A similar plot has been observed against σ^-[182]. This correlation suggests that an increase in the oxygen electron density leads to a decrease in the chemical shift, the opposite trend to that observed with aliphatic alcohols and ethers. In such cases a full examination of the variation of all the terms in equation 24 with substituent is required. A correlation has been demonstrated between the oxygen-17 chemical shift of aromatic ethers and alcohols and the carbon-13 chemical shift of the phenyl C-1 position[168].

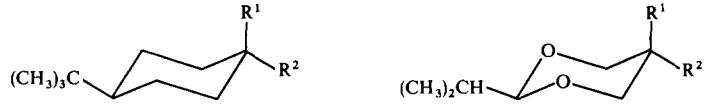
Polyfluorinated aryl ethers have oxygen-17 chemical shifts at a higher field compared with the corresponding hydrocarbon analogues[183]. This was explained in terms of a decreased conjugation between the non-bonding electron pair of the oxygen and the polyfluorinated benzene ring.

Whilst substitution of one *ortho* hydrogen in anisole by a methyl group only changes the chemical shift by 1 ppm, substitution of both *ortho* hydrogens decreases the chemical shift by 29 ppm. Such a change is indicative of steric hindrance preventing conjugation

of the p orbital on oxygen and the aromatic π system. A study of 19 methoxy aromatic compounds confirms this. The oxygen-17 signals of crowded methoxy groups (two *ortho* neighbours) are shifted upfield from the signals of uncrowded methoxy groups[184].

Oxygen-17 studies of cyclopropyl ethers do not reveal any σ,p conjugation, that is the cyclopropyl ring shows no p-acceptor abilities towards non-bonding electrons on oxygen.

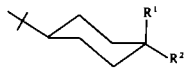
Eliel has examined the oxygen-17 chemical shifts of axial and equatorial OH and OR groups[171]. In the cyclohexane system the equatorial hydroxyl or methoxyl groups are



$R^1 = H$, $R^2 = OH$ or $R^1 = OH$, $R^2 = H$

downfield of axial counterparts by about 12 ppm. This behaviour is reversed in the series of 5-hydroxy- or 5-methoxy- 1,3-dioxanes, where the equatorial group resonates about 8 ppm upfield of the axial group. The corresponding 1,3-dithianes follow the cyclohexane series[185]. Again, all this mirrors the behaviour in the carbon analogues except that the carbon-13 chemical shift change is attenuated. It is proposed that equatorial OH or OR are upfield of axial groups in 1,3-dioxanes because in the equatorial form the oxygens are antiperiplanar. This upfield shift has been observed with first-row heteroatoms X in unsubstituted chains XCH_2CH_2Y, where Y is the observed nucleus. Eliel also demonstrated that steric compression of an axial OH with an axial methyl leads to a downfield shift of 7 ppm from its 'normal' value. Table 20 shows the effect of substitution

TABLE 20. Effect of substitution at the α carbon on the ^{17}O chemical shift in compounds of the type

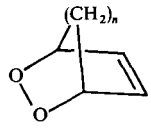


	R^1	R^2	$\delta^{17}O$	Effect of substitution (downfield)	Difference between axial and equatorial substituent effects
Substituent axial	H—	OH	38.0	0	
	CH_3—	OH	72.2	34.2	—
	C_6H_5—	OH	83.4	45.4	—
	$C_6H_5CH_2$—	OH	62.9	24.9	—
	HC≡C—	OH	75.3	37.3	—
	H—	OCH_3	5.9	0	—
	CH_3—	OCH_3	25.1	19.2	—
Substituent equatorial	OH	H	26.5	0	—
	OH	CH_3	49.1	22.6	11.6
	OH	C_6H_5	46.6	20.1	25.3
	OH	$C_6H_5CH_2$	41.7	15.2	9.7
	OH	HC≡C—	48.6	22.1	15.2
	OCH_3	H	−6.9	0	—
	OCH_3	CH_3	3.8	10.7	8.5

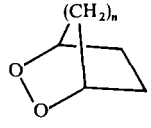
at the α carbon by various alkyl and aryl substituents[185]. Substitution by a methyl group in the methoxy ethers is 12–15 ppm less than in the corresponding alcohols. The effect of substitution of an equatorial methyl, phenyl or ethynyl group at the α carbon on the oxygen-17 chemical shift of the alcohols is about the same. However, this is not observed for axial substituents, where the effects are larger for the unsaturated groups. As a result the differences between the axial and equatorial series are also largest for these substituents.

An examination of conformational effects on oxygen-17 chemical shifts in cyclic aromatic ethers revealed the shifts to be sensitive to structural variations and were dependent upon both electronic and conformational effects; however, no quantitative relationship between chemical shift and geometric parameters was established[186].

Figure 7 showed that since each oxygen in peroxides is linked to an electronegative atom, they will resonate at very low field. Table 21 lists some typical values, ranging from 180 to 320. A systematic investigation of a range of dialkyl peroxides, **46–49**, shows



(46)



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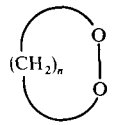
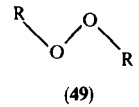


(48)



(49)

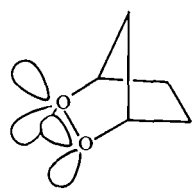
that chemical shifts are insensitive to solvent. To examine the origin of the oxygen-17 chemical shifts of peroxides, they were compared to the carbon-13 chemical shift of the corresponding carbon atom in a molecule where each O is replaced by a CH_2 group. An excellent linear correlation was found for the bicyclic secondary dialkyl peroxides which obey the eqution:

$$\delta(^{17}\text{ROOR}') = 12.4 \times \delta(^{13}\text{RCH}_2\text{CH}_2\text{R}') - 68.7\,\text{ppm}$$

A remarkably different correlation was found for the acyclic dialkyl peroxides:

$$\delta(^{17}\text{ROOR}') = 1.00 \times \delta(^{13}\text{RCH}_2\text{CH}_2\text{R}') - 220\,\text{ppm}$$

These correlations suggest that the chemical shift of cyclic peroxides is four times more sensitive to substitution than ethers, whereas acyclic peroxides are three times less sensitive than ethers. Such correlations also demonstrate that in both cases the paramagnetic term dominates the screening constant. The lack of any correlation between the chemical shift of the bicyclic peroxides and their ionization potential suggests that some factor other than net atomic charge seems to be predominant in determining the chemical shift. The difference in response factors to substitution between the bicyclic and acyclic peroxides was attributed to a conformational effect rather than ring strain. Coplanar non-bonding pairs in **50** may give rise to its extraordinarily low-field position.



(50)

Usually, spin–spin coupling constants in alcohols and ethers are obscured by the quadrupolar broadening. One-bond coupling constants have been reported for water

TABLE 21. Oxygen-17 chemical shift values for some peroxides

Peroxide	Chemical shift	Reference
H—O—O—H	180	187
CH_3CH_2—O—O—CH_2—CH_3	253	188
$CH_3(CH_2)_2$—O—O—$(CH_2)_2$—CH_3	249	188
$(CH_3)_2CH$—O—O—$CH(CH_3)_2$	255	188
$(CH_3)_3C$—O—O—$C(CH_3)_3$	260	188
$(CH_3)_3C$—O^x—O^y—H		
in H_2O	$x = 246$, $y = 206$	187
in hexane	$x = 249$, $y = 206$	187
	280	188
	254	188
	303	188
	250	188
	259	188
	232	188

(82 Hz)[189], methanol (85.5 Hz)[190] and ethanol (83.6 Hz)[190]. Two bond couplings have been determined by line shape analysis of the oxygen-17 NMR spectrum for oxirane (6 Hz), oxetane (5 Hz) and ethyl vinyl ether (16.5 Hz)[191].

Oxygen-17 NMR of alcohols and ethers has been used in organic chemistry for more than just structure elucidation. It has been used to identify the position of labels in mechanistic studies using oxygen-17 labelled compounds[192,193]. It has also been used to determine the oxygen functionalities in synthetic fuels[194] and to assess the ageing process in the Japanese spirit Awamori[195]!

III. REFERENCES

1. M. C. R. Symons, *J. Chem. Soc., Perkin Trans. 2*, 1618 (1974).
2. S. Weiner and G. S. Hammond, *J. Am. Chem. Soc.*, **91**, 2182 (1969).
3. M. C. R. Symons, *J. Am. Chem. Soc.*, **91**, 5924 (1969).
4. W. A. Bernhard, D. M. Close, J. Huttermann and H. Zehner, *J. Chem. Phys.*, **67**, 1211 (1977).
5. H. C. Box and E. E. Budzinski, *J. Chem. Phys.*, **62**, 197 (1975).
6. J. Y. Lee and H. C. Box, *J. Chem. Phys.*, **59**, 2509 (1973).
7. M. Iwasaki and K. Toriyama, *J. Am. Chem. Soc.*, **100**, 1964 (1978).
8. J. K. Becconsall, S. Clough, and G. Scott, *Trans. Faraday Soc.*, **56**, 459 (1960).
9. N. M. Atherton, A. J. Blackhurst and I. P. Cook, *Trans. Faraday Soc.*, **67**, 2510 (1971).

10. F. Shimoda, T. Hanafusa, F. Nemoto, K. Mukai and K. Ishizu, *Bull. Chem. Soc. Jpn.*, **52**, 3743 (1979).
11. K. Mukai, N. Tsuzuki, K. Ishizu, S. Ouchi and K. Fukuzawa, *Chem. Phys. Lipids*, **29**, 129 (1981).
12. K. Mukai, C. Morimoto and K. Ishizu, *Tetrahedron Lett.*, **24**, 5099 (1983).
13. T. J. Stone and W. A. Waters, *Proc. Chem. Soc.*, 253 (1962).
14. T. J. Stone and W. A. Waters, *J. Chem. Soc.*, 213 (1964).
15. W. T. Dixon, M. Moghimi and D. Murphy, *J. Chem. Soc., Faraday Trans. 2*, **70**, 1713 (1974).
16. W. T. Dixon and R. O. C. Norman, *J. Chem. Soc.*, 4857 (1964).
17. G. W. Burton, T. Doba, E. J. Gabe, L. Hughes, F. L. Lee, L. Prasad and K. U. Ingold, *J. Am. Chem. Soc.*, **107**, 7053 (1985).
18. H. A. Zahalka, B. Robillard, L. Hughes, J. Lusztyk, G. W. Burton, E. G. Janzen, Y. Kotake and K. U. Ingold, *J. Org. Chem.*, **53**, 3739 (1988).
19. M. Matsuo, S. Matsumoto and T. Ozawa, *Org. Magn. Res.*, **21**, 261 (1983).
20. J. Tsuchiya, E. Niki and Y. Kamiya, *Bull. Chem. Soc. Jpn.*, **56**, 229 (1983).
21. M. J. Davies, L. G. Forni and R. L. Willson, *Biochem. J.*, **255**, 513 (1988).
22. P. Neta and R. W. Fessenden, *J. Phys. Chem.*, **78**, 523 (1974).
23. E. Bascetta, F. D. Gunstone and J. C. Walton, *Chem. Phys. Lipids*, **33**, 207 (1983).
24. T. Momose, H. Nakatsuji and T. Shida, *J. Chem. Phys.*, **89**, 4185 (1988).
25. G. R. Buettner, *Free Rad. Biol. Med.*, **3**, 259 (1987).
26. M. J. Davies and T. F. Slater, *Biochem. J.*, **245**, 167 (1987).
27. D. L. Haire, U. W. Oehler, P. H. Krygsman and E. G. Janzen, *J. Org. Chem.*, **53**, 4535 (1988).
28. J. A. Howard and J. C. Tait, *Can. J. Chem.*, **56**, 176 (1978).
29. E. G. Janzen, P. H. Krygsman, D. A. Lindsay and D. L. Haire, *J. Am. Chem. Soc.*, **112**, 8279 (1990).
30. B. C. Gilbert, H. A. H. Laue, R. O. C. Norman and R. C. Sealy, *J. Chem. Soc., Perkin Trans. 2*, 1040 (1976).
31. F. P. Sargent and E. M. Gardy, *J. Phys. Chem.*, **80**, 854 (1976).
32. C. Chatgilialoglu, J. A. Howard and K. U. Ingold, *J. Org. Chem.*, **47**, 4361 (1982).
33. E. G. Janzen and C. A. Evans, *J. Am. Chem. Soc.*, **95**, 8205 (1973).
34. M. J. Davies and T. F. Slater, *Biochem. J.*, **240**, 789 (1986).
35. E. G. Janzen, G. A. Coulter, U. M. Oehler and J. P. Bergsma, *Can. J. Chem.*, **60**, 2725 (1982).
36. E. G. Janzen and G. A. Coulter, *Tetrahedron Lett.*, **22**, 615 (1981).
37. K. M. Schaich and D. C. Borg, *Free Rad. Res. Commun.*, **9**, 267 (1990).
38. W. T. Dixon and D. Murphy, *J. Chem. Soc., Farady Trans. 2*, **72**, 1221 (1976).
39. A. B. Barabas, W. F. Forbes and P. D. Sullivan, *Can. J. Chem.*, **45**, 267 (1967).
40. P. D. Sullivan, J. R. Bolton and W. E. Geiger, Jr., *J. Am. Chem. Soc.*, **92**, 4176 (1970).
41. F. Nemoto, N. Tsuzuki, K. Mukai and K. Ishizu, *J. Phys. Chem.*, **85**, 2450 (1981).
42. P. D. Sullivan and J. R. Bolton, *J. Am. Chem. Soc.*, **90**, 5366 (1968).
43. P. D. Sullivan, *J. Am. Chem. Soc.*, **89**, 4294 (1967).
44. J. T. Wang and F. Williams, *J. Am. Chem. Soc.*, **103**, 6994 (1981).
45. C. J. Rhodes and M. C. R. Symons, *J. Chem. Soc., Faraday Trans. 1*, **84**, 4501 (1988).
46. M. C. R. Symons and B. W. Wren, *J. Chem. Soc., Perkin Trans. 2*, 511 (1984).
47. D. N. Ramakrishna Rao and M. C. R. Symons, *J. Chem. Soc., Perkin Trans. 2*, 991 (1985).
48. G. Behrens, E. Bothe, G. Koltzenberg and D. Schulte-Frohlinde, *J. Chem. Soc., Perkin Trans. 2*, 883 (1980).
49. A. J. Bloodworth, A. G. Davies and S. Hay-Motherwell, *J. Chem. Soc., Chem. Commun.*, 862 (1988).
50. P. O'Neill, S. Steenken and D. Schulte-Frohlinde, *J. Phys. Chem.*, **79**, 2773 (1975).
51. W. T. Dixon and D. Murphy, *J. Chem. Soc., Perkin Trans. 2*, 1823 (1976).
52. W. F. Forbes, P. D. Sullivan and H. M. Wang, *J. Am. Chem. Soc.*, **89**, 2706 (1967).
53. A. Zweig, W. G. Hodgson and W. H. Jura, *J. Am. Chem. Soc.*, **86**, 4124 (1964).
54. V. N. Belevskii and S. I. Belopushkin, *Dokl. Akad. Nauk SSSR*, **310**, 1138 (1990).
55. H. Kubodera, T. Shida and K. Shimokoshi, *J. Phys. Chem.*, **85**, 2583 (1981).
56. L. D. Snow, J. T. Wang and F. Williams, *J. Am. Chem. Soc.*, **104**, 2062 (1982).
57. M. Matsushita, T. Momose and T. Shida, *J. Chem. Phys.*, **92**, 4749 (1990).
58. W. F. Forbes and P. D. Sullivan, *Can. J. Chem.*, **44**, 1501 (1966).
59. J. K. Brown, D. R. Burnham and N. A. J. Rogers, *Tetrahedron Lett.*, 2621 (1966).

60. J. K. Brown and D. R. Burnham, *Mol. Phys.*, **15**, 173 (1968).
61. R. Gerdil and E. A. C. Lucken, *J. Am. Chem. Soc.*, **87**, 213 (1965).
62. M. C. R. L. R. Lazana, M. L. T. M. B. Franco and B. J. Herold, *J. Am. Chem. Soc.*, **111**, 8640 (1989).
63. P. Maslak and R. D. Guthrie, *J. Am. Chem. Soc.*, **108**, 2628 (1986).
64. K. W. Bowers, in *Radical Ions* (Eds. E. T. Kaiser and L. Kevan), Chap. 5, Wiley, New York, 1968.
65. D. H. Eargle, *J. Org. Chem.*, **28**, 1703 (1963).
66. V. Cerri, M. Boyer and P. Tordo, *Gazz. Chim. Ital.*, **115**, 147 (1985).
67. J. K. Brown, D. R. Burnham and N. A. J. Rogers, *J. Chem. Soc. (B)*, 1149 (1969).
68. A. G. Evans, P. B. Roberts and B. J. Tabner, *J. Chem. Soc. (B)*, 269 (1966).
69. L. Bonazzola, J. P. Michaut and J. Roncin, *J. Phys. Chem.*, **93**, 639 (1989).
70. H. Chandra, D. N. R. Rao and M. C. R. Symons, *J. Chem Res. (S)*, 68 (1983).
71. S. F. Nelson, M. F. Teasley, D. L. Kapp and R. M. Wilson, *J. Org. Chem.*, **49**, 1845 (1984).
72. A. Bassindale and J. Iley, in *The Chemistry of Sulphenic Acids and Their Derivatives* (Ed. S. Patai), Chap. 4, Wiley, Chichester, 1990.
73. J. E. Bennett and R. Summers, *J. Chem. Soc., Faraday Trans. 2*, **69**, 1043 (1973).
74. K. U. Ingold and J. R. Morton, *J. Am. Chem. Soc.*, **86**, 3400 (1964).
75. A. J. Bloodwith, A. G. Davies and R. S. Hay-Motherwell, *J. Chem. Soc., Perkin Trans. 2*, 575 (1988).
76. D. V. Avila, A. G. Davies and I. G. E. Davison, *J. Chem. Soc., Perkin Trans. 2*, 1847 (1988).
77. S. Fukuzumi and Y. Ono, *J. Chem. Soc., Perkin Trans. 2*, 625 (1977).
78. S. Fukuzumi and Y. Ono, *J. Chem. Soc., Perkin Trans. 2*, 622 (1977).
79. B. Kalyanaraman, C. Mottley and R. P. Mason, *J. Biol. Chem.*, **258**, 3855 (1983).
80. P. Neta, R. E. Huei, S. Mosseri, L. V. Shastri, J. P. Mittal, P. Maruthamuthu and S. Steenken, *J. Phys. Chem.*, **93**, 4099 (1989).
81. K. Adamic, K. U. Ingold and J. R. Morton, *J. Am. Chem. Soc.*, **92**, 922 (1970).
82. J. E. Bennett, J. A. Eyre and R. Summers, *J. Chem. Soc., Perkin Trans. 2*, 797 (1974).
83. K. Mach, J. Nováková, V. Hanuš, and Z. Dolejšek. *Collect. Czech. Chem. Commun.*, **51**, 2675 (1986).
84. T. J. Kemp and M. J. Welbourn, *Tetrahedron Lett.*, 87 (1974).
85. Y. Hori, S. Soyama and H. Kashiwabara, *J. Chem. Phys.*, **75**, 1582 (1981).
86. D. Suryanarayana, W. Chamulitrat and L. Kevan, *J. Phys. Chem.*, **86**, 4822 (1982).
87. W. Chamulitrat and L. Kevan, *J. Phys. Chem.*, **88**, 3986 (1984).
88. M. D. Sevilla, D. Becker and M. Yan, *J. Chem. Soc., Faraday Trans.*, **86**, 3279 (1990).
89. C. L. Ayers, E. G. Janzen and F. J. Johnston, *J. Am. Chem. Soc.*, **88**, 2610 (1966).
90. D. J. Carlsson, S. Chmela and J. Lacoste, *Macromolecules*, **23**, 4934 (1990).
91. S. Schlick and B. McGarvey, *J. Phys. Chem.*, **87**, 352 (1983).
92. D. Suryanarayana, L. Kevan and S. Schlick, *J. Am. Chem. Soc.*, **104**, 668 (1982).
93. J. Zhu, W. J. Johnson, C. L. Sevilla, J. W. Herrington and M. D. Sevilla, *J. Phys. Chem.*, **94**, 7185 (1990).
94. J. Yanez, C. L. Sevilla, D. Becker and M. D. Sevilla, *J. Phys. Chem.*, **91**, 487 (1987).
95. D. Becker, J. Yanez, M. D. Sevilla, M. G. Alonso-Amigo and S. Schlick, *J. Phys. Chem.*, **91**, 492 (1987).
96. M. D. Sevilla, M. Yan, D. Becker and S. Gillich, *Free Rad. Res. Commun.*, **6**, 99 (1989).
97. E. Melamud and B. L. Silver, *J. Magn. Reson.*, **14**, 112 (1974).
98. P. W. Atkins and M. C. R. Symons, *The Structure of Inorganic Radicals*, Elsevier, Amsterdam, 1967.
99. B. H. Besler, M. D. Sevilla and P. MacNeille, *J. Phys. Chem.*, **90**, 6446 (1986).
100. S. Schlick and L. Kevan, *J. Phys. Chem.*, **83**, 3424 (1979).
101. L. Kevan and S. Schlick, *J. Phys. Chem.*, **90**, 1998 (1986).
102. M. D. Sevilla, M. Champagne and D. Becker, *J. Phys. Chem.*, **93**, 2653 (1989).
103. W. A. Pryor, S. K. Nuggehalli, K. V. Scherer and D. F. Church, *Chem. Res. Toxicol.*, **3**, 2 (1990).
104. D. Olivier, C. Marachi and M. Che, *J. Chem. Phys.*, **71**, 4688 (1979).
105. M. Che and A. J. Tench, *J. Chem. Phys.*, **64**, 2370 (1976).
106. M. Che and A. J. Tench, *Polymer Lett.*, **13**, 345 (1975).
107. S. Schlick and L. Kevan, *J. Am. Chem. Soc.*, **102**, 4622 (1980).

108. Y. Hori, S. Shimada and H. Kashiwabara, *Polymer*, **18**, 567 (1977).
109. S. Shimada, A. Kotake, Y. Hori and H. Kashiwabara, *Macromolecules*, **17**, 1104 (1984).
110. S. Shimada, Y. Hori and H. Kashiwabara, *Macromolecules*, **18**, 170 (1985).
111. D. Suryanarayana and L. Kevan, *J. Phys. Chem.*, **86**, 2042 (1982).
112. Y. Hori, Y. Makino and H. Kashiwabara, *Polymer*, **25**, 1436 (1984).
113. W. Chamulitrat and R. P. Mason, *J. Biol. Chem.*, **264**, 20968 (1989).
114. M. J. Davies and T. J. Slater, *Biochem. J.*, **240**, 789 (1986).
115. M. J. Davies, *Biochim. Biophys. Acta*, **964**, 28 (1988).
116. G. M. Rosen and E. J. Rauckman, *Mol. Pharmacol.*, **17**, 233 (1980).
117. M. V. Merritt and R. A. Johnson, *J. Am. Chem. Soc.*, **99**, 3713 (1977).
118. N. Ohto, E. Niki and Y. Kamiya, *J. Chem. Soc., Perkin Trans. 2*, 1770 (1977).
119. M. C. R. Symons, E. Albano, T. F. Slater and A. Tomas, *J. Chem. Soc., Faraday Trans. 1*, **78**, 2205 (1982).
120. T. Yamada, E. Niki, S. Yokoi, J. Tsuchiya, Y. Yamamoto and Y. Kamiya, *Chem. Phys. Lipids*, **36**, 189 (1984).
121. E. Niki, S. Yokoi, J. Tsuchiya and Y. Kamiya, *J. Am. Chem. Soc.*, **105**, 1498 (1983).
122. R. Konaka, S. Terabe, T. Mizuta and S. Sakata, *Can. J. Chem.*, **60**, 1532 (1982).
123. T. M. Lachocki, S. K. Huggehalli, K. V. Scherer, D. F. Church and W. A. Pryor, *Chem. Res. Toxicol.*, **2**, 174 (1989).
124. E. G. Janzen, C. A. Evans and J. I. Liu, *J. Magn. Reson.*, **9**, 513 (1973).
125. K. M. Schaich and D. C. Borg, *Lipids*, **23**, 570 (1988).
126. T. Matsui, H. C. Ko and L. G. Hepler, *Can. J. Chem.*, **52**, 2906 (1974).
127. M. Sjostrom and S. Wold, *Chem. Scr.*, **9**, 200 (1976).
128. R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 3146 (1963).
129. A. I. Rakhimov and A. V. Baklanov, *Zh. Org. Khim.*, **16**, 551 (1980).
130. S. Clementi and P. Linda, *J. Chem. Soc., Perkin Trans. 2*, 1887 (1973).
131. L. B. Jones and V. K. Jones, *Tetrahedron Lett.*, 1493 (1966).
132. C. J. Pouchert, *The Aldrich Library of NMR Spectra*, Aldrich Chemical Company, Milwaukee, 1983.
133. W. Bremser, B. Franke and H. Wagner, *Chemical Shift Ranges in Carbon-13 NMR Spectroscopy*, Verlag Chemie, Weinheim, 1982.
134. G. A. Olah, D. G. Parker, N. Yoneda and F. Pelizza, *J. Am. Chem. Soc.*, **98**, 2245 (1976).
135. D. Swern, A. Clements and T. M. Luong, *Anal. Chem.*, **41**, 412 (1969).
136. E. Breitmaier and W. Voelter, *Carbon-13 NMR Spectroscopy*, 3rd ed., Verlag Chemie, Weinheim, 1987.
137. S. J. Angyal and L. Odier, *Carbohydr. Res.*, **123**, 23 (1983).
138. A. C. Olivieri and T. S. Kaufman, *J. Chem. Educ.*, **66**, 53 (1989); J. Dubois and M. Carabedian, *Org. Magn. Reson.*, **14**, 264 (1980).
139. J. Huet, *Tetrahedron*, **37**, 731 (1981).
140. N. J. Clayden, *Magn. Reson. Chem.*, **27**, 692 (1989).
141. K. Matsuzaki, S. Okuzono and T. Kanai, *J. Polym. Sci., Polym. Chem. Ed.*, **17**, 3447 (1979).
142. T. Hjertberg, P. Zadorecki and M. Arwidsson, *Makromol. Chem.*, **18**, 899 (1986).
143. K. Honda, A. Tsugita, T. Yoneya and Y. Nishijima, *J. Soc. Cosmet. Chem.*, **32**, 255 (1981).
144. J. Hodson, *Chemosphere*, **17**, 2339 (1988).
145. R. J. Abraham and J. M. Bakke, *Org. Magn. Reson.*, **14**, 312 (1980).
146. R. R. Fraser, Gurudata, C. Reyes-Zamora and R. B. Swingle, *Can. J. Chem.*, **46**, 1595 (1968).
147. J. Oakes, *J. Chem. Soc., Faraday Trans. 2*, **69**, 1311 (1973).
148. M. M. Marciacq-Rousselot and M. Lucas, *J. Phys. Chem.*, **77**, 1056 (1973).
149. B. Berglund and R. W. Vaughan, *J. Chem. Phys.*, **73**, 2037 (1980).
150. C. M. Rohlfing, L. C. Allen, and R. Ditchfield, *J. Chem. Phys.*, **79**, 4958 (1983).
151. F. Kovac and B. Plesnicar, *J. Chem. Soc., Chem. Commun.*, 122 (1978); *J. Am. Chem. Soc.*, **101**, 5820 (1979).
152. B. Plesnicar, F. Kovac, M. Hodoscek and J. Koller, *J. Chem. Soc., Chem. Commun.*, 515 (1985).
153. M. Begtrup, *J. Chem. Soc., Perkin Trans. 2*, 544 (1980).
154. M. Begtrup, *J. Chem. Soc., Perkin Trans. 2*, 1609 (1983).
155. M. C. Moreau-Descoings, F. Guillaume-Vilport, J. P. Seguin, R. Uzan and J. P. Doucet, *J. Mol. Struct.*, **127**, 297 (1985).

156. M. Takasuka, *Spectrosc. Lett.*, **15**, 233 (1982).
157. D. Live and S. I. Chan, *J. Am. Chem. Soc.*, **98**, 3769 (1976).
158. M. Shamispur and A. I. Popov, *J. Am. Chem. Soc.*, **101**, 4051 (1979).
159. M. R. Johnson, C. A. Colburn, S. J. Ganion, B. Son, J. A. Mosbo and L. R. Sousa, *Magn. Reson. Chem.*, **26**, 197 (1988).
160. H. D. Durst, L. Echegoyan, G. W. Gokel and A. Kaifer, *Tetrahedron Lett.*, **23**, 4449 (1982).
161. B. Eliasson, K. M. Larsson and J. Kowalewski, *J. Phys. Chem.*, **89**, 258 (1985).
162. A. Talvitie and A. Borg-Karlson, *Finn. Chem. Lett.*, **93** (1979).
163. S. Watanabe, *J. Mol. Struct.*, **64**, 285 (1980).
164. T. Spoormaker and M. J. A. DeBie, *Recl. Trav. Chim. Pays-Bas*, **97**, 85 (1978).
165. H. Booth, J. M. Dixon, K. A. Khedhair and S. A. Readshaw, *Tetrahedron*, **46**, 1625 (1990).
166. S. Chandrasekaran, in *^{17}O NMR Spectroscopy in Organic Chemistry* (Ed. D. W. Boykin), CRC, Boca Raton, Fla., 1991, pp. 141–203.
167. J.-P. Kintzinger, in *NMR 17, Basic Principles and Progress. Oxygen-17 and Silicon-29* (Eds. P. Diehl, E. Fluck and R. Kosfeld), Springer-Verlag, Berlin, 1991, pp. 1–64.
168. S. Bank and K. L. Longley, *J. Labelled Compd. Radiopharm.*, **28**, 41 (1990).
169. J. K. Crandall and M. A. Centeno, *J. Org. Chem.*, **44**, 1183 (1979).
170. C. Delseth and J. P. Kintzinger, *Helv. Chim. Acta*, **61**, 1327 (1978).
171. E. L. Eliel, K. T. Liu and S. Chandrasekaran, *Org. Magn. Reson.*, **21**, 179 (1983).
172. T. Sugawara, Y. Kawada and H. Iwamura, *Chem. Lett.*, 1371 (1978).
173. M. Takasuka, *J. Chem. Soc., Perkin Trans. 2*, 1558 (1981).
174. T. Sugawara, Y. Kawada, M. Katoh and H. Iwamura, *Bull. Chem. Soc. Jpn.*, **52**, 3391 (1979).
175. M. T. Beraldin, E. Vauthier and S. Fliszar, *Can. J. Chem.*, **60**, 106 (1982).
176. P. Balakrishnan, A. L. Baumstark and D. W. Boykin, *Tetrahedron Lett.*, **25**, 169 (1984).
177. K. von Werner and B. Wrackmeyer, *J. Fluorine Chem.*, **31**, 183 (1986).
178. J. Reuben, *J. Am. Chem. Soc.*, **91**, 5725 (1969).
179. A. I. Popov, A. J. Smetans, J. P. Kintzinger and T. Thanh-Tam Nguyen, *Helv. Chim. Acta*, **63**, 668 (1980).
180. J. P. Kintzinger, C. Delseth and T. Thanh-Tam Nguyen, *Tetrahedron*, **36**, 3431 (1980).
181. G. A. Kalabin, D. F. Kushnarev, R. B. Valeyev, B. A. Trofimov and M. A. Fedotov, *Org. Magn. Reson.*, **18**, 1 (1982).
182. M. Katon, T. Sugawara, Y. Kawada and H. Iwamura, *Bull. Chem. Soc. Jpn.*, **52**, 3475 (1979).
183. G. G. Furin, A. I. Rezvukhin, M. A. Fedotov and G. G. Yakobson, *J. Fluorine Chem.*, **22**, 231 (1983).
184. M. A. Wysocki, P. W. Jardon, G. J. Mains, E. J. Eisenbraun and D. W. Boykin, *Magn. Reson. Chem.*, **25**, 331 (1987).
185. M. Manoharan and E. L. Eliel, *Magn. Reson. Chem.*, **23**, 225 (1985).
186. D. W. Boykin and G. E. Martin, *J. Heterocycl. Chem.*, **24**, 365 (1987).
187. J. J. Barieux and J. P. Schirmann, *Tetrahedron Lett.*, **28**, 6443 (1987).
188. M. G. Zagorski, D. S. Allan, R. G. Salomon, E. L. Clennan, P. C. Heah and R. P. L'Esperance, *J. Org. Chem.*, **50**, 4484 (1985).
189. S. W. Rabideau and H. G. Hecht, *J. Chem. Phys.*, **47**, 544 (1967).
190. H. Versmold and C. Yoon, *Ber. Bunsenges. Phys. Chem.*, **76**, 1164 (1972).
191. C. Delseth, J. P. Kintzinger, T. Thanh-Tam Nguyen and W. Niederberger, *Org. Magn. Reson.*, **11**, 38 (1978).
192. W. H. Bunnelle, *J. Am. Chem. Soc.*, **111**, 7613 (1989).
193. S. Chang and W. J. LeNoble, *J. Am. Chem. Soc.*, **106**, 810 (1984).
194. D. W. Grandy, L. Petrakis, D. C. Young and B. C. Gates, in *Magnetic Resonance. Introduction, Advanced Topics and Applications to Fossil Energy* (Eds. L. Petrakis and J. P. Fraissard), Reidel, Dordrecht, 1984, pp. 689–698.
195. T. Tamaki, K. Matsushita, K. Hioka and Y. Takamiya, *Nippon Nogei Kagaku Kaishi*, **60**, 191 (1986).

CHAPTER 7

Photoelectron spectroscopy of alcohols, phenols, ethers and peroxides

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Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

I. INTRODUCTION AND SCOPE

The application of photoelectron (PE) spectroscopy to small and medium-size organic molecules has emerged as a particularly fruitful technique and has contributed significantly to the understanding of their electronic structure and chemical bonding[1]. The objective of this article is to summarize the results of ultraviolet photoelectron spectroscopic (PES) studies of molecules which incorporate hydroxy or etheric functional groups, as well as to highlight the features of general interest for practicing chemists. Neither special experimental techniques in electron spectroscopy nor adjacent fields used in measurements nor theoretical models and methods employed in rationalization of the empirical data will be discussed in detail because this would obviously be beyond the scope of this chapter. Another self-imposed restriction is that only compounds containing C—O—X (X = H, C, O) linkages are discussed: inorganic hydroxy compounds or silyl ethers, for instance, are not covered. Similarly, compounds in which the character of the C—O—X linkage is obscured by other features (e.g. heterocyclic compounds[2,3]) are treated only to a limited extent, particularly if recent reviews are available. The literature coverage is up to 1991.

It is well known, both empirically and theoretically, that atoms retain their identity in molecular environments[4]. Their electronic structure is essentially that of free atoms perturbed by the formation of chemical bonds. Furthermore, some specific combinations of bonded atoms form characteristic molecular subunits—functional groups which, to a large extent, determine some gross properties of the compounds in question and frequently serve as fingerprints of the latter. Of particular importance are intramolecular interactions of several functional groups within the same molecule[5]. Such examples are provided by the title compounds, where it is interesting to see how the oxygen atom 'feels' other parts of the molecule or specific functional groups involved within a molecular frame.

In this connection it should be mentioned that the problem of oxygen lone pairs has a long history. There are two distinct ways of describing these lone pairs: (a) 'rabbit ears' representation provided by two hybrid orbitals approximately accommodating to tetrahedral directions[6] and (b) σ–π description involving an approximately sp^2 hybrid

and a pure p orbital of the π symmetry[7]. The rabbit ears picture is advantageous both conceptually and energetically in discussing the ground state properties within the valence bond framework (VB), as treated in detail by McWeeny[8] and Schultz and Messner[9]. This is compatible with the general conclusion that bent bonds offer a better description of multiple bonds than the customary σ–π dissection employed in molecular orbital (MO) theory. We note in passing that the VB formalism can be applied to molecular excited states too, when generated by ejection of a photoelectron. Their delocalized nature is represented by the hopping of the created positive hole either from a valence bond orbital to another valence bond orbital or simply from bond to bond[10]. However, we shall stick to a more transparent and common (albeit more elementary) picture provided by canonical molecular orbitals, which is closer to the σ–π representation of the oxygen lone pairs. Concomitantly, two lone pairs will be considered as energetically non-equivalent as far as the photoelectron event is considered compatible with MO description. The higher energy (lower IE) π-type lone pair (n_O^π) corresponds to the oxygen

2p atomic orbital perpendicularly aligned to a plane defined by the oxygen and central atoms of the two linked groups. The lower energy (higher IE) σ-type lone pair (n_O^σ) lies in the defined plane.

This simplified representation is not strictly valid for larger molecules involving several oxygen atoms and/or other chromophoric groups. Nevertheless, it is useful, since π- and σ-lone-pair orbitals can be viewed as a localized 'basis set' that can be combined with other localized orbitals to form delocalized molecular orbitals, at the same time leading to a conceptually appealing description of intramolecular interactions. This point will become evident later on, when interactions of lone pairs in terms of through-space[11] and through-bond[11] mechanisms are discussed in some detail.

II. EXPERIMENTAL BACKGROUND

The basic principles of PES, the instrumentation and interpretation procedures have been comprehensively discussed in several books[12–19] and review articles[20]. Hence, these concepts will be mentioned here only briefly in order to define the basic notions and introduce the necessary formalism.

In the photoelectron experiment, monochromatic light or X-radiation behaves like a beam of particles that hits valence electrons of the target molecule. If the energy of the incoming photons is sufficiently large, the electrons are ejected, leaving behind a radical cation ($M^{+\cdot}$) in one of the several possible electronic states:

$$M + h\nu \longrightarrow M^{+\cdot} + e \tag{1}$$

What is measured is the kinetic energy of the emitted electrons, $E_{kin(e)}$. The latter is related to the ionization energy, IE, involved in a given ionization event, by the energy conservation condition:

$$IE = E_{h\nu} - E_{kin(e)} \tag{2}$$

where $E_{h\nu}$ denotes the energy of the incident photons. For a fixed frequency ν, electrons are ejected by different kinetic energies and if the number of electrons emitted in a given time is plotted as a function of E_{kin} (or directly as $IE = h\nu - E_{kin}$), then this curve defines a spectrum. If the ionizing source is of medium or high energy such as produced in an inert gas discharge (for instance, 21.22 eV in the He I $2p \rightarrow 1s$ or 40.81 eV in He II $2p \rightarrow 1s$) and the specimen is in the gas phase, the information obtained is related to ionization energies of the valence shells of free molecules. Then the technique is called ultraviolet photoelectron spectroscopy (UPS or PES). On the other hand, if ν is in the range of the soft X-rays (up to a few thousand electron volts), the primary information is obtained for inner-core electrons and, consequently, the method is named X-ray photoelectron spectroscopy (XPS or ESCA).

The analysis of a PE spectrum consists of assigning each spectral band to an electronic state of the molecular ion and identifying the orbital from which electrons are ejected. The link between the position of bands and the energies of molecular orbitals is provided by Koopmans' approximation[21]

$$IE_v = -\varepsilon_{SCF} \tag{3}$$

stating that the vertical ionization energies are given by the negative canonical SCF orbital energies. Hence, the underlying physical picture is that of an independent electron moving in the average electrostatic field. Furthermore, it is implicitly assumed that MOs are frozen during the photoionization process or, equivalently, that ionization is completed in an infinitesimally short period of time (sudden approximation). A breakdown of Koopmans' approximation is expected whenever the above restrictions prove

to be too severe and a number of such cases have been thoroughly discussed in literature[22]. Nevertheless, interpretation of the PES spectra by the single-particle model has significantly contributed to our understanding of the electronic structure of molecules and has given a deep insight into the phenomenon of chemical bonding. The independent-electron picture coupled with the sudden approximation proved particularly useful in describing ionization from outer valence orbitals where it holds to good accuracy. This region of the PES spectrum is exactly the subject matter of the present review.

In order to illustrate the performance of Koopmans' approximation, let us regard H_2O as a prototype of molecules considered here. Orbital energies of outer valence electrons obtained by a near-Hartree–Fock (HF) calculation employing sudden approximation are given in Table 1. They are compared with the experimental data and results provided by some more involved methods to be discussed briefly below. We note first that Koopmans' approximation gives a qualitatively correct sequence of levels in accordance with the experimental IE values[23]. However, quantitative agreement appears to be poor. The computed values are substantially higher than the observed ones. Discrepancies can be traced down to reorganization and correlation effects, which are not present in the single-particle SCF procedure. The relaxation effect upon photoionization, caused by creation of a positive charge in the molecular ion, can be taken into account by the ΔSCF procedure, where both initial and final states are submitted to SCF calculations. It appears that the relaxation energies have an order of magnitude of 2–3 eV, which shifts the calculated IE values below the experimental values (Table 1). A proper description of the photoionization phenomenon is provided only by taking into account both the reorganization and correlation contributions[25,26]. This can be done in several distinct ways. We cite the results of Cederbaum[25]; he employed the many-body perturbation scheme based on Green's functions technique and that of Chong and coworkers[26] who utilized the Raleigh–Schrödinger perturbation theory of the third order. Both approaches yield IE values in harmony with experiment (Table 1). The survey of the data presented in Table 1 shows limitations of Koopmans' approximation. It is fair to say, however, that Hartree–Fock orbital energies provide IE values which are correct to the first order.

Apart from the comparison of the calculated and observed ionization energies, there are other criteria to aid interpretation of PE spectra. They encompass analyses of band shape and width, vibrational fine structure (if present), band intensities, measurement of the angular distribution parameter, studies of series of closely related species, discussion

TABLE 1. Comparison of experimental IE values of H_2O with orbital energies calculated assuming Koopmans' approximation and IE values calculated by more involved methods[a]

Final ionic state	IE^b	$-\varepsilon_{SCF}{}^c$	$\Delta E_{CSF}{}^d$	IE^e	IE^f
$^2B_1$	12.6	13.85	11.10	12.69	12.42
$^2A_1$	14.7	15.87	13.32	14.91	14.73
$^2B_2$	18.4	19.50	17.59	18.96	18.97
$^2A_1$	32.2	—	—	34.82	—
$^2A_1$	539.7	—	—	—	—

[a]All values in eV.
[b]Reference 24.
[c]Near-Hartree–Fock calculations, Reference 23.
[d]$\Delta E_{SCF} = E_{SCF}{}^+ - E_{SCF}{}^0$; near-Hartree–Fock calculations, Reference 23.
[e]Approximate many-body perturbation calculations, Reference 25.
[f]Third-order Raleigh–Schrödinger perturbation calculations, Reference 26.

of substituent effects, etc. Their interpretative merits will be illustrated by a number of examples discussed in the following paragraphs.

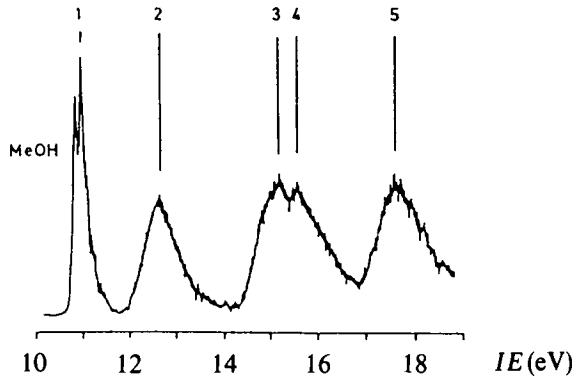
III. PES RESULTS AND DISCUSSION

A. Alcohols

Alcohols provide the most typical example of organic molecules, which were extensively studied earlier in the pioneering period of photoelectron spectroscopy. It is therefore, not surprising that most of their PE data were reported in the late sixties[27]. Hence, most of the measured ionization energies have been scrutinized in several books[13,17] and review articles[28]. This holds in particular for the simplest alicyclic representatives which will be discussed first.

1. Aliphatic alcohols

a. Methanol. In spite of its simplicity, the PE spectrum of MeOH (Figure 1) has been the subject matter of several photoelectron spectroscopic studies and considerable dispute[27,29,39]. A vast number of molecular orbital calculations for MeOH at semi-empirical[41] (CNDO/2[12,33], MONDO/2[33], INDO[33,42], SPINDO[40], MINDO/2[29]), as well as *ab initio*[43] (GTO[32,44], 6-31G[19], etc.) levels have been also published. A



	Reference 30[a]		Reference 32[b]		Reference 33[c]		Reference 38[d]	
Band	*IE*	Assgn.	*IE*	Assgn.	*IE*	Assgn.	*IE*	Assgn.
1	10.96	n_O^{π}	10.96	$2a''(n_O^{\pi})$	10.95	$a''(n_O^{\pi})$	10.95	$a''(n_O^{\pi})$
2	12.72		12.62	$7a'(n_O^{\pi})$	12.66	$a'(\pi_{CH_3})$	12.65	$a'(n_O^{\pi})$
3	15.15		12.51	$6a'(\sigma_{CO})$	15.09	$a'(\sigma_{CO})$	15.17	$a'(\sigma_{CO})$
4	15.55		15.64	$1a''(\pi'_{CH_3})$	15.69	$a''(\pi'_{CH_3})$	15.53	$a''(\pi'_{CH_3})$
5	17.50		17.62	$5a'(\sigma_{OH})$	17.53	$a'(\sigma_{OH})$	17.57	$a'(\pi_{CH_3})$

FIGURE 1. He I photoelectron spectrum, vertical ionization energies, *IE* values (eV) and band assignments of MeOH. Assignments aided by: [a]comparison with the PE spectra of related molecules, [b]sum rule considerations, [c]photoelectron angular distribution measurements and [d]*ab initio* calculations

representative selection of available PE assignments pertinent to the forthcoming discussion is shown in Figure 1, together with the PE spectrum of MeOH.

Perusal of the displayed data shows that there is generally good agreement among the measured *IE* values. It is also indisputable that the lowest *IE* of MeOH corresponds to the removal of an electron from an out-of-plane lone-pair (n_O^{π}) oxygen orbital and that this MO is delocalized to a considerable extent onto the neighbouring Me group. The latter is evidenced by the vibrational structure[32,36,37,39] of the corresponding PE band and its change on deuteration and substantiated by the results of calculations[12,19,29,32]. It should be emphasized, however, that the interpretation of fine structure offered in the literature is far from being unique. For the sake of completeness, the available proposals are summarized in Table 2. For details, the reader is referred to the literature[32,36,37,39].

The second band in the He I PE spectrum was originally assigned to the σ(C—O)-type orbital. This assignment, advanced by Baker and coworkers[30], was based on the comparative consideration of the second bands in the PE spectra of methanol and of 2-propanol and *t*-butanol. Katsumata and coworkers[35], on the other hand, ascribed the same band to the π_{CH_3}-type orbital with the aid of the sum rule. Both of these assignments were subsequently found to be in contradiction with the results of *ab initio* calculations and assignments based on the photoelectron angular distribution measurements, which indicated that IE_2, in fact, corresponds to the in-plane (n_O^{σ}) oxygen lone-pair orbital[38]. Controversies of the same kind are also encountered in regard to the assignment of all higher-lying PE bands in the He I spectrum. In contrast, identification of bands related to the removal of electrons from lower-lying MOs is rather straightforward. Thus, the ionization band at 22.26 eV obtained upon He II excitation is attributed to 4*a*′ MO, which is largely the 2s orbital of the carbon atom. Finally, binding energies of the core levels were reported by Siegbahn and coworkers[12] who used MgK_{α} excitation. Their values are 32.2 (3*a*′), 292.3 (2*a*′) and 538.9 (1*a*′) eV, respectively.

It is appropriate to mention that Ne*($^3P_0$, $^3P_2$) and He*(2^1S, 2^3S) Penning electron[45] and electron impact energy loss spectra[46] of MeOH have been also reported. Finally, from more recent publications, attention should be drawn to Koizumi's[47] study directed

TABLE 2. Summmary of some frequencies observed in the first band of the photoelectron spectra of CH_3OH and its deuterated analogues

Frequency (cm^{-1})				
CH_3OH	CH_3OD	CD_3OD	Assignment	Reference
Progression				
860	—	—	—	33
910	860	750	CO stretch	32
895	—	—	CO stretch	37
926	928	763	CH_3 rock	36
920	850	710	Angular deformation (σ_{COH}) + CH_3 rock	39
Other vibrational excitations				
1920	—	—	—	33
1270	1200	900	CH_3 symmetric bending	32
1371	—	—	—	37
1356	1300	1030	CH_3 symmetric bending	36
1270	1270	970	CH_3 symmetric bending	39

to elucidating the mechanism of excitation and decay for the superexcited state of MeOH together with a variety of other small molecules. The main conclusion of this work is that the superexcited state of most of the molecules studied dissociated to neutral fragments.

b. Ethanol and higher alcohols. Among higher homologues of MeOH, only the PE spectrum of EtOH has been rationalized in some detail[29,30,32–35,38,40]. Assignment of the measured *IE* values in the He I region was thoroughly discussed first by Katsumata and coworkers[35] by utilizing the sum rule, and subsequently by Nagakura's group[38] on the basis of photoelectron distribution measurements. In addition, assignments based on a comparison with calculated MO energies at either semiempirical or *ab initio* levels of theory are available (Table 3).

As in case of MeOH, all assignments agree insofar as the nature of the highest occupied MO (HOMO) is concerned, while some disagreement persists with respect to the nature of lower-lying orbitals.

Higher aliphatic alcohols studied by PES encompass n-propan-*X*-ols ($X = 1, 2$), n-butan-*X*-ols ($X = 1, 2$), n-pentan-*X*-ols ($X = 1$–3), n-hexan-*X*-ols ($X = 1$–3), n-heptan-*X*-ols ($X = 1$–4) as well as some of their isomeric forms[29,30,32,33,35,40,49]. The spectra are all fairly similar in appearance. They consist of a first band at an *IE* of about 10 eV, followed by σ bands covering the region of the PE spectrum from 10.5–17.5 eV. The shape of the first band is found to be similar to the shape of the first band in MeOH, thus suggesting that parent molecular orbitals similar to the b_1 MO of water are involved. The corresponding *IE*, however, decreases rapidly from 10.95 to 10.37 eV on ascending the series from MeOH to n-BuOH, but then assumes a nearly constant value of 11.30 eV. A similar 'saturation' effect is observed for the secondary alcohols (2-ols and 3-ols). The limiting *IE* may be taken as 10.24 eV in the former and 10.10 eV in the latter case. These trends are apparent in Figure 2, where the lowest *IE* values of aliphatic alcohols are plotted against the chain length. It appears that a limit to the effects of extra methylene groups upon the oxygen lone pair *IE* is to be expected for chain lengths above C_3. This indicates that, for small alkyl chains, the molecular ion is stabilized to a greater extent

TABLE 3. Vertical ionization energies *IE* (eV) and band assignments of EtOH

	Reference 35[a]			
IE (eV)	*trans*[d]	*gauche*[d]	Reference 38[b]	Reference 12[c]
10.64	$a''(n_O^{\pi})$	$(n_O^{\pi})^e$	$a''(n_O^{\pi})$	$3a''(n_O^{\pi})$
12.16	$a'(\sigma_{CC})$	$\pi_{C_2H_5}^{-}$	$a'(\sigma_{CC})$	$10a'(\sigma_{CC}, n_O^{\sigma})$
13.28	$a'(\pi_{CH_3})$	σ_{CC}	$a'(n_O^{\sigma})$	$2a''(\pi_{CH_3}, n_O^{\pi})$
13.85	$a'(\sigma_{CO})$	π_{CH_3}	$a'(\sigma_{CO})$	$9a'(\pi_{CH_3}, \sigma_{CO})$
14.55	$a''(\pi_{C_2H_5}{}^{-f})$	$\pi_{C_2H_5}^{+}$	$a''(\pi_{C_2H_5}^{-})$	$8a'(\sigma_{CO}, \sigma_{CC})$
15.96	$a''(\pi_{C_2H_5}{}^{+})$	σ_{CO}	$a''(\pi_{C_2H_5}^{+})$	$1a''(\pi_{CH_2}, n_O^{\pi})$
17.45	$a'(\sigma_{OH})$	σ_{OH}	$a'(\pi_{CH_3})$	$7a'(\sigma_{OH})$

[a] Assignment based on sum rule consideration.
[b] Assignment aided by photoelectron angular distribution measurements.
[c] Assignment made with the aid of 4-31G *ab initio* calculations.
[d] *trans* and *gauche* forms coexist in the gas phase, with the *trans* form being predominant[48].
[e] The underlined orbitals of the *gauche* conformer are *a''* like out-of-plane orbitals because EtOH has no symmetry in the *gauche* form.
[f] The π^- and π^+ denote antibonding and bonding types of combinations of the methyl pseudo π and methylene pseudo π orbitals, respectively.

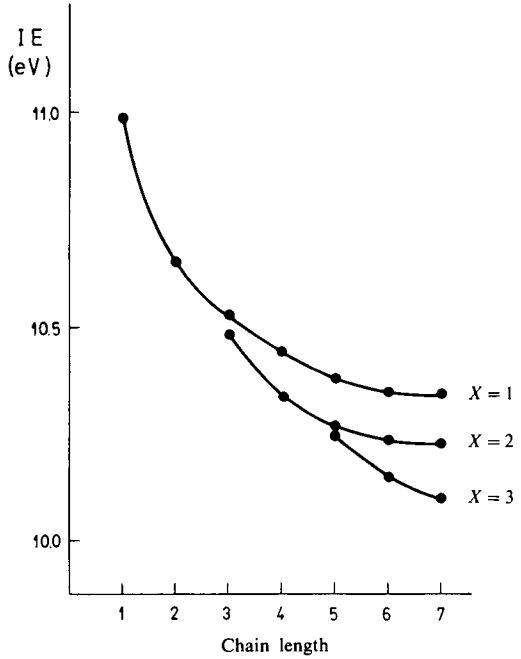


FIGURE 2. Plot of first *IE* values of n-alkan-*X*-ols ($X = 1$–3) against chain length

than the neutral molecule itself by the introduction of a methylene group. Above n-BuOH, there seems to be no difference between the stabilizing effects on the molecule and ion.

Contrary to the near-constancy of the n_O^{π} 'oxygen lone pair' *IE*, the bands associated with alkyl σ bands move to lower *IE* values with an increase in the size of the molecule. Finally, in heptan-1-ol, the first band is not resolved but only seen as a shoulder on the onset of the σ band. The PE spectra of secondary aliphatic alcohols, as well as the branched alcohols, have a more complete resolution of the first band.

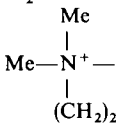
The extent of separation between the second and higher-lying bands depends strongly on the degree of branching of the carbon chain. In straight-chain alcohols (with the exception of the two lowest members, MeOH and EtOH), the second band is, as a rule, swamped under the higher-lying ionization events.

Let us finally mention that several attempts to corrrelate the *IE* (n_O^{π}) of aliphatic alcohols with a number of energetic and structural empirical parameters, such as proton affinity, heat of formation, Taft's σ^* constants, etc. have been made. Furthermore, correlation with the bonding energies of the inner-shell (1s) electrons[50], first *IE* values of the structurally related alkyl iodides, CT wavelengths of the corresponding complexes with TCN[51] and with calculated MO energies have been discussed in some detail.

2. *Heterosubstituted aliphatic alcohols*

Considerable attention in PE spectroscopic studies of aliphatic alcohols has been devoted to evaluating the influence of various substituents on oxygen lone-pair ionization energies[19,32,50]. The available data are summarized in Tables 4 and 5. They display

TABLE 4. Vertical ionization energies *IE* (eV) of 2-substituted ethanols (RCH_2CH_2OH)

R	*IE* (eV)[a]	References
Cl	10.90 (n_O^{π}); 11.45 (n_{CC}); 11.71 (n_{Cl}); 12.60 (n_O^{σ})	30, 52
F	10.98 (n_O^{π}); 12.48; (n_O^{σ}); 13.04 (n_F); 13.7 (n_F)	30, 52
I (*trans*)	9.60 ($^2E_{3/2}$); 10.17 ($^2E_{1/2}$); 10.96 (n_O^{π})	30, 52, 53
I (*gauche*)	9.73 (n_I); 10.34 (n_I); 10.96 (n_O^{π})	
Br (*trans*)	10.65 ($^2E_{3/2}$); 10.83 ($^2E_{1/2}$); 11.30 (n_O^{π})	30, 52
Br (*gauche*)	10.75 (n_{Br}); 10.93 (n_{Br}); 11.30 (n_O^{π})	
OH	10.55 (n_O); 11.22 (n_O); 12.38 (π_{CH}, $_2\sigma_{CC}$); 13.05	13, 19
OMe	10.13; 10.57; 12.01; 12.5; 13.44; 14.36; 15.16; 16.53; 17.41	19
OEt	9.97; 10.44; 11.87; 12.65; 13.4; 13.7; 14.3; 14.7; 15.5	19
SH	9.65; 10.86; 11.82; 12.62; 13.42; 14.55; (15.4); 16.04; 17.57	19
H_2N	9.88; 10.71; 12.23; 13.15; 14.03; (15.3)[b]; 16.09; (16.7)[b]; 17.67	53
Me_2N	8.85 (n_N); 10.38 (n_O^{π})	53
Et_2N	8.58 (n_N); 10.38 (n_O^{π})	53
		
$(CH_2)_2OH$	8.86 ($n_y^{NO\cdots H}$); 8.86 ($n_x^{NO\cdots H}$); 10.20 (n_x^{OH})	55

[a]Values refer to band maxima.
[b]Parentheses indicate uncertainty in measurements.

TABLE 5. Vertical ionization energies *IE* (eV), of polysubstituted aliphatic alcohols (ROH)[50]

R	*IE* (eV)
F_3C	9.71; 10.54; 11.98; 12.92; 14.07; 15.33
F_3CCH_2	11.70 (n_O^{π}); 12.60; 13.29; 15.35; 16.46; 17.01; 18.01; 20.56
$(F_3C)_2CH$	12.21 (n_O^{π}); 13.8; 15.6; 15.81; 16.72; 17.41; ~21; 22.8
$(F_3C)_3C$	9.71; 10.54; 11.98; 12.92; 14.07; 15.33
$(F_3C)_3CCH_2$	11.68 (n_O^{π}); 13.09; 14.19; 15.71; 16.58; 17.46; 18.68
$F_7C_3CH_2$	11.62; 13.23; 13.87; 15.8
Cl_3CCH_2	11.34; 11.78; 12.21 (n_O^{π}); 12.72; 13.29; 14.91; 15.46; 16.76; 18.31
$F_3CCH(OH)$	10.80 (n_O^{π}); 11.81; 13.26; 15.38; 16.83
$Cl(CH_2)_2CH(Br)$	10.36; 10.69; 11.23; 12.4; 13.16; 16.66
Cl_3CCMe_2	10.70; 11.30 (n_O^{π}); 12.45; 13.48; 15.93; 17.42

[a]Reference 32.

ionization energies for 2-substituted ethanols and either higher or more heavily substituted alcohols, respectively. It should be pointed out that analysis of the latter series is greatly obscured by strong overlapping of the ionization bands. Therefore, it is not surprising that ionization energies, as well as the assignment proposed in Reference 50, can be regarded only as tentative, although approached by a combination of several techniques. The only feature that should be singled out is the finding of significantly higher ionization energies for the oxygen lone pairs, as compared to structurally related parent alcohols.

Contrary to that, PE studies of compounds shown in Table 4 are in most cases easy to interpret and offer valuable information about the mechanism of mutual interaction

of a wide variety of chromophoric groups bound to neighbouring carbon atoms. The PE spectra of 2-haloethanols, 2-aminoethanols and β-hydroxyethyldimethylamine oxide will be discussed in more detail.

The PE spectra of 2-haloethanols (Hal = F, Cl, Br, I) were reported first by Baker and coworkers[30] and subsequently by Hoppiliard and Solgady[52]. In addition, Leavell and coworkers[53] discussed intramolecular hydrogen bonding in 2-iodo derivatives whereas Koppel and coworkers[50] remeasured the PE spectrum of 2-chloroethanol. Baker[30] explained the general features of the PE spectra, in particular the consequences of through-space interaction between the oxygen and halogen lone pairs, whilst Hoppilliard addressed the question of their conformation in the gas phase. It should be noted (Table 4) that the first ionization in the chloro- and fluoro-derivatives originates from the MO of a predominantly oxygen lone-pair character, while in the other two compounds involving Br and I atoms, n_{Hal} MO is of highest energy. As regards conformation, chlorine and fluorine derivatives were found to exist in the gas phase in the *gauche* form, while for their bromine and iodine counterparts, coexistence of the *gauche* and *trans* rotamers was predicted.

Of considerable interest is also the PES study of 2-aminoethanol and its *N,N*-dialkyl congeners performed by Leavell and coworkers[53] (Table 4). It illustrates the use of the PE technique in studying intramolecularly hydrogen-bonded systems. In order to get an insight into the influence of hydrogen bonding on the *IE* values of the highest occupied MOs in these compounds, the authors recorded PE spectra at different temperatures along with the spectra of 2-methoxyethylamine in which formation of hydrogen bond is precluded by methyl substitution (Table 6). By comparing two sets of data it was found that the *IE* of nitrogen lone-pair electrons in 2-aminoethanol is higher by 0.42 eV than in 2-methoxyethylamin. As the temperature is increased, the extent of stabilization becomes smaller. The observed trends are explained by the presence of an O—H···N hydrogen bond in the former compound. Let us mention in passing that the effect of intramolecular hydrogen bonding on the PIES activity of the n_O^{π} orbital in the same alcohols was recently discussed by Harada's group[54].

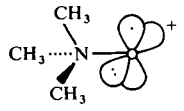
Leavell and coworkers[53] also applied PES technique to explore hydrogen bonding in *N,N*-dimethyl- and *N,N*-diethylaminoethanol, in 3-aminopropanol and its dialkyl congeners as well as in 2-iodoethanol (Table 4). In the case of 2-iodoethanol, a considerably smaller effect than those observed in amino alcohols is found, indicating the existance of significantly weaker hydrogen bonding in the former compounds. It should, however, be strongly pointed out that the approach presented above was based on the use of vertical *IE* values. Hence, the results are subject to the ambiguity that the observed trends are due to shifts in the Franck–Condon envelope rather than the opening or closing of the hydrogen bond.

To conclude the discussion about hydrogen bonding in this section, the results of PES study on β-hydroxyethyldimethylamine oxide reported by Wieczorek and coworkers[55]

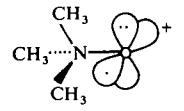
TABLE 6. Vertical ionization energies *IE* (eV) of lone-pair electrons of 2-aminoethanol and 2-methoxyethylamine[53]

Temperature (°C)	$HOCH_2CH_2NH_2$		$MeOCH_2CH_2NH_2$	
	$IE(n_N)$	$IE(n_O^{\pi})$	$IE(n_N)$	$IE(n_O^{\pi})$
23	9.87 ± 0.06	10.68 ± 0.03	9.45 ± 0.09	9.99 ± 0.07
100	9.79 ± 0.04	10.71 ± 0.04	—	—
200	9.68 ± 0.07	10.73 ± 0.04	9.43 ± 0.09	9.91 ± 0.07

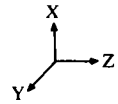
will be outlined. The amino-oxide grouping is known to form a particularly strong hydrogen bond. As far as the PE spectra are concerned it was expected that the degeneracy of the *N*-oxide (structures **Ia** and **Ib**) would enable a more subtle probe of the effects of



(Ia) (n_x^{N-O})

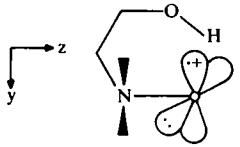


(Ib) (n_y^{N-O})

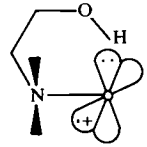


C_{3v}

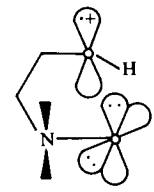
hydrogen bonding on the *IE* values than in the previously described *β*-aminoalcohols. Namely, this degeneracy would be lifted by symmetry-allowed interactions of NO and OH fragments, which would predominantly perturb the $n_y^{NO\cdots H}$ ionic structure **IIb** of



(IIa) $(n_x^{NO\cdots H})$



(IIb) $(n_y^{NO\cdots H})$

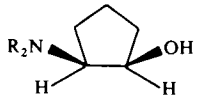


(IIc) $(n_x^{O\cdots H})$

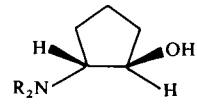
the considered molecule. By comparing the PE spectra of the parent molecule **I** with those of *β*-hydroxy- and *β*-methoxy derivatives, Wieczorek and coworkers came to the conclusion that the degenerate pair of *N*-oxide ionic states (**IIa** and **IIb**) is shifted by 0.49 eV to higher ionization energies relative to the non-hydrogen-bonded system. The ionization of the hydroxy lone pair (**IIc**), on the other hand, assumes only a slightly different value than the OMe lone-pair ionization energy in the methylated compound, indicating that formation of the hydrogen bond lowers the energy of the n_x^{O-H} state by about the same extent as conversion of an alcohol to its methyl ether (*ca* 0.4–0.6 eV). The experimental findings were corroborated by INDO calculations for the ionic states **IIa–IIc** modelled by the $NH_3O + H_2O$ complex.

3. *Saturated cyclic and polycyclic alcohols*

Much of the work associated with the study of the electronic structure of saturated cyclic and polycyclic alcohols has been focussed upon investigation of hydrogen bonding[56–58]. An exemplary case is represented by the PE study of *cis*- (**1a**) and *trans*-2-amino cyclopentanols (**2a**) and their *N,N*-dimethylamino congeners (**1b** and **2b**, respectively) conducted by Brown[56]. In both compounds, *cis* isomers exhibit nitrogen lone-pair (IE_1) ionizations at higher energy, and oxygen lone-pair ionizations (IE_2) at lower



(1a) R = H
(1b) R = Me



(2a) R = H
(2b) R = Me

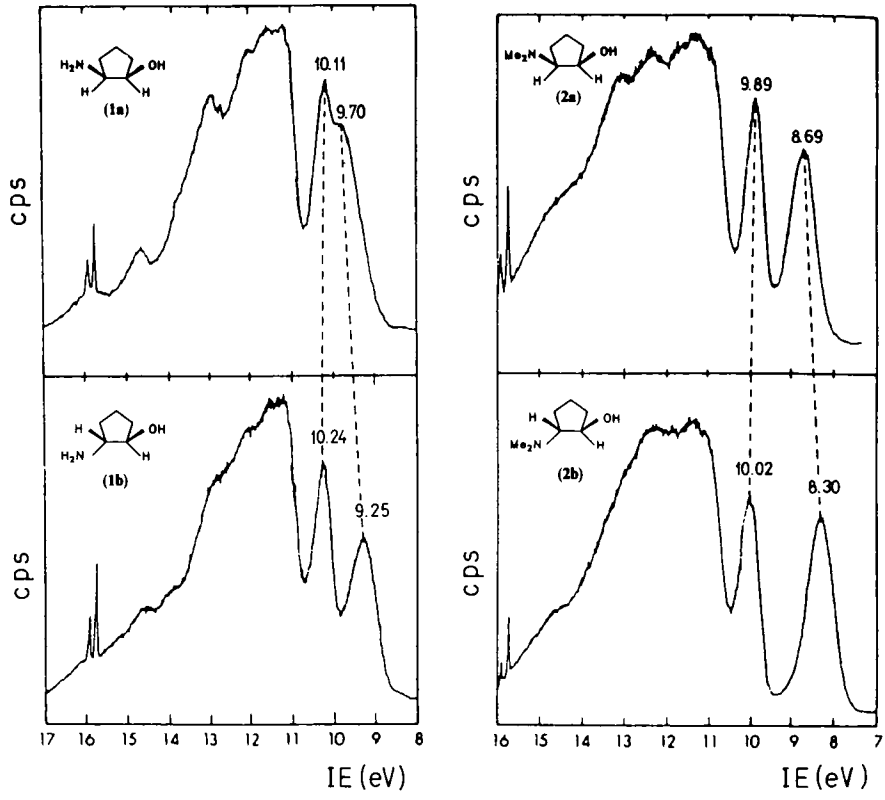


FIGURE 3. He I PE spectrum of *cis*- and *trans*-2-aminocyclopentanols (**1a** and **1b**) (left) and their *N,N*-dimethylamino congeners (**2a** and **2b**) (right)[56]

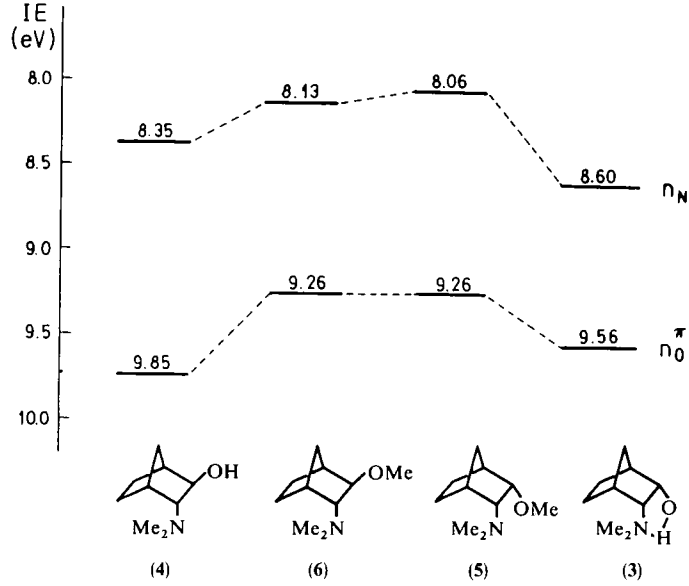
energy than their *trans* isomers (Figure 3). Thus, the difference in the IE_1 values for **1a** and **2a** is 0.45 eV, while that for the *cis*- and *trans*-*N,N*-dimethylamino derivatives **1b** and **2b** is 0.39 eV. It should be also noted that there is a somewhat smaller decrease of 0.13 eV in the oxygen lone-pair ionizations of the *cis* compounds over the *trans* compounds. Intuitively, one expects that, in hydrogen-bonded systems, the amino lone pair ought to become more bonding and move to higher ionization energy. Concomitantly, as the hydrogen of the OH moiety associates with the nitrogen lone pair, the oxygen ought to experience an increase in electron density, which should facilitate the removal of the electron from the oxygen lone pair[59]. In the light of this discussion, it is concluded that the differences in the PE spectra of the *cis*- and *trans*- aminocyclopentanols are due to hydrogen bonding in the *cis* isomers. That *cis*-amino alcohols in fact exist in an intramolecularly hydrogen-bonded state is amply illustrated by IR[56] and ESCA[60] spectroscopy.

Pertinent to the discussion of hydrogen bonding on the ionization pattern of amino alcohols is also the PE spectroscopic study of stereoisomeric 3-dimethylaminonorbornan-2-ols and their methoxy analogues (**3–6**) conducted by Bock's group[57].

In order to deduce whether hydrogen bonding is operative in *endo,endo* hydroxy

(3) R = H
(5) R = Me

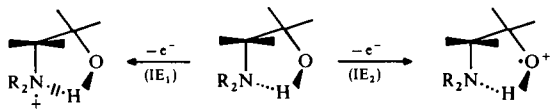
(4) R = H
(6) R = Me



(4) (6) (5) (3)

FIGURE 4. Comparison of n_O^{π} and n_N vertical ionization energies within the series **3–6**. Reproduced by permission of VCH Publishers from Reference 57

compound **3** in the gas phase, its ionization energies related to n_N and n_O^{π} orbitals were measured along with the same energies for compounds **4–6**. Comparison of the measured *IE* values displayed in Figure 4 shows that the PE spectrum of **3** exhibits a considerably smaller energy gap between the first two bands than the gap found in its *exo,endo* congener **4**. On the other hand, in methoxy derivatives (**5** and **6**), the first two ionization energies are of a similar order of magnitude. Lowering of the energy gap $\Delta IE_{2,1}$ in passing from **3** to **5** is rationalized in terms of hydrogen-bond formation in the former compound. Differences in ionization energies $+\Delta IE_1$ (n_N) and $-\Delta IE_2$ (n_O^{π}) are attributed to the changes in hydrogen-bond strength upon ionization. More specifically, n_N ionization is assumed to diminish the strength of the hydrogen bond through repulsive

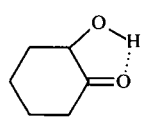


$\tilde{X}$ (n_N) $\tilde{A}$ (n_O^{π})

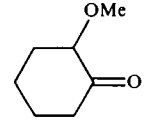
interaction between the positively charged nitrogen and hydrogen atom while in $\tilde{A}(n_O^{\pi})$, ionic state strengthening of the hydrogen bond (⁓) is expected.

It is interesting to note that the extent of n_N stabilization roughly corresponds to the extent of n_O^{π} destabilization. This is in sharp contrast to the situation encountered in α-aminocyclopentanol where a much stronger effect on n_N is observed[56].

Another class of compounds comprising intramolecular hydrogen bonds studied by PES are α-keto cyclic alcohols[58]. In order to assess the effect of hydrogen bonding in 2-hydroxycyclohexanone (**7**), for instance, its PE spectrum is compared to that of 2-methoxycyclohexanone (**8**), in which formation of hydrogen bond is prevented by methylation. It is tacitly assumed that hydroxyl and methoxy groups exhibit similar inductive effects and that PE spectral shifts, caused by possible conformational changes induced by methylation, are negligible. By comparing the PE spectra of the two compounds it was found that ionization assigned to the removal of the carbonyl n_o electron is by 0.6 eV higher in **7** than in **8**. Similarly, the ultraviolet spectra of these molecules also exhibit a marked blue shift of the $n \rightarrow \pi^*$ transition in the former compound of roughly 0.5 eV. In analogy to the previously discussed cases, the observed spectral shifts are ascribed to the formation of a hydrogen bond in **7**.



(7)



(8)

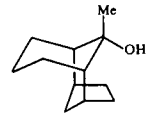
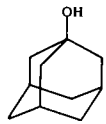
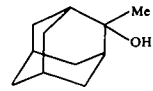
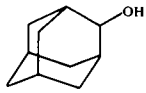
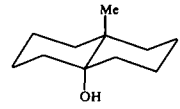
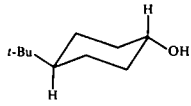
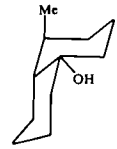
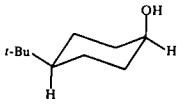
Apart from the molecules described above, PE spectra of several polycyclic alcohols have been also measured[61-64]. However, due to severe overlapping of ionization bands, analysis of their PE spectral features is most often confined only to the determination of the *IE* value related to the n_O^{π} oxygen lone-pair orbital which, as a rule, appears as the highest occupied MO. Results for some representative examples are shown in Table 7.

4. *Unsaturated alcohols*

a. Olefinic alcohols. Most PES studies of unsaturated alcohols have been devoted to the evaluation of the influence of the hydroxyl group on the C=C π-ionization energy. Typical examples are offered by the very early work of Katrib and Rabalais[65] dealing with substituted ethylenes and the more recent studies of Brown's group in which a series of cyclic allylic alcohols is considered[61,62]. In the first work the general features of the PE spectrum of allyl alcohol are described[65]. The spectrum exhibits nine ionization bands below 21 eV. The first band at 10.16 eV is attributed to ionization of C=C π electrons while the relatively sharp band at 10.93 eV is attributed to ionization of an oxygen (n_O^{π}) electron. The significant shift (0.28 eV) of the former towards higher energy, as compared to propene[19], followed by only 0.05 eV destabilization of the latter, when compared to methanol[19], was rationalized in terms of inductively caused electron density withdrawal toward the oxygen atom. The resonance effect appears to be of minor importance[65,66].

Replacement of one of the hydrogen atoms at the terminal allylic carbon atom leading to crotyl alcohol results in a lowering of the *IE* ($\pi_{C=C}$) and *IE*(n_O^{π}) to 9.70 and 10.70 eV, respectively[67]. For 3-penten-2-ol, further destabilization of the corresponding levels by 0.2 eV is encountered[67]. Let us mention in passing that the reported *IE* (n_O^{π}) values differ by only 0.15–0.28 eV from their counterparts in the corresponding saturated alcohols.

TABLE 7. Lone-pair ionization energies *IE* (eV) in some cyclic and polycyclic alcohols

Compound	IE (n_O^π)(eV)[a]	Reference	Compound	IE (n_O^π)	Reference
	9.65	61		9.5	64
	9.23	63		9.22	63
	9.25	63		9.41	61
	9.82	62		9.45	62
	9.91	62			

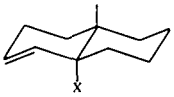
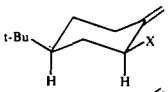
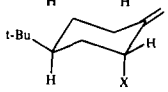
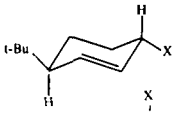
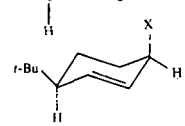
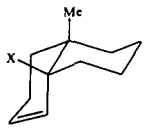
[a]Values refer to band maxima.

The smallest difference (0.15 eV) is found in the largest (3-pentenol/pentanol), and the largest difference (0.28 eV) in the lowest pair (propenol/propanol) of the described series.

The allylic alcohol fragment appears also in several cyclic and bicyclic alcohols studied by PES. One of the simplest examples is provided by 3-cyclopentenol[68]. For this compound, $IE(\pi_{C=C})$ and $IE(n_O^\pi)$ of 9.60 eV and 10.34 eV are reported. Particularly interesting representatives are provided by cyclic and bicyclic structures shown in Table 8.

PE spectra of these compounds were measured with the goal of evaluating the effect of the orientation of the allylic hydroxyl group on the π-ionization energies (**9–12**)[61] and determining the gas-phase conformation (**13–15**)[62]. In analysing the PE spectra of **9–12**, the π-related bands were found to be remarkably stabilized relative to the parent olefin (Table 8) for the coplanar arrangement of the allylic C—OR bond and π-system (**10** and **11**). Stabilization becomes significantly less pronounced as the allylic C—OR bond assumes a perpendicular arrangement relative to the plane of the double bond (**9** and **10**, Table 8). Experimental findings were rationalized by invoking interplay of the following factors: (i) inductive effect, (ii) hyperconjugative σ^*,π interaction and (iii) through-bond-mediated n_O^π,π interaction. While the inductive effect is independent of conformation, the other two types of interaction depend strongly on the relative orientation of the interacting subunits. The σ^*,π mode of interaction prevails in the coplanar and the through-bond interaction in the perpendicular conformation. The former acts stabilizing, and the latter destabilizing at the π level. Subsequently, the same approach was applied to the flexible alcohols **13–15**, with the intention of determining the preferred

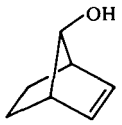
TABLE 8. Lowest ionization energies of olefinic alcohols **9–15** and corresponding hydrocarbons

Compound	X	IE(eV)[a] IE_1 (π)	IE_2 (n_O^{π})	$\Delta IE_{2,1}$
	H		9.05	
	OH (**9**)[b]	9.95	9.21	0.16
	H	8.92		
	OH (**10**)[c]	9.35	9.58	0.43
	H	9.09		
	OH (**11**)[b]	9.18	10.15[d]	0.09
	OH (**12**)[b]	9.37	9.97[d]	0.28
	H	8.94		
	OH (**13**)[c]	9.18	10.21[d]	0.24
	OH (**14**)[c]	9.33	10.07[d]	0.39
	H	8.92		
	OH (**15**)[c]	9.26	9.64	0.34

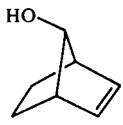
[a]Vertical IE values. All values are the average of at least three runs and have a precision of ± 0.02 eV, unless noted otherwise.
[b]Reference 61.
[c]Reference 62.
[d]Tentatively assigned; appears as a well-defined shoulder on the edge of the σ envelope.

orientation of the double bond and OH group. For all three alcohols, an increase in π-band ionization energy of 0.3 eV was observed, reminiscent of that observed for the coplanar arrangement of the two groups in **9** and **10**, respectively. Hence, it is concluded that the favoured conformation in the gas phase involves coplanar arrangement of the allylic C=C and C—O bonds.

Brown has also measured the PE spectra of *syn*- (**16**) and *anti*-7-norborneols (**17**)[69]. The ionization bands related to $\pi_{C=C}$ and oxygen lone-pair ionizations in the *syn* isomer are found at 9.41 and 9.71 eV, while in the *anti* isomer they are located at 9.19 and 10.04 eV, respectively. The pronounced increase in the lowest ionization energy, followed by diminution in the energy gap (0.5 eV) between the first two levels, in passing from the *anti* to the *syn* isomer, is ascribed to hydrogen-bond formation betweeen the hydroxylic hydrogen and the double bond in the latter compound. Theoretical evidence supporting the existence of π-hydrogen bonding in *syn*-7-norborneol was subsequently provided by Morokuma and Wipff[70].

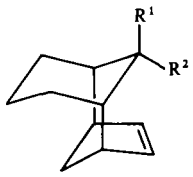


(16)



(17)

A similar, if somewhat smaller (0.1–0.2 eV), stabilization effect on the π-ionization energy was also deduced by Tombo and coworkers[64] in comparing the ionization pattern of the polycyclic alcohols **18b** and **18c** with the parent hydrocarbon system **18a**.



(18a) $R^1 = R^2 = H$

(18b) $R^1 = H$, $R^2 = OH$

(18c) $R^1 = Me$, $R^2 = OH$

b. Hydroxyacetylenes. He I photoelectron spectra of a series of hydroxy-substituted acetylenes have been reported by Andreocci and coworkers[71]. The assignment of the spectra (Table 9) is based on a comparison with the PE spectra of chemically related compounds and the results of CNDO/2 calculations performed for prop-2-yn-1-ol. The PE spectrum of the latter compound (Figure 5) contains five bands which originate from an ionization of seven energy levels. The first band is assigned to ionization of the $\pi_{C\equiv C}$ orbital. The second and third bands are attributed to two MOs, mainly formed by the 2p non-bonding out-of-plane oxygen (n_O^π) orbital and 2p HOC in-plane angle-determining oxygen orbitals. They are both shifted to higher energy (0.17 and 0.62 eV) by the inductive effect of the acetylenic group. The third double band (at 15.6 and 16.05 eV) is tentatively assigned to ionization of σ-orbitals associated with the σ_{C-C} and σ_{CH_2} bonds while, at higher energies, the ionizations of the bonding orbitals σ_{COH} (17.6 eV in MeOH) and $\sigma_{\equiv CH}$ (17.2 eV in propyne) coincide.

Introduction of one or more alkyl groups (Me and/or Et) into the propynol molecule causes a general progressive shift of *IE* values to lower values, and an increase in the relative intensity of the bands overlapping in the energy range 12–15 eV with the increasing length of the aliphatic chain. For instance, the *IE* value of the n_O^π orbital goes from 11.37 eV in prop-2-yn-1-ol to 10.82 eV in 3-methylpent-4-yn-3-ol. The inductive effect ($+I$) of the alkyl substituents in the α position to the triple bond is stronger on

TABLE 9. Selected vertical ionization energies *IE* (eV) of some substituted hydroxyacetylenes[71]

Compound	$IE(\pi_{C\equiv C})$	$IE(n_O^\pi)$	$IE(n_O^\sigma)$
$HC{\equiv}CCH_2OH$	10.45; 10.60	11.37	13.22
$HC{\equiv}CCH(Me)OH$	10.41; 10.64	11.21	12.70
$HC{\equiv}CCMe_2OH$	10.18; 10.37	10.89	12.21
$HC{\equiv}CCMe(Et)OH$	10.03; 10.32	10.82	11.73
$HC{\equiv}CCH_2CH(Me)OH$	10.24	10.83	10.98
$HO(Me)_2CC{\equiv}CC(Me)_2OH$	9.70	10.60	
$HC{\equiv}CCH(Ph)OH$[a]	10.69	11.27	13.29

[a]The *IE* values of the phenyl ring are given in the text.

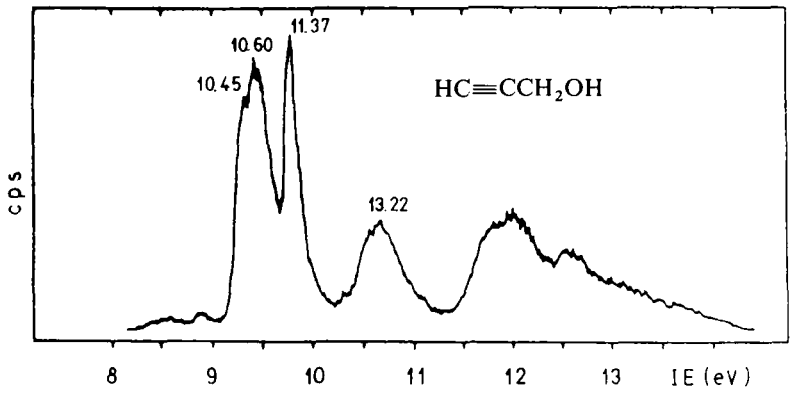


FIGURE 5. He I PE spectrum of prop-2-yn-1-ol. Vertical *IE* values (eV) are indicated above the bands. Reproduced by permission of Elsevier Science Publishers BV from Reference 71

the oxygen lone pair (shift of 0.55 eV) than on the $\pi_{C\equiv C}$ orbitals (shift of 0.32 eV) throughout the series. The position of the $\pi_{C\equiv C}$ band is unchanged in but-1-yn-3-ol (10.4–10.64 eV) with respect to the prop-2-yn-1-ol, and shifted to the lower *IE* value in the other molecules (10.18–10.37 eV in 2-methylbut-3-yn-2-ol and 10.03–10.32 eV in 3-methylpent-4-yn-2-ol).

The PE spectrum of the β-hydroxy derivative, pent-4-yn-2-ol, appears different from the others (Table 9). The acetylenic and hydroxy groups are separated by a CH_2 group, so they do not exert any strong mutual inductive effect. In fact, the spectrum looks like a superposition of the propyne and ethanol PE spectra. The first band ($\pi_{C\equiv C}$) is at 10.24 eV (cf. 10.36 in propyne)[71] whereas the second one (oxygen n_O^{π}) is at 10.83 eV (10.7 eV in EtOH). The third band, due to another n_O^{π} oxygen orbital at 11.98 eV (12.13 eV in EtOH), is well separated from the overlapped bands which, in the energy region 13–16 eV, correspond to the ionization of σ orbitals of the hydrocarbon skeleton.

The 2,5-dimethylhex-3-yn-2,5-diol is peculiar in being a di-substituted alkyne. A distinctive feature of the PE spectrum of this molecule lies in the first two bands, at 9.7 and 10.6 eV, which have a 1:1 intensity ratio, as expected owing to the presence of two OH groups in the molecule. The major shift of the first band ($\pi_{C\equiv C}$) to an *IE* value lower by 0.9 and 0.6 eV than those of prop-2-yn-1-ol and 3-methylpent-4-yn-3-ol, respectively, is consistent with the presence of four methyl groups in the α,α' positions to the triple bond.

In the PE spectrum of 1-phenylprop-2-yn-1-ol, the first band at 9.41 eV and the fourth one, which exhibits two maxima at 11.95 and 12.37 eV, respectively, are both related to ionizations from energy levels mainly related to orbitals of the aromatic ring. The corresponding bands in benzene are at 9.28 eV ($1e_{2g}^{-1}$) and at 11.4 and 12.1 eV ($3e_{2g}^{-1}$ and $1a_{2u}^{-1}$), respectively[19]. The two bands falling in the region free from ionizations of the phenyl moiety are identified as being related to the $\pi_{C\equiv C}$ (at 10.69 eV) and n_O^{π} (at 11.27 eV), respectively. Finally, the band at 13.29 eV is associated to ionization of the n_O^{σ} oxygen orbital.

It is of interest to mention that $\pi_{C\equiv C}$ and n_O^{π} *IE* values of the hydroxyacetylenes are directly related to their reactivity in catalytic cyclotrimerization reactions i.e. the compounds which give trimers in high yield have, as a rule, low $\pi_{C\equiv C}$ and n_O^{π} *IE* values[72]. The beneficial effects of the latter was attributed to alleviated coordination of the monomer to the catalyst.

B. Aromatic Hydroxy Compounds

Concomitant with the early interest in the PES characteristics of alcohols in general, phenol (**19**) and its congeners attracted considerable attention too.[27] Most of the work, particularly in the first stage, was triggered by the interest in both experimental and theoretical aspects of substituent effects on the benzene moiety. This is not surprising in view of the importance of the concept of aromaticity in organic chemistry. Leading references are summarized in Table 10.

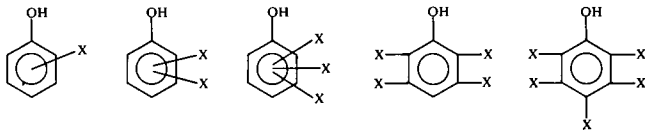
Substitution of a hydrogen atom in benzene by a OH group results in lowering of molecular symmetry and a splitting of the double degenerate e_{1g} benzene orbitals[73–76]. The latter effect is transparently rationalized in terms of the composite molecular approach in a manner shown schematically in Figure 6. As a consequence of the interaction between the Ph_S* component of the benzene e_{1g} orbital and n_O^π oxygen lone-pair orbital, the former entity becomes destabilized while n_O^π moves to lower energy. On the other hand, the Ph_A component does not interact with the n_O^π orbital for symmetry reasons and remains essentially unchanged relative to its position in benzene (9.28 eV)[19].

In the He I PE spectrum of phenol the two highest occupied MOs, localized mainly at the benzene moiety, give rise to two well-defined ionization bands at 8.73 and 9.40 eV, respectively, whereas the band related to transition from the oxygen lone-pair orbital n_O^π appears to be effectively buried within the highly overlapped ionization system starting from *ca* 11 eV. Most empirically based considerations of the spectra of phenol, put forward particularly in earlier PE studies, favour the assignment of the maximum at 11.59 eV to the latter ionization event. It should be noted, however, that an entirely different interpretation of the spectrum was offered by Palmer and coworkers[78]. Guided by the analysis of He I and He II PE spectra of phenol and supported by the results of *ab initio* calculations, these authors proposed the following binding energy order (in pseudo-benzene D_{6h} symmetry):

$$e_{1gS} < e_{1gA} < a_{2u} < e_{2gA} < e_{2gS} < n_O^\sigma < n_O^\pi = e_{1uA}$$

thus putting the π MO of the $1a_{2u}$ ring orbital at 11.59 eV and ascribing significantly larger *IE* values to the n_O^π lone-pair orbital (14.21 eV). The latter is rationalized in terms

TABLE 10. References to PE studies of substituted phenols



X					
		73–79			
Me	74,76,78,79	74,76,77,79	80		
t-Bu	74,80,81	74,80	80		
OH	78				
Br	73				
Cl	73	74			
F	78,82	82	82	82	74,82
NH_2	83				
NO_2	84	85			

*Ph_S and Ph_A designate e_{1gS} and e_{1gA} benzene MOs, respectively.

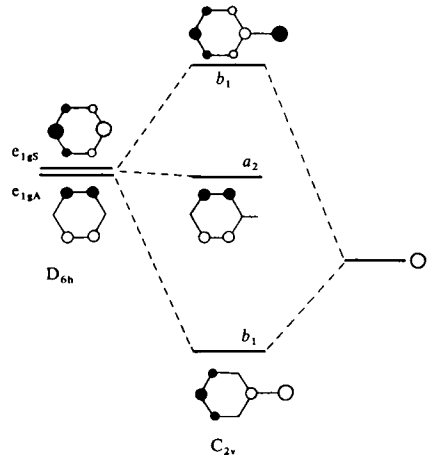


FIGURE 6. Interaction between the $e_{1g}(\pi)$ orbitals of benzene and n_O^{π}-type orbital of the hydroxyl group

of a_{2u}, n_O^{π} interaction. Analogous interpretation of PE ionization features of phenol is also advocated in Kimura and coworkers, recent handbook[19]. Changes in the first ionization energies of phenol by *ortho*-, *meta*-, and *para*-methyl substitution follow exactly the pattern expected within the first-order perturbation model (Figure 7)[86]. Thus, *ortho*- and *meta*-substitution leads to a decrease in IE_1 and IE_2 values of the same size (0.3 eV), whereas in the *para*-derivative IE_2 undergoes a less pronounced shift than IE_1 (0.15 vs 0.35 eV)[76,78]. Introduction of the second and third[80] methyl groups into the aromatic ring (**23**, **24** and **25**) results in further destabilization of the first two levels, with the extent of perturbation being roughly additive. Similar effects, but of somewhat greater magnitude, are also observed upon substitution by *t*-butyl group(s)[80]. Assignment of the higher-lying bands in all of the considered alkyl derivatives suffers from similar uncertainties as in the case of the parent phenol[19].

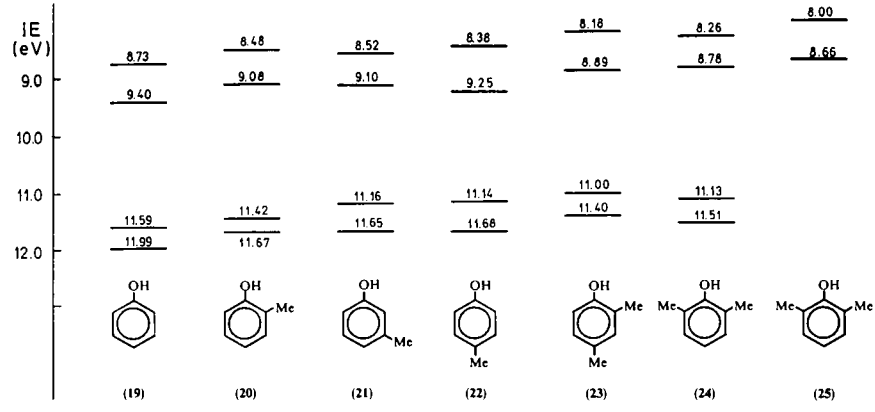
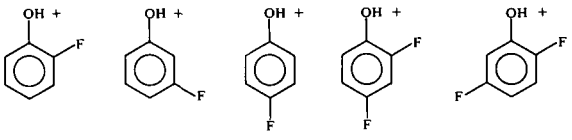


FIGURE 7. Comparison of the lowest ionization energies for methyl-substituted phenols **19–25**

PE spectra of a series of isomeric fluorophenols ranging from mono- (**26–28**) to penta- (**35**) substituted derivatives were measured by Maier and coworkers[82]. The ionization energies leading to the lowest four cationic states together with their symmetries inferred from the radiative decay studies are presented in Table 11. Perusal of the displayed data reveals that the ground ($\tilde{X}$) and the first excited state ($\tilde{A}$) of the fluorophenol radical cations result from removal of electrons from π-molecular orbitals. These are the lowest-energy PES events. Another point of interest is that the $\tilde{B}$ and $\tilde{C}$ states of the radical cations produced by photoionization of **22–29** are related to ejection of σ- and π-electrons, respectively. In spite of this, the vertical ionization energies leading to the $\tilde{B}$ state are greater than those of the π^{-1} process. Finally, in higher fluorophenols (**30–35**), the $\tilde{B}$ and $\tilde{C}$ states are found to be produced by ejection of σ- and π-electrons, respectively. Within the same study $\tilde{B}$–$\tilde{X}$ emission spectra of cations produced by photoionization of flourophenols **30–35** are presented.

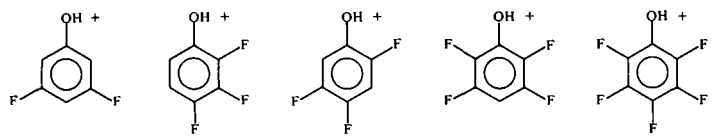
For compounds **26–28** He II spectra are also reported, the interpretation being guided by STO-3G calculations[78]. The same work offers a detailed comparison of the ionization pattern of fluorophenols with those of corresponding cresols (**20–22**) and dihydroxybenzenes (**36–38**). Similarly to cresols and fluorophenols, the PE spectra of dihydroxy-

TABLE 11. Photoelectron spectroscopic ionization energies leading to the indicated states of the fluoro-substituted phenol cations[a]



(26) (27) (28) (29) (30)

State	*IE*	Sym.	*IE*	Sym.	*IE*	Sym.	*IE*	Sym.	*IE*	Sym.
$\tilde{X}$	8.97	$^2A''$	9.05	$^2A''$	8.79	$^2A''$	8.98	$^2A''$	9.10	$^2A''$
$\tilde{A}$	9.60	$^2A''$	9.61	$^2A''$	9.71	$^2A''$	9.82	$^2A''$	9.69	$^2A''$
$\tilde{B}$	12.3	$^2A'$	12.5	$^2A'$	12.3	$^2A'$	12.7	$^2A'$	11.78	$^2A''$
$\tilde{C}$	11.70	$^2A''$	11.62	$^2A''$	11.57	$^2A''$	11.77	$^2A''$	12.8	$^2A'$



(31) (32) (33) (34) (35)

State	*IE*	Sym.	*IE*	Sym.	*IE*	Sym.	*IE*	Sym.	*IE*	Sym.
$\tilde{X}$	9.04	$^2A''$	9.19	$^2A''$	9.10	$^2A''$	9.40	$^2A''$	9.37	$^2A''$
$\tilde{A}$	9.23	$^2A''$	9.83	$^2A''$	9.89	$^2A''$	9.58	$^2A''$	9.57	$^2A''$
$\tilde{B}$	11.72	$^2A''$	11.87	$^2A''$	11.84	$^2A''$	12.00	$^2A''$	12.05	$^2A''$
$\tilde{C}$	13.4	$^2A'$	13.4	$^2A'$	13.5	$^2A'$	13.6	$^2A'$	13.7	$^2A'$

[a]In all cases the molecular symmetry is C_s. The *IE* values given correspond either to the most intense vibrational peak, or to the band maximum when the bands are structureless. Values given to two decimal places are to ± 0.02 eV, those given to one decimal place are to ± 0.1 eV. See text for explanation regarding the band B and C states for the first four compounds. Reproduced by permission of Elsevier Science Publishers BV from Reference 82.

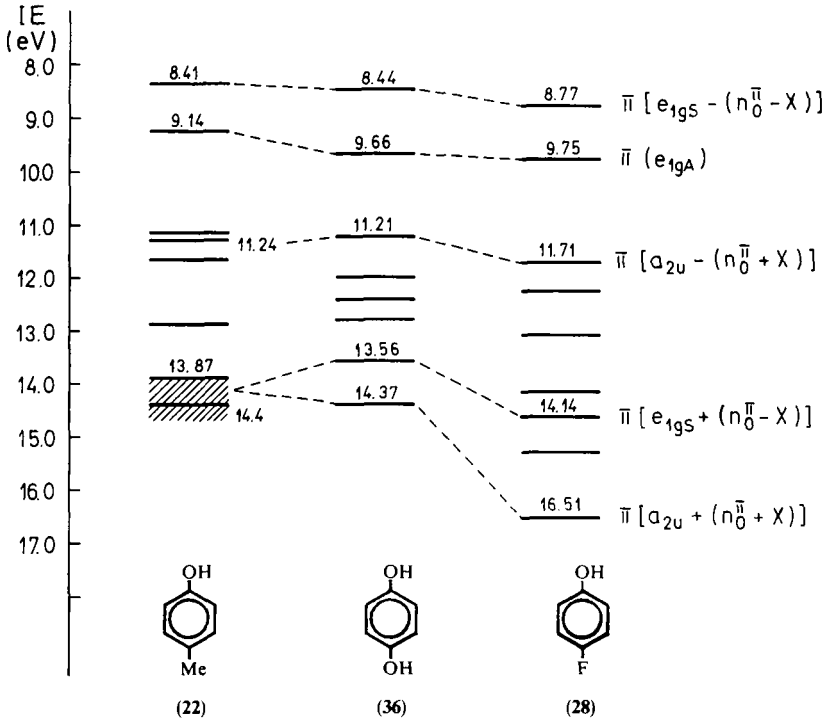


FIGURE 8. PES correlation diagram for compounds **22**, **28** and **36** (X = Me, OH and F, respectively)

benzene isomers exhibit three π-ionization events in the region below 12 eV. The lowest IE increases across the series *p*-dihydroxybenzene (**36**), catechol (**37**) and resorcinol (**38**), while IE_2 assumes the lowest value in **37**. A steady increase in the first ionization energies across the series **22–36–28** (Figure 8) is straightforwardly rationalized by invoking electronic properties of the substituents at hand. It is of interest to note that the splitting of the e_{1gS} ring orbital by interaction with Me and OH in *p*-cresol (**22**) and *p*-dihydroxybenzene (**36**) is significantly larger (5.3 eV) than that for the corresponding a_{2u} splitting (3.2 eV) whilst the two values are the same for *p*-fluorophenol (**28**). Different behaviour of the fluorine-substituted compounds is ascribed to the low extent of mixing of $(2p)^{\pi}_{F}$ with $(2p^{\pi}_{C})$; hence $1a_{2u}$ is virtually the $(2p^{\pi}_{F})$ lone-pair orbital.

A PE study of nitrophenols (**39–41**) performed by Kobayashi and Nagakura[84] throws some light on the extent to which the nitro group influences the ionization pattern of phenol. It is clearly seen in Figure 9, which shows the orbital correlation diagram obtained from the measured PE spectra, that the highest occupied orbitals of all isomers are lower by 0.6–0.7 eV than the highest occupied orbital of phenol. This may be reasonably well interpreted by considering the energy stabilization of the benzene-ring orbitals caused by the electron-withdrawing power of the nitro group. Similar consideration leads to assignment of the fifth band to the third highest occupied orbital of phenol. Near-constancy of IE_1, IE_2 and IE_5 across the series indicates that the contribution of the orbitals of the nitro group to the corresponding MOs is negligible. The third bands of all isomers are assigned to the a_1-like lone-pair orbital, largely localized on the nitro

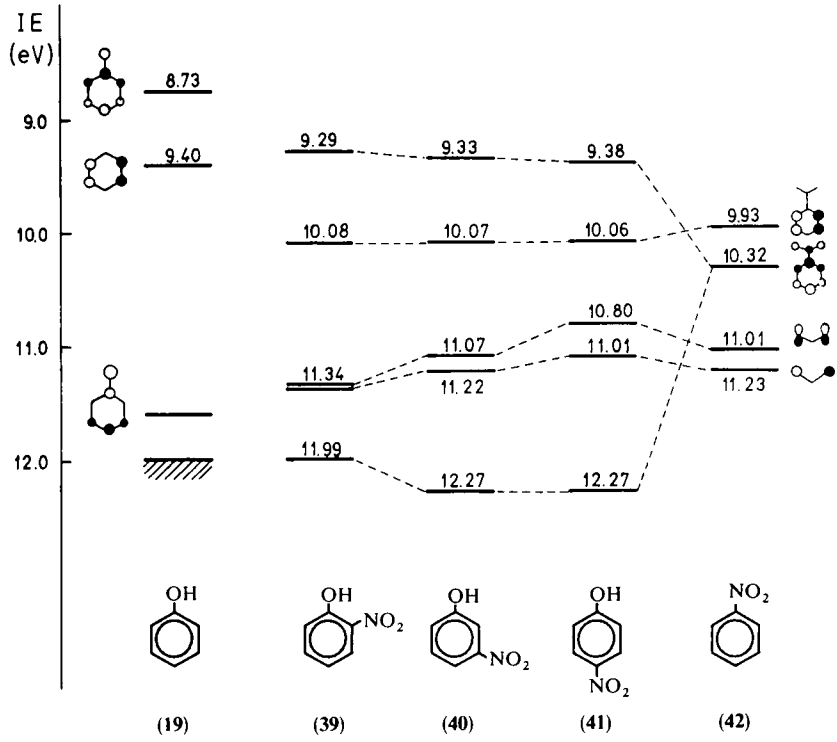


FIGURE 9. PES correlation diagram for nitrophenols **39–41**. Reproduced by permission of Elsevier Science Publishers BV from Reference 84

group, judging from the fact that their shapes and positions are similar to those of the third band of nitrobenzene (**42**)[87]. For the same reason, the fourth bands are attributed to the a_2-like π orbitals, largely localized on the nitro group. Another point of interest is that in the *meta*- (**40**) and *para*- (**41**) isomers the third and fourth bands appear as two distinct entities separated by 0.2 eV, while in the *ortho*- (**39**) derivative these two bands coincide. In order to trace the origin of this effect, the PE spectra of nitrophenols were compared with PE data for the corresponding nitroanisoles. Since $\Delta IE_{4,3}$ in the latter compounds is found to be almost independent of the position of the nitro group, the lowering of the a_1-like lone-pair orbital of the nitro group in *ortho*-nitro phenol is ascribed to hydrogen-bond formation[87]. By using similar arguments as above, the lowest ionization events in 2,4-dinitrophenol (**43**) (9.85 and 10.70 eV, respectively) are attributed to π MOs of e_{1gS} and e_{1gA} origin, respectively. The ionizations associated with nitro groups in **43** are centred around 11.7 eV. Each nitro group contributes a σ and a π orbital to yield IE_n^+, IE_n^-, IE_π^+ and IE_π^- events, but of close energies since both through-space and through-bond interactions between nitro groups are negligible.

Let us mention in passing that intramolecular hydrogen bonding is also invoked to rationalize ionization features of 4,6-dichlororesorcinol[88].

In contrast to phenols, there is only a limited number of PES studies dealing with higher homologues of phenol. We shall commence with the PE spectra of 1- (**44**) and

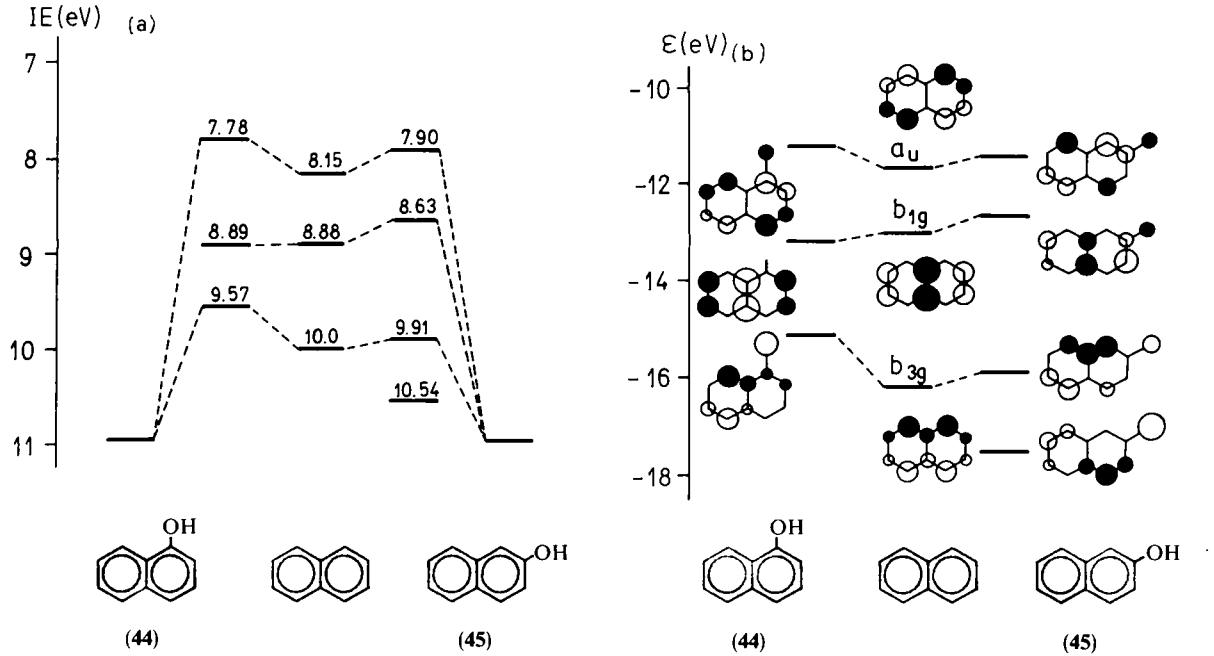


FIGURE 10. Comparison between measured *IE* values (in eV) (a) and orbital energies calculated by the CNDO/2 method (b) for naphthols **44** and **45**. Reproduced by permission of The Chemical Society of Japan from Reference 89

2-naphthol (**45**) that were reported by Utsunomiya and coworkers[89]. Following the composite molecule approach[17], the measured *IE* values of these two compounds are correlated with the PE data of their 'constituents' naphthalene[90] and methanol in Figure 10a, together with the theoretical orbital energy diagram and the shape of the highest occupied MOs calculated by the CNDO/2 method (Figure 10b). Differences in the ionization pattern between two isomeric naphthols are fully understood in terms of the localization properties of the highest occupied MOs of the naphthalene[13] moiety.

Another interesting contribution to PE investigations of aromatic hydroxy compounds is that of Millefiori and Millefiori, who discussed the consequences of intramolecular hydrogen bonding on the ionization energies in 1,4-, 1,8- and 2,6-dihydroxynaphthaquinones[91].

C. Ethers

In this section we will present first the general features of simple dialkyl ethers. Thereafter, a brief overview of the trends observed in heterosubstituted and unsaturated acyclic ethers will be given. Subsequent sections will be devoted to cyclic-, polycyclic- and polyethers. Finally, aromatic ethers will be considered in some detail.

1. Dialkyl ethers

Photoelectron spectra of dialkyl ethers have been measured by several research groups and used extensively in discussing ionization patterns of a vast number of complex molecules involving the ethers function [12,26,29,34,76,92–100]. A relevant selection of PE data is compiled in Table 12.

The most frequently discussed features of the spectra concern the position and shape of the band related to the n_O^{π} and n_O^{σ} ionization events. The corresponding *IE* values of MeOMe are 10.01 ($2b_1$) and 11.9 eV ($4a_1$), respectively. The higher-lying bands of MeOMe appearing at 13.55, 14.20 and 16.4 eV are assigned to $3b_2$, $1a_2$ and $2b_2 \cong 3a_1 \cong 1b_1$ MOs,

TABLE 12. Vertical ionization energies *IE* (eV) of dialkyl ethers (R^1—O—R^2)[a]

R^1	R^2	*IE* (eV)[a]	References
Me	Me	10.01; $b_1(n_O^{\pi})$; 11.90, $a_1(n_O^{\sigma})$; 13.55, $b_2(\sigma_{CO})$; 14.20, $a_2(\sigma_{CO})$; 16.4, $b_2(\sigma_{CO})$, $a_1(\sigma)$, $b_1(\pi_{Me})$	27, 34, 92–95, 99
Me	Et	9.86, $4a''(n_O^{\pi})$, 11.60, $13a'(n_O^{\sigma})$; 12.57, $12a'(\sigma_{CC})$; 13.13, $3a''(\pi_{Me})$; 13.94, $11a'(\pi_{Me})$; 14.70, $2a''(\pi_{Me})$; 15.72, $10a'(\pi_{Me})$; 16.53, $9a'(\sigma_{CO},\sigma_{CC})$; 17.14, $1a''(\pi_{CH_2},n_O^{\pi})$	19
Me	n-Pr	9.75 (n_O^{π})	100
Me	*i*-Pr	9.65 (n_O^{π})	100
Me	n-Bu	9.69 (n_O^{π})	100
Me	*i*-Bu	9.69 (n_O^{π})	100
Me	*t*-Bu	9.55 (n_O^{π})	100
Et	Et	9.61, $5a''(n_O^{\pi})$; 11.08, $16a'(n_O^{\sigma})$; 11.92–12.63	34
Et	*t*-Bu	9.39 (n_O^{π}); 10.70	97
n-Pr	n-Pr	9.32 (n_O^{π})	92
i-Pr	*i*-Pr	9.35 (n_O^{π})	118
n-Bu	n-Bu	9.51 (n_O^{π}); 10.96 (n_O^{σ})	97
t-Bu	*t*-Bu	8.94 (n_O^{π})	98

[a]Values refer to band maxima.

TABLE 13. Comparison of ionization energy shifts[a] (eV) and calculated dipole-induced potential-energy shifts (in parentheses) of $Me_2O \cdot HCl$ and $Me_2O \cdot HF$

	$Me_2O \cdot HCl$[b]	$Me_2O \cdot HF$[c]
n_O	0.6 (0.85)	1.0 (1.02)
π_{Me}	0.4 (0.53)	0.6 (0.61)
n_O, σ_{CO}	0.5 (0.75)	0.8 (0.97)
n_F or n_{Cl}	−1.0 (−0.34)	−1.6 (−0.56)

[a] *IE* (complex) − *IE* (monomer).
[b] Using *R*(O—H) = 1.9 Å and an out-of-plane angle of 34° (Reference 102).
[c] Using *R*(O—H) = 1.72 Å and planar geometry (Reference 103).

respectively. There is, however, still some disagreement as to whether $2b_2$ and $1b_2$ MOs are of σ_{CO} and σ_{CH_3} character or *vice versa*. It should be noted that the proposed assignment refers to the 'double eclipsed' (C_{2v}) structure of MeOMe which appears to be the most stable conformer according to electron diffraction measurements[101]. Rotation of one of the Me groups leading to the 'mono-eclipsed' structure should, according to the CNDO/2 calculations, lead to a slight destabilization of the highest occupied MO ($2b_1$) and a significant reduction in the energy gap between $3b_2$ and $4a_1$ MOs, with the latter orbital being more stable[94].

The trend of changes in *IE* values in higher ethers resembles closely that observed in the corresponding alcohols, i.e. as the alkyl group becomes more bulky, the lowest ionization energies decrease, while the area of higher-lying overlapping bands of the inner MOs moves towards first ionization events (Table 12).

PE studies of the gas-phase intramolecular complexes of Me_2O with HCl[102] and HF[103] are also of considerable interest. Their He I photoelectron spectra have been measured by using a specially developed nozzle (HCl)[102] ot pinhole (HF)[103] inlet system with high-pressure equilibrium mixtures of the respective gases. Spectra representing each complex in a 'pure' form are obtained by a spectrum-stripping procedure which removes the appropriate monomer spectra from each mixed spectrum. The experimental results indicate that the effect of hydrogen-bond formation is to raise the n_O^{π} *IE* of the Me_2O and to lower the π_{Hal} *IE* of the HHal component. The observed *IE* shifts occurring for the $Me_2O \cdot HCl$ and $Me_2O \cdot HF$ complexes are compared in Table 13. Stabilization of n_O^{π} is found to be mainly due to the electrostatic effect arising from the polar HHal moiety. π_{Hal} shifts, which appear to be appreciably higher, are rationalized in terms of charge transfer and electron-relaxation effect. Their contributions are comparable. The calculated charge transfers involved are small and amount to 0.06e and 0.05e from Me_2O to HF and HCl, respectively. The electronic-relaxation effect involves the highly polarizable Me_2O moiety in each complex, acting as a source of electron density which considerably stabilizes the localized valence hole in HF^+ or HCl^+. The calculations show that the drift of electron density is 0.13e to HF^+ in $Me_2O \cdot HF^+$ and 0.11e to HCl^+ in $Me_2O \cdot HCl^+$.

2. *Heteroalkyl ethers*

There has been considerable interest in evaluating the extent and mode of perturbation of oxygen lone-pair electrons by electronegative substituents and their influence on the corresponding PES levels. Leavell and coworkers[53] have reported PES data of several aminoalkyl methyl ethers and Hoppilliard and Solgady[52] the PE spectra of haloethyl methyl ethers ($MeOCH_2CH_2X$, X = Cl, F, Br, I). In both cases, introduction of the

substituent leads to an increase in the $IE(n_O^{\pi})$, but the effect is small. For instance, $IE(n_O^{\pi})$ within the $MeOCH_2CH_2X$ series assumes the following values: 9.72 (X = H), 10.18 (X = F), 10.05 (X = Cl), 10.13 (X = Br, *gauche*), 10.20 (X = Br, *trans*), 10.25 (X = I, *gauche*) and 10.23 eV (X = I, *trans*).

Another interesting conclusion that emerges from Hoppilliard and Solgady's study concerns the conformation of haloethyl ethers[52]. Observation that the bands related to ionization from the lone pairs of halogen atoms are degenerate (Cl derivative) or split by only 0.3 eV (F derivative) led these authros to conclude that the latter two compounds exist exclusively in the *trans* form in vapour phase. Additional support for greater stability of *trans* conformers was provided by *ab initio* calculations employing the STO-3G basis set. On the other hand, PE spectral features of the Br and I derivatives strongly indicate that these compounds coexist as *gauche* and *trans* conformers.

The effect of halogen substitution on the oxygen lone-pair orbitals was also discussed by Hardin and Sandorfy[104], who measured the PE spectra of fluoroethers of the $F(CF(CF_3)CF_2O)_nCHFCF_3$ ($n = 1$–4) type. However, due to the complexity of the spectra, only two observations from this work deserve attention: (a) the very high value of the lowest *IE* values (above 13 eV) and (b) close spacing of the bands related to ionization of the oxygen lone pair and C—C σ orbitals.

In a more recent study, Zverev and coworkers[100] have addressed the problem of mutual interaction between the OMe and Cl substituents on the *IE* values in a series of chloromethyl ethers ($ROCH_2Cl$, R = Me, Et, n-Pr, *i*-Pr and n-Bu), along with the question of intramolecular charge transfer. The n_O^{π} *IE* values for n-alkyl members of the series were found to vary from 10.84 eV ($MeOCH_2Cl$) to 10.35 eV ($n\text{-}BuOCH_2Cl$), while a value of 10.27 eV was recorded for $i\text{-}PrOCH_2Cl$. The following two bands (11.0–11.5 eV), assigned to chlorine lone-pair ionizations in all considered compounds, are found to be split by 0.3–0.4 eV, presumably as a result of conjugative interaction with the n_O^{π}. A marked increase in the first ionization energies, as compared to structurally related dialkyl ethers and alkyl chlorides, suggests, however, that the inductive effect is by far more important.

Finally, a compilation of PE data for a variety of dialkyl ethers, along with the newly measured PE data for two series of ethers of the general formulae XOMe ($X = CH_2Cl_2$, CH_2CF_3), have been reported by Molder and coworkers[105]. Assignment of the newly recorded spectra was attempted by using CNDO/2 calculations and by employing empirical relationships between the measured *IE* values and various energetic parameters (proton affinity, Taft's σ^* and σ_R^{π} constants, etc.). The main emphasis of the work is laid on the utility of various empirical correlations in assigning PE spectra that comprise highly overlapping bands.

3. *Olefinic ethers*

a. Vinylic ethers. He I PE spectra of vinyl ethers are characterized by two low ionization energies originating from π-type MOs[66,106–109]. The first one is mainly localized in the C=C bond whereas in the second MO in question the n_O^{π} character prevails. As splitting of these MOs depends strongly on the relative orientation[106–112] of the $\pi_{C=C}$ subunit and n_O^{π} lone pair (Figure 11), the difference in the corresponding *IE* values provides a sensitive probe for collinearity within the C=C—O—C moiety[110].

Particularly instructive in this respect is the work of Friege and Klessinger[106,107], who investigated conformational behaviour of a series of alkyl vinyl ethers depicted in Table 14 by employing the variable-temperature PE technique[113] and CNDO/2 calculations. We shall single out two compounds, **46a** and **47**, as representatives of sterically hindered and unhindered ethers. At room temperature, the PE spectrum of **47** shows two ionization bands (8.25 and 11.25 eV) separated by 3.0 eV. If the temperature

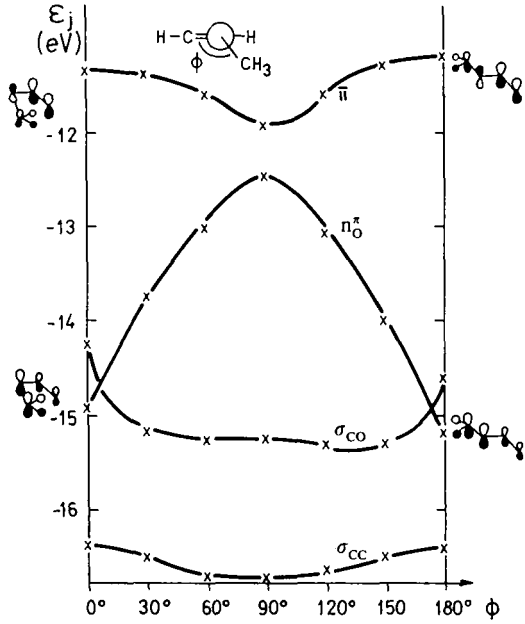


FIGURE 11. Calculated orbital energies (CNDO/2) for the highest occupied MOs of vinyl ether vs the COOC dihedral angle ϕ. Reproduced from Reference 106

TABLE 14. Vertical ionization energies IE (eV) of alkyl vinyl ethers (**46**) and of (*Z*)-2-methoxy-but-2-ene (**47**)[106,107]

	Most stable conformer				Less stable conformer		
Compound	IE_1	IE_2	$\Delta IE_{2,1}$	T(K)	IE_1	IE_2	$\Delta IE_{2,1}$
H_2C=CHOR							
46a R = Me	9.14	12.13	2.99	513	9.14	12.35	3.21
46b R = Et	9.15	11.68	2.53			not determined	
46c R = *i*-Pr	8.84	11.34	2.50	503	10.4	10.4	<0.2
46d R = n-Bu	9.10	11.32	2.22			not determined	
46e R = *t*-Bu	8.77	11.02	2.25				
47	8.25	11.25	3.00	508	9.6	10.1	0.5

is raised to 508 K, two new bands emerge (9.6 and 10.1 eV, respectively) separated by only 0.5 eV. The high-temperature PE spectrum of **46a**, on the other hand, exhibits no new bands. Instead, a change in the shape of the second band is observed, indicating the presence of a new ionization event at 12.35 eV. The latter is separated from the first band by 3.21 eV. In connection with the orbital correlation diagram given in Figure 11, these findings suggest different conformational equilibria in **46a** and **47**. In the sterically unhindered ether **46a**, *syn*-conformation predominates over *anti*-form whereas its sterically hindered counterpart **47** exhibits *anti-gauche* equilibrium, with the latter form

being less stable. These results are explained by assuming a strong steric repulsion occurring in *syn* conformation if the alkyl group is bulky or if the vinyl group carries additional substituents.

Conformational behaviour of alkyl vinyl ethers has also been studied by the IR, Raman, microwave and electron diffraction techniques[114]. All these methods indicate that alkyl vinyl ethers can exist in a second conformation in addition to a stable *syn* form. There is, however, some doubt whether this is a *gauche* conformation, as concluded from the electron diffraction and microwave measurements, or a planar *anti* form as inferred from the IR spectrum.

A structurally related family of molecules possessing the OMe group attached to the C=C double bond is provided by methoxybutadienes. PES data are available for 2-methoxy and 1-*trans*-methoxy-butadiene[115]. The π,n_O^{π} splitting energies in these molecules, as judged from their He I PE spectra, amount to 2.5 and 1.5 eV, respectively.

Finally, in divinyl ether, interaction between the ethylenic π-orbitals and n_O^{π}-type oxygen lone pairs gives rise to three ionization events in the low-energy region of the PE spectrum, at 9.0, 10.51 and 12.60 eV. Ionization related to the n_O^{σ} lone pair appears at 12.43 eV[116].

Incorporation of the C=C—O subunit into the ring system, like in 3,4-dihydropyran[108,117] leads to a significant reduction of the first *IE* value [8.68[108], (8.56)[117]] relative to the acyclic counterparts. Furthermore, the second *IE* value in 3,4-dihydropyran (11.0 eV) relates to electron ejection from the highly delocalized ribbon-type[118] σ orbital involving mainly the in-plane oxygen lone pair (n_O^{σ}). Finally, the third *IE* value corresponds to the n_O^{π} orbital, delocalized, to a considerable extent, over the adjacent methylene groups via a pseudo-π combination[117]. As an example of a bicyclic specimen with a C=C—O fragment, we chall mention 9-oxabicyclo[3.3.1]-nona-1-ene. For this molecule, Batich and coworkers[119] deduced a deviation from coplanarity of the vinyl ether system of approximately 70–75° by applying the LCBO model and assuming the angular dependence of the interaction term to be of the form $B = B_0 \cos\Theta$.

b. Homoallylic ethers. In contrast to compounds discussed in the previous subsection, direct conjugation of n_O^{π} lone pairs and double bonds in homoallylic compounds is intercepted by an insulating CH_2 group. PE spectra of several cyclic and bicyclic representatives of these highly interesting systems have been reported by Neijzen and coworkers[120]. Ionization energies due to the $\pi_{C=C}$ and n_O^{π} oxygen lone-pair orbitals of some characteristic examples are summarized in Table 15. Comparison with PE data of structurally related saturated ethers suggests that the n_O^{π}, π interaction is small and,

TABLE 15. Vertical ionization energies *IE* (eV) of monocyclic and bicyclic homoallylic methyl ethers[120]

Compound	*IE* (eV)	
	π	n_O^{π}
4-Methoxycyclopentene	9.12	9.57
4-Methoxycyclohexene	9.01	9.40
syn-7-Methoxycyclo[2.2.1]hept-2-ene	8.84	9.40
anti-7-Methoxybicyclo[2.2.1]hept-2-ene	9.02	9.52
endo-5-Methoxybicyclo[2.2.1]hept-2-ene	8.69	9.37
exo-5-Methoxybicyclo[2.2.1]hept-2-ene	8.68	9.51
endo-5-Methoxybicyclo[2.2.1]oct-2-ene	8.77	9.27

as expected, due to the presence of an intervening CH_2 group, mainly of through-bond character. The observed ionization energy shifts are dominated by inductive effects.

c. Acetylenic ethers. The He I PE spectrum of methoxyacetylene has been reported by Modena and coworkers[121]. The measured ionization energies and the corresponding assignment based on *ab initio* calculations, with inclusion of pseudo-potentials[122], are shown in Table 16.

d. Alkyl allenyl ethers. He I PE spectra of alkoxyallenes[123–125] are represented here by the following molecules: 1-methoxy-[123], 1,1,3,3-tetraethoxy-[124] and 1,1-diethoxy-3,3-bis(trifluoromethyl)allene[124]. The first three bands in the PE spectrum of 1-methoxyallene are encountered at 8.75, 10.33 and 12.0 eV, respectively. They are due to ionizations from out-of-phase linear combinations of allenic a'' MO and n_O^π oxygen lone pairs, a' component of the allenic 2e orbital and σ_{COC} a' MO, respectively. Considerable shift of the first band relative to its position in the PE spectrum of allene (10.5 eV)[126] results from a purely conjugative type of interaction.

In the low-energy region of the PE spectrum of 1,1,3,3-tetraethoxyallene, two bands, each related to two ionization events, are found at 8.13 and 10.17 eV[124]. The first two ionization events are assigned to ionization out of two degenerate MOs describing the $(EtO)_2$ C=C subunits (Figure 12). Each of them is composed of an out-of-phase linear combination of one of the allenic π-orbitals and n_O^π oxygen orbital of the adjacent oxygen atoms. Replacement of one of the pairs of the alkoxy groups by CF_3 leads to considerable splitting of the first two levels, as indicated in Figure 12. The first band (8.93 eV) is due to an ionization from the diethoxyethylene fragment while the second ionization event arises from the photoelectron ejection taking place within the $(CF_3)_2C{=}C$ group. It should be noted that CF_3 groups influence the adjacent π orbital entirely via the inductive effect.

e. Allenyl vinyl ethers. PE data for two ethers belonging to this class are reported: $CH_2{=}C{=}C$ (R)OCH$=CH_2$ (R=H, *i*-Pr)[117]. By comparing the measured PE data for these two ethers (Table 17) with those of divinyl ether and allyl alcohol[65], the lowest three bands are attributed to the antibonding combination of ethylenic, $C_\alpha{=}C_\beta$ allenic and n_O^π orbital, an orbital of predominant n_O^π character and to the $C_\beta{=}C_\gamma$ allenic π orbital. The IE_4 and IE_5 correspond to the n_O^σ and bonding combination of allenic $C_\alpha{=}C_\beta$ and ethylenic semi-localized π orbitals.

f. α-Keto ethers. PE spectra of 3-*endo*- (**48**) and 3-*exo*-methoxybicyclo[2.2.1]heptan-2-one (**49**) offer firm evidence for the existence of through-bond interaction involving

Table 16. Comparison between vertical ionization energies IE (eV) and calculated orbital energies ε (eV) for methoxyacetylene[125]

IE (eV)	$-\varepsilon$ (eV)	Symmetry, MO character
9.62	9.22	a'', $\pi_{CC,O}$ ($\alpha^+ - O^- - Me^+$)
10.3	9.75	a', π_{CC} (in plane)
13.4	13.32	a'', $\pi_{O,Me}$ ($\alpha^+ - O^+ - Me^-$)
	13.60	a', $\sigma_{O,Me}$
16.7	16.13	a', $\sigma_{O,Me}$
	16.60	a'', $\pi_{Me,O}$ ($\alpha^+ - O^+ - Me^+$)

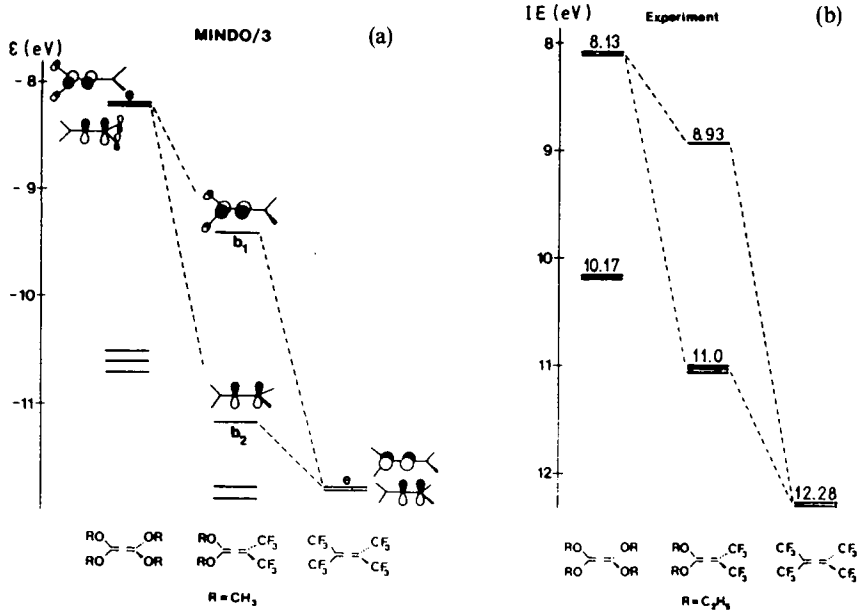
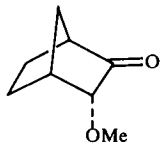


FIGURE 12. Comparison between orbital energies calculated by the MINDO/3 method (a) and measured *IE* values (in eV) (b) for 1,1,3,3-tetraethoxy-, 1,1-diethoxy-3,3-bis(trifluoromethyl)- and 1,1,3,3-tetrakis(trifluoromethyl)allene. Reproduced by permission of VCH Publishers from Reference 124

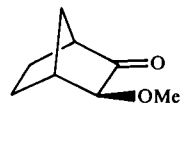
TABLE 17. Vertical ionization energies *IE*(eV) of allenyl vinyl ethers (CH_2=C=C(R)-OCH=CH_2)[117]

R	IE_1 (π)	IE_2 (n_O^{π})	IE_3 (π)	IE_4 (n_O^{π})	IE_5
H	8.78	10.22	10.55	12.54	12.54
n-Pr	8.44	9.90	10.20	12.16	11.75

the n_O^{π} and lone-pair electrons of the carbonyl oxygen[127]. The PE spectrum of **48** indicates the presence of two different conformers, which appear in a ratio 4:1. The more abundant conformer gives rise to ionizations at 8.71 (IE_1) and 10.4 (IE_2)eV, whereas the less represented conformer exhibits peaks at 9.0 and 9.9 eV. The relatively large energy difference $\Delta IE_{2,1} = 1.7$ eV and the comparatively small difference of 0.9 eV observed for the major and minor conformers, respectively, suggest a larger through-bond interaction

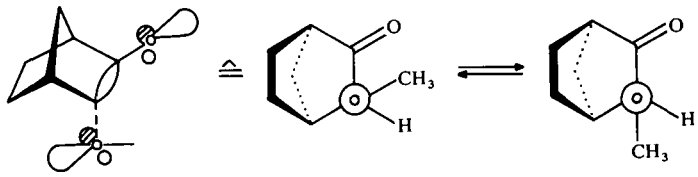


(48)



(49)

between the n_O^{π} and non-bonding carbonyl electron pairs in the former than in the latter conformer. The lower-energy bands (IE_1) correspond to the out-of-phase combination of ethereal and carbonyl oxygen lone pairs, whereas the higher-energy bands are associated with their in-phase combination. In the major conformer, the energy split of 1.7 eV is of a similar order of magnitude to that found in the PE spectra of α-methoxycyclohexanone (1.4 eV) and bicyclo[2.2.1]heptadi-2,3-one (1.5 eV). It is proposed on this basis that the major conformer corresponds to the *'homo-gauche'* structure **48G** and the less stable one to the *'homo-anti'* conformer **48A**. The more efficient through-bond interaction between n_O^{π} and n_{CO} in the former conformer results from a better overlap of the n_O^{π} with the σ C^2C^3 bond. In contrast, the PE spectrum of **49** is consistent with an equilibrium in which *'homo-anti'* conformer is slightly more stable than the corresponding *'homo-gauche'* rotamer. The major conformer is associated with two bands centred at $IE_1 = 9.1$ and $IE_2 = 9.7$ eV, respectively.



(48G) (48A)

4. Cyclic ethers

a. Oxiranes. Oxiranes represent a class of compounds that is interesting from both the theoretical and industrial points of view. It is therefore not surprising that many oxiranes have been subjected to PE investigations. Ionization energies of the parent oxirane were reported by Al-Joboury and Turner as early as 1964[27] and several other groups reported and/or discussed its electronic structure in the following years[128–133]. The assignments of the second and third ionization bands were particularly difficult to make, since various calculations[128–130] disagree over the relative energies. Double-zeta-level SCF calculations[128] show the highest occupied two orbitals (a_1 and b_1) to be almost accidentally degenerate, but calculations of the first two *IE* values correction for electronic reorganization and correlation energies indicate that the b_1 orbital, with a lone-pair character, is higher in energy. This is evidenced by experimental observations, since the vibrational Franck–Condon factors for the first band are typical of the out-of-plane oxygen lone-pair orbitals in ethers. The next two orbitals are Walsh orbitals, as predicted by the same calculations, with the a_2 (W_S) orbital of lower energy than the b_2 (W_A) orbital. The latter ordering was corroborated by STO-3G[132] and STO-4311G[133] calculations. Additional support is offered by calculations taking into account Koopmans' defects by a perturbation method[134]. These results were disputed, however, by 6-31G* calculations which predict the ordering $a_1 > b_1 > a_2 > b_2$[129]. We can take it to be confirmed that the sequence of the four highest occupied MOs in oxirane follows the order proposed by Basch and coworkers[128] ($b_1 > a_1 > b_2 > a_2$). Most conclusive evidence in favour of such assignment came through the thorough analysis of the PE spectral features of carefully selected series of substituted oxiranes[131] shown in Figure 13. Let us mention in passing that the PE spectra of halomethyloxiranes shown in Figure 13 have been also reported by Baker and coworkers[73] who, however, have not proposed any definitive interpretation of the recorded spectra.

McAlduff and Houk[131] have also measured the PE spectra of vinyl- and phenyloxirane. Vinyloxirane has three ionization energies virtually the same as in oxirane. These are

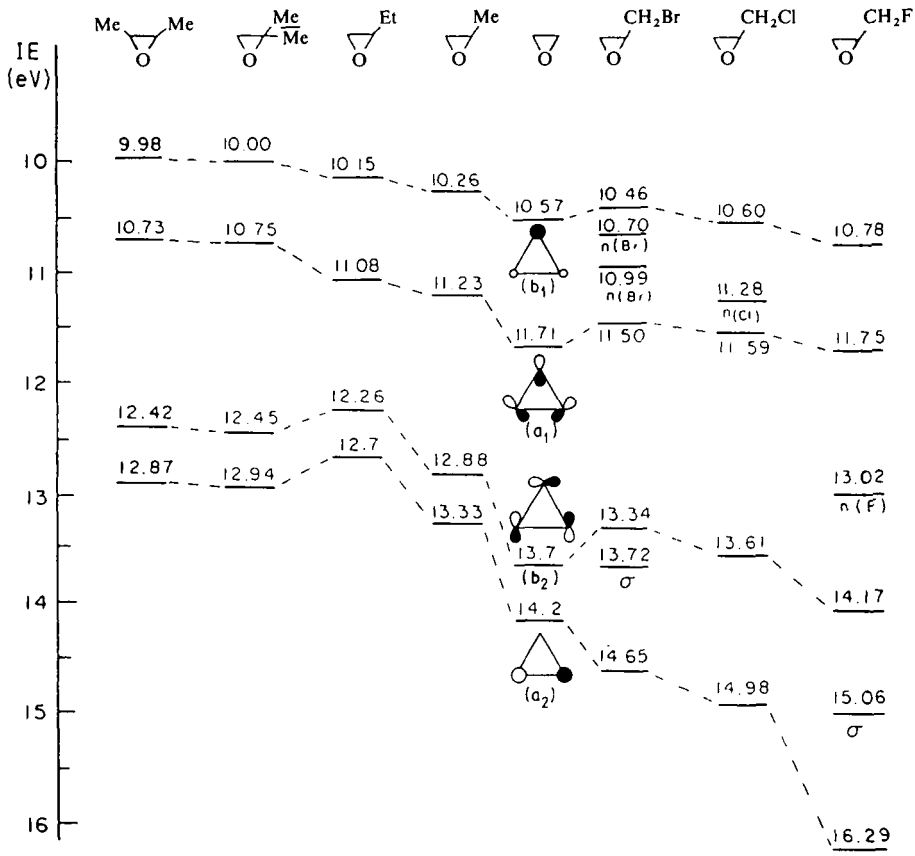


FIGURE 13. Correlation between ionization energies of oxirane and substituted oxiranes. Reproduced with permission from Reference 131

located at 10.58 (b_1), 13.88 (b_2) and 14.22 eV (a_2), respectively. In addition, the interaction of the ethylenic π orbital (10.52 eV) with a_1 Walsh orbitals of the oxirane ring results in two new orbitals, whose IE values are 9.94 and 12.21 eV, respectively. Other ionization in this region corresponds to the removal of an electron from the σ levels of the vinyl moiety. The measured IE value (12.71 eV) compares favourably with the corresponding energy in ethylene (12.38 eV)[135].

A similar type of interaction has been also encountered in the PE spectra of *cis*- and *trans*- diethynyloxirane[135]. The lowest ionizations of these compounds, related to lone-pair MOs, occur at 10.05 and 10.07 eV, respectively. The set of three closely spaced lower-lying bands (10.68–11.30 eV and 10.82–11.51 eV, respectively) is related to orbitals centred mainly on the acetylenic moiety, while the bands observed in the region $IE > 12$ eV seem to follow the pattern described for vinyloxirane[131,135].

The first ionization energies in phenyloxirane (9.07 and 9.47 eV) are related to Ph_S and Ph_A components of the degenerate e_{1g} benzene ring orbitals[131,136,137]. On the other hand, ionization energies at 10.30, 13.42 and 14.08 eV are assigned to MOs predominantly

localized at the oxirane moiety. In contrast to vinyloxirane, these ionization energies are lower than the corresponding ones in oxirane, indicating a stronger inductive and/or hyperconjugative donor ability of the phenyl group as compared to the vinyl moiety. Pertinent to this discussion is also a paper of Güsten and coworkers[137], who have compared ionization energies of phenyloxirane and several polyphenyl-substituted oxiranes (2,2-diphenyloxirane, *trans*-2,3-diphenyloxirane, 2,2,3-triphenyloxirane and 2,2,3,3,-tetraphenyloxirane) with those of the corresponding ethylenic congeners. Considerably smaller splitting of the lowest-energy benzene π orbitals is encountered for the former class of compounds.

PE studies have also been carried out on several oxiranes derived from polycyclic aromatic hydrocarbons[138]. Figure 14 shows He I photoelectron spectra along with the assignment and vertical ionization energies for the highest occupied orbitals in **50**, **51** and **52**. The measured PE spectra closely resemble the PE spectra of the parent

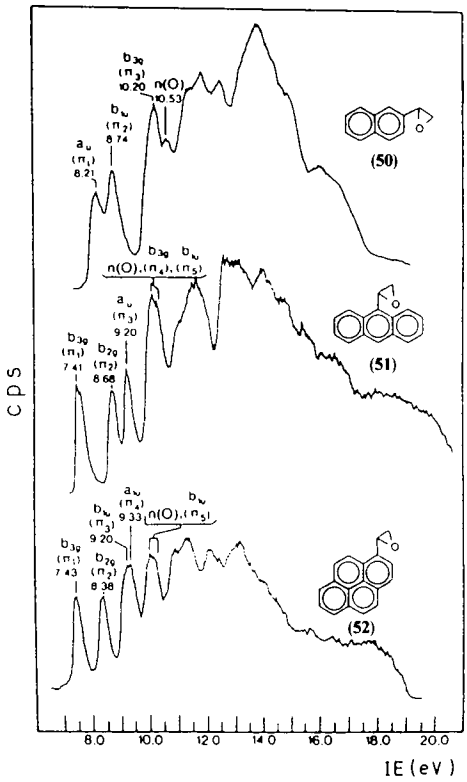
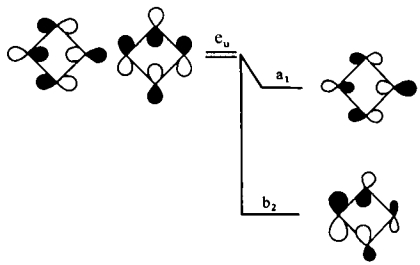


FIGURE 14. He I PE spectra of 2-oxiranylnaphthalene (**50**), 9-oxiranylanthracene (**51**) and 1-oxyranylpyrene (**52**). Assignments and vertical *IE* values are given for the highest occupied MOs. Reprinted with permission from I. Akiyama and coworkers, *J. Phys. Chem.*, **83**, 2992 (1979). Copyright (1979) American Chemical Society

hydrocarbons[139], the only difference being the appearance of an extra band in the energy region 10.0–10.5 eV. This band is associated with the n_O^{π} oxygen lone-pair orbitals of the epoxide group. The band arising from the more stable of these lone-pair orbitals appears in a region of poor resolution and has not been assigned. The similarity of the aryloxirane π systems and those in the parent hydrocarbons indicates that in molecules **50–52** the interaction between the π system of the aromatic hydrocarbon moiety and the lone-pair orbitals of the oxirane group is small. The same conclusion holds for phenantrene-9, 10-oxide and *trans*-7,8-dihydroxy-*anti*-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene described in the same study[138]. The above conclusions were substantiated by CNDO/S3[140] molecular orbital calculations.

b. Oxetane. The first *IE* value (9.63 eV) of oxetane is assigned to the n_O^{π} lone pair. The band shape (a very strong adiabatic transition, followed by rapidly diminishing intensity 0–1, 1–2 and 0–3 transitions) is typical of p-type non-bonding electron pairs. The second and third *IE* values are related to a_1 and b_2 orbitals which are derived from the degenerate e_u pair of cyclobutane[128,141]. Various molecular orbital calculations suggest that these orbitals retain much of the form of their homocyclic counterparts[132,142]. They are, however, lowered in energy and reinforced either at oxygen (a_1) or in the vicinity of the transannular carbon (b_2). It should be emphasized that semi-empirical calculations predict orbital a_1 to be of lower energy than b_2[142], while *ab initio* calculations employing either STO-3G or 4-31G basis set predict opposite ordering[132]. The latter sequence follows also from the appearance of the PE spectrum[132] (Figure 15) and correlation of the recorded PE data with those of structurally related acyclic and three-membered ring analogues.



c. Furan, 2,5-dihydrofuran and tetrahydrofuran. The numerous PE spectroscopic studies of the title compounds[143–181] have been primarily stimulated by the fact that these molecules are among the most important constituents of a variety of biochemical systems[143]. Additionally, they are of fundamental interest pertaining to the electronic structure of five-membered chalcogenides[144]. Most of the earlier results have been covered in two recent review articles[2,3]. We shall therefore only briefly recapitulate the most important conclusions regarding the electronic structure of the parent molecules to be followed by an overview of the substituent effects[155,158,159,170–179] and by pointing to the PE spectral features of structurally related, more complex systems [178–181].

We shall commence discussion by employing PE spectral data for tetrahydrofuran[117,145–147]. The main point of interest in the PE spectrum of this molecule concerns the band resulting from ionization of the n_O^{π} lone pair, at 9.57[145] eV (9.71 eV)[147]. Its shape ($\Delta E_{1/2} = 0.55$ eV) is indicative of considerable mixing of the oxygen lone-pair orbital with pseudo π-orbitals of the neighbouring CH_2 groups[147].

The PE spectrum of 2,5-dihydrofuran was first recorded by Bain and coworkers[145]

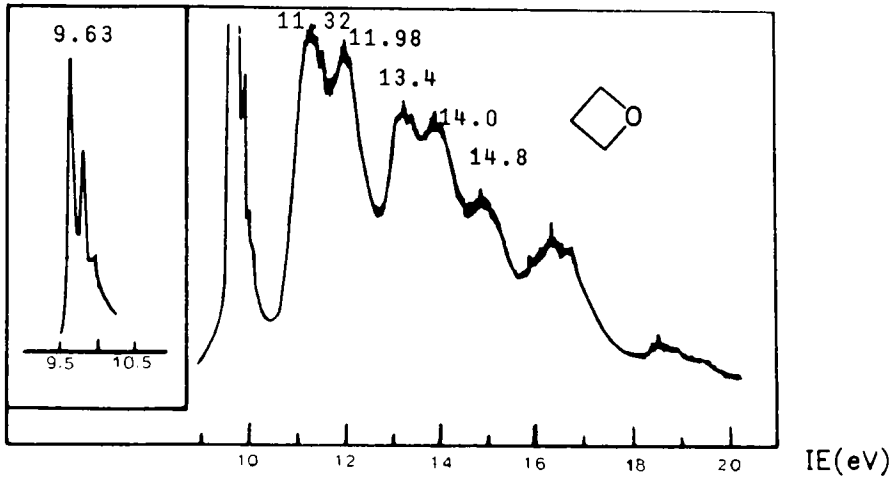
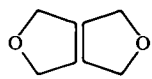


FIGURE 15. He I PE spectrum of oxetane. Vertical *IE* values (in eV) are indicated above the bands. Reprinted with permission from P. D. Mollere and K. N. Houk, *J. Am. Chem. Soc.*, **99**, 3226 (1977). Copyright (1977) American Chemical Society

and interpreted in terms of through-space interaction between the oxygen lone pair n_O^{π} and the double bond π orbital. Subsequently, however, Schmidt and Schweig[148] have shown that through-space interaction is negligible and that hyperconjugative interaction between the above specified orbitals via the two methylene groups is responsible for the observed split of 1.44 eV between the first two PE bands (9.18 and 10.62 eV, respectively). This important conclusion, which has crucial consequences for the nodal properties of the two highest occupied orbitals of 2,5-dihydrofuran, received strong support from PES results for structurally related heterocyclic molecules[149] and bicyclic oxides[145,150,151]. Close to the case at hand is also 3,7-dioxabicyclo[3.3.0]oct-1(5)-ene (**53**), for which the lowest ionization band, corresponding to electron removal from an orbital of predominantly π-double-bond character, appears at 8.85 eV. The second (9.80 eV) and third (10.60 eV) lowest ionization bands arise from out-of-phase and in-phase π-type orbitals, respectively located primarily on the oxygen atom. The in-phase combination is stabilized by through-bond interactions.



(53)

Contrary to its saturated analogoues discussed above, assignment of the PE spectrum of furan has been a matter of considerable dispute[152–162]. The six band systems identified in the low-energy region of its He I[152–159] and/or He II[95,160–162] spectra (Figure 16) have been interpreted as follows:

(I) *Reference 160:*

$$a_2(\pi) < b_1(\pi) < a_1(n_O^{\pi}) < b_2 < b_1(\pi) < \{a_1 < b_2\}$$

(II) *Reference 163:*

$$a_2(\pi) < b_1(\pi) < a_1(n_O^{\pi}) < a_1 < b_2 < \{b_2 < b_1(\pi)\}$$

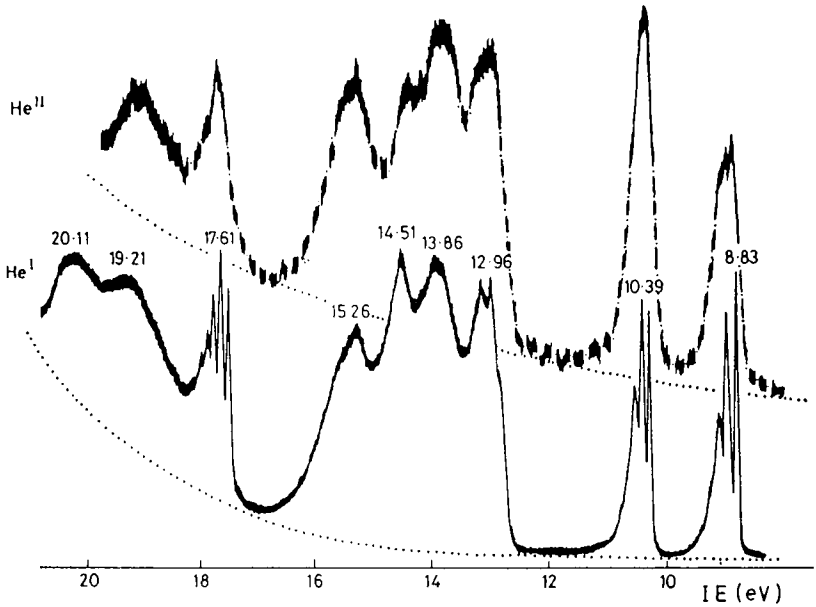


FIGURE 16. He I and He II PE spectra of furan. The corresponding base lines are indicated by dotted lines. Vertical *IE* values (in eV) are given above the bands in the He I PE spectrum. Reproduced by permission of The Royal Society of Chemistry from Reference 162

(III) *Reference 164:*

$$a_2(\pi) < b_1(\pi) < \sigma < \sigma < \sigma < \{\sigma < \sigma\} < b_1(\pi)$$

(IV) *Reference 165:*

$$a_2(\pi) < b_1(\pi) < a_1(n_O^{\pi}) < b_2 < a_1 < \{b_1(\pi) < b_2\}$$

(V) *Reference 166:*

$$a_2(\pi) < b_1(\pi) < a_1(n_O^{\pi}) < a_1 < b_1(\pi) < b_2 < b_2$$

(VI) *Reference 162:*

$$a_2(\pi) < b_1(\pi) < a_1(n_O^{\pi}) < a_1 < b_2 < b_1(\pi) < b_2$$

Assignment (I) is based on the results of PE measurements (both with He I and He II lines), mass spectrometry, Rydberg series and EHT calculations. Prediction of sequence (II) is guided by simulation of ESCA band intensities[163] and an orbital sequence given in Reference 160 and calculations of *ab initio* orbital energies corrected for correlation and reorganization effects by the many-body Green function method[163]. Assignment (III) results from angular distribution measurements, while orderings (IV) and (V) were obtained by HAM3 and MSCFX$_\alpha$ calculations, respectively. Finally, the most recent assignment (VI), offered by Klasinc and coworkers[158,162], was aided by a comparison of He I/He II intensity ratios and spectroscopically adjusted INDO-type calculations (INDO/RZ[167,168]) without and by applying the doublet-limited configuration interaction (LCI) procedure[169].

As to substituted furans, the most important of available PES data are summarized in Table 18[155,158,159,170–179].

The following are the main features of the results:

(i) α-substitution leads to an increase in the separation of the first two bands ($\Delta IE_{2,1} = IE_2 - IE_1$) in accordance with localization properties of the highest occupied MO levels. The only exception is encountered in 2-nitrofuran. The effect produced in the disubstituted derivatives is close to the sum of the effects produced by the two substituents separately.

(ii) The spectra of the halogen-containing compounds show, as expected, two bands due to ionization of the halogen lone pairs (in-plane and out-of-plane, respectively)[176]. The band at lower ionization energy is sharper and has therefore been attributed to the electrons occupying the in-plane halogen level. The wider band, at higher ionization energy, is due to ionization from the out-of-plane n_{Hal} level mixed into the π-electron system of the furan ring.

(iii) Comparison of 2-iodofuran with 3-iodofuran indicates that the effects of β-substitution are quite different from those of α-substitution[176]. While neither the $1a_2(\pi_3)$ nor the in-plane lone-pair bands exhibit significant shift in 2-iodofuran, the splitting of the $2b_1(\pi_2)$ and the out-of-plane lone-pair levels increases from 0.49 eV in 2-iodofuran

TABLE 18. Vertical ionization energies IE (eV) of substituted furans[a]

R	$IE_1(a_2)$	$IE_2(b_1)$	$\Delta IE_{2,1}$
2-H	8.87	10.32	1.45
2-Cl	8.68	10.34	1.66
2-Br	8.62	10.41	1.79
2-I	8.42	10.00	1.58
3-I	8.75	9.69	0.94
2,5-di-I	8.21	10.46	2.25
2-COOH	9.16	10.72	1.56
2-$COOCH_3$	9.00	10.56	1.56
2-$CONMe_2$	8.86	10.41	1.55
2-$COCF_3$	9.77	—	—
2-CHO	9.38	10.81	1.43
2-NO_2	9.75	11.13	1.38
2-CN	9.47	10.99	1.52
2-Me	8.38	10.03	1.65
2,5-di-Me	8.03	9.81	1.78
2-*t*-Bu	8.19	9.84	1.67
2,5-di-*t*-Bu	7.66	9.54	1.88
2-Vinyl	8.14	10.07	1.93
2-$SiMe_3$	8.44	9.67	1.51
2,5-di-$SiMe_3$	8.16	10.07	1.93
2-$SnMe_3$	8.33	9.96	1.63
2-CH_2SiMe_3	8.15	10.00	1.85
2-SCH_3	8.58	10.32	1.74
2-HgCl	8.96	10.40	1.44
3-HgCl	9.10	10.34	1.24
3-CH_2HgCl	8.80	9.91	1.11

[a]The ionizations energies are taken from References 155, 158, 159 and 170–179.

to 1.74 eV in 3-iodofuran. An explanation can again be found in the very different nodal properties of the $1a_2(\pi_3)$ and $2b_1(\pi_2)$ orbitals. Interaction of the latter with an out-of-plane lone-pair orbital of a halogen in an α-position is inhibited by the presence of a nodal plane. On the other hand, if the iodine is in the β-position, considerable splitting may occur because of the small energy gap of the interacting $2b_1(\pi_2)$ and iodine pair orbitals.

(iv) The filled $2b_1(\pi_2)$ and $1a_2(\pi_3)$ MOs are significantly destabilized (0.3–0.7 eV) by the $SiMe_3$ and $SnMe_3$ groups[177]. The interposition of a CH_2 group between the furan ring and the $SiMe_3$ group results in a destabilization (0.33 eV) of the uppermost $1a_2(\pi)$ MO. Moreover, the first two substituents lead to stabilization (0.3–0.4 eV) of the empty π^* MOs, causing a reduction of the HOMO/LUMO energy separation.

(v) The substitution of an HgCl group for an H atom of furan ring has a small stabilizing effect (< 0.1 eV)[178]. No sizeable variation is observed on going from the 2- to the 3-derivative despite the large variation in the wave-function coefficients. The electronic effect of the HgCl group is therefore essentially inductive and small.

(vi) The CH_2HgCl substituent exerts hyperconjugative destabilization on the ring π_2 and π_3 MOs via the C—Hg σ bond[178].

(vii) Analysis of the furan-like π_2 and π_3 MOs in both bis-2- and bis-3-furylmercury indicates that in these molecules there is a small charge-transfer interaction between the occupied ring π orbitals and the virtual $6p_\pi$ mercury atomic orbitals[178]. This interaction is larger in the bis-2-furyl derivative. Furthermore, p,π interaction in both compounds appears to be larger than the interaction of the π system with 5d atomic orbitals of mercury. These conclusions are corroborated by X-ray photoelectron data and iterative extended Hückel (IEHMO) calculations[178].

In addition to substituted furans displayed in Table 18, PES of several 1-(2-furyl)-2-arylethenes[179] as well as a PE study of the conformation of 2-(2-furyl)pyrole[158] are reported. Of considerable interest are also the PE spectra of furanophanes. The PE data for the following compounds are reported: *anti*-[2.2](2,5)furanophane, [2](2,5)-furano[2]paracyclophane, *anti*-[[2](2,5)furano[2](1,4)naphthalenophane, [2](2,5)furano-[2](9,10)-anthracenophane, *anti*-[2](2,5)furano[2](2,5)pyrrolophane[180] and octamethyl-tetrasila[2.2](2,5)furanophane[181].

d. Pyrane. The He I PE spectrum of pyrane exhibits a single low-energy ionization at 9.48 eV, which undoubtedly corresponds to the equatorial-type oxygen lone-pair orbital. The next higher ionization energy is found at 10.90 eV and is assigned to the axial lone pair[182,183].

e. Fused cyclic ethers. Several reports related to investigation of the electronic structure of benzo[2,3,144] and dibenzofurans[2,3,144] as well as one comparative study of the electronic structure of 2,3-dihydrobenzofuran (**54**)[96] and chroman (**55**)[96] have been reported. We shall briefly discuss the latter work, which is of considerable interest in view of the marked regiospecificity observed in reactions of a variety of structurally related systems. The latter is customarily discussed in terms of the Mills-Nixon effect[184] which is operative in fused aromatic systems involving small rings[185]. Comparison of the PE spectra of 2,3-dihydrobenzofuran and chroman (Figure 17) shows a marked difference related to the n_O^π oxygen lone-pair ionization energy, which decreases from 10.81 in **54** to 10.27 (and 10.63) eV in **55**. On the other hand, ionization energies of the outermost π orbitals are of the same order to magnitude in both **54** and **55**. This suggests that a decrease in conjugation with oxygen in **55** is made up by increased conjugation with the methylene group directly attached to the aromatic ring. Consideration of the consequences of differing conjugative effects on the reactivity of **54** and **55** led Behan and coworkers[96] to conclude that the orientational preferences observed in reactions of **54** and **55** are due to the cross-conjugation effect in the 'Wieland' transition state.

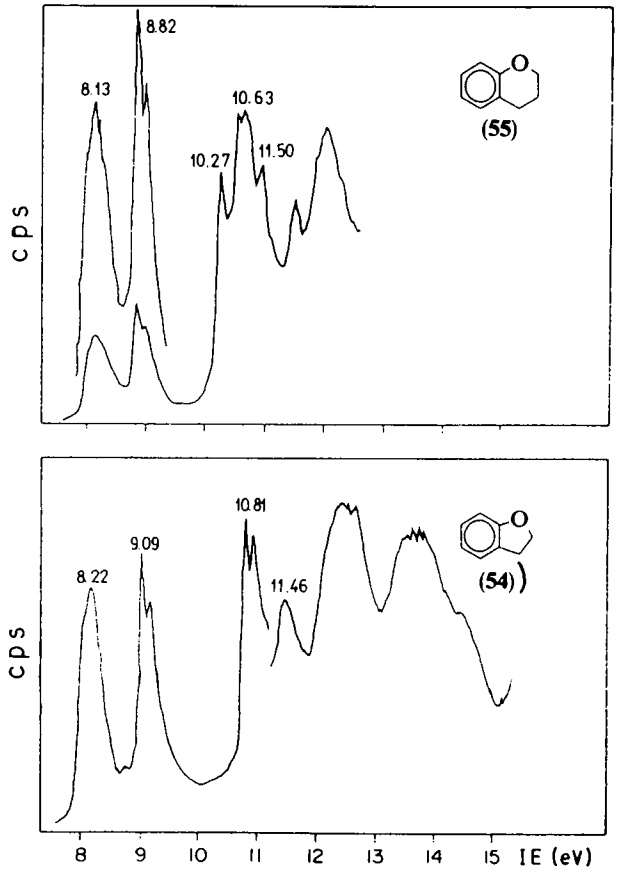


FIGURE 17. He I PE spectrum of 2,3-dihydrobenzofuran (**54**) and chroman (**55**). Vertical ionization energies are indicated above the bands. Reprinted with permission from J. M. Behan and coworkers, *Tetrahedron*, **32**, 167 (1976). Copyright (1976) Pergamon Press PLC

Another type of fusion is encountered in 6*H*-cyclohepta[*c*]furan-6-one (**56**) where the furan moiety is formally fused to the tropone ring[186]. The PE spectrum of **56** (Figure 18) shows three band systems below 12 eV. The first band with approximate maxima at 8.65 and 9.17 eV is assigned to three ionization events, while the bands at 10.98 and 11.70 eV correspond to one transition each. These five events are attributed to electron ejections from $2a_2(\pi)$, $4b_1(\pi)$, $9b_2(n_O^{\pi})$, $3b_1(\pi)$ and $1a_2(\pi)$ orbitals, aided by experimental correlation techniques and using ZDO calculations of the LCBO and HMO type as well as MINDO/3 and PPP calculations.

5. *Bicyclic ethers*

Most of the PE investigations of bicyclic ethers have been confined to the 7-oxabicyclo[2.2.1]heptane skeleton. A representative set of compounds (**57–66**) is shown,

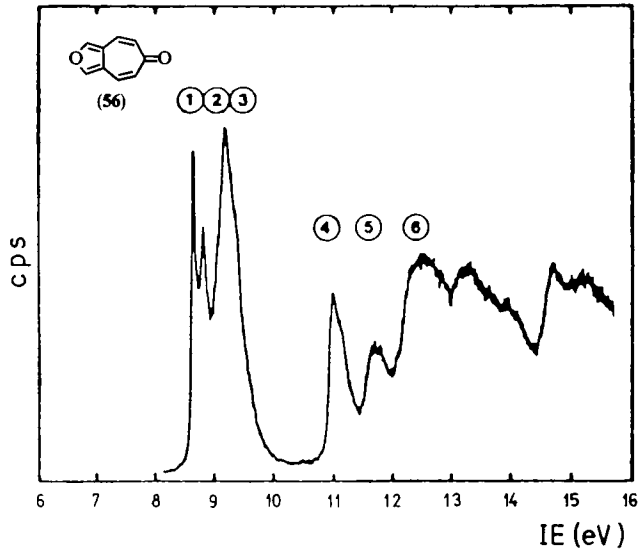
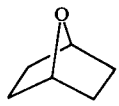


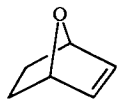
FIGURE 18. He I PE spectrum of 6*H*-cyclohepta[*c*]furan-6-one. Reproduced by permission of The Chemical Society of Japan from Reference 186

together with the corresponding IE (n_O^{π}) values:



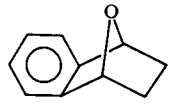
(57)

IE (n_O^{π}) 9.57 eV



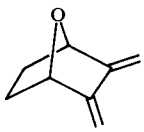
(58)

9.83 eV



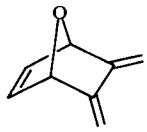
(59)

9.71 eV



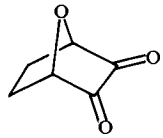
(60)

IE (n_O^{π}) 9.65 eV



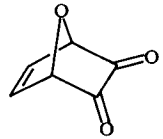
(61)

9.62 eV



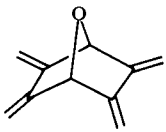
(62)

11.7 eV



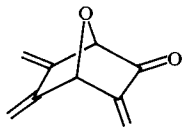
(63)

12.0 eV



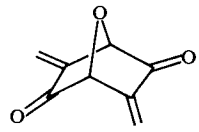
(64)

IE (n_O^{π}) 9.62 eV



(65)

10.55 eV



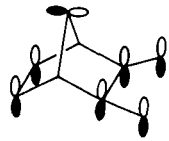
(66)

11.85 eV

The PE spectrum of the parent compound **57** is dominated by unusually high lone-pair ionization energy (9.57 eV)[145]. The effect is ascribed to the symmetry-enforced absence of interaction between the etheric lone pair n_O^{π} and the high-lying σ (ribbon) orbitals of the latter molecule.

Introduction of a double bond into **57** to yield 7-oxabicyclo[2.2.1]hept-2-ene (**58**) results in stabilization of the oxygen lone pair by 0.26 eV, presumably as a consequence of the through-bond type of coupling with the double-bond π system[145]. A similar effect, although of smaller magnitude (0.14 eV), is observed upon fusion of **57** to benzene yielding **59**[187]. The first two bands in the latter compound are assigned to orbitals derived from benzene e_{1gS} and e_{1gA} MOs, respectively[187].

In **60**, which incorporate two *exo* double bonds at the neighbouring ring positions of the bicyclic skeleton, the interaction between n_O^{π} and the semicyclic π-diene subunit is again negligible[188]. This is best illustrated by comparing $\Delta IE(\pi^+, \pi^-)$ in **60** (1.84 eV) and its methano analogue 2,3-dimethylenenorbornane (1.79 eV). The absence of interaction is easily understood in terms of the sizeable energy gap between the interacting subunits. However, insertion of *endo* double bond into the bicyclic frame to yield **61** results in mutual interaction of all three interacting subunits[188] (n_O^{π}, π_{endo}, π^+), leading to pronounced reinforcement of the π^+/π^- splitting (2.11 eV)[188]. Employing a simple LCBO model, the PE spectrum of **61** can be described by using the following interaction parameters:



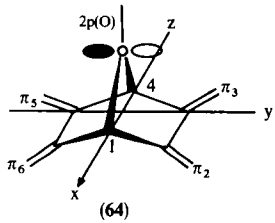
(61)

$$H_{11} = H_{22} = \varepsilon(\pi_{\text{semicycl.}}) = -9.90$$
$$H_{33} = \varepsilon(n_O) = -9.67$$
$$H_{44} = \varepsilon(\pi_{\text{cycl.}}) = -9.68$$
$$H_{12} = \tfrac{1}{2}\beta = -1.0$$
$$H_{13} = H_{23} = \sqrt{\tfrac{1}{2}}\beta''' = -0.07$$
$$H_{14} = H_{24} = \tfrac{1}{2}\beta' = -0.2$$
$$H_{34} = -\sqrt{2}\beta''' = 0.14$$

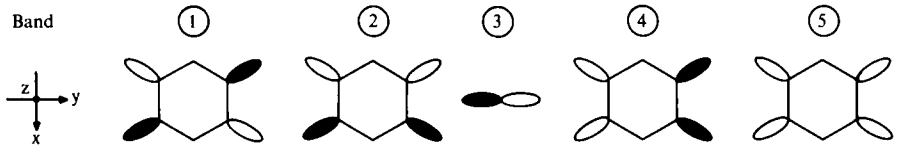
Detailed analysis of the PE spectra of several methylidene derivatives of **57** has been reported by Heilbronner's group. Assignment of the lower bands in the PE spectrum of **64** is rather straightforward, since it is almost completely symmetry conditioned[191]. The canonical π orbitals assigned to bands ①, ②, ④ and ⑤ are practically linear combinations of the localized two-centre π orbitals in positions $j = 2, 3, 5$ and 6, whereas band ③ is linked to an orbital localized on the oxygen atom at position 7, as shown in Scheme 1. In contrast, it is almost impossible to assign the strongly overlapping band system beginning with band ⑥ at $IE - 12.0$ eV, which is due to electron ejection from ribbon orbitals of the six-membered ring.

Related molecules studied also by Heilbronner's group[192] are carbonyl compounds **65**, and **66**. Replacement of the methylene groups by carbonyl moieties has the following consequences: (i) descent in symmetry from C_{2v} (**64**) to C_2 (**65**) and C_1 (**66**), respectively; (ii) lowering of self-energy of the two-centre basis π-orbital by roughly 3.0 eV and (iii) introduction of a lone-pair orbital of the carbonyl group/groups (n_{CO}) which in the latter case results in a pair of lone-pair orbitals. Their in-phase [n_{CO}^- (a)] and out-of-phase [n_{CO}^+ (b)] linear combinations [with respect to the $C_2(z)$ rotation] will interact with σ orbitals of appropriate symmetry. In addition, the (b) combination interacts with the n_O^{π} orbital of the ethereal oxygen at position 7. Taking all these facts into account, the assignment shown in Figure 19 is suggested. Let us mention is passing that the splitting between ether and carbonyl oxygen lone pairs in the considered compounds is well reproduced within the LCBO approach by using the cross-term $\langle n_O^{\pi}|H|n_{CO}\rangle = -0.55$ eV[192].

Interaction of the carbonyl groups in the 7-oxabicyclo[2.2.1]heptane moiety was also discussed by Gleiter's group[189] and Dougherty and coworkers[190]. The main point of



(64)



SCHEME 1

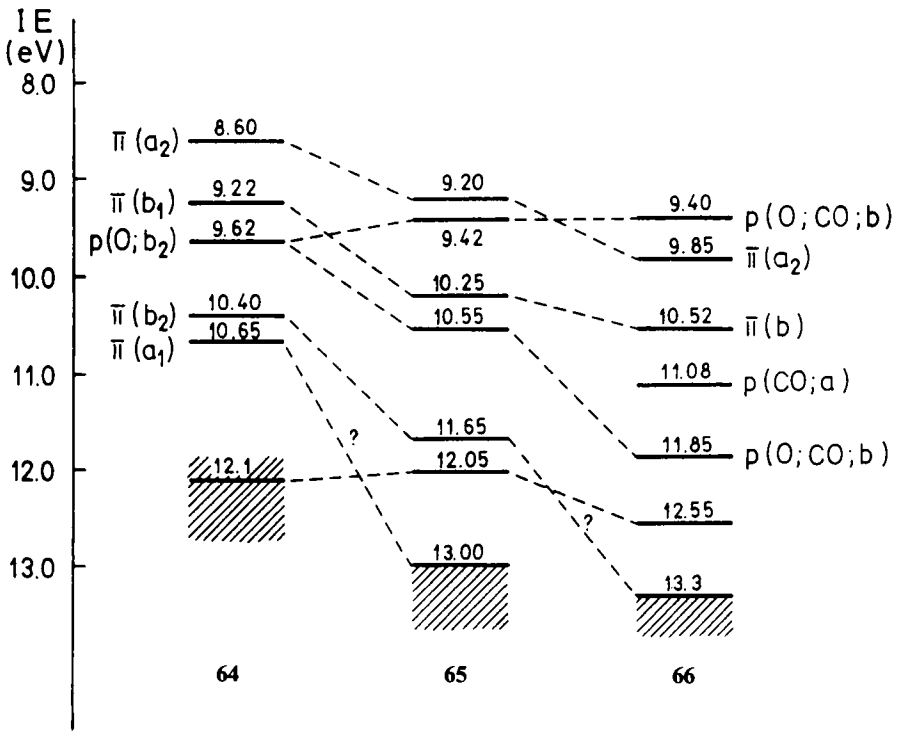
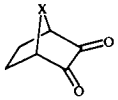
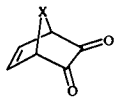


FIGURE 19. PES correlation diagram for compounds **64–66**. Reproduced by permission of *Helvetica Chimica Acta* from Reference 192

TABLE 19. Comparison of vertical ionization energies *IE* (eV) of bicyclic oxides **58** and **59** and related methano compounds[189,190]

Compound	X = CH_2		X = O	
	IE	Assign.[a]	*IE*	Assign.[a]
	9.0	$a'(n^+)$	9.2	$a'(n^+)$
	10.5	$a''(n^-)$	11.5	$a''(n^-)$
	11.2	$a''(\sigma)$	11.7	$a'(n_O^{\pi})$
	8.7	$a'(n^+)$	8.9	$a'(n^+)$
	10.6	$a'(\pi)$	10.8	$a'(\pi)$
	11.1	$a''(n^-)$	11.7	$a''(n^-)$
	12.1	$a''(\sigma)$	12.0	$a'(n_O^{\pi})$

[a] n^+ and n^- refer to in-phase and out-of-phase linear combinations of lone-pair orbitals of the carbonyl groups.

interest addressed in both studies concerns the interaction between the α,β-dicarbonyl subunit and the ether oxygen. A comparison of the ionization energies in **62** and **63** with those of related methano compounds (Table 19) reveals that replacement of the CH_2 bridge by oxygen leads to considerable enlargement of the n_{CO}^+/n_{CO}^- splitting energy. The latter was accounted for by a through-bond type of interaction between the n_{CO}^+ orbital and the pertinent lone-pair orbital of the 7-oxa bridge. It is noteworthy that the n_{CO}^+/n_{CO}^- energy gap in **63** is by 0.5 eV larger than in its saturated analogue **62**, thus resembling the trend already earlier encountered on passing from **61** to **60**[188].

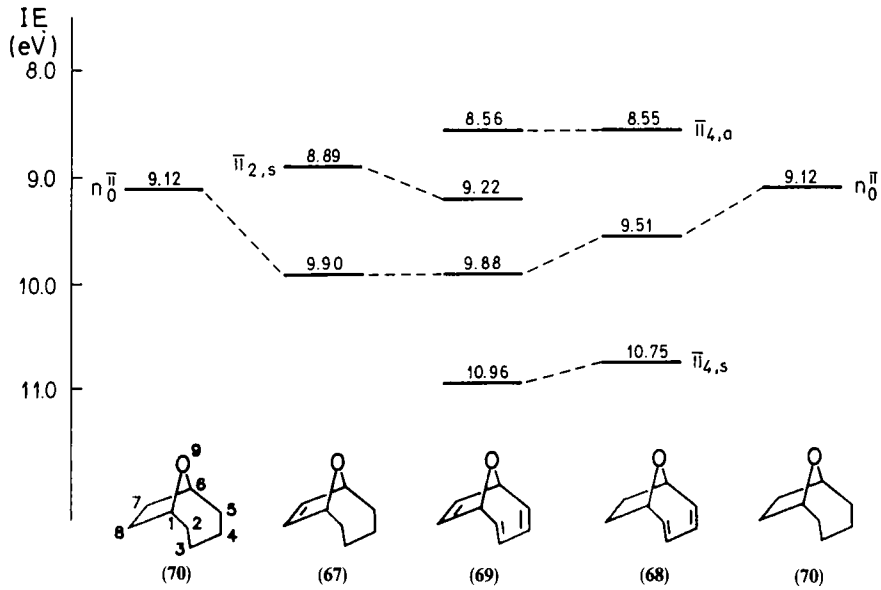


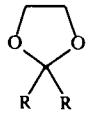
FIGURE 20. PES correlation diagram for compounds **67**–**70**[151]. The orbitals are classified in terms of (i) the segment (2 = ethylene, 4 = butadiene) on which they are mainly localized, and (ii) the molecular plane of symmetry (S = symmetric, A = antisymmetric).

A particularly thorough analysis, pertinent to the evaluation of n,π interactions in bicyclic ethers, has been made for 9-oxa-bicyclo[4.2.1]nona-7-ene (**67**), 9-oxa-bicyclo[4.2.1]nona-2,4-diene (**68**) and 9-oxa-bicyclo[4.2.1]nona-2,4,7-triene (**69**)[151]. The low-energy PE bands of the given compounds relating to ionizations from π and lone-pair levels are correlated in Figure 20. Before discussing the general features of the measured spectra it should be noted that, in the saturated analogue of the considered compounds (**70**), the lone-pair ionization occurs substantially easier (9.12 eV) than in the archetype furanoic moiety (10.32 eV)[19]. The reason for this lies in the non-bonded interaction of the lone pair and its proximal '*syn*'-directed protons bound to C^2 and C^5, respectively. A closer analysis of the displayed PE energies reveals that: (i) n_O^{π} levels are considerably stabilized (by 0.78 eV and 0.39 eV, respectively) on going from **70** to the mono-ene **67** and diene **68** species; (ii) the lone-pair ionization in **67** (9.90 eV) requires significantly higher energy than the same process in oxadiene **68** (9.51 eV); (iii) both the n_O^{π} and $\pi_{4,5}$ ionic states are noticeably stabilized (by 0.37 and 0.21 eV, respectively) on changing their environment from **68** to **67** and **69**, respectively. The above observations suggest that oxygen lone-pair, ethylene-π and butadiene-π systems are extensively involved in a hyperconjugative type of interaction. This conclusion receives strong support from the results of MINDO/2 and CNDO/S calculations, the latter being specifically designed to take into account the effect of conjugative coupling[193].

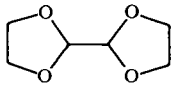
6. *Polyethers*

The main point of interest in the PES studies of molecules possessing two or more ethereal oxygen atoms concerns the extent to which oxygen lone-pair orbitals mutually interact[181,182,194–206]. The studied systems span a range extending from simple acyclic acetals to the macrocyclic ethers. Among the molecules, those exhibiting 1,3-*n*,*n*- and 1,4-*n*,*n*-interactions have been most thoroughly discussed. On the other hand, relatively little information is available on the interactions over longer carbon–carbon chains. One contribution dealing with spiroconjugation has also been published recently[206]. Typical representatives of each of the interaction patterns mentioned above are shown in structures **70–89**.

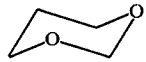
1,3-*n*,*n*-interactions:



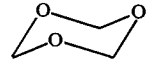
(**70a**) R = H[182,194]
(**70b**) R = Me



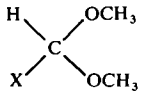
(**71**)[195]



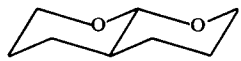
(**72**)[181,182]



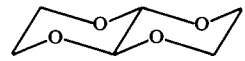
(**73**)[181,182,196]



(**74a**) X = H[197]
(**74b**) X = Me[198]

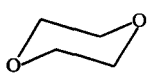


(**75**)[199]

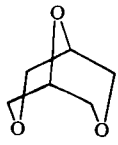


(**76**)[196]

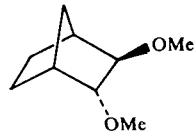
1,4-*n,n*-Interactions:



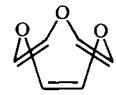
(77)[181,182,200]



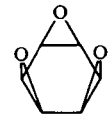
(78)[201]



(79)[127]



(80)[196]

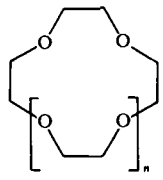


(81)[196]

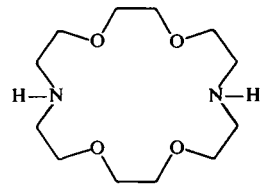
$MeO[CH_2CH_2O]_n—Me$

$n = 1,2,3$

(82)[202]

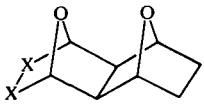


n = 1-3
(83a–c)



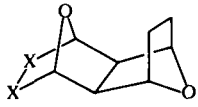
(84)[202]

1,5-*n,n*-Interactions:



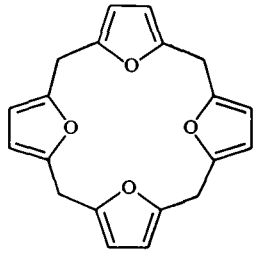
(85a) X—X = CH_2CH_2[189,205]

(85b) X—X = 



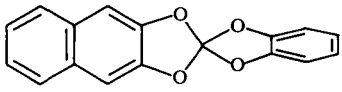
(86a) X—X = CH_2CH_2[189,205]

(86b) X—X = 

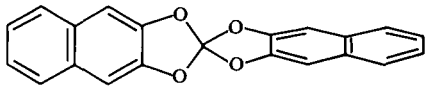


(87)[202]

Spiroconjugation:



(88)[206]



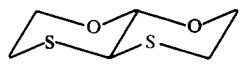
(89)[206]

In 1,3-dioxalane (**70a**) and 2,2-dimethyl-1,3-dioxalane (**70b**) two lone-pair oxygen orbitals interact predominantly via 'through-bond' coupling resulting in a splitting of 0.5 eV[182,194]. The CNDO/2 calcuations based on planar geometry predict the splitting of the same order of magnitude. In 1,3-dioxane (**72**) evidence for through-space interaction of equatorial lone-pair orbitals is deduced from CNDO/2 calculations, while axial lone-pair orbitals were found to interact mainly through-bond. The highest occupied MOs, according to CNDO/2 calculations, are n_{eq}^-, n_{ax}^+, σ, n_{ax}^-, σ and n_{eq}^+. The calculated energy difference between n_{eq}^- and n_{ax}^+ orbitals (0.30 eV) fits well the measured $\Delta IE_{2,1}$ value (0.26 eV).

In 1,3,5-trioxane (**73**), whcih exists in chair conformation (C_{3v}), the lone pairs interact both through-space and through-bond, the latter being mediated through CH_2

groups[181,182,196]. The original assignment, put forward by Schweigart and Turner[182], according to which the first PE band corresponds to one of the *e*-levels, was subsequently disputed by Palmer and Nisbet[196]. These authors prefer the ordering of levels where a_1 lies above *e* levels, thus implying that through-bond interaction between lone pairs and the pseudo π-orbital of the CH_2 group overrides the Jahn–Teller *e–e* coupling.

In a series of articles, Jørgensen and coworkers[195,197,199] have analysed the nature of *n,n*-interactions in acetals. The simplest acetal studied (**74a**) is known to exist in a *gauche, gauche* conformation[207]. Its He I PE spectrum displays five bands between 10 and 18 eV[197]. The first band arises from two ionizations (10.29 and 10.53 eV, respectively). Based on PRDDO molecular orbital calculations, these bands are assigned to two close-lying n_O^{π}-type lone-pair combinations. The peak at 11.4 eV is related to the n_O^{σ}–π_{CH_2} orbital, whereas the remaining two bands (12.98 and 13.42 eV, respectively) correspond to ionization of the unperturbed n_O^{σ} and π_{CH_3} levels, respectively. The same theoretical procedure, when applied to the *anti,anti* conformation of $CH_2(OMe)_2$, predicts an increase in the energy gap between the frontier orbitals, as a consequence of through-bond coupling of the in-phase combination of the n_O^{π} oxygen lone pairs via the pseudo π MO of the intervening CH_2 group. These predictions were fully confirmed by examining the PE spectra of *trans*-1,8-dioxa- (**75**), *cis*-1,4,5,8-tetraoxa- (**76**) and *trans*-1,8-dioxa-4,5-dithiodecalin (**90**), in which the acetal moiety is forced to adopt an *anti,anti* conformation due to the rigidity of the *trans*-decalin framework[195,199]. The PE spectrum of *trans*-1,8-dioxadecalin (**75**) exhibits two well-resolved low-energy ionization events at 9.08 and 9.93 eV, which correspond to two n_O^{π} lone-pair combinations[199]. The observed energy gap (0.85 eV) can be explained by destabilization of both the in-phase and out-of-phase n_O^{π} lone-pair combinations by interaction with the lower-lying σ_{CC} (C^2—C^3, C^6—C^7 and C^9—C^{10}) orbitals, the in-phase combination being destabilized more than its out-of-phase counterpart. The energy gap between related ionizations in *trans*-1,8-dioxa-4,5-dithiodecalin (**90**) was found to be slightly smaller (0.65 eV). The latter was tentatively ascribed to mixing of the oxygen and sulphur lone-pair orbitals. Intensive through-bond interactions for both the π and σ oxygen lone pairs were also invoked to explain the PE ionization pattern of *cis*-1,8,4,5-tetraoxadecalin (**76**)[195].



(**90**)

The PE spectrum of 1,4-dioxane (**77**)[181,182] exhibits three low-energy ionizations, of which only the first two were originally assigned. The first of them, appearing at 9.43 eV, was attributed to an ionization from the n_O orbital destabilized by out-of-phase interaction with the σ_{CC} ribbon orbital, while the following *IE* at 10.65 eV was related to an in-phase combination of the former with the σ_{CC}^* orbital of appropriate symmetry. Full assignment of the PE spectrum of **77** was subsequently offered by Jørgensen[195] and Gonbeau and coworkers[200] on the basis of PRDDO and *ab initio* STO-3G calculations. The STO-3G wave functions are localized by the Foster Boys technique and used for interpretative purposes within the simple LCBO formalism, which is illustrated in Figure 21. Both the PRDDO and LCBO approaches agree insofar that the electronic structure of 1,4-dioxane is dominated by through-bond coupling, but predict different ordering of the highest occupied MOs ($1a_g > 2a_g > 1b_u > 2b_u$ and $1a_g > 1b_u > 2a_g > 2b_u$, respectively). Through-bond interaction of the same size as in 1,4-dioxane has also been reported for 3,7,9-trioxabicyclo[3.3.1]nonane (**78**)[201].

Further evidence in favour of the through-bond interaction over the 1,4-coupling unit is obtained by combined PES and theoretical studies of the electronic structure of

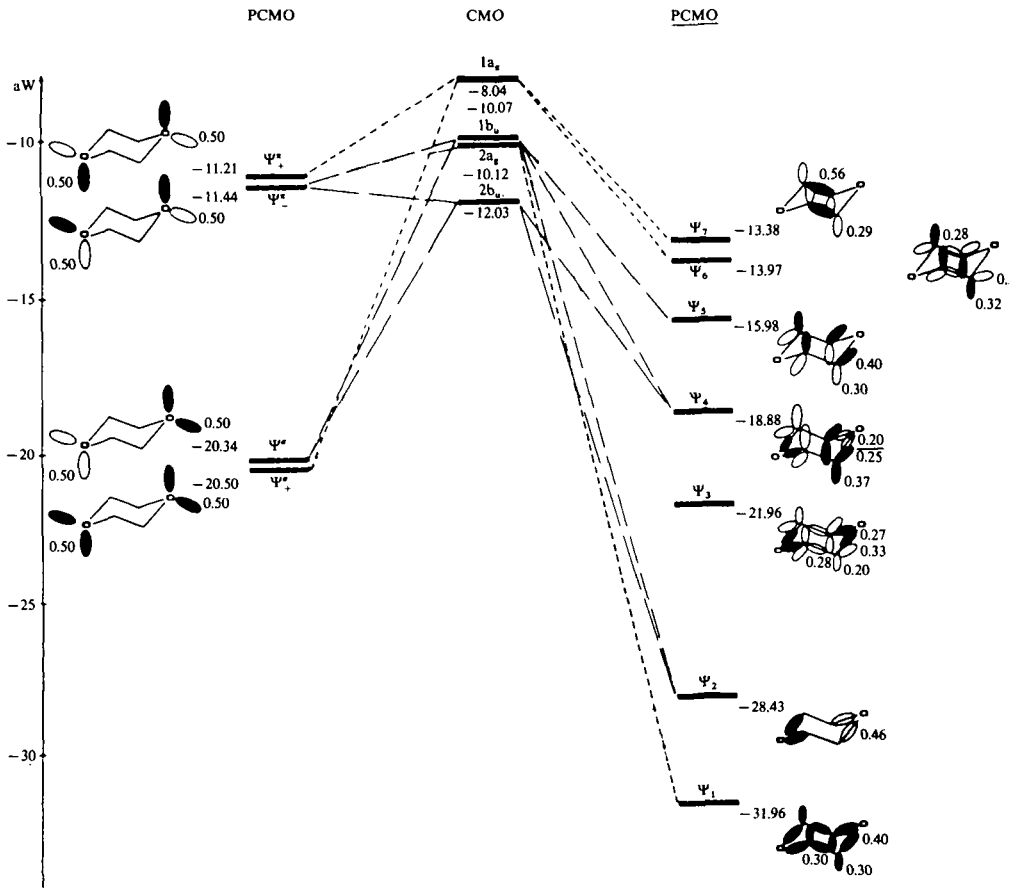


FIGURE 21. Localization and energies of PCMOs for 1,4-dioxane. Four highest occupied CMOs are given in the middle of the scheme together with their orbital energies. Reprinted with permission from D. Gonbeau and coworkers, *Tetrahedron*, **36**, 381 (1980). Copyright (1980) Pergamon Press PLC

$$\Delta\varepsilon(1a_g,\Psi^{\pi}_{+}) = 3.17\text{eV} \longleftarrow 1a_g = 0.74\Psi^{\pi}_{+} - 0.61\Psi_7 - 0.21\Psi^{\sigma}_{+} - 0.16\Psi_6$$
$$\Delta\varepsilon(1b_u,\Psi^{\pi}_{-}) = 1.36\text{eV} \longleftarrow 1b_u = 0.82\Psi^{\pi}_{-} - 0.35\Psi_5 + 0.31\Psi_4 + 0.31\Psi^{\sigma}_{-} + 0.13\Psi_2$$
$$\Delta\varepsilon(2a_g,\Psi^{\sigma}_{-}) = 10.38\text{eV} \longleftarrow 2a_g = 0.57\Psi^{\sigma}_{+} + 0.68\Psi_6 + 0.31\Psi^{\pi}_{+} - 0.25\Psi_3 - 0.22\Psi_1$$
$$\Delta\varepsilon(2b_u,\Psi^{\sigma}_{-}) = 8.30\text{eV} \longleftarrow 2b_u = -0.69\Psi^{\sigma}_{-} + 0.48\Psi^{\pi}_{-} - 0.45\Psi_2 - 0.3\Psi_4$$

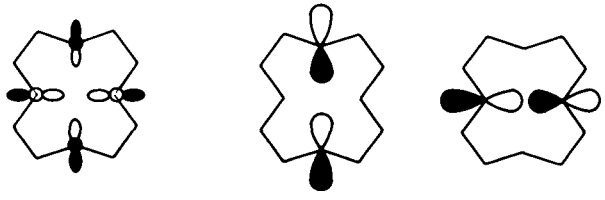
1,4,7-trioxonin (**80**) and benzene trioxide (**81**)[196]. Interestingly, the calculated electron distribution in the occupied levels suggests the occurrence of considerable mixing of $\pi_{C=C}$ semilocalized orbitals with each other and with σ oxygen lone-pair orbitals in **80**. Concomitantly, the corresponding $\sigma_{C=C}$ and n^{π}_{O} lone pairs mix significantly as well. The results refer to the crown form of the molecule (C_{3v}) which is found to be energetically preferred[196]. The theoretically predicted features are compatible with those deduced from the PE spectrum.

TABLE 20. Ionization energies *IE* (eV) of selected crown ethers and related macrocycles[a]

Compound	*IE* (eV)[b]
1,2-Dimethoxyethane (DME)	9.9; 11.7; 12.9
Diglyme[c]	9.8[d]
Triglyme[e]	9.8[d]
12-Crown-4[f]	9.3; 10.0; 11.4[d]
15-Crown-5	9.6; 11.3[d]
18-Crown-6	9.7; 10.4[d]
Cyclohexyl-14-crown-4	9.2[c]
Dicyclohexyl-18-crown-6[g]	9.45; 10.0
Benzo-14-crown-4	8.1; 9.8[d,h]
Benzo-15-crown-5	8.0; 9.6; 10.7
Dibenzo-18-crown-6	7.8; 8.7; 9.5[d]
Furano-crown	7.1; 7.5; 9.3; 10.8
Kryptofix 21[i]	8.4; 9.7; 11.3[d]
Kryptofix 22	8.4; 9.3; 11.3
Kryptofix 221	7.7; 9.3; 11.0; 12.3[d]
Kryptofix 222	7.8; 9.5; 11.3

[a]Reference 202.
[b]Values refer to band maxima.
[c]Diglyme = 2,5,8-trioxanonane.
[d]Merging of bands at higher energy.
[e]Triglyme = 2,5,8,11-tetraoxadodecane.
[f]Example of systematic nomenclature: 12-crown-4 = 1,4,7,10-tetraoxacyclododecane.
[g]Reference 203.
[h]Contains overlapping components.
[i]Example of systematic nomenclature: Kryptofix 21 = 1,4,10-trioxa-7,13-diazacyclopentadecane.

Closely related to the PE spectroscopic investigations of 1,4-dioxane and 1,4,7-trioxonin are also the PE studies of crown ethers and the related macrocycles. In these molecules, the presence of several heteroatoms possessing lone pairs leads to rather extensive lone-pair interactions[202-204]. The latter is evidenced by the broad appearance (eventually split into two strongly overlapping components) of the band in the region expected for the lone pairs, and its shift towards lower energies relative to those of the corresponding open-chain and cyclic model compounds (Table 20). To be more specific, the first band in the PE spectrum of polyether **83a**, for instance, exhibits two maxima at 9.3 and 10.0 eV. According to the CNDO/2 calculations they are associated with the equatorial type of the oxygen lone-pair orbitals (**12e**) and the bonding contribution of four n_O^{eq} orbitals together with the antibonding combination of four axial-type (n_O^{ax})



(12a) **(12e)**

lone-pair orbitals (**12a**). Since the former orbitals become more stable, and the **12a** orbitals less stable with the increasing ring size of polyethers, the bands due to these two orbitals may not be resolved for **83b** and **83c**. However, on account of its width, a similar degree of lone-pair interaction is presumed as in the case of **83a**.

An important question concerns the nature of the heteroatom lone pair interactions in macrocyclic ehters. The negligible change in the extent of interaction (as judged from the band shape) across the **83a–c** series, despite a large increase in the cavity size in the same direction, suggests that the through-bond interaction predominates. Further evidence for the prevailing through-bond character of interaction is provided by the ionization pattern of furano-crown ether **87**. The most striking feature in the PE spectra of kryptofixes **84a–c** is the presence of two distinct low lying *IE* bands. The first of them increases in intensity as the ratio of oxygen to nitrogen in the cryptands increases, suggesting its assignment to ionization from orbitals largely associated with nitrogen atoms. The second band is then related to orbitals located mainly at oxygen atoms.

Interesting systems for studying the mechanism of interaction of oxygen lone pairs over four sigma bonds are provided by molecules **85a,b** and **86a,b**[187,205]. Analysis of their He I PE spectra, substantiated by the AM1 and *ab initio* STO-3G calculations, reveals that the n_O^{π}-type lone-pair orbitals of ether oxygen atoms interact strongly irrespective of their conformational arrangement. Significantly larger n_O^{π}, n_O^{π} splitting energies in the *exo,exo* isomers (*ca* 1.0 eV) relative to those measured in their *endo,exo* congeners (*ca* 0.6 eV) are rationalized in terms of the differences in conformational disposition of the σ bonds within the σ-bond relay and a closer proximity of the oxygen atoms in the former isomers. As a consequence, both the through-space and through-bond modes of interaction are operative in **85a** and **85b**, whilst the splitting in **86a** and **86b** is governed by the through-bond coupling mechanism.

Effects of spiroconjugation on the PE spectral features of heterospiranes **88** and **89** were discussed by Gleiter and Uschmann[206]. The PE spectrum of the former compound was found to be very close to those of the superimposed PE spectra of naphtho[2,3-d]-[206] and benzo-1,3-dioxole[207] (Figure 22) indicating, at most, only a very weak interaction between the ring fragments. In the case of **89** any conclusion about the extent of spiro interaction is hampered by the strong overlapping of the PE bands.

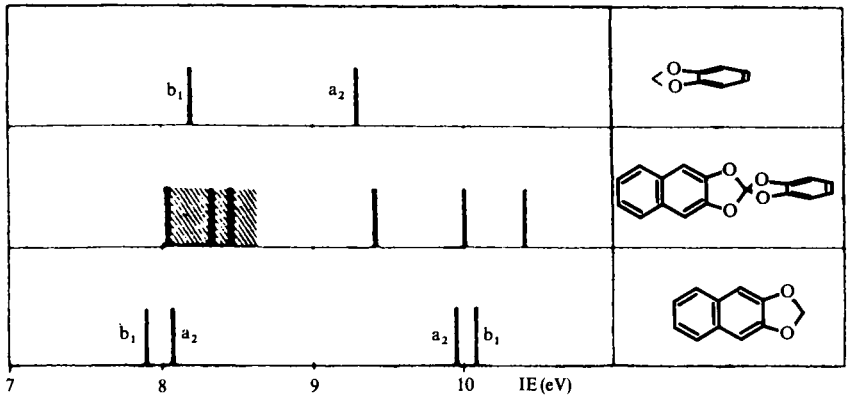


FIGURE 22. Comparison between the first bands in the PE spectrum of **88** with those of naphthol[2,3-*d*]- and benzo-1,3-dixole. Reprinted with permission from R. Gleiter and J. Uschmann, *J. Org. Chem.*, **51**, 370 (1986). Copyright (1986) American Chemical Society

To end this section, it should be mentioned also that the PE spectra of several unsaturated cyclic and aromatic molecules, incorporating two or more oxygen atoms, have been reported. Typical examples are provided by 1,4-dioxine[117], 1,3-dioxepine[208] and benzodioxin[209].

7. *Alkyl aryl ethers*

Similarly to phenols, interest in PES of alkyl aryl ethers can be traced back to the very first days of the technique[73,74]. These pioneering investigations determined also the main avenues of subsequent research in the field, i.e. studies of the electronic and conformational effects of substituents on the aromatic moiety.

The electronic structure of the parent anisole can be considered well understood. The influence of the methoxy group on the benzene π-ionization events and its manifestation in the He I PE spectrum was explored as early as 1968 by Baker and colleagues[73]. Additionally, Maier and Turner[74] assigned the band associated with the out-of-plane oxygen lone pair. This was achieved by comparing the PE spectrum of anisole and its pentafluorinated analogue C_6F_5OMe. These results combined with analyses of the vibrational fine structure[76] of individual bands and quantum chemical calculations yield the following ordering of the highest occupied MO levels: $e_{1gS} > e_{1gA} > n_O^{\pi} > e_{2gS} > e_{2gA} > a_{2u}$, where the symmetry characters of the D_{6h} point group of benzene are retained.

The PE spectroscopic splitting pattern of substituted anisoles is in most cases rationalized straightforwardly by using perturbation arguments[86]. In methyl-substituted anisoles[74,76] (Figure 23), for instance, one observes perturbation of the e_{1gS}- and e_{1gA}-type MOs of similar size upon *ortho* and *meta* substitution and a less pronounced disturbance of the latter level in the *para* derivative. However, in the cases of substituents that are capable of conjugative interaction[77,108,210–218] with the aromatic π system and in sterically hindered anisoles[97,107,211,212], rationalization of the ionization pattern is somewhat more involved. The PE spectra of dimethoxy- (**91–93**) and trimethoxybenzenes (**94–96**) have been selected as an illustration. The PE spectral features of dimethoxybenzenes will be discussed first[210–212]. Their interpretation is based on the *ab initio* STO-3G calculations (Figure 24). Theoretical findings are instructive and indicate that the conversion of anisole to *p*-dimethoxybenzene (**91**) leads to an enlargement of the energy gap between the highest occupied MOs by 60%, with HOMO being, as expected, significantly more influenced. The calculations further indicate that the HOMO of the *ortho*-substituted compound **93** is substantially higher in energy than that of the *meta*-isomer **92**. On the other hand, SHOMO of **93** is lower in energy than that of **92**. An explanation for this difference lies in higher-order effects[212]. As regards the comparison of the calculated and experimental ionization energies, there is adequate agreement for the whole series, from benzene through dimethoxybenzenes, displayed in Figure 24, with a notable exception provided by *ortho*-dimethoxybenzene where the experimental IE_1 value is by 0.8 eV higher than predicted by calculations. Furthermore, the measured IE_1 value is higher than that of *meta*-derivative **92**, implying that it departs from the general trends. This as well as other experimental values are, however, well reproduced by STO-3G calculations under the assumption that one of the methoxy C—O bonds is rotated out of the plane of the aromatic ring (see Figure 24a for details).

Turning to trimethoxybenzenes **94–96**[212], calculations predict a dramatic difference between the 1,2,4-trimethoxybenzene (**94**) on the one hand and the 1,2,3- (**95**) and 1,3,5-derivatives (**96**) on the other (Figure 24b). The 1,3,5-trimethoxybenzene has local C_{3h} symmetry, so that the HOMO and SHOMO are nearly degenerate, and both are raised approximately to the same extent as the HOMO of *meta*-dimethoxybenzene. This is as expected on the basis of the first-order perturbation analysis, since substitution of the third methoxy group, which converts *meta*-dimethoxybenzene to **96**, occurs at a

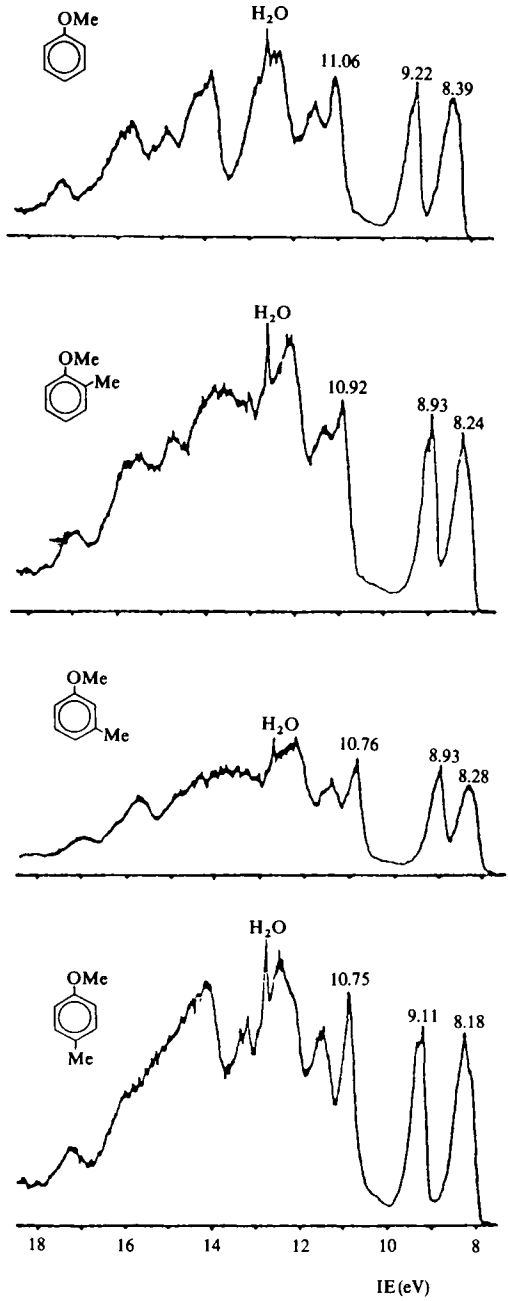


FIGURE 23. He I PE spectra of anisole and its methyl-sybstituted derivatives. Reproduced by permission of The Chemical Society of Japan from Reference 76

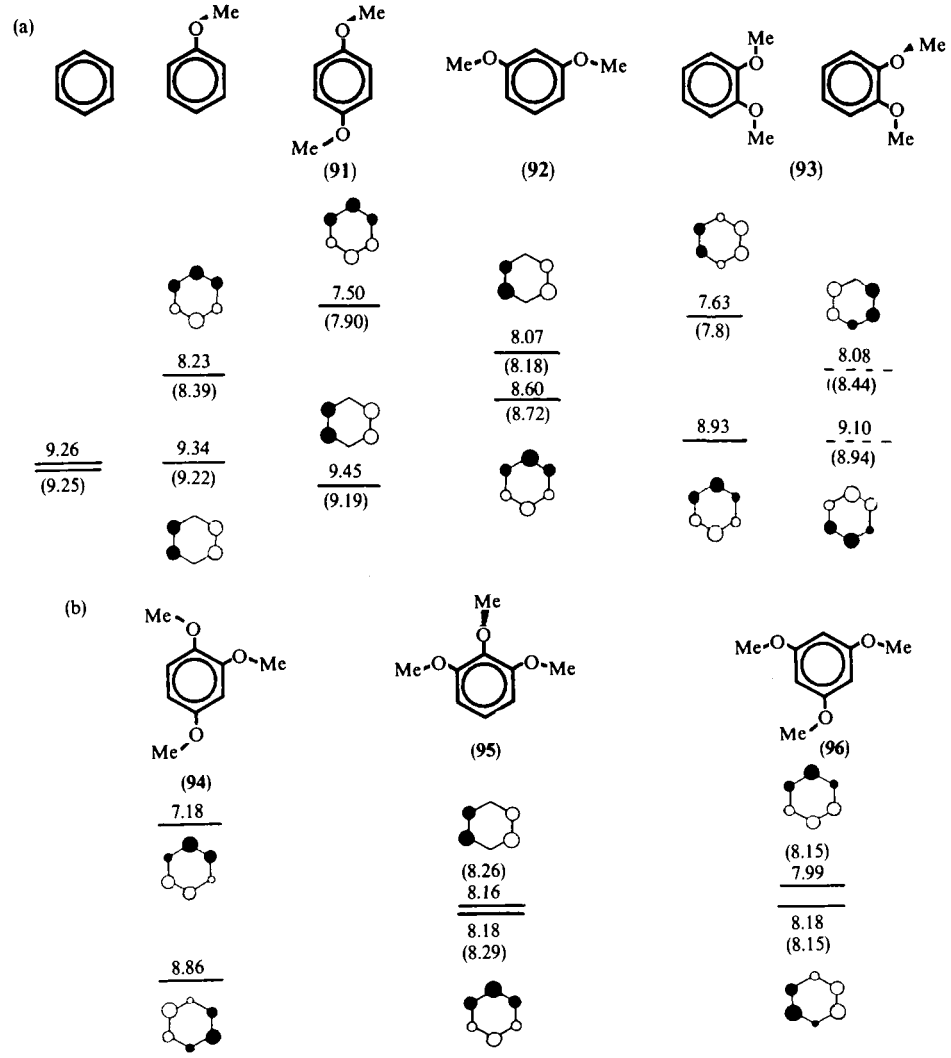


FIGURE 24. PES and orbital correlation diagram for dimethoxy- (a) and trimethoxybenzenes (b). Reprinted with permission from G. M. Anderson III and coworkers, *J. Am. Chem. Soc.*, **101**, 2344 (1979). Copyright (1979) American Chemical Society

nodal position in the HOMO of **92**. A first-order perturbation analysis employing the benzene MOs would also predict the same orbital energies in the 1,3,5- and 1,2,3-trimethoxybenzenes. However, slightly lower orbital energies are encountered in the latter compound as a consequence of the poorer donor ability of the middle methyl group (position 2) which, by necessity, adopts a perpendicular conformation. It should also be noted that the large split of the HOMO and SHOMO in the 1,2,4-trimethoxybenzene results from the dominant influence of the *para*-dimethoxy pattern, which is

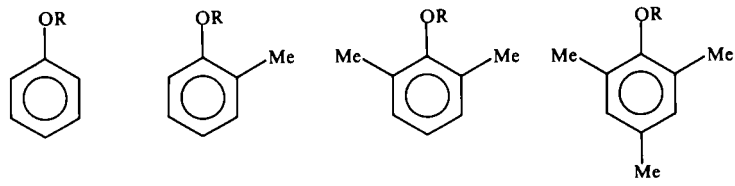
present only in this compound[212]. In effect, all three methoxy groups raise the HOMO energy, while only one, in position 2, raises the SHOMO energy. Photoelectron ionization energies are available only for compounds **95** and **96** and they are in good agreement with the calculated MO energies (Figure 24b). It is of interest to note that the effect of lowering the aromatic ionization energies by successive addition of methoxy groups to the benzene ring is rapidly attenuated. This results from the fact that the ionization energy lowering effect depends both on the coefficient at the site of substitution and, inversely, on the difference in energy between the aromatic π MOs and the oxygen lone-pair orbital. As the number of methoxy groups increases, the ring coefficient sizes decrease and the energy gap increases. Furthermore, polysubstitution will force one or more of the methoxy groups to assume a perpendicular conformation, which is less favourable for electron donation.

An ideal family of compounds for studying the effects of substituents on the conformation of aromatic ethers is provided by compounds **97–100**[97,107]. The PE spectra are very similar for the members of the series, as expected in view of their chemical resemblance. The same holds for their assignment. In analogy with anisole, the lowest (IE_1) and second (IE_2) ionization energies in all higher members of the series (**97–100**) are assigned to orbitals derived from benzene e_{1g} MOs, while the third band (IE_3) corresponds to the MO possessing a predominantly n_O^{π} character (cf. Figure 25). Perusal of the measured ionization energies for **97–100**, displayed in Table 21, reveals that an increase in the size of the alkoxy group, as well as substitution of both *ortho* positions in **97** leads to a significant reduction in $\Delta IE_{3,1}$. In contrast, there appears to be no further reduction in $\Delta IE_{3,1}$ on passing from *t*-butyl phenyl ethers **97d** and **98d** to their 2,6-dimethyl (**99d**) and 2,4,6-trimethyl (**100d**) counterparts. It should be noted that most of the difference in $\Delta IE_{3,1}$ arises from variation in the IE_3 values. The latter is due to the inductive effect of the alkyl moiety, except in the case of *t*-butyl derivatives, where the steric effect seems to prevail. Since the reduction in $\Delta IE_{3,1}$ in compounds **99** and

TABLE 21. Vertical ionization energies IE (eV) for alkyl aryl ethers **97–100**

Compound		$IE_1,(b_1)$		$IE_2,\pi(a_2)$	IE_3, n_O^{π}	$\Delta IE_{3,1}$
97	**a**	8.45[a] (8.67)[b]		9.25 (9.35)	11.14	2.69
	b	8.36 (8.46)		9.25 (9.32)	10.95 (11.03)	2.59 (2.49)
	c	8.42 (8.32)				2.45
	d	8.77 (8.66)		9.27		1.00 (0.93)
98	**a**	(8.43)		(8.82)		
	b		(8.53)		(9.98)[c]	(2.45)
	c		(8.49)		(9.81)	(2.37)
	d		(8.47)		(9.50)	(1.03)
99	**a**	8.24		8.94	10.93	2.69
	b	8.21		8.96	10.86	2.65
	c	8.24		8.94	10.76	2.52
	d	8.45		8.98	9.73	1.16
100	**a**	8.28		8.57	9.85	1.57
	b	8.28		8.57	9.75	1.47
	c	8.15		8.63	9.71	1.56
	d	8.27		8.50	9.49	1.22

[a]Reference 108.
[b]Reference 77 (in parentheses).
[c]Band position obscured.



(97) (98) (99) (100)

	(a)	(b)	(c)	(d)
	R = Me	Et	*i*-Pr	*t*-Bu

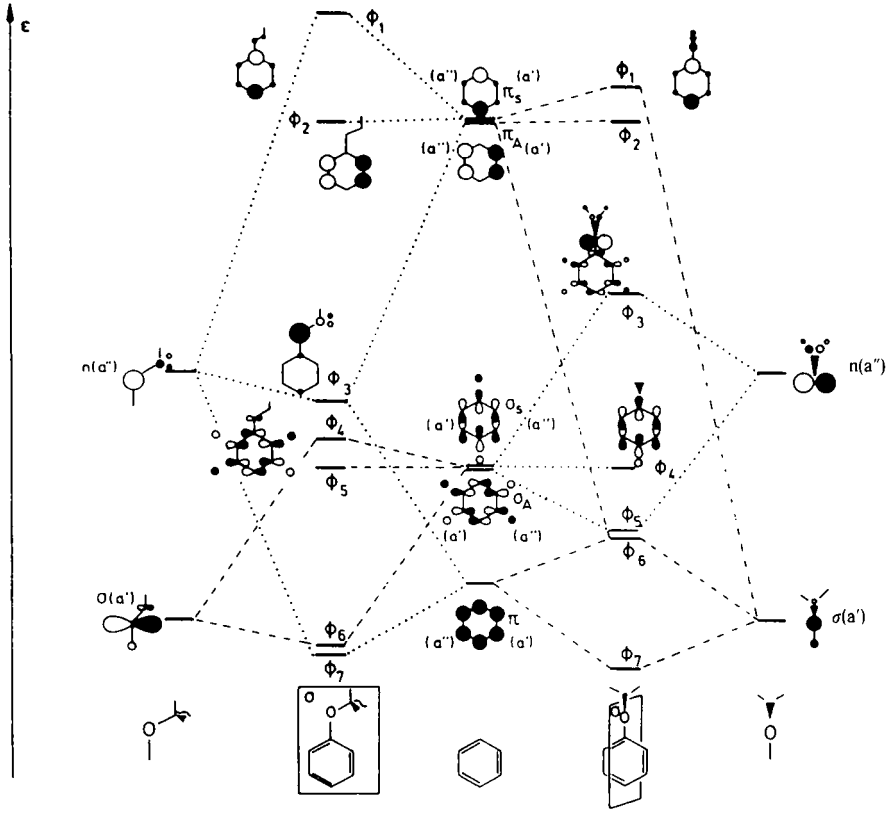


FIGURE 25. Qualitative interaction diagram between the highest occupied MOs of the ether group and benzene ring in planar (left) and orthogonal (right) conformation. Reproduced by permission of VCH Publishers from Reference 107

100 roughly corresponds to that observed in **97d** and **100d**, it is concluded that in the former compounds the alkoxy group adopts a perpendicular orientation. In the remaining molecules, planar conformations prevail. The above reasoning is corroborated by qualitative considerations illustrated by Figure 25 and quantum chemical calculations[107].

The nature of the relationship between the inductive effect of the alkyl groups and $IE(n_O^{\pi})$ in alkoxybenzenes was also addressed by Klessinger and coworkers[97] in a PES study of a variety of hydroquinone methyl alkyl ethers (Table 22). The energies of the first and second PE bands for all 13 compounds investigated within this study are assigned to ionizations from the π MOs related to the benzene moiety on the basis of qualitative considerations and correlation with excitation energies of the corresponding charge-transfer complexes with TCN. Attenuation of the third ionization energy $IE(n_O^{+})$ relative to its value in *para*-dimethoxybenzene across the series (Table 22) is interpreted in terms of the inductive effect of the alkyl groups. Quantitative evaluation of the inductive abilities was also attempted for particular alkyl groups[97].

Significant contributions to the understanding of substituent effects on the PES features of alkyl aryl ethers have been also made by Bernardi and colleagues[213], Kobayashi's group[84], Goetz and coworkers[83], Behan and coworkers[214], Ramsey[215] and Rao[216]. The most extensive among them is the study by Rao, in which the utility of correlations of first ionization energies with Hammett σ and Brown σ^{+} constants is thoroughly discussed. Similar analysis, but based on the use of adiabatic ionization energies vs p–σ^{+} constants, was reported by Behan and coworkers[214] who, in particular, discussed the limitations of such approaches.

As a part of his admirably systematic study of silyl substituents on benzene π-ionization energies, Ramsay reported the first ionization energies of 1-trichlorosilyl- and 1-trimethoxysilyl-4-methoxybenzene[215]. Like in the parent anisole, the first ionization energies of these compounds originate from benzene-like e_{1g} MOs and are found at 8.75 and 9.61 eV, respectively. The effect of a variety of substituents (Me, NO_2, SMe, OMe, NH_2, NMe_2) on the ionization energies related to the highest occupied π MOs in *p*-substituted anisoles was also addressed by Bernardi and colleagues[213]. The results are discussed in terms of the CNDO/2 calculations coupled with PMO analysis.

TABLE 22. Vertical ionization energies *IE* (eV) of hydroquinone methyl alkyl ethers[97,a]

Compound	$IE_1(\pi_1)$	$IE_2(\pi_2)$	$IE_3(n_O^{+})$
$MeOC_6H_4OR$			
R = Me	7.83	9.22	10.24
Et	7.72	9.17	10.15
n-Pr	7.80	9.17	10.13
i-Pr	7.83	9.19	10.04
n-Bu	7.74	9.16	10.09
CH_2CHMe_2	7.79	9.18	10.08
CHMeEt	7.83	9.13	10.01
t-Bu	8.00	9.18	9.64/10.55[b]
n-Heptyl	7.78	9.17	10.06
$n\text{-}C_{16}H_{33}$	7.72	9.07	10.04
CH_2(c-Pr)	7.78	9.17/9.37[b]	10.13/10.29[b]
$CH(c\text{-}Pr)_2$	7.80	9.20/9.61[b]	10.04
Adamantyl-(1)	7.82	9.05/9.19[b]	9.88/10.27[b]

[a] π_1 and π_2 denote out-of-phase linear combination of e_{1gS} benzene MO and n_O^{-} and e_{1gA}-like MO, respectively; n_O^{+} refers to bonding linear combination of n_O^{π} oxygen lone-pair orbitals.
[b] *IE* values related to ionization from σ_{CC} orbitals of the alkyl rests.

Finally, let us mention that Zverev and coworkers[217] have analysed the effect of chlorination of the methoxy group in anisole on the two lowest ionization energies. The observed increase in *IE* values across the series is attributed to the inductive effect of chlorine atoms.

In contrast to the PE studies of substituted benzenes, the PE investigations of fused aromatic ethers are few[120,218] and are limited to 1-methoxy- and 2-methoxynaphthalene[120,218] and 9-methoxyanthracene[218].

8. *Diaryl ethers*

Compared to the other categories of molecules considered in this chapter, PES studies of diaryl ethers are sparse. The most comprehensive work is that of Rodin and coworkers[219], who discussed conformation of PhOPh and its *p,p*-dibromo derivative by employing PE results and quantum chemical calculations. More recently, Nakanishi and coworkers[220] reported PES and PIES spectra of the parent PhOPh (Figure 26), together with exterior electron densities (EED) of MOs calculated by employing a lattice sum method[221]. It should be noted that the intensities of the n and π bands are larger than those of σ bands in PIES, indicating the wider distribution of n and π orbitals.

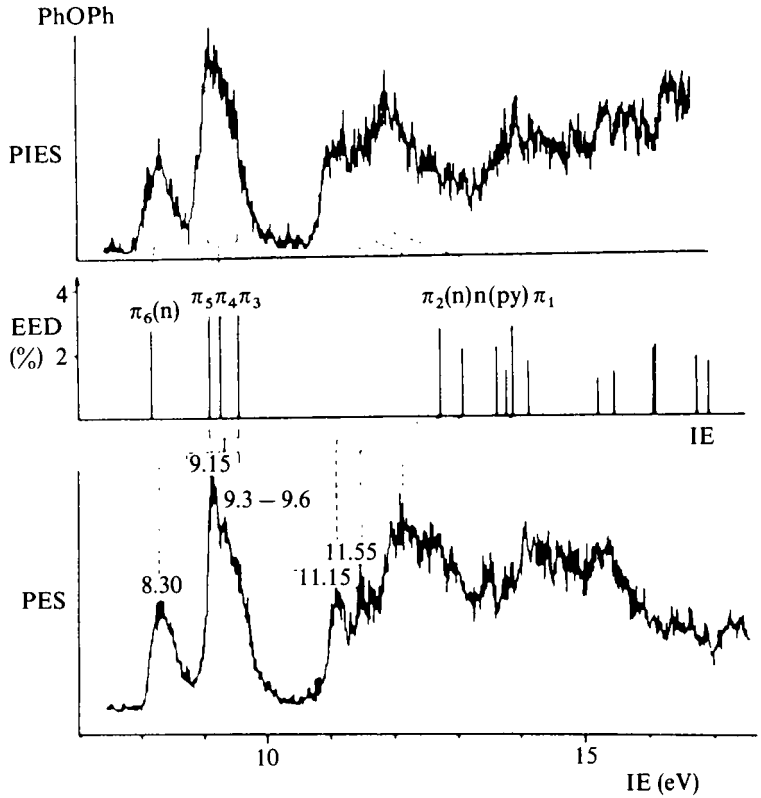


FIGURE 26. He I PE and PIES spectra of PhOPh. Reprinted with permission from W. Nakanishi and coworkers, *J. Org. Chem.*, **54**, 540 (1989). Copyright (1989) American Chemical Society

D. Miscellaneous Hydroxy and Alkoxy Compounds

Attention has been focused so far on compounds in which hydroxy or ether groups play a crucial role in determining the PE spectral features. There are, however, many PES studies that deal with highly complex molecules substituted by either hydroxy or alkoxy group(s) in which it is not possible to isolate their effects on the observed ionization pattern. Furthermore, there are a number of PE studies on hydroxy and/or alkoxy compounds dealing with some specific problems, such as reactivity, prototropic equilibria etc. Within this section, a few such cases will be mentioned for the sake of illustration only. No attempt will be made to cover all relevant contributions.

A number of papers in this category are related to the investigation of the electronic structure of molecules of pharmaceutical importance[67,222–224]. It is noteworthy that interest in this particular field was stimulated by an early observation of Karreman, Isenberg and Szent-Györgyi[225] that a number of drugs, including LSD, have HOMOs at an unusually high energy. Since that time, a number of empirical models have been proposed for correlating HOMO energies (or experimentally determined lowest ionization energies) of molecules and their pharmacological activity, measured in a variety of ways. Typical examples of the PES studies of drugs involving hydroxy or alkoxy groups are those of Houk and coworkers[222] performed on mescaline, derivatives of phenylamine and tryptophane. Another contribution to this topic is provided by Klasinc's group, who investigated morphine, codeine and ephedrine[223]. In discussing the relationship between the electronic structure and activity of the psychotropic drugs mentioned above, Houk and coworkers proposed a new model in which the average of the lowest *IE* values is correlated with the hallucinogenic activity[222]. As far as morphine, codeine and ephedrine are concerned, the molecular rather than the electronic structure seems to be more important for the analgesic activity[223].

Another representative study relating to the investigation of the electronic structure of biologically active compounds is that of Huke and Hillier on molecules allied with chromone[224].

A different type of complex molecule studied by PES is represented by lignine constituents that were investigated extensively by Klasinc's group[226] with the aim of extending the spectroscopic basis for the purpose of analysing the chemical behaviour of lignine itself.

In addition, several PE studies dealing with the influence of hydroxy and/or alkoxy group(s) on either the reactivity[227–229] or conformational properties of widely different molecules have been reported. Santiago and coworkeres[228], for instance, measured the ionization energies of several methoxybenzo-norbornadienes as part of a comprehensive study designed to explore substituent effects on the regioselectivity in triplet di-π-methano rearrangements of benzonorbornadiene[228]. Similarly, starting from the PE studies and detailed analysis of frontier orbitals, Paquette and Gleiter with coworkers[227] rationalized the directionality of singlet oxygen addition to 1,4-dimethoxynaphthalene laterally fused to bridged bicyclic systems. To close this series, we mention that Houk's group[229] has also measured the PE spectra of 7-(4-methoxyphenyl)- and 7-butoxy-norbornadiene with the aim of evaluating the influence of electronic effects on the stereoselectivity of Diels-Alder cycloadditions of hexachlorocyclopentadienes. The PE spectrum of 7-butoxynorbornadiene was also published by Astin and Mackenzie[230].

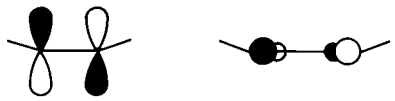
The important stereochemical problem of conformation of molecules was addressed by Cerfontain and his group in studying the PE spectral features of the α-oxooxime *O*-methyl ethers[231]. The PE spectra also provided valuable evidence of the significant through-space and through-bond interaction between the lone-pair orbitals of the keto and NOMe subunits.

Innumerable studies of prototropic equilibria also belong to this heading, to mention only those in β-diketones[232], β-thiooxoketones[233] and hydroxypiridines and related molecules[234].

Finally, a great deal of the PE studies aimed at elucidating substituent effects on the electronic structure of different classes of organic molecules comprise, almost as a rule, OH and/or OMe group(s). To illustrate their diversity, some of the compounds are listed: 2-methoxy-1,6-methano[10]annulene[235], *para*- and *meta*- methoxy benzamides[236], 9-hydroxy and 9-alkoxyphenalen-1-ones[237], 1-hydroxyethyl-2-methyl-5-nitroimidazole[238], etc.

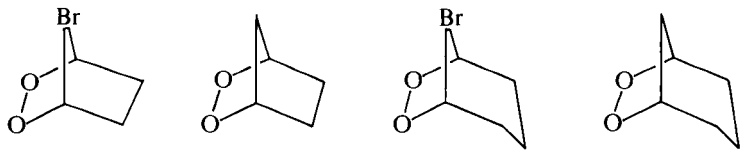
E. Peroxides

Theoretical aspects of the physico-chemical properties of peroxides were recently covered in this series by Cremer[239]. He also discussed the PE spectrum of H_2O_2 in detail and pointed to the most frequently exploited PE spectroscopic feature of organic peroxides, that is to the relationship between the splitting of photoelectron peaks representing oxygen lone pairs and the ROOR dihedral angle (Θ). The basis for understanding its origin is provided by numerous calculations of the conformational dependence of the energies of the highest occupied MOs in model compounds such as H_2O_2 and dimethyl peroxide[240]. Regardless of the level of sophistication, calculations show that the splitting of the two highest peroxide orbitals, designated as the out-of-phase linear combination of the n_O^{π} [$a_2(\pi^-)$] and the out-of-phase linear combination of the n_O^{σ} [$b_2(n^-)$] lone pairs on the two oxygen centers, respectively, should have two maxima corresponding to the values $\Theta = 0°$ and 180°. They are not necessarily equal. Further, the splitting vanishes at 90° where the two orbitals cross and become degenerate since the σ/π separation breaks down[241–244].



$a_2(\pi^-)$ $b_2(n^-)$

Typical examples of peroxides with Θ close to 0° are compounds **101a,b–102a,b**[246]. Analysis of their PE spectra shows a separation of 2.3 eV between the bands related to ionization from the considered MOs. In the PE spectra of **101a** and **101b** they appear at 9.3 and 11.5 eV and 8.96 and 11.26 eV, respectively, while in **102a** and **102b** the measured *IE* values are 9.3 and 11.6 eV and 9.05 and 11.3 eV, respectively. Assignment of the PE spectra of **102a** and **102b** deserves special attention, because of the finding that at least one of the σ levels is at a higher energy than the n^- combination. The change in the sequence of the highest occupied MOs in passing from **101b** to **102b** is rationalized by a simplified perturbation treatment including the highest occupied MOs of the peroxy group (π^-, n^-, n^+, π^+) and those of the cyclopentane and cyclohexane ring (Figure 27). The main interaction encountered between the ribbon orbitals of the six-membered ring and the peroxy unit is that between $a'(\sigma)$ and $a'(\pi^+)$, which leads to a destabilization of the ribbon orbital. In the case of the five-membered ring, fragment $a''(\sigma)$ interacts with $a''(\pi^-)$ and thus enlarges the gap between $a''(\pi^- - \sigma)$ and $a''(n^-)$. The n^+ and n^- MOs of the peroxy moiety do not interact with the ribbon orbitals of both rings since σ and n orbitals are almost orthogonal to each other.



(101a) **(101b)** **(102a)** **(102b)**

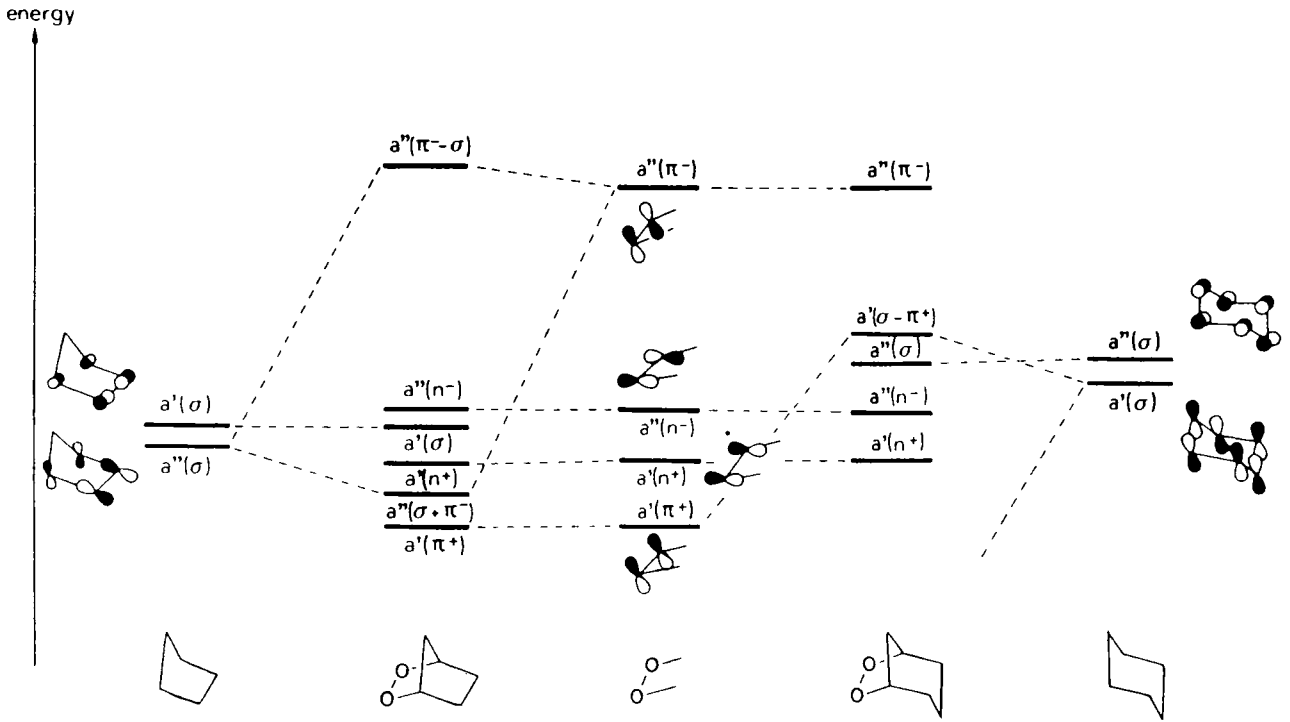
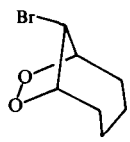
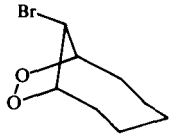


FIGURE 27. Qualitative interaction diagram between the highest occupied MOs of a peroxy group and those of a cycloalkane fragment. Only interactions with the two highest ribbon MOs a and a' of a six-membered (right) and five-membered ring (left) are shown. Reprinted with permission from R. Gleiter and coworkers, *J. Org. Chem.*, **49**, 3716 (1984). Copyright (1984) American Chemical Society

Enlargement of Θ from 0° to 14°, found in **103**, leads to a reduction in the split (ΔIE) of bands in the PE spectrum assigned to ionizations from π^- and n^- orbitals to 1.8 eV (Table 23). For compounds **104** and **105** where dihedral angles Θ are 44° and 50°, ΔIE values of 1.2 and 1.27 eV are encountered, while for compound **106** with Θ = 80° a split of only 0.4 eV emerged (Table 23).



(103)



(104)

(105)

(106)

In rationalizing the PE spectra of peroxides, considerable attention was payed to clarifying the nature of the relationship between the COOC dihedral angle and the split of the bands related to ionization from π^- and n^- MOs. Brown and coworkers[248] suggested a linear relationship between ΔIE and Θ, while Rademacher[244] and Gleiter with coworkers[245,246] advocated a linear relationship between ΔIE and cos Θ. This ambiguity has been ascribed to the lack of PES data for peroxides for which the dihedral angle has been determined experimentally[246].

The above examples provide just a brief cut through the PES investigations of peroxides. The PES data for a number of other examples are summarized in Table 23. Before concluding, we shall briefly summarize the main conclusions emerging from the PE investigations of hydroperoxides[49], ozonides[244,247] and tetroxanes[244]. The most thorough PE study of hydroperoxides is that of Ashmore and Burgess[49] who measured He I PE spectra of hydroperoxides of the general formulas: $Me(CH_2)_nOOH$, $n = 3–6$ and $Me(CH_2)_nCH(OOH)Me$, $n = 1–4$. The spectra are similar to those of the corresponding alcohols, with maxima of the bands characteristic of the hydroperoxide group typically lower by 0.1–0.2 eV than their counterparts in alcohols. The *IE* values measured are summarized in Table 24 along with assignment of the highest occupied MOs based on the INDO calculations. It should be noted, however, that INDO underestimates the energies of σ MOs with respect to lone-pair energies, leading to an incorrect ordering of the highest occupied MOs in the long-chain hydroperoxides.

The main differences between the spectra of homologous hydroperoxides lie in the shape of the first ionization band and in the onset of σ bands. The first band in 1-hydroperoxides exhibits two close-lying maxima at about 9.8–10.0 eV that are ascribed to MOs of mainly lone-pair character. The onset of the σ bands decreases from 10.8–10.4 eV as the alkyl group increases in size from n-butyl to n-heptyl, leading to merging of the first two bands in higher members of the series.

In the first bands of 2-hydroperoxides, only one maximum is discernable. However, their areas are greater than those of the σ bands. This finding indicates that they almost certainly originate from two ionization processes. The maxima of these bands are at 10.0 ± 0.05 eV in spectra of all three compounds. The separation of the first band from the σ band is less dependent on the size of the alkyl group and greater than that found in the 1-hydroxyperoxides.

It is of interest to note that the differences between the first vertical ionization energies of hydrogen peroxide and those of alkyl hydroperoxides are close to the differences between the first *IE* of water and those of alcohols. For instance, ΔIE_1 for hydrogen peroxide and n-butyl-1-hydroperoxide is 1.9 eV whereas for water and butanol it is 2.2 eV. The similar value for these shifts suggests that the effects leading to it are closely related and that the hydroperoxy group interacts quite strongly with the alkyl residue.

TABLE 23. PE data for peroxides[a]

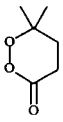
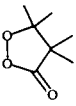
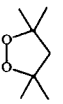
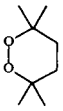
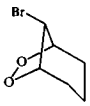
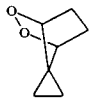
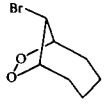
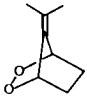
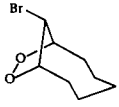
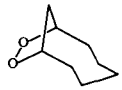
Structure	*IE* (eV)				References
H_2O_2	11.7 π^-	12.7 n^-			249
Alkyl peroxides					
MeOOMe	9.71 $b_g(\pi^-)$	11.61 $a_u(\pi^+)$	12.58 $a_g(n^-)$	14.02 $\sigma_{OC}{}^+$	249
i-Pr—OO—Pr-*i*	9.16 π^-	10.71 n^-			248
t-Bu—OO—Bu-*t*	8.78 $1b_g(\pi^-)$	10.46 $4a_g(n^-)$	10.85 $1a_u(\pi^+)$	11.7	242, 245, 249
Cyclic peroxides					
	8.98 $2a_2(\pi^-)$	10.94 $3b_1(n^-)$	11.41 $5a_1$	12.09 $1a_2$	244, 249
	9.86 π^-	11.13 n^-			251
	9.66 $\pi_{C=C}$	10.37	10.37		251
	10.0 π^-	10.2 n^-			249
	9.75 π^-	10.34 n^-			249
	10.1 n^-	10.7 π^-	11.4 σ		250
	9.29 π^-	10.60 n^-			249
	9.9 π^-	10.4 n^-	11.6 σ		250
	9.25 $1a_2(\pi^-)$	10.4 $3b_1(n^-)$	11.4, 11.8 $4a_1, 1b_2$		242
	9.5 $a(\pi^-)$	9.55 b	10.9 a	11.7	242
	9.3 π^-	10.33, 10.62 4p		11.5 n^-	246

TABLE 23. (*continued*)

Structure	*IE* (eV)				References
	8.96 $a''(\pi^-)$	11.26 $a''(n^-)$			246
	8.76 $a''(\pi^-)$	9.95 $a''(\pi)$	11.23 $a''(n^-)$		245
	9.3 π^-	10.3, 10.6 4p	10.8 σ	11.6 n^-	246
	9.05 π^-	10.6 σ	11.3 n^-		246
	8.82 $a''(\pi^-)$	10.83 $a''(n^-)$			245
	8.87 $a''(\pi^-)$	10.55 $a''(w)$	11.15 $a''(n^-)$		245
	9.2 π^-	10.3, 10.6 4p	11.0 n^-	11.6 σ	245
	8.9 π^-	10.6 n^-	11.3 σ		246
	8.97 π^-	10.37 n^-			246
	8.62 $a''(\pi^-)$	9.26 $a''(\pi)$	11.06 $a''(n^-)$		245
	9.00 π^-	9.70 π	10.34 n^-		245
	9.6 π^-	10.3, 10.5 4p		10.8 n^-	246
	9.2 π^-	10.4 n^-			246

(*continued*)

TABLE 23. (*continued*)

Structure	*IE* (eV)			References
	9.14 π^-	10.0 n^-		245
	9.06 π^-	10.07 n^-		245
	8.42 π^-	9.70 $\pi_{C=C}$	10.71 n^-	249
	8.50 π^-	10.36 n^-		249

[a]Vertical ionization energies and their orbital assignments (if available).

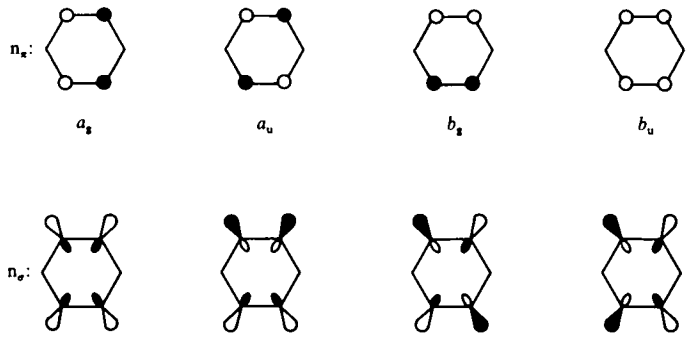
TABLE 24. PE data for some n-alkyl hydroperoxides[a]

Compound	1st band		*A*	σ onset	1st shoulder	σ bands
	v_1	v_2				
Butyl-1-OOH	9.75	10.32	9.36	10.81	11.45	16.6
Pentyl-1-OOH	9.83	10.28	9.50	10.67	11.14	—
Pentyl-2-OOH	10.05		9.35	10.58	11.05	16.35, 17.5
Hexyl-1-OOH	9.85	10.30	9.47	10.43	10.90	16.3
Hexyl-2-OOH	9.96		9.25	10.56	11.00	16.8, 17.5
Heptyl-1-OOH	9.88	10.30	9.48	10.41	10.84	11.55, 16.40
Heptyl-2-OOH	9.94		9.30	10.43	10.80	—

[a]Reference 49; all *IE* values in eV. Accuracy of the first *IE* value is generally $\pm$ 0.03 eV; other *IE* values $\pm$ 0.1 eV.

In discussing the PE spectra of ozonides, emphasis is laid on establishing the nature and extent of the mutual interaction between ether and peroxide subunits[247]. The symmetry characteristics of the oxygen lone-pair orbitals of 1,2,4-trioxolane, for instance, offer a unique opportunity to assess the inductive effects of the peroxide and ether oxygens on each other in the absence of interfering conjugative effects. From an analysis of the PES of 1,2,4-trioxolane, 1,2-dioxacyclopentane and tetrahydrofuran, Brown and Marcinko[247] concluded that ethereal oxygen exerts an inductive effect of *ca* 0.8 eV, while the peroxide group was found to stabilize the ether oxygen n_O^π lone pair by 1.4 eV. This conclusion was based on the assumption that the first two ionization events in the PE spectrum of 1,2,4-trioxolane correspond to ionization from n^- MO of the peroxide group and n_O^π MO of the etheric oxygen, respectively. It should be pointed out, however, that the MINDO/2 calculations performed by Rademacher and Elling[244] predicted a reversed MO ordering ($n_O^\pi > n^-$), indicating that both subunits exert inductive stabilization of 1.1 eV.

Rademacher and Elling have also measured the PE spectra of two 1,2,4,5-tetroxanes. On the basis of MINDO/2 calculations their lowest *IE* values were tentatively assigned to ionizations out of $b_g(n_\sigma)$, $a_g(n_\pi)$, $a_u(n_\pi)$ and $b_u(n_\pi)$ MOs shown below:



IV. CONCLUDING REMARKS

This review surveys the low-energy PE spectroscopic data of compounds involving hydroxyl, ether or peroxide groups accumulated over a period of 30 years—from the early days of this powerful technique until now. Similarities and differences between spectra within the series of molecules comprising the mentioned characteristic functional groups are discussed in some detail. The impressive number of compounds considered in the article illustrates the extensive interest of the PE spectroscopists in the properties of these systems. Part of this interest is certainly due to thier abundance and important role in synthetic and industrial chemistry. It is beyond doubt, however, that much of the work has been stimulated by theoretical questions concerning the modes of interaction between well-separated functional groups. This is of great conceptual significance, since the notion of functional groups is rooted in the idea of modified atoms in molecules[4]. In principle, the latter concept enables reduction of the very complex problem of the structure and properties of molecules to a problem of description of smaller subunits (atoms or atomic groupings) and their mutual interactions. Successful modelling of intramolecular interactions, as revealed by PES, supports the concept of modified atoms in molecular environments, which represents one of the cornerstones of phenomenological chemistry. To be more specific, we have discussed in great detail the interactions between the high-lying oxygen lone-pair orbitals with fragment orbitals describing other building blocks of the molecules in question. Particular attention is focused on interactions between lone pairs or mixing of lone-pair atomic orbitals with π or high-lying σ orbitals. Emphasis is laid on spectral features that reveal these interactions and *ultima linea* fingerprint the studied compounds. In most cases, interpretation of the results is based on a simple orbital model, which in turn is supported by more elaborate treatments wherever possible. It appears, however, that the description of intramolecular interactions by simple models, such as their dissection into through-bond and through-space modes, proves very useful in rationalizing the PES data, thus aiding our understanding of the behaviour of electrons in molecules.

Finally, we note in passing that complementary techniques, such as XPES[252] and PIES[253], related to inner and outermost electrons, respectively, have been applied to

several of the molecules considered here. The results, both experimental and theoretical, for inner valence spectra, shake-up spectra and core level shifts have been recently reviewed by Gelius and colleagues[252]. The latter technique is particularly important since it provides information about the outer shape of molecules, giving an idea of the spatial electron distribution of frontier molecular orbitals. This is essential for elucidating the various intermolecular processes, including chemical reactions[253].

In conclusion, it should be pointed out that a rich harvest can be expected in the future for the PES employing synchrotron radiation[254] and excited state[255] PES. Both techniques *inter alia* provide powerful methods for exploring the mechanism of photoionization, such as autoionization.

V. ACKNOWLEDGEMENTS

A part of this manuscript has been prepared at the Organisch-chemisches Institut der Universität Heidelberg and financial support of the Alexander von Humboldt Foundation is gratefully acknowledged. I would like to express my gratitude to Professor R. Gleiter for his hospitality, continuous encouragement and advice in my PES work over a number of years. Thanks are also due to Professor J. E. Frey for the results of Reference 51, Mr W. Wittwer for his help in the literature search and to MSc D. Margetic, Dipl. Eng. N. Novak and Dipl. Eng. Z. Glasovac for technical assistance in the preparation of the manuscript. Finally, I thank the Ministry of Science, Technology and Informatics of Croatia for supporting our ongoing research in the area of PE spectroscopy.

VI. REFERENCES

1. E.g. H.-D. Martin and B. Mayer, *Angew. Chem.*, **95**, 281 (1983); *Angew. Chem., Int. Ed. Engl.*, **22**, 283 (1983).
2. E. Heilbronner, J. P. Maier and E. Haselbach, in *Physical Methods in Heterocyclic Chemistry* (Ed. A. R. Katritzky), Vol. 6, Academic Press, New York, 1974, p. 1.
3. C. N. R. Rao and P. K. Basu, in *Physical Methods in Heterocyclic Chemistry* (Ed. R. P. Gupta), Wiley, New York, 1984, 231 p.
4. The interested reader should consult, for example, the books:
   (a) Z. B. Maksić (Ed.), *Theoretical Models of Chemical Bonding. Part 1. Atomic Hypothesis and the Concept of Molecular Structure*, Springer-Verlag, Berlin, 1991.
   (b) R. F. W. Bader, *Atoms in Molecules: A Quantum Theory*, Oxford University Press, Oxford, 1990.
5. R. Hoffmann, *Acc. Chem. Res.*, **4**, 1 (1971) and references cited therein.
6. (a) A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, Berlin, 1983.
   (b) P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, New York, 1983.
7. (a) O. Eisenstein, N. G. Anh, Y. Jean, A. Devaquet, J. Cantacuzene and L. Salem, *Tetrahedron*, **30**, 1717 (1974).
   (b) W. L. Jorgensen and L. Salem, *The Organic Chemist's Book of Orbitals*, Part I, Academic Press, New York, 1973.
8. R. McWeeny and F. E. Jorge, *J. Mol. Stuct. (Theochem)*, **169**, 459 (1988).
9. P. A. Schultz and R. P. Messner, in *Molecules in Natural Science and Medicine–An Enconium for Linus Pauling* (Eds. Z. B. Maksić and M. Eckert-Maksić), Ellis Horwood, Chichester, 1991, pp. 309–326.
10. R. P. Messner, *J. Mol. Struct. (Theochem)*, **169**, 137 (1988).
11. (a) For example, R. Gleiter, *Angew. Chem.*, **86**, 770 (1974); *Angew. Chem., Int. Ed. Engl.*, **13**, 696 (1974).
    (b) J. W. Verhoeven, *Recl. Trav. Chim. Pays-Bas*, **99**, 143 (1980).
    (c) M. N. Paddon-Row and K. D. Jordan, in *Modern Models of Bonding and Delocalization* (Eds. J. F. Liebman and A. Greenberg), VCH Publ., Stuttgart, 1988, pp. 115–194.

(d) M. Eckert-Maksić, in *Theoretical Models of Chemical Bonding*, Part 3. *Molecular Spectroscopy. Electronic Structure and Intramolecular Interactions* (Ed. Z. B. Maksić), Springer-Verlag, Berlin, 1991, pp. 153–198 and references cited therein.
12. K. Siegbahn, C. Nordling, G. Johansson, J. Hedman, P. F. Heden, K. Hamrin, U. Gelius, T. Bergmark, L. O. Werme, R. Manne and Y. Baer, *ESCA Applied to Free Molecules*, North-Holland, Amsterdam, London, 1969.
13. D. W. Turner, C. Baker, A. D. Baker and C. R. Brundle, *Molecular Photoelectron Spectroscopy*, Wiley–Interscience, London, 1970.
14. T. A. Carlson, *Photoelectron and Auger Spectroscopy*, Plenum Press, New York, 1975.
15. J. H. D. Eland, *Photoelectron Spectroscopy*, Butterworths, London, 1974.
16. C. R. Brundle and A. D. Baker, *Electron Spectroscopy: Theory, Techniques and Applications*, Vol. 1, Academic Press, New York, 1977.
17. J. W. Rabalais, *Principles of Ultraviolet Photoelectron Spectroscopy*, Wiley, New York, 1977.
18. R. E. Ballard, *Photoelectron Spectroscopy and Molecular Orbital Theory*, Adam Hilger, Bristol, 1978.
19. K. Kimura, S. Katsumota, Y. Achiba, Y. Yamazaki and S. Iwata, *Handbook of He I Photoelectron Spectra of Fundamental Organic Molecules*, Halsted Press, New York, 1981.
20. (a) D. W. Turner, in *Annual Review of Physical Chemistry* (Ed. H. Eyring), Ann. Rev. Inc., Palo Alto, Cal., 1970.
(b) D. Baker, *Acc. Chem. Res.*, **3**, 17 (1970).
(c) S. D. Worley, *Chem. Rev.*, **71**, 295 (1971).
(d) A. D. Baker, C. R. Brundle and M. Thompson, *Chem. Soc. Rev.*, **1**, 355 (1972).
(e) H. Bock and B. G. Ramsey, *Angew. Chem.*, **85**, 773 (1973); *Angew. Chem., Int. Ed. Engl.*, **12**, 734 (1973); H. Bock and P. D. Mollere, *J. Chem. Educ.*, **51**, 506 (1974); H. Bock, *Angew. Chem.*, **89**, 631 (1977); *Angew. Chem., Int. Ed. Engl.*, **16**, 631 (1977).
(f) D. Betteridge and M. A. Williams, *Anal. Chem.*, **46**, 125R (1974).
(g) T. A. Carlson, in *Annual Reviews of Physical Chemistry* (Ed. H. Eyring), Ann. Rev. Inc., Palo Alto, Cal., 1975.
(h) E. Heilbronner and J. P. Maier, in Reference 16, p. 205.
(i) M. E. Schwartz, in *Application of Electronic Structure Theory* (Ed. H. F. Schaefer), Plenum Press, New York, 1977, p. 357.
21. T. Koopmans, *Physica*, **1**, 104 (1934).
22. E.g. (a) L. S. Cederbaum and W. Domcke, *Adv. Chem. Phys.*, **36**, 205 (1977); L. S. Cederbaum, W. Domcke, J. Schirmer and W. von Niessen, *Adv. Phys. Chem.*, **65**, 115 (1986).
(b) S. P. McGlyn, K. Wittel and L. Klasinc, in *Theoretical Models of Chemical Bonding, Part 3. Molecular Spectroscopy, Electronic Structure and Intramolecular Interactions* (Ed. Z. B. Maksić), Springer-Verlag, Berlin, 1991, pp. 63–97.
23. W. Meyer, *Int. J. Quantum Chem.*, **S5**, 341 (1971).
24. Reference 19, p. 33.
25. L. S. Cederbaum, G. Hohlnreicher and W. von Niessen, *Mol. Phys.*, **26**, 1405 (1973).
26. D. P. Chong, F. G. Herring and D. McWilliams, *J. Chem. Phys.*, **61**, 3567 (1974).
27. M. I. Al-Joboury and D. W. Turner, *J. Chem. Soc.*, 4434 (1964); *J. Chem. Soc. (B)*, 373 (1967).
28. C. N. R. Rao, P. K. Basu and M. S. Hegde, *Appl. Spectrosc. Rev.*, **15**, 1 (1979).
29. M. J. S. Dewar and S. D. Worley, *J. Chem. Phys.*, **50**, 654 (1969).
30. A. D. Baker, D. Betteridge, N. R. Kemp and R. E. Kirby, *Anal. Chem.*, **43**, 375 (1971).
31. B. Brehm, V. Fuchs and P. Kebarle, *Int. J. Mass Spectrom. Ion Phys.*, **6**, 279 (1971).
32. M. B. Robin and N. A. Kuebler, *J. Electron Spectrosc.*, **1**, 13 (1972/1973).
33. (a) H. Ogata, H. Onizuka, Y. Nikei and H. Kamada, *Chem. Lett.*, 895 (1972).
(b) H. Ogata, H. Onizuka, Y. Nikei and H. Kamada, *Bull. Chem. Soc. Jpn.*, **46**, 3036 (1973).
34. A. W. Potts, T. A. Williams and W. C. Price, *Discuss. Faraday Soc.*, **54**, 104 (1972).
35. S. Katsumata, T. Iwai and K. Kimura, *Bull. Chem. Soc. Jpn.*, **46**, 3391 (1973).
36. K. A. G. MacNeil and R. N. Dixon, *J. Electron Spectrosc.*, **11**, 315 (1977).
37. L. Karlsson, R. Jadrny, L. Mattsson, F. T. Chau and K. Siegbahn, *Phys. Scr.*, **16**, 225 (1977).
38. C. Utsunomiya, T. Kobayashi and S. Nagakura, *Bull. Chem. Soc. Jpn.*, **53**, 1216 (1980).
39. J. P. Flament, Y. Hoppilliard, P. Jaudon and P. Youkharibache, *Nouv. J. Chim.*, **5**, 61 (1981).
40. J. B. Peel and G. D. Willet, *Aust. J. Chem.*, **28**, 2357 (1975).
41. J. J. P. Stewart, in *Reviews in Computational Chemistry* (Eds. K. B. Lipowitz and D. B. Boyd), VCH Publ., Stuttgart, 1990, pp. 45–81 provides a good overview of semiempirical methods.

42. A. B. Cornford, D. C. Frost, F. G. Herring and A. McDowell, *Can. J. Chem.*, **49**, 1135 (1971).
43. W. J. Hehre, L. Radom, P. v. R. Schleyer and J. Pople, *Ab initio Molecular Orbital Theory*, Wiley, New York, 1986.
44. W. H. Fink and L. C. Allen, *J. Chem. Phys.*, **46**, 2276 (1967).
45. D. S. C. Yee, A. Hamnett and C. E. Brion, *J. Electron Spectrosc.*, **8**, 291 (1976).
46. W. C. Tam and C. E. Brion, *J. Chem. Electron Spectrosc.*, **3**, 263 (1974).
47. H. Koizumi, *J. Chem. Phys.*, **95**, 6846 (1991).
48. J. P. Culot, Austin Symposium of Gas Phase Molecular Structures, Paper T8 (1972); see Ref. 19, p. 232.
49. F. S. Ashmore and A. R. Burgess, *J. Chem. Soc., Faraday Trans. 2*, **73**, 1247 (1977).
50. I. A. Koppel, U. H. Molder and R. J. Pikver, *Org. React.*, **20**, 45 (1983).
51. J. E. Frey, private communication (1991).
52. Y. Hoppilliard and D. Solgadi, *Tetrahedron*, **36**, 377 (1980).
53. S. Leavell, J. Steichen and J. L. Franklin, *J. Chem. Phys.*, **59**, 4343 (1975).
54. K. Ohno, K. Imai and Y. Harada, *J. Am. Chem. Soc.*, **107**, 8078 (1985).
55. J. S. Wieczorek, T. Koenig and T. Balle, *J. Electron Spectrosc.*, **6**, 215 (1975).
56. R. S. Brown, *Can. J. Chem.*, **54**, 642 (1976).
57. H. Kunz, M. Lindig, R. Bicker and H. Bock, *Chem. Ber.*, **111**, 2282 (1978).
58. R. S. Brown, *Can. J. Chem.*, **54**, 3203 (1976).
59. J. E. DelBene, *J. Am. Chem. Soc.*, **95**, 5460 (1973).
60. R. S. Brown and D. A. Allison, *J. Am. Chem. Soc.*, **99**, 3568 (1977).
61. R. S. Brown and R. W. Marcinko, *J. Am. Chem. Soc.*, **100**, 5721 (1978).
62. R. S. Brown, R. W. Marcinko and A. Tse, *Can. J. Chem.*, **57**, 1890 (1979).
63. N. Bodor, M. J. S. Dewar and S. D. Worley, *J. Am. Chem. Soc.*, **92**, 19 (1970).
64. G. M. R. Tombo, H. J. Ammann, K. Muller and C. Ganter, *Helv. Chim. Acta*, **66**, 50 (1983).
65. A. Katrib and J. W. Rabalais, *J. Phys. Chem.*, **77**, 2358 (1973).
66. G. W. Mines, *Spectrochim. Acta*, **29A**, 1377 (1973).
67. L. Klasinc, B. Ruščić, A. Sabljić and N. Trinajstić, *J. Am. Chem. Soc.*, **101**, 7477 (1979).
68. E. J. McAlduff, P. Caramella and K. N. Houk, *J. Am. Chem. Soc.*, **100**, 105 (1978).
69. R. S. Brown, *Can. J. Chem.*, **54**, 3206 (1976).
70. K. Morokuma and G. Wipff, *Chem. Phys. Lett.*, 400 (1980).
71. M. V. Andreocci, P. Bitchev, P. Carusi and A. Furlani, *J. Electron Spectrosc.*, **16**, 25 (1979).
72. E.g. A. Furlani, P. Bicev, M. V. Russo and M. Fiorentino, *Gazz. Chim. Ital.*, **107**, 373 (1977); G. Sartori, A. Furlani, P. Bicev, P. Carusi and M. V. Russo, *Isr. J. Chem.*, **15**, 230 (1976–77) and references cited therein.
73. A. D. Baker, D. P. Mayer and D. W. Turner, *J. Chem. Soc. (B)*, 22 (1968).
74. J. P. Maier and D. W. Turner, *J. Chem. Soc., Faraday Trans. 2*, **69**, 521 (1973).
75. T. P. Debies and J. W. Rabalais, *J. Electron Spectrosc.*, **1**, 355 (1973).
76. T. Kobayashi and S. Nagakura, *Bull. Chem. Soc. Jpn.*, **47**, 2563 (1974).
77. P. S. Dewar, S. Ernstbrunner, J. R. Gilmore, M. Godfrey and J. M. Mellor, *Tetrahedron*, **30**, 2455 (1974).
78. M. H. Palmer, W. Mayes, M. Speirs and J. N. A. Ridyard, *J. Mol. Struct. (Theochem)*, **52**, 293 (1979).
79. J. P. LaFemina, *Int. J. Quantum Chem.*, **36**, 563 (1989).
80. B. Cetinkaya, M. L. Lappert and R. J. Suffolk, *J. Chem. Res. (S)*, 316 (1983).
81. V. N. Baidin, A. D. Misharev and V. V. Takhistov, *Zh. Org. Khim.*, **21**, 1237 (1985).
82. J. P. Maier, O. Marthaler, M. Mohraz and R. H. Shiley, *J. Electron Spectrosc.*, **19**, 11 (1980).
83. H. Goetz, H. Hartan, H. Juds, F. Marschner and H. Pohle, *Justus Liebigs Ann. Chem.*, 556 (1977).
84. T. Kobayashi and S. Nagakura, *J. Electron Spectrosc.*, **6**, 421 (1975).
85. D. Dougherty, E. S. Younathan, R. Voll, S. Abdulnur and S. P. McGlynn, *J. Electron Spectrosc.*, **13**, 379 (1978).
86. E. Heilbronner and H. Bock, Das HMO Model und seine Anwendung, 2nd ed., Verlag Chemie, Weinheim, 1978.
87. C. Dearden and W. F. Forbes, *Can. J. Chem.*, **38**, 1837 (1960).
88. S. Millefiori, A. Millefiori and S. Pappalardo, *Spectrochim. Acta*, **40A**, 571 (1984).
89. C. Utsunomiya, T. Kobayashi and S. Nagakura, *Bull. Chem. Soc. Jpn.*, **48**, 1852 (1975).
90. F. Brogli, E. Heilbronner and T. Kobayashi, *Helv. Chim. Acta*, **55**, 274 (1972).
91. S. Millefiori and A. Millefiori, *Spectrochim. Acta*, **44A**, 17 (1988).

92. B. J. Cocksey, J. H. D. Eland and C. J. Danby, *J. Chem. Soc. (B)*, 790 (1971).
93. C. Cradock and R. A. Whiteford, *J. Chem. Soc., Faraday Trans. 2*, **68**, 281 (1972).
94. H. Bock, P. Mollere, G. Becker and G. Fritz, *J. Organomet. Chem.*, **61**, 113 (1973).
95. A. Schweig and W. Thiel, *Mol. Phys.*, **27**, 265 (1974).
96. J. M. Behan, F. M. Dean and R. A. W. Johnstone, *Tetrahedron*, **32**, 167 (1976).
97. M. Klessinger, P. Asmus and W. Kraetz, *Tetrahedron*, **31**, 517 (1975).
98. R. S. Brown, *Can. J. Chem.*, **53**, 3439 (1975).
99. F. Carnovale, T. H. Gan and J. B. Peel, *J. Electron Spectrosc.*, **20**, 53 (1980).
100. V. V. Zverev, A. A. Bredikhin, V. M. Vaker and A. N. Vereshchagin, *Zh. Strukt. Khim.*, **27**, 64 (1986).
101. K. Kimura and M. Kubo, *Nature*, **183**, 533 (1959).
102. F. Carnovale, M. K. Livett and J. B. Peel, *J. Am. Chem. Soc.*, **102**, 569 (1980).
103. F. Carnovale, M. K. Livett and J. B. Peel, *J. Am. Chem. Soc.*, **104**, 5334 (1982).
104. A. H. Hardin and C. Sandorfy, *J. Fluorine Chem.*, **5**, 435 (1975).
105. U. H. Molder, R. J. Pikver and I. A. Koppel, *Org. React.*, **20**, 208 (1983).
106. H. Friege and M. Klessinger, *J. Chem. Res. (S)*, 208 (1977).
107. H. Friege and M. Klessinger, *Chem. Ber.*, **112**, 1614 (1979).
108. A. A. Planckaert, J. Doucet and C. Sandorfy, *J. Chem. Phys.*, **60**, 4846 (1974).
109. H. Bock, G. Wagner, K. Wittel, J. Sauer and D. Seebach, *Chem. Ber.*, **107**, 1869 (1974).
110. M. Klessinger and P. Rademacher, *Angew. Chem.*, **91**, 885 (1979); *Angew. Chem., Int. Ed. Engl.*, **18**, 826 (1979).
111. F. Bernardi, N. D. Epiotis, R. L. Yates and H. B. Schlegel, *J. Am. Chem. Soc.*, **98**, 2385 (1976).
112. I. G. John and L. Radom, *J. Mol. Struct.*, **36**, 133 (1977).
113. (a) D. L. Ames and D. W. Turner, *J. Chem. Soc., Chem. Commun.*, 179 (1975).
(b) C. Muler, W. Schäfer, A. Schweig, N. Thom and H. Vermeer, *J. Am. Chem. Soc.*, **98**, 5440 (1976).
114. P. Fischer, in *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulphur Analogues* (Ed. S. Patai), Part 2, Wiley, Chichester, 1980, p. 761.
115. R. Sustman and R. Schubert, *Tetrahedron Lett.*, 2739 (1972).
116. S. W. Eroshchenko, L. M. Sinegovskaya, O. A. Tarasova, S. V. Amasova, Yu. L. Frolov and B. A. Trofimov, *Izv. Akad. Nauk SSSR, Khim.*, **9**, 2011 (1989).
117. M. Bloch, F. Brogli, E. Heilbronner, T. B. Jones, H. Prinzbach and O. Schweikert, *Helv. Chim. Acta*, **61**, 1388 (1978).
118. R. Hoffmann, Ph. D. Mollere and E. Heilbronner, *J. Am. Chem. Soc.*, **95**, 4860 (1973).
119. C. Batich, E. Heilbronner, C. B. Quinn and R. J. Wisemann, *Helv. Chim. Acta*, **59**, 512 (1976).
120. B. J. M. Neijzen, R. F. Schmitz, G. W. Klumpp and C. A. deLange, *Tetrahedron*, **31**, 873 (1975).
121. G. Modena, F. Marcuzzi, E. Tondello and D. Ajo, *J. Cryst. Spectrosc. Res.*, **18**, 747 (1988).
122. S. Topiol, J. W. Moskowitz and C. F. Melius, *J. Chem. Phys.*, **68**, 5 (1978).
123. J. Kroner, W. Kosbahn and W. Runge, *Ber. Bunsenges. Geselschaft*, **81**, 826 (1977).
124. R. Gleiter, R. W. Saalfrank, W. Paul. D. O. Cowan and M. Eckert-Maksić, *Chem. Ber.*, **116**, 2888 (1983).
125. L. M. Sinegovskaya, S. V. Eroshenko, O. A. Tarasova, Yu. L. Frolov, S. V. Amosova and B. A. Trofimov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 81 (1991).
126. C. Baker and D. W. Turner, *Chem. Commun.*, 480 (1969).
127. J. Cossy, J.-P. Pete, R. Gleiter, A. Flatow, P.-A. Carrupt and P. Vogel, *Tetrahedron*, **48**, 2401 (1992).
128. H. Basch, M. B. Robin, N. A. Kuebler, C. Baker and D. W. Turner, *J. Chem. Phys.*, **51**, 52 (1969).
129. W. A. Lathan, L. Radom, P. C. Hariharan, W. J. Hehre and J. A. Pople, *Fortschr. Chem. Forsch.*, **40**, 1 (1973).
130. A. Schweig and W. Thiel, *Chem. Phys. Lett.*, **16**, 541 (1973).
131. E. J. McAlduff and K. N. Houk, *Can. J. Chem.*, **55**, 318 (1971).
132. P. D. Mollere and K. N. Houk, *J. Am. Chem. Soc.*, **99**, 3226 (1977).
133. D. H. Aue, H. M. Webb, W. R. Davidson, M. Vidal, M. T. Bowers, H. Goldwhite, L. E. Vertal, J. E. Douglas, P. A. Kollman and G. L. Kenyan, *J. Am. Chem. Soc.*, **102**, 5151 (1980).
134. B. Kellerer, L. S. Cederbaum and G. Hohlneicher, *J. Electron Spectrosc.*, **3**, 107 (1974).
135. F. Brogli, E. Heilbronner, J. Wirz, E. Kloster-Jensen, R. G. Bergman, K. Peter, C. Vollhardt and A. J. Ashe III, *Helv. Chim. Acta*, **58**, 2620 (1975).
136. K. Shudo, T. Kobayashi and C. Utsunomiya, *Tetrahedron*, **33**, 1721 (1977).

137. H. Güsten, L. Klasinc, I. Novak and M. Šanjek, *Z. Naturforsch.*, **39a**, 1230 (1984).
138. I. Akiyama, K. C. Li, P. R. LeBreton, P. P. Fu and R. G. Harvey, *J. Phys. Chem.*, **83**, 2997 (1979).
139. R. Boschi and W. Schmidt, *Tetrahedron Lett.*, 2577 (1972); R. Boschi, E. Clar and W. Schmidt, *J. Phys. Chem.*, **60**, 4406 (1974).
140. N. O. Lipari and C. B. Duke, *J. Chem. Phys.*, **63**, 1748, 1758, 1768 (1975); C. B. Duke, W. R. Salaneck, T. J. Fabish, J. J. Ritsko, H. R. Thomas and A. Paton, *Phys. Rev.*, **B18**, 5717 (1978).
141. P. Bishof, E. Haselbach, and E. Heilbronner, *Angew. Chem., Int. Ed. Engl.*, **9**, 953 (1970).
142. P. D. Mollere, *Tetrahedron Lett.*, 2791 (1973).
143. Cf. A. R. Katritzky and C. W. Rees (Eds.), *Comprehensive Heterocyclic Chemistry*, Pergamon Press, Oxford, 1984.
144. For a recent review see: C. Cauletti and G. Distefano, in *The Chemistry of Organic Selenium and Tellurium Compounds*, Vol. 2 (Ed. S. Patai), Wiley, Chichester, 1978, pp. 1–50.
145. A. D. Bain, J. C. Bünzli, D. C. Frost and L. Weiler, *J. Am. Chem. Soc.*, **95**, 291 (1973).
146. S. Pignatoro and G. Distefano, *Chem. Phys. Lett.*, **26**, 356 (1974).
147. S. H. Gerson, S. D. Worley, N. Bodor, J. J. Kaminiski and T. W. Flechtner, *J. Electron Spectrosc.*, **13**, 421 (1978).
148. H. Schmidt and A. Schweig, *Chem. Ber.*, **107**, 725 (1974).
149. H. Schmidt and A. Schweig, *Tetrahedron Lett.*, 1437 (1973); A. Schweig, U. Weidner and G. Manuel, *Angew. Chem.*, **84**, 899 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 837 (1972).
150. M. Bloch, E. Heilbronner, T. B. Jones and J. L. Ripolli, *Heterocycles*, **11**, 443 (1978).
151. H. Schmidt, A. Schweig, A. G. Anastassiou and J. C. Wetzel, *Tetrahedron*, **32**, 2239 (1976).
152. J. H. D. Eland, *Int. J. Mass Spectrom. Ion Phys.*, **2**, 471 (1969).
153. A. D. Baker, D. Betteridge, N. R. Kemp and R. E. Kirby, *Anal. Chem.*, **42**, 1064 (1970); A. D. Baker and D. W. Turner, *Philos. Trans. R. Soc. London, Ser. A*, **268**, 131 (1970).
154. U. Gelius, C. J. Allan, G. Johansson, H. Siegbahn, D. A. Allison and K. Siegbahn, *Phys. Scr.*, **3**, 237 (1971).
155. P. Linda, G. Marino and S. Pignatoro, *J. Chem. Soc. (B)*, 1587 (1971).
156. G. Distefano, S. Pignatoro, G. Innorta, F. Fringuelli, G. Marino and A. Taticchi, *Chem. Phys. Lett.*, **22**, 132 (1973).
157. T. Munakata, K. Kuchitsu and J. Harada, *J. Electron Spectrosc.*, **20**, 235 (1980).
158. V. Galasso, L. Klasinc, A. Sabljić, N. Trinajstić, G. C. Pappalardo and W. Steglich, *J. Chem. Soc., Perkin Trans. 2*, 127 (1981).
159. T. Kobayashi, T. Kubota, K. Ezumi and C. Utsunomiya, *Bull. Chem. Soc. Jpn.*, **55**, 3915 (1982).
160. J. Derrick, L. Asbrink, O. Edqvist, B. O. Jonsson and E. Lindholm, *Int. J. Mass Spectrom. Ion Phys.*, **6**, 161, 177, 191 (1971); *Spectrochim. Acta*, **A27**, 2525 (1971).
161. P. Dechant, A. Schweig and W. Thiel, *Angew. Chem.*, **85**, 358 (1973); *Angew. Chem., Int. Ed. Engl.*, **12**, 308 (1973).
162. L. Klasinc, A. Sabljić, G. Kluge, J. Rieger and M. Scholz, *J. Chem. Soc., Perkin Trans. 2*, 539 (1982).
163. W. von Niessen, W. P. Kraemer and L. S. Cederbaum, *J. Electron Spectrosc.*, **8**, 179 (1976).
164. J. A. Sell and A. Kuppermann, *Chem. Phys. Lett.*, **61**, 355 (1979).
165. L. Asbrink, C. Fridh and E. Lindholm, *J. Electron Spectrosc.*, **16**, 355 (1979).
166. G. DeAlti, P. Decleva and A. Sgamellotti, *Gazz. Chim. Ital.*, **110**, 49 (1980); G. DeAlti and P. Decleva, *Chem. Phys. Lett.*, **77**, 413 (1981).
167. J. Ridley and M. Zerner, *Theor. Chim. Acta*, **32**, 111 (1973); **42**, 223 (1976).
168. G. Kluge and M. Scholz, *Z. Chem.*, **19**, 457 (1979).
169. G. Kluge and M. Scholz, *Int. J. Quantum Chem.*, **20**, 669 (1981).
170. F. Fringuelli, G. Marino, A. Taticchi, G. Distefano, F. P. Colonna and T. W. Flechtner, *J. Electron Spectrosc.*, **13**, 421 (1978).
171. T. Veszpremi, Y. Harada, K. Ohno and H. Mutoh, *J. Organomet. Chem.*, **252**, 121 (1983).
172. Z. Bozić, K. Humski, T. Cvitaš and L. Klasinc, *J. Chem. Soc., Perkin Trans. 2*, 1413 (1977).
173. T. Veszpremi, L. Nyulaszi, Gy. Zsombok, J. Reffy, T. Cvitaš, B. Kovač and L. Klasinc, *J. Mol. Struct. (Theochem)*, **202**, 1214 (1989).
174. L. Nyulaszi and T. Veszpremi, *Acta Chim. Acad. Sci. Hung.*, **126**, 27 (1989).
175. T. Veszpremi, L. Nyulaszi and J. Nagy, *J. Organomet. Chem.*, **331**, 175 (1987).
176. L. Nyulaszi, T. Veszpremi, J. Reffy, G. Zsombok, T. Cvitaš, B. Kovač, L. Klasinc and S. McGlynn. *Int. J. Quantum Chem., Symp.*, **25**, 479 (1991).

177. A. Modelli, G. Distefano, D. Jones and G. Seconi, *J. Electron Spectrosc.*, **31**, 63 (1983).
178. F. P. Colonna, G. Distefano, M. Guerra, D. Jones and A. Modelli, *J. Chem. Soc., Dalton, Trans.*, 2037 (1979).
179. I. Novak, L. Klasinc, G. Karminski-Zamola and K. Jakopčić, *Croat. Chem. Acta*, **56**, 281 (1983).
180. F. Bernardi, A. Bottoni, F. P. Colonna, G. Distefano, U. Folli and P. Vivarelli, *Z. Naturforsch. A, Phys. Kosmophys.*, **33a**, 959 (1978).
181. (a) B. Kovač, M. Allan, E. Heilbronner, J. P. Maier, R. Gleiter, M. W. Haenel, P. M. Keehn and J. A. Reiss, *J. Electron Spectrosc.*, **19**, 167 (1980).
(b) R. Gleiter, W. Schäfer, G. Krennrich and H. Sakurai, *J. Am. Chem. Soc.*, **110**, 4117 (1988).
182. D. A. Schweigart and D. W. Turner, *J. Am. Chem. Soc.*, **94**, 5599 (1972).
183. T. Kobayashi and S. Nagakura, *Bull. Chem. Soc. Jpn.*, **46**, 1558 (1973).
184. W. H. Mills and I. G. Nixon, *J. Chem. Soc.*, 2510 (1930).
185. Z. B. Maksić, M. Eckert-Maksić, M. Hodošcek, W. Koch and D. Kovaček, in *Molecules in Natural Science and Medicine. An Enconium for Linus Pauling* (Eds. Z. B. Maksić and M. Eckert-Maksić), Ellis Horwood, Chichester, 1991, pp. 333–349.
186. R. Gleiter, P. Bischof, M. C. Böhm, R. Guilard and H. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **57**, 856 (1984).
187. M. Eckert-Maksić and Lj. Maksimović, unpublished results.
188. H.-U. Pfeffer, M. Klessinger, G. Erker and W. R. Roth, *Chem. Ber.*, **108**, 2923 (1975).
189. R. Gleiter, R. Bartetzko, P. Hofmann and H.-D. Scharf, *Angew. Chem.*, **89**, 414 (1977); *Angew. Chem., Int. Ed. Engl.*, **16**, 400 (1977).
190. D. Dougherty, R. L. Blankespoor and S. P. McGlynn, *J. Electron Spectrosc.*, **16**, 245 (1979).
191. M. Mohraz, C. Batich, E. Heilbronner, P. Vogel and P.-A. Carrupt. *Recl. Trans. Chim. Pays-Bas*, **98**, 361 (1979).
192. K. Roser, P.-A. Carrupt, P. Vogel, E. Honegger and E. Heilbronner, *Helv. Chim. Acta*, **73**, 1 (1990).
193. K. W. Schulte and A. Schweig, *Theor. Chim. Acta*, **33**, 19 (1974); G. Kuehnlenz and H. H. Jaffe, *J. Chem. Phys.*, **58**, 2238 (1973) and references cited therein.
194. A. D. Baker, M. A. Brisk, T. J. Venauzi, Y. S. Kwon, S. Sadka and D. C. Liotta, *Tetrahedron Lett.*, 3415 (1976).
195. F. S. Jørgensen, L. Norskov-Lauritsen, R. B. Jensen and G. Schroll, *Tetrahedron*, **37**, 3671 (1981).
196. M. H. Palmer and J. Nisbet, *J. Mol. Struct.*, **67**, 65 (1980).
197. F. S. Jørgensen, *J. Chem. Res. (S)*, 212 (1981).
198. T. H. Gan, J. B. Peel and G. D. Willett, *Chem. Phys. Lett.*, **51**, 464 (1977).
199. F. S. Jørgensen and L. Norskov-Lauritsen, *Tetrahedron Lett.*, **23**, 5221 (1982).
200. D. Gonbeau, M. Loudet and G. Pfister-Guillouzo, *Tetrahedron*, **36**, 381 (1980).
201. R. Gleiter, M. Kobayashi, N. S. Zefirov and V. A. Palyalin, *Dokl. Akad. Nauk SSSR, Ser. Khim.*, **235**, 347 (1977); *Engl. Transl.*, **235**, 396 (1977).
202. A. D. Baker, G. H. Armen and S. Funaro, *J. Chem. Soc., Dalton Trans.*, 2519 (1983).
203. M. Kajitani, A. Sugimori, N. Sato, K. Seki, H. Inokuchi and Y. Harada, *Bull. Chem. Soc. Jpn.*, **52**, 2199 (1979).
204. T. Yamabe, K. Hori, K. Agaki and K. Fukui, *Tetrahedron*, **35**, 1065 (1979).
205. M. Eckert-Maksić and Lj. Maksimović, *J. Org. Chem.*, **56**, 3719 (1991).
206. R. Gleiter and J. Uschmann, *J. Org. Chem.*, **51**, 370 (1986).
207. R. Gleiter, R. Haider and H. Quast, *J. Chem. Res. (S)*, 138 (1978).
208. F. S. Jørgensen, M. Gajhede and B. Frei, *Helv. Chim. Acta*, **68**, 2148 (1985).
209. G. Distefano, V. Galasso, K. J. Irgolic and G. C. Papppalardo, *J. Chem. Soc., Perkin Trans. 2*, 1109 (1983).
210. H. Bock and G. Wagner, *Tetrahedron Lett.*, 3713 (1971); H. Bock, G. Wagner and J. Kroner, *Chem. Ber.*, **105**, 3850 (1972).
211. G. M. Anderson III, P. Kollman, L. N. Domelsmith and K. N. Houk, *J. Am. Chem. Soc.*, **101**, 2344 (1979).
212. L. N. Domelsmith and K. N. Houk, *Int. J. Quantum Chem., Quantum Biol. Symp.*, **5**, 257 (1978).
213. F. Bernardi, G. Distefano, A. Mangini, S. Pignatoro and G. Spunta, *J. Electron Spectrosc.*, **7**, 457 (1975).
214. J. M. Behan, R. A. W. Johnstone and T. W. Bentley, *Org. Mass Spectrom.*, **11**, 207 (1976).

215. B. G. Ramsey, *J. Organomet. Chem.*, **135**, 307 (1977).
216. C. N. R. Rao, *Tetrahedron*, **32**, 1561 (1976); R. Egdell, J. C. Green and C. N. R. Rao, *Chem. Phys. Lett.*, **33**, 600 (1975).
217. V. V. Zverev, V. M. Vakar, A. A. Bredikhin and A. N. Vereshchagin, *Zh. Strukt. Khim.*, **31**, 70 (1990).
218. L. Klasinc, B. Kovač and H. Güsten, *Pure Appl. Chem.*, **55**, 289 (1983).
219. O. G. Rodin, V. F. Traven, V. V. Redchenko, M. Yu. Eismont and B. I. Stepanov, *Zh. Obsch. Khim.*, **53**, 2537 (1983).
220. W. Nakanishi, S. Masuda, T. Ishida, K. Ohno and Y. Harada, *J. Org. Chem.*, **54**, 540 (1989).
221. K. Ohno and I. Ishida, *Int. J. Quantum Chem.*, **29**, 677 (1986).
222. L. N. Domelsmith, L. N. Munchausen and K. N. Houk, *J. Am. Chem. Soc.*, **99**, 4311 (1977).
223. V. Butković, B. Kovač, I. Novak, B. Ruščić, A. Sabljić, L. Klasinc and S. P. McGlynn, in *Modelling of Structure and Properties of Molecules* (Ed. Z. B. Maksić), Ellis Horwood, Chichester, 1987, pp. 251–268.
224. J. P. Huke and I. H. Hillier, *J. Chem. Soc., Perkin Trans. 2*, 1191 (1985).
225. G. Karreman, I. Isenberg and A. Szent-Györgyi, *Science*, **130**, 1191 (1959).
226. S. M. Shevchenko, M. Ya. Zarubin, B. Kovač, Lj. Paša-Tolić and L. Klasinc, *J. Wood Chem. Technol.*, 228 (1989); Lj. Paša-Tolić, B. Kovač, L. Klasinc and S. M. Shevchenko, *Croat. Chem. Acta*, **63**, 37 (1990); S. M. Shevchenko, M. Ya Zarubin, B. Kovač, Lj. Paša-Tolić and L. Klasinc, *Khim. Drev.*, **37**, 100, 104 (1990).
227. L. A. Paquette, F. Bellamy, M. C. Böhm and R. Gleiter, *J. Org. Chem.*, **45**, 4913 (1980).
228. C. Santiago, E. J. McAlduff, K. N. Houk, R. Snow and L. A. Paquette, *J. Am. Chem. Soc.*, **100**, 6149 (1978).
229. P. M. Mazzochi, B. Stahly, J. Dodd, N. Rondan, L. N. Domelsmith, M. D. Rozenboom, P. Caramella and K. N. Houk, *J. Am. Chem. Soc.*, **102**, 6482 (1980).
230. K. B. Astin and K. Mackenzie, *J. Chem. Soc., Perkin Trans. 2*, 1004 (1975).
231. T. S. V. Buys, H. Cerfontain, F. Stunnenberg and J. N. Louwen, *Recl. Trav. Chem. Pays-Bas*, **105**, 54 (1986).
232. K. N. Houk, L. P. Davis, G. R. Newkome, R. E. Duke and R. V. Naumon, *J. Am. Chem. Soc.*, **95**, 8364 (1973).
233. A. Schweig, H. Vermeer and U. Weidner, *Chem. Phys. Lett.*, **26**, 229 (1974); F. S. Jørgensen, L. Carlsen and F. Duus, *Acta Chem. Scand.*, **B34**, 697 (1980); F. S. Jørgensen, L. Carlsen and F. Duus, *J. Am. Chem. Soc.*, **103**, 1350 (1981); F. S. Jorgensen, R. S. Brown, L. Carlsen and F. Duus, *J. Am. Chem. Soc.*, **104**, 5922 (1982).
234. M. J. Cook, S. El-Abbady, A. Katritzky, C. Guimon and G. Pfister-Guillouzo, *J. Chem. Soc., Perkin Trans. 2*, 1652 (1977); C. Guimon , G. Garrabe and G. Pfister-Guillouzo, *Tetrahedron Lett.*, 2585 (1979); G. Pfister-Guillouzo, C. Guimon, J. Frank, J. Ellison and A. R. Katritzky, *Justus Liebigs, Ann. Chem.*, 366 (1981).
235. R. R. Andrea, H. Cerfontain, H. J. A. Lambrechts, J. N. Louwen and A. Oskam, *J. Am. Chem. Soc.*, **106**, 2531 (1984).
236. E. J. McAlduff, B. M. Lynch and K. N. Houk, *Can. J. Chem.*, **56**, 495 (1978).
237. F. Carnovale, T. H. Gan, J. B. Peel and K.-D. Franz, *Tetrahedron*, **35**, 129 (1979); F. Carnovale, T. H. Gan, J. B. Peel and K.-D. Franz, *J. Chem. Soc., Perkin Trans. 2*, 957 (1980).
238. F. Kajfež, L. Klasinc and V. Šunjić, *J. Heterocycl. Chem.*, **16**, 529 (1979).
239. D. Cremer, in *The Chemistry of Functional Groups, Peroxides* (Ed. S. Patai), Wiley Chichester, 1983, pp. 1–84.
240. E.g. T. Minato and D. P. Chong, *Can. J. Chem.*, **61**, 550 (1983).
241. G. Wagner and H. Bock, *Chem. Ber.*, **107**, 68 (1974).
242. C. Batich and W. Adam, *Tetrahedron Lett.*, 1467 (1974).
243. K. Kimura and K. Osafune, *Bull. Chem. Soc. Jpn.*, **48**, 2421 (1975).
244. P. Rademacher and W. Elling, *Justus Liebigs Ann. Chem.*, 1473 (1979).
245. R. Gleiter, P. Schang, W. Adam, H. Eggelte, I. Erden and A. J. Bloodworth, *J. Electron Spectrosc.*, **19**, 223 (1980).
246. R. Gleiter, W. Dobler, M. Eckert-Maksić, A. J. Bloodworth, H. J. Eggelte and D. Cremer, *J. Org. Chem.*, **49**, 3716 (1984).
247. R. S. Brown and R. W. Marcinko, *J. Am. Chem. Soc.*, **100**, 5584 (1978).
248. D. J. Coughlin, R. S. Brown and R. G. Salomon, *J. Am. Chem. Soc.*, **101**, 1533 (1979).

249. R. S. Brown, *Can. J. Chem.*, **53**, 3439 (1975); **54**, 805 (1976).
250. M. C. Böhm, R. Gleiter, W. Adam and N. Narita, *Z. Naturforsch.*, **88b**, 501 (1983).
251. T. Kondo, M. Tamimoto, M. Matsumoto, K. Nomoto, Y. Achiba and K. Kimura, *Tetrahedron Lett.*, **21**, 1649 (1980).
252. D. Nordfors, A. Nilsson, N. Martensson, S. Svensson, U. Gelius and H. Agren, *J. Electron Spectrosc.*, **56**, 117 (1991).
253. K. Ohno and Y. Harada, in *Theoretical Models of Chemical Bonding* (Ed. Z. B. Maksić), Part 3, Springer-Verlag, Berlin, 1991, pp. 199–233.
254. E.g. E. E. Koch (Ed.), *Handbook of Synchrotron Radiation*, Vol. 1, North-Holland, Amsterdam, 1983 and references cited therein.
255. E.g. K. Kimura, M. Takahashi, K. Okuyma and I. Plazbit, *J. Electron Spectrosc.*, **51**, 383 (1989) and references cited therein.

CHAPTER 8

Mass spectrometry of alcohols and ethers

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I. INTRODUCTION

By the time the last Supplement E was published mass spectrometry of organic compounds, including alcohols and ethers, looked very much like a mature discipline enjoying mild, steady-state progress[1]. This has changed dramatically ever since due to the introduction of new ionization methods that made it possible to obtain gaseous ions in the $> 10^5$ dalton range, new techniques for ion excitation, dissociation, neutralization and charge inversion, and new interpretation of fundamental dissociation processes of gas-phase ions. This growth has manifested itself by a multitude of articles devoted to various aspects of mass spectrometry, and spawned the emergence of three new specialized journals. Of necessity, this chapter will be very selective and deal with fundamental aspects pertinent to the chemistry of the hydroxyl and ether group in gaseous ions. Even this specialized area has undergone tremendous development as new concepts have been introduced over the last decade. Theoretical calculations have been especially helpful in providing structures and energy data of transition states[2] and stable intermediates, such

Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

as distonic ions[3–5] and ion–molecule complexes[6]. Simultaneously, the amount and quality of experimental thermochemical data has been growing steadily[7–9] to provide reference for and sometimes challenge theoretical calculations. Topics covered in this chapter will be the dissociations of alcohol and ether cation radicals by simple bond cleavage and rearrangement, and dissociations of protonated, alkylated and chelated alcohols and ethers as studied by various techniques.

II. CATION RADICALS

A. α-Cleavage Dissociations

Alkanol and saturated ether cation radicals undergo facile cleavage of the carbon–carbon bond next to the oxygen atom, the α-cleavage[10]. The energetics of α-cleavage can be estimated from the heats of formation of ions and radicals[7] as shown in Table 1 for methanol, dimethyl ether, ethanol, 2-propanol and 2-methyl-2-propanol. Since there is no barrier to the reverse reaction between the radical and the even-electron ion, the reaction endothermicities represent the corresponding C—C and C—H bond dissociation energies in the cation radicals.

α-Cleavage dissociations of methanol[2,11,12] and 2-methyl-2-propanol[13] have been studied by *ab initio* calculations that revealed further interesting details about the potential energy surface along the reaction coordinate. Dissociation of the C—H bond in methanol shows strong orientation effects in that it proceeds perpendicular to the O—H—C plane[11,12]. The calculated endothermicities are in excellent agreement with the experimental value. The calculations using the Møller–Plesset perturbational treatment (MP3 or MP4) and the 6-31(*d*, *p*) basis set, and including zero-point vibrational energy corrections, predict a very small barrier in the transition state which was found 63–68 kJ mol^{-1} above $CH_3OH^{+\cdot}$ and 7–10 kJ mol^{-1} above CH_2OH^+ and H$^\cdot$ at 0 K. At 298 K the calculated reverse barrier decreases to 2–4 kJ mol^{-1}, in fact well within the uncertainty limits of the most accurate energy measurements. At the even higher G1 level of theory[14] the calculations predicted no reverse energy barrier[2], and the 0 K endothermicity was 64.6 kJ mol^{-1}.[2]. Very good agreement between the experimental and calculated product and transition state energies was also found for other dissociations of the methanol ion[2].

Bond dissociation energies of carbon–carbon bonds α to the hydroxyl or ether oxygen atom decrease with increasing branching to reach a negative value for the 2-methyl-2-propanol cation radical (Table 1). In accordance with this trend, *ab initio* calculations [UHF/6-31G(*d*)][13] found no stable structure for a covalently bound 2-methyl-2-propanol ion. Vertical ionization of neutral 2-methyl-2-propanol leads to an unstable structure of 0.54 eV energy above the dissociation threshold corresponding to

TABLE 1. C—H and C—C bond dissociation energies (BDE) in alkanol and ether cation radicals

Ion	Products	ΔH_r(BDE, kJ mol^{-1})
$CH_3OH^{+\cdot}$	$CH_2OH^+ + H^\cdot$	75.7
$CH_3CH_2OH^{+\cdot}$	$CH_3CH^+OH + H^\cdot$	25.6
	$CH_2OH^+ + CH_3^\cdot$	73.6
$CH_3OCH_3^{+\cdot}$	$CH_3OCH_2^+ + H^\cdot$	91.7
$(CH_3)_2CHOH^{+\cdot}$	$(CH_3)_2C^+OH + H^\cdot$	4
	$CH_3CH^+OH + CH_3^\cdot$	25
$(CH_3)_3COH^{+\cdot}$	$(CH_3)_2C^+OH + CH_3^\cdot$	−14

$(CH_3)_2C^+—OH$ and $CH_3^{\cdot}$. The structure represents a point on a repulsive potential energy surface and collapses to products without an energy barrier. This calculated exothermicity is in excellent agreement with the energy excess (0.55 eV) found from kinetic energy release in photoelectron–photoion coincidence measurements of Baer and coworkers[15]. Although the classical 2-methyl-2-propanol ion structure is unstable, the calculations revealed a shallow minimum on the potential energy curve corresponding to an ion–molecule complex. The latter shows a very small binding energy (0.12 eV) and a long carbon–carbon bond (3.47 Å)[13].

It is noteworthy in this context that electron impact induced dissociations of perfluoro-2-methyl-2-propanol differ from those of 2-methyl-2-propanol[16]. The α-cleavage loss of $CF_3^{\cdot}$ from the molecular ion of the perfluoro compound competes with the loss of $F^{\cdot}$, and the resulting $(M - F)^+$ ion further undergoes facile elimination of hydrogen fluoride. Although the perfluoro-2-methyl-2-propanol ion chemistry has not been studied in detail, effects other than dissociation kinetics may well be involved, e.g., the fluorine loss may be due to dissociative preionization as found for other fluorinated organic molecules[17].

Ab initio calculations of both the methanol and 2-methyl-2-propanol cation radicals show substantial stereoelectronic effects on ion geometries, charge distribution and transition state energies. In symmetry nonrestricted calculations the methanol ion shows a long α-C—H bond (1.121 Å) which is perpendicular to the H—O—C plane. Dissociation of this long bond follows the minimum-energy-requirement path. By

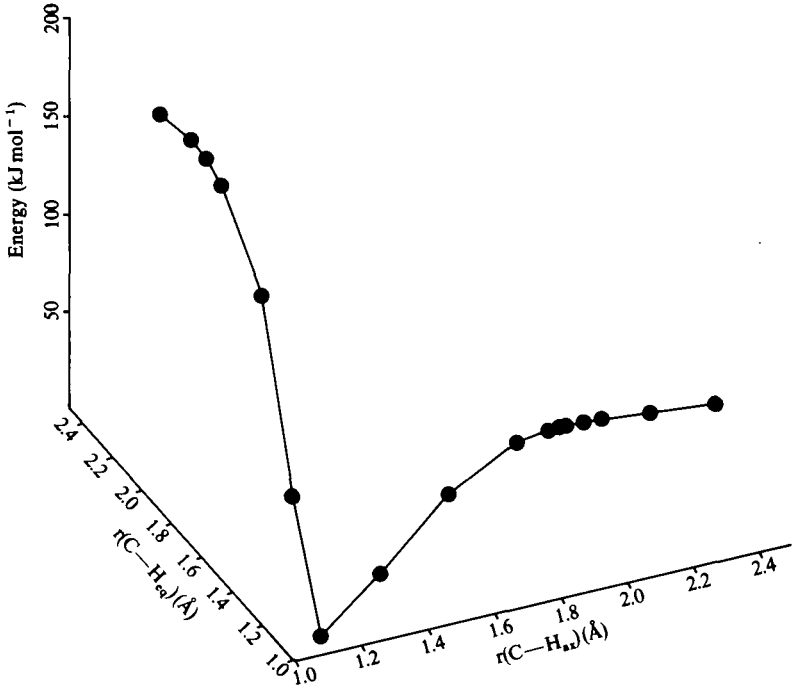


FIGURE 1. Potential energy diagram for the dissociation of C—H bonds in $CH_3OH^{+\cdot}$. $C—H_{ax}$: perpendicular to the C—O—H plane; $C—H_{eq}$: synperiplanar with the C—O—H plane. Reproduced by permission of Elsevier Science Publishers from Ref. 12

contrast, forced dissociation of the *anti*-C—H bond is highly endothermic ($\Delta E =$ 158 kJ mol^{-1}) and leads to a second-order saddle point (Figure 1). Such a dissociation is therefore dynamically forbidden[18]. In 2-methyl-2-propanol ion one of the out-of-plane methyl groups is lost exothermically, whereas the loss of the in-plane *anti*-methyl is disfavored. Also, the electron densities at the out-of-plane methyl groups are strongly affected by ionization from the oxygen n-orbital. Stereoelectronic effects on α-cleavage dissociations of C—H bonds in bicyclic ethers have been studied[19] as reviewed recently[12].

The absence of a reverse activation energy in α-cleavage dissociations of aliphatic alcohols, amino alcohols and diols has been utilized in appearance energy measurements that yielded heats of formation of a number of oxygen-containing radicals[20] and α-aminoalkyl radicals[21].

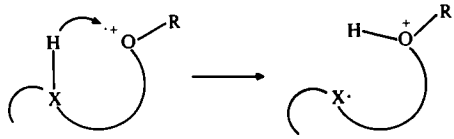
B. Hydrogen Rearrangements in Aliphatic and Cyclic Ethers

α-Cleavage processes dominate fast dissociations of aliphatic alcohol and ether cation radicals as observed under standard electron-impact ionization conditions (70 eV, ion-source lifetime $\leqslant 1$ μs). At low electron energies the α-cleavage dissociations compete with hydrogen and skeletal rearrangements resulting in eliminations of water, alcohols, alkanes, alkenes, alkenyl radicals, etc. Bowen and Maccoll have studied the 12 eV mass spectra of a series of aliphatic alcohols and ethers[22] using a water-cooled ionization source to prevent thermal dehydration. These authors found no detectable molecular ions at 12 eV for n-alkanols above n-butanol. The largest mass fragments from higher alkanols at 12 eV are the $(M - H_2O)^{+\cdot}$ ions of unspecified structure. The role in water elimination from cation radicals of thermal energy carried over from the neutral molecules has been discussed in detail[23,24].

Hydrogen and carbon skeletal rearrangements become predominant in slow dissociations of metastable alcohol and ether ions of 1–25 μs lifetime, corresponding to rate constants in the 10^4–10^6 s^{-1} range[25]. A large number of systems have been studied in great detail using various instrumental techniques, specific labeling, product analysis, appearance energy measurements, and semiempirical and *ab initio* calculations. Although there are some common features in dissociations of isomeric ions, factors like the ion size and the presence of double bonds and alicyclic or aromatic rings are often decisive in determining the particular ion chemistry. In the following the individual systems will be treated separately by their increasing molecular size.

A word of caution is in order when discussing dissociations of metastable ions. There has been a general trend to present these reactions as being representative of the chemistry of the given ion system. In fact, metastable ions are nothing more than leftovers after much faster dominant ion source dissociations; metastables very rarely amount to more than 1% of the ion current. The main advantage of these by-products is that they can be observed separately on a longer time scale, and that their unimolecular dissociations can be characterized by kinetic energy release which can provide very valuable information about the transition state.

Central to the elucidation of rearrangement reactions of alcohol and ether ions is the question of the relative stabilities of possible intermediates. An intraionic hydrogen rearrangement from an atom X (X = C, O, N, P, S, etc.) onto an oxygen acceptor forms a distonic intermediate[4] in which the charge and the radical site reside at different atoms (Scheme 1). One can express the heat of reaction for this isomerization, that is, the relative stability of the two isomers, by equation 1, where D(X—H) is the particular bond dissociation energy in the cation radical and HA is the hydrogen atom affinity[7] of the oxygen atom in a cation biradical. Assuming that the X and oxygen centers do not affect each other, D(X—H) can be approximated by the dissociation energy of an analogous



SCHEME 1

X—H bond in a neutral molecule[26], while HA(O) can be approximated by the hydrogen atom affinity in an analogous cation radical. These approximations give reasonable qualitative estimates showing that the rearranged ions should be 40–50 kJ mol^{-1} more stable than the classical structures produced upon ionization of neutral alcohols and ethers[27]. The utility for quantitative predictions of the above scheme has been discussed recently by Holmes and Lossing who found some discrepancies[28].

$$\Delta H_r = D(\text{X—H}) - \text{HA(O)} \qquad (1)$$

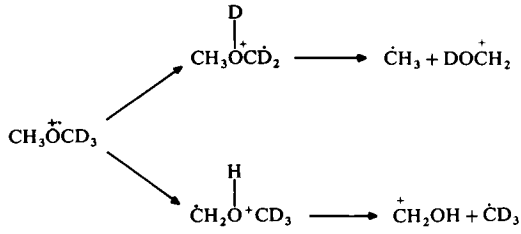
Firm evidence for the stability of distonic ions followed from the systematic calculations of Radom and coworkers[2–4,11,29–32] followed by experimental studies[5]. The calculated relative energies, E(classical) – E(distonic), show no smooth dependence on the relative position of the charge and radical site in the ion (Table 2), the γ-distonic ions[5,33] with the radical site at the third atom from the OH_2 group apparently being the least stable ones. Likewise, ether distonic ions appear to be comparably stable as their classical isomers[32]. The theoretical and experimental work on distonic ions in the gas phase, solution and solid matrix has been reviewed recently by Hammerum[5].

Loss of methyl from the dimethyl ether cation radical ($\mathbf{1}^{+\cdot}$) is an example of hydrogen rearrangement involving a distonic intermediate (Scheme 2). The dissociation forms CH_2OH^+ not CH_3O^+, the latter being unstable, as found through the collisionally activated dissociation spectrum[34]. *Ab initio* calculations found a two-minimum potential energy surface for the dissociation of $\mathbf{1}^{+\cdot}$ (Figure 2)[32]. The first step is the 1,2-hydrogen migration forming the distonic isomer $\mathbf{2}^{+\cdot}$. The rearrangement requires a substantial energy barrier (calculated as 146 kJ mol^{-1}) that lies 110 kJ mol^{-1} above the CH_2OH^+ and $CH_3^{\cdot}$ products. This is a typical example of a rate-determining isomerization[35]. Methyl loss from $CD_3OCH_3^{+\cdot}$ shows substantial kinetic isotope effects in both ion source

TABLE 2. Calculated relative energies of classical and distonic isomers

Isomer Distonic	Classical	E(classical) – E(distonic)(kJ mol^{-1})
$^{\cdot}CH_2OH_2^+$	$CH_3OH^{+\cdot}$	66[a], 46[b]
$^{\cdot}CH_2CH_2OH_2^+$	$CH_3CH_2OH^{+\cdot}$	39[a]
$^{\cdot}CH_2CH_2CH_2OH_2^+$	$CH_3CH_2CH_2OH^{+\cdot}$	−1[a]
$^{\cdot}(CH_2)_4OH_2^+$	$CH_3(CH_2)_3OH^{+\cdot}$	87[c]
$^{\cdot}OCH_2OH_2^+$	$HOCH_2OH^{+\cdot}$	143[a]
$^{\cdot}OCH_2CH_2OH_2^+$	$HOCH_2CH_2OH^{+\cdot}$	−26[a]
$^{\cdot}OCH_2CH_2CH_2OH_2^+$	$HOCH_2CH_2CH_2OH^{+\cdot}$	113[a]
$^{\cdot}CH_2O(H)^+CH_3$	$CH_3OCH_3^{+\cdot}$	3[d]

[a]MP2/6-31G(*d*) calculations, Reference 4.
[b]MP4/6-311G(*df*, *p*) calculations, Reference 11.
[c]MP2/6-31G(*d*) calculations, Reference 31.
[d]MP3/6-31G(*d*, *p*) calculations, Reference 30.



SCHEME 2

and metastable ion dissociations[36]. The more facile loss of $CD_3^{\cdot}$, $[M - CD_3]^+/[M - CH_3]^+ = 12:1$ and 2.1:1 in metastable ion and ion source dissociations, respectively, is consistent with the rate-determining hydrogen migration followed by rapid methyl elimination from the distonic intermediate. The energetics and kinetics of $CH_3OCD_3^{\cdot}$ dissociations have been investigated recently by the threshold photoelectron–photoion coincidence technique[37]. The $[M - CD_3]^+/[M - CH_3]^+$ ratio was found to be 2.5–1.5 for photon energies 0–1.25 eV above the dissociation onset. The latter was found 0.95 eV (92 kJ mol^{-1}) above the thermochemical threshold for CH_2OH^+ and $CH_3^{\cdot}$, in reasonable agreement with the calculated values. The experimental data could be fitted with RRKM calculations assuming 1.35 eV (130 kJ mol^{-1}) critical energy and a negative activation entropy (-12.5 J mol^{-1} K^{-1}) consistent with a tight transition state in the rate-determining step. Hydrogen atom tunneling in the methyl loss was suggested but not observed, because of the substantial competitive shift of the former dissociation with respect to the lowest-energy loss of hydrogen[37].

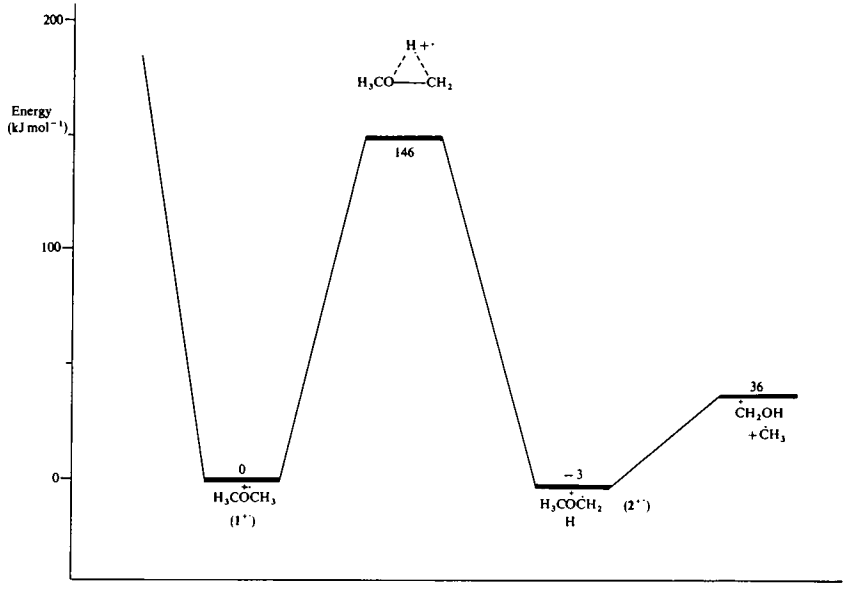
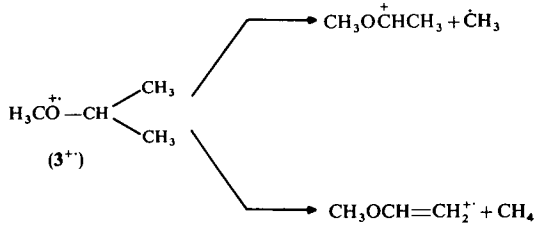


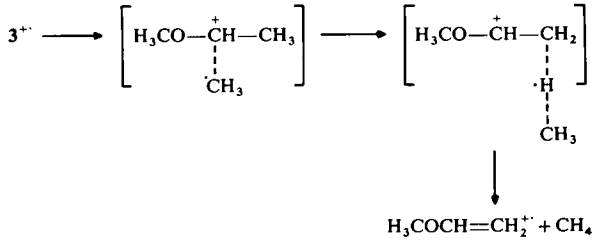
FIGURE 2. Potential energy diagram for the methyl loss from $CH_3OCH_3^{+\cdot}$[32]

Dissociations of the 2-methoxypropane cation radical ($3^{+\cdot}$) have been studied in detail by McAdoo and coworkers[38]. Upon electron-impact ionization, photoionization and collisional activation $3^{+\cdot}$ dissociates by losing one of the carbon-bound methyls to give $CH_3CH{=}O^+CH_3$ as the dominant (>99%) product. By contrast, metastable $3^{+\cdot}$ eliminate competitively CH_4 and $\dot{C}H_3$ in a proportion that depends on pressure (Scheme 3)[38,39]. Eliminations of $\dot{C}H_3$ versus $\dot{C}D_3$, and CH_3D versus CD_3H from metastable $CH_3OCH(CD_3)CH_3^{+\cdot}$ display very large kinetic isotope effects. Photoionization appearance energy measurements gave almost identical values for the products of methyl and methane eliminations (9.71 and 9.69 eV, respectively), *ca* 0.2 eV above the ionization energy of neutral **3** (9.50 eV).



SCHEME 3

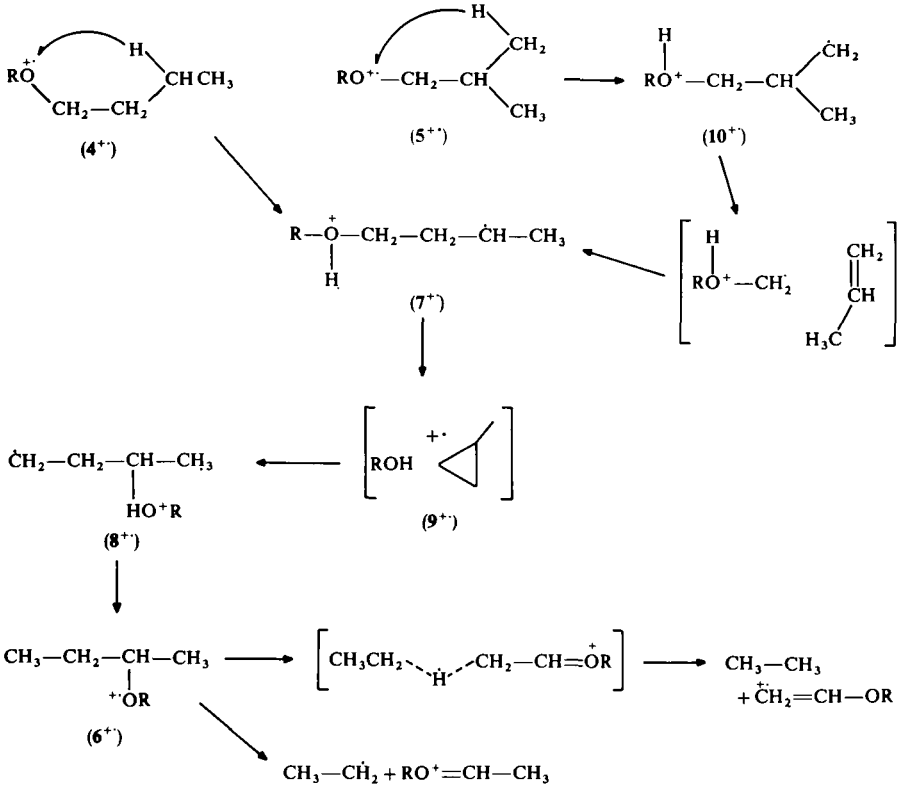
The competing elimination of $\dot{C}H_3$ and CH_4, and the rapid switching between these two dissociations near the threshold has been interpreted by the involvement of an ion–neutral complex in the transition state. Ion–neutral complexes, where the neutral is a molecule or a radical, are transient species held together by ion–dipole or ion-induced dipole interactions. For a comprehensive review see Reference 6. Since the original covalent bond between the ion and the neutral has been broken, the species can adopt a large number of different mutual configurations of closely spaced potential energies. These are thought to favor hydrogen transfer from positions otherwise inaccessible in the covalently bound ion, and thus promote hydrogen scrambling. Due to the large number of configurations in the complex, exit to both the reactant ion configuration and to products is limited by entropy decrease creating the so-called entropy bottleneck[40]. In slow threshold $3^{+\cdot}$ dissociations the methyl radical is assumed to linger in a complex with $CH_3C{=}O^+CH_3$ until it captures a hydrogen atom to form exothermically methane and $CH_2{=}CHOCH_3^{+\cdot}$ (Scheme 4). The latter dissociation is accompanied by a 4 kJ mol^{-1} kinetic energy release corresponding to the overall potential energy barrier to the methane elimination. It should be noted that the above interpretation is at odds with RRKM rate constant estimates which consistently predict fast methane elimination ($k \approx 2 \times 10^{10}\,s^{-1}$), incompatible with that from metastable ions ($k \approx 10^4$–$10^6\,s^{-1}$)[38].



SCHEME 4

An alternative mechanism involving a classical, i.e. bond-making–bond-breaking, rearrangement has also been suggested[39].

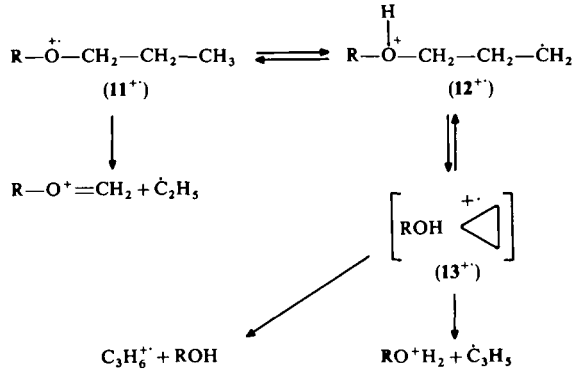
Metastable ion dissociations of a number of aliphatic ethers have been investigated in remarkable detail with the use of specific deuterium labeling, appearance energy and kinetic energy release measurements[41–44]. A peculiar feature of these dissociations is the different behavior of *sec*-alkyl ether cation radicals as compared with that of n- and *iso*-alkyl ether cation radicals. Thus metastable n-butyl ethyl ether ions ($\mathbf{4}^{+\cdot}$) eliminate ethyl radicals containing the butyl α- and β-methylenes plus a hydrogen atom from the γ-position. A similar mechanism apparently operates in the loss of ethyl from metastable isobutyl ethyl ether (Scheme 5, $\mathbf{5}^{+\cdot}$). The ethyl group lost contains the α-methylene and one of the methyl groups, the latter having undergone partial hydrogen exchange with the methine position[43]. By contrast to these, metastable ethyl *sec*-butyl ether ($\mathbf{6}^{+\cdot}$) eliminates mostly ethane (91%), whereas ethyl elimination is less abundant (9%). The ethane molecule eliminated contains most of the β-methylene hydrogens, the γ-methyl group and a hydrogen atom from the other methyl. The $(M - C_2H_6)^{+\cdot}$ ion products have alkyl vinyl ether structures, as confirmed through their collisionally activated dissociation spectra[44]. These diverse dissociations have been interpreted by invoking excited electronic states[42], and interconversion of the n- and iso-isomers, but not the *sec*-isomer in metastable ions. The recent work of Traeger and coworkers[44,45] has



SCHEME 5

brought a unified view of these dissociations supported by high-quality appearance energy measurements. The dissociation of the long-lived n-butyl alkyl ether ion $\mathbf{4}^{+\cdot}$ begins with a γ-hydrogen rearrangement forming the distonic isomer $\mathbf{7}^{+\cdot}$, which rearranges by 1,3-shift of the HOR group to another distonic isomer $\mathbf{8}^{+\cdot}$. The latter step may proceed in a complex of the alcohol molecule with the methylcyclopropane ion ($\mathbf{9}^{+\cdot}$) rather than a 1,3-shift which is usually disfavored in cation radical group migrations[46]. In order to be energetically accessible complex $\mathbf{9}^{+\cdot}$ should be stabilized by 80–90 kJ mol^{-1} against dissociation to components. Such stabilization would be comparable to the binding energies of other polar molecules with hydrocarbon cation radicals[6,30,47]. A reciprocal hydrogen migration converts $\mathbf{8}^{+\cdot}$ to $\mathbf{6}^{+\cdot}$ which loses the newly formed ethyl group by α-cleavage. The dissociation of metastable $\mathbf{5}^{+\cdot}$ is thought to begin with the γ-hydrogen transfer to form a distonic isomer $\mathbf{10}^{+\cdot}$ that further rearranges by 1,2-alkyl shift to $\mathbf{7}^{+\cdot}$, a common intermediate with $\mathbf{4}^{+\cdot}$. The $\mathbf{7}^{+\cdot} \rightleftarrows \mathbf{4}^{+\cdot}$ rearrangement appears to be reversible to account for the partial interchange of the β and γ hydrogen atoms in dissociating $\mathbf{5}^{+\cdot}$. The different behavior of metastable $\mathbf{6}^{+\cdot}$ versus the intermediate ion formed upon rearrangement of $\mathbf{4}^{+\cdot}$ and $\mathbf{5}^{+\cdot}$ can be due to greater internal energy of the latter, acquired by rearrangement through $\mathbf{9}^{+\cdot}$. The branching ratio for the competing ethyl and ethane eliminations from $\mathbf{6}^{+\cdot}$ shows indeed very strong energy dependence with the ethyl elimination dominating at > 20 kJ mol^{-1} above the dissociation threshold[44]. The threshold energies for ethyl elimination from $\mathbf{4}^{+\cdot}$ and $\mathbf{5}^{+\cdot}$ are 14–23 kJ mol^{-1} higher than that from $\mathbf{6}^{+\cdot}$[44]. The intermediate distonic isomers have been prepared independently by aldehyde elimination from dialkoxyalkanes and shown to eliminate alcohol and alkane molecules and alkyl radicals[48]. These studies nicely document the power of modern mass spectrometric methods in delivering a wealth of very detailed information about unusual and delicate reaction mechanisms.

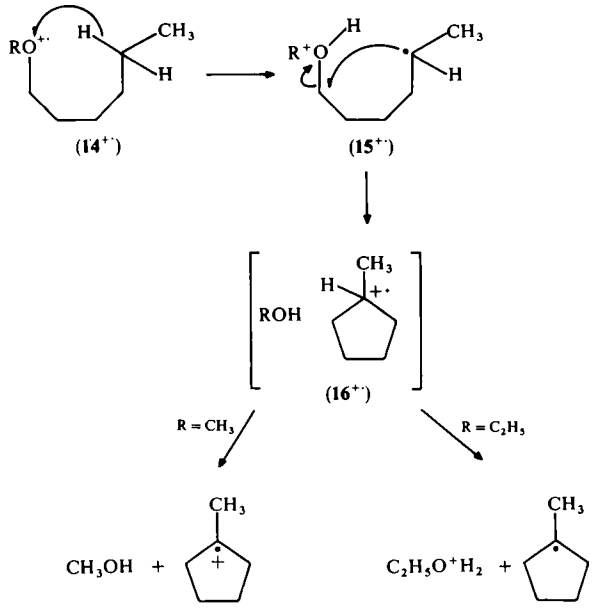
The role of ion–molecule complexes in metastable ether cation radical dissociations has further been examined with alkoxypropanes[49] and hexanes[50]. Both metastable methoxypropane and ethoxypropane ions ($\mathbf{11}^{+\cdot}$) eliminate allyl radical to form protonated methanol and ethanol, respectively (Scheme 6). This dissociation is accompanied by complete loss of positional identity of the propyl hydrogen atoms while those of the methyl and ethyl group are not scrambled. This extensive hydrogen exchange has been explained by reversible isomerizations involving the classical ether structures ($\mathbf{11}^{+\cdot}$), their γ-distonic isomers ($\mathbf{12}^{+\cdot}$) and alcohol–cyclopropane ion complexes ($\mathbf{13}^{+\cdot}$) prior to dissociation. The cyclopropane cation radical functions as a gaseous Brønsted acid to protonate the alcohol molecule in an exothermic reaction ($-\Delta H_r = 74$ kJ mol^{-1}).



SCHEME 6

α-Cleavage loss of ethyl from $\mathbf{11}^{+\cdot}$ and direct dissociation of $\mathbf{13}^{+\cdot}$ to give a $C_3H_6^{+\cdot}$ ion have also been observed[49]. It should be noted, however, that the branching ratios for the competing channels are quite sensitive to the ion internal energy and/or availability of other low-energy dissociation pathways. For example, dissociations of metastable ethoxypropane ions involve hydrogen exchange between the ethyl and the propyl group, giving rise to additional fragments.

The competitive eliminations of alcohol and protonated alcohol from 1-methoxy and 1-ethoxyhexane ions are strongly dependent on the reaction thermochemistry. Thus metastable 1-ethoxyhexane ion ($\mathbf{14}^{+\cdot}$, $R = C_2H_5$) forms $C_2H_5OH_2^+$ involving tranfer of both hydrogen atoms from C-5[50]. Following the formation of distonic ion $\mathbf{15}^{+\cdot}$, a second hydrogen atom transfer occurs in a complex of ethanol with the methylcyclopentane cation radical ($\mathbf{16}^{+\cdot}$), as also observed in an ion–molecule reaction between ethanol and labeled methylcyclopentane ion produced from a different precursor (Scheme 7). The hydrogen transfer in the complex is favored by $20\,kJ\,mol^{-1}$ over a simple complex dissociation to the methylcyclopentane ion and ethanol molecule[50]. By contrast, proton transfer to the less basic methanol does not take place in the analogous methylcyclopentane ion–methanol complex that dissociates by losing methanol[50]. It is noteworthy that the latter reaction is only $2\,kJ\,mol^{-1}$ less endothermic than the proton transfer to dominate the metastable ion spectrum. Interestingly, formation of both $CH_3OH_2^+$ from 1-methoxyhexane and $C_2H_5OH_2^+$ from 1-ethoxyhexane is observed in the corresponding 70 eV electron impact mass spectra, although the latter reaction is preferred.



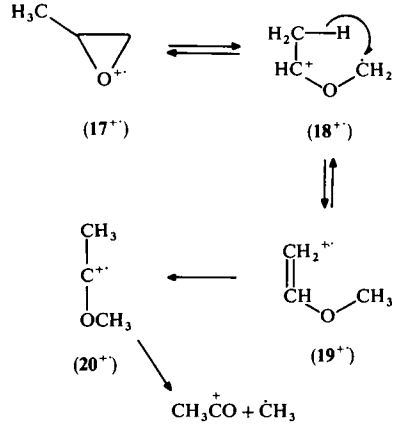
SCHEME 7

Dissociations of the methoxycyclohexane cation radical at different ion lifetimes have been studied in great detail by the field-ionization kinetics technique[51] with the help of deuterium-labeled derivatives[52]. 1,4-Elimination of methanol exhibits only 19%

stereoselectivity even at $< 10^{-10}$ s lifetimes. This contrasts the loss of water from the cyclohexanol cation radical in which the stereospecific 1,4-elimination is a major process. The majority of methoxycyclohexane molecular ions undergo ring opening followed by hydrogen rearrangement to isomeric methoxyhexenes that eliminate methanol by 1,3- and 1,4-mechanisms. The branching ratio for the (overall) 1,4- and 1,3-elimination of methanol is time-dependent with the latter dominating at $> 10^{-9}$ s ion lifetimes. Extensive isomerizations also precede eliminations of ethyl[53] and propyl[54] from long-lived methoxycyclohexane and methoxyhexene cation radicals.

Distonic ions are the natural intermediates in ring-cleavage dissociations of cyclic ethers. Oxiranes in particular have been studied extensively by experiment and theory. Recent *ab initio* calculations[55] found the $^2B_1$ state of the oxirane cation radical to be 85 kJ mol^{-1} less stable than the $^2A_2$ state of the ring-opened isomer $^+CH_2OCH_2^{\cdot}$. There is a small barrier to ring opening (17 kJ mol^{-1}) which is predicted to be reached upon vertical ionizaton of neutral oxirane.[55]. The other ring-opened isomer, $^+CH_2CH_2O^{\cdot}$, is predicted to be unstable and collapse without barrier to $CH_3CHO^{+\cdot}$. These calculations, in line with solid state electron spin resonance (ESR) studies[56], and ion–cyclotron resonance experiments[57,58], suggest that the ring-closed form of the oxirane cation radical undergoes very fast ring opening to form the more stable $^+CH_2OCH_2^{\cdot}$ isomer. Ion–molecule reaction of the oxirane ion with pyridine has also been interpreted in favor of the ring-opened structure[59]. By contrast, a different interpretation of the ESR splitting patterns in the matrix trapped oxirane cation radical[60], and a recent neutralization–reionization mass spectrometric (NRMS) study[61] argued that a stable ring-closed oxirane ion has been detected. It is worth noting at this point that neither of the gas-phase experiments provides a quantitative assessment of the ring-closed versus ring-opened oxirane isomers. Rather, extremely selective detection of a given species via a specific ion–molecule reaction[57–59] or electron transfer[61], both taking place with negligibly low efficiencies, could lead to overly generalizing conclusions about the composition of the original ion mixture. For a recent review on the oxirane ion see Reference 62.

Ring opening is a major process in dissociations of gaseous methyloxirane cation radical (**17**$^{+\cdot}$, Scheme 8)[63]. The ring-opened distonic isomer **18**$^{+\cdot}$, calculated to be *ca* 100 kJ mol^{-1} more stable than **17**$^{+\cdot}$[62,64], undergoes extensive hydrogen exchange between the methyl and methylene groups, while the methine hydrogen atom does not



SCHEME 8

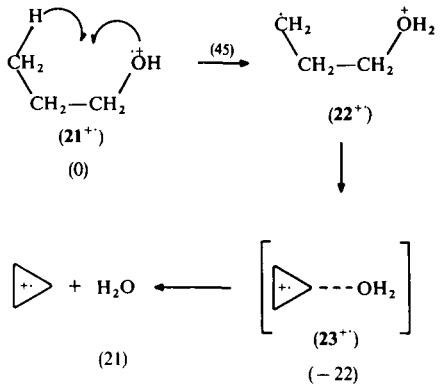
participate. This leads to the formation of the methyl vinyl ether cation radical ($\mathbf{19}^{+\cdot}$) that further isomerizes to the methoxymethylcarbene ion ($\mathbf{20}^{+\cdot}$) on the way to losing the methyl group and producing the most stable acetyl ion. The last isomerization represents the rate-determining step of a substantial critical energy ($170\,kJ\,mol^{-1}$)[62,65]. The loss of methyl is accompanied with a large kinetic energy release ($73\,kJ\,mol^{-1}$) which is common for dissociations of both metastable $\mathbf{17}^{+\cdot}$ and $\mathbf{19}^{+\cdot}$[63]. A minor process of low kinetic energy release ($4\,kJ\,mol^{-1}$) presumably proceeds through $\mathbf{17}^{+\cdot}$ isomerization to an excited acetone ion that loses either methyl group, although presumably at different rates[63,66,67]. The existence of a stable methyloxirane ion has been disputed on the basis of selective ion–molecule reactions and photodissociation experiments[68], again in contradiction to the results of previous collisionally activated dissociation studies[62,63].

Ion dissociations of a large number of substituted oxiranes have been studied[69] and found to mostly follow the ring-opening-isomerization pathway[63]. The intermediate methyl alkenyl ether ions lose alkyl groups by allylic cleavage of the γ-C—C bond. Ion dissociations of functionalized oxiranes[70] and cyclohexene oxide have been studied[71].

C. Hydrogen Rearrangements in Aliphatic and Cyclic Alcohols

Alkanol cation radicals undergo a variety of hydrogen rearrangements involving the hydroxy group or the hydrocarbon skeleton. Ionization in alkanols is usually depicted to result in the removal of an electron from the oxygen nonbonding orbital creating a very reactive ion. However, the oxygen lone-pair orbital energies (e.g. 10.94 eV in methanol)[72] are close to those of the σ_{CC} orbitals in branched alkanes (e.g. 10.94 eV in isopentane)[72], or cycloalkanes (e.g. 10.32 eV in cyclohexane)[72], so there could be two closely spaced electronic states contributing to ion reactivity. Hydrogen transfer from a methyl, methylene or a methine group to the hydroxy group is exoergic, implying a low activation barrier. Hydrogen transfer between sp^3 carbon centers in a saturated hydrocarbon ion is unlikely in a bound structure, but can proceed in an ion–radical complex formed by C—C bond dissociation[6,73]. Likewise, carbon-to-carbon hydrogen rearrangements are very frequent in cyclic alcohol cation radicals in which a bond dissociation creates two unsaturated reaction sites. These three basic rearrangement types will be treated separately.

As discussed above, ionization from the hydroxy group creates a reactive cation radical that can get stabilized by hydrogen transfer rearrangement to a distonic ion (Scheme 9). Heterolysis of the C—OH_2^+ bond then results in loss of water. The loss of water is extremely facile in ionized n-alkanols that, starting with n-pentanol, do not show molecular ions in their electron impact mass spectra even at a low temperature and electron energy[22]. *Ab initio* calculations (UHF/4-31G) indicated an exoergic rearrangement of the propanol ion ($\mathbf{21}^{+\cdot}$) to its γ-distonic isomer $\mathbf{22}^{+\cdot}$, and an early, five-membered cyclic, transition state (Scheme 9)[74,75]. Although the relative energies of $\mathbf{21}^{+\cdot}$, TS($\mathbf{21}^{+\cdot} \rightarrow \mathbf{22}^{+\cdot}$) and $\mathbf{22}^{+\cdot}$ (0, 92 and $-67\,kJ\,mol^{-1}$, respectively)[75] may not be expressed accurately by these calculations (see below), the net charge distributions give a chemical clue as to the nature of the hydrogen transfer. The negatively charged oxygen atom in the propanol molecule acquires a net positive charge (0.09) in $\mathbf{21}^{+\cdot}$ as a result of n_o ionization. Upon γ-hydrogen transfer, the oxygen net charge decreases to -0.06 in the transition state and -0.26 in $\mathbf{22}^{+\cdot}$. Most of the positive charge in the latter is carried by the oxygen-bound hydrogen atoms ($+0.38$ each), while the γ-carbon atom net charge changes from -0.18 in $\mathbf{21}^{+\cdot}$ to -0.13 in $\mathbf{22}^{+\cdot}$. Hence, the driving force for the rearrangement can be interpreted qualitatively as being due to increasing the negative charge on the most electronegative atom.

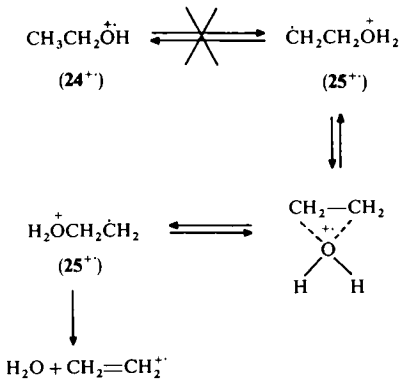


SCHEME 9

Threshold photoelectron–photoion coincidence measurements[76] gave the 0 K relative energies shown in Scheme 9 (values in parentheses, kJ mol^{-1}). In addition, the ion–molecule complex **23**$^{+\cdot}$ has been considered as an intermediate in the elimination of water. The complex has been found to dissociate at an anomalously slow rate compared with RRKM-based predictions[76]. This anomaly was explained by considering an extremely anharmonic potential energy surface, resulting in a large number of vibrational energy levels (estimated as 10^4) that increase the quantum state density of the complex. Angular momentum effects may also play an important role in slowing down the complex dissociation[76]. Carbon skeleton rearrangements appear to be unimportant in dissociations of **21**$^{+\cdot}$. It should also be noted that nondissociating **21**$^{+\cdot}$ and **22**$^{+\cdot}$ do not interconvert, as confirmed by their distinct collisionally activated dissociation[77] and neutralization–reionization mass spectra[78]. The propanol ion **21**$^{+\cdot}$ appears to be an intermediate in the dissociations of metastable $CH_3OH^+CH_2\dot{C}H_2$ and $\dot{C}H_2OH^+CH_2CH_3$ that both lose water[79,80]. The intermediacy of the $CH_3OH\cdots CH_2{=}CH_2^{+\cdot}$ complex in these rearrangements has been disputed[79,80].

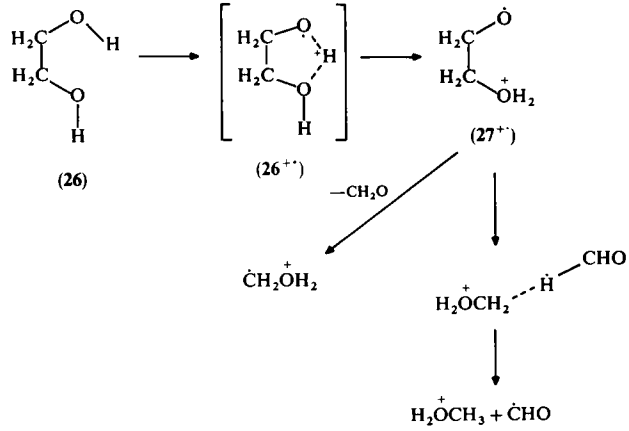
Ionized ethanol (**24**$^{+\cdot}$) is 46 kJ mol^{-1} less stable than its β-distonic isomer **25**$^{+\cdot}$ (cf. Table 2). Nevertheless, **24**$^{+\cdot}$ does not isomerize to **25**$^{+\cdot}$ in metastable ion or collisionally activated dissociations. Metastable **25**$^{+\cdot}$ loses water with a remarkably small kinetic energy release ($< T > = 0.04$ kJ mol^{-1})[47,81], and the hydroxyl hydrogen atoms are not exchanged with those of the ethylene unit[81,82]. On the other hand, the water molecule can migrate almost freely between the ethylene termini as deduced from the identical collisionally activated dissociation spectra of $^{\cdot}CD_2CH_2OH_2^+$ and $^{\cdot}CH_2CD_2OH_2^+$; both these isotopomers lose equal (small) fractions of CH_2 and CD_2[80]. *Ab initio* calculations suggest a 7–13 kJ mol^{-1} energy barrier for the degenerate isomerization of **25**$^{+\cdot}$ whereas the dissociation to $CH_2{=}CH_2^{+\cdot}$ and H_2O is calculated to require 79–83 kJ mol^{-1} (see References 30 and 47), close to the experimental value from appearance energy measurements (89 kJ mol^{-1})[47]. These isomerizations are depicted in Scheme 10.

In contrast to n-propanol ion **21**$^{+\cdot}$, hydrogen rearrangement in the 1,2-ethanediol ion **26**$^{+\cdot}$ appears to be extremely facile. *Ab initio* calculations of Yates and coworkers[83] suggest that electron impact ionization of the *cis* form of neutral **26** forms an unstable cation radical that rearranges without barrier to its distonic isomer **27**$^{+\cdot}$. The latter can lose formaldehyde to form an ylid ion $^{\cdot}CH_2OH_2^+$, or eliminate $^{\cdot}$CHO to give protonated methanol (Scheme 11). The latter reaction is analogous to the formation of protonated dimethyl ether in the dissociations of ionized methoxyethanol[27]. In spite of the theoretically predicted rapid isomerization of **26**$^{+\cdot}$, the electron impact mass spectrum



SCHEME 10

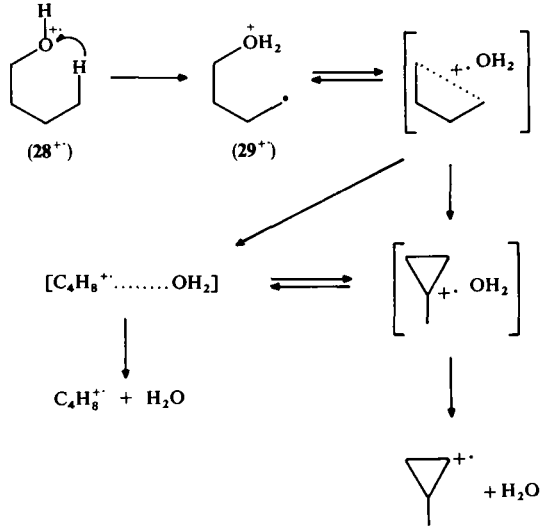
of **26** does show a molecular ion and fragments due to its dissociations by simple bond cleavage (*m/z* 31, 100%). This was attributed to the *trans* form of $\mathbf{26}^{+\cdot}$ that has to isomerize by rotation about the carbon–carbon bond in order to reach the reactive *cis* form. Nevertheless, the latter is found by theory to be unstable[81] and would represent a transition state rather than an intermediate. A number of other stable $C_2H_6O_2^{+\cdot}$ isomers have been identified by theory and experiment[84,85].



SCHEME 11

Loss of water from ionized n-butanol ($\mathbf{28}^{+\cdot}$) has been studied in great detail by experiment and theory. *Ab initio* calculations[29] suggested a very small or nonexistent barrier to transfer onto the hydroxyl group of one of the methyl δ-hydrogens; the calculated activation energy was actually negative, $-46\,\mathrm{kJ\,mol^{-1}}$[33]. The δ-distonic ion ($\mathbf{29}^{+\cdot}$) was calculated to be $87\,\mathrm{kJ\,mol^{-1}}$ more stable than $\mathbf{28}^{+\cdot}$ (Table 2). However, loss of water from $\mathbf{29}^{+\cdot}$ does not proceed by simple bond cleavage to yield cyclobutane cation radical or its ring-opened isomer, at least not near the dissociation threshold. Appearance energy measurements by the threshold photoelectron–photoion coincidence technique[15]

set the 298 K dissociation threshold at 708 kJ mol^{-1}, compatible with the formation of butene or methylcyclopropane ions, but not the cyclobutane ion that would require 743 kJ mol^{-1}. The elimination of water is extremely facile, with the dissociation threshold lying only 18 kJ mol^{-1} above the adiabatic ionization energy. Nevertheless, n-butanol gives a detectable molecular ion at 12 eV electron impact ionization[22]. The loss of water from $\mathbf{28}^{+\cdot}$ exhibits a peculiar dynamics in that the threshold dissociation can be fitted with a two-component decay scheme whereby one of the rate constants is 10^4 smaller than what would be predicted from the statistical rate theory[15]. Mechanistically, it is well established by deuterium labeling that $\mathbf{28}^{+\cdot}$ undergoes extensive hydrogen exchange among all carbon positions and the hydroxyl group[86] prior to elimination of water. Facile interconversion of nondecomposing $\mathbf{28}^{+\cdot}$ and $\mathbf{29}^{+\cdot}$ has been inferred from their nearly identical collisionally activated dissociation and neutralization–reionization mass spectra[78]. The $C_4H_8^{+\cdot}$ product from $\mathbf{28}^{+\cdot}$ contains the methylcyclopropane cation radical that was identified by its gas-phase reaction with ammonia[88]. The cyclobutane ion is not produced to any appreciable amount, while the formation of linear $C_4H_8^{+\cdot}$ isomers, unreactive towards ammonia, could not be excluded[87]. the loss of water from $\mathbf{28}^{+\cdot}$ can be depicted by the mechanism shown in Scheme 12. The initial δ-hydrogen transfer in $\mathbf{28}^{+\cdot}$ generates $\mathbf{29}^{+\cdot}$ that is at equilibrium with the $C_4H_8^{+\cdot}$ (cyclobutane?)–water complex. A 35 kJ mol^{-1} ion–dipole stabilization energy would be necessary to make this complex accessible within the dissociation limit. The C_4H_8 part then undergoes 1,2-hydrogen rearrangement to form a new complex that dissociates to water and methylcyclopropane ion or its ring-opened form. It should be noted that the stable 1-butene ion has also been considered as a likely $C_4H_8^{+\cdot}$ product in these dissociations[76,87].

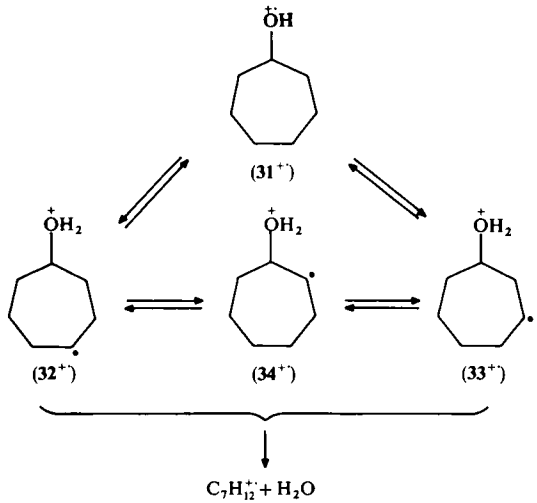


SCHEME 12

The methylcyclopropane cation radical has also been indicated as a product of water elimination from the isobutanol cation radical, based on both photoionization appearance energies[76] and product analysis through ion–molecule reactions[87].

Elimination of water from the n-heptanol cation radical ($\mathbf{30}^{+\cdot}$) in ion source dissociations has been postulated to yield the n-propylcyclobutane ion[88]. In keeping with this, hydrogen atoms from the δ position are transferred preferentially (69%) and contained in the water molecule eliminated. Other mechanisms are also operative leading to hydrogen transfer from the β (10%), γ (12.6%), ε (4.8%) and ζ (4%) positions. Unlike the butanol ion $\mathbf{28}^{+\cdot}$, reversible hydrogen exchange between the hydroxyl group and the carbon skeleton is negligible in $\mathbf{30}^{+\cdot}$. In spite of careful product analysis, no definite conclusion could be reached as to the structure of the $(M - H_2O)^{+\cdot}$ ion from $\mathbf{30}^{+\cdot}$, as the collisionally activated dissociation spectra of eight different $C_7H_{14}^{+\cdot}$ isomers were very similar[88]. Appearance energy measurements, carried out with polyenergetic electrons and evaluated by the vanishing current method, set the upper energy limit for the $C_7H_{14}^{+\cdot}$ formation at 10.37 eV, or 51 kJ mol^{-1} above the ionization energy of **30** (9.84 eV)[7]. Note that this critical energy for the water elimination from $\mathbf{30}^{+\cdot}$ is higher than that measured for the analogous dissociation of $\mathbf{28}^{+\cdot}$ (18 kJ mol^{-1}). The estimated threshold energy (665 kJ mol^{-1}) allows for the formation of propylcyclobutane (estimated threshold of 641 kJ mol^{-1}), butylcyclopropane (637 kJ mol^{-1}) and other more stable cyclic and linear $C_7H_{14}^{+\cdot}$ cation radicals. By comparison, the $C_5H_{10}^{+\cdot}$ product of water elimination from ionized 1-pentanol was identified as the ethylcyclopropane cation radical through collisional charge stripping spectra, consistent with thermochemical measurements[89]. The $C_5H_{10}^{+\cdot}$ appearance energy (10.04 eV) practically coincides with the pentanol ionization energy (10.00 eV) suggesting a very low critical energy for the loss of water. Nevertheless, the dissociation threshold lies above the combined heats of formation of water and any of plausible $C_5H_{10}^{+\cdot}$ isomeric structures, thus providing no differentiation[87]. The formation of the more stable ethylcyclopropane ion following δ-hydrogen transfer in ionized 1-pentanol was explained by 1,2-hydrogen rearrangement in the intermediate distonic ion[89], similar to that postulated in Scheme 12.

The stereochemical aspects of elimination of water from the cycloheptanol molecular ion ($\mathbf{31}^{+\cdot}$) have been studied[90]. The water molecule eliminated contains hydrogen atoms from the δ, γ and β positions, and the hydroxyl hydrogen undergoes exchange with the ring hydrogen atoms (Scheme 13). Kinetic analysis, based on extensive deuterium

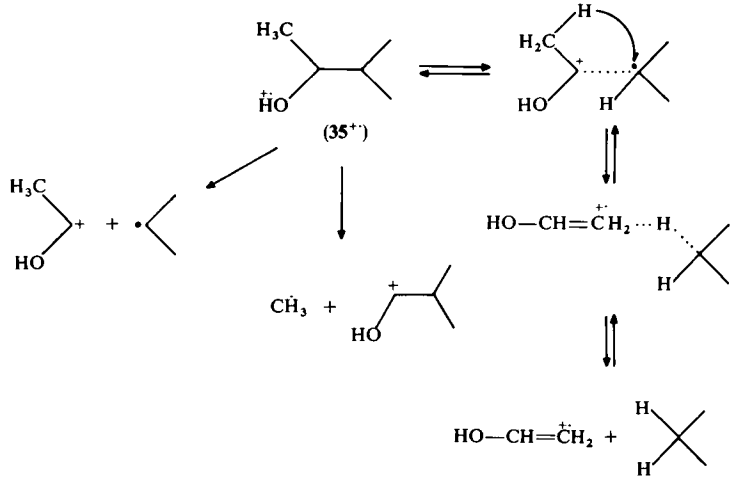


SCHEME 13

labeling, indicated that about 40% of cycloheptanol ions dissociate after the first hydrogen transfer onto the hydroxyl group to form the distonic isomers $\mathbf{32}^{+\cdot}$, $\mathbf{33}^{+\cdot}$, while the rest undergo reversible hydrogen transfers $\mathbf{32}^{+\cdot} \rightleftarrows \mathbf{34}^{+\cdot} \rightleftarrows \mathbf{33}^{+\cdot}$ combined with hydrogen migration among the ring positions in $\mathbf{31}^{+\cdot}$. Proton transfer between the $C_7H_{12}^{+\cdot}$ ion and the water molecule has not been considered, but appears unlikely on thermochemical grounds due to the low basicity of water. Elimination of water is the predominant dissociation of both metastable ion and 14 eV electron impact mass spectra of $\mathbf{31}^{+\cdot}$, consistent with its low-energy threshold (9.5 eV) that coincides with the ionization energy of **31**. The $C_7H_{12}^{+\cdot}$ products have not been identified, although formation of an isomeric mixture is likely. The 1,3-elimination of water shows modest stereospecificity; 19% of the *cis*-γ-H appears in the water eliminated compared to 9% of the *trans*-γ-H[90].

Stereospecific eliminations of water from monoterpene alcohols under electron impact ionization[91] and collisional activation[92] have been reported recently. Stereospecific fragmentations in the electron impact mass spectra of gibberellins and kaurenes are due to transfer of skeletal hydrogen atoms[93]. For a review of stereospecific dissociations of gaseous alcohol cations see Reference 94.

In the absence of γ-, δ- and more remote hydrogen atoms, alkanol cation radicals as a rule dissociate by α-cleavage. In slowly dissociating metastable ions this can be accompanied by hydrogen transfer between the cation and radical moieties, especially if these remained locked in an ion–dipole complex. This can be exemplified by the dissociations of the 3-methyl-2-butanol ion ($\mathbf{35}^{+\cdot}$), studied recently[95,96]. While the electron impact mass spectrum is dominated by $CH_3CH{=}OH^+$ and $(CH_3)_2CHCH{=}OH^+$ from α-cleavage dissociations, metastable $\mathbf{35}^{+\cdot}$ undergoes competitive eliminations of methane and propane, yielding stable enol ions[97], $(CH_3)_2C{=}CHOH^{+\cdot}$ and $CH_2{=}CHOH^{+\cdot}$, respectively. While the elimination of propane is 27 kJ mol^{-1} endothermic and occurs at the thermochemical threshold, the elimination of methane is exothermic and goes over an energy barrier estimated at 24 kJ mol^{-1} [96]. A puzzling feature of these rearrangements is the preferential transfer of deuterium atoms from C-1 and C-3 onto the isopropyl group, and retention of light hydrogen in the $CH_2{=}CHOH^{+\cdot}$ ion (Scheme 14). For instance, 1,1,1-D_3-$\mathbf{35}^{+\cdot}$ eliminates $C_3H_6D_2$ and C_3H_7D in a 10:1 ratio, far in excess of the 1:1 statistical ratio. Interpretation of this phenomenon by



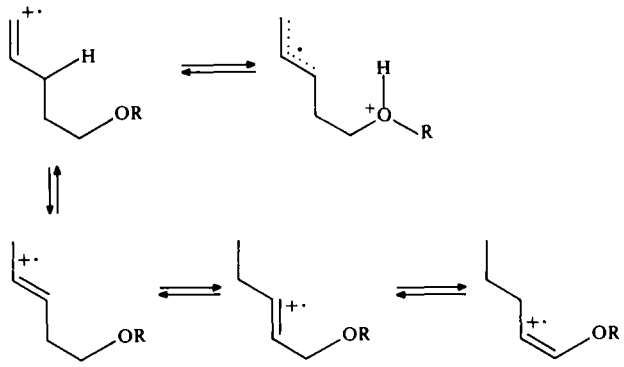
SCHEME 14

kinetic isotope effects is unclear, since the rate constants should be affected to the same extent in the forward and reverse isomerizations, provided these proceed through a common transition state or complex as suggested[96]. However, if there is a multitude of transition states of very similar energies due to the looseness of the reaction counterparts in the complex, unequal isotope effects could result in deuterium retention in the propane molecule. Alternatively, isotope effects on the complex dissociation could cause that a higher fraction of the $CH_3CD_2CH_3 \cdots CHD{=}CHOH^{+\cdot}$ complex survives for 10^{-5} s to reach the observation window. Interestingly, a lower selectivity (3:1) is observed at shorter ion lifetimes[96] and completely stochastic dissociation occurs upon collisional activation[95].

Ion–molecule reactions of $CH_2{=}CHOH^{+\cdot}$ with alkanes have been studied by the ion–cyclotron resonance technique[98]. The main reaction channel is a hydrogen atom transfer forming $CH_3CH{=}OH^+$. However, the presence of a bound propane $\cdots CH_2{=}CHOH^{+\cdot}$ complex is indicated by the formation of $(CH_3)_2CH{=}OH^+$ which must involve carbon–carbon bond formation in $\mathbf{35}^{+\cdot}$ as a possible intermediate. In contrast to unimolecular dissociations of metastable $\mathbf{35}^{+\cdot}$, loss of methane from the complex is a minor process, giving rise to a weak peak of $C_4H_8O^+$. This may be due to the higher initial energy of $\mathbf{35}^{+\cdot}$ formed by the exothermic ion–molecule reaction that would prefer α-cleavage dissociations. Dissociations of metastable neopentanol cation radical to give 2-methylpropene ion and methanol presumably involve skeletal isomerizations and hydrogen exchange in a variety of intermediates[95,99,100].

D. Rearrangements in Unsaturated and Aromatic Ethers and Alcohols

Introduction in an alcohol or ether molecule of a carbon–carbon double bond or an aromatic ring changes dramatically the cation radical chemistry. Ionization of an unsaturated or aromatic alcohol or ether takes place from a π(C=C) orbital to give the ion ground electronic state. On the one hand, this removes the inherent instability of the ionized hydroxy or ether group, so hydrogen transfers to the oxygen function are no longer exothermic, although they may play an important role. On the other hand, double bond isomerizations or hydrogen transfers to the aromatic system become very facile and very often determine the dissociation course. In addition, the ionized alkene moiety can function as a Brønsted acid and use its allylic hydrogens to protonate the hydroxy or ether group (Scheme 15). Since proton affinities of alkenyl radicals are comparable to those of alcohols and ethers, the proton transfer is nearly thermoneutral,

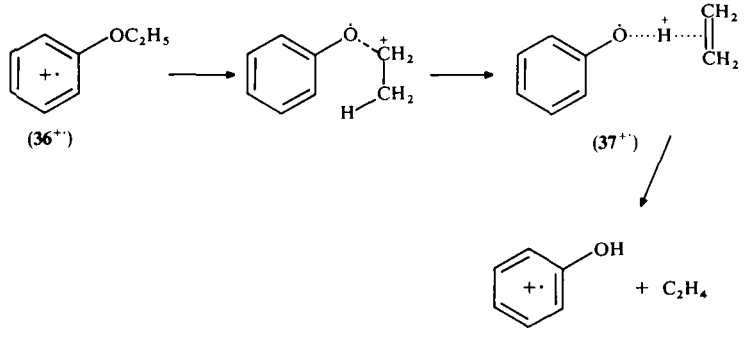


SCHEME 15

allowing fast hydrogen exchange in a distonic ion or an ion–molecule complex[98]. Double bond migration towards the hydroxy or ether group results in the formation of an enol or enol ether ion. These are very stable and often function as a sink on potential energy surface. Consequently, low-energy dissociations of metastable ions from isomeric unsaturated alcohols or ethers are often indistinguishable due to common stable intermediates. Enol ion dissociations have been covered in detail recently[97]. Methyl loss from pent-3-en-2-ol cation radical is a case example of multiple isomerization as studied by the field-ionization kinetics method[101]. Rearrangements preceding alkyl loss are also common in dissociations of alkenyl methyl ether cation radicals[53,102].

Eliminations of alkenes from alkyl phenyl ether cation radicals have been studied extensively for 25 years following the original labelling study that showed nonspecific hydrogen transfer[103]. The $C_6H_6O^{+\cdot}$ was identified as ionized phenol[104,27], and the neutral products from n-butyl phenyl ether ion were identified by the electron-bombardment flow technique as a 2:1:1 mixture of 1-butene and (*E*)- and (*Z*)-2-butenes[105]. Morton suggested a mechanism for these dissociations in which cleavage of the O—C_{alkyl} bond gives rise to a complex of the phenoxy radical and the alkyl ion. If the latter is an n-alkyl cation, it undergoes reversible hydrogen rearrangement to the more stable *sec*-alkyl ion which eventually transfers a hydrogen atom onto the phenoxy radical to form phenol and an alkene cation radical. Morton's mechanism has been revisited recently in a series of studies employing metastable ion dissociations, kinetic energy release and appearance energy measurements[106–112].

Elimination of ethene from ionized phenetole (**36**$^{+\cdot}$) has been the subject of recent dispute.[108–111]. The dissociation has an activation barrier, measured as 228 kJ mol^{-1} above **36**$^{+\cdot}$ and 136 kJ mol^{-1} above the thermochemical threshold. However, only 6.3 kJ mol^{-1} kinetic energy is released upon fragmentation of metastable **36**$^{+\cdot}$[110]. The actual energy barrier has been estimated from RRKM fits of the measured kinetic curves as 139 kJ mol^{-1} above **36**$^{+\cdot}$[111], suggesting a large kinetic shift (89 kJ mol^{-1}) even for slowly dissociating ions. Riley and Baer thus argued that their estimated transition state energy is incompatible with the estimated heat of formation of the $C_6H_5O \cdots C_2H_5^+$ complex (> 245 kJ mol^{-1} above **36**$^{+\cdot}$). The kinetic curves and activation parameters were interpreted in favor of a classical (i.e. bound) four-membered cyclic transition state, suggested earlier by Bouchoux (Scheme 16)[113]. In the same vein, the absence of hydrogen migration in dissociations of labeled *sec*-pentyl phenyl ethers was interpreted as contradicting Morton's mechanism[114]. It is interesting to note that without the above appearance energy corrections the ion–molecule complex would become somewhat more plausible on energy grounds. Also, very similar appearance energies (10.3–10.5 eV) have

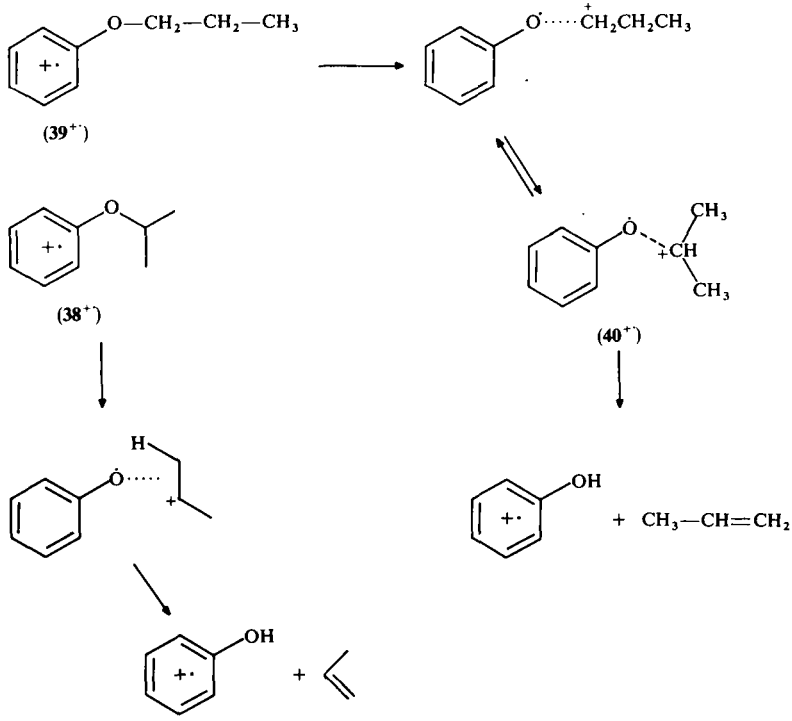


SCHEME 16

been obtained by different workers for $C_6H_5OH^{+\cdot}$ ions of different lifetimes (10^{-6}–7×10^{-4} s).

A yet different point of view has been advocated by Holmes and coworkers based on their labeling studies[109,110]. These authors find preferential transfer of the methyl hydrogen atoms onto the phenoxyl oxygen in $\mathbf{36}^{+\cdot}$, with the specificity reaching 96% with ions dissociating after 30 μs. Based on this, the modest kinetic isotope effects observed and the known instability of the classical $C_2H_5^+$ cation, a symmetrical hydrogen-bridged intermediate ($\mathbf{37}^{+\cdot}$) has been suggested as a plausible dissociating species (Scheme 16).

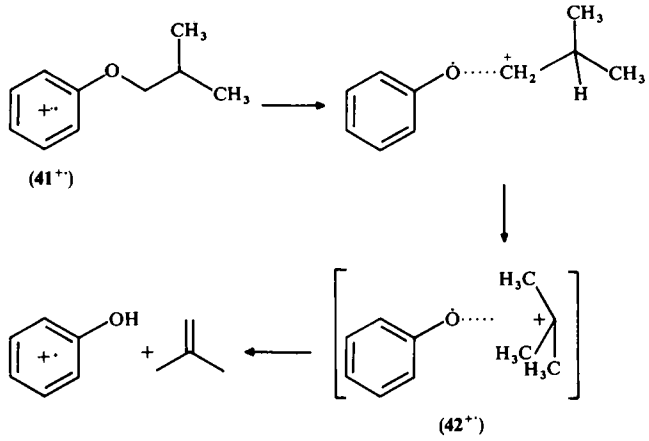
Critical energy measurements for dissociations of other alkyl phenyl ether cation radicals pointed out the importance of energy excess in the intermediate[110]. For example, metastable 2-propyl phenyl ether ($\mathbf{38}^{+\cdot}$) eliminates propene with 97% specific transfer of one of the methyl hydrogen atoms, consistent with only 45 kJ mol^{-1} energy excess in the transition state. This internal energy, even if confined in the 2-propyl cation in the ion–radical complex, would be insufficient to bring about hydrogen migrations involving the unstable 1-propyl cation as a transition state[115]. By contrast, the 97 kJ mol^{-1} excess energy in the transition state for the dissociation of the n-propyl phenyl ether ion ($\mathbf{39}^{+\cdot}$) should be sufficient to cause several 1,2-hydrogen shifts in the propyl cation in complex $\mathbf{40}^{+\cdot}$ prior to propene elimination (Scheme 17)[108].



SCHEME 17

The complexity of these dissociations and their sensitivity towards subtle energetic factors is highlighted by the behavior of metastable isobutyl phenyl ether cation radical ($\mathbf{41}^{+\cdot}$, Scheme 18). Upon dissociation the isobutyl group rearranges to a *t*-butyl cation

that transfers a proton to the phenoxy radical. The proton transfer is purely statistical with modest isotope effects, showing that $C_6H_5O^{\cdot}$ and $(CH_3)_3C^+$ are bound in a loose ion–molecule complex ($\mathbf{42}^{+\cdot}$) in which all the methyl hydrogen atoms become accessible with equal probability.

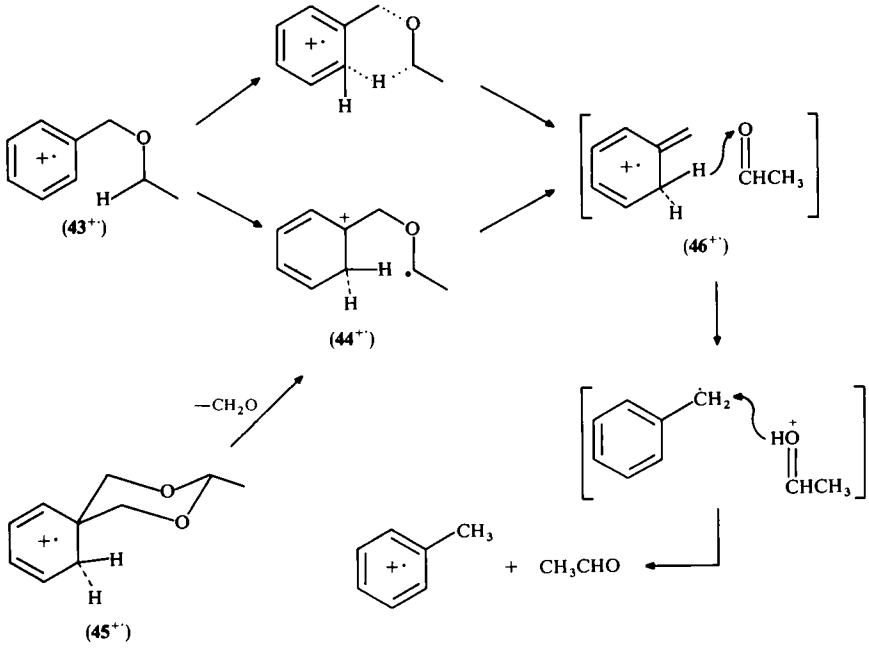


SCHEME 18

It appears from these studies that there is no simple rule that would encompass all the subtle facets of this highly interesting gas-phase ion chemistry. Fortunately, these aromatic systems are still too large to be treated by *ab initio* calculations at a sufficiently high theoretical level, so for some time experimentalists will remain at large in postulating and arguing their mechanisms.

The mechanism of the γ-hydrogen rearrangement in benzyl alkyl ether cation radicals has been the subject of another dispute[116–119]. The benzyl ethyl ether ion ($\mathbf{43}^{+\cdot}$) eliminates acetaldehyde to form $C_7H_8^{+\cdot}$ whose collisionally activated dissociation spectrum was different from that of toluene ion[116,119,120], while a specific transfer of the γ-hydrogen has been confirmed by deuterium labeling (Scheme 19). Deuterium isotope effects in ring-substituted metastable $\mathbf{43}^{+\cdot}$ were independent of the nature of the substituent and showed moderately large values ($k_H/k_D = 1.8–2.2$). these findings were interpreted by a concerted mechanism of acetaldehyde elimination from $\mathbf{43}^{+\cdot}$[116], the main argument having been the magnitude of the isotope effects that were deemed to arise from hydrogen transfer in a rate-determining step. The concerted mechanism was challenged in another study that claimed hydrogen–deuterium exchange between the alkyl chain and the aromatic ring in dissociating labeled $\mathbf{43}^{+\cdot}$[117]. Such an exchange, although observed at a very low extent (2%), would nevertheless suggest an intermediate in a stepwise elimination (Scheme 19) but could not possibly result from a concerted elimination. However, the hydrogen–deuterium exchange has not been reproduced in two later studies[118,119] and appears likely to have arisen from artifacts in the mass-unresolved collisionally activated dissociation spectra[119]. The stepwise mechanism was refuted on the basis of detailed kinetic analysis that indicated that some hydrogen–deuterium exchange would have taken place had there been a stable intermediate, e.g. distonic ion $\mathbf{44}^{+\cdot}$. However, the latter was found by MNDO calculations to be more stable than $\mathbf{43}^{+\cdot}$, and the two structures were separated by a small energy barrier calculated as 21 kJ mol^{-1}. RRKM calculations predicted a range of deuterium isotope effects depending on the input critical energy data. The extreme sensitivity towards the energy

barrier of the calculated rate constants made it difficult to interpret the kinetic data unequivocally[118]. $^{18}O/^{16}O$ isotope effects in metastably dissociating α,α'-diethoxy-*p*-xylenes were also interpreted (with some caution) as favoring the concerted mechanism[118].



SCHEME 19

A subsequent study focussed on the generation of $\mathbf{44}^{+\cdot}$ which was obtained from a spirocyclic precursor ($\mathbf{45}^{+\cdot}$) and found to give a collisionally activated dissociation spectrum different from that of $\mathbf{43}^{+\cdot}$. Metastable $\mathbf{44}^{+\cdot}$ eliminates acetaldehyde with a very small kinetic energy release ($T_{av} = 1.1$ kJ mol^{-1}) compared to that in dissociations of metastable $\mathbf{43}^{+\cdot}$ (7 kJ mol^{-1})[119]. In a reverse ion–molecule reaction acetaldehyde was found to react with the methylenecyclohexadiene cation-radical, generated from isopentylbenzene as precursor, to produce $\mathbf{44}^{+\cdot}$, not $\mathbf{43}^{+\cdot}$. The unimolecular dissociations of $\mathbf{43}^{+\cdot}$ and $\mathbf{44}^{+\cdot}$ are made further complicated by isomerization of the originally formed methylenecyclohexadiene ion to the more stable toluene ion. The latter reaction occurs spontaneously in high-energy $C_7H_8^{+\cdot}$, or it can be catalyzed by the acetaldehyde molecule in an ion–molecule complex (e.g. $\mathbf{46}^{+\cdot}$)[119]. The existence of stable $\mathbf{44}^{+\cdot}$ and its formation in the ion–molecule reaction suggested that it and $\mathbf{43}^{+\cdot}$ are separated by an energy barrier in line with the previous calculations[118]. Hence it was argued that there cannot be separate transition states corresponding to two very similar processes. e.g. the $\mathbf{44}^{+\cdot}$ forming hydrogen transfer *without* C—O bond cleavage on the one hand, and a hydrogen transfer *with* concomitant C—O bond cleavage, corresponding to the concerted mechanism, on the other. The possibility of the hydrogen transfer taking place in a $C_6H_5CH_2^+ \cdots {}^{\cdot}OCH_2CH_3$ ion–molecule complex has also been suggested, although so far there has been no experimental evidence to support such a mechanism[119].

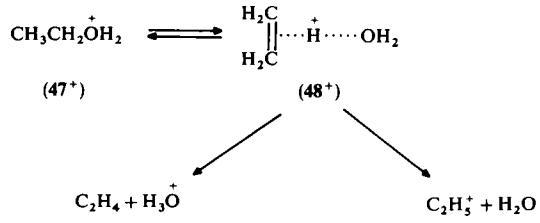
Interestingly, substantial deuterium isotope effects are often encountered in unimolecular dissociations involving ion–molecule complexes[6,110].

III. EVEN-ELECTRON CATIONS

A. Simple Protonated Alcohols

Upon protonation or cationization under chemical ionization conditions, alcohols and ethers undergo a variety of unimolecular dissociations, including C—O bond heterolysis, and hydrogen and skeletal rearrangements. The basic aspects of chemical ionization mass spectrometry of alcohols and ethers have been reviewed by Harrison[121] and reviews on rearrangements in even-electron ions have also appeared[122–124].

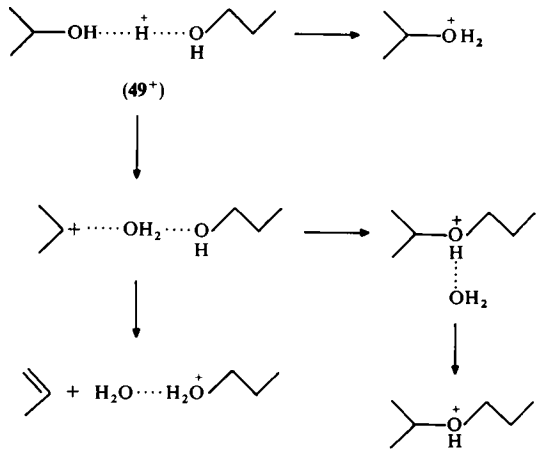
Protonated ethanol, $CH_3CH_2OH_2^+$ ($\mathbf{47}^+$), dissociates upon collisional activation by two competing reactions to form $C_2H_5^+$ and H_3O^+. These dissociations involve substantial hydrogen exchange between the hydroxyl and the ethyl group in both $CH_3CH_2OH_2^+$ and the $C_2H_5^+ \cdots H_2O$ complex produced by an ion–molecule reaction[124]. Only H_3O^+ is observed in dissociations of metastable $CH_3CH_2OH_2^+$ in keeping with the lower endothermicity for the formation of $C_2H_4 + H_3O^+$ (132 kJ mol^{-1}) compared to that of $C_2H_5^+ + H_2O$ (153 kJ mol^{-1})[125–128]. Since the carbon and oxygen atoms in $C_2H_5OH_2^+$ are coordinationally saturated, proton migration in a classical bound structure would have to involve high-energy carbon-protonated intermediates, incompatible with the reaction thermochemistry. As shown by *ab initio* calculations[128,129] following mechanistic interpretation of experimental data[124], the hydrogen exchange is facile in an ion–molecule complex ($\mathbf{48}^+$, Scheme 20). In the most extensive calculations carried out so far[129], $\mathbf{48}^+$ is calculated to be 53 kJ mol^{-1} less stable than $\mathbf{47}^+$ and the isomerization requires 95 kJ mol^{-1} activation energy. Interestingly, both $C_2H_5^+$ and H_3O^+ are formed from $\mathbf{48}^+$ in a continuously endothermic fashion without a reverse potential energy barrier. Solvation of the water moiety in $\mathbf{48}^+$ with a water or ethanol molecule does not change significantly the relative energies of the classical and proton-bound structures[128]. However, the energy barriers to rearrangements are greater in the solvated ions, e.g. 178 and 163 kJ mol^{-1} for $C_2H_5OH_2^+ \cdots H_2O$ and $C_2H_5OH_2^+ \cdots HOC_2H_5$, respectively, compared to that calculated for $\mathbf{47}^+$ at the same level of theory (120 kJ mol^{-1})[128]. The presence of a high-energy barrier explains the behavior of the $C_2H_5OH_2^+ \cdots HOC_2H_5$ cluster which does not lose ethylene, but instead undergoes condensation to form protonated diethyl ether[128]. Condensation and loss of ethylene are also the major processes in the thermal decomposition of $\mathbf{47}^+$[130]. Kinetic measurements carried out with the use of the selected-ion-flow-drift tube method yielded rate constants for thermal decomposition of $\mathbf{47}^+$[131]. In a yet different approach, a neutralization–reionization study of protonated ethanol appears to be consistent with the existence of $\mathbf{47}^+$ and $\mathbf{48}^+$, in spite of some ambiguities in spectra interpretation[132].



SCHEME 20

Protonation of 1-propanol and 2-propanol gives rise to distinct ions as confirmed by their collisionally activated dissociation spectra[133]. By contrast, ion–molecule reactions of $C_3H_7^+$ ions with water produce a single ion isomer identified as protonated 2-propanol. The fragmentation patterns in collisionally activated dissociation of these ions are compatible with the classical bound structures, but do not seem to lend support to nonclassical proton-bound structures suggested in an earlier study[127].

In the same vein, proton-bound dimers of 1-propanol and 2-propanol (e.g. **49**$^+$) dissociate upon collisional activation by losing an alcohol molecule, propene, or water. These dissociations appear to be straightforward, with no hydrogen exchange having been observed for derivatives labeled in either propyl group[134]. However, further dissociation of protonated propyl isopropyl ether from **49**$^+$ does involve extensive hydrogen exchange between the oxygen function and the isopropyl group, presumably in an ion–molecule complex (Scheme 21).



SCHEME 21

B. Stereochemistry

Stereochemical aspects of protonated alcohol dissociations have been studied intensively in systems of increasing complexity. Most of this highly interesting work has been reviewed recently[12,94], or constitutes a significant part of a forthcoming monograph on organic stereochemistry by mass spectrometry[135]. It therefore suffices to list here some of the systems examined most recently; these included: cyclohexane and cyclopentane diols[136–138], triols[136] and their acetates[139], [4.3.3]propellane diols[140,141], ribose and arabinose[142], hexose isomers[143,144], terpenes[145], nucleosides[146] and eburnane alkaloids[147].

C. Aliphatic Ethers

Even-electron ions produced from aliphatic and aromatic ethers under chemical ionization conditions as a rule represent very stable species[121]. In contrast to protonated alcohols, C—O bond heterolysis in a protonated ether ion, $R^1—OH^+—R^2$, is greatly disfavored against hydrogen rearrangements forming an alkane or alkene molecule and

an even-electron product ion. For example, both protonated dimethyl ether, $(CH_3)_2OH^+$, and trimethyloxonium ion, $(CH_3)_3O^+$, dissociate by loss of methane[148]. The (C, H_3, O^+) product from $(CH_3)_2OH^+$ is very likely to be the stable CH_2OH^+ ion that was shown to retain the deuterium atom if produced from $(CH_3)_2OD^+$[148,149]. Dissociation of metastable $(CH_3)_2OH^+$ shows large kinetic energy release (38.6 kJ mol^{-1}), suggesting a rate-determining energy barrier in the hydrogen rearrangement step. Upon neutralization with Xe, $(CH_3)_2OH$ dissociations display large kinetic isotope effects. While $(CH_3)_2OH$ dissociates rapidly to become undetectable after 1 μs, $(CH_3)_2OD$ survives to give the corresponding ion as one of the major species in the neutralization–reionization mass spectrum[149]. Interestingly, neutral $(CH_3)_2OD$ loses light hydrogen to form ylide $CH_2OD^+CH_3$, or with concomitant rearrangement to produce the more stable CH_2DOCH_3 molecule[149].

The appearance energy of $CH_3OCH_2^+$ by loss of methane from $(CH_3)_3O^+$ has been measured by low-energy collisionally activated dissociation[150] and found to be only *ca* 30 kJ mol^{-1} below the thermochemical threshold for C—O bond heterolysis to CH_3^+ and dimethyl ether (909 kJ mol^{-1}). It was suggested that the elimination proceeds through an ion–molecule complex with a very long C ··· O distance that allows for almost free rotation of the ion and neutral components. The reported energy data indicate a very large energy barrier (297 kJ mol^{-1}) for the unimolecular methane elimination from $(CH_3)_3O^+$, consistent with the latter being a symmetry-forbidden process[151].

Ion–molecule clustering in dilute mixtures of $(CH_3)_2O$ in krypton has been studied at variable temperatures and electron energies[152]. The main products reported are $(CH_3OCH_3)_nH^+$ ($n = 1$–4), $[CH_3OCH_2^+](CH_3OCH_3)_n$ and $[(CH_3)_3O^+](CH_3OCH_3)_n$.

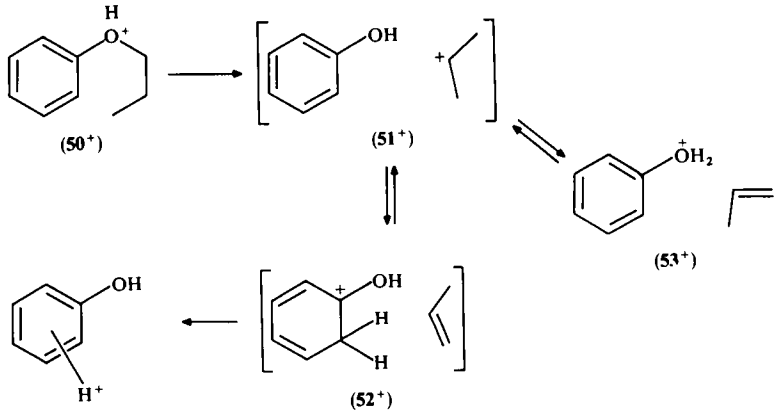
Fragmentations of metastable protonated alkyl n-propyl and alkyl isopropyl ethers (alkyl = CH_3, C_2H_5, *iso*-C_3H_7) have been investigated in detail by experiment and theory[153]. These even-electron ions fragment mostly to give rise to ROH_2^+ and $C_3H_7^+$, similar to the dissociations of proton-bound alcohol dimers (Scheme 21). The formation of ROH_2^+ is accompanied by a substantial exchange of the oxygen-bound proton with those of the isopropyl group. This is assumed to occur in a propane–$CH_3OH_2^+$ ion–molecule complex. The latter was found by *ab initio* calculations [6–31G(*d*)/3–21G] to be a stable species 96 kJ mol^{-1} above *i*-C_3H_7—OH^+CH_3, but 52 kJ mol^{-1} below the dissociation threshold. By contrast, no stable structure was found for the postulated complex of *i*-$C_3H_7^+$ with CH_3OH. The C—O bond heterolysis appears to be continuously endothermic up to final product separation. Nevertheless, the calculated potential energy surface is very flat beyond 2.7 Å C ··· O separation, thus allowing a large number of low-energy vibrational states in this region. This possibly creates an entropy bottleneck, explaining the slow dissociation of the protonated ether by 'simple' bond cleavage[153]. Another ion–molecule reaction study, carried out under both high- and low-pressure conditions, reported rate constants for the reactions of $C_2H_3^+$, $C_3H_5^+$, $C_3H_7^+$, $C_2H_5O^+$ and $(CH_3)_2OH_2^+$ with di-isopropyl ether[154].

D. Aromatic Ethers

In contrast to aliphatic ethers in which protonation occurs at the oxygen atom to give the most stable ion structure, the site of proton attachment in aromatic ethers is less certain, although both ring and oxygen protonation is likely to occur[155] (see also Reference 156 for discussion of protonation sites in aromatic compounds). In spite of this dichotomy, dissociations of aromatic ethers have usually been depicted as being initiated by ether oxygen protonation[157–159].

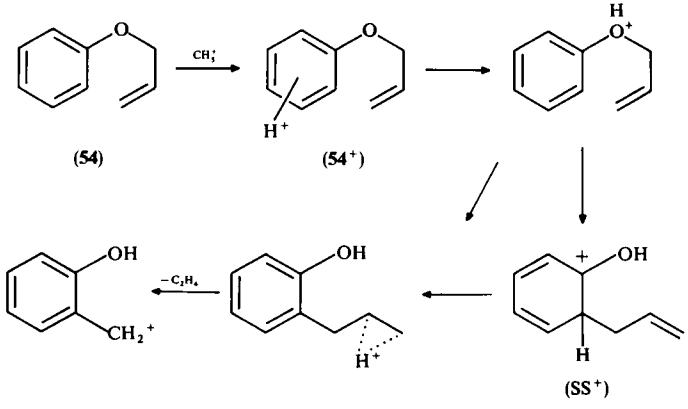
Protonated phenyl propyl ether (**50**$^+$) eliminates propene to give protonated phenol[157,158]. Careful deuterium labeling and kinetic analysis allowed Morton to distinguish between two alternative mechanisms termed gas-phase solvolysis and

elimination–readdition. The former is shown in Scheme 22. Ion **50**$^+$ undergoes C—O bond heterolysis with concomitant rearrangement of the unstable 1-propyl cation to the 2-propyl isomer to form complex **51**$^+$, which is held together by ion–dipole interaction. Protonation of phenol by 2-$C_3H_7^+$ is an exothermic process ($-\Delta H_r = 70\,kJ\,mol^{-1}$), so the newly formed complex **52**$^+$ breaks apart without much hydrogen exchange. However, significant exchange is assumed to take place following proton transfer to the phenolic hydroxyl group, which is less basic than the ring and can transfer one of its protons back to the propene molecule. This results in equilibration of **51**$^+$ and **53**$^+$, leading to extensive proton exchange between the phenolic hydroxyl and the propyl group[157,158].



SCHEME 22

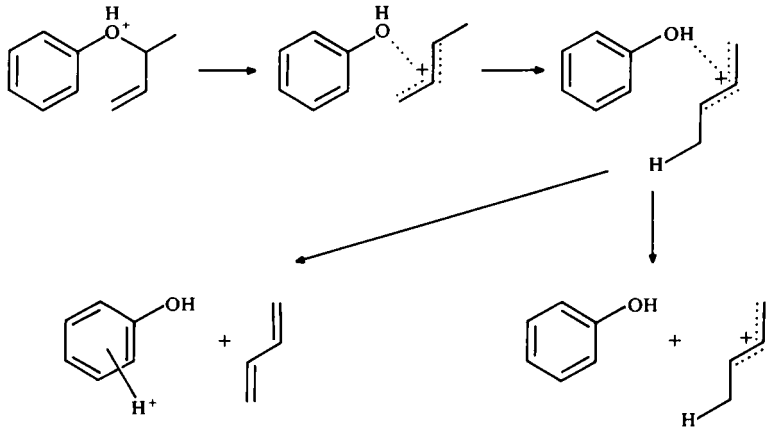
Protonated phenyl allyl ethers undergo two competing alkene losses in ion source and metastable ion dissociations[159–161]. One has been formulated as a gas-phase Claisen rearrangement (Scheme 23). Protonation with CH_5^+ in the ring in **54** leads to complete scrambling of six hydrogen atoms[161]. The rearrangement is triggered by proton transfer to the ether oxygen followed by C—O bond heterolysis and formation of the C—C



SCHEME 23

bond. Hydrogen rearrangement in intermediate **55**$^+$ then results in expulsion of the terminal alkene and formation of an ion at *m/z* 107, presumably *o*-hydroxybenzyl or hydroxytropylium[161].

The other alkene loss becomes more prominent with branched and cycloalkenyl phenyl ethers and yields protonated phenol and the complementary protonated diene ion (Scheme 24). A mechanism suggested for this dissociation invokes the formation of an ion–molecule complex following heterolysis of the C—O bond in an oxygen-protonated molecular ion. Unimolecular dissociations of these complexes exhibit low kinetic energy release (*ca* 2 kJ mol^{-1}), consistent with a loose transition state[159]. The relative intensities of the complementary product ions roughly correlate with the estimated ion heats of formation[159]. It should be noted in this context that the kinetic energy spectra used in these studies tend to discriminate against low-energy, low-mass product ions, so an appropriate instrument function should be taken into account when quantifying ion relative intensities. Carbon–carbon bond-forming rearrangements in protonated aryl benzyl ethers have also been reported[162].



SCHEME 24

In concluding this chapter one can remark that gas-phase ion dissociations, both unimolecular and collisionally activated, exhibit a variety of unusual features that distinguish them from ion reactions in solution. The absence of solvent and intermolecular energy exchange makes gas-phase ion chemistry a distinct discipline with its own rules and intricacies. With the still closer interplay of experiment and theory being fostered in this field, one may predict a further buoyant development that will make this chapter obsolete at the time of the next Supplement.

IV. ACKNOWLEDGEMENT

Generous support by the National Science Foundation (Grant CHE-9102442), University of Washington Graduate Research Fund and the Center for Process Analytical Chemistry is gratefully acknowledged. Acknowledgment is also made to the donors of the Petroleum Research Fund administered by ACS for partial support.

V. REFERENCES

1. C. C. Van de Sande, in *Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulphur Analogues* (Ed. S. Patai), Part 1, Wiley, Chichester, 1980, p. 299.
2. L. Radom, *Org. Mass Spectrom.*, **26**, 359 (1991).
3. B. F. Yates, W. J. Bouma and L. Radom, *J. Am. Chem. Soc.*, **106**, 5805 (1984).
4. B. F. Yates, W. J. Bouma and L. Radom, *Tetrahedron*, **42**, 6225 (1986).
5. S. Hammerum, *Mass. Spectrom. Rev.*, **7**, 123 (1988).
6. D. J. McAdoo, *Mass Spectrom. Rev.*, **7**, 363 (1988).
7. S. G. Lias, J. E. Bartmess, J. F. Liebman, J. L. Holmes, R. D. Levin and W. G. Mallard. *J. Phys. Chem. Ref. Data, Suppl.1*, **17** (1988).
8. M. Meot-Ner (Mautner) and L. W. Sieck, *J. Am. Chem. Soc.*, **113**, 4448 (1991).
9. S. T. Graul, M. E. Schnute and R. R. Squires, *Int. J. Mass Spectrom. Ion Processes*, **96**, 181 (1990).
10. H. Budzikiewicz, C. Djerassi and D. H. Williams, *Mass Spectrometry of Organic Compounds*, Holden Day, San Francisco, 1967.
11. B. F. Yates, W. J. Bouma and L. Radom, *J. Am. Chem. Soc.*, **109**, 2250 (1987).
12. F. Turecek, *Int. J. Mass Spectrom. Ion Processes*, **108**, 137 (1991).
13. W. Beveridge, I. W. Garioch, J. A. Hunter, C. A. F. Johnson and J. E. Parker, *Org. Mass Spectrom.*, **26**, 416 (1991).
14. L. A. Curtiss, C. Jones, G. W. Trucks, K. Raghavachari and J. A. Pople, *J. Chem. Phys.*, **93**, 2537 (1990).
15. J. D. Shao, T. Baer and D. K. Lewis, *J. Phys. Chem.*, **92**, 5123 (1988).
16. S. Huang and A. Tuinman, *Org. Mass Spectrom.*, **25**, 225 (1990).
17. R. Locht and J. Momigny, *Int. J. Mass Spectrom. Ion Processes*, **71**, 141 (1986).
18. J. N. Murrell and K. J. Laidler, *Trans. Faraday Soc.*, **64**, 371 (1968).
19. F. Turecek and V. Hanus, *Tetrahedron*, **39**, 1499 (1983).
20. J. L. Holmes, F. P. Lossing and P. M. Mayer, *J. Am. Chem. Soc.*, **113**, 9723 (1991).
21. D. Griller and F. P. Lossing, *J. Am. Chem. Soc.*, **103**, 1586 (1981).
22. R. D. Bowen and A. Maccoll, *Org. Mass Spectrom.*, **19**, 379 (1984).
23. A. Amirav, *Org. Mass Spectrom.*, **26**, 1 (1991).
24. F. Turecek, *Org. Mass Spectrom.*, **26**, 1074 (1991).
25. J. L. Holmes and J. K. Terlouw, *Org. Mass Spectrom.*, **15**, 383 (1980).
26. D. F. McMillen and D. M. Golden, *Ann. Rev. Phys. Chem.*, **33**, 493 (1982).
27. T. H. Morton, *Tetrahedron*, **38**, 3195 (1982).
28. J. L. Holmes and F. P. Lossing, *Int. J. Mass Spectrom. Ion Processes*, **92**, 111 (1989).
29. W. J. Bouma, R. H. Nobes and L. Radom, *J. Am. Chem. Soc.*, **104**, 2929 (1982).
30. W. J. Bouma, R. H. Nobes and L. Radom, *J. Am. Chem. Soc.*, **105**, 1743 (1983).
31. W. J. Bouma, R. H. Nobes and L. Radom, *Org. Mass Spectrom.*, **17**, 315 (1982).
32. L. Radom, W. J. Bouma, R. H. Nobes and B. F. Yates, *Pure Appl. Chem.*, **56**, 1831 (1984).
33. A. E. Dorigo, M. A. McCarrick, R. J. Loncharich and K. N. Houk, *J. Am. Chem. Soc.*, **112**, 7508 (1990).
34. J. D. Dill, C. L. Fischer and F. W. McLafferty, *J. Am. Chem. Soc.*, **101**, 6531 (1979).
35. D. H. Williams, *Acc. Chem. Res.*, **10**, 280 (1977).
36. K. Eckart, W. Zummack and H. Schwarz. *Org. Mass Spectrom.*, **19**, 642 (1984).
37. O. Dutuit, T. Baer, C. Metayer and J. Lemaire, *Int. J. Mass Spectrom. Ion Processes*, **110**, 67 (1991).
38. D. J. McAdoo, J. C. Traeger, C. E. Hudson and L. L. Griffin, *J. Phys. Chem.*, **92**, 1524 (1988).
39. T. Weiske, S. Akkok and H. Schwarz, *Int J. Mass Spectrom. Ion Processes*, **76**, 117 (1987).
40. J. A. Dodd, D. M. Golden and J. I. Brauman, *J. Chem. Phys.*, **80**, 1894 (1984).
41. C. E. Hudson and D. J. McAdoo, *Org. Mass Spectrom.*, **14**, 109 (1979).
42. C. E. Hudson, R. D. Lerner, R. Aleman and D. J. McAdoo, *J. Phys. Chem.*, **84**, 155 (1980).
43. H. E. Audier, G. Bouchoux, Y. Hoppilliard and A. Milliet, *Org. mass Spectrom.*, **17**, 382 (1982).
44. J. C. Traeger, C. E. Hudson and D. J. McAdoo, *J. Phys. Chem.*, **94**, 5714 (1990).
45. D. J. McAdoo and C. E. Hudson, *Org. Mass Spectrom.*, **25**, 664 (1990).
46. T. Weiske and H. Schwarz, *Tetrahedron*, **42**, 6245 (1986).
47. R. Postma, P. J. A. Ruttink, J. K. Terlouw, J. L. Holmes and P. C. Burgers, *Chem. Phys. Lett.*, **123**, 409 (1986).

48. A. Milliet and G. Sozzi, *Org. Mass Spectrom.*, **25**, 522 (1990).
49. H. E. Audier, G. Sozzi, A. Milliet and S. Hammerum, *Org. Mass Spectrom.*, **25**, 368 (1990).
50. M. S. Ahmed, C. E. Hudson, J. C. Traeger, C. S. Giam and D. J. McAdoo, *J. Am. Chem. Soc.*, **112**, 6443 (1990).
51. N. M. M. Nibbering, *Mass Spectrom. Rev.*, **3**, 445 (1984).
52. T. A. Molenaar–Langeveld and N. M. M. Nibbering, *Org. Mass Spectrom.*, **21**, 637 (1986).
53. T. A. Molenaar-Langeveld, R. H. Fokkens and N. M. M. Nibbering, *Org. Mass Spectrom.*, **23**, 364 (1988).
54. T. A. Molenaar-Langeveld and N. M. M. Nibbering, *Org. Mass Spectrom.*, **18**, 426 (1983).
55. R. H. Nobes, W. J. Bouma, J. K. MacLeod and L. Radom, *Chem. Phys. Lett.*, **135**, 78 (1987).
56. X.-Z. Qin, L. D. Snow and F. Williams, *J. Am. Chem. Soc.*, **107**, 3366 (1985).
57. B. C. Baumann and J. K. MacLeod, *J. Am. Chem. Soc.*, **103**, 6223 (1981).
58. P. N. T. van Velzen and W. J. van der Hart, *Chem. Phys. Lett.*, **83**, 55 (1981).
59. C. G. de Koster, J. J. Van Houte and J. van Thuijl, *Int. J. Mass Spectrom. Ion Processes*, **98**, 235 (1990).
60. M. C. R. Symons and B. W. Wren, *J. Chem. Soc., Perkin Trans. 2*, 511 (1984).
61. C. Wesdemiotis, B. Leyh, A. Fura and F. W. McLafferty, *J. Am. Chem. Soc.*, **112**, 8655 (1990).
62. G. Bouchoux, *Mass Spectrom. Rev.*, **7**, 1 (1988).
63. F. Turecek and F. W. McLafferty, *J. Am. Chem. Soc.*, **106**, 2528 (1984).
64. W. J. Bouma, J. K. MacLeod and L. Radom, *J. Am. Chem. Soc.*, **102**, 2246, 7928 (1980).
65. R. Bombach, J. P. Stadelman and J. Vogt, *Chem. Phys.*, **72**, 259 (1982).
66. C. Lifshitz, T. Peres, N. Ohmichi and I. Pri Bar, *Int. J. Mass Spectrom. Ion Processes*, **72**, 253 (1986).
67. C. Lifshitz, *Org. Mass Spectrom.*, **23**, 303 (1988).
68. W. J. van de Guchte and W. J. van der Hart, *Org. Mass Spectrom.*, **25**, 309 (1990).
69. G. Bouchoux, Y. Hoppilliard and P. Jaudon, *Org. Mass Spctrom.*, **22**, 98 (1987).
70. H.-F. Grutzmacher and D. Pankoke, *Org. Mass Spectrom.*, **24**, 647 (1989).
71. M. Alai and R. T. B. Rye, *Org. Mass Spectrom.*, **19**, 506 (1984).
72. K. Kimura, S. Kastsumata, Y. Achiba, T. Yamazaki and S. Iwata, *Handbook of He(I) Photoelectron Spectra of Fundamental Organic Molecules*, Japan Scientific Societies Press, Tokyo, 1981.
73. R. D. Bowen and D. H. Williams, *J. Am. Chem. Soc.*, **102**, 2752 (1980).
74. M. Yamamoto, T. Takeuchi and K. Nishimoto, *Int. J. Mass Spectrom. Ion Phys.*, **46**, 239 (1983).
75. T. Takeuchi, S. Ueno, M. Yamamoto, T. Matsushita and K. Nishimoto, *Int. J. Mass Spectrom. Ion Processes*, **64**, 33 (1985).
76. J.-D. Shao, T. Baer, J. C. Morrow and M. L. Fraser-Monteiro, *J. Chem. Phys.*, **87**, 5242 (1987).
77. J. L. Holmes, A. A. Mommers, J. E. Szulejko and J. K. Terlouw, *J. Chem. Soc., Chem. Commun.*, 165 (1984).
78. C. Wesdemiotis, P. O. Danis, R. Feng, J. Tso and F. W. McLafferty, *J. Am. Chem. Soc.*, **107**, 8059 (1985).
79. J. R. Cao, M. George and J. L. Holmes, *Org. Mass Spectrom.*, **26**, 481 (1991).
80. D. J. McAdoo, M. S. Ahmed, C. E. Hudson and C. S. Giam, *Int. J. Mass Spectrom. Ion Processes*, **100**, 579 (1990).
81. J. K. Terlouw, W. Heerma and G. Dijkstra, *Org. Mass Spectrom.*, **16**, 327 (1981).
82. D. J. McAdoo and C. E. Hudson, *Org. Mass Spectrom.*, **21**, 779 (1986).
83. B. F. Yates, W. J. Bouma, J. K. MacLeod and L. Radom, *J. Chem. Soc., Chem. Commun.*, 204 (1987).
84. P. C. Burgers, J. L. Holmes, C. E. C. A. Hop, R. Postma, P. J. A. Rutink and J. K. Terlouw, *J. Am. Chem. Soc.*, **109**, 7315 (1987).
85. R. Postma, S. P. van Helden, J. H. van Lenthe, P. J. A. Rutink, J. K. Terlouw and J. L. Holmes, *Org. Mass Spectrom.*, **23**, 503 (1988).
86. D. J. McAdoo and C. E. Hudson, *Org. Mass Spectrom.*, **22**, 615 (1987).
87. M. S. Ahmed, C. E. Hudson, C. S. Giam and D. J. McAdoo, *Org. Mass Spectrom.*, **26**, 1089 (1991).
88. J. Haib and D. Stahl, *Org. Mass Spectrom.*, **25**, 592 (1990).
89. D. Harnish, J. L. Holmes, F. P. Lossing, A. A. Mommers, A. Maccoll and M. N. Mruzek, *Org. Mass Spectrom.*, **25**, 381 (1990).
90. F. Turecek, M. Smutek and V. Hanus, *Org. Mass Spectrom.*, **16**, 483 (1981).

91. A. Selva, F. Ferrario, P. Ventura and R. Pellegata, *Org. Mass Spectrom.*, **22**, 523 (1987).
92. M. Decouzon, J.-F. Gal, S. Geribaldi, M. Rouillard and J.-M. Sturia, *Org. Mass Spectrom.*, **25**, 312 (1990).
93. J. K. MacLeod and L. C. Monahan, *Org. Mass Spectrom.*, **24**, 573 (1989).
94. F. Turecek, *Collect. Czech. Chem. Commun.*, **52**, 1928 (1987).
95. S. Hammerum and H. E. Audier, *J. Chem. Soc., Chem. Commun.*, 860 (1988).
96. M. George and J. L. Holmes, *Org. Mass Spectrom.*, **25**, 605 (1990).
97. F. Turecek, in *The Chemistry of Enols* (Z. Rappoport, Ed.), Chap. 3, Wiley–Interscience, Chichester, 1990, p. 95.
98. P. Mourgues, H. E. Audier and S. Hammerum, *Org. Mass Spectrom.*, **26**, 339 (1991).
99. M. C. Bissonnette, M. George and J. L. Holmes, *Org. Mass Spectrom.*, **25**, 689 (1990).
100. M. C. Bissonnette, M. George and J. L. Holmes, *Int. J. Mass Spectrom. Ion Processes*, **101**, 309 (1990).
101. H. W. Zappey, S. Ingemann and N. M. M. Nibbering, *Org. Mass Spectrom.*, **26**, 241 (1991).
102. R. D. Bowen, A. D. Wright, S. R. Thomas, K. R. Jennings and A. Maccoll, *Org. Mass Spectrom.*, **26**, 421 (1991).
103. J. K. MacLeod and C. Djerassi, *J. Am. Chem. Soc.*, **88**, 1840 (1966).
104. A. Maquestiau, Y. Van Haverbeke, R. Flammang, C. De Meyer, K. G. Das and G. S. Reddy, *Org. Mass Spectrom.*, **12**, 631 (1977).
105. F. P. Burns and T. H. Morton, *J. Am. Chem. Soc.*, **98**, 7308 (1976).
106. J. Lemaire, I. Dimicoli and R. Botter, *Chem. Phys.*, **115**, 129 (1987).
107. R. W. Kondrat and T. H. Morton. *Org. Mass Spectrom.*, **23**, 555 (1988).
108. E. L. Chronister and T. H. Morton, *J. Am. Chem. Soc.*, **112**, 133 (1990).
109. M. C. Blanchette, J. L. Holmes and F. P. Lossing, *Org. Mass Spectrom.*, **24**, 673 (1989).
110. D. Harnisch and J. L. Holmes, *J. Am. Chem. Soc.*, **113**, 9729 (1991).
111. J. Riley and T. Baer, *J. Am. Soc. Mass Spectrom.*, **2**, 464 (1991).
112. F. M. Benoit and A. G. Harrison, *Org. Mass Spectrom.*, **11**, 599 (1976).
113. G. Bouchoux, *Org. Mass Spectrom.*, **13**, 184 (1978).
114. G. Sozzi, H. E. Audier, P. Mourgues and A. Millet, *Org. Mass Spectrom.*, **22**, 746 (1987).
115. W. Koch, B. Liu and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **111**, 3479 (1989).
116. D. J. M. Stone, J. H. Bowie, D. J. Underwood, K. F. Donchi, C. E. Allison and P. J. Derrick, *J. Am. Chem. Soc.*, **105**, 1688 (1983).
117. C. Wesdemiotis, R. Feng and F. W. McLafferty, *J. Am. Chem. Soc.*, **107**, 715 (1985).
118. C. E. Allison, M. B. Stringer, J. H. Bowie and P. J. Derrick, *J. Am. Chem. Soc.*, **110**, 6291 (1988).
119. F. Turecek, D. E. Drinkwater and F. W. McLafferty, *J. Am. Chem. Soc.*, **112**, 993 (1990).
120. P. C. Burgers, J. K. Terlouw and K. Levsen, *Org. Mass Spectrom.*, **17**, 295 (1982).
121. A. G. Harrison, *Chemical Ionization Mass Spectrometry*, CRC Press, Boca Raton, 1983.
122. E. E. Kingston, J. S. Shannon and M. J. Lacey, *Org. Mass Spectrom.*, **18**, 183 (1983).
123. F. W. McLafferty, *Org. Mass Spectrom.*, **15**, 114 (1980).
124. A. G. Harrison, *Org. Mass Spectrom.*, **22**, 637 (1987).
125. P. H. Dawson, *Int. J. Mass Spectrom. Ion Processes*, **50**, 287 (1983).
126. M. F. Jarrold, A. J. Illies, N. J. Kirchner and M. T. Bowers, *Org. Mass Spectrom.*, **18**, 388 (1983).
127. M. Meot-Ner (Mautner), M. M. Ross and J. E. Campana, *J. Am. Chem. Soc.*, **107**, 4839 (1985).
128. G. Bouchoux and Y. Hoppilliard, *J. Am. Chem. Soc.*, **112**, 9110 (1990).
129. D. J. Swanton, D. C. J. Marsden and L. Radom *Org. Mass Spectrom.*, **26**, 227 (1991).
130. M. Meot-Ner (Mautner) and L. W. Sieck, *Int. J. Mass Spectrom. Ion Processes*, **92**, 123 (1989).
131. S. C. Smith, M. J. McEwan, K. Giles, D. Smith and N. G. Adams, *Int. J. Mass Spectrom. Ion Processes*, **96**, 77 (1990).
132. C. Wesdemiotis, A. Fura and F. W. McLafferty, *J. Am. Soc. Mass Spectrom.*, **2**, 459 (1991).
133. J. K. Terlouw, T. Weiske, H. Schwarz and J. L. Holmes, *Org. Mass Spectrom.*, **21**, 665 (1986).
134. H. E. Audier, C. Monteiro, P. Mourgues and D. Robin, *Rapid Commun. Mass Spectrom.*, **3**, 84 (1989).
135. J. S. Splitter and F. Turecek (Eds.), *Applications of Mass Spectrometry to Organic Stereochemistry*, VCH Publ., Stuttgart, 1993 (in press).
136. C. Guenat, R. Houriet, D. Stahl and J. Winkler, *Helv. Chim. Acta*, **68**, 1647 (1985).
137. W. J. Meyerhoffer and M. M. Bursey, *Org. Mass Spectrom.*, **24**, 169 (1989).
138. W. J. Meyerhoffer and M. M. Bursey, *Org. Mass Spectrom.*, **24**, 246 (1989).

139. L. D'Haenens, C. C. van de Sande, M. Schelfaut and M. Vandewalle, *Org. Mass Spectrom.*, **22**, 330 (1987).
140. P. Ashkenazi, W. Blum, B. Domon, A. L. Gutman, A. Mandelbaum, D. Muller, W. J. Richter and D. Ginsburg, *J. Am. Chem. Soc.*, **109**, 7325 (1987).
141. P. Ashkenazi, B. Domon, A. L. Gutman, A. Mandelbaum, D. Muller, W. J. Richter and D. Ginsburg, *Isr. J. Chem.*, **29**, 131 (1989).
142. W. J. Meyerhoffer and M. M. Bursey, *Biomed. Environm. Mass Spectrom.*, **18**, 801 (1989).
143. R. Guevremont and J. L. C. Wright, *Rapid Commun. Mass Spectrom.*, **1**, 12 (1987).
144. Y.-P. Tu, Y.-Z. Chen, S.-N. Chen, M.-L. Wang and Z.-Z. Jing, *Org. Mass Spectrom.*, **25**, 9 (1990).
145. R. B. Cole and J.-C. Tabet, *Org. Mass Spectrom.*, **26**, 59 (1991).
146. J. H. Banoub, G. Mackenzie, G. Descotes, R. W. Humble, G. Shaw, M. Becchi and D. Fraisse, *Biomed. Environm. Mass Spectrom.*, **19**, 97 (1990).
147. O. Laprevote, A.-M. Bui, B. C. Das, B. Charles and J.-C. Tabet, *Org. Mass Spectrom.*, **26**, 621 (1991).
148. D. Farcasiu and R. G. Pancirov, *Int. J. Mass Spectrom. Ion Processes*, **74**, 207 (1986).
149. J. L. Holmes and M. Sirois, *Org. Mass Spectrom.*, **25**, 481 (1990).
150. D. Wang, R. B. Squires and D. Farcasiu, *Int. J. Mass Spectrom. Ion Processes*, **107**, R7 (1991).
151. W. Tumas, R. F. Foster and J. I. Brauman, *J. Am. Chem. Soc.*, **110**, 2714 (1988).
152. A. J. Illies, *Org. Mass Spectrom.*, **25**, 73 (1990).
153. H. E. Audier, C. Monteiro, D. Berthomieu and J. Tortajada, *Int. J. Mass Spectrom. Ion Processes*, **104**, 145 (1991).
154. R. Barry, F. Strobel, M. Haas, D. Ridge and B. Munson, *Int. J. Mass Spectrom. Ion Processes*, **89**, 133 (1989).
155. K. V. Wood, D. J. Burinsky, D. Cameron and R. G. Cooks, *J. Org. Chem.*, **48**, 5236 (1983).
156. A. W. McMahon, F. Chadikun, A. G. Harrison and R. E. March, *Int. J. Mass Spectrom. Ion Processes*, **87**, 275 (1989).
157. R. W. Kondrat and T. H. Morton, *Org. Mass Spectrom.*, **26**, 410 (1991).
158. R. W. Kondrat and T. H. Morton, *J. Org. Chem.*, **56**, 952 (1991).
159. P. Meyrant, R. Flammang, A. Maquestiau, E. E. Kingston, J. H. Beynon and J. G. Liehr, *Org. Mass Spectrom.*, **20**, 479 (1985).
160. E. E. Kingston, J. H. Beynon, J. G. Liehr, P. Meyrant, R. Flammang and A. Maquestiau, *Org. Mass Spectrom.*, **20**, 351 (1985).
161. H. van der Wel, N. M. M. Nibbering, E. E. Kingston and J. H. Beynon, *Org. Mass Spectrom.*, **20**, 535 (1985).
162. E. E. Kingston, J. S. Shannon and M. J. Lacey, *Org. Mass Spectrom.*, **22**, 30 (1987).

CHAPTER 9

Electronic effects of ether and hydroxyl groups

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Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

I. INTRODUCTION

A. The Scope of this Chapter

Previous articles by the present contributor in *The Chemistry of Functional Groups* series have dealt with the electronic effects of the sulphonio group[1], of the sulphinyl and sulphonyl groups[2], of SOOH and related groups[3], and of amidino, guanidino and related groups[4]. In the last two cases[3,4] the amount of information available was very restricted. In the first two cases[1,2] there was copious information in the literature from which to draw, but fairly comprehensive surveys were practicable. The present case is quite different: the amount of material bearing on the electronic effects of hydroxyl and ether groups is enormous. It is therefore necessary to be selective both in the topics covered and in the illustrative examples provided. There will, of course, be considerable emphasis on work published in the last ten years or so, but much important information regarding the electronic effects of hydroxyl and ether groups is in much older papers; the more modern work can only be appreciated in the context of the older contributions. Further, articles of this kind present an opportunity for directing attention to important older papers which have either been generally overlooked or which tend now to be obscured in the welter of subsequent work.

An exception to the existence of copious information is provided by the third type of group featured in the present volume: there is only very little material on the electronic effects of peroxide groups. It seemed therefore appropriate to omit these from the title of this chapter, but the topic is dealt with briefly towards the end of the chapter (Section X.D).

The study of the directing and activating effects of the hydroxyl and ether groups played an important role in the early investigation of aromatic substitution, and hence of the development of the electronic theory of organic reactions. It is therefore appropriate that the present Introduction should include a specifically historical section.

The quantitative study of the electronic effects of hydroxyl and ether groups is naturally much concerned with the Hammett equation and its extensions. The next main section therefore contains a summary of the salient features of the Hammett equation and cognate linear free-energy relationships, along the general lines of corresponding sections in certain of the contributor's previous articles in the series[1,2]. This prepares the ground for a discussion of the electronic effects of hydroxyl and ether groups as manifested in substituent effects on the strengths of carboxylic and other acids; alicyclic, aliphatic and aromatic systems are covered. The discussion of aromatic systems leads to a further main section on the *ortho*-effect, in which electronic effects are moderated by steric and other influences, and a section on the cumulative effects of substituents in aromatic systems. This includes a discussion of steric enhancement of resonance, a phenomenon which is not so well known as steric inhibition of resonance. Later sections deal with the important topics of the role of hydroxyl and ether groups in studies of solvolysis reactions and of electrophilic aromatic substitution. The possibility of including unipolar substituents in Hammett and similar treatments has long been a matter of controversy and this problem is discussed with special reference to the O^- substituent. The emphasis of this chapter is deliberately 'chemical', but modern experimental and theoretical techniques have an important role in connection with substituent effects, so they are discussed briefly. Multiparameter treatments such as the Yukawa–Tsuno equation have long been important and further treatments have been devised in recent years. A section is therefore devoted to some of these, with an indication of the place of hydroxyl and ether groups therein. Finally, some of the material regarding substituent constants from earlier sections is summarized, with some extension particularly to groups that have been scarcely mentioned or have been omitted altogether in earlier parts of the chapter.

B. Historical Introduction

Soon after the structural relationships between the *ortho*-, *meta*- and *para*-disubstituted derivatives of benzene had been established, attempts to formulate orientation rules began. It was recognized early on that the substituent already present tended to direct further substitution either to the *ortho*- and *para*-positions or to the *meta*-position. The problem of formulating orientation rules was thus essentially to classify substituents as *ortho/para* or *meta* directing and then to correlate the two classes with chemical character. The earliest attempts at this were by Hübner[5] in 1875 and Noelting[6] in 1876. The latter actually suggested that *meta* directing groups were of a 'strongly acid character', which showed remarkable insight in view of the rudimentary ideas as to the nature of acidity that were prevalent at that time. Empirical orientation rules were gradually refined, notably by Armstrong (1887)[7], Crum Brown and Gibson (1892)[8], Vorländer (1902)[9] and Hammick and Illingworth (1930)[10]. By the time of the last-mentioned it was well recognized that the factor underlying the mode of action of a substituent was its electronic structure, as we shall see below. However, it should be mentioned in passing that prior to the development of the electronic theory of organic chemistry, Flürscheim had treated the 'alternation' characteristic of directing effects in terms of an electrical (but not 'electronic') concept of 'alternating chemical affinity' (1902 and later[11]).

In 1910 Holleman published a remarkable book about the direct introduction of substituents into benzene which brought together the then known information about aromatic substitution[12]. In this book there was for the first time an emphasis on the importance of quantitative measurements of the percentage yields of isomers in aromatic substitution and on the value of measurements of relative velocities of substitution under standard conditions. The latter led to the recognition that *ortho/para* orienting substituents tended to increase the rate of substitution compared with benzene, whereas *meta* orienting substituents decreased the reaction rate. Holleman was able to rank substituents in order of 'relative directing power', thus:

ortho/para directing groups:

$$\underset{\text{strongly directing}}{OH > NH_2 > NR_2 > NHAc > Cl > Br > Me > I}\ \text{weakly directing}$$

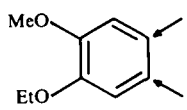
meta directing groups (all more weakly directing than the *ortho/para* directing groups)

$$COOH > SO_3H > NO_2$$

By World War I it was certainly well recognized that both OH and OR groups were strongly *ortho/para* directing and activating; indeed so activating that with some reagents and under some conditions, the reaction did not stop with the introduction of one further group but polysubstitution was prone to occur, e.g. phenol reacts with bromine water to give tribromophenol[13].

In the nineteen-twenties the examination of the directing effects of ether groups was prominent in the work of various research groups, particularly those involved in the controversies regarding electronic theories of organic chemistry which raged from 1924 for several years[14–16]. Thus in 1926–27 Robert Robinson and his associates published a series of papers on 'The Relative Directive Powers of Groups of the Forms RO and RR'N in Aromatic Substitution'. Part IV of the series by Allan, Oxford, Robinson and Smith[17] in 1926 contains the earliest fairly comprehensive statement of the main features of the electronic theory which Robinson was developing, this being given as necessary background to 'A Discussion of the Observations Recorded in Parts I, II, and III'. (There were in all eight Parts in the series). The 'observations' were of the percentages of isomers formed in the nitration of appropriate substrates, which were made the basis of a numerical scale of 'relative directing power'. Thus the percentages of isomers formed in

the nitration of **1** indicated that EtO has a higher directive power than MeO, and on a scale with MeO set at 100, EtO = 135. Further experiments in this catechol ether series found $Pr^iO = 150$, $Pr^nO = 128$, $Bu^nO = 123$, $PhCH_2O = 113$. Thus the effect of lengthening the alkyl chain appeared to reach a maximum at EtO. On the other hand, in the quinol ether series (**2**), MeO ≈ 100, EtO = 163, $Pr^nO = 180$, $Bu^nO = 186$, i.e. the directive power increased with chain length at least to Bu^nO[18]. The effect of substituents in the benzyl group of **3** was investigated and directive powers found as follows[17,19]: MeO = 100, $PhCH_2O = 113$, *m*-$MeOC_6H_4CH_2O = 92$, *p*-$ClC_6H_4CH_2O = 82$, *m*-$ClC_6H_4CH_2O = 69$, *m*- or *p*-$NO_2C_6H_4CH_2O = 67$.



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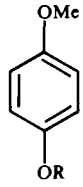

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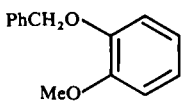

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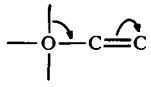
All the above and many related results were shown by Robinson to be accommodated by his electronic theory of organic chemistry, in which alkoxy- or hydroxy-substituted benzenes were classified as 'hetero-enoid' or 'crotenoid' systems, favouring the 'anionoid' reactivity of benzene through conjugative polarization represented as **4**. Robinson could not include OH in his numerical scale of directive power. 'The case of OH itself as against OMe cannot be considered on similar lines on account of the possibility of ionization or removal of the proton from OH by the reagent'[20,21].



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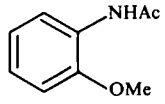
At around the same time Ingold and his collaborators began a series of publications on 'The Nature of the Alternating Effect in Carbon Chains'. Part I of the series appeared in 1925[22]; the series ended with Part XXXII in 1930[23]. Several of the earlier Parts were concerned with aspects of the controversy about electronic theories of organic chemistry which arose between Ingold and Robinson[14–16]. Ingold initially favoured the approach of Flürscheim[11], but by Part V[24] of the series was formulating reactivity in terms of electrons[16]. Part II[25] of the series was on 'The Directing Influence of the α-Methoxyvinyl Group in Aromatic Substitution'. The *ortho/para* directing nature of this group, $—C(OMe)=CH_2$, was considered by Ingold to constitute a test case in favour of Flürscheim's treatment, but Robinson was able to show that it could easily be accommodated by his electronic theory[26]. Parts III[27], V[24] and VI[28] of Ingold's series were much concerned with the 'relative directive efficiencies' of oxygen, nitrogen and fluorine, and the studies involved determining the percentages of the various isomers formed in the nitration of such substrates as **5** to **7**. As Ingold's version of the electronic theory developed, OR and OH groups were classified as $-I$ and $+T$ in their electronic effects, signifying electron attraction through the *Inductive Effect* and electron release by the *Tautomeric Effect*[29]. Later the latter was subdivided into the *Mesomeric Effect M* (polarization) and *Electromeric Effect E* (polarizability)[30]. Ingold recognized early on that the $+T$ effect of $—O^-$ would be enormously augmented by the negative charge,

in accord with the long known rapid and exclusive *ortho/para* substitution of phenols in alkaline solution[31].



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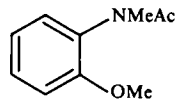

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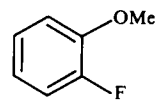
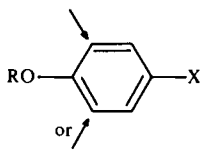


(7)

Work of a rather different nature involving the directive effects of alkoxy groups was pursued in the nineteen-twenties by Orton and colleagues, and after Orton's death in 1930 was continued by Brynmor Jones in a long series of papers on 'Halogenation of Phenolic Ethers and Anilides'[32,33]. This work concerned the measurement of the velocities of halogenation (usually chlorination) of many series of phenolic ethers in 99% acetic acid. In these studies the complication of isomer formation in electrophilic aromatic substitution was eliminated by using substrates in which either the *para* or the *para* and one *ortho* position was already occupied by a group such as CH_3, Cl, NO_2, etc. In this way the velocity of substitution was brought within the range of convenient measurement and only one product was obtained, as in **8** or **9**.



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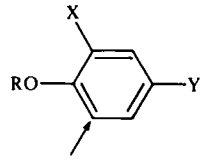

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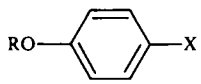
Of general interest for chemical kinetics in this extensive work was the demonstration of the additive effects of the various substituents involved and the finding that the effects of substituents on reaction velocity were exerted largely through the energy of activation rather than the non-exponential factor of the Arrhenius equation[33]. Much information was obtained on the activating influences of the various alkoxy groups. Thus from the



X = F, Cl, Br, or COOH

(10)

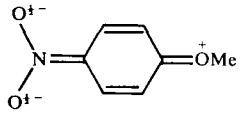
chlorination of series **10**, the activating effects of the groups OR (as reaction velocities relative to OMe as 100) were found to be[33]:

R =	Me	Et	Pr^n	Pr^i	$PhCH_2$
	100	199	222	440	68

With lengthening of the alkyl chain to between 4 and 7 carbon atoms, the activating effect reached a limit at *ca* 220, but appeared to diminish slightly for very long chains, e.g. to 201 at $C_{16}H_{33}$. The adverse effect of Ph manifested above in $PhCH_2$ diminished with the introduction of further CH_2 groups, thus:

R =	Me	$PhCH_2$	$Ph(CH_2)_2$	$Ph(CH_2)_3$
	100	68	119	171

Hydroxyl and ether groups also played an important role in the elucidation of structural effects through dipole moment measurements in the nineteen-thirties[34]. There was great interest in comparing the dipole moments of corresponding aliphatic and aromatic compounds, e.g. MeOMe and PhOMe. It was found that these frequently differed somewhat, in a direction which appeared to confirm the occurrence in the aromatic compound of a movement of electrons corresponding to the mesomeric effect that had been postulated in the electronic theory of organic chemistry. This led to the concept of 'mesomeric moment' and various ways of estimating this from observed dipole moments were devised. Thus Groves and Sugden[35] suggested values of 0.40D for the mesomeric moment of PhOMe and of 1.2D for that of PhOH. (Observed dipole moments are usually between 1D and 4D.) It was found, however, that mesomeric moments associated with a given group may vary when other substituents are present in the molecule. Bennett and Glasstone[36] measured the dipole moments of several *para*-substituted anisoles (among various series of compounds) and compared the experimental values with those calculated from the corresponding monosubstituted compounds. In the case of *para*-nitroanisole, the observed dipole moment was 4.74D, compared with a calculated value of 3.47D, corresponding to enhanced mesomeric effects through participation of the canonical structure **11** in the resonance hybrid. However, much of the way in which dipole moment measurements were interpreted in the nineteen-thirties is now regarded as over-simplified[37], but there was great interest at the time in the relationship of the signs of the mesomeric moments to the *ortho/para* or *meta* orienting influence of the groups, i.e. whether electrons were moving from the substituent into the ring or *vice versa*[34].



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II. THE HAMMETT EQUATION[38]

A. Introduction

The Hammett equation is the best-known example of a linear free-energy relationship (LFER), that is, an equation which implies a linear relationship between free energies (Gibbs energies) of reaction or activation for two related processes[39]. It describes the influence of polar *meta*- or *para*-substituents on reactivity for side-chain reactions of benzene derivatives.

The Hammett equation (1937)[40–44] takes the form of equation 1 or 2:

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

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

The symbol k or K is the rate or equilibrium constant, respectively, for a side-chain reaction of a *meta*- or *para*-substituted benzene derivative, and k^0 or K^0 denotes the statistical quantity (intercept term) approximating to k or K for the 'parent' or 'unsubstituted' compound. The *substituent constant* σ measures the polar (electronic) effect of replacing H by a given substituent (in the *meta*- or *para*-position) and is, in principle, independent of the nature of the reaction. The *reaction constant* ρ depends on the nature of the reaction (including conditions such as solvent and temperature) and

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

Substituent	σ_m	σ_p	σ_p^+	σ_p^-
Me	−0.07	−0.17	−0.31	—
OMe	0.12	−0.27	−0.78	—
SMe	0.15	0.00	−0.60	0.21
OH	0.12	−0.37	−0.92	—
SH	0.25	0.15	—	—
NMe_2	−0.15	−0.63	−1.7	—
F	0.34	0.06	−0.07	—
Cl	0.37	0.23	0.11	—
CF_3	0.43	0.54	—	0.65
CN	0.56	0.66	—	0.88
NO_2	0.71	0.78	—	1.24
CO_2H	0.37	0.45	—	0.73

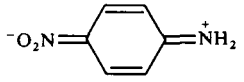
[a]These values, drawn from various sources, are presented solely for illustration. The table should not itself be used uncritically as a source of σ values for correlations. See rather References 41 and 45. The values for OMe and OH will be discussed later in this chapter.

measures the susceptibility of the reaction to polar effects. Hammett chose the ionization of benzoic acids in water at 25 °C as a standard process. For this, ρ is defined as 1.000, and the value of σ for a given substituent is then $\log (K_a/K_a^0)$, where K_a is the ionization constant of the substituted benzoic acid and K_a^0 that of benzoic acid itself. Selected values of σ for well-known substituents are given in Table 1. They are readily interpreted qualitatively in simple electronic terms, i.e. through the inductive (I) effect and the resonance or conjugative (R) effect.

Jaffé[46] showed that while many rate or equilibrium data conform well to the Hammett equation (as indicated by correlation coefficient), many such data are outside the scope of the equation in its original form and mode of application. Deviations are commonly shown by *para*-substituents with considerable $+R$ or $-R$ effect[47]. Hammett himself found that *p*-NO_2 ($+R$) showed deviations in the correlation of reactions of anilines or phenols. The deviations were systematic in that a σ value of *ca* 1.27 seemed to apply, compared with 0.78 based on the ionization of *p*-nitrobenzoic acid. Other examples were soon discovered and it became conventional to treat them similarly in terms of a 'duality of substituent constants'.

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

In the ionization of the *p*-nitroanilinium ion, the free base is stabilized by delocalization of electrons involving the canonical structure **12**. An analogous structure is not possible for the *p*-nitroanilinium ion. In the ionization of *p*-nitrophenol, analogous delocalization is possible in both phenol and phenolate species, but is more marked in the ion. Thus,



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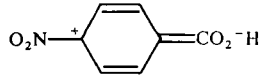

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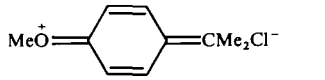
in both the aniline and the phenol system *p*-NO_2 is effectively more electron-attracting than in the ionization of benzoic acid, where the reaction centre is incapable of a $-R$ effect, and indeed shows a small $+R$ effect (**13**).

An example of a reaction series in which large deviations are shown by $-R$ *para*-substituents is provided by the rate constants for the solvolysis of substituted *t*-cumyl chlorides, $ArCMe_2Cl$[48]. This reaction follows an S_N1 mechanism, with intermediate formation of the cation $ArCMe_2^+$. A $-R$ *para*-substituent such as OMe may stabilize the activated complex, which resembles the carbocation–chloride ion pair, through delocalization involving structure **14**. Such delocalization will clearly be more pronounced than in the species involved in the ionization of *p*-methoxybenzoic acid, which has a reaction centre of feeble $+R$ type (**15**). The effective σ value for *p*-OMe in the solvolysis of *t*-cumyl chloride is thus -0.78, compared with the value of -0.27 based on the ionization of benzoic acids.



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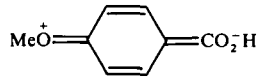

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The special substituent constants for $+R$ *para*-substituents are denoted by σ^-, and those for $-R$ *para*-substituents are denoted by σ^+ [48]. They are based respectively on the reaction series discussed above. Selected values are given in Table 1. Characteristic σ^- or σ^+ values are sometimes distinguished for *meta*-substituents also, but only for a minority of substituents which show very marked $+R$ or $-R$ effects do these differ significantly from ordinary σ values. The range of applicability of the Hammett equation is greatly extended by means of σ^- and σ^+, notably to nucleophilic (by σ^-) and to electrophilic (by σ^+) aromatic substitution.

However, the 'duality of substituent constants' and the attempt to deal with cross-conjugation by selecting σ^+, σ or σ^- in any given case is somewhat artificial. The contribution of the resonance effect of a substituent relative to its inductive effect must in principle vary continuously as the electron-demanding quality of the reaction centre is varied, i.e. whether it is electron-rich or electron-poor. A 'sliding scale' of substituent constants would be expected for each substituent having a resonance effect and not just a pair of discrete values: σ^+ and σ for $-R$, or σ^- and σ for $+R$ substituents[49].

B. Multiparameter Extensions[43,50,51]

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

In the Yukawa–Tsuno equation (1959)[52] (equation 3), the sliding scale is provided by multiple regression on σ and $(\sigma^+ - \sigma)$ or $(\sigma^- - \sigma)$, depending on whether the reaction is more or is less electron-demanding than the ionization of benzoic acid. (There is a corresponding form of the equation for equilibria.) The quantity $r^{\pm}$ gives the contribution of the enhanced $\pm R$ effect in a given reaction. (The equation was modified in 1966[53] to use σ^0 instead of σ values, see below, but the essential principles are unaltered.)

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

In the form of treatment developed by Taft and his colleagues since 1956[54–56], the Hammett constants are analysed into inductive and resonance parameters, and the sliding scale is then provided by multiple regression on these. Equations 4 and 5 show the basic relationships, the suffix BA signifying benzoic acid.

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

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

The σ_I scale is based on alicyclic and aliphatic reactivities (see below), and the factor 0.33 in equation 4 is the value of a 'relay coefficient', α, giving the indirect contribution of the resonance effect to σ_m. However, the ionization of benzoic acids is not regarded as an entirely satisfactory standard process, since it is subject to some slight effect of cross-conjugation (see structure **15** above). Consideration of 'insulated series', not subject to this effect, e.g. the ionization of phenylacetic acids, is used as the basis of a σ^0 scale, which can be analysed by equations 6 and 7. (Note the different value of α.) By a different procedure Wepster and colleagues[49] devised an analogous σ^n scale (n = normal, i.e. free from the effects of cross-conjugation). Analysis of σ^+ and σ^- constants correspondingly involves σ_R^+ and σ_R^-.

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

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

Multiple regression on σ_I and σ_R-type parameters employs the 'dual substituent-parameter' equation, which may be written as in equation 8[58]. (The combining of the k and k^0 terms implies that there is no intercept allowed, and k^0 is now the actual value for the parent system, cf below.)

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

For any given reaction series the equation is applied to *meta*- and *para*-substituents separately, and so values of ρ_I and ρ_R characteristic both of reaction and of substituent position are obtained. The various σ_R- type scales are linearly related to each other only approximately. In any given application the scale which gives the best correlations must be found[59].

Values of σ^0, σ_I and σ_R-type parameters for certain substituents are given in Table 2. It should be mentioned that Exner has developed a slightly different procedure for analysing sigma values[60] into inductive and resonance components[43,44,61] (Section IX.B).

A slightly different procedure for carrying out multiple regression on σ_I and σ_R-type parameters employs the 'extended Hammett equation' of Charton[62], which may be written as in equation 9. For the substituent X, Q is the absolute value of the property to be correlated ($\log k$ or $\log K$ in the case of reactivity), i.e. not expressed relative to X = H, h is introduced as the appropriate intercept term and the regression coefficients are α and β. (Charton has used various symbols at various times.)

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

The correlation analysis of spectroscopic properties in terms of σ_I and σ_R-type parameters has been very important. Substituent effects on ^{19}F NMR shielding in

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

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

[a]See the footnote to Table 1.

fluorobenzenes have been studied in great detail by Taft and colleagues[57,63,64]. For δ_m^F linear regression on σ_I is on the whole satisfactory, but a term in σ_R^0 with a small coefficient is sometimes introduced. The correlation analysis of δ_p^F, however, requires terms in both σ_I and σ_R-type parameters, with σ_R^0 being widely applicable. Many new values of these parameters have been assigned from fluorine chemical shifts. In recent years there has also been extensive use of correlation analysis of ^{13}C NMR data[65,66].

The correlation analysis of infrared data has been much examined by Katritzky, Topsom and colleagues[67,68]. Thus the intensities of the ν_{16} ring-stretching bands of mono- and di-substituted benzenes may be correlated with the σ_R^0 values of the substituents and these correlations may be used to find new σ_R^0 values.

Finally, in this account of multiparameter extensions of the Hammett equation, we comment briefly on the origins of the σ_I scale. This had its beginnings around 1956[56] in the σ' scale of Roberts and Moreland[69] for substituents X in the reactions of 4-X-bicyclo[2.2.2]octane-1 derivatives. However, at that time few values of σ' were available. A more practical basis for a scale of inductive substituent constants lay in the σ^* values for XCH_2 groups derived from Taft's analysis of the reactivities of aliphatic esters into polar, steric and resonance effects[56,70–72]. For the few σ' values available it was shown that σ' for X was related to σ^* for XCH_2 by the equation $\sigma' = 0.45\sigma^*$. Thereafter the factor 0.45 was used to calculate σ_I values of X from σ^* values of XCH_2[73]. These matters will be referred to again later in this chapter, and other methods of determining σ_I values will also be mentioned.

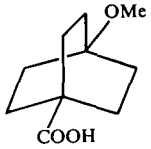
III. SUBSTITUENT EFFECTS ON THE STRENGTHS OF CARBOXYLIC AND OTHER ACIDS[74]

A. Alicyclic and Aliphatic Systems

1. *Alkoxy groups*

The greater part of the information available concerns the methoxy group and this will therefore be considered first.

The simplest indicator of the electronic effect of a substituent X is its influence on the ionization constant of an organic acid into which it is substituted. For the least complicated behaviour, the group should not be conjugated with the molecular skeleton and should be somewhat remote from the acidic centre. The change in acid strength produced by X is conveniently expresssed as ΔpK_a, defined as $(pK_a)_H - (pK_a)_X$, so that an increase in acid strength is associated with a positive value of ΔpK_a. In Table 3 the ΔpK_a value of 0.47 for 4-methoxybicyclo[2.2.2]octane-1-carboxylic acid (**16**) and of 1.81 for the 4-methoxyquinuclidinium ion (**17**) are clear indications of the electronegative or electron-attracting nature of OMe. The influence of this reaches the acidic centre either by induction through the bonds of the molecular skeleton or through the electric field of the substituent as moderated by the dielectric behaviour of the molecular cavity and the solvent. The respective roles of these two modes of transmission have long been a matter of controversy[75]. Both are 'inductive' in the most general meaning of this term



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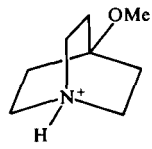

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TABLE 3. The influence of the methoxy group on the strengths of alicyclic and aliphatic acids[74]

Acid	Solvent	Temp. (°C)	pK_a X = H	pK_a X = OMe	ΔpK_a[a]	σ_I[b] (calc)
1. 4-X-Bicyclo[2.2.2]octane-1-carboxylic acid	50% w/w EtOH–H_2O	25	6.87	6.40	0.47	0.300
2. 4-X-Quinuclidinium ion	H_2O	25	11.12	9.31	1.81	0.326
3. *trans*-4-X-Cyclohexane-1-carboxylic acid	H_2O	24.91	4.90	4.66	0.24	0.321
4. *trans*-4-X-Cyclohexane-1-carboxylic acid	50% v/v EtOH–H_2O	24.91	6.40	6.02	0.38	0.328
5. XCH_2COOH	H_2O	25	4.756	3.570	1.186	0.301
6. XCH_2COOH	50% w/w EtOH–H_2O	25	5.84	4.79	1.05	0.282

[a] $\Delta pK_a = (pK_a)_H - (pK_a)_{OMe}$.
[b] From the appropriate regression equations in Charton's review[78,80].

in physics and we shall continue the traditional practice of describing them collectively as the 'inductive effect'.

The data in Table 3 for the behaviour of the OMe group in the 4-position of cyclohexane-1-carboxylic acid also demonstrate the electron-attracting inductive effect, although there may be some acid-strengthening contribution from converting the parent acid which contains appreciable *ax*-COOH in $eq \rightleftharpoons ax$ equilibrium into the essentially diequatorial *trans*-4-methoxycyclohexane-1-carboxylic acid[76]. The pK_a values of acetic acid and methoxyacetic acid (Table 3) also show the electron-attracting inductive effect of OMe, although with the substituent so close to the reaction centre, some contribution of a steric effect cannot be ruled out. However, the behaviour of substituted acetic acids containing very bulky alkyl groups shows that a steric effect in that situation is acid-weakening and involves the inhibition of solvation of the carboxylate ion[77].

The data for the bicyclooctane system are the basis for primary σ_I values according to Charton[78], calculated through equation 10[79].

$$\sigma_I = \Delta pK_a/1.56 \tag{10}$$

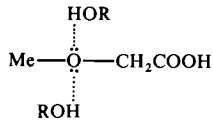
The resulting value for OMe is 0.300, as in the last column of Table 3, cf COOEt, 0.30; CF_3, 0.40; Cl, 0.47. These values and values for various other substituents are used by Charton to correlate data for the other systems featured in Table 3, through the general linear regression equation 11[80].

$$pK_a = L\sigma_I + h \tag{11}$$

OMe shows slight deviations from these regressions as indicated by the back-calculated values of σ_I in Table 3. (Note: data for OMe have themselves contributed to the individual regressions with the value $\sigma_I = 0.30$.) On the whole, however, the value of 0.30 seems reasonably applicable throughout these systems. It should be noted that this value is rather higher than the value derived by Taft[56] from the analysis of substituent effects in aliphatic ester reactions. This yielded $\sigma^* = 0.52$ for CH_2OMe, which gave $\sigma_I = 0.23$ for OMe by application of the equation $\sigma_I = 0.45\sigma^*$ (see Section II.B). In more recent years Taft has come to favour a value of around 0.30, as determined in various ways, some of which are mentioned later in this chapter[81].

The bimolecular reaction of carboxylic acids with diazodiphenylmethane (DDM) involves a slow proton transfer to form a diphenylmethanediazonium carboxylate ion-pair. The reaction has been greatly used during the past 40 years as a kinetic probe

of acidity[82]. The value $\sigma_I = 0.30$ for OMe seems also to express fairly well the effect of this substituent on $\log k$ (second-order rate coefficient) for the reaction of acetic acid with DDM at 30 °C in MeOH, EtOH, Pr^iOH, Bu^tOH, $MeO(CH_2)_2OH$ or $BuO(CH_2)_2OH$ as solvents[83]. These data are considered by Charton in his review[78] and back-calculation from the regressions[84] gives values of σ_I for OMe of 0.308, 0.295, 0.290, 0.274, 0.276 and 0.287, respectively. There thus appears to be a slight tendency for the value of σ_I to be lower in the less polar alcohols. This could be connected with a change in the hydrogen-bonding of alcohol molecules to the OMe group in $MeOCH_2COOH$, as in **18**. Hydrogen-bonding in protic solvents, particularly water and aqueous organic mixtures, may be seen as a factor enhancing the electron-attracting effect of OMe.



(18)

For the reaction of DDM with substituted acetic acids in several aprotic solvents at 30 °C, OMe shows significant deviations from the regressions in Charton's review[78], the back-calculated σ_I values in dimethyl sulphoxide, ethyl acetate and toluene being 0.258, 0.213 and 0.257, respectively[85]. (The data for the OMe compound in ethyl acetate had apparently been omitted from the regression as obviously deviant. It should be mentioned that in the case of ethyl acetate as solvent, the observed second-order rate coefficients vary markedly with concentration. The rate coefficients subjected to correlation analysis were measured at a standard concentration of carboxylic acid.) These low values of σ_I may be due to the reduced role of MeO–solvent hydrogen-bonding in the aprotic solvents.

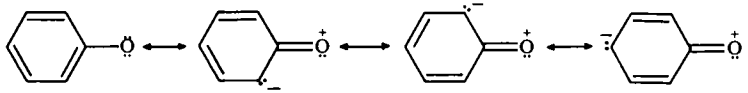
Rather old data are available for the pK_a values in water at 25 °C of the series of acids $MeO(CH_2)_nCOOH$, where $n = 1$ to 4[86]. The values of n, pK_a are: 1, 3.53; 2, 4.46; 3, 4.68; 4, 4.72. We may regard these values as a coherent body of data suitable for internal comparison. They show clearly the increasing 'damping' effect of the $(CH_2)_n$ chain as n is increased. In the limit the pK_a value will tend towards that of a long-chain fatty acid between 4.8 and 4.9. A decremental factor of about 2.7 per CH_2 has been suggested for the effect on the σ_I values of polar substituents[56]. On the basis of $\sigma_I = 0.30$ for OMe and the above factor, σ_I for $MeOCH_2$ should be about $0.30/2.7 = 0.11$. Such a value is in fact indicated by the pK_a value of 10.46 for the 4-methoxymethylquinuclidinium ion, when inserted in the appropriate regression equation in Charton's review[80].

Further old data from the same source[86] are available for the acids $ROCH_2COOH$ in water at 25 °C, with R = Me, Et, Pr^n, Bu^n and Bu^i. The pK_a values are 3.53, 3.60, 3.66, 3.66 and 3.67, respectively, and as before we may reasonably treat these values as a coherent body of data suitable for internal comparison. The values suggest that the inductive effect of alkoxy groups decreases slightly with the size of the alkyl group, but rapidly comes to a limit. The total decrease would amount to no more than 0.03 units of σ_I. Such a decrease would at one time have been attributed to the electron-releasing inductive effect of alkyl groups increasing with size, but might now be attributed rather to increased polarizability (see later in this chapter, Section IX.D and E).

2. *Phenoxy groups*

Not nearly so many data are available for phenoxy as for methoxy. The pK_a value of phenoxyacetic acid in water at 25 °C is 3.171, cf 4.756 for acetic acid. When inserted into the appropriate regression equation in Charton's review[80], this pK_a value yields

$\sigma_I = 0.40$, i.e. OPh is somewhat more electron-attracting than OMe, for which $\sigma_I = 0.30$. This may be attributed partly to sp^2 hybridized carbon being slightly electron-attracting relative to sp^3 hybridized carbon, but probably a more important factor is the delocalization of the unshared pairs of electrons of the oxygen atom of PhO into the benzene ring, as in **19**, thereby increasing the ability of the oxygen to attract electrons from the rest of the molecule.



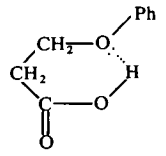
(19)

The value of $\sigma_I = 0.40$ for phenoxy seems fairly satisfactory for the correlation analysis of data on the pK_a values of substituted acetic acids in aqueous organic solvents[80]. This seems also to be true for the reactions of substituted acetic acids with DDM in a variety of protic and aprotic solvents (cf above)[83–85], i.e. any variation of σ_I with solvent for phenoxy is less marked than for methoxy. The delocalization of the unshared pairs of electrons of the oxygen atom into the benzene ring should presumably reduce interaction with solvents through hydrogen-bonding. The value of σ_I for OPh suggested originally by Taft[56] on the basis of $\sigma_I = 0.45\sigma^*$ was 0.38.

pK_a values in water at 25 °C for various acids $XC_6H_4OCH_2COOH$ have been measured[74]. These can be the basis of σ_I values for groups XC_6H_4O. Thus Charton[78] tabulates values of 0.47 for 4-$NO_2C_6H_4O$ and of 0.39 for 4-$MeOC_6H_4O$, but values of σ_I for more than twenty further substituents could be calculated from the available pK_a data. The same data may also be treated through the Hammett equation in connection with σ^0 values (see Section III.C.1).

pK_a data (water, 25 °C) are available for a few ring-disubstituted phenoxyacetic acids[74]. The value of 3.356 for 2,6-$Me_2C_6H_3OCH_2COOH$ is particularly interesting; on insertion in the appropriate regression equation[80] it gives $\sigma_I = 0.354$ for 2,6-$Me_2C_6H_3O$, cf 0.40 for OPh and 0.386 for 2-MeC_6H_4O. The relatively large reduction in σ_I by 2,6-Me_2 compared with 2-Me may suggest that there is some steric inhibition of resonance of the type indicated in **19** above when flanking methyl groups are introduced. (See later in this chapter for further consideration of steric inhibition, and also steric enhancement of resonance, Section V.C.)

The pK_a value for 3-phenoxypropanoic acid in water at 25 °C was found by Bowden and coworkers to be 4.32[83]. Substituted into the appropriate regression equation[80] this gives $\sigma_I = 0.12$ for $PhOCH_2$. Very similar values may be calculated from pK_a determinations in 50% w/w EtOH–H_2O and 80% w/w 2-methoxyethanol–H_2O by the same authors[83]. This is slightly lower than may be calculated by applying the methylene decremental factor of 2.7 to the σ_I value for OPh, i.e. $0.40/2.7 = 0.15$[56]. As in the case of OPh itself, there is little indication of any solvent dependence of σ_I for $PhOCH_2$ being manifested in the reaction of the substituted acetic acids with DDM[83], except possibly in the aprotic solvents ethyl acetate and toluene[85]. In such rather non-polar solvents, however, internal hydrogen-bonding could intervene as in **20**. This would reduce reactivity towards DDM and thus mimic a decrease in σ_I.

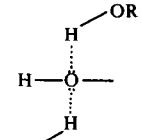


(20)

3. Hydroxyl groups

The substitution of 4-OH into bicyclo[2.2.2]octane-1-carboxylic acid reduces the pK_a value by 0.37 (Table 4), cf 0.47 for OMe (Table 3). Thus in this situation OH appears to be slightly less electron-attracting than OMe, and Charton[78] uses the data to calculate $\sigma_I = 0.24$ for OH, cf 0.30 for OMe. Comparison of the ΔpK_a columns of Tables 3 and 4 indicates that in the various systems OH tends to be slightly less electron-attracting than OMe, but back-calculation from the regression equations in Charton's review[80] gives σ_I values that are on the whole rather greater than the value defined above from the bicyclooctane system. Taft's original value from the analysis of ester reactions was 0.27[56].

It must be recognized that the electronic behaviour of OH is liable to be more complicated by interference from solvent than that of OMe, for in addition to hydrogen-bonding of solvent *OH* to substituent *O*, there is the possibility of hydrogen-bonding of solvent *O* to substituent *OH*, e.g. **21** and **22**. As we have seen in Section III.A.1, the former type of hydrogen-bonding may be deemed a factor tending to enhance electron-attracting power, but the latter type of hydrogen-bonding will tend to reduce it. Thus the inductive effect of OH as indicated by its influence as a substituent on the acidity of various substrates in various solvents (water, aqueous organic solvents, one-component alcohols, aprotic solvents) may vary in quite a complex way, particularly in comparison with the behaviour of OMe.



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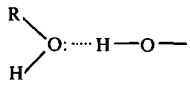


(22)

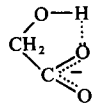
In this connection the behaviour of the acids $HOCH_2COOH$ and $MeOCH_2COOH$ in reactivity towards DDM is particularly interesting[83]. In MeOH, EtOH and Pr^{i}OH the methoxy acid is the more reactive, as one might expect from the acidity data in Tables 3 and 4. However, in Bu^{t}OH the hydroxy acid is the more reactive. This corresponds to a slight rise in effective σ_I of OH through the series of alcohols (0.275,

TABLE 4. The influence of the hydroxyl group on the strengths of alicyclic and aliphatic acids[74]

Acid	Solvent	Temp. (°C)	pK_a X = H	pK_a X = OH	ΔpK_a[a]	σ_I[b] (calc)
1. 4-X-Bicyclo[2.2.2]octane-1-carboxylic acid	50% w/w	25	6.87	6.50	0.37	0.237
2. 4-X-Quinuclidinium ion	H_2O	25	11.12	9.44	1.68	0.301
3. *trans*-4-X-Cyclohexane-1-carboxylic acid	H_2O	24.91	4.90	4.69	0.21	0.281
4. *trans*-4-X-cyclohexane-1-carboxylic acid	50% v/v EtOH–H_2O	24.91	6.40	6.08	0.32	0.273
5. XCH_2COOH	H_2O	25	4.756	3.83	0.926	0.237
6. XCH_2COOH	50% w/w EtOH–H_2O	25	5.84	4.86	0.98	0.267

[a] $\Delta pK_a = (pK_a)_H - (pK_a)_{OH}$.
[b] From the appropriate regression equations in Charton's review[78,80].

0.273, 0.280, 0.289[84]), while σ_I for OMe falls (0.308, 0.295, 0.290, 0.274[84]). Presumably the distinctive behaviour of OH as a substituent is connected with changes in the hydrogen-bonding of *O*H of the alcoholic solvent to O*H* of $HOCH_2COOH$. In $2\text{-}MeO(CH_2)_2OH$ as solvent the hydroxy acid is the more reactive, but in $2\text{-}BuO(CH_2)_2OH$ the situation is reversed. Results for two aprotic solvents show an interesting contrast: in DMSO the methoxy acid is the more reactive, but in ethyl acetate the rate constants are in the ratio 4.5:1 in favour of the hydroxy acid. It is probable that in ethyl acetate the reaction of the hydroxy acid with DDM is facilitated by internal hydrogen-bonding in the nascent carboxylate ion, as in **23**. (Cf the later discussion of the reaction of salicylic acid with DDM, Section IV.D.) The rate of reaction of PhCH(OH)COOH with DDM in ethyl acetate is also subject to peculiar enhancement[83].



(23)

The pK_a value for $4\text{-}HOCH_2$-bicyclo[2.2.2]octane-1-carboxylic acid gives a value of $\sigma_I = 0.045$ for CH_2OH, which indicates rather severe damping by the methylene group[79]. Further, the pK_a value of β-lactic acid is 4.51 in water at 25 °C, and when inserted into Charton's regression equation[80] this gives a σ_I value of 0.07, likewise rather low. The quinuclidinium ion system gives 0.11, which seems more reasonable in relation to the value of σ_I for OH of 0.30 from the same system (Table 4). This is the value tabulated by Charton[78], who regards it as confirmed by consideration of the pK_a value of $HOCH_2CH_2NH_3^+$. Charton also gives a value of σ_I of 0.06 for $HO(CH_2)_2$ on the basis of the substituted methylammonium system. Thus there seems to be some confusion as to the damping effect of methylene groups on the electron-attracting power of OH.

B. Aromatic Systems

1. Alkoxy groups in benzoic acid

As in the case of Section III.A.1 the greater part of the information available concerns the methoxy group and this will therefore be considered first.

The pK_a values in water at 25 °C of *m*-methoxybenzoic acid and *p*-methoxybenzoic acid were measured accurately (conductivity method) by Dippy and his colleagues in the nineteen-thirties as 4.088 and 4.471, respectively, compared with 4.203 for benzoic acid itself[87]. On the basis of these values Hammett[88] proposed σ values of 0.115 for *m*-OMe and -0.268 for *p*-OMe respectively (see Section II.A). During half a century these values have often been slightly modified, sometimes by rounding to the second place of decimals as 0.11 or 0.12 and -0.27, respectively, and sometimes undergoing changes in the second place of decimals as a result of considering later work on the pK_a values, e.g. 0.10 and -0.28, respectively. In a later Section of this chapter (X.B.1) we shall mention a critical assessment of the σ constants based on determinations of pK_a by various authors using various experimental methods. For the present discussion the values of 0.12 and -0.27, respectively, will be satisfactory.

The acid-weakening effect of *p*-OMe is attributed to the influence of the electron-attracting inductive effect ($+I$) being outweighed by the electron-releasing mesomeric or resonance effect ($-R$)[47]. The small acid-strengthening effect of *m*-OMe is explained as the resultant of the inductive effect and a small 'relayed' influence of the resonance effect. If σ_p is regarded simply as a sum of σ_I and σ_R (Section II.B) and σ_I is

taken as 0.30 (Section III.A.1.), a value of -0.57 is indicated for σ_R. The relay factor of 0.33 for the influence of the resonance effect accounts nicely for the value of σ_m as $\sigma_I + 0.33\sigma_R = 0.30 - 0.19 = 0.11$, cf 0.12 above.

The values $\sigma_m = 0.12$ and $\sigma_p = -0.27$ are certainly fairly successful at expressing through the Hammett equation the effect of OMe on the ionization of benzoic acid in various aqueous–organic media and on the rates of reactions of benzoic acids with diazodiphenylmethane (DDM) in various alcohols as solvents. However, careful analysis of the data for some of these systems reveals slight but systematic deviations, which indicate that the electronic effects of *m*- and *p*-OMe show a small solvent dependence (cf the behaviour of OMe as a substituent in aliphatic systems above).

We will take the ionization of substituted benzoic acids in aqueous ethanol as an example. The behaviour of *p*-OMe stands out most clearly when the data for *para*-substituted benzoic acids are treated by the extended Hammett equation (Section II.B) in terms of σ_I and σ_R, rather then by the original simple equation. When the pK_a data (25 °C) for nine acids *p*-XC_6H_4COOH (X = H, Me, NO_2, F, Cl, Br, I, CN, OMe) in 75% v/v aqueous ethanol[89] are subjected to such treatment, expression 12 is obtained:

$$pK_a = 6.274 - 1.778\,\sigma_I - 1.432\,\sigma_R \qquad (12)$$

$$(\pm 0.042) \quad (\pm 0.043)$$

$$n = 9,\ R = 0.9990,\ s = 0.0285,\ \psi = 0.0540$$

(In this multiple regression and later multiple regressions, Charton's values of σ_I and σ_R are used[78]; n = number of data points, R = multiple correlation coefficient, s = standard error of estimate and ψ = Exner's statistic of goodness of fit[90,91]. The $\pm$ values in parentheses are standard errors of regression coefficients.)

From equation 12 the back-calculated value of pK_a for X = OMe is 6.57, compared with the observed value of 6.61. Thus a slight deviation of *p*-OMe is indicated. If the data for *p*-OMe are excluded from the regression, equation 13 is obtained:

$$pK_a = 6.275 - 1.769\,\sigma_I - 1.368\,\sigma_R \qquad (13)$$

$$(\pm 0.030) \quad (\pm 0.040)$$

$$n = 8,\ R = 0.9994,\ s = 0.0204,\ \psi = 0.0420$$

The insertion of $\sigma_I = 0.30$ and $\sigma_R = -0.58$[78] for OMe into this expression gives $pK_a(\text{calc}) = 6.54$, which is 0.07 less than $pK_a(\text{obs})$. Such a deviation appears to be significant, and would be accounted for if, in 75% ethanol, σ_I for OMe is slightly less positive or σ_R more negative than in water or highly aqueous organic mixtures, or (which seems more likely) a combination of these changes might occur. It was suggested earlier (Section III.A.1) that hydrogen-bonding of H_2O to OMe might enhance the electron-attracting inductive effect. For OMe bonded in an aromatic system, hydrogen-bonding of H_2O to OMe may be seen as tending to reduce electron delocalization into the ring, i.e. the $-R$ effect. It must be emphasized that, in contrast, when data for the same acids in 50% v/v aqueous ethanol[89] are analysed as above, no such discrepancy for OMe appears. On the other hand, more marked discrepancies appear on analysis of data for *para*-substituted benzoic acids in various low alcohols. For instance, for seven acids *p*-XC_6H_4COOH (X = H, Me, F, Cl, Br, NO_2, OMe) in ethanol at 25 °C, equation 14 is obtained:

$$pK_a = 10.098 - 1.698\,\sigma_I - 1.504\,\sigma_R \qquad (14)$$

$$(\pm 0.084) \quad (\pm 0.092)$$

$$n = 7,\ R = 0.9968,\ s = 0.0546,\ \psi = 0.1062$$

The calculated deviation for OMe is 0.06. When OMe is excluded from the regression, we obtain equation 15:

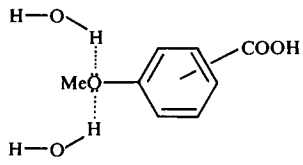
$$pK_a = 10.101 - 1.675\,\sigma_I - 1.384\,\sigma_R \qquad (15)$$
$$(\pm 0.063) \quad (\pm 0.088)$$
$$n = 6,\ R = 0.9982,\ s = 0.0399,\ \psi = 0.0848$$

pK_a(calc) for OMe is 10.40, compared with pK_a(obs), 10.52. A similar discrepancy may be demonstrated from data for the same acids in butanol: pK_a(calc) = 8.87, pK_a(obs) = 8.97.

For *m*-OMe there is evidence for a solvent effect from the behaviour of this substituent in the reaction of substituted benzoic acids with DDM. Aslam and collaborators[92] studied the kinetics of this reaction in various alcohols and a small number of aprotic solvents. After appropriate estimations of ρ values, the rate coefficients for the reactions of *m*-methoxybenzoic acid were used to calculate effective σ values for *m*-OMe. These varied from 0.048 (ethanol) to 0.021 (ethyl acetate), i.e. they were consistently less positive than the value of 0.12 based on the ionization of benzoic acids in water.

Many years ago it was suggested by Hancock[93] on the basis of rate measurements for substituted benzoic acids reacting with substituted diazodiphenylmethanes in toluene that the values of σ_m and σ_p for OMe which were effective in this system were -0.003 and -0.361, respectively. In toluene solution the inductive and mesomeric effects of OMe should be entirely free from any interference by hydrogen-bonding with the solvent.

Thus various items of data accord with the view that in substantially aqueous media, the electron-attracting influence of OMe on a benzene ring is enhanced by hydrogen-bonding, which increases the $+I$ effect and reduces the $-R$ effect, cf structure **24**.



(24)

We turn now to the influence of other alkoxy groups on the strength of benzoic acid. Brynmor Jones and Speakman[94] determined the pK_a values in water at 20 °C of *m*- and *p*-alkoxybenzoic acids by potentiometric titration. Their experimental method was standardized by experiments on benzoic acid, whose pK_a value was taken to be 4.23 at 20 °C. The values are shown in Table 5. In the *meta* series the pK_a values increase with

TABLE 5. The influence of alkoxy groups on the strength of benzoic acid in water, 20 °C[94]

Substituent	pK_a *m*-X	pK_a *p*-X
H	4.23	4.23
OMe	4.11	4.52
OEt	4.17	4.80
OPr^n	4.20	4.78
OPr^i	4.15	4.68
OBu^n	4.25	—

chain length of the alkyl group, corresponding to the *m*-OR groups becoming less electron-attracting in the order MeO > EtO > Pr^{n}O > Bu^{n}O. This corresponds to the 'traditional' order of increasing electron release by alkyl groups[56]. However, this would require Pr^{i}O > Pr^{n}O, the opposite of what is observed. The irregularity was also observed in the *para* series, the Pr^{i}O acid being stronger than the Pr^{n}O acid. In the *para* series the increase in electron-releasing ability with chain length seems rapidly to come to a limit.

2. *Phenoxy group in benzoic acid*

Dippy's value for the pK_a of *m*-phenoxybenzoic acid in water at 25 °C was 3.951, giving a σ_m of 0.252 for OPh[87]. In recent years these values have essentially been confirmed by potentiometric titration (glass electrode)[95]. The higher value for OPh than for OMe (0.12) is most obviously interpreted in terms of the greater inductive effect of OPh ($\sigma_I = 0.40$, compared with 0.30 for OMe, see Section III.A.1 and 2), with some slight contribution from a reduced relayed electron-releasing resonance effect. A contribution of -0.15 from the latter would be required, which suggests a σ_R value of about -0.45, assuming the relay factor of 0.33 to be applicable (Section II.B).

Dippy's value for the pK_a of *p*-phenoxybenzoic acid in water at 25 °C was 4.523, giving a σ_p of -0.320 for OPh[87]. No direct confirmation of these values appears to have been obtained by any other authors. It is very difficult to explain why the σ_p value of OPh should be more negative than that of OMe (-0.27), and this value is now regarded sceptically by several authorities in the field[61,96]. (It is curious that σ values for OPh were not tabulated by Hammett[88], although Dippy's results[87] must presumably have been available to him.) Charton[81] appears to ignore this value of σ_p for OPh, and instead tabulates a value of -0.08, which is said to be based on data in 44.1% w/w aqueous ethanol (50% v/v) communicated privately by B.M. Wepster. These data, and many related ones, have now been published by Wepster[96]. In fact Wepster's paper contains pK_a values for this acid in several aqueous–organic solvents. An earlier paper[89] had given pK_a values for the *m*-phenoxy acid in some of the same aqueous–organic solvents. All these values are given in Table 6, with the corresponding pK_a values of benzoic acid itself for comparison (all values at 25 °C).

Wepster's papers are much concerned with deviations from the Hammett equation that are shown by some substituted benzoic acids in some aqueous–organic mixtures. He attributes these to hydrophobic interactions and has developed an extended Hammett equation which incorporates Hansch's hydrophobic substituent constant π[97], as in equation 16:

$$\Delta = \rho\sigma + h\pi \tag{16}$$

($\Delta = pK_a^0 - pK_a$). The equation expresses very well the data for a wide range of substituents in a wide range of aqueous–organic solvents, the value of h required varying from 0 to -0.16. Thus an increase in the hydrophobic character of the acid (substituent), corresponding to a more positive value of π, results in an acid-weakening effect, which is attributed to the anion being deprived of stabilization through solvation by water. Clearly these findings have implications for the determination of σ values by pK_a measurements involving aqueous–organic mixtures as solvents. However, for some substituents for which π is numerically small (whether positive or negative relative to H as 0.00) the hydrophobic effect is of minor significance. Such a substituent is OMe, for which $\pi = -0.02$, and a possible hydrophobic effect could be ignored in our earlier discussion (Section III.B.1) of the effect of *p*-OMe on the ionization of benzoic acid in 50% and 75% ethanol. However, the value of π for OPh is 2.05, one of the largest values for any substituent considered by Wepster, and the hydrophobic effect is undoubtedly of importance for the pK_a values in Table 6.

TABLE 6. The pK_a values of benzoic acid and of *m*- and *p*-phenoxybenzoic acid in various aqueous–organic solvents, 25 °C[89,96]

Solvent	pK_a values		
	H	*m*-OPh	*p*-OPh
50% v/v EtOH	5.48	5.32	5.50
75% v/v EtOH	6.29	6.08	6.31
85% v/v EtOH	6.77	6.55	—
32% v/v *t*-BuOH	5.28	5.41	5.55

This is shown very strikingly by the pK_a value for the *m*-OPh acid in 32% *t*-BuOH, in which solvent h is about -0.16. Thus the hydrophobic effect on OPh in this solvent weakens the acid by about 0.33 pK_a units, to make the acid weaker than benzoic acid itself, cf the situation in water above. Without this effect the pK_a value would be about 5.08, with *m*-OPh thus producing an acid-strengthening effect of about 0.20. For 50% ethanol h is about -0.05, so the hydrophobic effect for OPh is about -0.10, which leaves the *m*-OPh acid still stronger than benzoic acid. Further assessment of the data for *m*-OPh in the light of the various correlation equations and values of ρ and h in Wepster's papers[89,96] suggests that in the aqueous–organic mixtures the effective value of σ_m is somewhat smaller than the value based on the pK_a value of the acid in water as determined by Dippy, probably below 0.20, rather than 0.252.

As regards *p*-OPh, the results in Table 6 show this to be apparently only slightly acid-weakening in 50% or 75% ethanol, but rather more so in 32% *t*-BuOH. In the last-mentioned solvent, the acid-weakening is certainly due considerably to the hydrophobic effect. In the absence of the hydrophobic effect *p*-OPh seems to have little acid-weakening effect on benzoic acid, and may even have a slight acid-strengthening effect; cf the supposed σ_p value of -0.32 in water, also the value of -0.08 inferred by Charton[81] from Wepster's results as communicated privately.

The situation regarding the electronic effect of OPh as indicated by the influence of this group on the ionization of benzoic acid is not very clear at present.

3. *Hydroxyl group in benzoic acid*

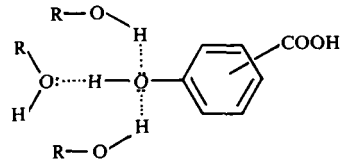
The pK_a value of *m*-hydroxybenzoic acid in water at 25 °C was determined as 4.08 by Bray and coworkers[98]. [Strictly this should be designated $(pK_a)_1$ to distinguish the carboxylic ionization from the much weaker second ionization, that of OH, but it will be understood that in this discussion we are dealing only with the first ionization.] On this basis the σ_m value for OH is often taken as 0.123. However, a more recent determination[89] suggests $\sigma_m = 0.07$, and there are other determinations of the pK_a value which suggest slightly different values of σ_m. Thus while it is clear that the σ_m value of OH in water as solvent is close to that of OMe (0.115), it is impossible to say for certain whether *m*-OH is slightly more electron-attracting than *m*-OMe, or *vice versa*. The possibility of $H_2O \cdots HOC_6H_4COOH$ hydrogen-bonding in aqueous solution (see **24**) would lead one to favour a σ value for *m*-OH less than that for *m*-OMe; cf the lower σ_I value of OH (Section III.A.3).

There seems to be no doubt that, as indicated by the pK_a values of substituted benzoic acids in water, *p*-OH is more electron-releasing than *p*-OMe, for the pK_a values are clearly in the order *p*-OH > *p*-OMe. However, a variety of values are available. Bray and coworkers[98] found pK_a of the *p*-OH acid to be 4.53, leading to $\sigma_p = -0.327$, cf -0.27 for *p*-OMe, but higher pK_a values have been obtained, e.g. 4.58[74]. In any event

the behaviour of *p*-OH in benzoic acid, relative to that of *p*-OMe, seems in accord with what one would suppose would be the effect of $H_2O \cdots HOC_6H_4COOH$ hydrogen-bonding on the inductive and resonance effects of OH, diminishing the $+I$ effect and increasing the $-R$ effect.

Wepster has data for the behaviour of *m*-OH and *p*-OH as substituents in benzoic acid in various aqueous–organic solvents[89,96]. The π value of OH is -0.67, so the $h\pi$ term in Wepster's extended Hammett equation 16 is liable to be of some significance, leading to an acid-strengthening effect, but not nearly so important as the acid-weakening effect for OPh ($\pi = 2.08$; Section III.B.2). In 50% ethanol, *m*-OH slightly strengthens benzoic acid, but this appears to be due to the hydrophobic effect. Correction for the latter makes *m*-OH acid-weakening by virtue of its electronic effect. This is seen explicitly in the behaviour in 75% and 85% ethanol, although not in 32% *t*-BuOH, where the hydrophobic effect is naturally dominant, with $h = -0.16$. It is clear that the electron-attracting influence of *m*-OH manifested in water as solvent is much reduced in the more alcoholic media and ultimately the influence becomes one of electron-release. However, the σ value of *p*-OH seems fairly steady at -0.35 in the various aqueous organic media, when the hydrophobic effect is allowed for.

pK_a data for *m*-hydroxybenzoic acid in various low alcohols[74c] show that in such an environment the acid is weaker than benzoic acid, with an apparent σ_m value of about -0.1. The pK_a data for the *p*-OH acid to not present an altogether uniform picture, but for the most part an enhanced electron-release is indicated with a more negative σ value than in water, perhaps as high as -0.45. A tendency for *m*-OH or *p*-OH to become more electron-releasing in alcoholic media than in water is not what would be expected from the earlier indications of the solvent effect on σ_I (Section III.A.3). It must therefore be supposed that what is observed for *m*-OH or *p*-OH is connected with the influence of the solvent on the resonance effect. One must beware of inferring overmuch from rather scanty data; all one can be really certain of is that the behaviour is complicated and doubtless due to competition between the two possible modes of hydrogen-bonding, structure **25**.



(25)

The electron-releasing nature of *m*-OH as a substituent in benzoic acids in non-aqueous solvents has been confirmed by rate studies of the reaction with DDM[92]. In seven alcohols (including 2-methoxyethanol) the apparent value of σ_m for OH varies from -0.087 to -0.126, but in acetone and ethyl acetate the values are less negative, -0.047 and -0.035, respectively. Aslam and coworkers[92] suggested that the small size of water molecules might facilitate hydrogen-bonding to the *O* of OH, compared with the situation for alcohols, thereby making this type of hydrogen-bonding dominant in highly aqueous solution.

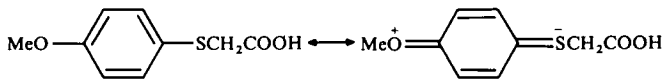
C. Various Systems and Acids

1. The methoxy group in acids of the type Ph—G—COOH

The σ_p value of -0.27 (Section III.B.1) for OMe based on the ionization of substituted benzoic acids is not found to be applicable to the ionization of phenylacetic acids, i.e.

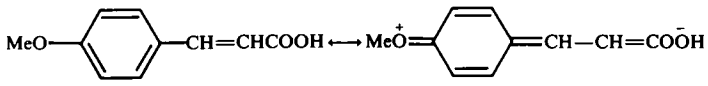
Ph—G—COOH, with G = CH_2. The pK_a value in water at 25 °C of phenylacetic acid itself is 4.31 and that of *p*-methoxyphenylacetic acid is 4.36, the ρ value being about 0.47. From this ρ value and $\sigma_p = -0.27$, the pK_a value of the *p*-OMe acid should be about 4.43. Thus the apparent σ value of *p*-OMe in this acid is about -0.10. The explanation of the discrepancy compared with the behaviour in benzoic acid lies in the occurrence of cross-conjugation in *p*-methoxybenzoic acid, which is more pronounced in the undissociated acid than in the anion, and therefore stabilizes the former relative to the latter; see structure **15** and Section II.B. The insertion of CH_2 between the phenyl ring and the carboxylic function inhibits such cross-conjugation and makes *p*-OMe (and other substitutents which are electron-releasing by the $-R$ effect) less electron-releasing than when substituted in benzoic acid. The behaviour of substituents in such 'insulated' systems as phenylacetic acid is expressed by the σ^0 scale of substituent constants (Section II.B). The rather small effects on pK_a values, consequent upon the modest ρ values (see further below), makes such systems not very suitable for accurate determination of σ^0 values. They are better determined from reactions characterized by larger ρ values, such as the alkaline hydrolysis of ethyl phenylacetates in aqueous–organic solvents, for which the ρ values are about 1.0 (see Sections IV.C and X.B). Such studies give the σ^0 value of *p*-OMe in the region -0.10 to -0.15.

Several other well-known moieties will serve as G to insulate the phenyl ring from the carboxylic acid function, e.g. CH_2CH_2, OCH_2, SCH_2, SO_2CH_2. The pK_a data are somewhat sparse and often there are anomalous items therein, which may arise from larger than usual experimental errors, perhaps including errors due to impurities in the substrate. The ρ values are small and not very well established. Thus the data are not well suited to examining the applicability, or otherwise, of a σ^0 value for *p*-OMe in the region of -0.10 to -0.15. For example, for *p*-OMe in 3-phenylpropanoic acid, $\Delta pK_a = -0.04$, and combined with a ρ value of about 0.17 this gives an apparent σ value of -0.24. However, if ± 0.01 error (possibly optimistic) is attached to ΔpK_a, then the apparent σ value lies between -0.18 and -0.35, which provides little discrimination between the applicability of σ or σ^0. Further, some of the supposed insulating groups may in fact provide opportunities for special interactions which could influence pK_a values. Thus the ability of sulphur to expand its valence shell beyond the octet could permit resonance as in **26**. The ΔpK_a value of -0.13 for *p*-OMe as a substituent in 2-phenylthioacetic acid, coupled with a ρ value of only about 0.26, may certainly suggest some peculiar acid-weakening effect of *p*-OMe in this system.



[(26)]

The introduction of a CH=CH bridge as G in *trans*-cinnamic acid presents a quite different situation. The ρ value for the ionization of *trans*-cinnamic acids in water at 25°C is about 0.45 and a ΔpK_a value of -0.10 for *p*-OMe seems more or less in accord with the applicability of the ordinary σ_p value of -0.27, rather than the σ^0 value in the region of -0.10 to -0.15. Presumably there is cross-conjugation through the cinnamic acid molecule, as in **27**, and this serves as an acid-weakening factor, as with benzoic



(27)

acid. The influence of the *p*-OMe group on the rate of alkaline hydrolysis of ethyl *trans*-cinnamate (85.4% w/w aqueous ethanol, 24.8 °C), for which the ρ value is about 1.2, confirms the relevance of the ordinary σ value of *p*-OMe in the cinnamic acid system[99].

m-OMe enhances the acidity in water of various insulated systems Ph—G—COOH, but since the ΔpK_a values are in the range 0.02 to 0.05, it is difficult to tell whether σ^0 for *m*-OMe differs significantly from σ, 0.11, which would also produce ΔpK_a values in this range. If we take σ^0 for *p*-OMe as -0.12 (the mid-point of the range -0.10 to -0.15), then σ_R^0 would be -0.42. With a relay factor of 0.5 for the σ^0 scale (Section II.B), this would give σ^0 for *m*-OMe as 0.09, little different from the value of σ. Data for the alkaline hydrolysis of substituted ethyl phenylacetates[100] suggest a σ^0 value of about 0.04 for *m*-OMe and a similar value is given by data for ethyl *trans*-cinnamates[99]. However, this information is for reactions in a highly alcoholic medium, 84.8% w/w aqueous ethanol, in which some reduction in the electron-attracting effect of *m*-OMe might be expected (see Section III.B.1).

2. *The methoxy group in phenol, thiophenol and anilinium ion*

The influence of *p*-OMe on the ionization of phenol, thiophenol and anilinium ion in water at 25 °C is particularly interesting. These are all processes which are greatly facilitated by $+R$ *para*-substituents such as NO_2, SO_2Me, CN, etc. The ρ values are most reliably determined by linear regression of $-pK_a$ on σ for the *meta*-substituted substrates only, and the following equations 17 to 19 are typical:

Phenols

$$-pK_a = -9.936 + 2.205\sigma \quad (17)$$
$$(\pm 0.078)$$
$$n = 9,\ r = 0.9957,\ s = 0.0579,\ \psi = 0.105$$

Thiophenols

$$-pK_a = -6.571 + 1.915\sigma \quad (18)$$
$$(\pm 0.103)$$
$$n = 5,\ r = 0.9957,\ s = 0.0657,\ \psi = 0.120$$

Anilinium ions

$$-pK_a = -4.567 + 2.847\sigma \quad (19)$$
$$(\pm 0.079)$$
$$n = 11,\ r = 0.9965,\ s = 0.0603,\ \psi = 0.092$$

The insertion of observed pK_a values for the *p*-methoxy-substituted compounds into the above expressions gives the following apparent values of σ_p for OMe: -0.124, -0.107 and -0.277, respectively. The first two values correspond fairly well to the σ^0 value for *p*-OMe being applicable, rather than the benzoic acid-based σ value of -0.27. This is reasonable since the cross-conjugative effect as shown in the benzoic acid system is absent in the phenolic and thiophenolic systems. However, the effective σ value in the ionization of *p*-methoxyanilinium ion corresponds fairly well to the ordinary σ_p value. It seems likely that the close correspondence is mere coincidence, but that what is actually involved is the *resonance saturation* of the two opposing powerful $-R$ groups in *p*-methoxyaniline having the effect of apparently enhancing the $-R$ effect of OMe. Such resonance saturation appears first to have been pointed out by Wepster[101]. A very

careful analysis of the effect of this on the species involved on both sides of the equilibrium is required in order to explain the apparent enhancement of the $-R$ effect of OMe and to understand why no such enhancement is manifested in the ionization of *p*-methoxyphenol and *p*-methoxythiophenol. For this analysis, Wepster's paper should be consulted[101]. Other powerful $-R$ groups, such as OH in *p*-hydroxyanilinium ion, also show this phenomenon. In this connection it is significant that Ehrenson, Brownlee and Taft[59] found it necessary to define two σ_R^- scales, σ_R^-(A) and σ_R^-(P), based respectively on the behaviour of substituents in anilines and phenols. The values for OMe are -0.45 and -0.36, respectively (see Section II.B).

IV. THE *ORTHO*-EFFECT

A. Introduction

The term *ortho*-effect has long been used to cover the peculiar influence of a substituent in the position *ortho* to a reaction centre, which often differs very markedly from that of the same substituent in the *meta*- or *para*-position[70,71,102]. Steric phenomena have long been recognized as playing a major part in the *ortho*-effect. Primary steric effects of various kinds, including steric hindrance to the approach of the reagent or to solvation, and secondary steric effects have been invoked. In certain systems hydrogen-bonding and other intramolecular interactions have been postulated.

One of the main difficulties in understanding the *ortho*-effect, however, lies in adequately specifying the electronic effects of *ortho*-substituents. The relative contributions of I and R effects to the influence of *ortho*-substituents are liable to be very different from those operating at the *meta*- or *para*-position. There have been many attempts to develop scales of 'sigma-*ortho*' constants analogous to σ, σ^0, σ^+, σ^-, etc. (Section II) for the *meta*- and *para*-position, but such scales are never found to be of very general application[70,71]. The composition of the electronic influence of *ortho*-substituents with respect to I and R effects seems greatly subject to variation with the nature of the reaction, the side-chain, the solvent, etc. The inductive effect of an *ortho*-substituent operates at much shorter range than that of a *meta*- or *para*-substituent, but the orientations of substituent dipoles with respect to the reaction centre are very different from those for *meta*- or *para*-substituents. It is sometimes supposed that the resonance effect of an *ortho*-substituent tends to the inherently weaker than that of the same substituent in the *para*-position, because *ortho*-quinonoid instead of *para*-quinonoid structures may be involved in its operation. However, the resonance effect also is being delivered at rather short range from the *ortho*-position.

The most fruitful treatment of the electronic effects of *ortho*-substituents involves the use of the same σ_I and σ_R-type constants as are employed in correlation analysis for *meta*- and *para*-substituents. Obviously it is a considerable assumption that these are valid for *ortho*-substituents and the implication is that in the correlation analysis any peculiarities in the electronic effects may be adequately expressed through the coefficients of the inductive and resonance terms. Really satisfactory correlation analysis for any given reaction system requires a large amount of data and can only rarely be accomplished.

In this account we will concentrate on the *ortho*-effects of alkoxy (mainly methoxy), phenoxy and hydroxyl groups as manifested in the ionization of carboxylic and other acids, in the alkaline hydrolysis of esters and in the reactions of substituted benzoic acids with diazodiphenylmethane (DDM). Only in the case of the last-mentioned system can really satisfactory correlation analysis be taken as the basis for discussing the groups of special interest for this chapter. For the other systems discussion will have to be rather qualitative or, at best, semi-quantitative.

B. Ionization of Carboxylic and other Acids

1. Benzoic acid

Like all *ortho*-substituted benzoic acids, with no electron-releasing substituents elsewhere in the ring, *ortho*-methoxybenzoic acid in solution in water is stronger than the parent acid. Its pK_a value (25 °C) is 4.09, cf benzoic acid, 4.21 and *para*-methoxybenzoic acid. 4.48. The general acid-strengthening effect of *ortho*-substituents in benzoic acid is usually attributed to the substituent twisting the carboxyl group out of the plane of the benzene ring, thereby reducing the extent of conjugation of the ring with the side-chain. This has the result of destabilizing the undissociated form of the acid relative to the carboxylate ion, thereby enhancing acid strength. The deconjugation effect is shown very clearly in *ortho-t*-butylbenzoic acid, whose pK_a value is 3.54; cf the acid-weakening effect of the group in the *para*-position, $pK_a = 4.40$. This 'secondary steric effect' will, of course, be supplemented by the polar effect of the *ortho*-substituent. In the case of *o*-OMe this will certainly be acid-weakening in nature. The *o*-OMe acid stands rather apart from other *ortho*-substituted benzoic acids by having $pK_a > 4$; cf *o*-ethylbenzoic acid, $pK_a = 3.79$. this acid provides a suitable comparison: the OMe and Et groups are fairly similar in size and shape, and the secondary steric effects they produce should be comparable. It seems likely that the considerable $-R$ effect of OMe is responsible for the net acid-strengthening being only modest, 0.12 pK_a unit.

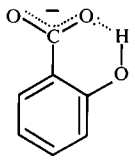
The pK_a value of 2,6-dimethoxybenzoic acid in water is 3.44 This may be compared with 3.25 for 2,6-dimethylbenzoic acid (both values in water at 25 °C). In both these acids the carboxyl group is no doubt practically orthogonal to the ring, with maximum reduction in conjugation of the ring and the carboxyl group. The dimethoxy acid is weaker than the dimethyl acid because of the greater electron-releasing polar effect of the methoxy groups.

The mutual relationship of the pK_a values of *o*-methoxybenzoic acid and benzoic acid is, however, solvent-dependent. In 44.1% w/w aqueous ethanol the pK_a value of *o*-methoxybenzoic acid is 5.83; cf 5.76 benzoic acid, and 5.59 and 6.04 for the *meta* and *para* isomers, respectively. Similar results are shown in other aqueous organic solvents. This changed relationship is probably due to an enhancement of the resonance effect of *o*-OMe in the less aqueous medium, with but little change in the secondary steric effect. However, a detailed understanding of such behaviour cannot be based solely on consideration of one substituent; correlation analysis of the data for various *ortho*-substituents is needed. See the various papers of Charton[103] and of Bowden[104].

In Section III.B.2 it was concluded that the pK_a value obtained by Dippy[87] for *p*-phenoxybenzoic acid of 4.523 is unreliable. For *o*-phenoxybenzoic acid the usually quoted pK_a value of 3.527 in water at 25 °C was also obtained by Dippy[87]. There is no particular reason to regard this also as unreliable, but no confirmatory value appears to exist. The unreliability of the value for the *para* acid means, however, that we are deprived of the natural reference point for discussion of the *ortho* acid. The previous discussion concluded that *p*-OPh has probably only a slight effect on the strength of benzoic acid in water, and this may be acid-strengthening. It seems reasonable therefore to attribute most of the enhancement of strength by *o*-OPh to the secondary steric effect of this fairly bulky group, with possibly a small component from an electron-attracting polar effect.

The pK_a value of *o*-hydroxybenzoic acid in water at 25 °C is 3.03, indicating a surprisingly large enhancement of acid strength. Since OH must be regarded as a rather small substituent, the enhancement cannot be attributed to a secondary steric effect. As long ago as 1934 Branch and Yabroff[105] suggested that the anion of salicylic acid is stabilized by internal hydrogen-bonding, as in **28**. Such internal hydrogen-bonding was

considered to be greatly favoured by the possibility of forming a six-membered ring. In the 2,6-dihydroxybenzoate ion there is the possibility of internal hydrogen-bonding involving both OH groups, as in **29**[106]. This results in a very considerable further increase in acid strength, the pK_a value being about 1.05.



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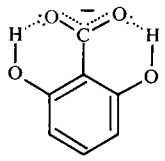


(29)

2. Other carboxylic acids containing aromatic rings

For acids of the general formula XC_6H_4GCOOH in which the aromatic ring is not conjugated with COOH through the connecting entity G (Section III.C.1), the *o*-methoxy-substituted acid tends to be weaker in water than the parent acid, X = H, and even weaker than the *para* isomer. Thus for several acids the nature of G and the pK_a values for X = *o*-OMe, *p*-OMe and H, are respectively as follows: $(CH_2)_2$, 4.804, 4.69, 4.66; (OCH_2), 3.231, 3.213, 3.171; (SCH_2), 3.75, 3.701, 3.567. In these acids there is, of course, no acid-strengthening secondary steric effect to compete with the acid-weakening polar effect of *o*-OMe. Presumably the $-R$ effect is enhanced by proximity to the reaction centre, but correlation analysis for a considerable number of acids would be necessary to be confident of this explanation. Steric inhibition of solvation of the ion is a possible additional factor.

When G is (CH=CH), *trans*-cinnamic acid, the pattern of pK_a values is different: (CH=CH), 4.462, 4.539, 4.437. The *p*-OMe acid is now the weakest. It was previously suggested (Section III.C.1) that in cinnamic acid there may be cross-conjugation involving benzene ring, CH=CH and COOH. The slightly enhanced acidity of the *o*-OMe acid compared with the *p*-OMe acid may indicate some operation of an acid-strengthening secondary steric effect of *o*-OMe.

There appears to be no information about the behaviour of OPh as an *ortho*-substituent in acids of the general formula XC_6H_4GCOOH.

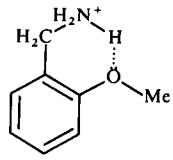
As might be expected, the peculiar acid-strengthening effect of *o*-OH in the benzoic acid system is not usually manifested in the acids XC_6H_4GCOOH, because the structure does not permit the formation of the internal hydrogen-bond in the carboxylate ion. Thus 3-(*o*-hydroxyphenyl)propanoic acid is weaker than its parent acid (pK_a values in water at 25 °C, 4.75 and 4.66, respectively), and *o*-hydroxy-*trans*-cinnamic acid is weaker than its parent acid (pK_a values 4.614 and 4.437, respectively). These values appear to indicate an electron-releasing effect of OH from the *ortho*-position that is comparable with that from the *para*-position. However, *o*-hydroxyphenoxyacetic acid is *stronger* than its parent acid (pK_a values 3.02 and 3.171, respectively). Bowden and Parkin[107] attributed this to internal hydrogen-bonding in the carboxylate ion, even though at first sight this seems rather improbable: an eight-membered ring would be involved. (The same authors[107] also found that the *o*-OH acid was more reactive towards DDM in ethanol than phenoxyacetic acid itself. This was in contrast to the behaviour of the 3-phenylpropanoic acids.)

3. Anilinium ions and phenols

The possible components of the *ortho*-effect in the ionization of anilinium ions and phenols are rather complex. In addition to the operation of the polar effect of the

ortho-substituent at rather short range, there are possibilities of steric inhibition of conjugation of the reaction centre with the ring, steric inhibition of solvation of the ion and, in the case of suitable substituents, several possibilities of internal hydrogen-bonding. Thus it is not always easy to arrive at an unambiguous interpretation of the pK_a value of an *ortho*-substituted anilinium ion or phenol.

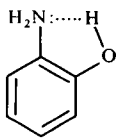
The *ortho*-methoxyanilinium ion has a pK_a value of 4.527 in water at 25 °C, so this ion is a slightly stronger acid than the anilinium ion itself at a pK_a value of 4.596. The pK_a value of the *p*-OMe derivative is 5.357, the acidity of this compound being depressed by the effect of *resonance saturation* (Section III.C.2). The *o*-OMe compound is perhaps not affected to as great an extent by this phenomenon, so some increase in acidity compared with the *p*-OMe compound may be expected. The most obvious factor which could make the *o*-OMe compound a stronger acid than the anilinium ion itself is steric inhibition of solvation of the ion. This is certainly a factor when very bulky *ortho*-substituents are involved, e.g. the *o*-*t*-butylanilinium ion has the very low pK_a value of 3.78. (It is also possible that in the *ortho*-substituted anilinium ion system there is a general enhancement of inductive effects relative to resonance effects. The issue might be clarified by correlation analysis for an adequate number of suitable substituents.) By contrast, the pK_a value of the *o*-methoxybenzylammonium ion is 9.74, compared with 9.51 for the *p*-OMe derivative and 9.37 for the benzylammonium ion itself. The stabilizing effect of *o*-OMe on the ion here seems most likely due to internal hydrogen-bonding, as in **30**. Presumably the different effects of *o*-OMe in the two situations are due to a change in the relative importance of internal hydrogen-bonding and of steric inhibition of solvation when NH_3^+ is made more remote from the ring by insertion of a CH_2 group.



(30)

The *o*-ethoxyanilinium ion with a pK_a value of 4.47 is a slightly stronger acid than the *o*-OMe derivative, possibly due to greater steric inhibition of solvation by the slightly more bulky group.

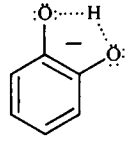
The *o*-OH group slightly weakens the anilinium ion as an acid, with a pK_a value of about 4.65, but not nearly to the same extent as the *p*-OH group at $pK_a = 5.65$. The last-mentioned value is subject to the effect of resonance saturation, as mentioned above for the *p*-OMe derivative, and this phenomenon may not be so marked for *o*-OH as for *p*-OH. There are clearly various possibilities of hydrogen-bonding in the *o*-OH system. It seems likely that much of the enhancement in acid strength compared with the *p*-OH system is due to O*H* bonding to the lone-pair of electrons in the NH_2 group of the free base, as in **31**.



(31)

o-Methoxyphenol and phenol itself have closely corresponding pK_a values at around 9.99, while the *p*-OMe derivative is at 10.20. Thus *o*-OMe is clearly facilitating phenol ionization relative to *p*-OMe, although two of the most obvious factors which might be operating would both disfavour ionization: internal hydrogen-bonding and steric inhibition of solvation of the phenolate ion. The last-mentioned certainly appears to operate with very bulky groups; cf the pK_a value of the *o*-*t*-Bu compound at 10.62. It may be that in phenol ionization the inductive effects of *ortho*-substituents in general are enhanced relative to resonance effects, so that *o*-OMe behaves as more or less electronically indifferent. This is another issue which might be clarified by correlation analysis involving an adequate number of suitable substituents.

For *o*-hydroxyphenol the pK_a value for the ionization of the first hydrogen ion is 9.45, but to make it comparable with values for other phenols, this should be statistically corrected by 0.30 unit to 9.75. The corresponding corrected value for the *p*-OH compound is 10.15. The operation in the *o*-OH compound of a factor favourable to ionization is clear and this is most likely to be internal hydrogen-bonding as in **32**. No doubt the symmetry of this structure is a stabilizing factor.



(32)

C. Alkaline Hydrolysis of Esters

There have been many kinetic studies of the alkaline hydrolysis of esters. The systems we will consider here are ethyl *ortho*-substituted-benzoates, -phenylacetates and -*trans*-cinnamates. The discussion will largely be restricted to *o*-OMe. *o*-OH cannot of course be studied under the conditions used for determining rate coefficients of alkaline ester hydrolysis, since this substituent would then be present as $—O^-$. (This unipolar substituent is considered separately later, in Section VII.)

It will frequently be convenient for making comparisons to express the second-order rate coefficients as $\log k$ values, since this is the form proper to linear free-energy relationships. The units of rate coefficients in this present discussion are litre $mol^{-1}\,s^{-1}$. Alkaline ester hydrolysis is characterized by ρ values that are considerably more positive than those for the ionization of the corresponding carboxylic acids, i.e. alkaline ester hydrolysis is strongly facilitated by electron-attracting groups and disfavoured by electron-releasing groups.

We begin with the hydrolysis of ethyl *trans*-cinnamates. This has long been recognized as a system in which the peculiar effects of *ortho*-substituents are minimized by the remoteness of the reaction site from the ring and by the *trans* stereochemistry of the system[108]. The values of $\log k$ for the *ortho*- and *para*-methoxycinnamates are -3.287 and -3.277, respectively, for reactions in 85.4% w/w aqueous ethanol at 24.8 °C, compared with -2.857 for the parent compound[99]. Ordinary benzoic acid-based σ values appear to be applicable to the effects of *m*- and *p*-substituents and the ρ value is about 1.2 (as mentioned in passing in Section III.C.1). The approximately equal $\log k$ values for the *o*-OMe and *p*-OMe systems suggest that any tendency for the polar effect of OMe to increase on moving the substituent closer to the reaction centre (and this seems to happen with electron-attracting substituents such as Cl) is more or less cancelled by reduction of the $-R$ effect in *ortho*-position compared with *para*-position, *ortho*-quinonoid structures now being involved in the electron-releasing resonance effect.

The situation is rather different for the alkaline hydrolysis of ethyl phenylacetates under the same conditions[100]. All the *ortho*-substituted derivatives which were studied by Watkinson's group reacted more slowly than their *para* isomers, in fact more slowly than the parent compound, irrespective of the electronic effects characteristic of each substituent. The values of $\log k$ for *o*-OMe, *m*-OMe and *p*-OMe derivatives and the parent compound are -2.842, -1.987, -2.092 and -2.036, respectively, i.e. the order of reactivity is *m*-OMe > H > *p*-OMe > *o*-OMe. σ^0 values rather than benzoic acid-based σ values are of course applicable (Sections II.B and III.C.1) and the ρ value is about 1.2. Studies of the Arrhenius parameters and of the effect on the rate coefficients of varying the composition of the aqueous ethanol solvent convinced Watkinson and coworkers[100] that the *ortho*-substituents exert steric inhibition of solvation of the transition state of alkaline ester hydrolysis. In the case of *o*-OMe some of the retarding influence must be due to the electron-releasing nature of the group, but this will certainly not be greater than in the case of *p*-OMe. Most of the retarding effect of *o*-OMe must be attributed to the postulated steric effect.

There is a vast amount of data on the kinetics of alkaline hydrolysis of substituted ethyl benzoates in aqueous organic solvents, but data serving properly to establish the effect of *o*-OMe or *o*-OPh are rather sparse. However, in 56% w/w aqueous acetone at 25 °C, $\log k$ values for the *o*-OMe, *o*-OPh and *p*-OEt derivatives are -2.94, -2.79 and -3.22, compared with -2.62 for ethyl benzoate itself[109]. Ordinary benzoic acid-based σ values are applicable and the ρ value is about 2.4. It is generally supposed that primary steric effects of *ortho*-substituents are liable to be very important in this system, i.e. steric hindrance to the approach of the reagent. Thus *o*-Me exerts a strong retarding effect: $\log k$ is -3.52, compared with -2.92 for *p*-Me. Although an experimental value for *p*-OMe is not available under the above conditions, it would certainly be little different from that of *p*-OEt. The reactivity order *o*-OMe > *p*-OMe probably arises from an enhancement of the $+I$ inductive effect relative to the $-R$ resonance effect which is sufficiently marked to outweigh any retarding steric effect. The above information for *o*-OPh is difficult to interpret in detail. Hoefnagel and Wepster[96] have found that alkaline ester hydrolysis in aqueous organic solvents is subject to the hydrophobic influences of substituents. The high π value of OPh (Section III.B.2) makes it prone to participate in such effects, which would tend to decrease $\log k$. In the absence of a hydrophobic effect, the *o*-OPh ester might be more reactive than ethyl benzoate itself.

D. The Reactions of *ortho*-Substituted Benzoic Acids with Diazodiphenylmethane(DDM)

Our discussion of the *ortho*-effect above was frequently hampered by a lack of data for the wide range of *ortho*-substituted compounds which is necessary to set in context the behaviour of groups such as OMe, OPh and OH of immediate interest for this chapter. As indicated in Section IV.A, such an undertaking is best carried out through correlation analysis by means of an appropriate form of extended Hammett equation[103]. This was done some years ago by the author and his colleagues[82,110] for the reactions of *ortho*-substituted benzoic acids with DDM. Rate coefficients (litre mol^{-1} min^{-1}) at 30 °C were measured for the reactions of benzoic acid and 32 *ortho*-substituted benzoic acids in 11 alcohols (including 2-methoxyethanol) as solvents[82]. The reaction involves a rate-determining proton transfer from the carboxylic acid to the DDM to form a diphenylmethanediazonium–carboxylate ion-pair; subsequent fast product-governing stages have been variously formulated[82]. A more restricted study was carried out for the reactions at 30 °C of the substituted benzoic acids with DDM in 7 aprotic solvents[110], in which the proton transfer is believed to be rate-limiting rather than rate-determining.

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

equation 20:

$$\log k = h + \alpha\sigma_I + \beta\sigma_R + \phi\upsilon \tag{20}$$

where σ_I and σ_R are respectively the inductive and resonance constants of Taft's analysis of ordinary Hammett σ constants (see Section II.B), values derived by Charton being actually used[78]; υ is the steric substituent constant developed by Charton[111-113].

A full discussion of the *ortho*-effect as revealed in this work would be unduly lengthy here; we must restrict ourselves to the more limited task of indicating the role of OMe, OEt, OPh and OH. We discuss first the work involving alcohols as solvents[82].

To apply the extended Hammett equation 20, i.e. to determine the regression coefficients h, α, β and ϕ, it is first necessary to select a set of substituents which can be expected to be 'well-behaved'. Particular problems for σ_R and υ may be caused by conformational effects. Also, internal hydrogen-bonding may occur as a further factor governing reactivity, for which parametrization is not included in the above extended Hammett equation. For the present discussion, a first point of interest is that it proves possible to include OMe, OEt and OPh among the well-behaved substituents, 18 in number, with σ_I, σ_R and υ values, respectively, as follows: OMe, 0.30, −0.59, 0.36; OEt, 0.28, −0.58, 0.48; OPh, 0.40, −0.48, 0.57. For these substituents, values of σ_I and σ_R have been referred to in various places earlier in this chapter. They are subject to variations of one or two units in the second place of decimals in some cases. The values of υ do not vary over the three groups by as much as might have been expected at first sight, in so far as OPh might seem to be a much bulkier group than the other two. The small spread of υ values expresses the expectation that the substituents will adopt conformations to minimize steric interactions: the Me, Et and Ph groups will be oriented away from the reaction site, so that the effective bulk of the groups is largely governed by the oxygen atom. The inclusion of OMe, OEt and OPh among the well-behaved substituents means that steric interaction between these groups and COOH does not seriously influence the $-R$ substituent effect; nor is hydrogen-bonding between COO*H* and the *O* of the substituent apparently a factor influencing reactivity. (Presumably the carboxyl group is preferentially solvated by the alcoholic solvent; cf the situation in aprotic solvents below.)

The regression equations were established for data in eleven alcohols as solvents and were then used to assess the peculiar behaviour of another 15 *ortho*-substituents in respect of conformational effects and intramolecular hydrogen-bonding. As an example, the regression for 2-methoxyethanol as solvent is given as equation 21:

$$\log k = -0.305 + 1.624\,\sigma_I + 0.964\,\sigma_R + 0.346\,\upsilon \tag{21}$$

$$(\pm 0.074) \quad (\pm 0.082) \quad (\pm 0.060)$$

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

The regression coefficients are positive for the σ_I and σ_R terms becaue electron-attracting groups accelerate the reaction and electron-releasing groups retard it. The positive regression coefficient for the υ term corresponds to the reaction being subject to steric acceleration by *ortho*-substituents through deconjugation of COOH with the benzene ring; cf Section IV.B.1.

For the various regression equations, $\alpha\sigma_I$ is always the most important term, with a value of α varying from 1.25 in the most polar alcohol (methanol) to 1.98 in the least (2-methylbutan-2-ol). Depending on the solvent, either $\beta\sigma_R$ or $\phi\upsilon$ comes next in importance. The value of β varies from 0.54 to 0.995 and tends to increase with decrease in polarity of the solvent. Thus the inductive effect of the *ortho*-substituent is always substantially more important than the resonance effect. The value of φ varies from 0.35

to 0.49 and is thus relatively insensitive to solvent, indicating that steric interaction between COOH and *ortho*-substituent is very much a matter internal to the molecule.

The interplay of the various factors makes the value of k for the *o*-OPh acid always 2 to 3 times greater than that of the parent acid, while the *o*-OMe and *o*-OEt acids may either be slightly more reactive than the parent acid or slightly less so, e.g. in methanol these acids are about 40% (in k) more reactive than benzoic acid, but in 2-methoxyethanol they are about 20% less reactive than the parent. Also the order of rate constants as between *o*-OMe and *o*-OEt is solvent-dependent; thus in methanol, *o*-OMe $\approx$ *o*-OEt; in benzyl alcohol, *o*-OMe > *o*-OEt; and in 2-methoxyethanol, *o*-OMe < *o*-OEt.

Values of $\log k$ for *ortho*-hydroxybenzoic acid were calculated from the various regression equations by using values of σ_I, σ_R and υ for OH of 0.24, −0.62 and 0.32, respectively. $\log k$(obs) is much higher than $\log k$(calc) in all solvents, e.g. in 2-methoxyethanol $\log k$(obs) = 0.993, while $\log k$(calc) is −0.402. Thus the value of k is enhanced about 25-fold. The enhancement is greatest in the less polar solvents, but it is still by a factor of about 10 even in the more polar alcohols. This rate increase is certainly due to the proton transfer being encouraged by hydrogen-bonding of the *o*-O*H* to the nascent CO*O*$^-$; cf the enhancement of acidity as measured by the ionization constant in water, see Section IV.A.1 and structure **28**. Such hydrogen-bonding may be termed 'favourable'; cf below.

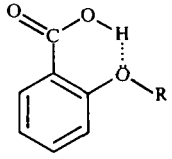
We turn now to the studies in aprotic solvents[110]. Here the series of acids used could not be complete for every solvent, for reasons of insolubility and other factors. (There were also other complications in this part of the work[110].) For acetone all 18 acids involving substituents previously held to be 'well-behaved' could be studied. However, the inclusion of OMe and OEt in the set for establishing the regression equation greatly diminished the goodness of fit, although OPh could be included without serious damage. Equation 22 was obtained when OMe and OEt were excluded:

$$\log k = -0.626 + 2.263\,\sigma_I + 1.415\,\sigma_R + 0.264\,\upsilon \qquad (22)$$

$$(\pm 0.103) \quad (\pm 0.142) \quad (\pm 0.084)$$

$$n = 16,\ R = 0.990,\ s = 0.097$$

From this equation the values of $\log k$(calc) for the *o*-OMe and *o*-OEt acids are −0.687 and −0.869, respectively, compared with $\log k$(obs) values of −1.305 and −1.458, respectively. Thus the reactions of these are retarded by about 0.6 units of $\log k$, and this is undoubtedly due to hydrogen-bonding of O*R* to COO*H*, as in **33**. Such hydrogen-bonding may be termed 'unfavourable'. Presumably it does not occur when the acids are dissolved in alcohols because the COOH is then greatly solvated by surrounding alcohol molecules. Similar behaviour of the *o*-OMe and *o*-OEt acids was found in the other aprotic solvents in which these acids could be studied. Back-calculation of $\log k$ for *o*-OPh revealed a slight retarding effect of unfavourable hydrogen-bonding in the aprotic solvents. Probably this is less important for OPh than for OMe or OEt because of the electron-attracting nature of Ph.



(33)

As one might expect, the favourable hydrogen-bonding effect for *o*-OH in aprotic

solvents is enormous: rate enhancement by 2.46 log units (nearly 300-fold in k) in acetone and 3.4 log units (over 2500- fold in k) in chlorobenzene.

Detailed analyses of this kind have subsequently been made by other authors for the effects of *ortho*-substituents in other reactions, e.g. the kinetics of the reactions of *ortho*-substituted benzoate ions with ethyl bromoacetate[114] or phenacyl bromide[114,115], the kinetics of oxidation of *ortho*-substituted benzyl alcohols by ethyl chlorocarbamate[116] and various reactions of *ortho*-substituted phenylmercaptoacetic acids[117]. The number of *ortho*-substituents studied was usually about 10, including OMe and sometimes OEt. These substituents seem usually to be well-behaved for the purpose of establishing a regression equation of the form of 20. The solvents involved have usually been aqueous–organic mixtures.

V. THE CUMULATIVE EFFECTS OF SUBSTITUENTS

There is a vast amount of data in the literature on the cumulative effects of two or more substituents in a benzene ring on a variety of processes[74] such as the ionization of the carboxyl group, NH_3^+, or OH, the rates of reactions of benzoic acids with diazodiphenylmethane (DDM); alkaline ester hydrolysis; Menschutkin reactions, etc. Many of the studies involved substituents of interest to this chapter, such as OMe, OEt or OH. In the space available we can present only a small selection of data, to indicate the kind of behaviour which may be found and the types of interaction between substituents which may occur.

A. The Effect of Two Methoxy Groups or Two Hydroxyl Groups on the Strength of Benzoic Acid

The pK_a values for dimethoxybenzoic acids in water at 25 °C are in Table 7 (that of the 2,5 isomer does not appear to have been measured). Observed ΔpK_a values relative to benzoic acid are tabulated for comparison with those calculated from ΔpK_a values for the relevant monomethoxy acids on a strictly additive basis, i.e. according to the general equation 23 for the substituents X and Y:

$$(\Delta pK_a)_{X,Y} = (\Delta pK_a)_X + (\Delta pK_a)_Y \tag{23}$$

As might be expected, the 3,5 acid conforms well to strictly additive behaviour, as do also the 2,4, 3,4 and 2,3 acids. Some mutual interference of the $-R$ resonance effect of the 4-substituent and the deconjugative secondary steric effect of the 2-substituent might have been expected, but evidently this does not occur, or in some way there is a cancellation of opposing effects. The behaviour of the 3,4 acid is certainly surprising

TABLE 7. Cumulative effect of two methoxy groups on the strength of benzoic acid in water at 25 °C[74]

Isomer $(OMe)_2$	pK_a	ΔpK_a(obs)[a]	ΔpK_a(calc)[a]
2,3	3.98	0.223	0.228
2,4	4.36	−0.157	−0.155
2,6	3.44	0.763	0.226
3,4	4.36	−0.157	−0.153
3,5	3.97	0.233	0.230

[a] pK_a benzoic acid, 4.203; ΔpK_a values: *o*-OMe, 0.113; *m*-OMe, 0.115; *p*-OMe, −0.268.

since, with 3,4-disubstituted benzoic acids, interaction between the substituents often tends to lead to some departure from strict additivity, e.g. in the case of 3,4-Cl_2 or 3,4-$(NO_2)_2$. The additive behaviour of the 2,3-$(OMe)_2$ acid is also surprising since 2,3-disubstituted acids often show 'buttressing' effects of having three adjacent groups on the ring, e.g. in the case of 2,3-Me_2. The non-additivity shown by the 2,6 isomer has already been discussed in connection with the *ortho*-effect (Section IV.B.1): the combined secondary steric effects of two *ortho*-substituents are usually considerably greater than twice the effect of one substituent.

The pK_a values for dihydroxybenzoic acids in water at 25 °C are in Table 8[118], whose arrangement is similar to that of Table 7. Here good additivity is shown by the 2,3, 2,4 and 2,5 acids, in spite of the possibility of interactions between the substituents by hydrogen-bonding in the case of 2,3 or through the molecule as a result of having two powerful $-R$ groups in *para* position to each other in the case of 2,5. The non-additive behaviour of the 2,6 acid has already been discussed in connection with the *ortho*-effect (Section IV.B.1): the stabilization of the carboxylate ion by internal hydrogen-bonding to *o*-OH is greatly enhanced by the presence of two *o*-OH substituents to form a symmetrical hydrogen-bonded structure.

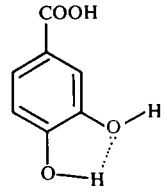
The surprises in Table 8 are provided by the deviations from additivity shown by the 3,4 acid (cf the 2,3 isomer) and especially by the 3,5 acid. The pK_a values of these acids as measured by Dippy and collaborators[118] are close to the values of 'concentration-based' constants measured many years earlier by Ostwald[119], 4.48 and 4.04, respectively. For the 3,5 acid there are also values of 4.14 at 20 °C and 4.10 at 30 °C[120], suggesting a value of about 4.12 at 25 °C, i.e. somewhat higher than Dippy's value, which would make the departure from additivity even more striking. We must therefore suppose these deviations from additivity to be real.

As far as the behaviour of the 3,5 isomer was concerned, Dippy[118] wrote in 1959. 'It is not possible to envisage any mutual interaction between the two hydroxyl groups in this structure and the phenomenon cannot yet be explained'. Thirty-three years later this seems still to be true. For the 3,4 acid it is easy to envisage hydrogen-bonding between the groups which would lead to the acid being somewhat weaker than required by strict additivity of substituent effects, as in **34**. However, hydrogen-bonding interaction between OH groups might also have been expected in the 2,3 acid, which shows good additivity as noted above. It is possible that various interactions between the OH groups, COOH and CO_2^- are occurring, some acid-strengthening and some acid-weakening, and that the apparently good additivity shown by the 2,3 acid arises from a fortuitous cancelling of opposing effects.

TABLE 8. Cumulative effect of two hydroxyl groups on the strength of benzoic acid in water at 25 °C[74]

Isomer $(OH)_2$	pK_a	ΔpK_a(obs)[a]	ΔpK_a(calc)[a]
2,3	2.914	1.289	1.296
2,4	3.325	0.879	0.846
2,5	2.951	1.252	1.296
2,6	1.051	3.152	2.346
3,4	4.491	−0.288	−0.204
3,5	4.039	0.164	0.246

[a] pK_a benzoic acid, 4.203; ΔpK_a values: *o*-OH, 1.173; *m*-OH, 0.123; *p*-OH, −0.327.



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B. The Effect of Two Methoxy Groups or of Two Hydroxyl Groups on the Rate of Reaction of Benzoic Acid with Diazodiphenylmethane

Aslam and coworkers[92] measured rate coefficients at 30 °C for the reactions of 2,3-, 2,5- and 2,6-dimethoxybenzoic acids and the corresponding dihydroxybenzoic acids with diazodiphenylmethane (DDM) in seven alcohols, ethyl acetate or acetone. The cumulative effects were assessed by comparing observed $\Delta \log k$ values (i.e. relative to $\log k$ for benzoic acid) with those calculated from the data for the appropriate monosubstituted acids through the general equation 24:

$$(\Delta \log k)_{X,Y} = (\Delta \log k)_X + (\Delta \log k)_Y \tag{24}$$

The original paper[92] displays detailed tables of the additivity assessments, of which we will give only a brief summary here.

The 2,5-$(OMe)_2$ and 2,5-$(OH)_2$ acids show fairly strict additivity in all the solvents studied, in spite of the possibility of interaction between the opposed powerful $-R$ groups. (The additivity is slightly less good in the aprotic solvents.) The 2,3-$(OMe)_2$ acid, however, tends to react somewhat faster than predicted, both in alcohols and aprotic solvents, which contrasts with the fairly strictly additive behaviour shown in the ionization in water (Section V.A). In the alcoholic solvents the steric interaction of the 3-OMe against the 2-OMe may be supposed to enhance the secondary steric effect of the *o*-OMe. In the case of the aprotic solvents part of the enhanced reactivity could be due to the buttressing interfering with the unfavourable hydrogen bonding (see Section IV.D). Slight positive deviations from addivitity also occur with the 2,3-$(OH)_2$ acid. Again this contrasts with the behaviour shown in the ionization in water. In this case a hydrogen-bond between 3-O*H* and 2-*O*H may promote the favourable hydrogen-bonding of 2-O*H* to the reaction centre (Section IV.D).

As might be expected, substantial positive deviations from additivity occur with the 2,6-$(OMe)_2$ and 2,6-$(OH)_2$ acids. (The latter were too reactive to study in the aprotic solvents.) For the 2,6-$(OMe)_2$ acid the deviations may be attributed to non-additivity in the secondary steric effect of *o*-OMe. In the aprotic solvents the twisting of COOH produced by the second OMe could also interfere with the unfavourable hydrogen-bonding of the first OMe. For the 2,6-$(OH)_2$ acid the substantial positive deviations may be attributed to non-additivity in the favourable hydrogen-bonding effect (Sections IV.B.1 and IV.D).

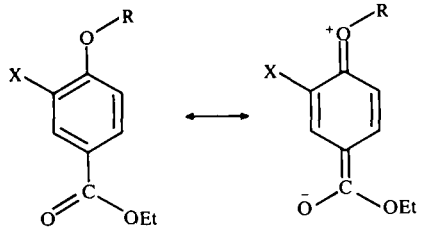
C. Steric Enhancement of Resonance

It is sometimes supposed that steric interference with the resonance effect of a substituent necessarily takes the form of *inhibition* of resonance by preventing the necessary alignment of p-orbitals on the substituent and on the ring carbon to which the substituent is attached. Such inhibition of resonance may certainly be observed in the case of an alkoxy group. Thus rate constants, $10^4 k\ \text{min}^{-1}$, for the solvolysis of substituted

benzyl chlorides (90% aqueous ethanol, 25 °C) are as follows for the substituents indicated: H, 8.3[121]; *m*-Me, 10.8[121]; *p*-OMe, 130[122]; 3,5-Me_2-4-OMe, 3.7[122]. Both *m*-Me (slightly) and *p*-OMe (strongly) facilitate reaction by promoting the S_N1 benzyl cation-forming process. However, the combined effect in the 3,5-Me_2-4-OMe derivative is to retard reaction. This can only be explained in terms of steric inhibition of the $-R$ effect of OMe making this group now a net electron-attracting substituent by virtue of its $+I$ effect. The effect of only one flanking methyl group is quite different. The value of 10^4k for the 3-Me-4-OMe compound is 510[122], which shows that the steric effect of the 3-Me *enhances* the $-R$ effect of 4-OMe by encouraging the latter to adopt conformations in which conditions for orbital overlap are favourable[123].

The steric enhancement of resonance was first postulated by Baliah and Uma[124] on the basis of a study of the dipole moments of some substituted anisoles[123]. For example, the dipole moment of *p*-nitroanisole as calculated from the individual moments of nitrobenzene and anisole is 4.51 D. The experimental value is 4.74 D, the enhancement of 0.23 D being attributable to the resonance interaction of OMe and NO_2. However, in the case of 2-methyl-4-nitroanisole the observed moment is 5.29 D, compared with a calculated value of 4.71 D. The greater discrepancy of 0.58 was attributed to the steric enhancement of the resonance interaction of 4-NO_2 and 1-OMe by 2-Me. 2,6-Dimethyl-4-nitroanisole gives an experimental value of 4.77 D, compared with a calculated value of 4.89 D, indicating now the steric inhibition of resonance by the flanking methyl groups[123].

Evidence for steric enhancement of resonance comes from a variety of kinetic studies[123]. Brynmor Jones and Robinson[125] measured rate constants for the alkaline hydrolysis of 3,4- and 3,5-disubstituted ethyl benzoates in 85.4% aqueous ethanol at 25 °C. Additivity of substituent effects was assessed in terms of $k_{X,Y}(\text{calc}) = k_X k_Y / k_H$, and k(calc) was compared with k(obs) through the ratio k(calc)/k(obs). 3,5-Disubstituted esters variously involving Me, Br or OMe gave values of k(calc)/k(obs) within a few percent of unity and this also applied to 3,4-Me_2 and 3-Cl-4-Me. However, for eight combinations of 3-X-4-OR (X = Cl, Br or NO_2; R = Me, Et or Pr^i) k(calc)/k(obs) varied from 1.28 to 1.60. This may be taken as evidence that the 3-substituent enhances the resonance interaction of the 4-OR group with the ester function. The 3-substituent encourages the 4-OR group to adopt a conformation in which R is *trans* to it, as in **35**. The probability of OR being coplanar with the ring is increased as the OR group can no longer rotate freely.



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Rate data of Crocker and Brynmor Jones[126] for the reactions of substituted *N*,*N*-dimethylanilines with allyl bromide yield similar evidence for the steric enhancement of resonance. For the 3-halogeno-4-methoxy-*N*,*N*-dimethylanilines, the values of k(calc)/k(obs) increase in the order F < Cl < Br < I, indicating greater steric enhancement of resonance with increasing bulk of the 3-substituent.

Baliah[123] also cites results on the alkaline hydrolysis of 4-methoxy-substituted methyl benzoates[127], which show enhancement of resonance by 3-substitution and inhibition

of resonance by 3,5-disubstitution. Evidence for steric enhancement has also been obtained from diamagnetic susceptibility measurements[123].

Brynmor Jones and Watkinson[99] measured rate constants for the alkaline hydrolysis of 14 disubstituted ethyl cinnamates, including 3-X-4-OR compounds. the results, however, do not give any indication of steric enhancement of resonance, e.g. the 3-NO_2-4-OMe and 3-Cl-4-OMe compounds show strict additivity to within a few percent in the k(calc)/k(obs) ratio (approx. 1.07), very different from the behaviour of the corresponding ethyl benzoates[125], for which the ratio is about 1.43.

D. Cumulative Effects of Substituents in Different Rings

The systems discussed in the earlier parts of this Section V have all involved the cumulative effects of two (or more) substituents in the same ring. There is also considerable interest in multiple substitution when the substituents X and Y are in different rings, either in the reactions of a substrate Ar^1Ar^2Z, or in reactions of the type:

$$Ar^1Z^1 + Ar^2Z^2 \rightarrow \text{products}$$

A system which combines both these possibilities is the reaction of substituted diazodiphenylmethanes (DDM; possibility of substituents in one or both of the rings) with substituted benzoic acids. This reaction, in toluene at 25 °C, was studied as long ago as 1958 for 46 combinations of substituents[93]. The rate coefficients were treated with an appropriate form of Hammett equation (see equation 25), embodying the assumption of strict additivity of substituent effects:

$$\log k = \log k^0 + \rho_D \Sigma\sigma_D + \rho_B \Sigma\sigma_B \qquad (25)$$

the subscripts D and B referring to substituents in DDM and benzoic acid, respectively. The results conformed well to this equation, with $\log k^0 = -0.1089$, $\rho_D = -1.620$ and $\rho_B = 2.376$ ($R = 0.9975$, $s = 0.0783$). The OMe group featured in several cases as a substituent in one or the other or both of the reactants and (as already mentioned in connection with solvent dependence of substituent constants, Section III.B.1) values of $\sigma_m = -0.003$ and $\sigma_p = -0.361$ were found applicable throughout.

When correlation analysis for systems of the above type gives poor results under the assumption of strict additivity of substituent effects, the inclusion of a 'cross-term' involving $\sigma_X\sigma_Y$ may be examined. Applications of such a procedure have been pursued in only a rather desultory fashion until recent years, but there have now been much more systematic and extensive studies. Thus, Lee's group[128] have studied the rates of S_N2 reactions of X-substituted-anilines, with Y-substituted-1-arylethyl Z-substituted-arenesulphonates in methanol. In the correlation analysis it is necessary to include cross-interaction terms $\rho_{XY}\sigma_X\sigma_Y$, $\rho_{XZ}\sigma_X\sigma_Z$ and $\rho_{YZ}\sigma_Y\sigma_Z$, in addition to the ordinary Hammett terms $\rho_X\sigma_X$, $\rho_Y\sigma_Y$ and $\rho_Z\sigma_Z$. Numerous possible combinations of X = p-Me, H, p-Cl, m-NO_2; Y = p-OMe, p-Me, H, p-Cl; and Z = p-Me, H, p-Cl, p-NO_2 were studied. The correlation analysis found $\rho_{XY} = -0.23$, $\rho_{YZ} = 0.10$ and $\rho_{XZ} = -0.60$. The substantial value of ρ_{XZ}, implying interaction between the substituent in the nucleophile and that in the leaving group, was considered to support an 'intermolecular S_Ni reaction', with a four-centre transition state.

The interest for the present chapter in such studies by Lee and colleagues lies in the frequent use of p-OMe as a substituent. For instance, there is a study of seven reaction series (in MeOH as solvent) involving halides as leaving groups and aromatic amines as nucleophiles[129]. (This paper yields a rapid overall impression of the authors' procedures and the uses made of cross-interaction constants.) In most of the series p-OMe is one of the substituents used in the amine and often in the organic halide as well. In Lee's work as a whole, a great variety of substrates and, to a lesser extent, of nucleophiles

are being used in a range of media, both one-component solvents and binary organic mixtures. It is by no means always clear what values of substituent constants are being used in the correlation analysis, or indeed what values should be used in the various situations. (Phrases like 'ordinary substituent constants' occur in some of the papers.) For *p*-OMe this is not a trivial matter. Nor is it a trivial matter for the outcome of the correlation analysis, since *p*-OMe is frequently the most electron-releasing substituent used. Further examination of Lee's extensive work would be out of place here. We conclude by giving the reference for one of his most recent papers, which has numerous citations of his earlier papers[130].

VI. SUBSTITUENT EFFECTS IN HIGHLY ELECTRON-DEMANDING REACTIONS

A. Substituent Effects in Solvolysis Reactions

The enormous accelerating influence of alkoxy groups in the *para* position on the solvolysis of benzyl chloride ($PhCH_2Cl$) or tosylate (p-$MeC_6H_4SO_2OCH_2Ph$) in aqueous–organic solvents has long been known. Thus the introduction of *p*-OMe into the latter substrate increases the rate constant by a factor of over 30,000 for the reaction at 25 °C in 49.6% w/w aqueous acetone[131]. The activating effect of *p*-OMe in this case is somewhat distorted by a change in mechanism. The parent compound probably reacts mainly by a bimolecular mechanism, with a process involving an intermediate carbocation $PhCH_2^+$ playing only a small part. Substituents may alter the relative importance of the mechanisms, and in particular $-R$ *para*-substituents such as OMe can stabilize $ArCH_2^+$ by cross-conjugation so that reaction occurs almost entirely via the carbocation.

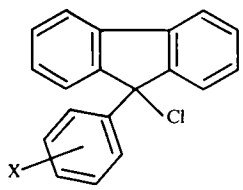
The electronic effects are shown more clearly in a reaction series in which there is no change of mechanism. The best known of these is the solvolysis of tertiary cumyl chlorides $ArCMe_2Cl$ in 90% v/v aqueous acetone, in which the mechanism is uniformly S_N1. It is not possible to study both the parent and the *p*-OMe substituted compound at the same temperature, but extrapolation to 25 °C finds the rate constant to be enhanced by a factor of 3360 by *p*-OMe. This is the basis of the well-known σ_p^+ value of -0.78 for OMe (see Section II.A)[132]. (This may be compared with an average value based on electrophilic aromatic substitution of -0.76, as tabulated by Exner[45].)

In the *meta*-position OMe retards the solvolysis of cumyl chloride, with an apparent σ_m^+ value of 0.134. This is, of course, very similar to the ordinary Hammett σ_m value of 0.115 (Section III.B.1). (The rate constants for various *meta*-substituted substrates and the corresponding benzoic acid-based σ values were used to establish the correlation equation for the cumyl chloride solvolysis, with a ρ value of -4.54 at 25 °C. Thus it was assumed that those *meta*-substituents would behave normally and not show enhanced $-R$ effects. The close correspondence of the apparent σ_m^+ to σ_m confirms that this assumption is valid, even for a group such as OMe that is liable to show pronounced resonance effects.)

The phenoxy group has rarely been used as a substituent in solvolysis reactions. The σ_p^+ values which are sometimes quoted at *ca* -0.5[45] are mainly based on studies of electrophilic aromatic substitution. However, some fairly old rate data[133–135] for the solvolysis of benzhydryl chlorides $XC_6H_4CHPhCl$ in ethanol at 25 °C may be used to give a value of σ_p^+ for OPh. The ρ value for this reaction is about -4.6, and $\Delta \log k$ for the *p*-OPh compound is 2.46. These figures give a σ_p^+ value of -0.53 for OPh, in the general region of the values based on electrophilic aromatic substitution. No doubt the value for OPh is not so negative as that of OMe, because of the electron-attracting nature of the phenyl in OPh, due largely to its ability to delocalize the lone-pair electrons of O.

Values of σ_p^+ that are sometimes quoted[45] for OEt (−0.82), OR (alkoxy groups in general, apart from OMe, −0.83) and OH (−0.92) are based on studies of electrophilic aromatic substitution (Section VI.B), rather than of solvolysis reactions, There is some doubt as to the significance of the long-accepted value of −0.92 for OH (Section X.C).

The value of −0.78 of σ_p^+ for OMe has been much used in connection with the solvolysis of substrates in which the −*R* effect of OMe can operate to stabilize a nascent carbocationic centre. Bolton, Chapman and Shorter[136] established a Hammett line for the solvolysis of 9-aryl-9-chlorofluorenes (**36**) in ethanol–acetone (9:1, v/v) at 25 °C by using only the log *k* and σ values for the *meta*-substituted derivatives (cf Wepster[49]). The value of ρ was found to be −3.51. Effective σ values of *para*-substituents were then calculated. The value for *p*-OMe was found to be −0.786, very close to the usual σ_p^+ value of −0.78. Johnson[137] has claimed that simple correlation analysis employing σ^+ is satisfactory for the treatment of the S_N1 solvolysis of about twenty tertiary *p*-nitrobenzoates of general formula *p*-$NO_2C_6H_4CO_2R$, where R contains an aryl group attached to a tertiary carbinyl centre. All the systems involve *p*-OMe as a substituent. However, his views have been criticized by some of those who believe strongly that the σ_p^+ value of −0.78 for OMe is but one point, albeit an important one, in a 'spectrum' of values measuring the enhanced electron-releasing power of this substituent in electron-demanding reactions[138,139].



(**36**)

This brings us to the point of view that proper correlation analysis of such reactions should involve some form of multiparameter extension of the Hammett equation (Section II.B), to express the idea of the 'sliding-scale' of substituent effects[49]. The multiparameter extension of the Hammett equation which is most commonly used for solvolysis reactions is the Yukawa–Tsuno equation, either in the form of equation 26[52]:

$$\log k = \log k^0 + \rho[\sigma + r^+(\sigma^+ - \sigma)] \tag{26}$$

or in the form of equation 27[53]:

$$\log k = \log k^0 + \rho[\sigma^0 + r^+(\sigma^+ - \sigma^0)] \tag{27}$$

using σ^0 instead of σ as the more proper origin for assessing enhanced resonance effects. (The Yukawa–Tsuno equation is called by its originators the Linear Aromatic Substituent Reactivity, or LArSR, relationship.) The Yukawa–Tsuno equation remains popular in spite of certain limitations[42,43,50] and of the considerable advocacy in certain quarters that the Dual Substituent-parameter equation[59] or the Extended Hammett Equation[78] (Section II.B) is to be preferred. Not unnaturally the Japanese authors are concerned to rebut the various types of criticism of their LArSR treatment and they certainly continue to make good use of it in connection with the solvolysis of aromatic substrates. *p*-OMe is always among the substituents used. Parts 12 to 17 of their series 'Substituent Effects' appeared between 1978 and 1987. The topics studied included the solvolyses of 3′ and 4′-substituted 1-(4-biphenylyl)ethyl chlorides[140], 1-(7-substituted 2-fluorenyl)ethyl chlorides[141] and 6- and 7-substituted 1-(2-naphthyl)ethyl chlorides[142]. Outside the 'Substituent Effects' series there are studies of the solvolysis of 1-methylbenzyl chlorides[143] and the acetolysis of neophyl *p*-bromobenzenesulphonates[144,145].

In connection with the use of multiparameter extensions of the Hammett equation for the correlation analysis of solvolysis data, it would be appropriate to mention briefly the modification of the Yukawa–Tsuno equation introduced by Young and Jencks[146]. This takes the form of equation 28,

$$\log k/k_0 = \rho\sigma^n + \rho^r(\sigma^+ - \sigma^n) \tag{28}$$

in which σ^n is the 'normal' or 'unexalted' substituent constant of Wepster[49]. The first term on the right-hand side gives the contribution of the normal substituent effect, while the second gives the contribution of the exalted substituent effect. Like the Yukawa–Tsuno equation the Young–Jencks equation may be applied to *meta* and *para* series together. The modified equation is claimed not to present an anomaly encountered in applying the Yukawa–Tsuno equation to reversible reactions for which equilibrium constants and rate constants of forward and reverse reactions may be measured. The present author has previously given an appraisal of the modified equation[43].

There is some information about the effects of *ortho*-substituents, including *o*-OMe, on rates of solvolysis of certain substrates. In the cumyl chloride series the enhancement of rate by *o*-OMe is by a factor of 105 at 25 °C; cf 3360 for *p*-OMe[147]. The smaller factor may be due in considerable measure to a reduction in the $-R$ effect for *o*-OMe compared to *p*-OMe, consequent upon an *ortho*-quinonoid structure being involved in the effect. However, the behaviour of several other *ortho*-substituents suggests that steric effects play a part, so it seems probable that some of the reduction in the activating effect of OMe is steric in origin, i.e. in the transition state there is steric compression between the *ortho*-substituent and the carbinyl methyl groups. In the 9-aryl-9-chlorofluorene system the increase in rate produced by *o*-OMe is by a factor of only 13; cf 606 for *p*-OMe[136]. Again this seems likely to be due to a combination of a reduced $-R$ effect and a steric effect, transition state steric compression of the *ortho*-substituent with the hydrogen atom in the 1- or 8-position of the fluorene ring being involved.

B. Substituent Effects in Electrophilic Aromatic Substitution

1. Introduction

The Historical Introduction (Section I.B) showed the important role of electrophilic aromatic substitution in the development of the electronic theory of organic reactions, and in particular the part played by the study of the directing and activating effects of alkoxy groups, etc. We come now to more modern studies of these groups in connection with electrophilic aromatic substitution.

A very comprehensive account of electrophilic aromatic substitution has recently been written by Roger Taylor[148]. This book contains many mentions of the groups of interest in the present chapter and for a detailed account the reader should consult Taylor's volume. The present account concentrates on giving an overall impression of the influences of these groups on *ortho:meta:para* ratios in isomer proportions and in partial rate factors, and the dependence of these characteristics on reagents and conditions. The incorporation of data for hydroxyl and ether groups in linear free-energy relationships will receive some emphasis. In connection with the last-mentioned we repeat that electrophilic aromatic substitution was not within the scope of the original Hammett equation, but was brought within it by H. C. Brown[48] through the introduction of the special substituent constant σ^+ to deal with enhanced $-R$ resonance effects (Section II.A). The treatment of electron-demanding reactions was refined by Yukawa and Tsuno through equation 26 above[52].

If we represent electrophilic aromatic substitution of a benzene derivative by the

general equation

$$XC_6H_4Y + E \longrightarrow XC_6H_4E + Y$$

then for the most important reactions, Y = H and the possibility of isomer formation is of great interest.

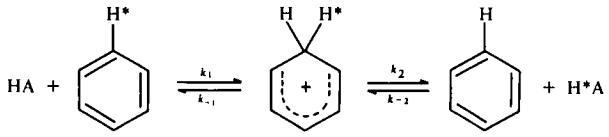
The statistical ratio for the proportions of isomer formation in the substitution of ring hydrogen of C_6H_5X is, of course, $o:m:p = 2:2:1$, but these proportions are rarely, if ever, found. The theoretical ratio is distorted by electronic and other effects, so that most groups are predominantly *ortho/para* or *meta* directing (Section I.B[5-12]). Only relatively few groups show intermediate behaviour in which significant amounts of all three isomers may be produced. The substituents of interest to this chapter are largely *ortho/para* directing and the main interest is in the proportions of *ortho* and *para* isomers formed and in the ratios of partial rate factors f, often considered in the form $\log f_o/\log f_p$. (The partial rate factor is a measure of the reactivity of the position in question relative to that of one position in benzene[149]. The term is also used in the sense of relative rate constant when the displacement of a moiety other than H is involved, i.e. in the above equation, Y ≠ H. It is then equivalent to k/k^0 in the Hammett equation and other linear free-energy relations, when written in forms in which k^0 is the actual value for the parent compound rather than the antilog of an intercept term.)

Ortho-substitution is subject to many of the peculiarities encountered in the *ortho*-effect (Section IV). Thus the electronic effects of substituents are liable to have a different inductive/resonance composition from that relevant for *para*-substitution. The inductive effect is operating at short range, but with different orientations of substituent dipoles relative to the reaction centre, and the resonance effect may be diminished through involving *ortho*-quinonoid structures. Also, *ortho*-substitution is liable to steric influences of various kinds. For OMe, OPh, OH, etc. one of the particular matters of interest is the way in which *ortho/para* ratios vary with the reaction, the reagent, reaction conditions such as solvent or acidity, etc. These matters are also of importance in the general case of electrophilic aromatic substitution, i.e. of replacing Y by E, and Y ≠ H.

In this discussion it will be convenient to classify and arrange the types of electrophilic aromatic substitution as in Taylor's book[148,150].

2. Hydrogen exchange[151]

a. Acid-catalysed hydrogen exchange. Most studies of hydrogen exchange have been carried out under acidic conditions. Such exchange involves an $A\text{-}S_E2$ mechanism, as in **37**. Hydrogen exchange is commonly studied as the detritiation of appropriately tritiated aromatic compounds. Partial rate factors for detritiation of OMe and OPh substituted tritiobenzene TC_6H_4X in trifluoroacetic acid at 70 °C are shown in Table 9[152]. The order *p*-OMe > *p*-OPh shows that the O atom in OMe is better able to release electrons by the $-R$ effect than that in OPh. This is, of course, due to the possibility of resonance interaction of O with either phenyl ring in diphenyl ether, and to phenyl being inductively electron-withdrawing relative to methyl. The similarity of the values of $\log f_o/\log f_p$



(37)

TABLE 9. Partial rate factors in detritiation in TFA at 70 °C[152]

X	*o*	*m*	*p*	log f_o/log f_p
OMe	7.30×10^4		1.9×10^5	0.92
OPh	6.90×10^3	*ca* 0.12	3.1×10^4	0.855

suggests that there is no steric hindrance by the *ortho*-substituents. The reduction in f_o compared with f_p indicates the reduced $-R$ effect from the *ortho* position.

Both *m*-OMe and *m*-OPh are deactivating (f_m for OMe is 0.25 in 63% w/w aqueous perchloric acid[152]). Thus the relayed resonance effect, even under considerable electron demand from the reaction centre, does not outweigh the $+I$ effects of these substituents.

The *p*-OMe group is not so activating as might be expected. Correlation analysis of the data for several substituents shows that, in this reaction, *p*-OMe has an apparent σ^+ value of about -0.60; cf the usual σ^+ value of -0.78. This has been attributed to hydrogen-bonding of OMe to the TFA solvent[153].

b. Base-catalysed hydrogen exchange. This reaction proceeds via slow deprotonation of the aromatic compound by the base to form the carbanion Ar^-. Substituent effects are therefore rather different from those operating in acid-catalysed exchange. Data are available for deuterium exchange of various substituted benzenes PhX with various bases. Partial rate factors for substituents of interest in this chapter are as follows, KNH_2 being the base[154]: *o*-OMe, 8000; *m*-OMe, 10; *p*-OMe, 0.1; *m*-OPh, 41; *p*-OPh, 3.7. These results, and those for other substituents, show that inductive effects are dominant, with electron-attracting groups naturally facilitating the loss of the hydrogen ion. This accounts for the orders *m*-OPh > *m*-OMe and *p*-OPh > *p*-OMe, the deactivation by *p*-OMe being the result of intervention by the $-R$ effect. Base-catalysed hydrogen exchange is subject to steric hindrance by some *ortho*-substituents, but there is no sign of this in the great activating effect of *o*-OMe, which may be attributed to the inductive effect operating at short range.

Data also exist for 1,4-$(OMe)_2$ and 1,2-$(OMe)_2$ compounds and for other polysubstituted benzenes involving at least one OMe[154]. The cumulative effects of substituents appear to be fairly additive.

3. *Replacement of a substituent by hydrogen*[155]

Taylor[148] discusses a considerable number of reactions of this nature, and for several of them there is information about the influence of groups of interest for the present chapter[155]. Our discussion will be restricted mainly to protiodemercuriation and protiodesilylation (both acid- and base-catalysed).

a. Protiodemercuriation. Partial rate factors are available for the protiodemercuriation of symmetrical diarylmercury compounds $(RC_6H_4)_2Hg$ by hydrochloric acid in 90% aqueous dioxan at 30 °C[156]. The data for *meta*- and *para*-substituents R conform well to the Yukawa–Tsuno equation with $\rho = -3.8$ and $r^+ = 0.5$, confirming that the reaction is a typical electrophilic substitution, the protonation of the aromatic ring to form the Wheland intermediate being rate-determining. Partial rate factors for alkoxy substituents are as follows[156]: *p*-OEt, 99.7; *p*-OMe, 80.3; *m*-OMe, 0.83; *o*-OMe, 2.14. The order *p*-OEt > *p*-OMe may be attributed to the order of electron release of the alkyl groups being Et > Me, possibly due to the higher polarizability of the ethyl group. The relative effects of *p*-OMe and *m*-OMe are fairly well in accord with their σ_p^+ and σ_m^+ (or σ_m)

values and the Yukawa–Tsuno correlation referred to above. The order *p*-OMe ≫ *o*-OMe may suggest that the reaction is subject to steric hindrance by the *ortho*-substituent.

b. Acid-catalysed protiodesilylation. The mechanism of this reaction and substituent effects on the rate have been much studied, particularly for protiodetrimethylsilylation in which the $SiMe_3$ group is replaced by H. Partial rate factors for the reactions in methanol–aqueous perchloric acid or acetic acid–aqueous sulphuric acid may be correlated (as $\log f$) by means of the Yukawa–Tsuno equation, with $\rho = -5.3$ and $r^+ = 0.65$[157]. The values of ρ and r^+ indicate an early transition state. Partial rate factors for substituents of interest for the present chapter are shown in Table 10[157].

The orders *p*-OH ≫ *p*-OMe and *o*-OH ≫ *o*-OMe are considered anomalous, and contrast with *p*-SMe (65.2) > *p*-SH (11.3) and *o*-SMe (18.4) > *o*-SH (4.42). The sulphur group orders are those which would be expected on the basis of the electron-releasing behaviour of Me compared with H and/or the hyperconjugative abilities of Me—Y and H—Y bonds, as inferred from their behaviour when Y is C. Various explanations have been suggested, e.g. that OH tends to behave in some way in anionic form as O^- or O^-H^+ in the media in question. This might be encouraged through hydrogen-bonding with the solvent, and would certainly greatly enhance the $-R$ effect of the substituent. The orders *p*-OMe > *p*-OPh and *o*-OMe > *o*-OPh are, of course, what would be expected from the usual inductive and resonance effects of these groups. The $\log f_o/\log f_p$ ratios are low compared with those shown in acid-catalysed hydrogen exchange. This has been attributed to the resonance effects being smaller in protiodesilylation, so that the short-range $+I$ effect at the *ortho* position becomes more evident. The deactivation by *m*-OMe and *m*-OPh indicates, as we have seen previously (Section VI.B.2.a), that the relayed resonance effect from the *meta* position is not able to outweigh the $+I$ effect even under considerable electron demand.

It is of interest that the very high value of f, *ca* 1.8×10^8, for $2,4,6\text{-}(OMe)_3C_6H_2SiMe_3$ is fairly closely in accord with additive contributions from the methoxy groups involved.

The f_p values (Table 10) for CH_2OMe, CH_2OEt and CH_2OH may be compared with the value of 18 for CH_3. The value of f_p is naturally reduced by the electron-attracting nature of OMe, OEt and OH bonded to CH_2. In view of the complicated possibilities of hydrogen-bonding of the medium to OR and particularly OH, one cannot really say whether CH_2OH having the lowest f_p value is in accord with expectation (cf Section III.A). However, the order $CH_2OMe < CH_2OEt$ might have been expected, rather than the reverse as found. Steric hindrance to solvation in the CH_2OEt substrate has been suggested as the cause of the inversion.

TABLE 10. Partial rate factors for acid-catalysed protiodetrimethylsilylation of $XC_6H_4SiMe_3$ at 50 °C[157]

X	f(MeOH–HClO$_4$)	$\log f_o/\log f_p$	f(AcOH–H$_2$SO$_4$)
4-OH	10,700	0.89	
2-OH	3,720		
4-OMe	1,270	0.82	1010
2-OMe	335		
4-OPh	88.5	0.48	
2-OPh	8.73		
3-OPh	0.36		
3-OMe			0.38
4-CH_2OMe			1.27
4-CH_2OEt			0.70
4-CH_2OH			0.64

Results are also available for the effects of OH, OMe and OPh in acid-catalysed protiodegermanylation[158].

c. Base-catalysed protiodesilylation. The mechanism of base-catalysed protiodesilylation is analogous to that of base-catalysed hydrogen exchange (Section VI.B.2.b), i.e. attack on an aryl anion is involved and the usual substituent effects are reversed. Thus partial rate factors for base-catalysed protiodetrimethylsilylation in 1:6 v/v H_2O:DMSO at 40 °C are 2.17 and 0.24 for *m*-OMe and *p*-OMe, respectively[159]. Powerful $-R$ groups do not deactivate strongly, however, and in Hammett-type correlations σ^0 (Section II.B) may be used with some success.

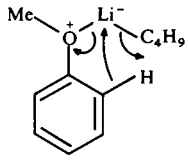
4. Metallation[160]

The replacement of hydrogen by metal is an important class of aromatic substitution reactions. Electrophilic substitution is usually assumed to be involved, but except in the case of mercuriation the exact nature of the reactions has rarely been well established[160].

Lithiation[161] with Bu^nLi:

$$ArH + Bu^nLi \longrightarrow ArLi + butane$$

shows a strong preference for substitution in the *ortho* position to substituents such as OMe and NMe_2, suggesting that coordination of substituent to reagent may be involved, as in **38**. Anisole is lithiated exclusively in the *ortho* position and phenetole almost entirely so[161]. The 1,3-$(OMe)_2$ compound is 97% lithiated in the 2-position, but the 1-OMe-3-Me substrate goes to the extent of 40% in 2- and 60% in 6-position. Another consequence of coordination to the reagent is a preference for the 8-position for attack on 1-methoxynaphthalene.



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Mercuriation[162] may be carried out under various different conditions and numerous mechanistic aspects have been elucidated, e.g. the reactions are subject to catalysis by mineral acids and salts. In uncatalysed mercuriation by mercury(II) acetate in acetic acid, the principal reactive entity is probably $HgOAc^+$. The partial rate factors have been measured for several monosubstituted benzenes. There is a general preference for *para* mercuriation, and log *f* values correlate with σ^+, giving a ρ value of -4.0 at 25 °C. For OMe, $f_o = 188$, $f_p = 2310$; for OPh, $f_p = 194$. *Ortho* mercuriation appears to be subject to steric hindrance[162].

Various electrophiles have been identified in thalliation[163], depending on the conditions. There is often a preference for *para* substitution, but with thallium tris(trifluoroacetate) anisole is attacked at room temperature in the *ortho* position, suggesting that a coordination mechanism is involved.

5. Reactions involving electrophilic carbon[164]

There are numerous reactions of this type (Taylor[164] gives 308 references), in many of which carbon in alkyl halides, acyl halides, alcohols, esters, ethers, etc. is activated

TABLE 11. Isomer distributions and reactivities relative to benzene in $TiCl_4$-catalysed benzylation of anisole with $XC_6H_4CH_2Cl$ at 25 °C[165]

X	Relative reactivity anisole/benzene	Isomer distribution(%)		
		ortho	*meta*	*para*
4-NO_2	7.0	54	< 0.5	46
H	14	47	< 0.3	53
4-OMe	15,500	30	—	70

by means of a Lewis acid. The best known of these substitutions are the Friedel–Crafts reactions. Isomer distributions and reactivities relative to benzene are shown in Table 11 for the $TiCl_4$-catalysed benzylation of anisole with $XC_6H_4CH_2Cl$ at 25 °C. The isomer distribution tends towards the statistical between the *ortho* and *para* positions as the reactivity of the benzyl halide is increased, and at the same time there is a decrease in the anisole:benzene rate ratio.

With many combinations of reagent and Lewis acid, however, the reactions of substrates containing alkoxy or hydroxyl groups are inhibited by coordination of the Lewis acid with the substituent. This often limits studies of directing and activating effects to alkyl groups and halogens, but partial rate factors have been measured for the acetylation of a wide range of substrates PhX with acetyl chloride and $AlCl_3$ in 1,2-dichloroethane. There is a strong preference for *para* substitution, and this apears to be exclusive in the case of anisole with $f_p = 1.8 \times 10^6$ [166]. On the other hand, partial rate factors for the arylation of PhX with phenyldiazonium tetrafluoroborate in acetonitrile at 40 °C Show rather less discrimination between the positions, with values for OMe of $f_o = 3.14$, $f_m = 0.68$ and $f_p = 3.53$[167].

6. *Reactions involving nitrogen electrophiles*[168]

a. Diazonium coupling[169]. This involves electrophilic substitution by ArN_2^+:

$$ArN_2^+X^- + Ar'H \rightarrow ArN{=}NAr' + HX$$

ArN_2^+ is a poor electrophile and considerable activation of the substrate is required. Such reactions are therefore limited to amines and phenols as substrates. The bulky nature of the electrophile encourages substitution in the *para* rather than the *ortho* position, but if the former is blocked, the latter may be attacked.

b. Nitrosation. Nitrosation by nitrous acid under various conditions may involve several different reactive entities[170]. The rate is very sensitive to the effects of substituents in the substrate PhX. For *para* nitrosation of PhX by $NaNO_2$ in 10.4 M $HClO_4$ at 52.9 °C, $\rho = -6.9$, and f_p values for OPh, OMe and OH are 3780, 210,000 and 168,000, respectively.

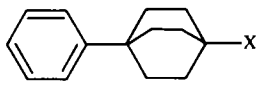
c. Nitration[171]. This has been the most studied of all electrophilic aromatic substitutions (cf Section I.B, the Historical Introduction). Nitration may be carried out by means of a wide variety of reagents and under a wide variety of conditions. However, the mechanism in many cases is essentially the same, involving the nitryl cation NO_2^+, or some species closely related thereto.

Nitration by nitric acid in strong mineral acids shows the feature of 'limiting' or 'encounter' rate, in which the aromatic substrate removes the NO_2^+ almost as rapidly

as it is generated. Relative rates of nitration then show little variation with substrate. Thus for nitration in 68.3% w/w sulphuric acid at 25 °C, relative rates are: benzene, 1.0; toluene, 17; anisole, 13; *o*-methylanisole, 22; *p*-methylanisole, 21; 1-methoxynaphthalene, 35; phenol, 24[172]. There is more interest in variation of *ortho:para* ratios with acidity. Thus nitration of anisole in aqueous perchloric acid gives ratios that vary from 1.58 in 50.6% w/w acid to 0.80 in 72.7% acid[173]. There are similar decreases in the ratios for nitration in sulphuric acid as the percentage of acid is increased, both for anisole and for phenol[174,175]. These changes have been attributed to increased hydrogen-bonding to the substituent with increasing acidity. Presumably hydrogen-bonding of OMe and OH to the medium blocks the *ortho* positions.

Nitric acid in acetic anhydride contains various nitrating species, including protonated acetyl nitrate. It might be expected that this would have a large steric requirement. Nevertheless phenyl ethers do not give unduly low *ortho:para* isomer proportions under these conditions, e.g. OMe, 1.54 (45 °C); CH_2OMe, 1.21 (25 °C); OPh, 1.04 (0 °C)[176]. It has been suggested that coordination of the reagent with the substituent may favour *ortho* substitution. (Taylor[176] gives a comprehensive Table of isomer distributions and partial rate factors for nitration of amines, anilides and ethers under various conditions.)

On the other hand, very low ratios f_o/f_p are given by nitration of 4-X-1-phenylbicyclo[2.2.2]octanes (**39**) by HNO_3–Ac_2O at 25 °C[177]. For OMe $f_o = 4.84$, $f_m = 4.12$, $f_p = 63.5$; cf X = H, 10.9, 6.87, 123, respectively. Presumably the bulky bicyclooctyl group disfavours *ortho* substitution relative to *para* substitution. In view of the electron-attracting nature of OMe attached to the bicyclooctane system (Section III.A.1) it is not surprising that each H/OMe pair of f values shows the order H > OMe. However, at first sight it may seem surprising that *meta* substitution is increased so little in relative importance by the introduction of OMe. The effect is qualitatively similar for X = hal, CN, COOMe, NO_2. Evidently the electronic behaviour of bicyclooctyl as a $-I$, $-R$ group continues to dominate, only slightly modified by the remote electron-attracting group X.



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7. *Reactions involving oxygen and sulphur electrophiles*[178]

Hydroxylations with peracids and with other hydroxylating agents give extraordinarily high *ortho:para* isomer ratios with anisole, phenetole and other substrates, but this is due to the destruction of much of the *para* isomer formed in subsequent preferential oxidation.

Numerous different reactive entities have been identified under the various conditions of sulphonation, and *ortho:para* ratios vary markedly with the conditions. Also the products first formed under kinetic control are liable to change in composition during prolonged reaction times in which thermodynamic control may supervene. In these circumstances substantial amounts of *meta* isomer may be formed in a system expected to yield mainly *ortho* and *para* products.

Partial rate factors for sulphonation in 77.8% sulphuric acid (in which the electrophile is probably $H_3SO_4^+$) at 25 °C are $f_0 = 3400$ and $f_p = 7300$ for phenol, and $f_o = 2000$ and $f_p = 7100$ for anisole[179]. These are modest values for the electrophilic substitution of these substrates and probably indicate that the substituents are extensively hydrogen-bonded to the solvent. The log f_o/log f_p values are 0.91 and 0.85, respectively,

the lower value for anisole probably signifying the occurrence of steric hindrance to *ortho* substitution.

8. *Electrophilic halogenation*[180]

As mentioned in the Historical Introduction (Section I.B), much pioneering work on halogenation, particularly of phenolic ethers, was done in the nineteen-twenties and nineteen-thirties[32,33].

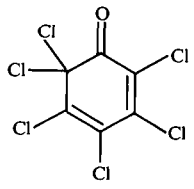
Halogenation usually involves one of three types of reactant[181]: (i) molecular halogen, (ii) molecular halogen in the presence of a Lewis acid, (iii) some form of positive halogen, such as Cl^+ or its solvated form $ClOH_2^+$.

a. Fluorination. Relatively little is known about substituent effects in electrophilic substitution by fluorine, but partial rate factors have been measured for reaction of F_2 with PhX in $CFCl_3$ at $-78\,°C$[182]. For several substituents $f_o \approx f_p$ or $f_o < f_p$, but for OMe: $f_o = 123$, $f_m = 8.1$, $f_p = 76.1$. This parallels the behaviour of anisole in some other reactions in which coordination of electrophile with substituent is believed responsible for a marked *ortho* preference, but this can hardly be the case here.

b. Chlorination. The *ortho:para* ratio for anisole reacting with *t*-butyl hypochlorite is 0.65 and is independent of acidity. The ratio for phenol varies from 0.43 at pH 4.0 to 4.3 at pH 10.0. This change may be attributed to an increased amount of reaction via phenoxide ion at higher pH[183].

In the chlorination of anisole by molecular chlorine the ratio *ortho:para* is subject to a complicated solvent effect. Also the chlorination of anisole in the presence of cyclodextrin causes the *ortho:para* ratio to drop to below 0.05. The enclosure of the anisole molecule by the cyclodextrin molecule leaves only the *para* position reasonably exposed to attack[184].

Anisole is chlorinated almost exclusively in the *para* position by 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone or by 2,3,4,4,5,6-hexachlorocyclohexa-2,5-dienone[185], structures **40** and **41** respectively. This seems likely to be due to steric hindrance. However, the former reagent gives considerable *ortho* substitution in phenol, particularly in non-polar solvents. This is probably due to hydrogen-bonding between carbonyl group and phenolic hydrogen, with resultant facilitation of the transfer of chlorine from CCl_2 to the *ortho* position in phenol, as in **42**.



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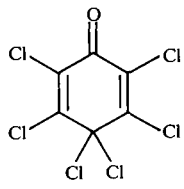

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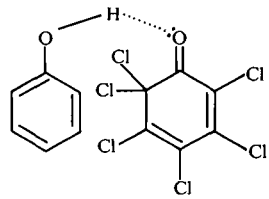

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c. Bromination. Partial rate factors for *para* substitution of phenolic ethers PhX by Br_2 in water are as follows[186]: OMe, 3.5×10^9; OEt, 2.8×10^{10}; OPr^n, 3.74×10^{10}; OPr^i, 5.85×10^{10}; OBu^n, 2.76×10^{10}; OPh, 3.33×10^7. The general effect of chain length and branching of the alkoxy group is in accord with the traditional view of the way these factors influence electron release by alkyl groups[56], with OPh being considerably less electron-releasing in accordance with the electron-attracting properties of Ph itself. It

has been suggested that the order $OPr^n > OBu^n$ could be due to slight steric hindrance to the resonance effect of the larger alkoxy group.

Partial rate factors for *para* substitution of PhX by bromine in aqueous acetic acid are: OH, 3.7×10^{12}; OMe, 1.1×10^{10} [186]. As we have remarked before (Section VI.B.3.b), the order OH > OMe is considered anomalous. The order may arise from the different modes of hydration of the two groups (Section III.B.3), but it has also been suggested that part of the greater $-R$ effect of OH is due to hyperconjugation $H^+O^-=$. Some workers consider this to be unlikely because C—C hyperconjugation is well established as greater than C—H hyperconjugation. However, recent work on the molecular bromination of phenol in acetic acid provides some support for the hyperconjugative explanation of the order OH > OMe[187]. Second-order rate constants ($dm^3\,mol^{-1}\,s^{-1}$) at 25 °C are as follows: phenol in CH_3COO^1H, 17.5, and in CH_3COO^2H, 11.7; anisole in CH_3COO^1H, 0.20, and in CH_3COO^2H, 0.60. The dissolution of phenol in CH_3COO^2H of course converts it into PhO^2H. In the case of anisole, the observed solvent isotope effect is attributed to differences in hydrogen-bond donor–acceptor interaction involving the hydroxyl hydrogen of acetic acid and the oxygen of the OMe group. Such an effect should also operate in the case of phenol, but a somewhat reversed isotope effect is actually observed. The authors suggest that a rate enhancement comparable with that observed for anisole is more than cancelled out by a rate decrease due to the electron-releasing effect of O^2H being weaker than that of O^1H. This seems to require a contribution from hyperconjugation of OH in addition to electron delocalization involving the lone pairs of oxygen.

The late Peter B. D. de la Mare (1920–1989) was much concerned with the role of hyperconjugation throughout his long research career. It therefore seems appropriate to refer to a lecture on this topic which he gave a few years before his death[188]. He also wrote an extensive review on linear free-energy relationships in electrophilic chlorination and bromination of organic compounds[189].

It has also been suggested that the order OH > OMe could be due to steric inhibition of the resonance effect being greater by Me than by H; cf the suggestion above to explain the order $OPr^n > OBu^n$. Steric inhibition of resonance is clearly shown by the effect of flanking methyl groups on the activating influence of OMe and OH in bromination. Taylor gives the following relative rates of bromination of anisoles and phenols[186]: anisole, 1.0; 2-methylanisole, 6; 2,6-dimethylanisole, 0.4; phenol, 90; 2-methylphenol, 450; 2,6-dimethylphenol, 550. The deactivating effect of 2,6-Me_2 in anisole, compared with the activating effect of 2-Me, are clear indications of steric inhibition of the $-R$ effect of OMe by 2,6-Me_2. In phenol the behaviour is less dramatic, but steric inhibition is indicated by the small activating effect of the second Me compared with the first. Thus OMe is clearly more sensitive than OH to steric inhibition of resonance.

d. Iodination. The mechanism of iodination with iodine is not well understood, but the reaction shows large substituent effects[190]. The PhO^- ion is about 10^{10} times more reactive than undissociated phenol, while phenols are about five times more reactive than their methyl ethers.

VII. ELECTRONIC EFFECT OF THE UNIPOLE O^-

A. Introduction

Earlier sections have referred several times to the enhanced electron-releasing properties of O^- as a substituent on a benzene ring compared with OH or OMe, e.g. in Sections I.B, VI.B.8.b and VI.B.8.d. This behaviour is readily attributable to a reversal of the inductive effect as compared with OH or OMe, O^- being thus a $-I$ substituent,

and an enhanced $-R$ effect. These characteristics are particularly evident in some types of electrophilic substitution, but it is easy to find examples in some less electron-demanding reactions.

The effect of O^- in the ionization of benzoic acid cannot be observed, but it is possible to do so in the alkaline hydrolysis of ethyl benzoate, for which reaction the effect of OH cannot easily be studied. For the alkaline hydrolysis of m-XC_6H_4COOEt in 76% w/w aqueous ethanol at 35 °C, values of $\log k$ (second-order rate constant, litre mol^{-1} s^{-1}) are as follows[74c]: X = H, −2.76, OMe, −2.46; O^-, −4.00. The ρ value is about 2.5. Thus m-O^- is strongly electron-releasing in character (cf m-OH), with an apparent σ value of about −0.50. For the alkaline hydrolysis of p-XC_6H_4COOEt in 56% w/w aqueous acetone at 25 °C $\log k$ values are as follows[74c]: X = H, −2.62; OEt, −3.22; O^-, −5.06. The ρ value is again about 2.5, so the apparent σ value of p-O^- is about −0.98; cf p-OH, −0.327 (Section III.B.3).

The electronic effect of O^- is also revealed in the second ionization constants of the dihydroxybenzenes. The $(pK_a)_2$ values for m- and p-dihydroxybenzenes in water at 25 °C are about 11.2 and 11.5, respectively[74]. Comparison with other substituted phenols requires a statistical correction of −0.30 to allow for there being two O^- sites in the doubly-charged anion. Thus, taking the pK_a value of phenol as 10.00, the corrected $(\Delta pK_a)_2$ values of the dihydroxybenzenes are −0.9 and −1.2, respectively. It we apply a ρ value of about 2.2 for the ionization of phenols, the apparent sigma values are −0.41 for m-O^- and −0.55 for p-O^-. The former is not too far from the value of −0.50 derived above from the ethyl benzoate hydrolysis; the discrepancy may reflect the difference between a σ value from the benzoate system and a σ^0 value from the phenolic system (Sections II.B and III.C.2). The discrepancy for p-O^- is much larger and could be due to a resonance saturation effect of two powerful $-R$ entities in *para* position to each other in the doubly-charged anion (cf Section III.C.2).

To complete the picture for the dihydroxybenzenes, we mention that the $(pK_a)_2$ value of o-dihydroxybenzene is about 12.10[74] (the value appears to be difficult to determine accurately, and the real value may be higher, perhaps nearer 13), which gives 11.8 on statistical correction. Thus the second ionization of the *ortho* compound is considerably weaker than that of the *meta* or *para* isomer. No doubt this is partly due to strain arising from the proximity of two negatively charged centres in the doubly-charged anion, and also partly to the stabilization of the singly-charged ion by internal hydrogen-bonding; see Section IV.B.3, structure **32**.

B. The Behaviour of Unipolar Substituents with Respect to the Hammett Equation

In the Introduction above, the Hammett equation was applied to the effects of O^- on reactivities, the implied assumption being that this was a valid and meaningful procedure. While the calculation of apparent sigma values is a convenient way of comparing the effects of O^- under given conditions with those of other substituents, the simple Hammett equation is not really applicable to unipolar substituents. For the latter it is not possible to define sigma values on the basis of suitable reference systems, and then to apply these widely and successfully to many different processes.

The Hammett treatment is essentially based on dipolar substituents. In the original presentation of the Hammett equation (1937)[88,191], substituent constants were not tabulated for any unipolar substituent. When Jaffé (1953)[46] reviewed the state of the Hammett equation, he tabulated σ values for several 'cationic' or 'anionic' substituents, e.g. m- and p-NMe_3^+, m-NH_3^+, m- and p-CO_2^-, p-SO_3^-, m- and p-O^- and others. He seemed fairly optimistic that the extension of the Hammett equation to embrace ionic substituents would prove a successful development. He commented[192]:'Since the

available data indicate no greater uncertainty for substituent constants of ionic substituents than for those of neutral groups, the Hammett equation also appears to be applicable to substituents which carry an integral charge'. However, he also pointed out that ionic substituents will interact strongly with polar solvents, and that their substituent constants might be expected to be particularly solvent-dependent.

In fact, problems that may be expected to arise in the attempt to include unipolar substituents within the scope of the Hammett equation may readily be envisaged. A given reaction of a substrate containing a unipolar substituent will be of a charge type different from that of the same reaction of a substrate containing a dipolar substituent. This difference has immediate consequences. The reactions of substrates of different charge type will respond differently to changes in ionic strength and in dielectric constant of the medium, i.e. whether equilibria or rates are involved, reactants of different charge type will show different primary salt effects and different solvent effects.

Suppose we establish a Hammett relation for a given reaction series involving dipolar substituents under given conditions. We may then use appropriate data for unipolar substituents to measure apparent sigma values for those substituents. (This is essentially what we did for *m*- and *p*-O^- above.) If we now consider another set of data for the same reaction but under markedly different conditions of ionic strength and/or dielectric constant of the medium, we may derive a new Hammett relation for the dipolar substituents, and try also to include the unipolar substituents on the basis of the sigma values previously derived. The general result will be that the latter will not be found applicable under the new conditions, because the substrates involving unipolar substituents, on the one hand, and those involving dipolar substituents, on the other, have responded differently to the changes in the medium. Thus any simple definition of sigma values for unipolar substituents to be used in a treatment which is dominated by dipolar substituents is in principle impossible. The inclusion of dipolar and unipolar substituents in one treatment can only be done by including specific consideration of the effects of ionic strength and dielectric constant in an elaboration of the Hammett equation. In essence this is what Wepster has tried to do[193] (Section VII.C).

It is not surprising that the attempt during the past forty years to include unipolar substituents in simple Hammett treatment has produced what the present author has described elsewhere as a 'long history of anomalies, failures, and warnings'[4,43]. Thus authors have persistently found that sigma values of unipolar substituents show marked dependence on ionic strength and dielectric constant of medium and that values based on behaviour in a given reaction under given conditions prove totally inapplicable to another reaction under different conditions, for no immediately obvious reason. The present author has summarized this history in various publications[1,43]. For present purposes the history may be exemplified by showing the sigma values for *m*- and *p*-O^- which have been proposed at various times[45,97]. Before this is done, it needs to be mentioned that the study of the effects of unipolar substituents necessarily involves the presence in the reaction solution of an oppositely charged 'gegen' ion. In the case of the O^- substituent this has often been Na^+ or K^+. Under certain conditions ion-pair formation may occur, so that the substrate being studied is an equilibrium of O^- and O^-M^+ substituted species. This is a further complication in the attempt to understand apparent sigma values of a unipolar substituent. Compilers of sigma values often neglect to mention the identity of the gegen ion, and sometimes this is even difficult to determine from the original source of the data.

Jaffe'[46] gave values of -0.71 for σ_m and -0.52 for σ_p of O^-. The σ_m value was based on the alkaline hydrolysis of benzamides in 60% ethanol and may be regarded as essentially on the benzoic acid scale. However, it differs considerably from the value of -0.50 which we calculated above from the alkaline hydrolysis of ethyl benzoates. The σ_p value was based on the ionization in 50% methanol of $ArC(=NH)NH^+(C_4H_9)_2$ and its

status must be regarded as uncertain[45]. The identities of the gegen ions are not clear.

The situation is clearer for values based on the alkaline hydrolysis of aryl tosylates or aryl benzoates (i.e. substituents in the alcohol moiety of the ester)[194]. The gegen ion was K^+, the solvent was water and extrapolations to zero ionic strength were carried out. The values should have the status of σ^0 constants. The two ester systems gave concordant values for σ_m^0 with an average of -0.87, and the aryl benzoate system gave σ_p^0 as -0.82. There is also a value for σ_p^0 of -0.75, based on the alkaline hydrolysis of aryl 2,4-dinitrophenates in dioxan–water, K^+ being the gegen ion[195].

Hine arrived at values of σ_m and σ_p for O^- by application of a form of Hammett equation sometimes referred to as the Hine equation[196]. Data for various reaction series in water were involved, and the status of the values arrived at, a kind of average, is not clear; nor is the identity of the gegen ion(s) clear. The values were $\sigma_m = -0.47$ and $\sigma_p = -0.81$.

Taft and coworkers[63,64] determined σ_I and σ_R^0 values for O^- from ^{19}F NMR shielding (Section II.B) as -0.16 and -0.60, respectively. The solvent was methanol–water, but the identity of the gegen ion is not clear, These values may be compared with values of 0.29 and -0.43 for OH, respectively, also based on ^{19}F NMR shielding. The value of σ_R^0 for O^- is essentially confirmed by a value of -0.59 based on infrared intensities by Brownlee and collaborators[197] (Section II.B), D_2O being the solvent and Na^+ the gegen ion. From Taft's values of σ_I and σ_R^0 for O^-, values of σ_m^0 and σ_p^0 may be calculated as -0.46 and -0.76, respectively (Section II.B, equations 6 and 7).

The reader may be left to try and decide whether the occasional approximate numerical agreements in the above sigma values as determined by different authors by various methods are anything more than coincidence.

Two different σ_p^+ values for O^- have been proposed. Wepster[198] derived a value of -2.3 through a complicated manipulation of data; cf the usually quoted value for OH of -0.92 (Section VI.A). The same paper arrives at a σ_p^n value[49] (Section II.B) of -0.50 (cf -0.76 for σ_p^0 above). A value of σ_p^+ for O^- of -1.6 was based on acid-catalysed hydrogen exchange by Clementi and Katritzky[199].

C. Wepster's Treatment of Unipolar Substitutents

The essence of this treatment lies in considering a 'Bjerrum field effect term' as a separate component of the Hammett equation. Wepster's paper[193] occupies some 25 pages of the *Journal of Organic Chemistry* and contains extensive tabulation of experimental results (partly Wepster's own work, but mainly from the literature, with many references) and of the results of applying the new treatment. The experimental results are for the effects of both unipolar and dipolar substituents in a variety of reactions and they have been analysed in terms of the classical ideas developed by Lewis and Bjerrum and recently revived by Palm and his coworkers[200]. The outcome is that the Hammett equation needs only a simple extension to cover the effects of both dipoles and poles. The present author has previously written a fairly lengthy summary of Wepster's paper, while recommending that seriously interested readers should consult the original paper[43]. Here, however, only a brief summary will be attempted, with an indication of application to O^-.

The attempt to correct experimental data to zero ionic strength is fundamental to the treatment, even though often this can be done only approximately. The model of non-conjugative substituent effects which is used is a combination of Lewis's model of the inductive effect as a through-bonds displacement of electrons, and the electrostatic model of the field effect as devised by Bjerrum in his treatment of the first and second ionization constants of aliphatic dicarboxylic acids in water. As Wepster acknowledges,

these models have their limitations, but he claims that their combination has nevertheless led to a very successful treatment.

The Hammett equation is rewritten as

$$\Delta = \rho\sigma \tag{29}$$

where Δ is the substituent effect ($\log K - \log K_H$ or $\log k - \log k_H$; note the use of the actual reactivity for the parent system), $\rho \equiv \rho_m$ is the reaction constant as obtained by using standard σ_m values[49], and σ is the substituent constant which may either be Wepster's own σ^n in the absence of 'mesomeric *para* interaction' (as he terms cross-conjugation), or an exalted value, perhaps σ^+ or σ^-. From the rewritten Hammett equation and the above models, Wepster writes equations 30 and 31:

$$\Delta = \delta^L + \delta^B \tag{30}$$

$$\Delta = \rho^L\sigma^L + \delta^B \tag{31}$$

δ^L signifies the effect through the molecule (the superscript standing for Lewis) and δ^B is the electrostatic effect (the superscript standing for Bjerrum); σ^L is a sigma value free from the Bjerrum field effect and ρ^L is a reaction constant based on such (*meta*) σ^L values. The Bjerrum term is based on the well-known expressions in electrostatics for the interaction energies of two point charges, in the case of a unipolar substituent, or of point charge and dipole, in the case of a dipolar substituent, the interactions being moderated by the dielectric constant of the solvent.

The extension of the Hammett equation to unipolar substitutents formally requires a redefinition of the σ values of dipolar substituents as σ^L values, but the changes involved are very small and in practice $\sigma^L \approx \sigma^n$ for such substituents, and $\rho^L = \rho_m$ as defined above. σ^L values (strictly σ^{Ln}) for many unipolar substituents were derived from experimental results on various acid–base equilibria and applied to other reactions through equation 31. The general success of the treatment was shown graphically and by statistical tabulation. Individual σ^{Ln} values and those for structural series were specially discussed.

The values of σ_m^{Ln} and σ_p^{Ln} for O^- were found to be -0.28 and -0.45, respectively. These values were not so securely established as those of some unipolar substituents, since the data available were very limited. (The data were for *m*- and *p*- dihydroxybenzenes. It is not clear to the present author whether statistical corrections were made. See Section VII.A.) The values are distinctive by being negative. Those of other negatively charged substituents are positive, e.g. the corresponding values for COO^- are 0.24 and 0.26, respectively, and for SO_3^- they are 0.49 and 0.51, respectively. Presumably the negative values for O^- mean that an appreciable part of the $-I$ effect passes through the molecule, in addition to the part which constitutes the Bjerrum field component. Naturally the values include the whole of the $-R$ effect. If we assume that the composition of σ^{Ln} values in inductive and resonance effects of unipolar substituents is given approximately by the same equations as are operative for the σ^0 values of dipolar substituents, equations 6 and 7 in Section II.B, we may tentatively suggest values of σ_I^{Ln} and σ_R^{Ln} for O^- of -0.10 and -0.35, respectively.

As a tailpiece to our discussion of Wepster's treatment, it should be mentioned that the problem of 'charged substituents in correlations of electronic substituent effects' has been discussed from a different point of view by Marriott, Reynolds and Topsom[201]. These authors were concerned with the dual substituent-parameter equation (Section II.B) and the redefinition of the σ_I scale as a σ_F (through-space electrostatic effect) scale. From the electrostatic model of the so-called inductive effect it follows that the non-conjugative substituent effect will vary with distance r from the reaction centre

as $1/r$ for a unipole and $\cos\theta/r^2$ for a dipole. (θ is the angle between the dipole and the line of length r joining the centre of the dipole to the reaction centre.) Thus a σ_F scale which was established for unipoles and dipoles on one system could not be applied to another system which was characterized by different values of r and θ. The values of σ_F for the unipolar substituents would then inevitably be out of scale with those for the dipolar substituents. These arguments were supported by reference to a theoretical scale of σ_F values obtained by *ab initio* molecular orbital calculations. This scale mainly involved dipolar substituents but three unipoles were included: NH_3^+, O^- and COO^-.

VIII. THE IMPACT OF MODERN EXPERIMENTAL AND THEORETICAL TECHNIQUES ON SUBSTITUENT CONSTANTS

A. Experimental Techniques

The emphasis in the foregoing parts of this chapter has been deliberately 'chemical'. We have tried to explore the role of substituent constants in relation to understanding the effect of structure on reaction rates and equilibria, with particular reference to the behaviour of hydroxyl and ether groups as substituents. In Section II.B brief reference was made to the use of substituent constants in the correlation analysis of spectroscopic data, particularly ^{19}F and ^{13}C NMR substituent chemical shifts and infrared frequencies and intensities. Occasional reference has been made to such matters thereafter, but they must now be explored in somewhat greater detail.

Attempts were made to apply Hammett benzoic acid-based σ_m and σ_p constants to the correlation analysis of spectroscopic data. Some significant correlations were obtained, but many of the correlations were rather poor, trends rather than precise relationships. Success in this area was found to involve the separation of inductive and resonance effects and the application of the dual substituent-parameter (DSP) equation. Indeed the development of the DSP equation became closely connected with the correlation analysis of ^{19}F NMR shielding of substituted fluorobenzenes at an early stage, around 1957[202]. σ_I and σ_R^0 were applied extensively to ^{19}F NMR data[57], and within a few years the correlations were being used to investigate 'the effect of solvent on the inductive order'[63], and 'the effect of structure and solvent on resonance effects'[64]. New σ_I and σ_R^0 values were based on the correlations. What happened with ^{19}F NMR set a pattern which was followed by later work. Established σ_I and σ_R^0 values for substituents which were expected to be 'well-behaved' were used to set up regression equations. In the very early days the established substituent constants were all based on chemical reactivity (rate constants or equilibrium constants). ^{19}F NMR data for groups for which no appropriate substituent constants were available were then substituted into the regression equations to obtain '^{19}F NMR-based values' of the substituent constants. Further, for the substituents which had been used to establish the regression equations, back-calculation from the NMR data led to '^{19}F NMR-based values' for those substituents as well. Thus for many substituents both 'reactivity-based' and '^{19}F NMR-based' values of σ_I and σ_R^0 became available. For certain substituents there was a proliferation of values based on reactivity under various conditions or on ^{19}F NMR in different solvents. Slightly later, correlation analysis of infrared data led in particular to new σ_R^0 values and to a lesser extent new σ_I values, which were described as 'IR-based'[67,68]. Somewhat later the same development occurred in connection with ^{13}C NMR, leading to '^{13}C NMR-based' values[65,66].

Naturally these developments all involved many of the substituents with which we are concerned in this chapter, particularly OMe, OH and OPh.

Thus OMe was characterized by Taft[54,56] with a σ_I value of 0.23, based on the appropriate σ^* value in his analysis of reactivities in ester reactions. The application of ^{19}F NMR found for OMe a σ_I value of 0.25 'normal solvents', 0.26 in dioxan, 0.29 in 'weakly protonic solvents', and 0.51 in trifluoroacetic acid[63]. The last-mentioned high value was attributed to the effect of strong hydrogen-bonding of CF_3COOH to *O*Me. A recent compilation of substituent constants gives a ^{19}F NMR-based value of 0.30, from a chemical shift determined in cyclohexane solution[81]. This is higher than the earlier value determined in cyclohexane, which was regarded as a 'normal solvent', probably due to a combination of new data and a new regression equation. The σ_I value recommended by Ehrenson, Brownlee and Taft[59] was 0.27 and Charton's reactivity-based value is 0.30[78] (Section III.A.1).

For the σ_R^0 constant of OMe, the reactivity-based value (Taft and Lewis[54,55]) was -0.41, and the ^{19}F NMR-based value was -0.43[64]. The latter value is also given in the more recent compilation[81]. An IR-based value of σ_R^0 for OMe (solution of anisole in CCl_4) was -0.428[197]. (Note: the sign of σ_R^0 is not actually given by the correlation of infrared intensities, because the square of σ_R^0 is involved.) The value recommended by Ehrenson's group[59] was -0.45 and Charton's value is -0.44[78].

The situation for OH, OPh, and other substituents of interest for this chapter is easily explored in the references given above. The variation of spectroscopically based values of σ_I and σ_R^0 with structure usually parallels what has been found through the study of chemical reactivitites, although numerical discrepancies in the constants of a few units in the second place of decimals may sometimes occur. The influences of hydrogen-bonding to the solvent which are manifested in the reactivity studies are parallelled in the solvent effects on spectroscopically based parameters.

There is a continual tendency for the values of σ_I and σ_R^0 (and other σ_R-type constants) to be adjusted in the light of new measurements. Thus measurements in 1979[203] of *para* ^{13}C substituent chemical shifts for a series of mono-substituted benzenes in very dilute solution in cyclohexane, carbon tetrachloride or deuteriochloroform were the basis for a redefinition of the σ_R^0 scale and some amendment of σ_R^0 values. For most substituents the changes compared with the values recommended earlier[59] were very small, e.g. σ_R^0 for OMe came out as -0.42 compared with -0.45.

Reynolds and coworkers[204] based a similar operation on ^{13}C substituent chemical shifts of *meta*- and *para*-substituted styrenes. Iterative multiple regression was used for the redefinition of the σ_I and σ_R^0 scales. The authors also took the opportunity to replace the symbol σ_I by σ_F, having become convinced that the so-called inductive effect was entirely a field effect (see the present author's discussion of this matter[43]). The authors presented an extensive table in which their values of the substituent parameters are compared with those obtained by other authors. The σ_R^0 value of OMe was essentially confirmed at -0.42, but for σ_I the rather low value of 0.24 was found.

Happer[205] determined ^{13}C substituent chemical shifts for *meta*- and *para*-substituted styrenes in seven different solvents. Data for the side-chain carbons, and in the *meta* series for the ring carbon *para* to the substituent, were analysed as a basis for assessing solvent effects on σ_I, σ_R^0, σ_R(BA) and σ_R^-. The influence of solvent on the inductive order of substituents was studied by Laurence and collaborators through infrared measurements on 4-substituted camphors[206]. From these Laurence[207] has tabulated new σ_F values applicable to solutions in carbon tetrachloride or other solvents of low dielectric constant. OMe comes out very low at 0.20, and OH is at 0.27, cf the ^{19}F NMR-based values of 0.30 in cyclohexane and 0.32 in carbon tetrachloride, respectively[81].

Mention must also be made of the use of studies of chemical reactions in the gas phase as a means of determining substituent constants. The investigation of substituent effects and linear free-energy relationships in the gas phase has become an enormous

subject with which we can deal only briefly. Part of this subject was established a long time ago and consists in the study of such reactions as the pyrolysis of esters by the techniques of gas kinetics (see the review by Smith and Kelly[208]). One purpose of such work is to see how far substituent constants based on processes in solution may be applied successfully in the gas phase. This leads to the possibility of determining substituent constants in the complete absence of solvent. Work of this nature continues today and frequently involves alkoxy groups and other substituents of interest in this chapter[209–211].

However, the major activity in gas-phase studies now depends on the use of modern techniques such as ion cyclotron resonance (ICR). Thus Fujio, McIver and Taft[212] used the ICR equilibrium constant method to study the gas-phase acidities of 38 *meta*- or *para*-substituted phenols relative to phenol. The treatment of results by linear free-energy relationships and comparisons with behaviour in solution led to a number of interesting conclusions. For instance, a sigma value for *m*-OMe is very close to the corresponding value for aqueous solutions, but the electron-releasing properties of *p*-OMe are appreciably reduced in the gas phase compared with aqueous solution. Taft and Topsom have recently written an extensive review of the electronic effects of substituents in the gas phase[213].

B. Theoretical Techniques

The application of *ab initio* molecular orbital theory to suitable model systems has led to theoretical scales of substituent parameters, which may be compared with the experimental scales. Calculations (3-21G or 4-31G level) of energies or electron populations of simple molecular systems were made by Marriott and Topsom in 1984[214]. The results were well correlated with σ_F (i.e. σ_I) values for a small number of substituents whose σ_F values on the various experimental scales (gas phase, non-polar solvents, polar solvents) are concordant. The regression equations are the basis of theoretical σ_F values for about fifty substituents. Among the values calculated are those of OMe at 0.26 and OH at 0.29. A theoretical scale of substituent resonance effects was based on calculations of electron populations in substituted ethylenes[215]. A suitable regression equation was again set up by using standard substituents, but in this case the quantum-mechanical quantity was correlated with infrared-based σ_R^0 values. The equation was the basis of theoretical σ_R^0 values of more than forty substituents. A further redefinition of the theoretical scale was made recently[216] as a result of a change of views as to the most suitable level of MO approximation. In the latest version σ_R^0 for both OMe and OH comes out as -0.39. For OMe this is somewhat less negative than the experimental values (see above), which are in the range -0.41 to -0.45. The value for O^- was -2.1, far more negative than any of the experimental values (see Section VII.B).

It seems rash to regard these theoretical substituent parameters as in any way replacing those founded on experimental results. Topsom has recently reviewed theoretical studies of electronic substituent effects[217].

Among theoretical studies of substituents of interest to this chapter was one involving MINDO/3 and STO-3G SCF calculations of the effect of a hydrogen-bonded water molecule on the ability of a hydroxyl group to stabilize a carbocationic centre[218]. With such a water molecule present (i.e. in aqueous solution) OH is more effective than OMe, but in its absence (gas phase) OMe is the more effective.

OMe and OH have been involved, along with other substituents, in various other theoretical treatments of substituent effects, e.g. the correlation analysis of substituent effects on the acidity of benzoic acids by the AM1 method[219] and direct prediction of linear free-energy substituent effects from 3D structures using comparative molecular field analysis, the relevant data set being 49 substituted benzoic acids[220].

IX. SOME FURTHER MULTIPARAMETER TREATMENTS OF SUBSTITUENT EFFECTS

A. Introduction

Earlier sections of this chapter contain accounts of the Yukawa–Tsuno equation[52,53], the Dual Substituent-Parameter (DSP) equation[58,59] and Extended Hammett (EH) equation[62] (see Section II.B), with the particular intention of showing how these may be applied to data sets involving the substituents of particular interest for this chapter, chiefly OMe, OH and OPh. These equations are not now the only possibilities for multiparameter treatment. In this section we shall give accounts of some of the other approaches. The accounts will necessarily be brief, but key references will be given, with indications as to how the substituents of interest for this chapter fit into the various treatments.

B. Exner's Analysis

This is essentially a method of providing an alternative set of σ_I and σ_R parameters for use in the DSP equation or EH equation. In the mid-nineteen sixties Exner[61] found evidence that the inductive effect from the *para* position of benzoic acid was stronger than that from the *meta* position by a factor of 1.14. He also suggested that σ_I values current at that time and based on alicyclic and aliphatic reactivities were out of scale with σ_m and σ_p by a factor of 1.10, and should be multiplied by this to introduce the π-inductive component. This led Exner to a revised analysis of σ_m and σ_p in terms of inductive and resonance components. He calculated revised σ_I values by multiplying the alicyclic/aliphatic values by 1.10, and then multiplying these further by 1.14 before subtraction from σ_p values to obtain revised values of σ_R.

The most dramatic changes were for some $+R$ substituents, such as NO_2 and CN, whose σ_R values dropped to zero. The changes for OMe and OH were less dramatic: for OMe, σ_I and σ_R became 0.31 and -0.63, respectively (cf 0.25 and -0.52 from calculation without applying the above factors); for OH, σ_I and σ_R became 0.28 and -0.68, respectively (cf 0.25 and -0.62 from calculation without applying the above factors).

The status of Exner's revised σ_I and σ_R values has been debated for a quarter of a century. A number of prominent workers in the field are rather critical of Exner's approach. For a recent appraisal of the situation, see an article by the present author[43]. Exner has continued to propagate his view on this matter in his recently published book[44].

C. C.G. Swain's Treatments

These began with a paper by Swain and Lupton in 1968[221]. The approach was slightly modified and greatly extended by Hansch's group[222] in 1973. During the first 15 years or so of its life, the Swain–Lupton treatment was applied extensively, but was also severely criticized. A revised version appeared in 1983 in a paper by Swain and coworkers[223]. This revised version was in its turn severely criticized, but also applied. The Swain–Lupton treatment was reviewed by the present author in 1978[50] and again more briefly in 1982[51]. A more recent review[43] covers also the revised version and an account of a mini-symposium in print in which several of Swain's critics set forth their views, and Swain replied[224–227].

The Swain–Lupton treatment[221] was a reaction against the proliferation of scales of polar substituent constants. The authors maintained that the polar effect of any given

substituent could be adequately expressed in terms of just two basic characteristics: a field constant $\mathfrak{F}$ and a fixed resonance constant $\mathfrak{R}$. Swain and Lupton maintained that the correlation analysis of chemical reactivity data and spectroscopic data of aromatic systems could be carried out satisfactorily in terms of $\mathfrak{F}$ and $\mathfrak{R}$ (cf the four σ_R-type parameters introduced for the DSP equation), *meta* and *para* series being dealt with separately, as in the case of the DSP equation. The assumptions involved in establishing the $\mathfrak{F}$ and $\mathfrak{R}$ scales provoked much criticism. Nevertheless, the treatment achieved fair success when applied to chemical reactivity data and some spectroscopic data, particularly NMR[50,51]. The most notable success, however, was in the correlation analysis of biological activity data[228].

The revised version[223] developed new scales of field and resonance effects, the awkward symbols $\mathfrak{F}$ and $\mathfrak{R}$ being replaced by the more straightforward F and R. Some of the criticisms made of the earlier form of the treatment had been met by the modifications, but the critics were still not satisfied[224–226].

A compilation of F and R constants as revised by Hansch, for numerous substituents, appeared in the book by Hansch and Leo[97]. A more recent compilation of substituent constants includes F and R values, revised yet again by Hansch[81]. Values are provided for OMe, OH and OPh, and of many other substituents of interest in this chapter.

D. The Poly Substituent-parameter (PSP) Equation

This equation is an elaboration of the dual substituent-parameter (DSP) equation. Its development has been relatively recent, but Taft and Topsom, who have been closely associated with it, have already written a long review article[213] involving the equation, and this article will probably acquire the status in respect of the PSP equation that the article of Ehrenson, Brownlee and Taft[59] has in connection with the DSP equation. The name Poly Substituent-parameter equation was devised by the present author in a short account thereof[43]. Hopefully that account and the present briefer one will encourage study of Taft and Topsom's article[213].

The new treatment had its origins partly in *ab initio* molecular orbital calculations of substituent effects and partly in extensive studies of gas-phase proton transfer reactions from about 1980 (Section VIII.A). Various aspects of this work essentially drew attention to the importance of substituent polarizability. In 1986 Taft, Topsom and their colleagues[229] developed a scale of 'directional substituent polarizability parameters', σ_α, by *ab initio* calculations of directional electrostatic polarization potentials at the 3-21G//3-21G level for a large set of CH_3X molecules. The σ_α values were shown to be useful in the correlation analysis of gas-phase acidities of several series of substrates[229], and such work has subsequently been extended by Taft and Topsom[213].

Values of σ_α are available for over thirty substituents. H is the standard at 0.00 and the values range from +0.13 for F to −0.81 for Ph. The values for OMe, OEt and OH are −0.17, −0.23 and −0.03, respectively. To set these values in context we mention that the σ_α values for NH_2, NO_2, Me and Cl are −0.16, −0.26, −0.35 and −0.43, respectively.

The PSP equation is written by Taft and Topsom[213] in various forms. Equation 32 is a convenient form with which to begin this discussion:

$$-\delta\Delta G^\circ = \rho_F\sigma_F + \rho_R\sigma_R + \rho_\alpha\sigma_\alpha + \rho_\chi\sigma_\chi \qquad (32)$$

The equation is written in terms of Gibbs energy changes, rather than $\log K$ or $\log k$, because much of its application initially was to gas-phase reactions for which the use of Gibbs energies is conventional. Corresponding equations in terms of $-\delta\Delta E^\circ$ or $-\delta\Delta H^\circ$ have also been used. The negative sign is introduced to make the signs of ρ values correspond to the conventions of the Hammett equation. σ_F is Taft and Topsom's

preferred symbol for the inductive constant σ_I (see Section VIII.A), σ_R is a resonance constant closely related to σ_R^0, σ_α is the substituent polarizability parameter as above and σ_χ is the substituent electronegativity parameter.

The inclusion of σ_χ is to deal with the possibility that consideration of substituent electronegativity may be helpful in understanding substituent effects. Values of σ_χ come from *ab initio* calculations. On this scale H is taken as a standard at $\sigma_\chi = 0.00$ and the values range from -0.15 for SMe to $+0.70$ for F. OMe, OEt and OH are at 0.55, 0.55 and 0.54, respectively. To set these values in context we mention that the σ_χ values for NH_2, NO_2, CH_3 and Cl are 0.33, 0.46, 0.00 and 0.16, respectively. However, except at very short range, electronegativity effects of substituents are found not to be important, and the PSP equation may be simplified to equation 33:

$$-\delta\Delta G^\circ = \rho_F\rho_F + \rho_R\sigma_R + \rho_\alpha\sigma_\alpha \tag{33}$$

Taft and Topsom's article[213] and also Topsom's[217] should be consulted for details of the setting up of the scales of substituent parameters. The equation has been applied to a wide range of gas-phase reactivities. (In the multiple regressions an intercept term is often permitted, but usually this turns out to be indistinguishable from zero, as it should be if equation 33 is valid.) For aliphatic or alicyclic saturated systems the resonance term is duly negligible. The roles of field, resonance and polarizability effects are discussed and the interpretation of the various ρ values is attempted.

When the equation is applied to reactions in solution, it is found that polarizability effects tend to be much smaller than in the gas phase, but the PSP equation has to be adapted to include Substituent Solvation Assisted Resonance (SSAR). The PSP equation then assumes the form of equation 34:

$$-\delta\Delta G^\circ(\text{soln.}) = \rho_F\sigma_F + \rho_R\sigma_R + \rho_S\Delta\sigma_R \tag{34}$$

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

The SSAR phenomenon affects only $+R$ substituents such as CN and NO_2. σ_F(aq.) values are tabulated[213] for several substituents including NH_2 and NMe_2, but not for OMe or OH. However, a recent study applied the PSP equation to good effect in discussing the gas-phase and aqueous solution basicities of about fifty 2-, 3-, or 4-substituted pyridines, and some 2,6-disubstituted compounds[230]. The substituents studied included 2-, 3-, and 4-OMe, but these tended to show significant deviations from various relations and graphical plots. It was suggested that such deviations arise from specific solvent–substituent interactions.

E. Charton's LDR Equation

This has been developed since 1986. The title letters stand for *L*ocalized *D*elocalized *R*esponse. The localized effect is Charton's preferred name for the inductive effect and delocalized effect is his preferred name for the resonance effect. Indeed, he would like to change the usual symbols from σ_I to σ_L and σ_R to σ_D for the purposes of the Extended Hammett (EH or LD) equation[78]. The response referred to is that of the substituent to the electronic demand of the site (i.e. reaction site in the correlation analysis of reactivity). Thus this equation, like the PSP equation, is concerned with the parametrization of substituent polarizability.

We shall describe the treatment only rather briefly, because a detailed article[231] and a useful introductory account[232] have already appeared. (The latter includes a table of substituent constants for about thirty common substituents.)

The LDR equation may be written as in equation 35:

$$Q_X = L\sigma_{l,X} + D\sigma_{d,X} + R\sigma_{e,X} + h \tag{35}$$

where Q_X is the substituent-influenced property, σ_l is the localized effect parameter, identical to σ_I, σ_d is the intrinsic delocalized effect parameter for minimal electronic demand of the active site and σ_e gives the sensitivity of X to changes in electronic demand of the active site; h is, of course, the intercept term. Quantities σ_d and σ_e are defined by equation 36:

$$\sigma_D = \sigma_e\eta + \sigma_d \tag{36}$$

where η expresses the electronic demand of the active site and σ_D (i.e. σ_R) is the relevant delocalized electronic parameter which would be used in the EH treatment of the system, i.e. a σ_R-type quantity. The main article mentioned above[231] should be consulted for the methods whereby the substituent parameter scales were established. Several hundred data sets have now been treated by means of the LDR equation, and the various sigma parameters have been tabulated for more than 120 substituents.

As already mentioned, the σ_l values correspond closely to those of σ_I as derived by Charton[78], while the values of σ_d are broadly similar to Charton's values of σ_R[78]. However, individual values may sometimes differ by a few units in the second place of decimals, consequent upon σ_d being derived from σ_D (i.e. σ_R) in equation 36 by subtracting an electronic response term. Thus for OMe, OEt, OPh and OH, σ_d values are -0.55, -0.55, -0.51 and -0.57, respectively; cf -0.58, -0.57, -0.48 and -0.62, respectively, for Charton's σ_R values[78]. H is the standard for σ_e at 0.00, and the scale runs from $+0.041$ for F to -0.29 for PPh_2. The values for OMe, OEt, OPh and OH are -0.064, -0.070, -0.083 and -0.044, respectively. To set these values in context we mention that for NH_2, NO_2, Me and Cl the values of σ_e are -0.13, -0.077, -0.030 and -0.011, respectively.

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

It is claimed that, 'The LDR equation is the first successful model for electrical effects of substituents bonded to carbon in all substrates'[233].

X. SUBSTITUENT CONSTANTS: RECAPITULATION AND SOME EXTENSION

A. Introduction

It seems useful at the end of this long chapter to bring together and summarize some of the material which is scattered throughout it. Also, there are some relevant substituents which have not so far been mentioned. These include the one peroxidic substituent for which there appears to be any information.

It should have become very apparent in this chapter that the electronic effects of ether and hydroxyl groups are liable to vary greatly with the reaction studied and the reaction conditions, particularly the solvent. This means that the introduction of data for such groups into a correlation analysis must be done with circumspection. If values of substituent constants are chosen that are in fact not applicable in the given case, a fair correlation may be obtained, but it will be biassed. This is liable to be a particular danger with, for example, OMe and OH groups because on some of the sigma scales the values for these groups lie at one extreme on the scale, e.g. the ordinary Hammett σ_p values of about -0.3 are often the most negative values in a data set. This feature

arises, of course, owing to the behaviour of these groups as very strong $-R$ substituents. Also, reliable values of some substituent constants are not available. Thus it is always a good procedure to carry out correlations both including and excluding data for ether and hydroxyl groups.

Whether or not it is possible to introduce data for ether and hydroxyl groups successfully into the correlation analysis of any given data set, substituent constants for these groups are important as providing standards of behaviour under given conditions. So in this section we will summarize the situation regarding σ and σ^0 values for the most important substituents: OMe, OPh and OH, and include some information additional to what is scattered in earlier parts of this chapter. We shall also tabulate values of such constants for a variety of ether and hydroxyl-containing groups, mainly unmentioned in the earlier discussions. We shall also tabulate σ_p^+ values, with yet more discussion of the peculiar behaviour of OH as a substituent.

We shall not introduce further consideration of σ_I and σ_R-type constants. If readers wish to use the dual substituent-parameter or extended Hammett equation (Section II.B), then they should take the necessary substituent constants either from Ehrenson, Brownlee and Taft[59] or from Charton[78]. Each of these collections of inductive and resonance parameters has been arrived at by a coherent procedure, albeit a different one. Overall there is reasonable agreement between the substituent parameters in the two collections, but values of some constants for certain individual substituents do differ significantly. Values from one collection should not be mixed with values from the other collection in any given correlation. Of course it is often possible and useful to do parallel correlations with values drawn from one collection or the other. Hopefully, essentially the same conclusions will be reached from the two correlations. It is also possible to use Exner's σ_I and σ_R values in such correlations[61], but it is very important not to mix such values with those from the other collections, since Exner's values are on a different basis (Section IX.B).

B. Values of σ and σ⁰ for *m*- or *p*-OMe, -OPh and -OH, and for other Ether and Hydroxy Groups[234]

1. Methoxy group

Some five determinations of the pK_a value of *m*-methoxybenzoic acid in water (involving several different experimental techniques) are of sufficient precision to merit consideration. The values are in close agreement and give a mean value for σ_m of 0.114, essentially confirming Hammett's original value based on Dippy's work[87,191]. This may be rounded to 0.11, with a limit of uncertainty of ± 0.01.

Three modern determinations of the pK_a value of *p*-methoxybenzoic acid all find values appreciably higher than Dippy's value[87]. If all four values are taken into consideration, we arrive at a σ_p value of -0.288. This may be rounded to -0.29, with a limit of uncertainty of ± 0.02. This now seems preferable to the traditional value of -0.27 based on Dippy's work and used elsewhere in this chapter.

These values of σ_m and σ_p will also apply in fairly aqueous mixtures of water and organic solvents, but their applicability at low water content and in purely organic solvents is highly doubtful. The OMe group tends to become more electron-releasing under these conditions (Section III.B.1). It should be mentioned here that Pytela, Ludwig and colleagues[95,235] have made extensive measurements of pK_a values of substituted benzoic acids in non-aqueous media and the results have been submitted to principal component analysis and factor analysis to produce sets of substituent constants. The material is too complicated to be discussed here, but the substituents examined included *m*- and *p*-OMe, *m*- and *p*-OH and *m*-OPh.

The pK_a values for p-XC_6H_4GCOOH in water, where G is a suitable 'insulating' moiety (Section III.C.1), suggest a σ_p^0 value for OMe of about -0.10, but the small ρ values make these systems unsuitable for precise determination of σ^0 values. Yukawa's group[236] considered other suitable reactions characterized by higher ρ values. These were mainly alkaline hydrolyses of esters. The 21 values of σ_p^0 for OMe which were derived varied from -0.092 to -0.162. Several of the more negative values were excluded and the remainder gave a mean value of -0.108. The authors concluded that -0.10 would be a 'reliable' value. The more negative values, averaging -0.15, were mainly based on experimental data involving non-aqueous solvents or aqueous–organic solvents of low water content. Measurements of σ_m^0 found a mean value of 0.082 with considerable scatter about the mean, and a distinction between σ_m and σ_m^0 for OMe seems hardly worth making.

2. *Phenoxy group*

The value of 0.25 for σ_m of OPh, based on Dippy's work[87], may be accepted with reasonable confidence, since it has recently been confirmed[95] (Section III.B.2), but the value of -0.32 for σ_p, based on Dippy's work, must be rejected. The determination of a more reliable σ_p value from measurements in aqueous–organic mixtures is rendered difficult by the large hydrophobic effect of the phenoxy group (Section III.B.2). The indications are that the true σ_p value for OPh is very small, possibly around -0.08 as suggested by Charton[78], but it might actually be slightly positive, perhaps about 0.04, as suggested by Wepster[96]. In any case no σ_m or σ_p value for this substituent can be used with confidence, since for many processes and in many media the influence of this substituent may depend more on the hydrophobic effect than on the electronic effect.

Yukawa's group[236] have suggested a value of σ_p^0 for OPh as 0.05, based on appropriate ester hydrolysis in 70% aqueous acetone, but it is not known whether there would be any hydrophobic effect operating for the reaction and medium in question.

3. *Hydroxyl group*

The two main determinations of pK_a for m-hydroxybenzoic acid in water are not in good agreement, and at present the value of σ_m for OH appears to be 0.10 with a limit of uncertainty of ± 0.03. The situation for p-OH is worse. The pK_a value of p-hydroxybenzoic acid in water appears not to be highly reproducible and values in the range 4.53 to 4.67 at 25 °C have been recorded. The lowest of these, 4.53 by Bray and coworkers[98], gives a σ_p value of -0.327, but a pK_a value of 4.58 seems to be more highly regarded. This gives a σ_p value of -0.37, but this should be regarded as having an uncertainty of at least 0.04.

It must be emphasized that these values for σ_m and σ_p apply in water or in highly aqueous solutions. In less aqueous solutions the electronic effect may be obscured by a (negative) hydrophobic effect, and when this is allowed for, m-OH appears as slightly electron-releasing. In alcohols and other non-aqueous media m-OH is clearly electron-releasing, with an apparent σ_m value of about -0.1, and p-OH becomes even more electron-releasing than it is in water.

The values which have been suggested for σ_p^0 of OH show rather a spread. Yukawa and collaborators[236] suggest a value of -0.16, which at least bears a sensible relationship to the value of σ_p, and to the value of σ_p^0 of OMe. However, a single value will hardly be widely applicable since σ_p^0 for OH would be expected to vary with solvent, and the status of the suggested value in this respect is unclear.

4. Other ether and hydroxy groups

The values in Table 12 have been taken from Exner's critical compilation[45] or from the more recent compilation of Hansch, Leo and Taft[81]. No additional critical assessment has been done for the present compilation. References to the original literature may be

TABLE 12. Sigma values for ether and hydroxy groups

Substituent	σ_m[c]	Source[a]	σ_p[c]	Source[a]	Status[b]
CH_2OMe	0.08	H	0.01	H	
CH_2OR	0.02	E	0.01	E	σ
CH_2OH	0.01	E	0.01	E	σ
	0.00	H	0.00	H	
CH_2OPh	0.04	E	0.05	E	σ
	0.06	H	0.07	H	
CH(OH)Me			−0.07	E	
	0.08	H	−0.07	H	
CH(OH)Ph			−0.03	E	
CH(OMe)Ph			−0.01	E	
$CH_2CH(OH)Me$	−0.12	H	−0.17	H	
$CH_2C(OH)Me_2$	−0.16	H	−0.17	H	
$C(OMe)_3$	−0.03	H	−0.04	H	
	(−0.03)	E	(−0.04)	E	σ^0
$CH(OR)_2$	(−0.04)	E	(−0.05)	E	σ^0
oxiranyl	0.05	E, H	0.03	E, H	σ^0
2-C_4H_3O	0.06	E	0.02	E	σ
$C(OH)(CF_3)_2$	0.29	H	0.30	H	
OEt	0.10	E, H	−0.24	E, H	σ
			−0.14	E	σ^0
OPr^n	0.10	H	−0.25	H	
OPr^i	0.10	H	(−0.45)	H	
OBu^n	0.10	H	(−0.32)	H	
$OPen^n$	0.10	H	(−0.34)	H	
OCH_2Ph			(−0.41)	E	
OCH_2COOH			−0.18	E	
			(−0.33)	E	
$OCH{=}CH_2$	0.21	H	−0.09	H	
$OCH_2CH{=}CH_2$	0.09	H	−0.25	H	
OCH_2F	0.20	E, H	0.02	E, H	σ^0
$OCHF_2$	0.31	E, H	0.18	E, H	σ
OCF_3	0.38	E, H	0.35	E, H	σ
	0.35	E	0.32	E	σ
OCF_2CHF_2	0.34	E, H	0.25	E, H	σ
OCF_2CF_3	0.48	E, H	0.28	E, H	
OCF_2CHFCl	0.35	E, H	0.28	E, H	σ
OCH_2Cl	0.25	E, H	0.08	E, H	σ^0
$OCHCl_2$	0.38	E, H	0.26	E, H	σ^0
$OCCl_3$	0.43	E, H	0.35	E, H	σ^0

[a] E = Exner's compilation[45]; H = compilation of Hansch, Leo and Taft[81].

[b] The entries in this column give Exner's opinion as to whether the values tabulated are on the benzoic acid-based σ scale or are σ^0 values free from any effects of cross-conjugation. A blank in an entry from Exner means that he regards the status as uncertain. Hansch and coworkers express no opinions on this matter, and while many of the entries in their large compilation are undoubtedly on the benzoic acid-based σ scale, some are certainly σ^0 values (as may be appreciated from some of the entries above).

[c] Values in parentheses are 'particularly uncertain' (Exner) or 'suspected of being inaccurate' (Hansch and coworkers).

found in both compilations mentioned above. Exner also gives an indication of the method of determination. Particular attention is directed to the footnotes in Table 12. It must be said that in addition to the values put in parentheses as uncertain by Exner and by Hansch and colleagues, the values for some of the substituents seem inherently improbable or they do not bear a sensible relationship to the values for other substituents. More experimental work seems to be needed!! However, it is hoped that the values in Table 12 may be of some help to readers as indications of roughly what effect a particular substituent may have. Readers engaged in correlation analysis should approach these values with caution and should carefully probe the origins of any values in which they are particularly interested.

For some substituents in Table 12, particularly substituents in the *meta* position, any distinction between σ and σ^0 may be of little importance. We take this opportunity of commenting on the use of σ^0 values for $-R$ substituents in reaction series requiring the use of σ^- values for $+R$ substituents. This matter has been touched on briefly in Section III.C.2. It is often assumed that in reactions such as the dissociation of phenols or of anilinium ions $-R$ substituents will behave according to their σ^0 values. We have seen in Section III.C.2 that this is not always the case in view of the possibility of 'resonance saturation'[101] when a $-R$ *para*-substituent is opposed by a $-R$ reaction centre. Therefore the assumed equivalence of σ_p^0 and σ_p^- for $-R$ substituents should always be regarded with caution.

C. Values of σ^+ for OMe, OPh and OH, and for other Ether and Hydroxy Groups

Taylor[237] has done a careful critical assessment of σ^+ values based usually either on *t*-cumyl chloride solvolysis (the original defining system[48]), or other suitable solvolyses, or electrophilic aromatic substitution. He tabulates values for groups of interest to this chapter as in Table 13.

Only for OMe is a distinctive σ_m^+ value tabulated, at 0.05. For many of the groups an ordinary σ_m value should be applicable in electron-demanding reactions, although such applications should always be approached with caution.

The value of -0.59 tabulated for OH was obtained under non-polar conditions, and makes OH less electron-releasing than OMe. This is in accord with expectations regarding C—O and H—O hyperconjugation (see Sections VI.B.8 and VIII.B). The usually quoted value for OH of -0.92 is based on electrophilic aromatic substitution[238]. Even more negative values have been obtained. Thus a study of the kinetics of hydrolysis of 2-bromo-4-dibromomethylphenol in 95% aqueous dioxan led to a value of -1.36 for σ_p^+ of OH[239]. This all emphasizes that the behaviour of *p*-OH depends very much on the medium as well as on the electron-demanding quality of the reaction.

TABLE 13. Values of σ^+ for ether and hydroxy groups

Substituent	σ_p^+	Substituent	σ_p^+	Substituent	σ_p^+
OMe	−0.78	OCH_2Ph	−0.65	CH_2OMe	−0.05
OEt	−0.81	OPh	−0.53	CH_2OEt	0.00
OPr^n	−0.83	OH	−0.59	CH_2OH	+0.01
OPr^i	−0.85	$3,4\text{-}CH_2CH_2O$	−0.98[a]	OCF_3	+0.07
OBu^n	−0.81	$3,4\text{-}OCH_2O$	−0.675[b]		

[a]For the 5-position of coumarin.
[b]For the 5-position of benzo-1,3-dioxole.

D. The Electronic Effects of the 2-Hydroperoxy-2-propyl Group, CMe_2OOH

This is the only peroxy substituent for which the author has been able to find any information. Ogata and Haba[240] studied the kinetics of autoxidation (dissolved O_2) of *meta*- and *para*-substituted isopropylbenzenes in chlorobenzene at 60 °C using azobisisobutyronitrile as initiator. From the rates for substrates with substituents of known σ values, the Hammett ρ value was found to be -0.50, the quality of fit being rather modest ($r = 0.955$). The rates for the *m*- or *p*-CMe_2OOH-substituted compounds gave $\sigma_m = 0.06$ and $\sigma_p = -0.14$ for this group. A small electron-attracting effect from the *meta* position seems reasonable, but the σ_p value is almost identical to that of Pr^i, which is -0.15. This seems a little odd in view of the presence of two rather electron-attracting oxygen atoms in the group. The authors also used the reaction to determine σ values for CMe_2OH, finding $\sigma_m = 0.47$ and $\sigma_p = 0.60$. These values seem unreasonably large, in view of the almost zero electronic effect of CH_2OH, and the small σ values of CH(OH)Me (Table 12). It is possible that the factors influencing the rate of the reaction in question are not well understood.

XI. REFERENCES AND NOTES

1. J. Shorter, in *The Chemistry of the Sulphonium Group* (Eds. C. J. M. Stirling and S. Patai), Chap. 9, Wiley, Chichester, 1981.
2. J. Shorter, in *The Chemistry of Sulphones and Sulphoxides* (Eds. S. Patai, Z. Rappoport and C. J. M. Stirling), Chap. 10, Wiley, Chichester, 1988.
3. J. Shorter, in *The Chemistry of Sulphinic Acids, Esters and their Derivatives* (Ed. S. Patai), Chap. 17, Wiley, Chichester, 1990.
4. J. Shorter, in *The Chemistry of Amidines and Imidates*, Vol. 2 (Eds. S. Patai and Z. Rappoport), Chap. 13, Wiley, Chichester, 1991.
5. H. Hübner, *Chem. Ber.*, **8**, 873 (1875).
6. E. Noelting, *Chem. Ber.*, **9**, 1797 (1876).
7. H. E. Armstrong, *J. Chem. Soc.*, **51**, 258 (1887).
8. A. Crum Brown and J. Gibson, *J. Chem. Soc.*, **61**, 367 (1892).
9. D. Vorländer, *Ann. Chem.*, **320**, 122 (1902).
10. D. Ll. Hammick and W. S. Illingworth, *J. Chem. Soc.*, 2358 (1930).
11. B. Flürscheim, *J. Chem. Soc.*, **95**, 718 (1909) and earlier papers.
12. A. F. Holleman, *Die direkte Einführung von Substituenten in den Benzolkern*, Veit, Leipzig, 1910.
13. In presenting this summary of the early part of the development of theories of aromatic substitution, the author is greatly indebted to the more extended account in W. A. Waters, *Physical Aspects of Organic Chemistry*, 4th ed., Chap. XVIII, Routledge and Kegan Paul, London, 1950.
14. M. D. Saltzman, *J. Chem. Educ.*, **57**, 484 (1980).
15. M. D. Saltzman, *Nat. Product Rep.*, **4**, 53 (1987), Robinson Centenary Issue.
16. J. Shorter, *Nat. Product Rep.*, **4**, 61 (1987), Robinson Centenary Issue.
17. J. Allan, A. E. Oxford, R. Robinson and J. C. Smith, *J. Chem. Soc.*, 401 (1926).
18. J. Clarke, R. Robinson and J. C. Smith, *J. Chem. Soc.*, 2647 (1927).
19. A. E. Oxford and R. Robinson, *J. Chem. Soc.*, 2239 (1927).
20. Reference 17, footnote on p. 406.
21. References 14–16 give numerous references to the various accounts in which Robinson described the features of his electronic theory of organic reactions. The most comprehensive account was in R. Robinson, *Outline of an Electrochemical (Electronic) Theory of the Course of Organic Reactions*, Institute of Chemistry, London, 1932, 52pp. The book by Waters (Reference 13) contains much information on Robinson's theory.
22. C. K. Ingold, *J. Chem. Soc.*, 513 (1925).
23. J. W. Baker and C. K. Ingold, *J. Chem. Soc.*, 431 (1930).
24. C. K. Ingold and E. H. Ingold, *J. Chem. Soc.*, 1310 (1926).
25. C. K. Ingold and E. H. Ingold, *J. Chem. Soc.*, 870 (1925).
26. See report of discussion at a meeting of the Chemical Society, *Chem. Ind. (London)*, 227 (1925).

27. C. K. Ingold, *J. Chem. Soc.*, 87 (1924).
28. E. L. Holmes and C. K. Ingold, *J. Chem. Soc.*, 1328 (1925).
29. C. K. Ingold, *Annu. Rep. Prog. Chem.*, **24**, 148 (1927).
30. C. K. Ingold, *Chem. Rev.*, **15**, 225 (1934).
31. C. K. Ingold, *Annu. Rep. Prog. Chem.*, **23**, 129 (1926).
32. Part I, A. E. Bradfield, Brynmor Jones and K. J. P. Orton, *J. Chem. Soc.*, 2810 (1929); Part XVIII, Brynmor Jones and E. N. Richardson, *J. Chem. Soc.*, 3939 (1956).
33. The earlier Parts of the work on the kinetics of halogenation were summarized by A. E. Bradfield and Brynmor Jones, *Trans. Faraday Soc.*, **37**, 726 (1941).
34. H. B. Watson, *Modern Theories of Organic Chemistry*, 2nd ed., Chap. 4, Oxford University Press, Oxford, 1941.
35. L. G. Groves and S. Sugden, *J. Chem. Soc.*, 1992 (1937).
36. G. M. Bennett and S. Glasstone, *Proc. R. Soc. (London)*, **145A**, 71 (1934).
37. O. Exner, *Dipole Moments in Organic Chemistry*, Chap. 6 Georg Thieme, Stuttgart, 1975.
38. This section is largely based on previous accounts in References 1 and 2, in which certain material was adapted (by kind permission of Oxford University Press) from J. Shorter, *Correlation Analysis in Organic Chemistry; An Introduction to Linear Free-Energy Relationships*, Chap. 2, Oxford Chemistry Series, 1973.
39. J. Shorter, *Correlation Analysis of Organic Reactivity*, Chap. 1, Research Studies Press, Wiley, Chichester, 1982.
40. L. P. Hammett, *Physical Organic Chemistry*, 2nd ed., Chap. 11, McGraw-Hill, New York, 1970.
41. O. Exner, in *Advances in Linear Free-Energy Relationships* (Eds. N.B. Chapman and J. Shorter), Chap. 1, Plenum Press, London, 1972.
42. Reference 39, Chap. 3.
43. J. Shorter, in *Similarity Models in Organic Chemistry, Biochemistry, and Related Fields* (Eds. R. I. Zalewski, T. M. Krygowski and J. Shorter), Chap. 2, Elsevier, Amsterdam, 1991.
44. O. Exner, *Correlation Analysis of Chemical Data*, Plenum, New York and SNTL, Prague, 1988.
45. O. Exner, in *Correlation Analysis in Chemistry: Recent Advances* (Eds. N. B. Chapman and J. Shorter), Chap. 10, Plenum Press, New York, 1978.
46. H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
47. The symbol and sign conventions used for substituent effects in this chapter are those most frequently used by writers on correlation analysis in organic chemistry. *I* or *R* effects which withdraw electrons from the ring are regarded as positive. See Reference 39, pp. 229–230 for a more detailed consideration of symbol and sign conventions.
48. H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).
49. H. van Bekkum, P. E. Verkade and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **78**, 815 (1959).
50. J. Shorter, in Reference 45, Chap. 4.
51. Reference 39, Chap. 3.
52. Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Jpn.*, **32**, 971 (1959).
53. Y. Yukawa, Y. Tsuno and M. Sawada, *Bull. Chem. Soc. Jpn.*, **39**, 2274 (1966).
54. R. W. Taft and I. C. Lewis, *J. Am. Chem. Soc.*, **80**, 2436 (1958).
55. R. W. Taft and I. C. Lewis, *J. Am. Chem. Soc.*, **81**, 5343 (1959).
56. R. W. Taft, in *Steric Effects in Organic Chemistry* (Ed. M. S. Newman), Chap. 13, Wiley, New York, 1956.
57. R. W. Taft, S. Ehrenson, I. C. Lewis and R. E. Glick, *J. Am. Chem. Soc.*, **81**, 5352 (1959).
58. S. Ehrenson, *Prog. Phys. Org. Chem.*, **2**, 195 (1964).
59. S. Ehrenson, R. T. C. Brownlee and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1 (1973).
60. It should be mentioned that the expression 'σ value' or 'σ constant' has acquired both a specialized and a more general meaning. The former denotes substituent constants based on the ionization of benzoic acids; the latter signifies polar (electronic) substituent constants in general. Thus the meaning of σ often has to be understood in context, but expressions such as 'sigma value' or 'σ-type constant' are preferable when the more general meaning is intended.
61. O. Exner, *Collect. Czech. Chem. Commun.*, **31**, 65 (1966).
62. See, for example, M. Charton, *J. Am. Chem. Soc.*, **91**, 6649 (1969).
63. R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 709 (1963).
64. R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 3146 (1963).

65. D. F. Ewing, in Reference 45, Chap. 8.
66. D. J. Craik and R. T. C. Brownlee, *Prog. Phys. Org. Chem.*, **14**, 1 (1983).
67. A. R. Katritzky and R. D. Topsom, in Reference 41, Chap. 3.
68. G. P. Ford, A. R. Katritzky, and R. D. Topsom, in Reference 45, Chap. 3.
69. J. D. Roberts and W. T. Moreland, *J. Am. Chem. Soc.*, **75**, 2167 (1953).
70. Reference 39, Chap. 4.
71. J. Shorter, in Reference 41, Chap. 2.
72. Reference 38, Chap. 3.
73. R. W. Taft, *J. Am. Chem. Soc.*, **79**, 1045 (1957).
74. Except where a more specific reference is given, pK_a values quoted explicitly, or quoted implicitly through correlation equations, in this chapter have been taken from the following compilations:
(a) G. Kortüm, W. Vogel and K. Andrussow, *Dissociation Constants of Organic Acids in Aqueous Solution*, Butterworths, London, 1961 (for I.U.P.A.C.). This is a reprint from *Pure and Applied Chemistry*, Vol. 1, Nos. 2 and 3.
(b) E. P. Serjeant and B. Dempsey, *Ionisation Constants of Organic Acids in Aqueous Solution*, Pergamon Press, Oxford, 1979 (I.U.P.A.C. Chemical Data Series, No. 23).
(c) V. A. Palm (Ed.), and several Compilers (From the Laboratory of Chemical Kinetics and Catalysis, Tartu State university, Estonia), *Tables of Rate and Equilibrium Constants of Heterolytic Organic Reactions*, Moscow, 1975–79 (in 10 volumes)
Detailed references may be found in the above sources. Some use has also been made of Tables in Charton's review[78], where detailed references are also given. Reference 74c has also been used as a source of rate constants in the present chapter, where no more specific reference is given.
75. For a recent review of the 'through-bonds' versus 'through-space' controversy, see J. Shorter, in Reference 43, especially pp. 117–120.
76. Chapman, J. Shorter and K. J. Toyne, *J. Chem. Soc.*, 1077 (1964).
77. K. Bowden, N. B. Chapman and J. Shorter, *J. Chem. Soc.*, 3370 (1964).
78. M. Charton, *Prog. Phys. Org. Chem.*, **13**, 119 (1981).
79. Equation 58 on p. 137 of Reference 78.
80. Equation 36 on p. 131 of Reference 78, with slightly different symbols. The correlation equations which are relevant to Tables 3 and 4 are nos. 36, 33, 35, 6 and 53 in Charton's Table 9, for our entries 2 to 6, respectively.
81. C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, **91**, 165 (1991).
82. M. H. Aslam, A. G. Burden, N. B. Chapman, J. Shorter and M. Charton, *J. Chem. Soc., Perkin Trans. 2*, 500 (1981).
83. K. Bowden, M. Hardy and D. C. Parkin, *Can. J. Chem.*, **46**, 2929 (1968).
84. The relevant correlations in Charton's review[78] are nos. 55–60 of his Table 9, respectively.
85. The relevant correlations in Charton's review[78] are nos. 6–8 of his Table 14, respectively.
86. M. H. Palomaa, *Chem. Zent.*, **2**, 595 (1912) cited in Reference 74c.
87. J. F. J. Dippy, *Chem. Rev.*, **25**, 151 (1939) and references therein.
88. L. P. Hammett, *Physical Organic Chemistry*, Chap. 7, McGraw-Hill, New York, 1940.
89. A. J. Hoefnagel and B. M. Wepster, *J. Chem. Soc., Perkin Trans. 2*, 977 (1989).
90. O. Exner, *Collect. Czech. Chem. Commun.*, **31**, 3222 (1966).
91. Reference 39, Chap. 7.
92. M. H. Aslam, N. B. Chapman, M. Charton and J. Shorter, *J. Chem. Res. (S)*, 188 (1981); *(M)*, 2301 (1981).
93. C. K. Hancock and J. S. Westmoreland, *J. Am. Chem. Soc.*, **80**, 545 (1958).
94. Brynmor Jones and J. C. Speakman, *J. Chem. Soc.*, 19 (1944).
95. M. Ludwig, V. Baron, K. Kalfus, O. Pytela and M. Večeřa, *Collect. Czech. Chem. Commun.*, **51**, 2135 (1986).
96. A. J. Hoefnagel and B. M. Wepster, *Collect. Czech. Chem. Commun.*, **55**, 119 (1990).
97. C. Hansch and A. J. Leo, *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley, New York, 1979.
98. L. C. Bray, J. F. J. Dippy, S. R. C. Hughes and L. W. Laxton, *J. Chem. Soc.*, 2405 (1957).
99. Brynmor Jones and J. G. Watkinson, *J. Chem. Soc.*, 4064 (1958).
100. J. G. Watkinson, W. Watson and B. L. Yates, *J. Chem. Soc.*, 5437 (1963).
101. A. J. Hoefnagel, M. E. Hoefnagel and B. M. Wepster, *J. Am. Chem. Soc.*, **98**, 6194 (1976).

102. Reference 34 p. 241.
103. e. g. M. Charton and B. I. Charton, *J. Org. Chem.*, **33**, 3872 (1968) and other papers in *J. Am. Chem. Soc.* or *J. Org. Chem.* in 1968–71.
104. e.g. K. Bowden and G. E. Manser, *Can. J. Chem.*, **46**, 2941 (1968) and other papers in the same Journal at around that time.
105. G. E.K. Branch and D. L. Yabroff, *J. Am. Chem. Soc.*, **56**, 2568 (1934).
106. W. Baker, *Nature*, **137**, 236 (1936).
107. K. Bowden and D. C. Parkin, *Can. J. Chem.*, **46**, 3909 (1968).
108. K. Kindler, *Justus Liebigs Ann. Chem.*, **464**, 278 (1928).
109. E. Tommila, in various papers as quoted by Reference 74c.
110. M. H. Aslam, N. B. Chapman, J. Shorter and M. Charton, *J. Chem. Soc., Perkin Trans. 2*, 720 (1981).
111. M. Charton and B. I. Charton, *J. Org. Chem.*, **43**, 1161 (1978) and earlier papers referred to therein.
112. M. Charton, in *Topics in Current Chemistry 114: Steric Effects in Drug Design* (Eds. M. Charton and I. Motoc), Springer-Verlag, Berlin, 1983, pp. 57–91.
113. M. Charton, in Reference 43, Chap. 11.
114. C. Srinivasan, A. Shunmugasundaram and N. Arumugam, *J. Chem. Soc., Perkin Trans. 2*, 213 (1984).
115. P. Ananthakrishna Nadar and A. Shunmugasundaram, *Ind. J. Chem. Sect. A*, **14**, 805 (1976).
116. S. Jain (née Mittal) and K. K. Banerji, *Bull. Chem. Soc. Jpn.*, **61**, 1767 (1988).
117. C. Srinivasan and P. Subramaniam, *Proc. Ind. Acad. Sci. (Chem. Sci.)*, **100**, 31 (1988).
118. J. F. J. Dippy, S. R. C. Hughes and L. G. Bray, *J. Chem. Soc.*, 1717 (1959).
119. W. Ostwald, *Z. Phys. Chem.*, **3**, 170 (1989) cited in Reference 74c.
120. A. N. Pant, R. N. Soni and S. L. Gupta, *Ind. J. Chem.*, **9**, 270 (1971), cited in Reference 74c.
121. T. Balasubramanian, Ph.D. thesis, Annamalai University, 1976, cited in Reference 123.
122. G. Baddeley, N. H. P. Smith and M. A. Vickars, *J. Chem. Soc.*, 2455 (1956), cited in Reference 123.
123. V. Baliah, in *Selected Topics in Physical Organic Chemistry* (Professor R. Anantaraman Commemoration Volume), p. 83, Dept. of Chemistry, University of Kerala, Trivandrum, India, 1985. This is a review of steric enhancement of reasonance.
124. V. Baliah and M. Uma, *Tetrahedron Lett* (25), 21 (1960).
125. Brynmor Jones and J. Robinson, *J. Chem. Soc.*, 3845 (1955).
126. H. P. Crocker and Brynmor Jones, *J. Chem. Soc.*, 1808 (1959).
127. V. Baliah and P. V. V. Satyanarayana, *Ind. J. Chem., Sect. B*, **19**, 619 (1980).
128. I. Lee, H. Y. Kim and H. K. Kang, *J. Chem. Soc., Chem. Commun.*, 1216 (1987).
129. I. Lee, C. S. Shim, S. Y. Chung, H. Y. Kim and H. W. Lee, *J. Chem. Soc., Perkin Trans. 2*, 1919 (1988).
130. I. Lee, K. W. Rhyu, H. W. Lee, C. S. Shim and H. K. Oh, *J. Phys. Org. Chem.*, **3**, 751 (1990).
131. J. K. Kochi and G. S. Hammond, *J. Am. Chem. Soc.*, **75**, 3445, 3452 (1953).
132. Reference 48 and earlier papers.
133. J. F. Norris and C. Banta, *J. Am. Chem. Soc.*, **50**, 1804 (1928).
134. J. F. Norris and J. T. Blake, *J. Am. Chem. Soc.*, **50**, 1808 (1928).
135. J. F. Norris and A. Martin, *J. Am. Chem. Soc.*, **50**, 1795 (1928).
136. R. Bolton, N. B. Chapman and Shorter, *J. Chem. Soc.*, 1895 (1964).
137. C. D. Johnson, *J. Org. Chem.*, **43**, 1814 (1978).
138. J. S. Lomas and A. Argile, *J. Org. Chem.*, **44**, 2024 (1979).
139. R. Taylor, *J. Org. Chem.*, **44**, 2024 (1979).
140. Y. Tsuno, W.-Y. Chong, Y. Tairaka, M. Sawada and Y. Yukawa, *Bull. Chem. Soc. Jpn.*, **51**, 596 (1978).
141. Y. Tsuno, Y. Tairaka, M. Sawada, T. Fujii and Y. Yukawa, *Bull. Chem. Soc. Jpn.*, **51**, 601 (1978).
142. Y. Tsuno, M. Sawada, T. Fujii and Y. Yukawa, *Bull. Chem. Soc. Jpn.*, **52**, 3033 (1979).
143. M. Fujio, T. Adachi, Y. Shibuya, A. Murata and Y. Tsuno, *Tetrahedron Lett.*, **25**, 4557 (1984).
144. Y. Tsuno, K. Funatsu, Y. Maeda, M. Mishima and M. Fujio, *Tetrahedron Lett.*, **23**, 2879 (1982).
145. M. Fujio, K. Funatsu, M. Goto, M. Mishima and Y. Tsuno, *Tetrahedron*, **43**, 307 (1987).
146. P. R. Young and W. P. Jencks, *J. Am. Chem. Soc.*, 99, 8238 (1977).
147. H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **79**, 1913 (1957).
148. R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, Chichester, 1990.

149. Reference 148, p. 40.
150. Some references to the original literature will be given in this section, but where the situation for citations is complicated, an appropriate reference to Taylor's book[148] will be given. Citations of the original literature can then easily be identified by the interested reader.
151. Reference 148, Chap. 3.
152. Reference 148, p. 88.
153. R. Baker, R. W. Bott, C. Eaborn and P. M. Greasley, *J. Chem. Soc.*, 627 (1964).
154. Reference 148, p. 120.
155. Reference 148, Chap. 4.
156. Reference 148, p. 133.
157. Reference 148, pp. 144–151.
158. Reference 148, pp. 156–158.
159. Reference 148, pp. 154–156.
160. Reference 148, Chap. 5.
161. Reference 148, pp. 173–175.
162. Reference 148, pp. 175–181.
163. Reference 148, pp. 181–182.
164. Reference 148, Chap. 6.
165. Reference 148, p. 200.
166. Reference 148, p. 230.
167. Reference 148, p. 215.
168. Reference 148, Chap. 7.
169. Reference 148, pp. 258–260.
170. Reference 148, pp. 261–263.
171. Reference 148, pp. 263–314.
172. R. G. Coombes, R. B. Moodie and K. Schofield, *J. Chem. Soc. (B)*, 800 (1968).
173. R. B. Moodie, K. Schofield and P. N. Thomas, *J. Chem. Soc., Perkin Trans. 2*, 318 (1978).
174. J. W. Barnett, R. B. Moodie, K. Schofield, J. B. Weston, R. G. Coombes, J. G. Golding and G. D. Tobin, *J. Chem. Soc., Perkin Trans. 2*, 248 (1977).
175. R. G. Coombes, J. G. Golding and P. Hadjigeorgiou, *J. Chem. Soc., Perkin Trans. 2*, 1451 (1979).
176. Reference 148, pp. 298–299.
177. S. Sotheeswaran and K. J. Toyne, *J. Chem. Soc., Perkin Trans. 2*, 2042 (1977).
178. Reference 148, Chap. 8.
179. H. Cerfontain, Z. R. H. Schaasberg-Nienhuis, R. G. Coombes, P. Hadjigeorgiou and G. P. Tucker, *J. Chem. Soc., Perkin Trans. 2*, 659 (1985).
180. Reference 148, Chap. 9.
181. Reference 148, p. 363.
182. Reference 148, p. 364.
183. Reference 148, p. 366.
184. Reference 148, p. 370.
185. A. Guy, M. Lemaire and J.-P. Guette, Tetrahedron, **38**, 2339 (1982).
186. Reference 148, p. 393.
187. O. M. E. El-Dusouqui and M. N. Mousa, *J. Chem. Soc., Perkin Trans. 2*, 1171 (1991).
188. P. B. D. de la Mare, *Pure Appl. Chem.*, **56**, 1755 (1984).
189. P. B. D. de la Mare, in Reference 123, p. 1.
190. Reference 148, p. 385.
191. L. P. Hammett, *J. Am. Chem. Soc.*, **59**, 96 (1937).
192. Reference 46, p. 239.
193. Hoefnagel, M. E. Hoefnagel and B. M. Wepster, *J. Org. Chem.*, **43**, 4720 (1978).
194. V. M. Nummert, *Org. React. (Tartu)*, **11**, 621 (1975).
195. S. S. Gitis, A. V. Ivanov, A. Ya. Kaminskii, and Z. A. Kozina, *Reakts. Spos. Org. Soedinenii*, **3**(3), 142 (1966); English edition, 264.
196. J. Hine, *J. Am. Chem. Soc.*, **82**, 4877 (1960).
197. R. T. C. Brownlee, R. E. J. Hutchinson, A. R. Katritzky, T. T. Tidwell and R. D. Topsom, *J. Am. Chem. Soc.*, **90**, 1757 (1968).
198. A. J. Hoefnagel and B. M. Wepster, *J. Am. Chem. Soc.*, **95**, 5357 (1973).
199. S. Clementi and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 2*, 1077 (1973).
200. I. A. Koppel, M. M. Karelson and V. A. Palm, *Org. React. (Tartu)*, **11**, 101 (1974).

201. S. Marriott, W. F. Reynolds and R. D. Topsom, *J. Org. Chem.*, **50**, 741 (1985).
202. R. W. Taft, *J. Am. Chem. Soc.*, **79**, 1045 (1957).
203. J. Bromilow, R. T. C. Brownlee, V. O. Lopez and R. W. Taft, *J. Org. Chem.*, **44**, 4766 (1979).
204. W. F. Reynolds, A. Gomes, A. Maron, D. W. MacIntyre, A. Tanin, G. K. Hamer and I. R. Peat, *Can. J. Chem.*, **61**, 2376 (1983).
205. D. A. R. Happer, *J. Chem. Soc., Perkin Trans. 2*, 1673 (1984).
206. C. Laurence, M. Berthelot, M. Lucon, M. Helbert, D. G. Morris and J.-F. Gal, *J. Chem. Soc., Perkin Trans. 2*, 705 (1984).
207. C. Laurence, in Reference 43, Chap. 5.
208. G. G. Smith and F. W. Kelly, *Prog. Phys. Org. Chem.*, **8**, 75 (1971).
209. N. Al-Awadi and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1581 (1986). (This is Part 19 of The Mechanism of Thermal Eliminations.)
210. R. August, C. Davis and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1265 (1986). (This is Part 21 of Electrophilic Aromatic Reactivities via Pyrolysis of Esters.)
211. R. August, I. McEwen and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1683 (1987). (This is Part 22 of The Mechanism of Thermal Eliminations).
212. M. Fujio, R. T. McIver, and R. W. Taft, *J. Am. Chem. Soc.*, **103**, 4017 (1981).
213. R. W. Taft and R. D. Topsom, *Prog. Phys. Org. Chem.*, **16**, 1 (1987).
214. S. Marriott and R. D. Topsom, *J. Am. Chem. Soc.*, **106**, 7 (1984).
215. S. Marriott and R. D. Topsom, *J. Chem. Soc., Perkin Trans. 2*, 1045 (1985).
216. S. Marriott, A. Silvestro and R. D. Topsom, *J. Chem. Soc., Perkin Trans. 2*, 457 (1988).
217. R. D. Topsom, *Prog. Phys. Org. Chem.*, **16**, 125 (1987).
218. K. B. Astin, *Tetrahedron Lett.*, **21**, 3713 (1980).
219. T. Sotomatsu, Y. Murata and T. Fujita, *J. Comput. Chem.*, **10**, 94 (1989).
220. K. H. Kim and Y. C. Martin, *J. Org. Chem.*, **56**, 2723 (1991).
221. C. G. Swain and E. C. Lupton, *J. Am. Chem. Soc.*, **90**, 4328 (1968).
222. C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nakaitani and E. J. Lien, *J. Med. Chem.*, **16**, 1207 (1973).
223. C. G. Swain, S. H. Unger, N. R. Rosenquist and M. S. Swain, *J. Am. Chem. Soc.*, **105**, 492 (1983).
224. W. F. Reynolds and R. D. Topsom, *J. Org. Chem.*, **49**, 1989 (1984).
225. A. J. Hoefnagel, W. Oosterbeek and B. M. Wepster, *J. Org. Chem.*, **49**, 1993 (1984).
226. M. Charton, *J. Org. Chem.*, **49**, 1997 (1984).
227. C. G. Swain, *J. Org. Chem.*, **49**, 2005 (1984).
228. C. Hansch, in Reference 45, Chap. 9.
229. W. J. Hehre, C.-F. Pau, A. D. Headley, R. W. Taft and R. D. Topsom, *J. Am. Chem. Soc.*, **108**, 1711 (1986).
230. J.-L. M. Abboud, J. Catalán, J. Elguero and R. W. Taft, *J. Org. Chem.*, **53**, 1137 (1988).
231. M. Charton, *Prog. Phys. Org. Chem.*, **16**, 287 (1987).
232. M. Charton and B. Charton, *Bull. Soc. Chim. France*, 199 (1988).
233. Reference 231, p. 288.
234. The author is the chairman of a Working Party on Structure–Reactivity Parameters and Equations under the auspices of the IUPAC Commission for Physical Organic Chemistry. At present (1992) σ values which are based directly on the pK_a values of substituted benzoic acids in water are under critical appraisal. Some of the material in this Section of the chapter is from the material being considered by the Working Party. It is hoped that reports will appear in due course in *Pure and Applied Chemistry*.
235. O. Pytela, M. Ludwig and M. Večeřa, *Collect. Czech. Chem. Commun.*, **51**, 2143 (1986).
236. Y. Yukawa, Y. Tsuno and M. Sawada, *Bull. Chem. Soc. Jpn.*, **45**, 1198 (1972).
237. Reference 148, Chap. 11.
238. S. Clementi and P. Linda, *J. Chem. Soc., Perkin Trans. 2*, 1887 (1973).
239. P. B. D. de la Mare and P. A. Newman, *J. Chem. Soc., Perkin Trans. 2*, 1797 (1984).
240. Y. Ogata and M. Haba, *J. Org. Chem.*, **38**, 2779 (1973).

CHAPTER **10**

Syntheses and uses of isotopically labelled hydroxyl compounds and ethers

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Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

ABBREVIATIONS

AChE	acetylcholinesterase
BBB	blood brain barrier
BDPE	1,1-bis(*p*-hydroxyphenyl)-2-bromo-2-phenylethylene
BOP–Cl	*N*,*N*-bis(2-oxo-3-oxazolidynyl)-phosphorodiamidic chloride
BNPPA	2,2-(1,1-binaphthyl)phosphoric acid
DBCP	1,2-dibromo-3-chloropropane
DBP	2,3-dibromopropanol
DBU	1,5-diazabicyclo[5,4,0]undec-5-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEA	diethylamine
2DG	2-deoxy-D-glucose
DMPA	dimethylphenethyl amine
DMA	*N*,*N*-dimethylaniline
DPPA	diphenylphosphoryl azide
DPPB	1,2-bis(diphenylphosphino)benzene
EOB	end of bombardment
ER	estrogen receptor
FA	flavellagic acid
FDA	2-deoxy-2-fluoro-D-altrose
DCCD (DCC)	1,3-dicyclohexylcarbodiimide
6-FD	6-fluorodopa
FDG	2-deoxy-2-fluoro-D-glucose
FMR	fluorometaraminol
FDGal	2-deoxy-2-fluoro-D-galactose
GHSV	gas hourly space velocity
HLD	high density lipoproteins
$pHOBDPNH_2$	α-amino-4-hydroxybenzylidenediphosphonate
J.r.	Johnson reagent (CrO_3 in acetone)
K.I.E.	kinetic isotope effect
LDL	low density lipoproteins
MAO	monoamine oxidase
MDO–NPA	10,11-methylenedioxy derivative of NPA
MHED	*m*-hydroxyephedrine
MIDG	methyl-2-deoxy-2-iodo-β-D-glucopyranoside
MBDG	methyl-2-deoxy-2-bromo-β-D-glucopyranoside
MNU	*N*-methyl-*N*-nitrosourea
MPA	methylphenethyl amine
MTBG	methyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-bromo-β-D-glucopyranoside

MTIG	methyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-β-D-glucopyranoside
NADPH	β-nicotinamide adenine dinucleotide phosphate (reduced form)
NCA	no carrier added
NCS	*N*-chlorosuccinimide
NMPB	*N*-methyl-4-piperidyl benzilate
NPA	*N*-n-propylnorapomorphine
PET	positron emission tomography
3-PPP	3-(3-hydroxyphenyl)-*N*-propyl-piperidine
QNB	quinuclidinyl-benzylate
r.y.	radiochemical yield or radiation yield
RP–HPLC	reversed-phase high pressure liquid chromatography
TBAF	tetrabutylammonium fluoride
TBPP	tetrabenzyl pyrophosphate
TFA	trifluoroacetic acid
THC	tetrahydrocannabinol
TPP	triphenylphosphine
TRB	tropanyl benzilate

I. INTRODUCTION

The syntheses and reactivity of hydroxyl and ether functional groups are presented, among others, in the textbooks and monographs cited in Reference 1. Many of the well established reaction schemes have been utilized in the synthesis of isotopically labelled alcohols and ethers. Even so, the methods applied for preparation of isotopically labelled organic compounds differ greatly from general organic syntheses. The reaction schemes had to be adjusted to the availability of radioactive compounds of very high specific activity or very high enrichment with stable isotopes. Reactions presented in this chapter were required to surmount the technical difficulties encountered in studies employing highly radioactive materials with fast decay. Syntheses with short-lived isotopes became very important in contemporary diagnostic applications (heart, brain and tumor scanning). Drugs which can carry radioactive isotopes to cancerous tissues and destroy them, are increasingly required. Many labelled compounds have been synthesized to investigate the mechanism of biochemical processes in living organisms or to investigate the mechanism of chemical processes of industrial importance or for environmental studies. In Section V some contemporary studies of catalytic processes are reviewed. Due to lack of space, we limited the Isotope Effect section to the most representative examples listed in Vol. 109 of *Chemical Abstracts*, whereas Sections II–V review virtually all studies which appeared in the last decade.

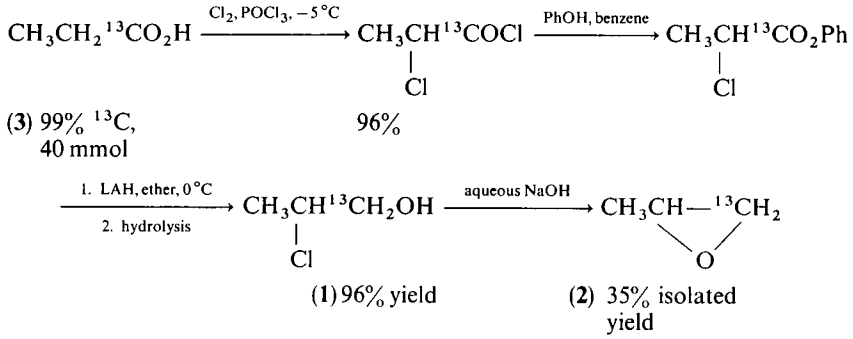
II. SYNTHESIS AND APPLICATIONS OF THE TITLE COMPOUNDS LABELLED WITH CARBON-13, NITROGEN-15 AND OXYGEN-18

A. Synthesis of the Title Compounds Labelled with ^{13}C and ^{15}N

1. Synthesis of ^{13}C-labelled propylene oxide

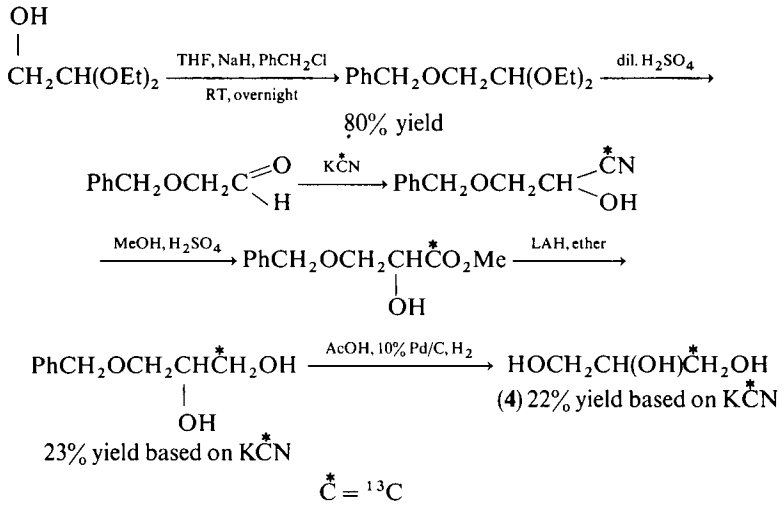
2-Chloro[1-^{13}C]propane-1-ol (**1**) has been obtained as intermediate product in the four – step synthesis of 1-methyl[2-^{13}C]ethylene oxide (**2**) using propanoic acid[1-^{13}C] (**3**) as the starting material[2a] (equation 1). No separation of intermediates was necessary. The propylene oxide **2** has been ^{13}C-labelled since the use of deuterium labelling failed

to establish the fragmentation pattern of $[C_3H_6O]^+$ ions and to ascertain whether methylene fragments cleaved symmetrically due to H—D scrambling[2b].



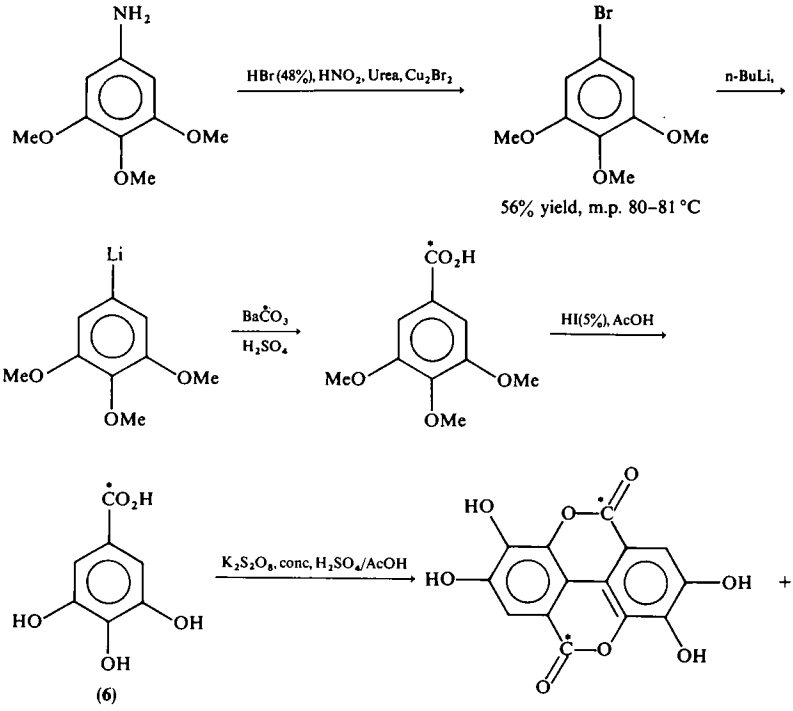
2. Synthesis of glycerol[1-^{13}C]

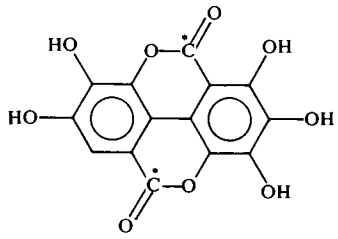
Glycerol[1-^{13}C] (**4**) has been synthesized[3] by the cyanohydrin method[4,5] (equation 2) for biosynthetic investigations, for NMR studies of whole cells and as an intermediate needed for preparations of other isotopically labelled compounds[6].



3. Synthesis of ^{13}C- and ^{14}C-labelled ellagic acid

Ellagic acid (EA) (2,3,7,8-tetrahydroxy[1]benzopyrano[5,4,3-cde][1]benzopyran-5,10-dione) (**5**), is a natural product present in soft fruits, nuts and vegetables, inhibits effectively the activity of several chemical carcinogens including polycyclic aromatic hydrocarbons, *N*-methyl-*N*-nitrosourea (MNU) and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine[7–16]. EA has been ^{13}C and ^{14}C labelled[17] according to equation 3, to investigate its complex with DNA that masks or protects the *O'*-guanine-N7 site from methylation[13,18] by MNU. The methanolic solution of EA[^{14}C] was stored in ambar reaction vials over argon at −80 °C. EA dissolved in refluxing pyridine and, treated with isobutyryl chloride for 24 h,



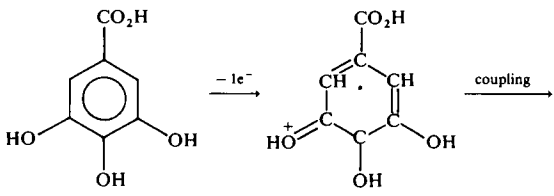


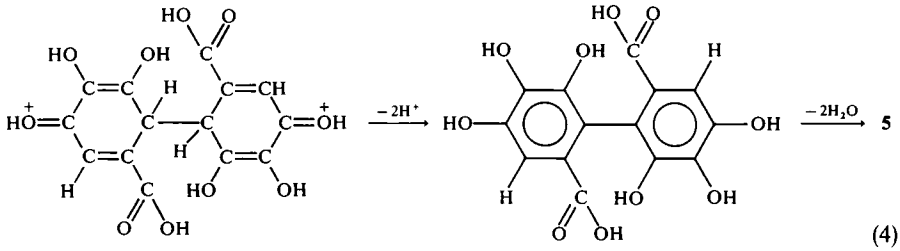
enrichment at CO = 97%,
99% radiochem. purity
sp. activity 110 mCi mmol^{-1}

(3)

(F.A.) $\dot{C} = {}^{13}C$ or ${}^{14}C$

gave 80% of EA–tetraisobutyrate (m.p. 270 °C). The crucial intermediate, carboxyl-^{13}C and $-{}^{14}C$ gallic acid **6**, has been prepared by modification of a previously reported synthesis[19] of this acid. It has been proposed that the $K_2S_2O_8$ oxidative coupling of **6** to yield EA proceeds as shown in equation 4 via a phenoxy radical species dimerizing



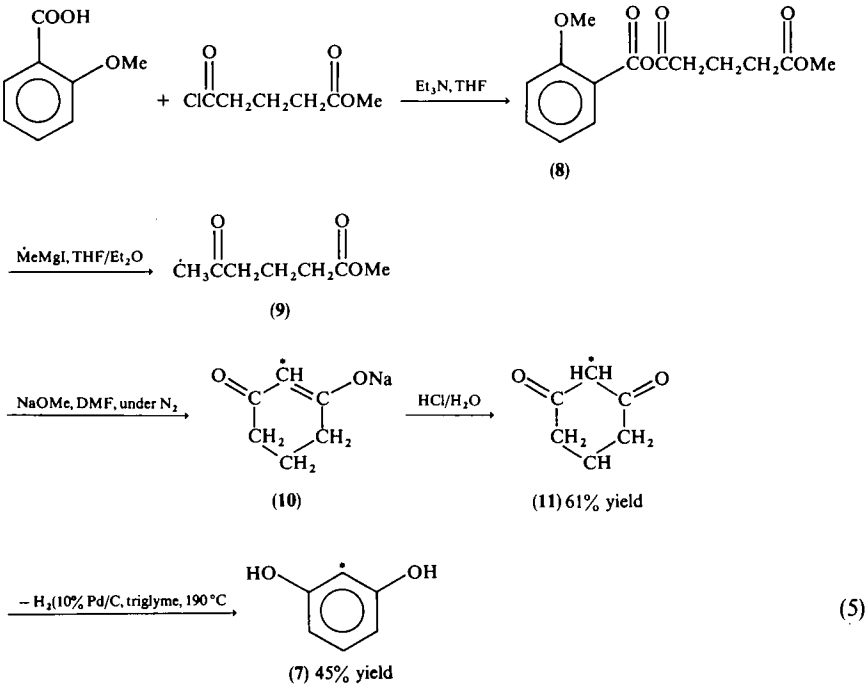


(4)

to a biphenyl intermediate with properly oriented carboxyl and hydroxyl groups required for lactonization. Use of 96% H_2SO_4 gave flavellagic acid (F.A.) as major (90%) product and E.A. as minor product (10% yield).

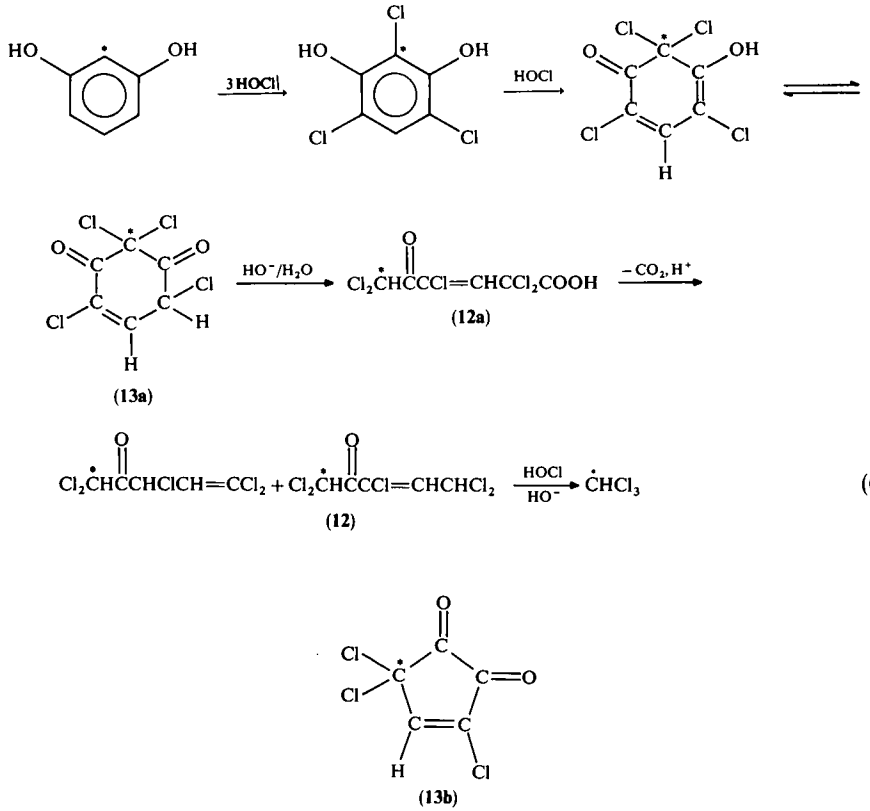
*4. Synthesis of 1,3-dihydroxybenzene[2-^{13}C] (**7**) and its application*

a. **7** has been ^{13}C-labelled[20] (equation 5) to investigate the mechanism of formation of carcinogenic trihalomethane pollutants, such as $CHCl_3$ and $CHBr_3$ during the disinfection of water containing humic substances with chlorine[21–26]. The mixed dicarboxylic anhydride **8** was obtained by treatment of *o*-methoxybenzoic acid with methyl 4-(chloroformyl)butyrate in the presence of Et_3N. Grignard reaction of **8** with methyl-^{13}C magnesium iodide gave methyl 5-oxohexanoate[6-^{13}C] (**9**) which by intramolecular Claisen condensation, produced the sodium enolate of 1,3-cyclohexanedione-[2-^{13}C] (**10**) and finally the 1,3-cyclohexanedione[2-^{13}C] (**11**). Dehydrogenation of **11** over a palladium–carbon catalyst produced the desired product **7**.



(5)

b. Chlorination and bromination of **7** with ten-fold excess of Cl_2 and Br_2 in H_2O gave $^{13}CHCl_3$ and $^{13}CHBr_3$, respectively, with at least 95% of the haloforms originating from the $C_{(2)}$ position of the aromatic ring. Several trihalomethyl-substituted compounds, such as $Cl_3{}^{13}CCOOH$, were also identified in the products[27]. The presence of by-products like $Cl_2\overset{*}{C}HC(=O)CCl{=}CHCHCl_2$ (**12**) and $Cl_2CHC(=O)CHClCH{=}CCl_2$ lend support to the scheme shown in equation 6. The structure **13b** has been suggested[28] for one of the detected products derived from **13a**.



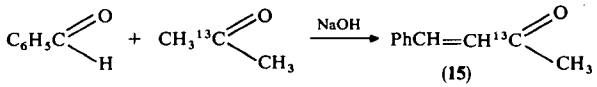
$$Cl_2\dot{C}HC(=O)CHClCH{=}CCl_2 + Cl_2\dot{C}HC(=O)CCl{=}CHCHCl_2 \xrightarrow[HO^-]{HOCl} \dot{C}HCl_3 \qquad (6)$$

(12)

(13b)

5. Synthesis of ^{13}C warfarin labelled at the hemiketal carbon

Warfarin (**14**), clinically effective oral anticoagulant and rodenticide, has been labelled[29] with ^{13}C (98.6%) at the anomeric carbon $C_{(2)}$ by condensing acetone[2-^{13}C] with benzaldehyde and subsequent addition of the produced **15** to 4-hydroxycoumarin in methanol (equation 7). The obtained diastereomeric warfarin methyl ketals (**16**) yielded, after deprotection, the racemic warfarin [2-^{13}C (98%)].



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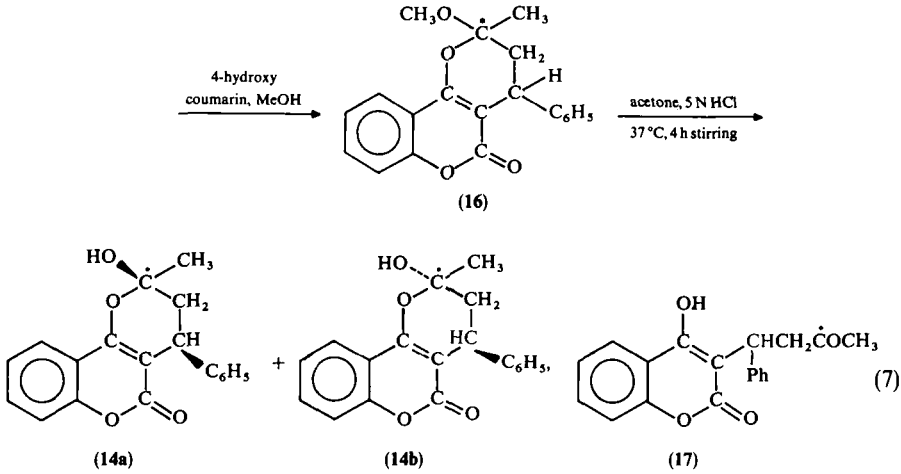


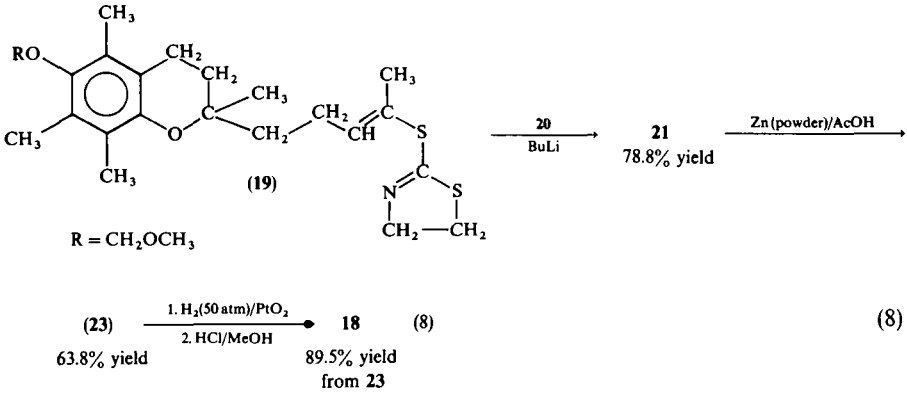
31% yield based on acetone-[^{13}C]

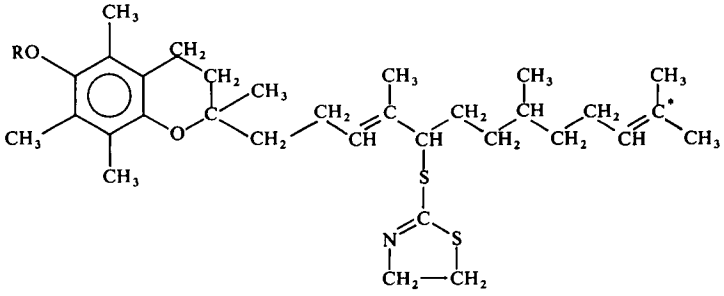
The racemic **14**-[2-^{13}C] has been resolved[30] by precipitating the less soluble (*S*)-(**14**)-[2-^{13}C] quinidine salt from acetone as colourless crystals. The more soluble (*R*)-(**14**)-[2-^{13}C] quinidine salt remaining in the acetone solution could be recovered by evaporation of the solvent.

In relatively non-polar solvents, warfarin exists[31] as a mixture of two diastereomeric hemiketals **14a** and **14b** and as an open-chain keto form **17**.

6. *Synthesis of carbon-13 labelled vitamin E, [12'-^{13}C]all-rac-α-tocopherol*

[12'-^{13}C]*all-rac*-α-tocopherol (**18**) has been synthesized in order to investigate the interaction between the isoprenoid side chain of vitamin E and lipid components in biomembrane[32]. Condensing 6-methoxymethoxy-2,5,7,8-tetramethyl-2-(5-mercaptothiazolinyl-4-methyl-3-penten-1-yl) chroman (**19**) with [7-^{13}C]geranyl bromide **20** and subsequent desulphurization, reduction and hydrolysis of the produced [12'-^{13}C]-6-methoxymethoxy-2,5,7,8-tetramethyl-2-[(3*E*,7*E*,9*E*)-5-mercaptothiazolinyl-4,8,12-trimethyl-3,7,9-tridecatrien-1-yl]chroman (**21**) (equation 8), **18** was obtained in 33.7% on the basis of [2-^{13}C]acetone[32]. [7-^{13}C]geranyl bromide **20** used in the syntheses of **18** has





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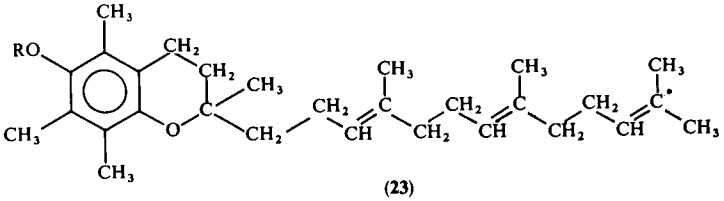

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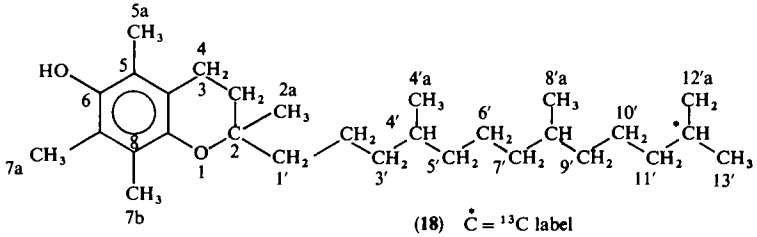
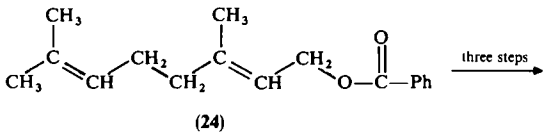


(18) $\dot{C} = {}^{13}C$ label

been prepared from (6-benzoyloxy-4-methyl-4-hexenyl)triphenylphosphonium bromide **22** (equation 9). The overall yield of **18** starting from **24** was 28.6%. Synthesis of [4'a-^{13}C]*all-rac*-α-tocopherol has been reviewed elsewhere[33a].



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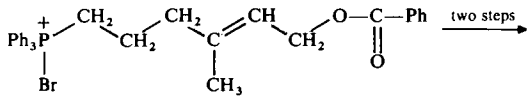
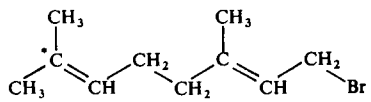
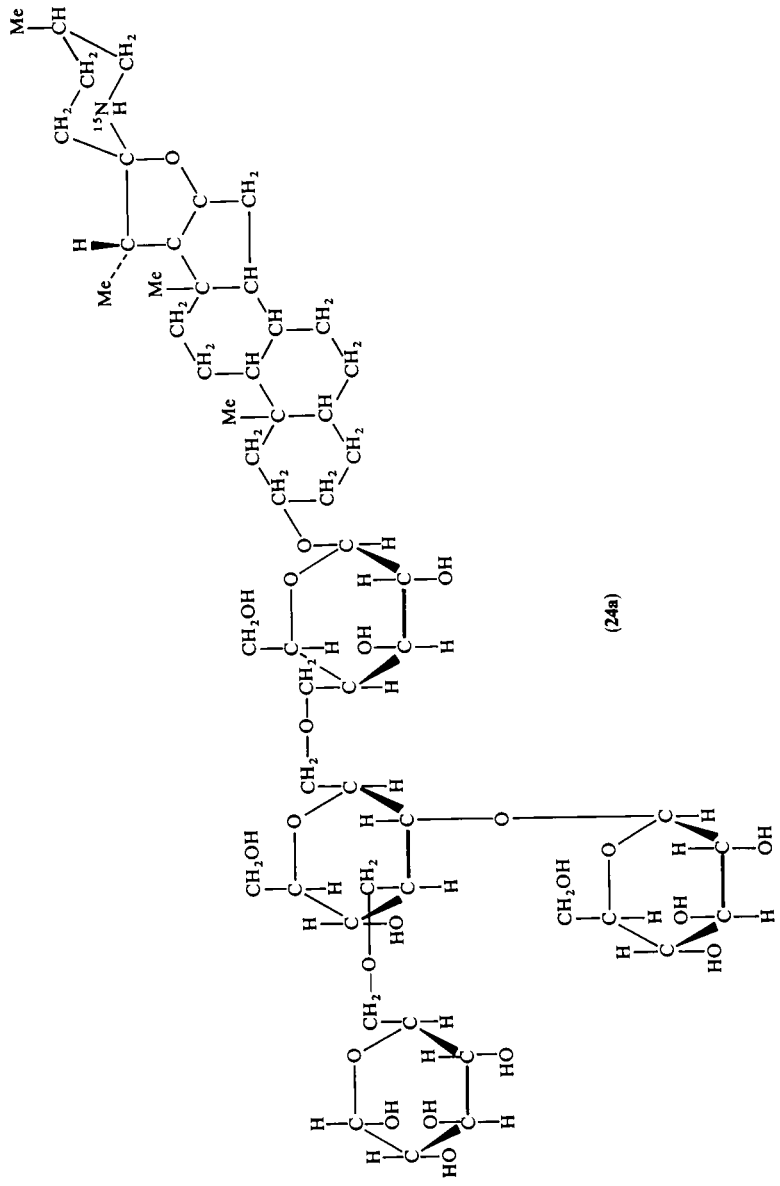


(22) 89.4%



(20)

(9)



(24a)

7. Synthesis of ^{15}N-tomatine

Tomatine, a steroidal glycoalkaloid, **24a**, found in the tamato plant and also in other species, is considered as a possible useful precursor of steroidal pharmaceuticals[33b]. It has been isolated (with 95% isotopic purity) from foliage of tomato plants grown hydroponically with ^{15}N-containing nutrient solution of salts[33c,d]. **24a** could be converted to ^{15}N-tomatidine by acid hydrolysis[33c]. The isotopic purity of the latter was estimated by MS to be about 95%.

B. Synthesis of the Title Compounds Labelled with Oxygen-18

1. Synthesis of labelled phenol and naphthol

Phenol[^{18}O] **25** and naphthol[^{18}O] **26** needed[34], for preparation of L-tyrosine-[4′-^{18}O] and propanolol[^{18}O], have been obtained in the past[35] using acid exchange in $H_2{}^{18}O$, but this procedure requires large quantities of $H_2{}^{18}O$ and recycling. Among other approaches[36–41], the reaction of Grignard reagents with oxygen gas has been found the most convenient and effective route[34] for production of the ^{18}O-enriched alcohols[42,43] or phenols. The yield obtained from aryl halides has been improved by addition of aliphatic halide: The oxygen reacts with ArMgX to form the peroxide (equation 10), which is reduced by reaction with more ArMgX (equation 11).

$$\mathrm{ArMgBr} + \mathrm{O_2} \longrightarrow \mathrm{ArOOMgBr} \tag{10}$$

$$\mathrm{ArOOMgBr} + \mathrm{ArMgBr} \longrightarrow 2\,\mathrm{ArOMBr} \tag{11}$$

Since alkyl Grignard reagents are better reducing agents than aryl ones, this improves the yield of the aryl hydroxyl compound (equation 12).

$$\mathrm{ArOOMgBr} + \mathrm{RMgBr} \longrightarrow \mathrm{ArOMgBr} + \mathrm{ROMgBr} \tag{12}$$

Both PhMgBr and 1-NaphMgBr reacted with oxygen-18 and yielded the ^{18}O-labelled products **25** and **26**[34].

Ph^{18}OH	1-Naph^{18}OH
(**25**)	(**26**)
34% yield	23% yield based on ^{18}O

2. Synthesis of specifically ^{18}O-labelled pyrimidine deoxyribosides

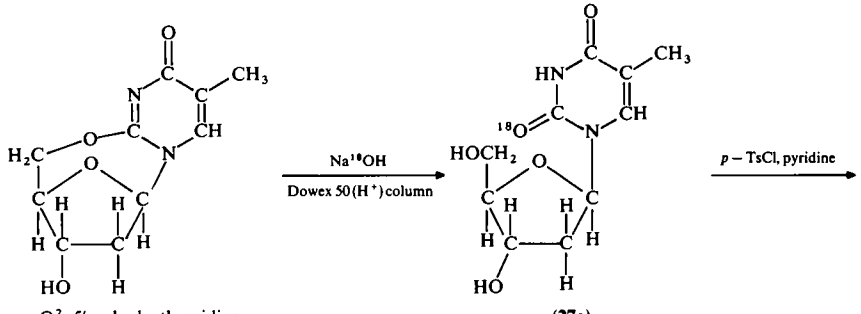
There is a growing use of pyrimidine nucleosides labelled with stable isotopes, such as deuterium[45–48] and oxygen-18[44,49,50], particularly in GC/MS studies[51]. The general method of specific ^{18}O-labelling of nucleosides has been elaborated using the antitumor agent[52] thymidine as a model[53] (equation 13). The position and the level of ^{18}O have been determined using mass spectrometry. Product **27b** had 98.7% of ^{18}O incorporated in the sugar according to MS determinations.

III. SYNTHESIS AND APPLICATION OF THE TITLE COMPOUNDS LABELLED WITH HEAVY RADIOISOTOPES

A. Synthesis with Radiocarbon-^{14}C

1. Preparation of [U-^{14}C]solanesol

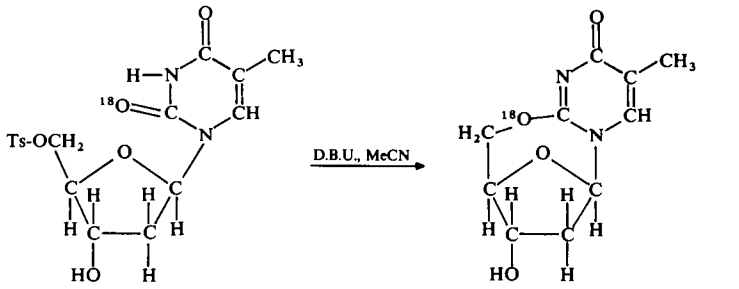
[U-^{14}C]solanesol, **28**, has been isolated[54] from $^{14}CO_2$-chamber grown tobacco leaves. Purification yielded **28** with a total activity of 0.474 mCi, specific activity of



O^2, 5′-anhydrothymidine

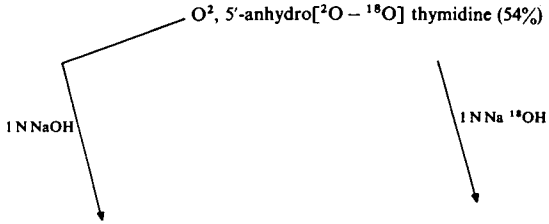
(27a)

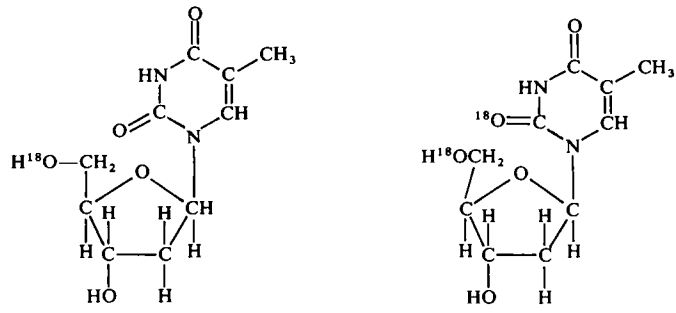
[O^2—^{18}O]thymidine (92.8% incorporation of ^{18}O)



27% yield

O^2, 5′-anhydro[^2O – ^{18}O] thymidine (54%)



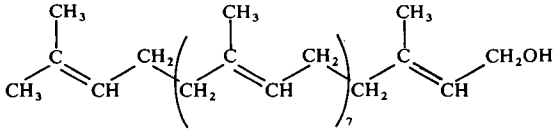


(27b)
5′-^{18}O thymidine
66%

(27c)
O^2, 5′-^{18}O thymidine
65%

(13)

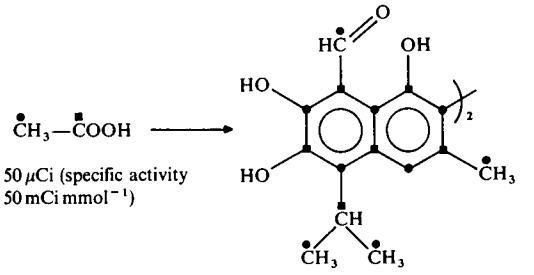
0.5 mCi mmol^{-1}, radiochemical purity of 95% and chemical purity of 97%. This trisesquiterpene alcohol has been required to investigate the contribution of solanesol to the flavour and aroma of tobacco smoke[55,56].



(28)

2. Preparation of ^{14}C-labelled gossypol

Carbon-14 labelled gossypol **29**, a pigment formed in plants of the genus *Gossypium* (*Malvaceae*)[57], was biosynthesized previously from ^{14}C- and ^{13}C-acetates[58–61] (equation 14). It has been prepared recently[62] by incorporation of sodium acetate-[1,2-^{14}C] in the growth medium of cotton seedlings roots. Unlabelled gossypol was added during the purification procedure to aid crystallization of gossypol as its acetic acid complex. Further purification gave the product **29**. The ^{14}C gossypol–acetic acid complex has been needed for study of detoxification in insects and microorganisms and also to investigate its male antifertility activity in humans[63] or its toxicity to the cotton plant pathogen, *Verticillium dahliae*[58], etc. Gossypol, tritium labelled in the 4,4′ positions, has also been synthesized[64] but it is unsuitable for metabolism studies in which that position is oxidized.



50 μCi (specific activity 50 mCi mmol^{-1})

(29)

specific activity 1900 dpm mg^{-1}

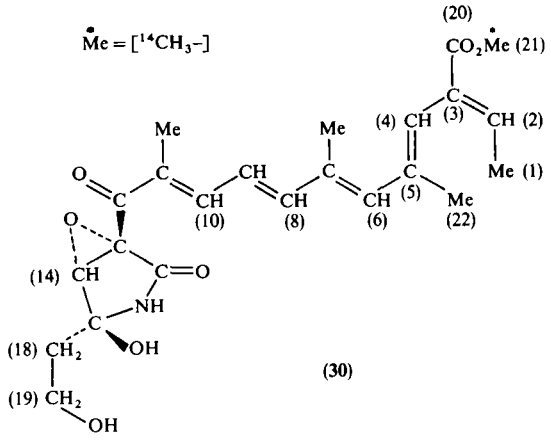
(14)

● denotes carbon-14 or carbon-13 derived from the methyl group of the acetate

■ denotes carbon-14 or carbon-13 derived from the carboxyal group of the acetate

3. Synthesis of [21-^{14}C]fusarin C

Fusarin C, **30**, isolated from cornmeal cultures of *Fusarium moniliforme*, is mutagenic and toxic to bacteria and mammalian cells when metabolized by microsomal enzymes[65] and is often contaminating corn in China and South Africa. It has been radiolabelled in two steps[66] by enzymatic hydrolysis of the 21-methyl ester group with liver microsomes from rats in the absence of NADPH and subsequent quantitative remethylation using diazomethane[^{14}C].

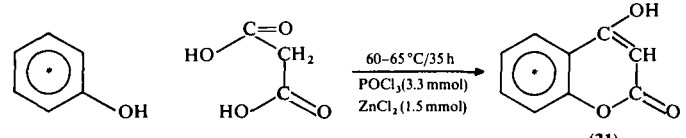


(30)

The product **30** (0.33 μmol, 20 μCi) had the same specific activity (60 mCi mmol^{-1}) as the [^{14}C]methyl nitrosourea used for preparation of diazomethane[^{14}C] and was found convenient for studying its metabolism and binding to DNA due to inhibition of the esterase activity in the presence of low concentrations of diisopropyl fluorophosphate.

4. Synthesis of 4-hydroxy[phenyl-U-^{14}C]coumarin

4-hydroxycoumarin, **31**, is the fundamental moiety of a number of anticoagulant rodenticides[67]. It has been synthesized[68] with a uniformly labelled benzene ring also for metabolic studies on a microscale by condensing phenol[U-^{14}C] and malonic acid[69] (equation 15).



(15)

specific activity
87 mCi mmol^{-1}
0.5 mmol, 250 μCi

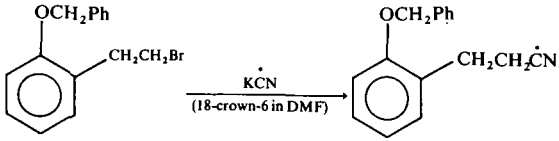
0.5 mmol

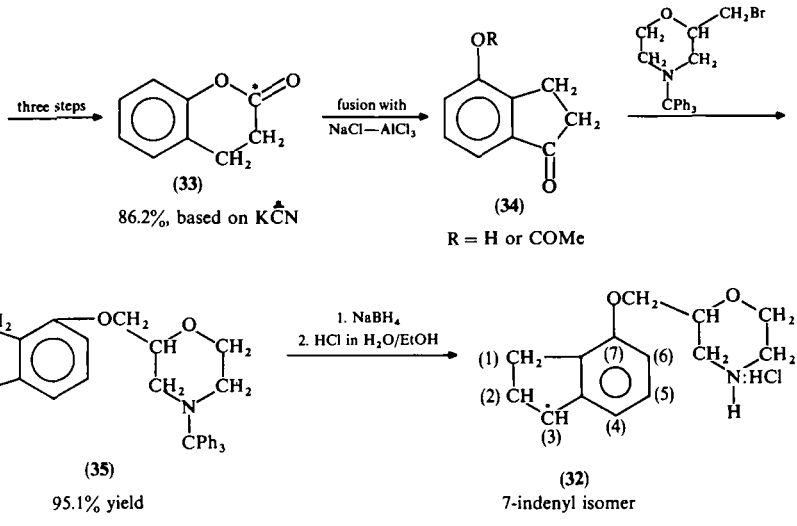
(31)

20% yield
specific activity 107 μCi/mmol^{-1}

5. Synthesis of ^{14}C-labelled indeloxazine hydrochloride (YM-08054)

This compound, (±)-2[(inden-7-yloxy)methyl]morpholine hydrochloride **32**, a new cerebral activator[70], has been ^{14}C-labelled[71] for neuropharmacological and metabolic studies in a ten-step synthesis in 42.8% radiochemical yield (r.y.) from K^{14}CN (equation 16).

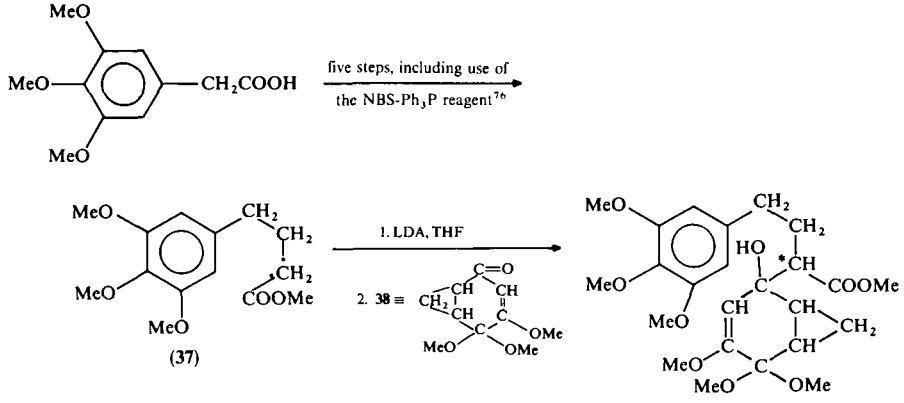


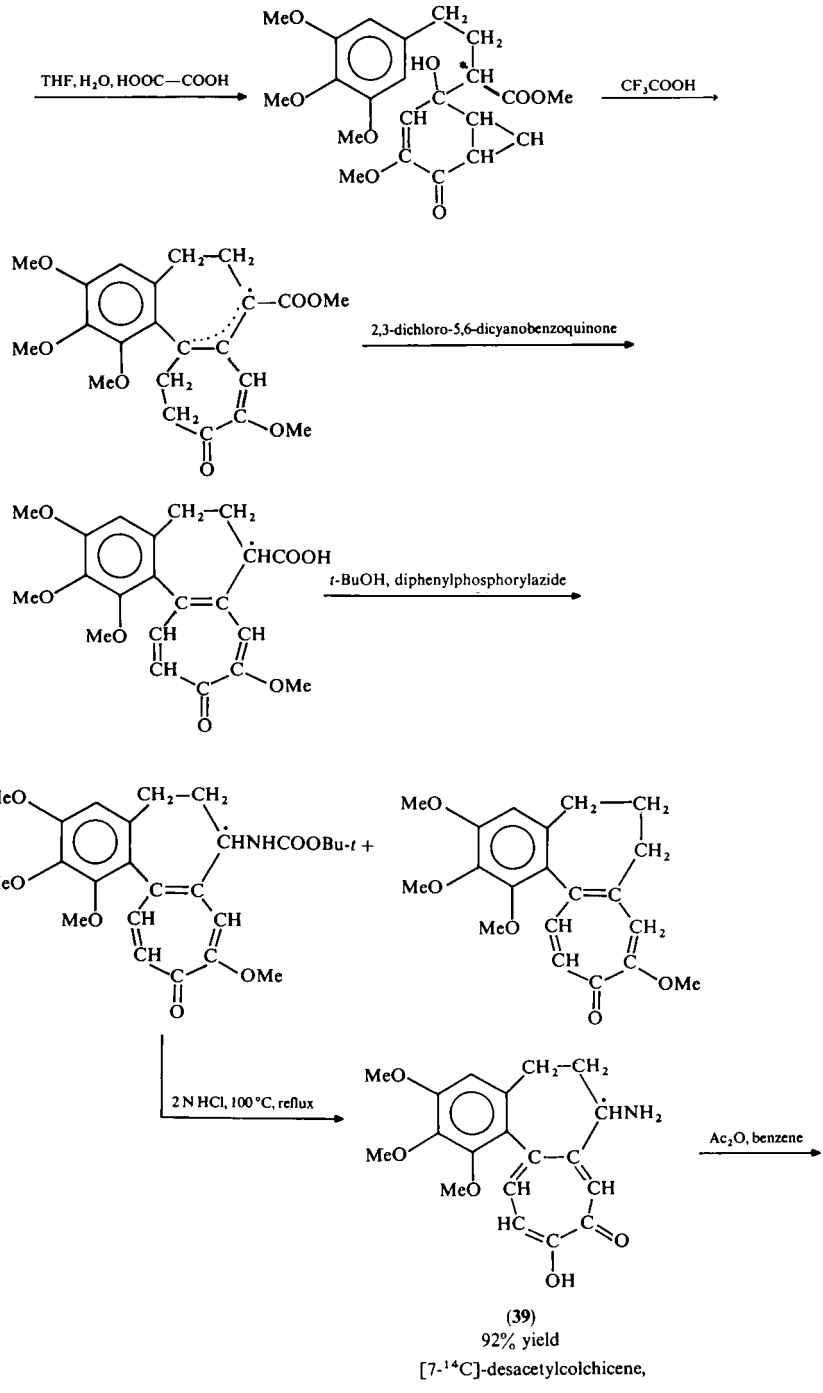


(16)

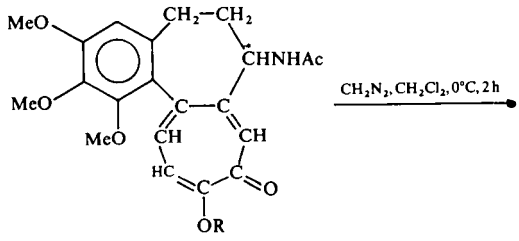
6. *Synthesis of (±)-colchicine[7-^{14}C]*

Colchicine, **36**, an alkaloid occurring in members of the *Liliacesa*, whose specific mechanism of therapeutic and cytotoxic action is still imperfectly known[72–74], has been ^{14}C-labelled recently at the 7-position of the 'B-ring' in a sixteen-step reaction sequence[75], the main features are illustrated by equation 17. Conversion of the ester **37** to (±) desacetylcolchiceine **39** has been carried out following the procedure by Evans and coworkers[73]. Besides colchiceine **40** (80% yield) the diacetylated by-product **41** has also been produced in 2% yield. O-methylation of crude **40** with diazomethane provided **36** and **42** in 1.7:1 ratio. The final product, (±)-colchicine[7-^{14}C] **36**, has been obtained in 2.5% overall yield from the $Ba^{14}CO_3$ used to generate $^{14}CO_2$ in the first stages of the reaction. The radiolabelled **36** was indistinguishable from the natural (±)-colchicine, except for its optical rotation.

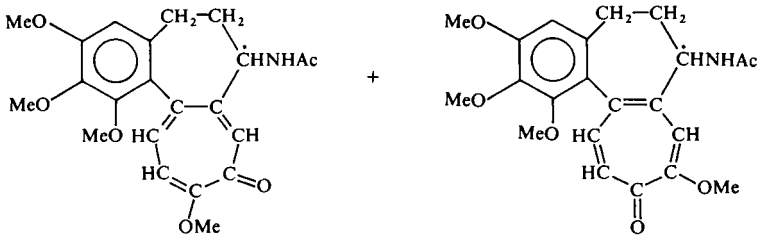




(39)
92% yield
[7-^{14}C]-desacetylcolchicene,



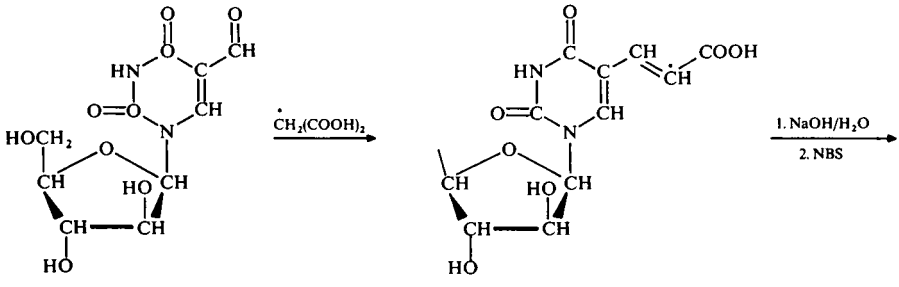
(40) R=H
(41) R=Ac



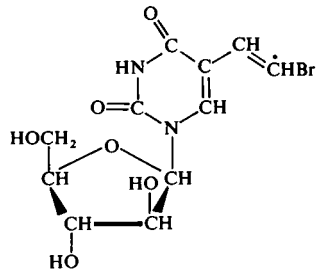
(17)

Colchicine (**36**)
radiochemical purity 98%

(**42**)



(**43**) (**44**)



(18)

(**42a**)

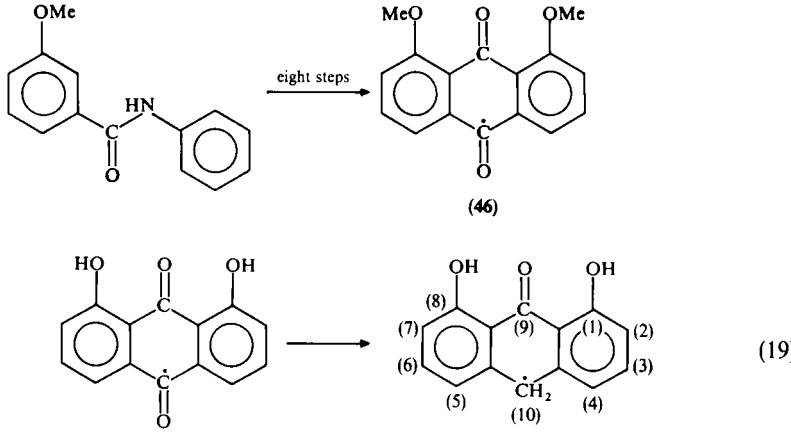
26.6% r.y. based on
^{14}C-labelled malonic acid, radiochemical purity > 98%

7. Synthesis of ^{14}C-labelled BV-araU

This compound, 1-β-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil, **42a**, an antiviral agent against herpes simplex virus type 1 (HSV-1), has been ^{14}C-labelled by reaction of 1-β-D-arabinofuranosyl-5-formyluracil aldehyde, **43**, with malonic acid[2-^{14}C] and further treatment with NBS.[77,78] (equation 18).

8. Synthesis of ^{14}C-anthralin

The unstable 1,8-dihydroxy-9-anthrone[10-^{14}C], **45**, used extensively in the topical treatment of psoriasis, has been synthesized[79,80] for drug metabolism and skin penetration studies from the stable precursor 1,8-dimethoxyanthraquinone[10-^{14}C], **46**, which could be stored and converted efficiently into **45** when required (equation 19).

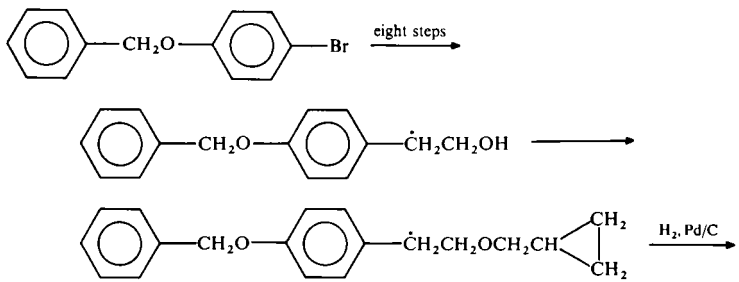


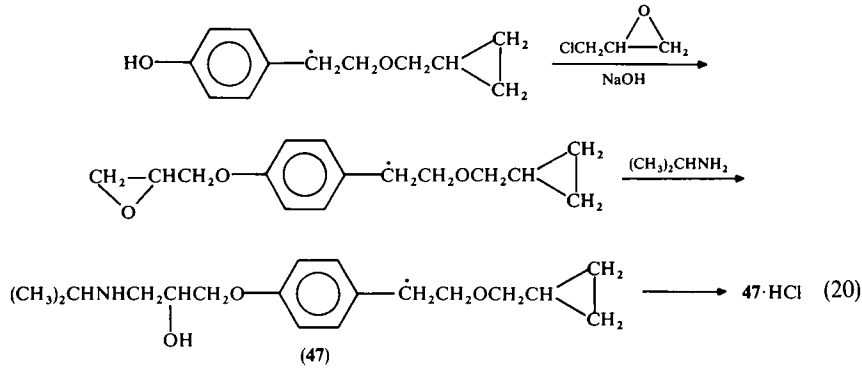
(19)

(45) 94% specific activity 57 mCi mmol^{-1}

9. Synthesis of SL-75.212 (betaxolol) labelled with ^{14}C

The above compound, the β-blocker 1-[4-(2-cyclopropyl methoxyethyl-[1-^{14}C])-phenoxy]-3-isopropylamino-2-propanol, **47**, has been obtained[81] in twelve steps (equation 20) and applied for quantitative pharmacokinetic studies[82,83]. The desired product, SL 75.212 [ethyl-1-^{14}C], **47**, obtained as the hydrochloride in better than 99% radiochemical purity (specific activity 57 mCi mmol^{-1}), was stored under nitrogen in sealed ampoules. After 4 years, four impurities comprising about 25% of the total activity were formed.

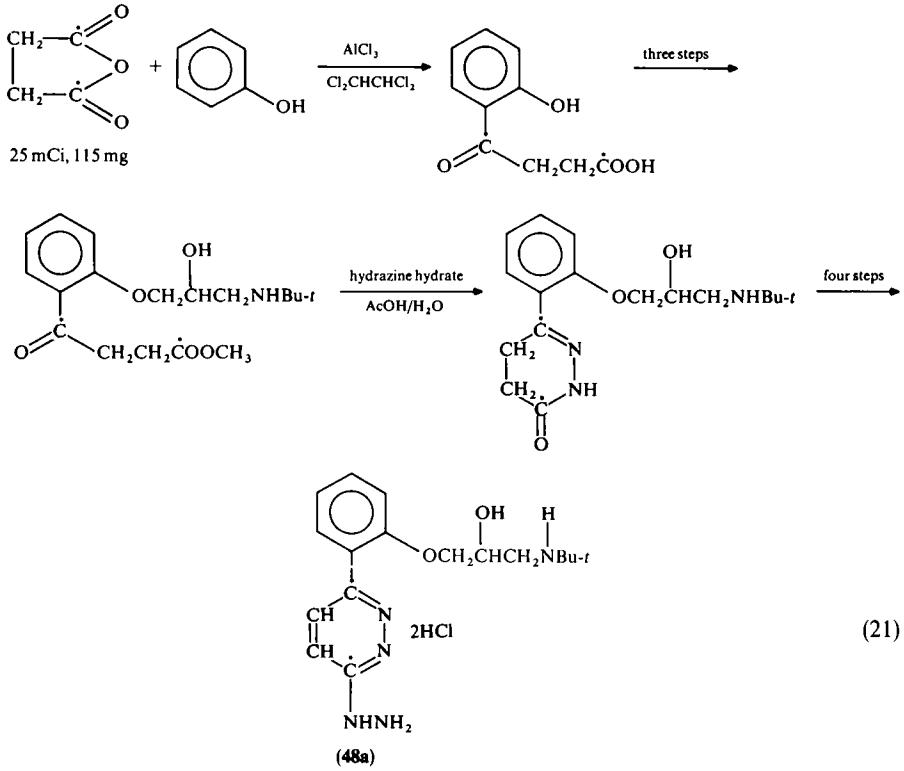




(20)

10. Synthesis of ^{14}C-labelled prizidilol dihydrochloride

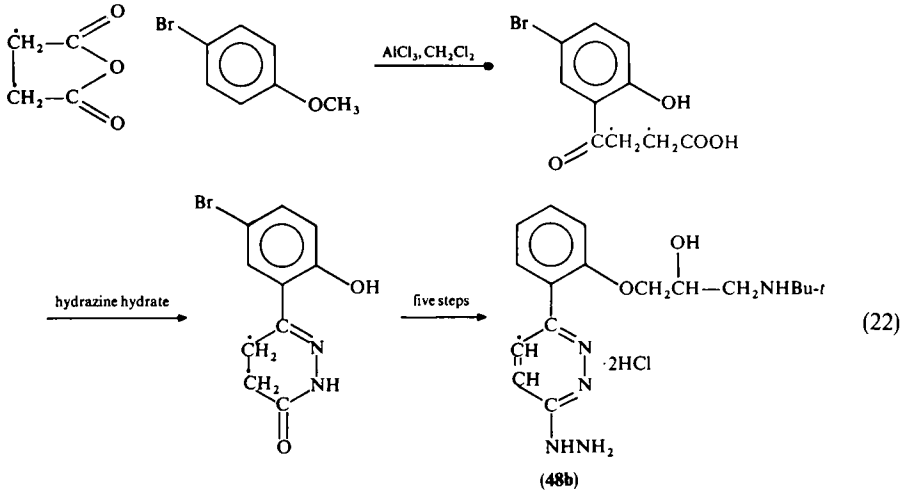
Prizidilol, **48a,b**, is an antihypertensive drug reducing blood pressure in animals and man[84,85], as a result of precapillary vasodilatation and competitive β-adrenoreceptor blockade, possessing a 2-hydroxy-3-alkylaminopropoxy side chain. It was originally ^{14}C-labelled[86] according to a 10-step procedure (equation 21) which gave the



(21)

523 μCi, 8 mg, radiochemical purity of 97.6%

dihydrochloride **48a** in rather poor (0.91%) overall yield. The drug-^{14}C has been subsequently obtained in an improved 7-stage synthesis (equation 22) in 8% yield.



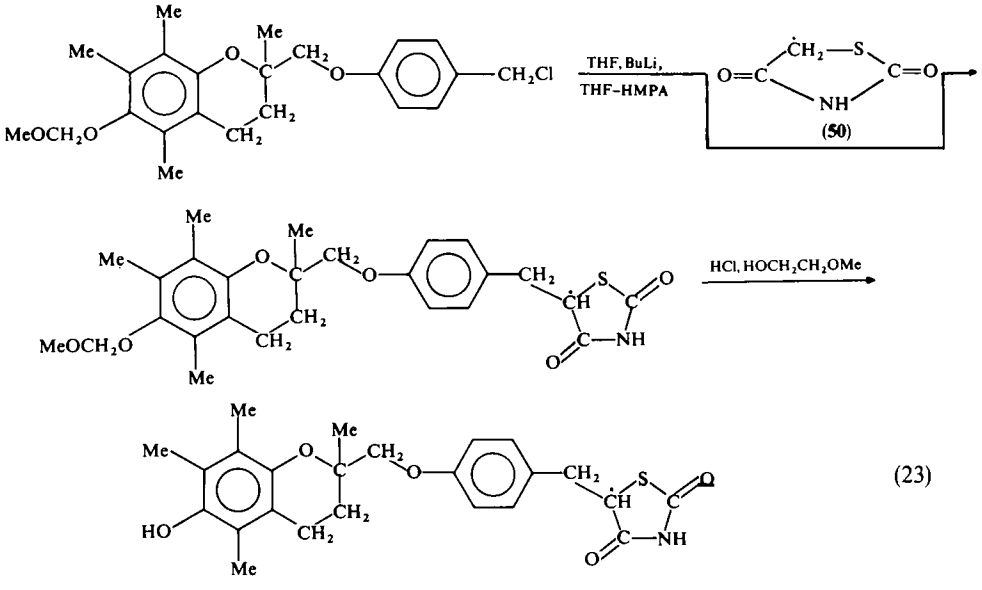
(22)

(48b)

475 mg, 9.357 mCi, radiochemical purity > 97.8%

11. Synthesis of ^{14}C-labelled CS-045

This new oral antidiabetic agent **49**, the hindered phenol (±)-5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-[5-^{14}C]-thiazolidine-2,4-dione, possesses also



(23)

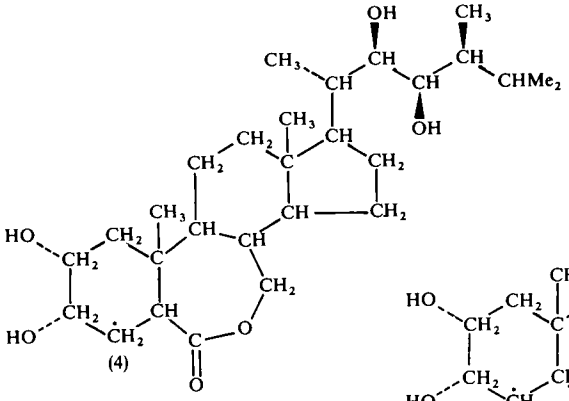
(49)

185 MBq, 0.748 mmol, specific activity 561.2 kBq mg^{-1}

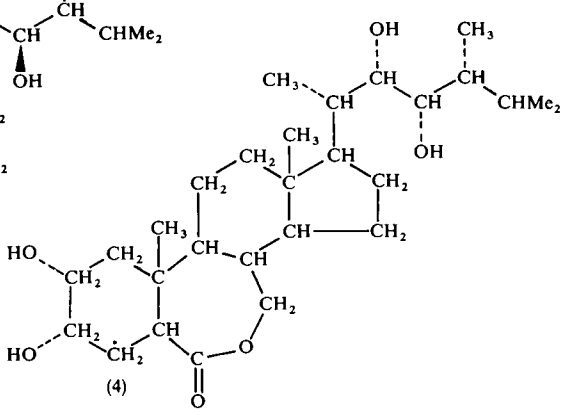
significant lipid peroxide activity[87,88]. It has been radiolabelled by introducing ^{14}C at the 5-position of the thiazolidine ring[89] of **49** using [5-^{14}C]thiazolidine-2,4-dione **50**, prepared by reacting [2-^{14}C]bromoacetic acid with thiourea (equation 23)[90].

12. Synthesis of (22R,23R)- and (22S,23S)-[4-^{14}C]-24-epibrassinolide

The above compounds, plant growth regulating substances and promising candidates for application in agriculture[91] have been labelled with ^{14}C at position 4 of the epibrassinolides **51** and **52** in an overall radiochemical yield of 3.22% and 4.46% respectively based on $Ba^{14}CO_3$ (equation 24)[92,93].

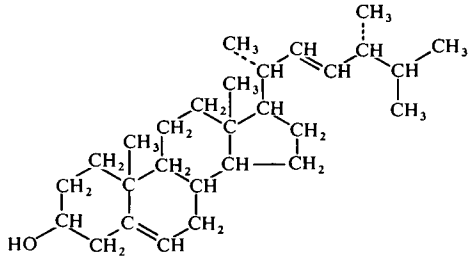


(51) [4-^{14}C]

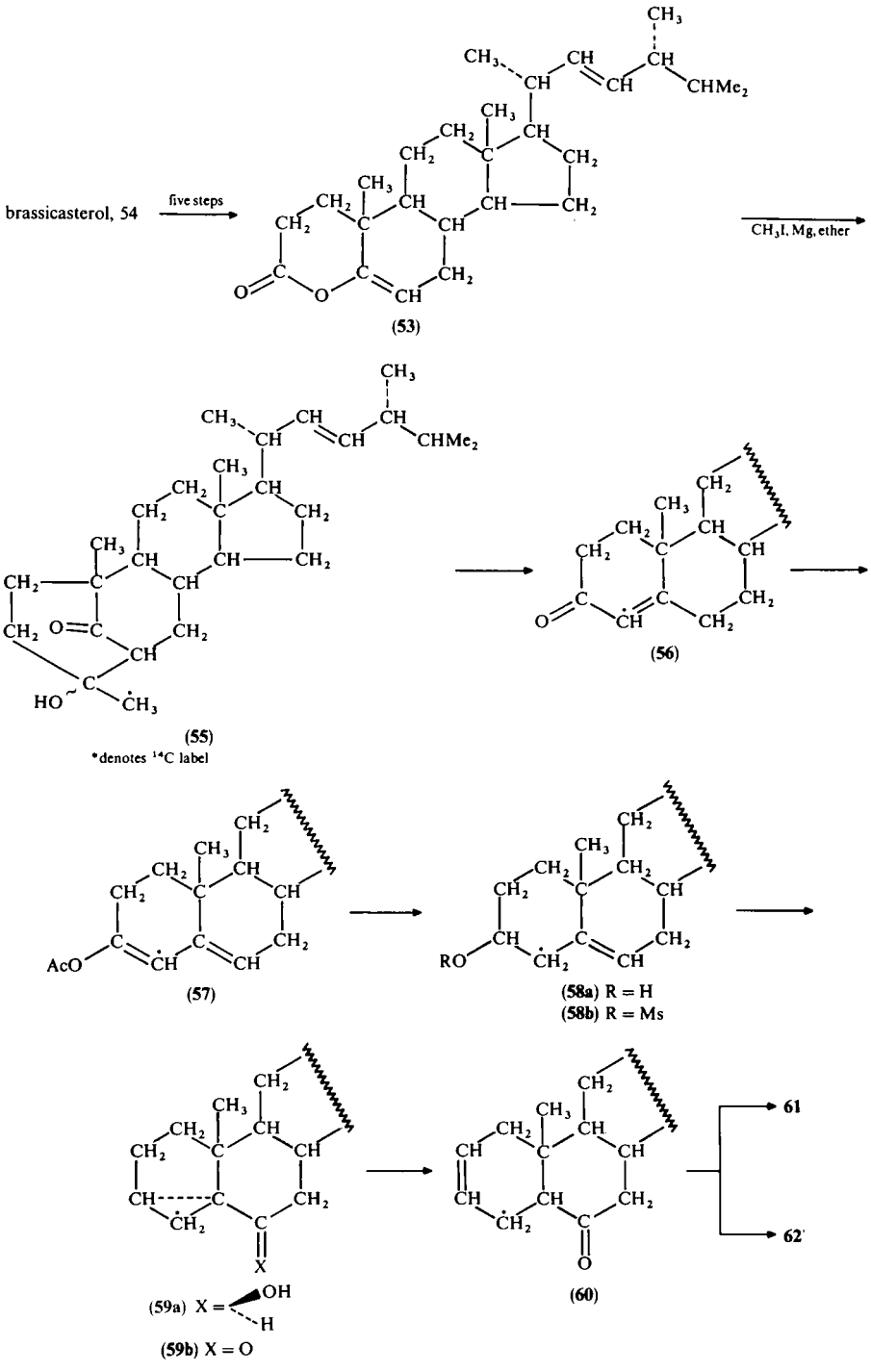


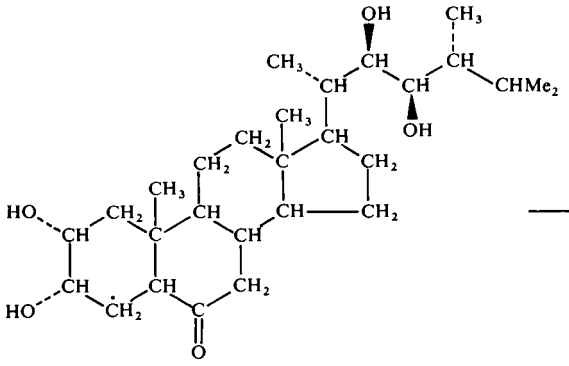
52 [4-^{14}C]

The enol lactone **53**, synthesized from brassicasterol **54**, gave in Grignard reaction with $^{14}CH_3I$ the bridged ketone **55**, which in turn furnished [4-^{14}C]brassicasterone **56** in 70% yield (from $^{14}CH_3I$). Enol acetylation of **56** with mixture of isopropenyl acetate and *p*-toluene sulphonic acid gave the acetate **57**. This was reduced with sodium borohydride to [4-^{14}C]brassicasterol **58** and its isomers, which were eliminated by Jones' oxidation method[94]. 3,5-cyclo-6-ol **59a** was obtained from **58a** by mesylation to give **58b**, followed by treatment with sodium carbonate. **59a** was oxidized[94] to 3,5-cyclo-6-one **59b** which, treated subsequently with LiBr and camphorsulphonic acid, provided the



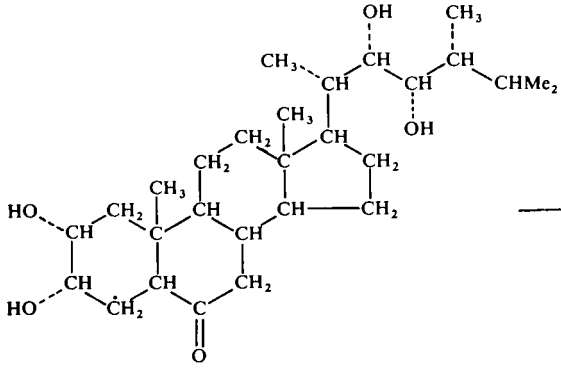
(54)


brassicasterol, 54
five steps
CH3I, Mg, ether
(53)
(55)
*denotes 14C label
(56)
(57)
(58a) R = H
(58b) R = Ms
(59a) X = OH, H
(59b) X = O
(60)
61
62



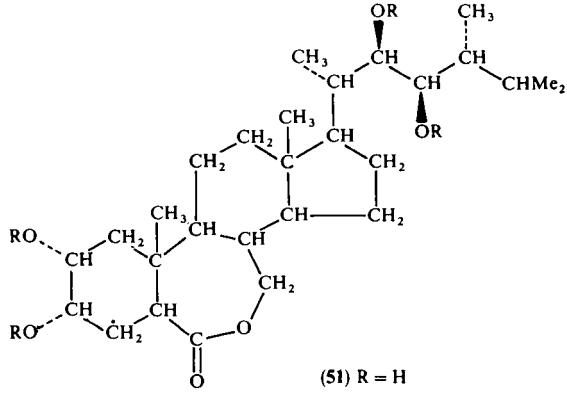
(61)

(51) R = H
(63) R = Ac
(24)

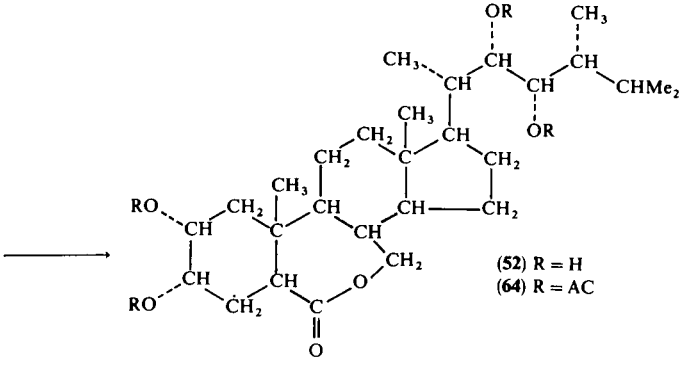


(62)

(52) R = H
(64) R = Ac
(24)



(51) R = H
(63) R = Ac

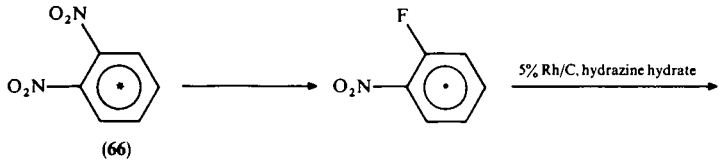


(24)

2,22-diene-6-one **60**. Oxidation of **60** with osmium tetroxide produced a stereoisomeric mixture of 2,3,22,23-tetraols from which the 22*R*,23*R*-tetraol **61** and 22*S*,23*S*-tetraol **62** were isolated by repeated chromatography and recrystallization. **61** and **62** oxidized in dichloromethane with trifluoroperacetic acid produced (22*R*,23*R*)-7-oxa-lactone **51** and (22*S*,23*S*)-7-oxalactone **52** in 3.22% and 4.46% overall radiochemical yields respectively based on the $Ba^{14}CO_3$ used. The radiochemical purity of **51** and **52** is 98%, specific activity 10.68 μCi mg^{-1} and 12.09 μCi mg^{-1} (5.13 mCi mmol^{-1} and 5.8 mCi mmol^{-1}) respectively.

13. Synthesis of 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(2-chloro-4-trifluoromethyl-phenoxy)[ring U-^{14}C]phenyl) urea

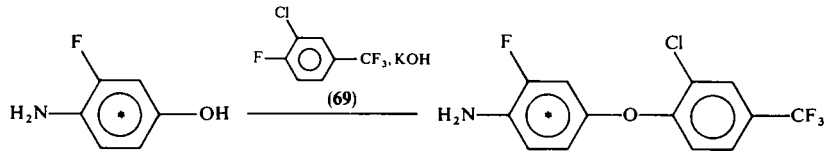
The title compound, **65**, also called flufenoxuron, is a potent new acylurea insecticide and acaricide[95], and was needed for various metabolic and residue studies. It has been labelled[95–97] with ^{14}C starting with *o*-dinitro[ring-U-^{14}C]benzene **66** (equation 25), **67** was synthetized by the method of Clark and Smith[96], reduced and transformed to **68**. The latter with **69** gave **70**, which on reaction[98] with the isocyanate **71** furnished the final product **65**.



(66)

specific activity 851 MBq mmol^{-1}
242.3 mg

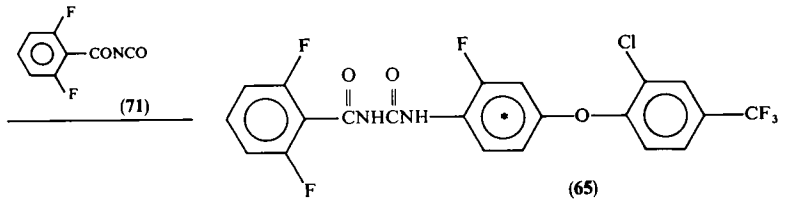
(67) 96% yield 1.46 GBq, 851 MBq mmol^{-1}



(70)

29 GBq,
88%

0.52 GBq, 40%
90% radiochemical purity



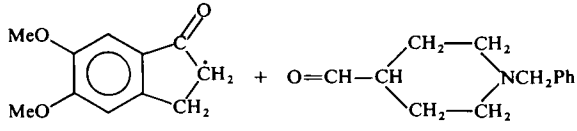
(25)

*denotes ring-U^{14}C

0.36 GBq, 24% overall yield specific activity
851 MBq mmol^{-1}, > 99% radiochem. and chemical purity

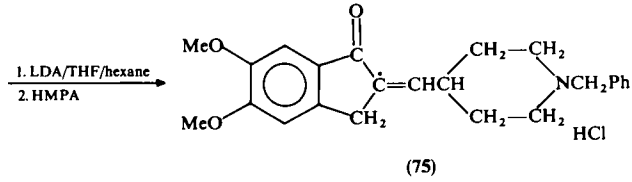
14. Synthesis of ^{14}C-labelled E2020

The title compound, 1-benzyl-4-[(5,6-dimethoxy[2-^{14}C]-1-indanon)-2-yl]-methylpiperidine hydrochloride **72**, a novel piperidone derivative potently inhibiting acetylcholinesterase[99], has been synthesized[100,101] for studying the pharmacokinetic profile of E2020. Condensation of the [2-^{14}C]-1-indanone **73** with 1-benzyl-4-formylpiperidine **74** followed by hydrogenation of the intermediate **75** yielded **72** in 99% radiochemical purity and a specific activity of 44.6 mCi mmol^{-1} (equation 26). The starting labelled material, **73**, is commercially available and is produced according to equation 27.

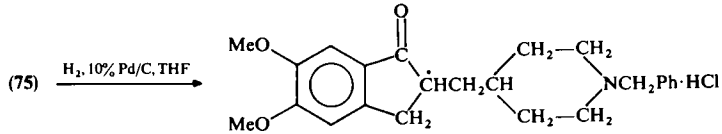


(73)
100 mCi, 2.22 mmol

(74) white crystals

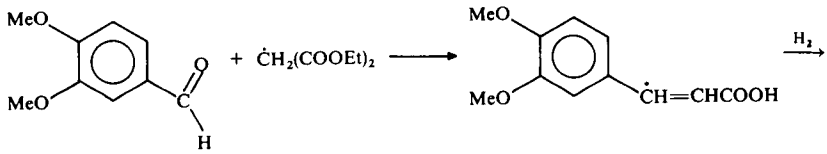


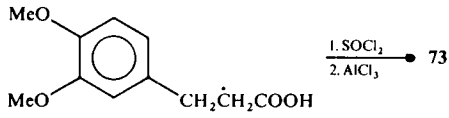
(75)



(26)

(72)



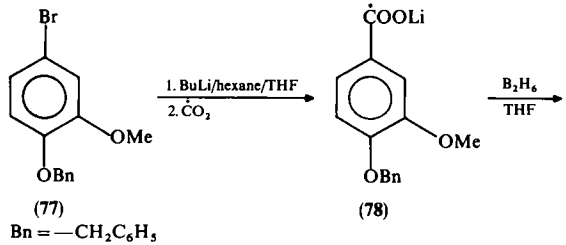


(27)

(27)

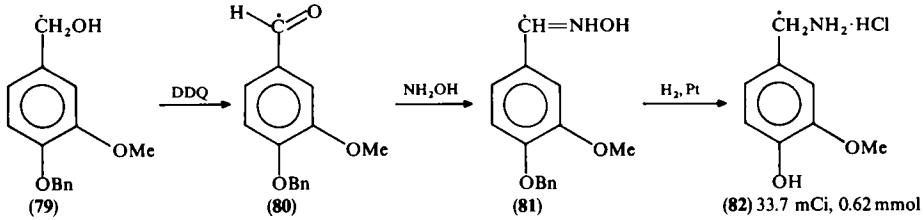
15. Synthesis of ^{14}C-labelled capsaicin

The title compound, (*E*)-*N*-4-(hydroxy-3-methoxybenzyl-α-^{14}C]-8-methyl-6-nonenamide **76**, stimulates prostaglandin formation[102,103], is important also as a food and cosmetic additive and is intensively sharp and pungent substance found in fruits of the genus *Capsicum* species. It was synthesized[104], as in equation 28, for metabolism/binding studies.

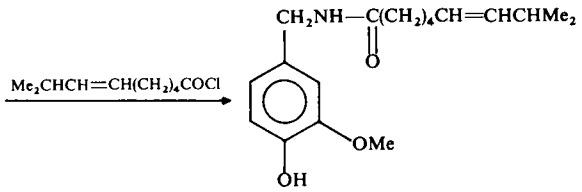


(77)
Bn = —$CH_2C_6H_5$
*denotes ^{14}C

(78)



(79) (80) (81) (82) 33.7 mCi, 0.62 mmol



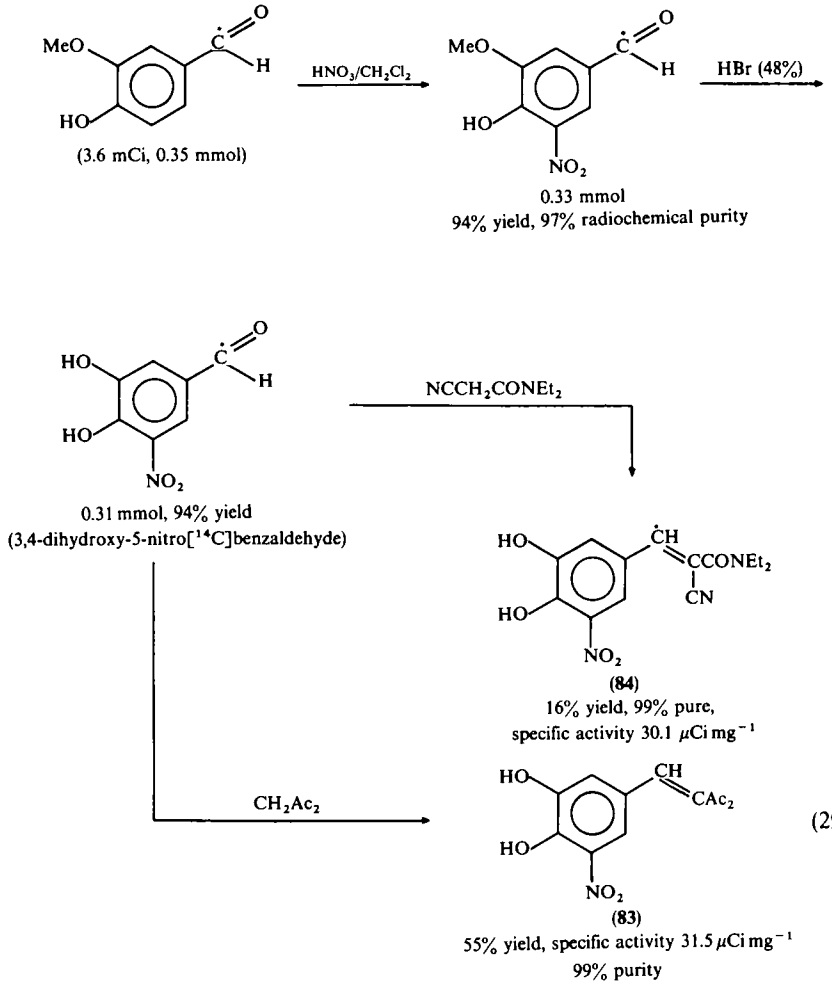
(28)

(**76**) 5.1 mCi,
specific activity 53.6 mCi mmol^{-1}

The reaction includes carbonation of **77** by $^{14}CO_2$, to yield the acid **78** in 90% radiochemical yield, reduction of the latter with diborane to produce the benzyl alcohol **79**, oxidation of **79** to **80** with DDQ[105] and preparation of oxime the **81**. Hydrogenolysis of **82** resulted in formation of the key intermediate, 4-hydroxy-3-methoxybenzylamine-α-^{14}C hydrochloride **82** in 64% yield, and finally capsaicin-^{14}C **76** (97% chemical and radiochemical purity) was obtained in 15% yield by coupling **82** with (*E*)-8-methyl-6-nonenoyl chloride[106].

16. Synthesis of two ^{14}C-labelled catechol-O-methyl transferase inhibitors

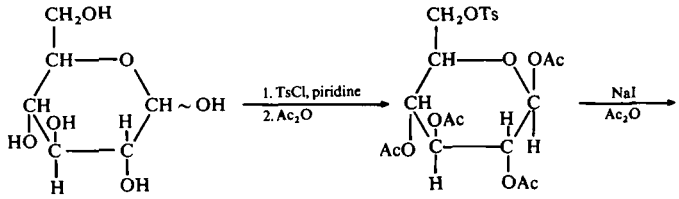
^{14}C-labelled 3-(3,4-dihydroxy-5-nitrophenylmethylidene)-2,4-pentanedione **83** and ^{14}C-labelled (*E*)-*N*,*N*-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide **84** have been synthesized[107] from [carbonyl-^{14}C]vanillin as shown in equation 29.



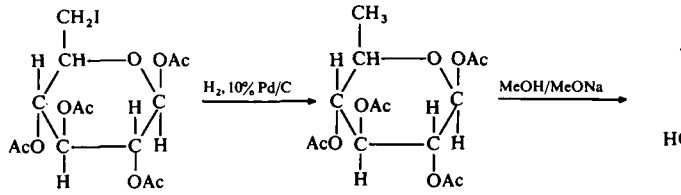
(29)

*17. Synthesis of 6-deoxy-D-[U]^{14}C-glucose (**85**)*

This was required for transport studies of non-metabolizable sugars in the yeasts *Rhodotorula glutinis* and *Saccharomyces cerevisiae*. It has been synthesized[108] following the procedure[109] outlined in equation 30, which was also successfully applied for the synthesis of 6-deoxy-D-[6-$^{3}H_1$]glucose[110] using D-[U-^{14}C]glucose **86** as starting material.



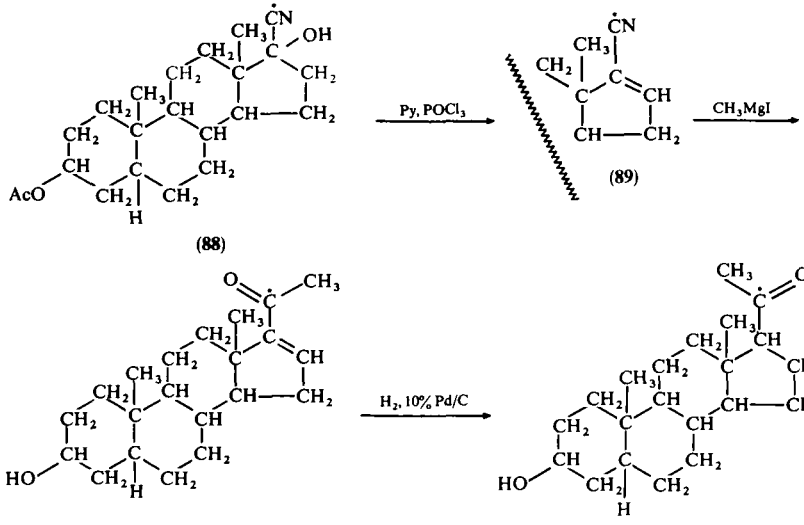
(86)
D-[U-^{14}C]glucose
76.6 MBq



(85) 22% yield
specific activity 912.6 MBq mmol^{-1} (30)

*18. Synthesis of [20-^{14}C]-3β-hydroxy-5β-pregnan-20-one (**87**)*

This compound has been ^{14}C-labelled[111–113] at $C_{(20)}$ following the procedure[114] illustrated by equation 31 for study the biosynthesis of bufadienolides in animals[111,113]. Condensation of 3β-acetoxy-5β-androstan-17-one with K^{14}CN gave[115] cyanohydrin **88**, dehydratation of which afforded the α,β-unsaturated nitrile **89**. The latter with MeMgI produced[116] 3β-hydroxy-5β-pregn-16-en-20-one **90** and finally hydrogenation of **90** afforded **87**.



(88)

(89)

(90) (104 mg, m.p. 170–173 °C,
specific activity 0.66 mCi mmol^{-1})

C = ^{14}C label
(87) (93 mg, m.p. 141–144 °C,
specific activity 0.65 mCi mmol^{-1}) (31)

The synthesis of ^{14}C-labelled alcohols $C_6H_5{}^{14}CH_2OH$, $C_6H_5{}^{14}CH(OH)CH_3$ and $C_6H_5CH(OH)^{14}CH_3$ used as intermediates in preparation of ^{14}C-labelled styrenes, which have been needed for corresponding kinetic isotopic effect studies[117–119], were described in review chapters[120,121]. Syntheses and application of ^{14}C-labelled methanol and dimethyl ether have also been reviewed[122].

B. Synthesis of Compounds Labelled with Carbon-11

1. *A comparative study of the reaction of $[^{11}C]CO_2$ with alkyl metal reagents*

The effect of various parameters, such as organometallic reagent, solvent, temperature and concentration, on the control of radiochemical yields obtained in the reaction of the universal precursor, isotopically labelled carbon dioxide with organometallic reagents, has been investigated by Nagren and Langstorm[123] (equation 32).

$$^{11}CO_2 \xrightarrow{CH_3M} CH_3{-}{}^{11}\underset{\underset{O}{\|}}{C}{-}OM \xrightarrow{CH_3M} CH_3{-}{}^{11}\underset{\underset{OM}{|}}{\overset{\overset{OM}{|}}{C}}{-}CH_3 \xrightarrow{H^+}$$

$$CH_3{}^{11}\underset{\underset{O}{\|}}{C}CH_3 \xrightarrow{CH_3M} CH_3{-}{}^{11}\underset{\underset{CH_3}{|}}{\overset{\overset{OM}{|}}{C}}{-}CH_3 \xrightarrow{H^+} CH_3{-}{}^{11}\underset{\underset{CH_3}{|}}{\overset{\overset{OM}{|}}{C}}{-}CH_3 \qquad (32)$$

(M = MgBr, MgCl, MgI, Li)

2. *Synthesis of no-carrier added ^{11}C-labelled methyl choline analogues*

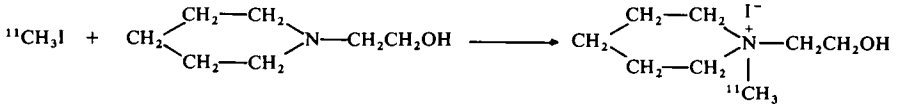
Two no-carrier added [^{11}C-methyl]labelled analogues of choline, [^{11}C-methyl]pyrrolidinocholine **91** and [^{11}C-methyl]piperidinocholine **92**, have been prepared[124–126] in 40% and 36% radiochemical yields using, as starting materials, 1-(2-hydroxyethyl)pyrrolidine **93**, 1-(2-hydroxyethyl)piperidine **94** and $^{11}CH_3I$ obtained from $^{11}CO_2$ produced by irradiation of nitrogen gas with 10 MeV protons by a $^{14}N(p,\alpha)^{11}C$ nuclear reaction (equations 33a,b,c). Preparations prepared in acetonitrile with specific activity between 1000–2000 Ci mmol^{-1}, ready for the PET (position emission tomography) study, have been used to scan the high affinity choline uptake system in monkey and human brain[126–128].

$$^{11}CO_2 \xrightarrow{LiAlH_4,\,THF} {}^{11}CH_3OH \xrightarrow{HI} {}^{11}CH_3I \qquad (33a)$$

$$^{11}CH_3I + \underset{\text{(93)}}{\overset{CH_2{-}CH_2}{\underset{CH_2{-}CH_2}{>}}NCH_2CH_2OH} \longrightarrow \underset{\text{(91)}}{\overset{CH_2{-}CH_2}{\underset{CH_2{-}CH_2}{>}}\overset{{}^{11}CH_3}{\overset{|}{N^+}}{-}CH_2CH_2OH\ I^-}$$

15–40 mCi, radiochemical purity > 99%

(33b)



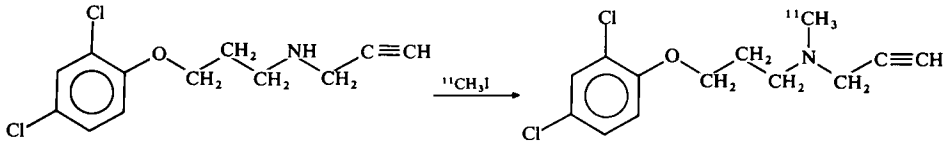
(92)

15–25 mCi, chemical and radiochemical purity > 99%

(33c)

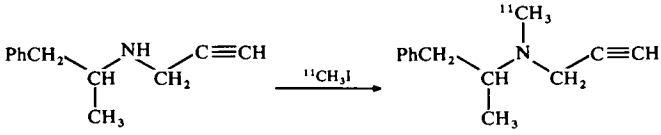
3. Synthesis of ^{11}C-labelled clorgyline, L-deprenyl, dimethylphenethyl amine (DMPA) and methylphenethyl amine (MPA)

These compounds, **95**, **96**, **97**, **98**, and **99** have been ^{11}C-labelled[129] for *in vivo* studies of the functional activity of monoamine oxidase (MAO) in brain. The MAO enzyme deaminates oxidatively endogenous neurotransmitter amines and exogenously administered drugs[130]. Compounds **95**, **96** and **97**, applied for PET study of enzyme dynamics and disease, have been obtained by *N*-alkylation of the free bases of the corresponding desmethyl compounds (equations 34–36). The radiochemical yields based on $^{11}CH_3I$ were 93%, 85% and 93% for **95**, **96** and **97**, respectively, with specific activities of the order of 200 Ci/mmol^{-1}.



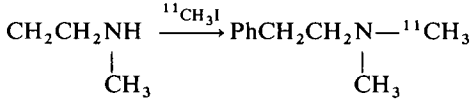
(95)

(34)



(96)

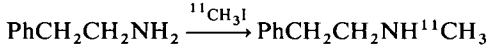
(35)



(97)

(36)

Methylphenethyl amine (MPA), **98**, has been prepared also by *N*-alkylation of the free base of the desmethyl compound (equation 37) in similar yield. Dimethylphenethyl amine (DMPA), **99**, ^{11}C-labelled in the phenethyl group, has been also synthetized[129] (equation 38). **95** and **96** deactivate the MAO enzyme by covalent bonding to its active site[130].



(98)

(37)

$$PhCH_2MgCl \xrightarrow{^{11}CO_2} PhCH_2{}^{11}COOMgCl \xrightarrow{LiAlH_4/THF}$$

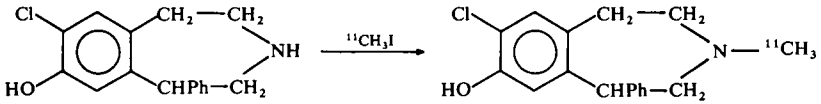
$$PhCH_2{}^{11}CH_2OH \xrightarrow{HI} PhCH_2{}^{11}CH_2I \xrightarrow{Me_2NH}$$

$$PhCH_2{}^{11}CH_2NMe_2 \text{ (overall yield, 10–15\%)} \qquad (38)$$

(99)

*4. Syntheses of ^{11}C-SCH 23390 (**100**)*

This compound ((*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-[^{11}C]methyl)-5-phenyl-1 H-3-benzazepin-7-ol, **100**, a dopamine D-1 receptor antagonist suitable for the *in vivo* study of the dopamine D-1 receptor-rich area in the human brain, has been synthesized[131,132] by *N*-alkylation of the desmethyl compound as shown in equation 39.



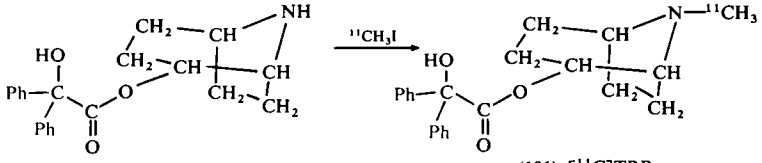
(100)

80% radiochemical yield based on $^{11}CH_3I$ Radiochemical purity > 99%
specific activity ~ 11.1 GB_2 mmol^{-1} (300 Ci mmol^{-1})

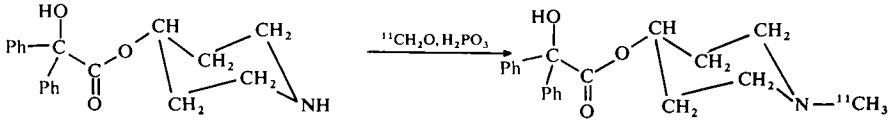
(39)

5. Synthesis of ^{11}C-labelled (+) 2α-tropanyl benzilate (TRB) and N-methyl-4-piperidyl benzilate (NMPB)

Both centrally active antimuscarinic drugs, TRB (**101**) and NMPB (**102**), have been ^{11}C-labelled[133] by methylation of the corresponding desmethyl derivatives with [^{11}C]formaldehyde[134] or with [^{11}C]methyl iodide (equations 40 and 41). The biodistribution of [^{11}C]TRB and [^{11}C]NMPB (specific activity 75–400 Ci mmol^{-1} at the time of injection) in rats was examined at various times after the injection. Brain uptakes for the two compounds, largely receptor mediated, were similar but in contrast; while heart uptake of **102** was low, the heart uptake of **101** was significant. Analysis of tissue radioactivity after 30 min showed that more than 97% of the activity in the brain had the same R_f as authentic TRB. About 90% of heart activity and about 40% in the whole blood was unmetabolized.



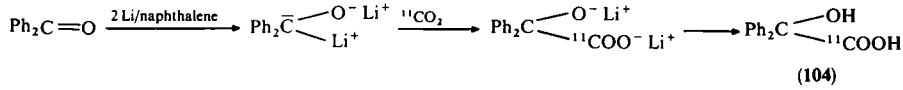
(101) [^{11}C]TRB (40)



(102) [^{11}C]NMPB (41)

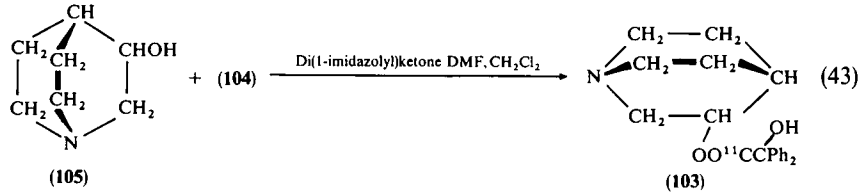
6. Synthesis of no-carrier added (N.C.A.) [^{11}C]QNB

The [^{11}C]quinuclidinyl benzylate **103** has been synthesized[135–138] in two main stages (equations 42 and 43) for visualizing central muscarinic receptors by PET[138]. In the first step [^{11}C]benzilic acid **104** has been formed[135–137] by carbonation of the benzophenone dianion with $^{11}CO_2$ (equation 42) in about 60% yield. In the second step the esterification of **104** by quinuclidinol-3 **105** takes place.



(104)

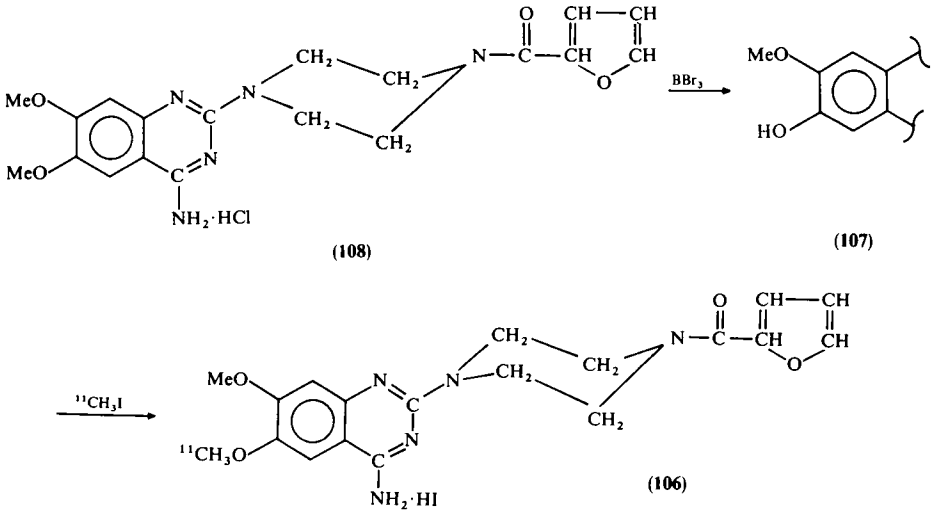
(42)



(43)

7. Synthesis of ^{11}C-labelled prazosin

The antihypertensive drug prazosin **106**, an α-1 adrenoreceptor antagonist, has been labelled with ^{11}C in the 7-methoxy group by preparing the desmethylated compound **107** and reacting it with [^{11}C]CH_3I (equation 44)[139,140]. **107** has been prepared from prazosin hydrochloride (**108**).

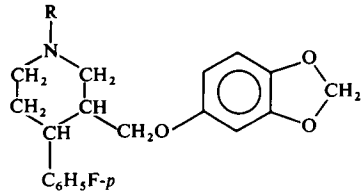


99.9% ratiochemical purity; 15–20% radiochemical yield, specific activity 3500 Ci mmol^{-1}

(44)

*8. Synthesis of ^{11}C-labelled N-methylparoxetine (**110**)*

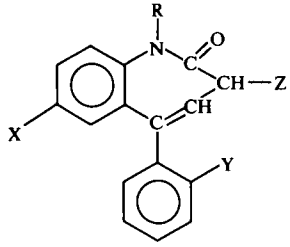
This compound was needed for a study of serotonin uptake sites, since it is highly concentrated on serotonin-containing nerve terminals. It has been prepared[141] by ^{11}C-*N*-methylation of paroxetine **109**. The synthesis gave 15% radiochemical yield, corrected for radioactive decay. The specific activity at the end of the synthesis was 1.3 Ci μmol^{-1}, while it was about 3.8 Ci μmol^{-1} at the end of the bombardment ('E.O.B.'), i.e. at the end of the ^{14}N(p,α) ^{11}C under reaction.



(**109**) R = H (paroxetine)
(**110**) R = $\dot{C}H_3$ (*N*-methylparoxetine)

9. Synthesis of ^{11}C-labelled 3-methoxybenzodiazepines

The direct nucleophilic substitution of [^{11}C]methanol in 3-chlorobenzodiazepines possessing reactive halogen has been applied for obtaining [^{11}C]methoxy-labelled benzodiazepines[142] for *in vivo* PET studies. Reaction of 3-chlorodiazepam **112** (obtained from $SOCl_2$ and temazepam **113**) with N.C.A. [^{11}C]methanol produced the desired [^{11}C]3-methoxydiazepam **111**, obtained in >50% radiochemical yield based on [^{11}C]methanol and >99% radiochemical purity. [^{11}C]potassium methoxide had been used also for transforming simple n-alkyl and benzyl chlorides to the corresponding methyl ethers in 50–60% radiochemical yields[143].

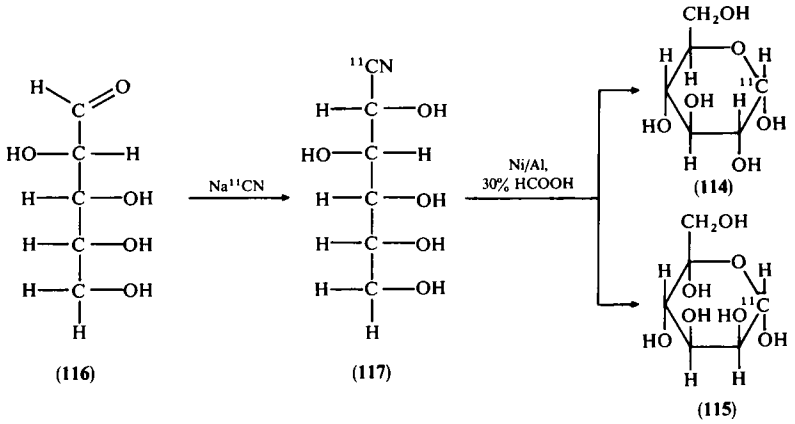


(**111**) X = Cl, Y = H, Z = O$\dot{M}$e, R = Me
(**112**) X = Z = Cl, Y = H, R = Me
(**113**) X = Cl, Y = H, Z = OH, R = Me

10. Synthesis of D-[1-^{11}C]-glucose and related compounds

D-[1-^{11}C]-Glucose **114** and D-[1-^{11}C]-mannose **115** are attractive tracers for the measurement of regional glucose metabolism in humans, especially for the quantitative mapping of the first step of glycolysis in the brain and the heart[144]. Both have been synthesized[145,146a] as shown in equation 45. D-arabinose **116** with aqueous Na^{11}CN gave the aldononitrile **117** in good yield. Reduction of the latter produced compounds **114** and **115**, in about 40–50% r.y. The overall r.y. of **114** was 15%; the total synthesis time including HPLC separations and purifications was 70 min.

Starting from 100 mCi of ^{11}C-cyanide, about 9 mCi or ^{11}C-1-glucose and ^{11}C-1-mannose mixture was synthesized in 30 minutes[146b,147] in an automatic apparatus



(116) (117) (114) (115) (45)

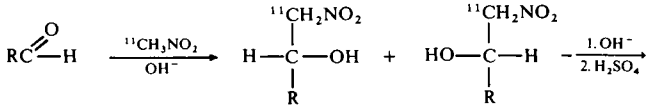
which carried out the complete sequence of ^{11}C-cyanide preparation, its addition to arabinose, acidification and reduction with H_2/Pd in a high-pressure autoclave and separation of the labelled product. The latter, in 5–7 mCi portions, has been injected intravenously to rabbits with an intramuscularly transplanted VX2 cancinoma. A large field scintillation camera was adjusted to discriminate the 511-keV photons which permitted one to vizualize specifically the tumor and the brain owing to metabolic trapping of the radiocarbon in the tumor-specific large lactate pool or in the tumor-specific glucogenic-amino acid pool[148].

Various nitroalkanes (Me, Et, Pr) were produced[149] by passing ^{11}C-alkyl iodates in nitrogen through a column containing silver nitrate (equation 46)[149,150].

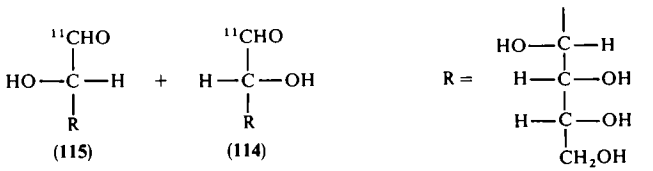
$$R^{11}CH_2I \xrightarrow{AgNO_3} R^{11}CH_2NO_2 \qquad (46)$$

(118)

Thus D-[1-^{11}C]glucose has been synthesized via [^{11}C]nitromethane (equation 47) by reacting **118** with D-arabinose in a basic solution[150,151]. Mannose **115** was the major product (mannose **115**:glucose **114** = 3:1). The r.y. of D-[1-^{11}C]glucose and D-[1-^{11}C]-mannose was 20–30% based on [^{11}C]methyl iodide; the overall synthesis time was 50 min. **114** will be used to measure the regional cerebral glucose utilization with PET.



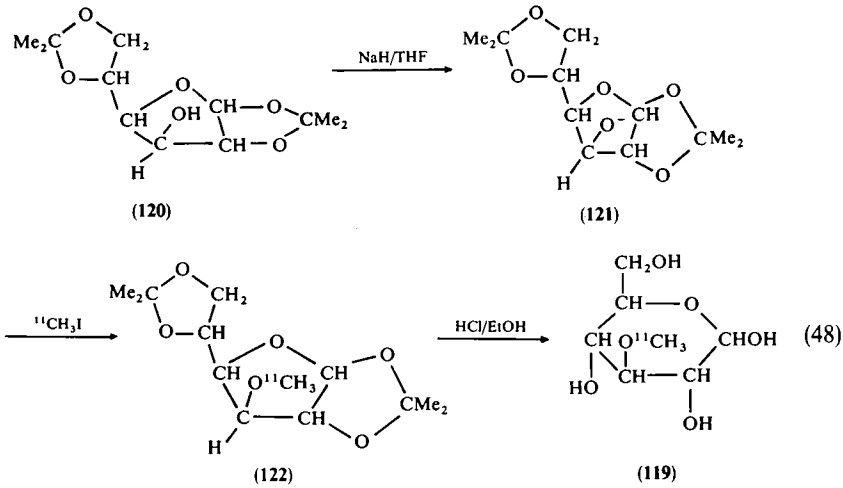
^{11}C-labelled epimeric nitroalcohols



(115) (114) (47)

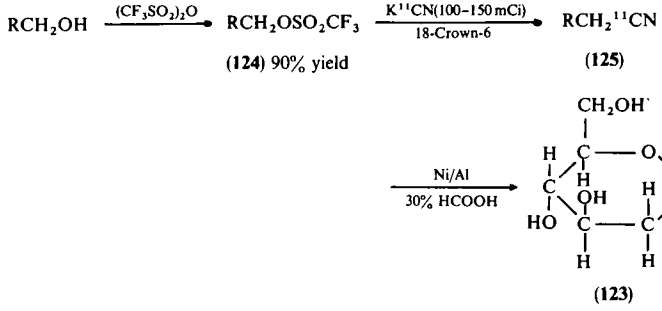
Carbon-11 labelled glucose has also been synthesized by different biosynthetic methods, for instance from $H^{11}CO_3^-$ utilizing algae as the biosynthetic medium[152,153].

The synthesis of 3-*O*-[^{11}C]methyl-D-glucose **119**, the analogue of glucose used with PET to study glucose transport in heart and brain[154], has been modified recently and performed[155] as shown in equation 48. **120** with sodium hydride produced the oxyanion **121** which, with $^{11}CH_3I$, gave the intermediate **122**. The latter was hydrolysed to yield the radiochemically pure product **119**, in 49% radiochemical yield based on $^{11}CH_3I$ (40 min from the end of radionuclide production).

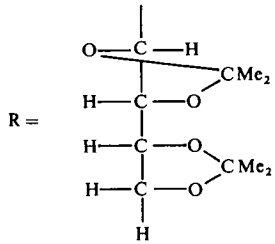


(48)

2-Deoxy-D-[1-^{11}C]glucose (^{11}C-2DG, **123**) was prepared[156] as shown in equation 49 in >99% radiochemical purity. The overall radiochemical yield achieved in 45–50 min total synthesis time was 25–35%. The previous procedure[157] has been improved by using 18-crown-6 as a catalyst[158] and modifying the purification procedure.

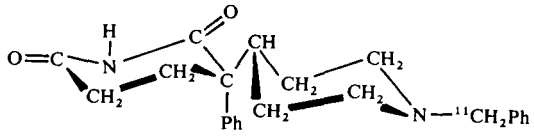


(49)

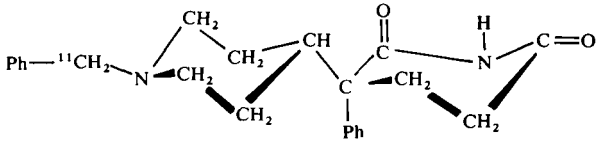


11. Synthesis of ^{11}C-labelled dexetimide and ^{11}C-labelled levetimide

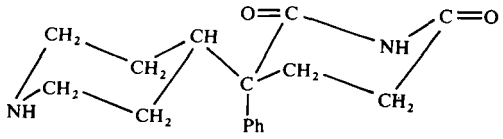
Both compounds **126** and **127**, used for studying muscarinic cholinergic receptors in the living human brain by PET, have been synthesized[159] (equation 50) during about 35 minutes from the end of bombardment in five main steps. The r.y. based on [^{11}C]benzyl iodide was about 20%, the r.y. based on $^{11}CO_2$ was approximately 8%, specific activity at the end of synthesis was 0.905 Ci μmol^{-1} and specific activity at the end of bombardment about 3 Ci μmol^{-1}.



(126) dexetimide



(127) levetimide



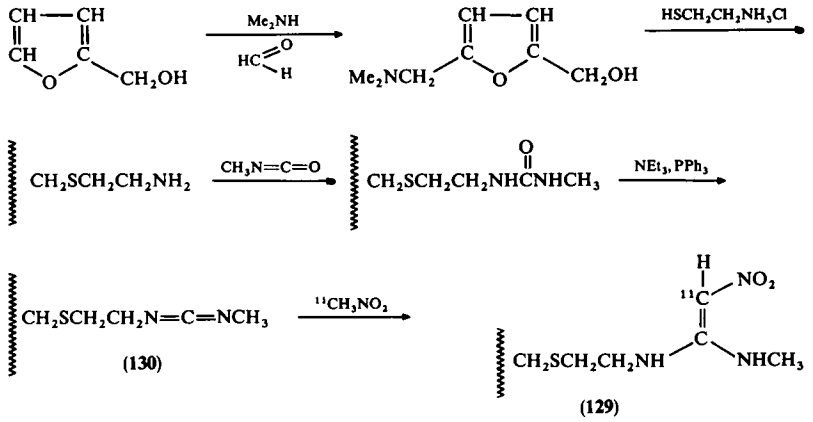
(128)

$$\text{PhMgCl} \xrightarrow[\text{2. LiAlH}_4\text{/THF}]{\text{1. }^{11}CO_2\text{, THF}} \text{Ph}-{}^{11}CH_2OH \xrightarrow{\text{HI}} \text{Ph}{}^{11}CH_2I \xrightarrow[\text{80 °C, HPLC, purification}]{\text{128}(CH_2Cl_2,CH_3CN)} \textbf{127 (or 126)} \qquad (50)$$

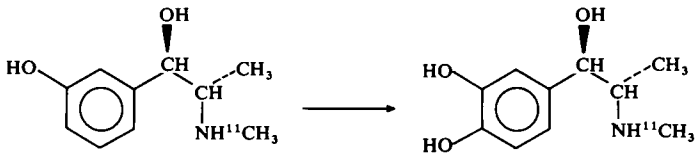
12. Synthesis of [^{11}C]ranitidine

Ranitidine hydrochloride **129**, needed in treatment of peptic ulceration, has been ^{11}C-labelled[160] to visualize the H_2-receptors in the heart by PET (equation 51). For the last step, the nitromethane carbanion is prepared under anhydrous conditions[161] in one of three different ways each giving different yields of **129**: (1) $^{11}CH_3NO_2$ + NaH/DMF gives 5% yield of **129**, (2) $^{11}CH_3NO_2$ + BuLi/DIPA/*i*-Pr_2NH gives 10% yield and (3) $^{11}CH_3NO_2$ + KOH/DMF gives 15% yield.

(1R,2S)-(—)-[^{11}C]-meta-hydroxyephedrine (MHED), **131**, has been synthesized and used to study neuronal heart diseases and neuroendocrine tumors[162]. It is metabolized rapidly in humans to α-methylepinephrine (equation 52) by the action of liver microsomal hydroxylase[163a,164a], but no metabolites of MHED appear in the heart. The search for completely non-metabolizable [^{11}C]-labelled neuronal tracer on a PET-imaging time scale is under current investigation[162].



(51)



(131) MHED

(52)

C. [^{15}O]-Labelled Compounds

Preparation of [^{15}O]-butanol. Oxygen-15 labelled butanol, used for assessment of regional cerebral blood flow measurements by the PET method, has been prepared by rapid reaction of molecular oxygen with tributylborane[163b–166] (equation 53).

$$Bu_3B + {}^{15}O_2 \longrightarrow Bu{}^{15}OH \tag{53}$$

To avoid difficulties associated with separations of the excess tributylborane and the dibutylborinic acid by-product from butanol-^{15}O, a polymeric organoborane has been prepared[167] by lithiating a polystyrene resin and reacting it with methyl dibutylborinate. The new reagent ('butanol kit'), stored under argon, is utilized to generate butanol by sequentially passing $^{15}O_2$ and sterile water through a column containing polymer **132** (equation 54).

$$\text{Ⓟ-}BBu_2 \xrightarrow[H_2O]{{}^{15}O_2} Bu{}^{15}OH \tag{54}$$

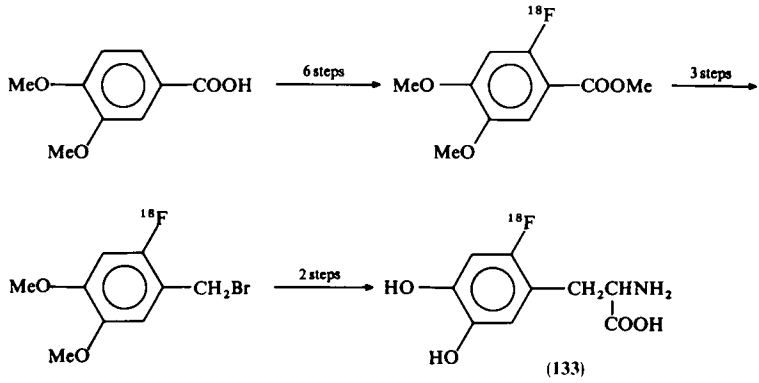
(132)

The procedure for ^{15}O-butanol production for clinical use has been improved recently[168] by separating the boric acid derivatives contaminating the radioactive compound from the sample by passing the product through an additional column of an anion exchange resin with high exchange capacity and small particle size (to reduce dead volume). ^{15}O (2.037 min) was produced from 10 min, 25 μA, 8.5 MeV deuteron bombardment in ^{14}N(d,n)^{15}O nuclear reaction[166b]. The subsequent procedure from EOB to the preparation of 9.5–14 mg of butanol in the form of an injectable solution takes 3.75 min.

D. Synthesis of [^{18}F]-Labelled Compounds

*1. Synthesis of [^{18}F]-labelled DL-6-fluorodopa (**133**)*

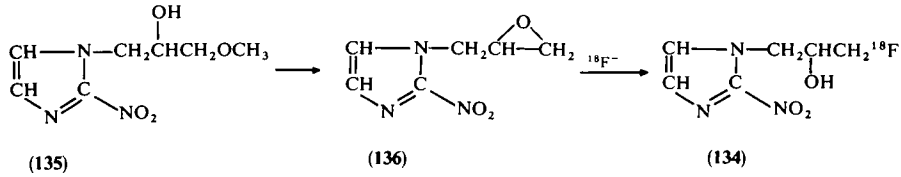
The synthesis of ^{18}F-labelled 6-FD **133** in 12% overall chemical yield was based on veratric acid and involved 11 steps[169] (equation 55). It was used to conduct quality control testing in the radiosynthesis of ^{18}F-labelled 6-fluorodopa, in the *in vivo* visualization of dopaminergic neuronal distributions in man.



(133) (55)

2. Synthesis of fluorine-18 labelled 1-(2-nitro-1-imidazoyl)-3-fluoro-2-propanol

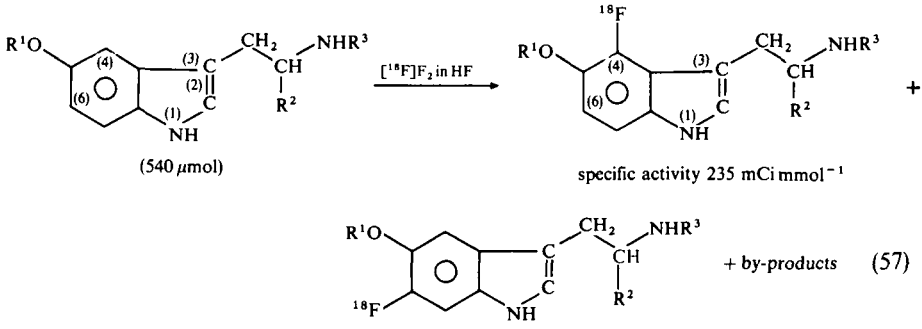
These hypoxic radiosensitizers **134** and **135** have been ^{18}F-labelled[170] (equation 56) for autoradiographic visualization of hypoxic regions of tumors[171] by the PET method[172]. Fluoride-[^{18}F], prepared by irradiation of ^{18}O-enriched water with protons, has been converted to $Bu_4N^{18}F$ by exchange. The reaction of the latter with epoxide **136** in DMS or dimethylacetamide gave a mixture of products from which **134** has been isolated by HPLC in 17% yield.



(135) (136) (134) (56)

3. Synthesis of ^{18}F-labelled fluoromelatonins and 5-hydroxyfluorotryptophans

For the potential use in PET to image the bonding sites for melatonin and for metabolic studies, 6-fluoromelatonin as well as 4- and 6-fluoro-5-hydroxytryptophan have been obtained[173,174] by reaction of [^{18}F]fluorine with melatonin or 5-hydroxytryptophan in hydrogen fluoride at −70 °C (equation 57). The fluorine entered position 4 preferentially. Catechols dissolved in anhydrous hydrogene fluoride at low temperature react also with [^{18}F]fluorine yielding [^{18}F]fluorocatechols[175]. The [^{18}F]F_2 used in the above synthesis has been produced in the ^{20}Ne(d,α)^{18}F nuclear reaction with 15-MeV deuterons in a Tandem Van de Graff accelerator[176].

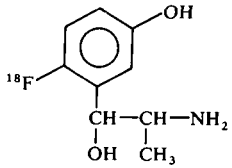


5-hydroxytryptophan: $R^1 = H$, $R^2 = COOH$, $R^3 = H$

melatonin: $R^1 = CH_3$, $R^2 = H$, $R_3 = Ac$

4. Synthesis of 6-[^{18}F]fluorometaraminol (FMR)

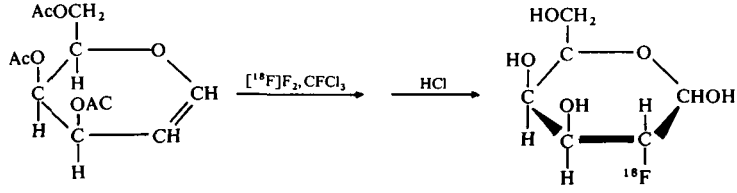
The false neurotransmitter, FMR (**137**), has been ^{18}F-labelled[177] and validated as a heart agent that selectively maps adrenergic nerve density. Its potential use in detecting neuronal damage on the diseased heart and its clinical utility as well as the utility of the other no-carrier-added ^{18}F-labelled sympathomimetic amines for probing discrete aspects of the peripheral adrenergic nerve complex has been discussed[178].



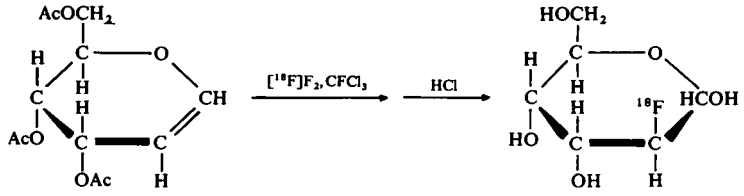
(**137**)

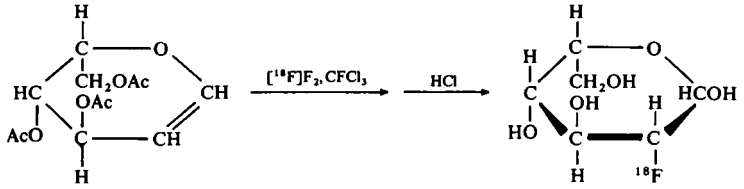
5. Synthesis of ^{18}F-deoxy-aldohexoses and their comparative study

a. ^{18}F-2-deoxy-2-fluoro-D-glucose (^{18}F-FDG) and ^{18}F-2-deoxy-2-fluoro-D-mannose (^{18}F-FDM) have been widely used for glucose metabolism studies[179] and for cancer diagnosis[180], respectively. The new positron-emitting radiopharmaceuticals, ^{18}F-deoxyaldohexoses: ^{18}F-2-deoxy-2-fluoro-D-galactose (^{18}F-FDGal) (**138**), ^{18}F-2-deoxy-2-fluoro-D-altrose (^{18}F-FDA) (**139**) and ^{18}F-2-deoxy-2-fluoro-L-glucose (L-^{18}F-FDG) (**140**), have been synthesized[181,182] by treating the corresponding tri-*O*-acetyl aldohexals with $[^{18}F]F_2$ (equations 58a, b, c).



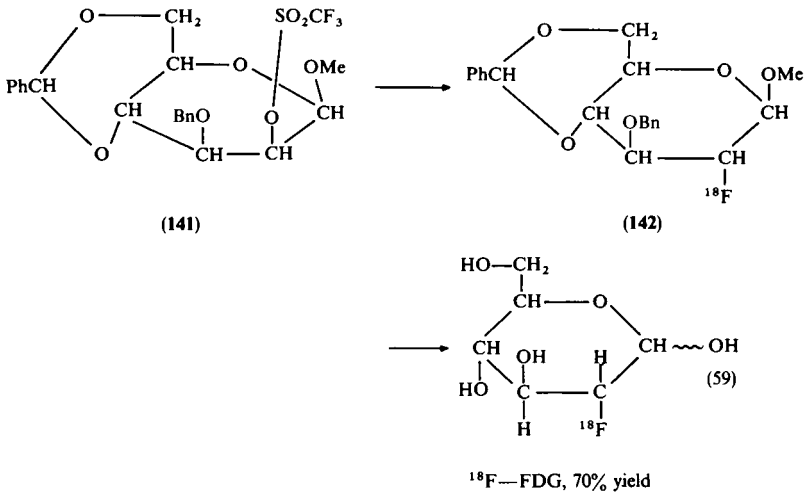
^{18}F-FDGal (**138**), 15–26% r.y.





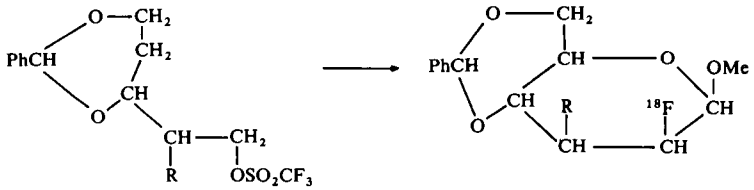
The radiochemical purities of **138**, **139** and **140** were >95%, >99% and 98%, respectively. The total time required for the synthesis of these compounds was about 120 min from the end of the target bombardment in the cyclotron. Their specific activities (expressed in $mC\,mg^{-1}$) were found to be 11–14, 15–19 and 11–12, respectively. The biodistribution studies of **138**, **139** and **140** have shown[182] that **139** was rapidly excreted from all organs, **140** was rapidly excreted from the kidney but slower from other tissues and **138** was accumulated in the liver. It has been suggested that the metabolism of **138** and **140** can be stopped at the phosphorylation position.

^{18}F-FDG has also been obtained[183a] by treatment of the triflate **141** with CsF and Et_4NF and subsequent hydrolysis of the 2-deoxy-2-fluoro-D-glucopyranoside (**142**) with 50% $MeSO_3H$ (equation 59).



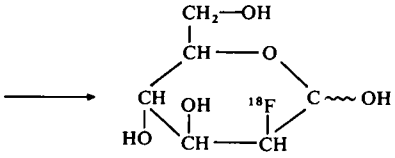
^{18}F-FDM, 2-deoxy-2-fluoro-D-mannose (**143**), used for glycoprotein biosynthesis and for cancer diagnosis in humans by PET, has been prepared similarly (equation 60) by

fluorination of triflates (**144**) with tetraalkylammonium fluorides and hydrolysis of **145a** or of **145b**, both in 82–85% isolated yield[183a].



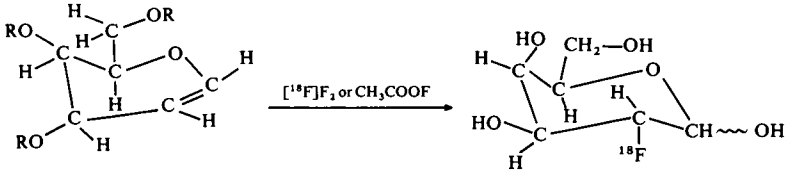
(**144a**) R = OBn
(**144b**) R = OAc

(**145a**) R – R = OBn
(**145b**) R = OAc
(**145c**) R = OH



FDM (**143**) (60)

b. Synthesis of 3-deoxy-2-[^{18}F]fluoro-D-galactose. 2-Deoxy-2-[^{18}F]fluoro-D-galactose (**146**) has been prepared recently from tri-*O*-acetyl-D-galactal (**147**) and gaseous [^{18}F]acetyl hypofluorite or [^{18}F]F_2 (equation 61). The product **146** was obtained in over 90% epimeric purity, even with [^{18}F]F_2 as fluorinating reagent in a polar protic solvent such as AcOH or water[183b].



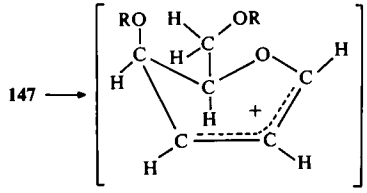
(**147a**) R = acetyl
(**147b**) R = H

(**146**) (61)

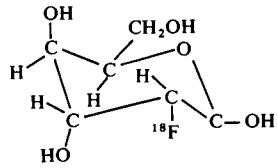
Besides the main product **146**, two radioactive contaminants **148** (0.8%) and **149** (8.5%) have been isolated by HPLC. It is suggested that they are formed by fluorination of the resonance-stabilized carbocation intermediate **150** (equation 62). Compound **146** can be utilized as a tool for control of the selectivity and effectiveness of tumor chemotherapy involving anti-pyrimidines[184].

6. *Synthesis of ^{18}F-labelled fluoroandrogens and fluoroprogestins*

Fluoroandrogen (**151**) and fluoroprogestin (**152**), useful for distinguishing hormone-responsible breast tumors and prostate tumors from those that are hormone-non-responsible[185], have been ^{18}F-labelled[186] by bromofluorination of 9(11)-estren-3-on-17β-ol **153** to give 9α-bromo-11β-fluoroestran-3-on-17β-ol, followed by reductive debromination (equation 63), or, alternatively, by rapid displacement of the 17α-propargyl methanesulphonate of 19-nortestosterone (**154**) by fluoride (equation 64).

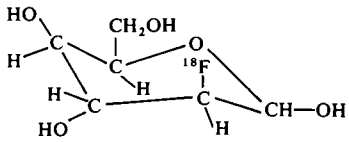


(150)

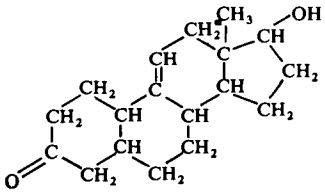


(148) α-2-deoxy-2-fluoro-D-idose (62)

146

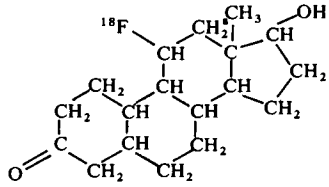


(149) α-2-deoxy-2-fluoro-D-glucose



1. $H^{18}F$ py, 1,3-dibromo-5,5-dimethylhydantoin
2. Bu_3SnH

(153)



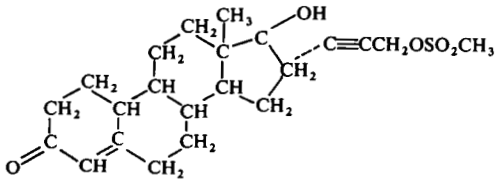
(151) (63)

7. Synthesis of chloro derivatives of estradiol as precursors of ^{18}F-labelled analogues

The 4-halo derivatives of estradiol steroids, **155–162**, are chemically stable compounds which can be labelled with ^{18}F via nucleophilic substitution[187]. Their estrogen receptor binding affinities were determined and the radiosyntheses of the most promising derivatives with ^{18}F for *in vivo* studies have been projected[188].

8. Synthesis of ^{18}F-labelled ligands

Tosylates **163**, **164** and **165** have been fluorinated with ^{19}F or ^{18}F and deprotected to give ligands **166**, **167** and **168** for *in vivo* measurement of the β-adrenergic receptor[189].



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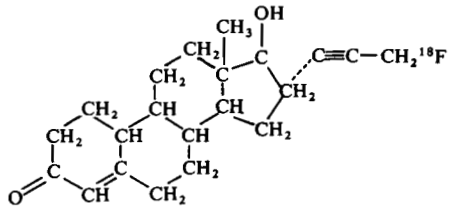
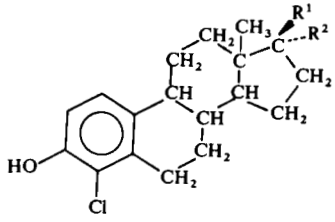
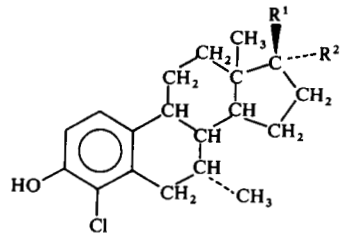


(64)

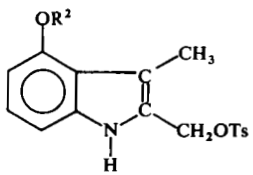
(152)



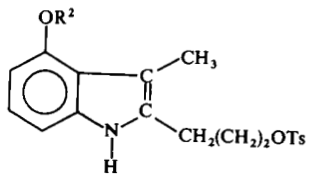
(155) $R^1 = OH$, $R^2 = H$
(156) $R^1 + R^2 = O$
(157) $R^1 = OH$, $R^2 = CH_3$
(158) $R^1 = OH$, $R^2 = C{\equiv}CH$
(159) $R^1 = OH$, $R^2 = C{\equiv}CCl$



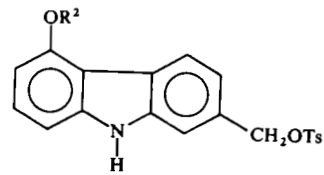
(160) $R^1 = OH$, $R^2 = H$
(161) $R^1 + R^2 = O$
(162) $R^1 = OH$, $R^2 = C{\equiv}CH$



(163)



(164)



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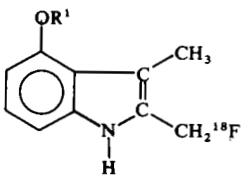

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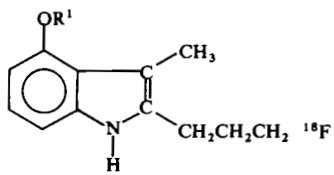

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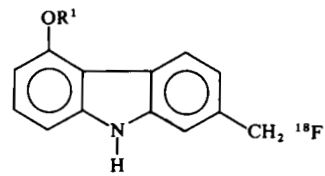

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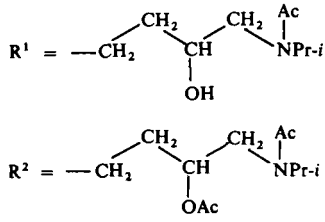
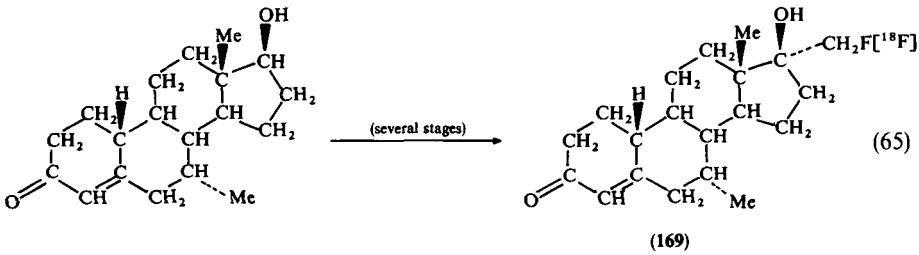


9. Synthesis and tissue distribution studies with tritium and fluorine-18 labelled androgens

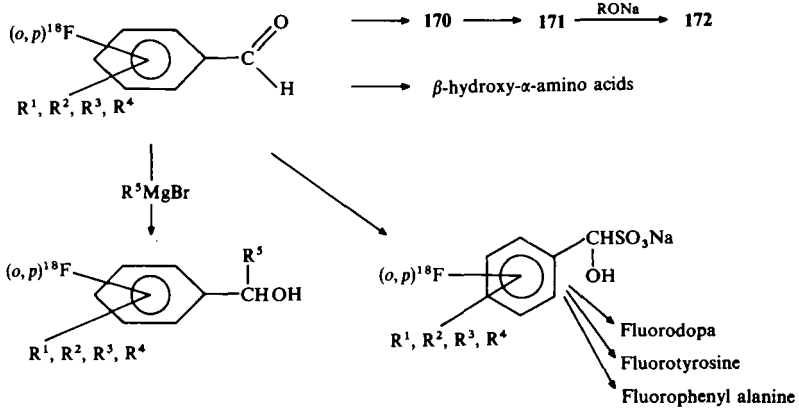
Commercially available high-specific-activity mibolerone (**169**) has been fluorine-18 labelled[190] for imaging the prostate tumor's invasion and metastasis (equation 65). Prostatic tissue and most prostate tumors contain receptors for androgens.



(65)

(169)

Very recently an additional fluorination pathway, using substituted [^{18}F]-fluoro aromatic aldehydes, has been proposed by Lemaire and coworkers[191]. The proposed scheme leads also to [^{18}F]-labelled alcohols (equation 66).

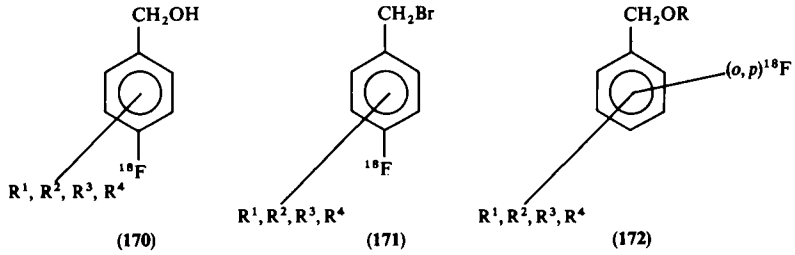


(66)

E. Synthesis of Hydroxyl Compounds Labelled with Bromine Isotopes

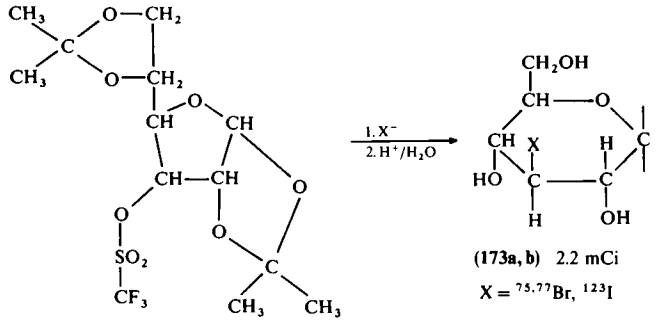
1. Synthesis of D-*glucose derivatives labelled with*^{75,77} *Br and with* ^{123}*I*

Sugars are important substrates for the energy metabolism in brain and heart of mammals but only D-glucose (also mannose derivatives, but at a slower rate) and some



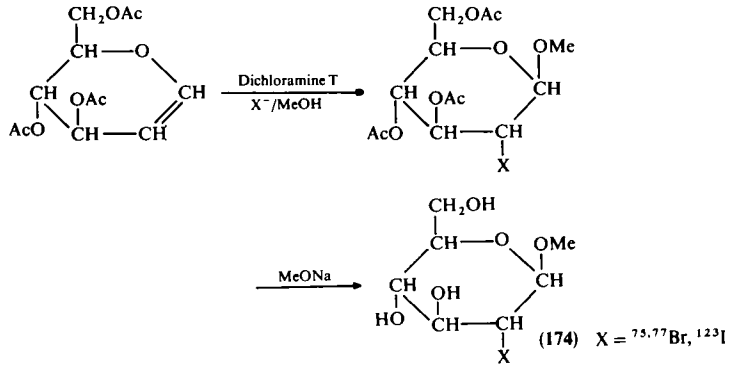
its analogues are transported by the hexose carrier at the BBB. These analogues have all-*trans* and all-equatorial arrangement of electronegative substituents.

[^{123}I]-3-Deoxy-3-iodo-D-glucose (**173a**) and [^{75,77}Br]-3-deoxy-3-bromo-D-glucose (**173b**) have been prepared[192] from 1,2:5,6-di-isopropylidene-D-allose via its triflate in 10–20% yield (equation 67). ^{75}Br ($T_{1/2} = 1.6$ h) and ^{77}Br ($T_{1/2} = 56$ h) were produced in ^{75}As(^{3}He, $3n$)^{75}Br and ^{75}As(α, $2n$)^{77}Br nuclear reactions[194,193] and isolated as N.C.A. [^{75,77}Br]-bromide ions in aqueous solutions. ^{123}I with 13.3 h half-life was produced in the ^{124}Te(p, $2n$)^{123}I nuclear reaction[195] and isolated also as N.C.A. [^{123}I] ion in aqueous solution.

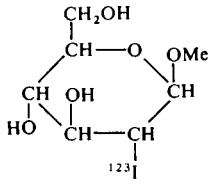


(67)

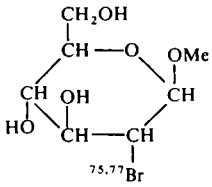
An attempt to synthesize 2-deoxy-2-halo-D-glucose, **174**, labelled with ^{75,77}Br and ^{123}I according to equation 68, was unsuccessful. Nevertheless, several ^{75,77}Br- and ^{123}I-labelled intermediates of possible use as tracers for glucose utilization have been prepared on the route to compound **174**, namely the methyl glucosides **175** and **176**, and the acetylated methyl glucosides **177** and **178**. All the above compounds have been studied biochemically and pharmacokinetically in mice[192].



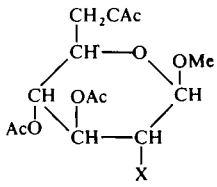
(68)



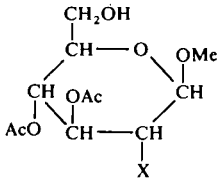
(175)



(176)



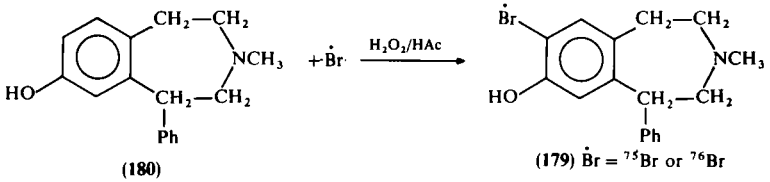
(177) X = ^{75,77}Br



(178) X = ^{75,77}Br

2. Synthesis of the 8-bromo analogue of SCH 23390 (BrSCH or SKF 83556) labelled with ^{75}Br or ^{76}Br

Compound **179** has been prepared[196] by the reaction of its *des*-chloro analogue **180** with radiobromide (equation 69). The identity of the product **179** was confirmed by NMR, mass spectrometry and pharmacological methods, and it was used to study the distribution of [^{75}Br]-BrSCH in mouse or in monkey brain[197].



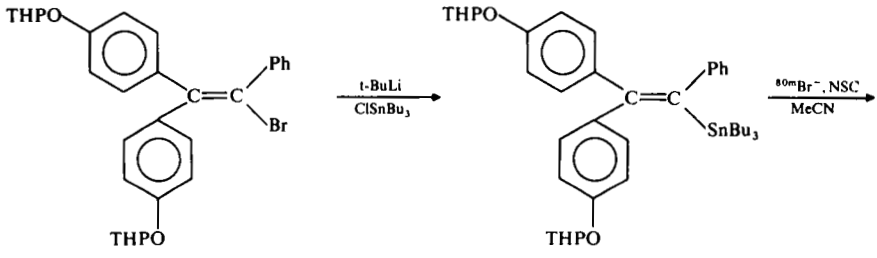
(180) (179) $\dot{Br}$ = ^{75}Br or ^{76}Br (69)

3. Synthesis of ^{80m}Br-labelled 1,1-bis(p-hydroxyphenyl)-2-bromo-2-phenylethylene (BDPE)

This compound **181** is an excellent ligand to bind the estrogen receptor and is of potential use in the diagnosis and treatment of cancers of the female reproductive system[198,199]. It has been labelled[200] with ^{80m}Br [half-life of 4.4 h, producing 6–7 Auger electrons from each decay, obtained in the nuclear reaction ^{83}Kr$(d, n, \alpha)^{80m}$Br, at $E_d = 23$ MeV] according to equation 70. The phenolic groups of BDPE were protected as tetrahydropyranyl ethers (**182**), **181** was shown by sedimentation analysis to bind strongly to the estrogen receptor and to carry Auger electron emitting nuclides to cells that contain the latter.

4. Synthesis of ^{82}Br- and ^{77}Br-labelled (17α, 20E)-21-bromo-19-norpregna-1,3,5(10),20-tetraene-3,17β-diol

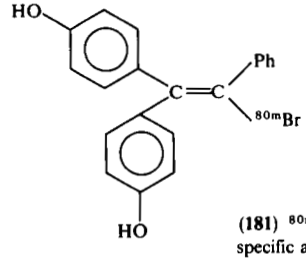
Estrogens radiolabelled with ^{18}F and ^{123}I are most frequently used for quantitation of estrogen receptors in human mammary carcinoma and in determining prognosis of



(182)

THP = tetrahydropyranyl

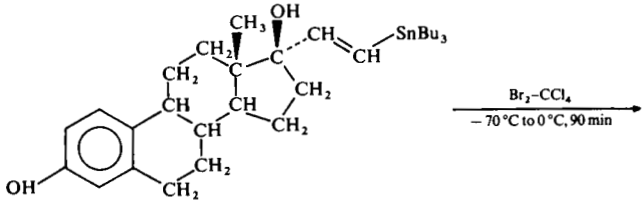
(183)



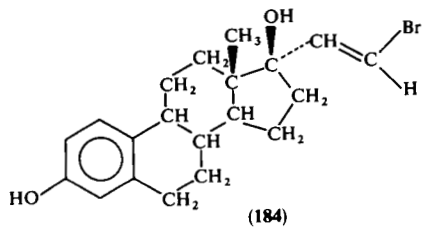
(181) ^{80m}Br-BDPE, 65% r.y.
specific activity 150 Ci mmol^{-1}

(70)

long-term survival[201,202]. Applications of bromine isotopes have been discussed by Stocklin[203], and by Huang and Friedman[204]. ^{75}Br (positron emitter, $T_{1/2} = 101$ min) and ^{80m}Br (Auger electron emitter, $T_{1/2} = 4.4$ h) have the greatest potential for radiodiagnostic and radiotherapy applications. ^{77}Br ($T_{1/2} = 56$ h) and ^{82}Br ($T_{1/2} = 35.3$ h) have poorer clinical characteristics, but are more easily produced and have been used for synthesis of several radiobrominated estrogens[205–211]. Labelling of 17α-*E*-bromovinylestradiol **184** with ^{82}Br and ^{77}Br has been carried out[212] by halodestannylation (equation 71). The reaction of **185** with ammonium [^{82}Br]bromide or sodium [^{77}Br]-bromide in the presence of *N*-chlorosuccinimide (NCS) produced 17*E*-[^{77}Br] and [^{82}Br] bromovinylestradiols in 80–90% r.y. The radiochemical purity was greater than 98%.

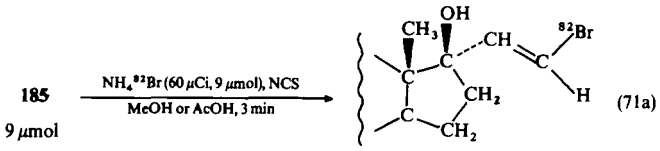


(185)

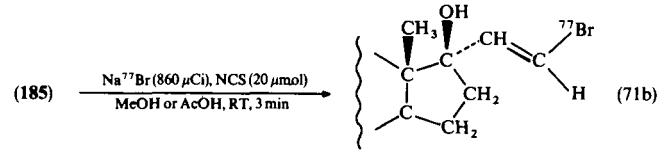


(184)

(71)



(184a) (71a)

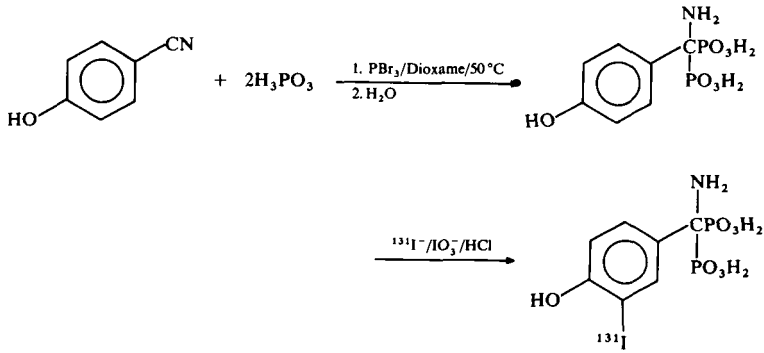


(184b) 575 μCi (71b)

F. Synthesis of Hydroxyl and Ether Compounds Labelled with Iodine Isotopes ^{131}I, ^{125}I, ^{123}I and ^{122}I

1. Synthesis of α-amino-(3-[^{131}I]-4-hydroxybenzylidene)diphosphonate (pHOBDPNH$_2$)

[^{131}I]-pHOBDPNH$_2$, **186**, is a better β^--particle source for palliative therapy of intractable pain than ^{32}P and ^{89}Sr beta emitters[213]. It has been prepared[214,215] in less than one hour by electrophilic aromatic substitution with $^{131}I^-$ and IO_3^- (equation 72). The organ distribution, the total bone uptake and total body retention of **186** in rats have been measured. The biological half-life of **186** was 46.3 days; ^{131}I-pHOBDPNH$_2$ disappeared rapidly from the blood pool. The oxidative cleavage *in vivo* of ^{32}P—C bonds (the source of ^{32}P-phosphate parcipating in blood cell formation and causing blood cell depression) leads to metabolites containing the ^{131}I-*p*-HO-benzylidene group which do not participate in blood cell formation. The high affinity of **186** to bone metastases was found by scintigraphy. The first palliative therapies with **186** were promising: 1 to 3 days after administration of 6–12 mCi of **186** the pain relief was observed in four out of five treated patients.

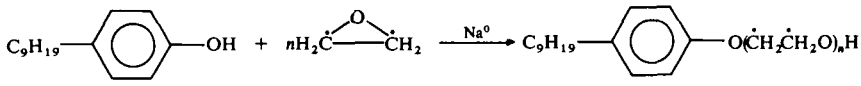


(72)

(186)
specific activity 15.6 Ci mmol^{-1}
~95% r.y.

2. Preparation of [^{131}I]iodinated nonoxynol-9

Nonoxynol-9, nonylphenoxy(polyethoxy ethanol) (N-9) is a widely used non-ionic surfactant in vaginal spermicides. Using commercially available ^{14}C-labelled N-9 (^{14}C-polyethylene glycol moiety), **187**, prepared by reacting one equivalent of nonylphenol with nine equivalents of ethylene oxide 1,2-^{14}C in the presence of a catalytic amount of metallic sodium[216,217] (equation 73), it has been suggested that considerable absorption of **187** through the vaginal wall into the systemic circulation of barren and pregnant rats[218] takes place. The commercial product is a mixture of ethoxymer species with different molecular weights[219].



$\overset{*}{C}$ = ^{14}C label

(**187**)

nonoxynol-9, average $n = 9$ (73)

The ^{131}I iodinated **187** has been synthesized to solve various radioanalytical problems related to **187** and its tissue distribution as a function of time by external scintigraphy. After various methods failed, the synthesis of ^{131}I-**187** has been accomplished in high yield reacting K^{131}I with *in situ* formed arylthallium bis(trifluoroacetate) (equations 74 and 75).

$$ArH + Tl(OCOCF_3)_3 \xrightarrow[RT,\,30\,min]{CF_3COOH} ArTl(OCOCF_3)_2 + CF_3COOH \quad (74)$$

$$ArTl(OCOCF_3)_2 + 2K^{131}I \longrightarrow Ar^{131}I + TlI + 2CF_3COOK \quad (75)$$

0.4 mCi (40% yield)

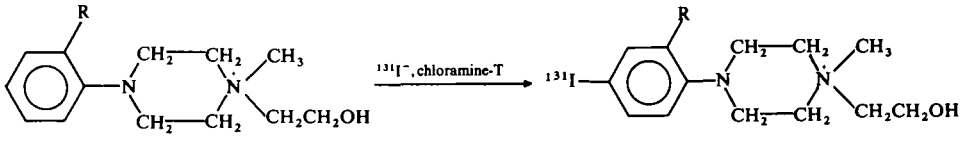
The iodination is predominantly *ortho* to the alkoxide substituent of **187**, in agreement with previous observations that thallation usually occurs in the *o*- or *p*-positions when carried out at room temperature and in the *meta* position under reflux[220]. The highest incorporation of [^{131}I] was achieved in the ethoxymer species containing nine ethylene oxide units. The N-9-[^{131}I] should be a good model compound for studying the *in vivo* disposition of N-9 from vaginal administration of the compound in rats.

3. Labelling of radiopharmaceuticals with iodine-122

In the course of preliminary studies for evaluating the conditions for the synthesis of radiopharmaceuticals labelled with the short-lived positron emitter ^{122}I ($T_{1/2} = 3.6$ min, $E_{max} = 3.1$ MeV), obtained from ^{122}Xe ($T_{1/2} = 20.1$ h), ^{131}I-iodinations of two phenylpiperazinium derivatives of **188** have been carried out. The reactions were quenched by addition of sodium metabisulphite (equation 76) and the radiochemical yields determined by HPLC[221]. Subsequently, rapid exchanges of ^{122}I for ^{127}I to produce ^{122}I-HIPDM (80% yield in 3 min) were achieved for cerebral blood flow studies and as brain agents[222] at 100 °C in the presence of a trace of KIO_3. The resulting product was of more than 98% radiochemical purity. (^{122}I-HIPDM = ^{122}I-labelled *N,N,N'*-trimethyl-*N'*-[2-hydroxyl-3-methyl-5-iodobenzyl]-1,3-propanediamine).

4. Synthesis of ^{131}I-labelled vinylic iodides in high specific activity

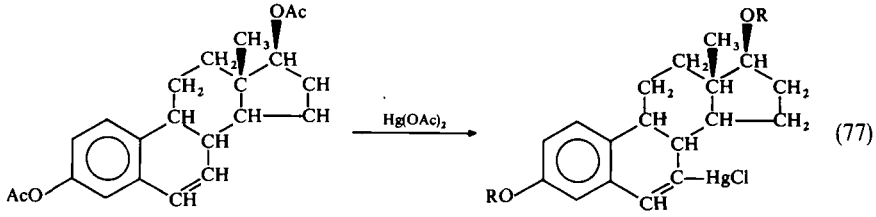
Several high specific activity N.C.A. radiolabelled iodinated steroids have been synthesized[223,224] for steroid receptor mapping using organometallic compounds as



(188) (76)

R	T (°C)	Radiochemical yields (%) 0.5	1 min	5 min
Me	70	41 ± 9	55 ± 4	52 ± 5
H	25	82 ± 8	93 ± 3	93 ± 4

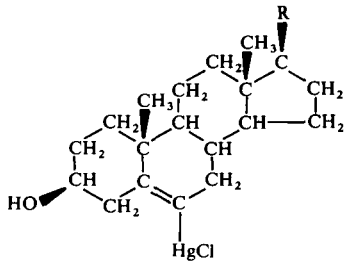
substrates[225,226]. Thus 7-chloromercuri-estradiol-6-ene, **189**, was obtained from estradiol-6-ene-3,17-diacetate, **190**, with mercuric acetate via the 7-chloromercuriestradiol-6-ene-3,17-diacetate, **191** (equation 77). Both **189** and **191** reacted smoothly with bromine and iodine to yield the corresponding 7-halo-estradiol-6-ene.



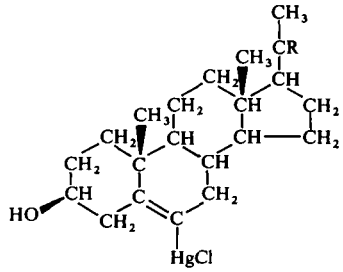
(190) (77)

(189) RO = OH
(191) RO = OAc

[^{131}I]-6-iodoandrost-5-en-3β,17β-diol, [^{131}I]-6-iodoandrost-5-en-3β-ol,17-one, [^{131}I]-6-iodopreg-5-en-3β-ol-20-one and [^{131}I]-6-iodopregn-5-en-3β,20-diol have also been synthesized[224] from the precursors **192–195** in which the labelling position is activated by mercury towards electrophilic substitution by radiohalogens. 6-Chloromercuricholest-5-en-3β-ol reacted efficiently[227] with [^{131}I]iodine yielding [^{131}I]-6-iodocholest-5-en-3β-ol[224] of high specific activity. The chloromercury compounds **192–195** undergo



(193) R = =O
(192) R = 

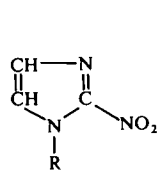


(194) R = =O
(195) R = 

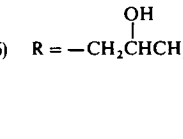
smooth reaction with [^{131}I]iodine monochloride in ethanol to give the corresponding iodinated products. The chloromercury derivatives could be stored for long periods at room temperature (in the presence of water and oxygen).

5. Synthesis of radioiodinated 2-nitroimidazoles for non-invasive estimation of hypoxic tumors

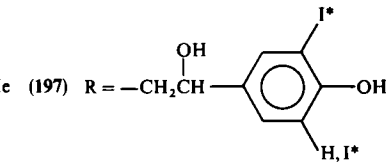
Misonidazole **196** has found clinical application for the enhancement of radiation therapy of tumors[227]. 2-Nitroimidazoles with the structures like **197**, **198** and **199** have been synthesized[228] as potential non-invasive hypoxic tumors markers. The acetophenone precursors in water, in contact with a solution of Iodogene[228] in chloroform treated with ^{125}I or ^{131}I, gave mild and selective iodination. Monoiodo and diiodo derivatives of **197**, **198** and **199** were obtained by adjusting the quantity of non-radioactive iodine in the solution. Selective accumulation of the radioactivity in tumors relative to other tissues was found after intravenous administration of [^{125}I]-diiodo-**198** to male $B_6D_2F_1$ mice bearing a Lewis lung tumor[227]. Minimal excretion of the compound, with 90% of the injected activity still in the body at 24 hours after injection, has been found.



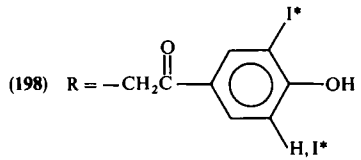
I* = ^{125}I, ^{131}I



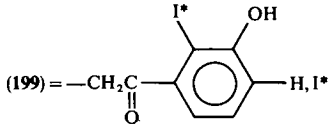
(196) R = —CH$_2$CHCH$_2$OMe



(197) R = —CH$_2$CH—



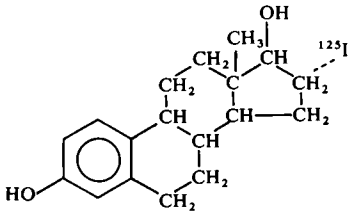
(198) R = —CH$_2$C—



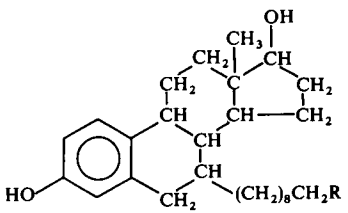
(199) = —CH$_2$C—

*6. Synthesis of 16α-[^{125}I]iodo-17β-estradiol (**200**) and [^{125}I]-labelled 7α-undecyl substituted estradiol derivatives*

The reference compound **200** has been obtained according to the method of Hochberg[229]. 7α-(11-hydroxy undecyl)-17β-estradiol **201** has been obtained according to



(200)



(201) R = —CH$_2$CH$_2$OH
(202) R = —CH$_2$CH$_2$Br
(203) R = —CH$_2$CH$_2$^{125}I
(204) R = —CH=CH$_2$
(205) R = —CH$_2$CH$_2$F

the procedure of Bucourt and coworkers[230]. **201** has been converted into **203** via **202**, as shown in equation 78.

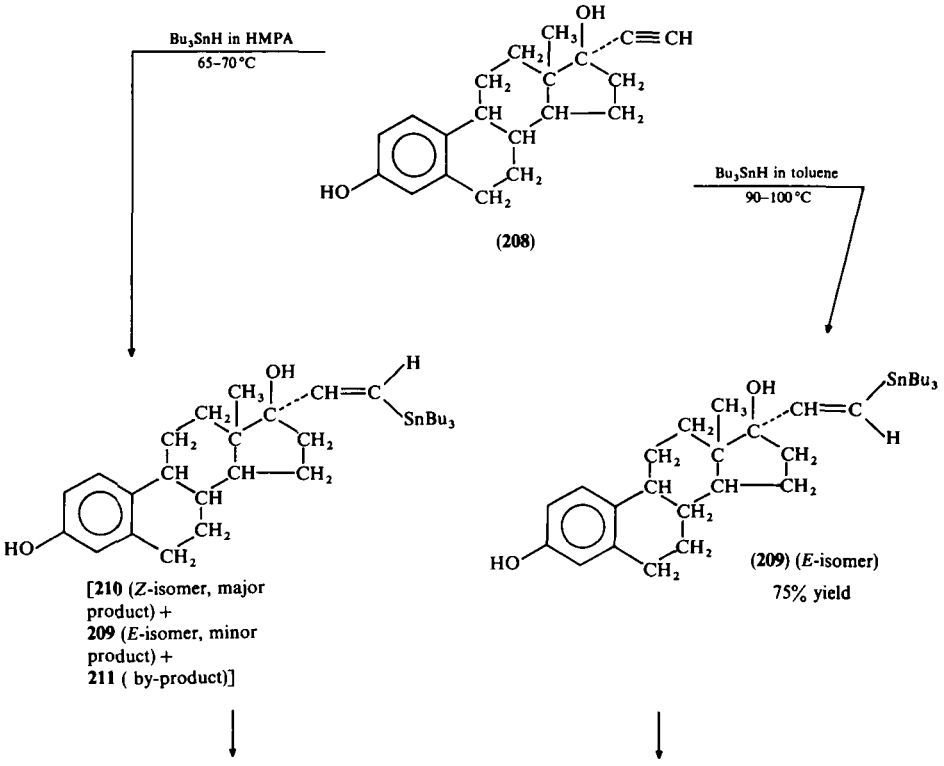
$$\mathbf{201} \xrightarrow{CBr_4,\ PPh_3 \text{ in dry } CH_3CN/THF/CH_2Cl_2\ (4:1:1)} \mathbf{202} \xrightarrow{[^{125}I]NaI} [^{125}I]\mathbf{203} \qquad (78)$$

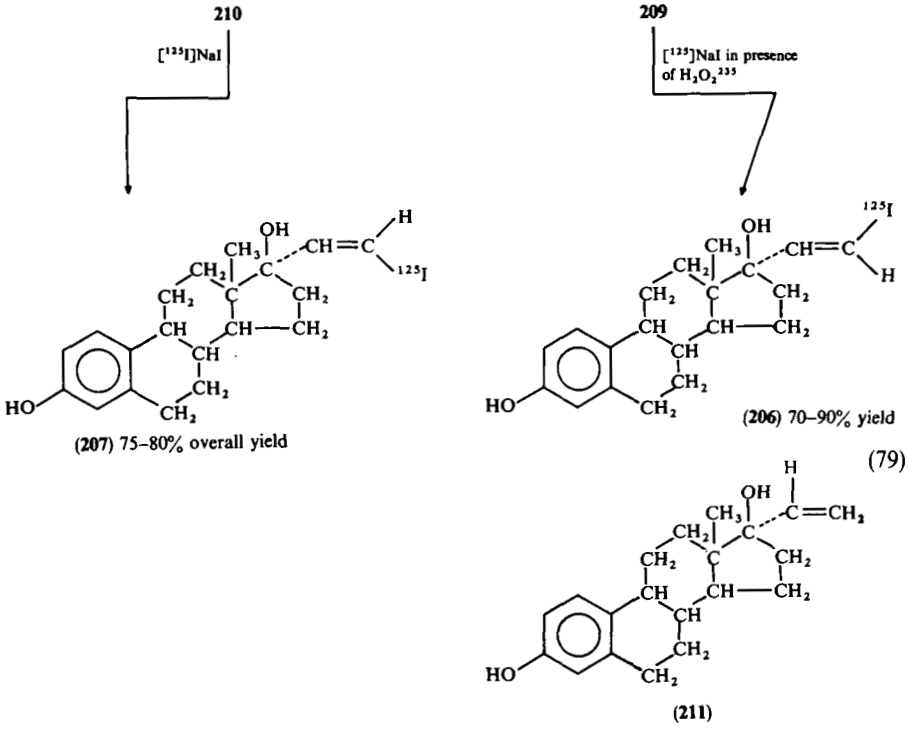
30% r.y. specific activity 175 Ci mmol^{-1}

The dehydrobrominated product **204** has also been produced as a by-product. Synthesis of the non-radioactive 7α-(11-fluoro undecyl) derivative **205** was achieved by substitution of the bromine in **202** with Bu_4NF, when the 3- and 17β-hydroxyl groups of **202** were protected as tetrahydropyran derivatives[231]. The presence of the long linear spacer molecule in **202–205** allows an attached functional group to protrude from the receptor binding pocket. Estrogen receptor binding affinity and target tissue uptake of compounds **201–205** have been studied[231].

7. *Synthesis of the 20-Z and 20-E isomers of 17α-[^{125}I]iodovinylestradiols*

a. Both the 20-*E* (**206**) and 20-*Z* (**207**) isomers, needed for receptor imagining in conjunction with the management of breast cancer, have been synthesized[232–234] by introducing iodine (or radioiodine) to the vinyl substituent by destannylation (equation 79).

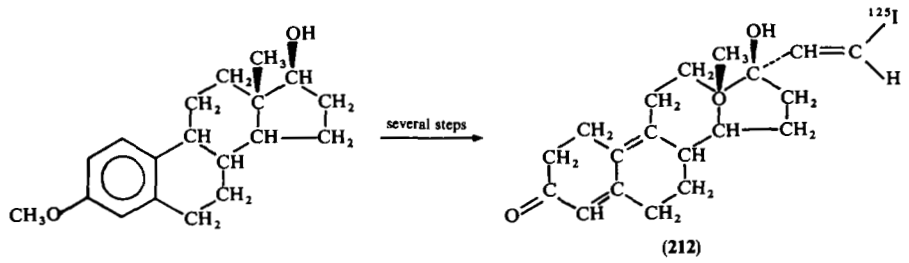




(79)

The ratio of the **210:209** isomers depends on temperature, the higher temperatures favouring formation of 20-*E* isomer. The intermediates **209** and **210** are converted to the corresponding 17α,20-*E*- and 17α,20-*Z*-iodovinylestradiols **206** and **207** in excellent yields, and were characterized by their ^{1}H and ^{13}C NMR spectra. The tissue distribution and uterus uptake of [^{125}I]**206** and [^{125}I]**207** showed that 20-*Z* isomer has higher relative bonding affinity (RBA) for the estrogen receptor. RBA values relative to ^{3}H estradiol were 33 and 47 for **206** and **207**, respectively.

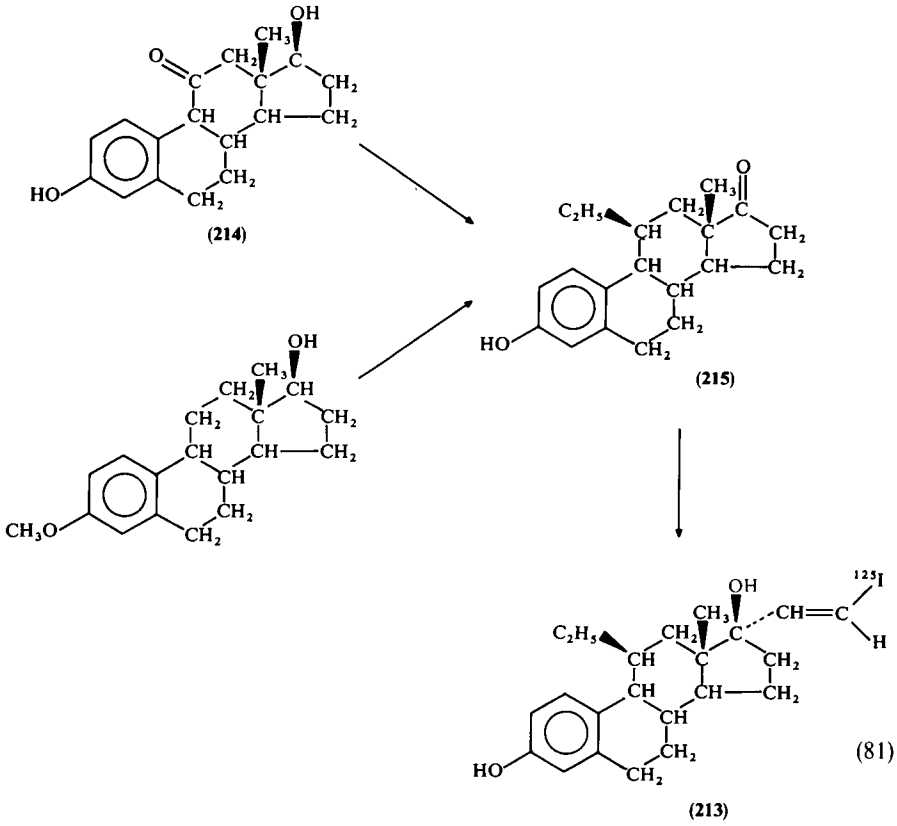
b. Synthesis of [^{123}I]-labelled 17α-iodovinyl-17β-hydroxy-4,9-dien-3-one (**212**) has been undertaken[235] by Hanson and coworkers (equation 80). It has been suggested that this radiohalogenated progestin is a better imaging agent for the diagnosis of hormone-responsible tumors than other agents because 9,10-double-bond impacts enhanced affinity for the receptor[236].



(80)

*8. Synthesis of [^{125}I]-17α-iodovinyl-11β-ethylestradiol (**213**)*

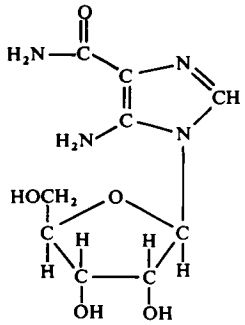
This compound has been synthesized by two pathways[238,239] (equation 81) for imaging estrogen receptor-rich tissues, such as breast and ovarian carcinomas. It has been reported that its receptor affinity is substantially greater than that of estradiol[237]. Both methods provided 11β-ethylestrone **215**, which was converted first to the 17α-tributylstannylvinyl intermediate and then to **213**. The product is useful both as an imaging agent (^{123}I-label) or as a radiotherapeutic agent (^{131}I).



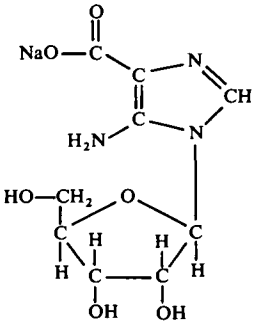
(81)

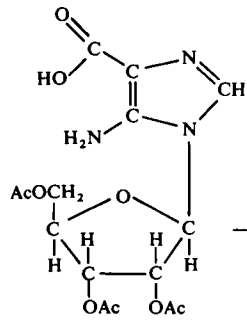
9. Synthesis of radiolabelled [^{125}I]-p-iodophenyl analogue of a naturally occurring imidazole ribonucleoside

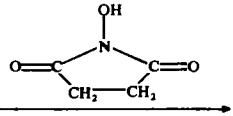
Nucleosides radiolabelled with ^{125}I ($T_{1/2} = 60$ d) are incorporated into nucleic acids via phosphorylation and may serve as indicators of tumor growth. The naturally occurring nucleoside, 5'-phosphate of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICA riboside, **216**), has been radiolabelled[239] with ^{125}I (equation 82). The key intermediate **217** has been synthesized by **218** with *p*-[^{125}I]iodoaniline. Deacylation of **217** gave 5-amino-1-β-D-ribofuranosyl-imidazole-4-[*N*-(*p*-[^{125}I]iodophenyl]carboxamide) **219**. Compound **219** showed uptake in proliferating tissues like tumor and bone-marrow tumor bearing nude mice.

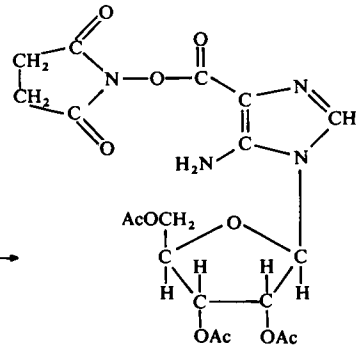


(216)

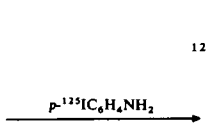


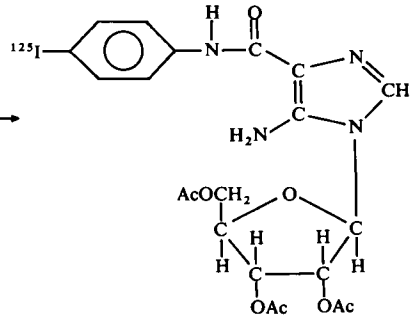


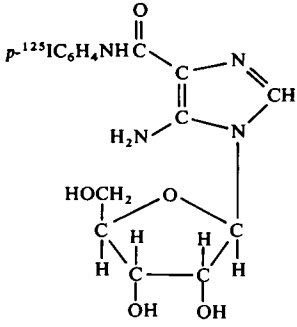




(218)





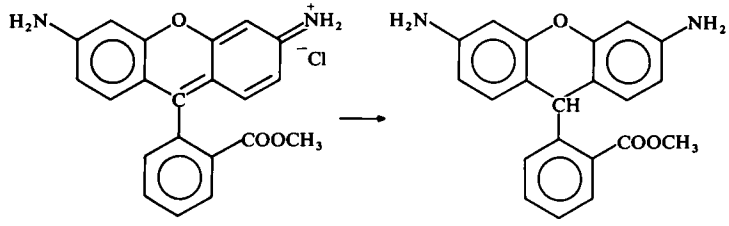


(219)

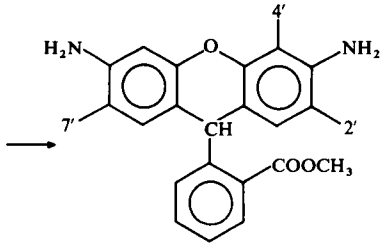
(82)

10. Synthesis of ^{125}I-labelled iodinated derivatives of rhodamine

Rhodamine 123 (**220**), a cationic dye used as a fluorescent stain for mitochondria, is retained for a longer period by certain types of cancer cells (2–5 days) than by normal cells (1–16 h)[240]. **220** has therefore been ^{125}I-labelled[241] for tumor imaging or radiotherapeutic use by ^{125}I-iodination of dihydrorhodamine **221** with Na^{125}I, separating the derivatives **222–226** by flash chromatography and identifying by TLC autoradiography (equation 83). The presence of one or more iodine atoms in the molecules **222–226** did not affect their ability to localize in the cell cytoplasm.



(220) (221)

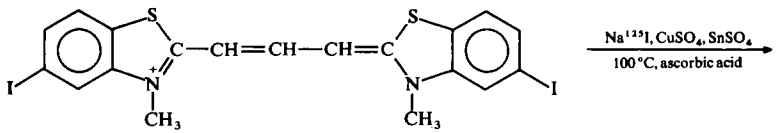


(222–226)

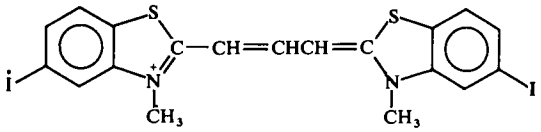
(83)

Compound	Positions 4′	2′	7′	% distribution of radioiodinated products
222	H	^{125}I	H	50
223	^{125}I	H	H	18
224	H	^{125}I	^{125}I	24
225	^{125}I	H	^{125}I	7
226	^{125}I	^{125}I	^{125}I	1

Another lipophilic cationic cyanine dye, a specific tumor localizing tracer, 3,3′-dimethylthiacarbocyanine (**227**), has also been labelled[242a] with ^{125}I in the 5,5′ positions (equation 84) and has been found promising for diagnosis and therapy of some tumors.



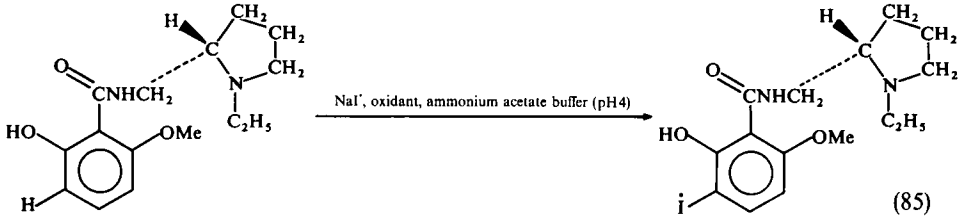
(227)



(84)

11. Synthesis of [^{123}I]- or [^{125}I]-labelled IBZM

Radioiodinated IBZM {(S)-(−)-3-iodo-2-hydroxy-6-methoxy-N-[(1-ethyl-2-pyrrolidynyl)methyl]benzamide} (**228**), a useful dopamine D-2 receptor imaging agent, has been synthesized[242b] (equation 85) using BZM (**229**) and Na*I[^{125}I] ($T_{1/2} = 60$ days, $E_\gamma = 30$–65 keV) or Na*I[^{123}I] ($T_{1/2} = 13$ h, $E_\gamma = 159$ keV). Among all oxidizing agents tested, peracetic acid appeared to be the best. **228** was obtained in >95% r.y., in 93–95% radiochemical purity in 2 minutes at room temperature.



(229) (228)

(85)

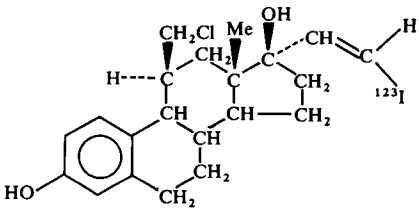
specific activity 600 Ci mmol^{-1} for ^{125}IBZM

The utility of peracetic acid as an oxidant for N.C.A. radiohalogenation ([^{77}Br], [^{131}I] and [^{125}I]) has been noted by other researchers also[243,244]. The active iodinating moiety is generated by oxidizing I^- to I^+, which is the electrophilic reagent involved[245].

*12. Synthesis of ^{123}I-labelled Z-11β-chloromethyl-17α-iodovinyl estradiol (Z-IV; **230**)*

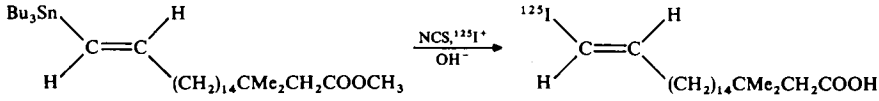
230 has been ^{123}I-labelled[246] for radioimaging and for targeted radiotheraphy, since Auger electrons emitted by ^{123}I release most of their energy within a few nanometers of the parent isotope and, if the decay occurs in the vicinity of DNA, less than 100 disintegrations are sufficient to kill a cancer cell. Attaching ^{123}I to steroids with high affinity to the nuclear associated estradiol receptor (ER) fulfils this condition. *In vitro* cytotoxicity studies showed that *Z*-**230** is 1000 times more toxic for MCF-7 human breast carcinoma cells than for human bone marrow cells.

The endothelial permeability and uptake of ^{14}C-labelled cholestrol, ^{125}I-labelled high-density lipoproteins and ^{131}I low-density lipoproteins in aortocoronary femoral vein bypass graft in dogs has been investigated[247].



(230)

(*E*)-19-Iodo[^{125}I]-3,3-dimethyl-18-nonadecenoic acid (**231**) has been ^{125}I-labelled (equation 86) to evaluate regional myocardial fatty acid uptake[248]. Fast (90 min) high yield (84%) Cu(I)-assisted preparation of 1231-15 (4-^{123}I-phenyl)-9-methylpentadecanoic acid has also been carried out[249], and the preparation of other ^{123}I-containing acids is being studied[249].



(231) (86)

IV. SYNTHESES OF THE TITLE COMPOUNDS LABELLED WITH DEUTERIUM AND TRITIUM

A. Synthesis and Uses of Deuterium-labelled Compounds

1. Synthesis of six specifically deuterated analogues of 1,2-dibromo-3-chloropropane (DBCP)

DBCP (**232**) was widely used as a nematocide until 1977[250], but its commercial production was suspended when it was found[251] to be carcinogenic, mutagenic and an acute gonadal toxicant[252,253]. Six selectively deuterated analogues of DBCP (**233–238**) have been synthesized[254] since it was found[255] that the toxicities are caused by metabolites of **232**, and hence deuterated analogues of **232** should be less toxic if the biological process involves C—H bond rupture or is accompanied by a secondary deuterium isotope effect.

	$BrCH_2CBrHCH_2Cl$ (**232**)	
$BrCD_2CHBrCH_2Cl$	(**233**)	$BrCH_2CDBrCH_2Cl$ (**234**)
$BrCH_2CHBrCD_2Cl$	(**235**)	$BrCD_2CDBrCH_2Cl$ (**236**)
$BrCD_2CHBrCD_2Cl$	(**237**)	$BrCD_2CDBrCD_2Cl$ (**238**)

Deuterated analogues (**240–245**) of 2,3-dibromopropanol (DBP), **239**, have been prepared and used in various synthetic schemes[256]. Some of these analogues were prepared previously[257] for toxity studies with flame-retardant tris(2,3-dibromopropyl)-phosphate.

	$BrCH_2CHBrCH_2OH$ (**239**)	
$BrCH_2CHBrCD_2OH$	(**240**)	$BrCH_2CDBrCH_2OH$ (**241**)
$BrCD_2CHBrCH_2OH$	(**242**)	$BrCD_2CDBrCH_2OH$ (**243**)
$BrCD_2CHBrCD_2OH$	(**244**)	$BrCD_2CDBrCD_2OH$ (**245**)

The deuterated analogues **240**, **241** and **242** have been prepared by bromination[257] of the appropriate allyl alcohols with bromine in CCl_4. **243** has been prepared[254,258] by reducing [3-$^2H_1$]propargyl alcohol, $CD{\equiv}CCH_2OH$, with $LiAlD_4$, hydrolysis and subsequent bromination (equation 87).

$$\underset{(\mathbf{246})}{CD{\equiv}CCH_2OH} \xrightarrow{LiAlD_4} CD_2{=}CDCH_2OH \longrightarrow \underset{(\mathbf{243})}{CD_2BrCDBrCH_2OH} \quad (87)$$

The synthesis of **244** and **345** was carried out as shown in equations 88 and 89.

$$CD_2BrCHBrCH_2OH \xrightarrow{\text{Jones reagent}} CD_2BrCHBrCOOH \xrightarrow{SOCl_2}$$

$$CD_2BrCHBrC(=O)Cl \xrightarrow{NaBD_4} CD_2BrCHBrCD_2OH \xrightarrow{NCS/TPP} CD_2BrCHBrCD_2Cl \quad (88)$$

(237)

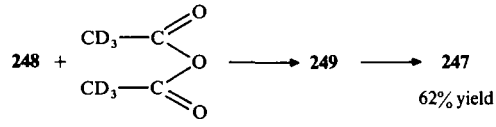
$$CD_2BrCDBrCH_2OH \xrightarrow{\text{Jones reagent}} CD_2BrCDBrCOOH \xrightarrow{SOCl_2}$$

$$CD_2BrCDBrC(=O)Cl \xrightarrow{NaBD_4} CD_2BrCDBrCD_2OH \xrightarrow{NCS/TPP} CD_2BrCDBrCD_2Cl \quad (89)$$

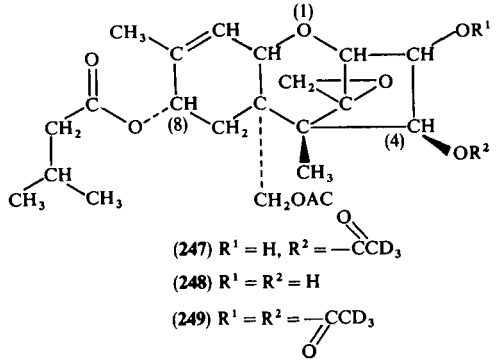
(238)

2. Synthesis of deuterium-labelled T-2 toxin

Isotopically pure trideuterated T-2 toxin **247**, a useful internal standard for mycotoxin analysis[259], has been prepared[260] by acetylation of HT-2 toxin (**248**) with hexadeuterated acetic anhydride and subsequent selective hydrolysis (equation 90).

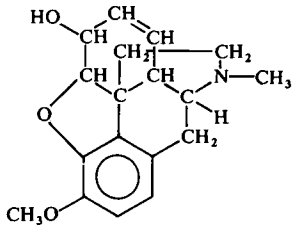


(90)

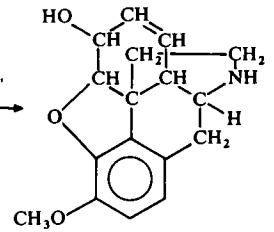


3. Synthesis of multiply deuterated N-n-propyl-norapomorphine-N-($^2H_7$) and derivatives

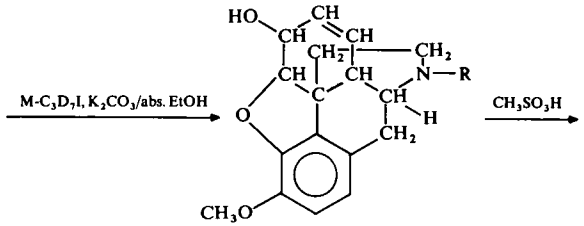
The title compound, *R*(−)-*N*-n-propylnorapomorphine (NPA, **250a**), has potent dopaminergic activity[261]. Its 10,11-methylenedioxy derivative (MDO–NPA, **251a**)—a prodrug in treating Parkinson's disease and related neurological disorders—is currently being investigated. **252** and 10,11-dimethoxy-NPA-**253** are of interest in the study of potential metabolites of NPA[262]. Seven deuterium atoms (as $—C_3{}^2H_7$ moiety) have therefore been incorporated[263,264,268a] into the relatively stable *N*-alkyl side chain of $^2H_7$-*R*(−)-apomorphine (equation 91) for use in metabolic and pharmacokinetic studies and as internal standard for GC–MS assays. Morphine has been deuterium-labelled previously in the aromatic ring structure[265,266] but these deuterated analogues are unsuitable for isotope dilution and MS studies, because H/D exchange occurs readily[266,267].



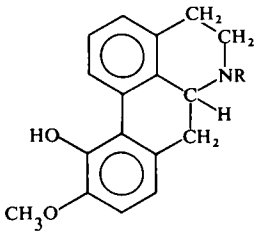
(**254**), codeine, 14 g



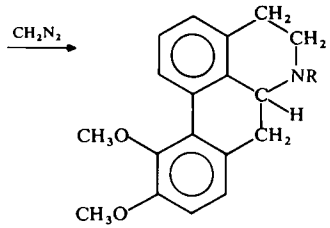
(**255**) norcodeine 9.4 g (70.4% yield)
m.p. 185–186 °C



(**256**) 99.7%, oil

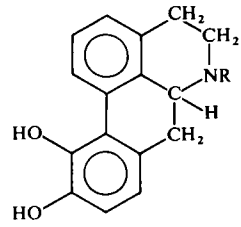


n-m-Propylnorapocodeine-$^2H_7$
(**252**)
(41%) m.P. 168–170 °C)

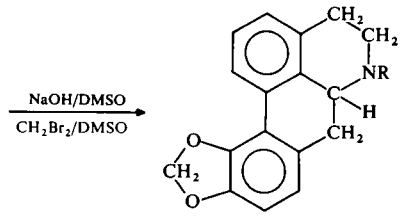


(**253**) oil, 100%
253·**HCl**—white solid, m.p. 161–162 °C

(**250a**)R = $CH_2CH_2CH_3$
white solid, sintered at
260 °C, decomp. 278–279 °C
(**250b**)R = $CD_2CD_2CD_3$ (95.6%)



(**250**) (*continued*)



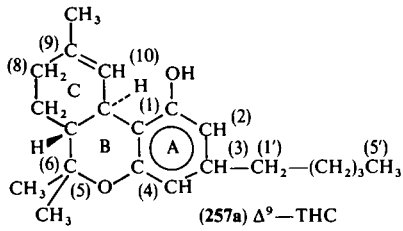
(91)

(251)
52% yield, (251) m.p. of HCl salt 260–262 °C
(251a) R = $CH_2CH_2CH_3$ (MDO–NPA)
(251b) R = $CD_2CD_2CD_3$
[*R*(−)—MDO—NPA – $^2H_7$]

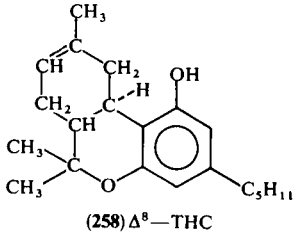
4. Synthesis of deuterium-labelled cannabinoids

Cannabis has been known since ancient times to elicit psychotomimetic response in man, but recently therapeutic applications of certain tetrahydrocannabinols (THCs) **257** are under investigation, including the interaction of cannabinoids with membrane phospholipids[268b,c]. Cannabinoids isotopically labelled with deuterium in selected positions were needed for a study of their orientation in membrane bilayers by solid-state NMR spectroscopy[269].

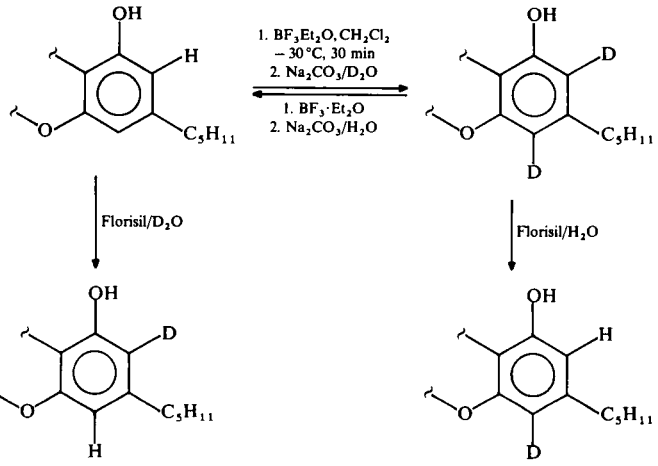
Several methods for incorporation of deuterium into THC have been applied[270–273].



(257a) Δ⁹—THC



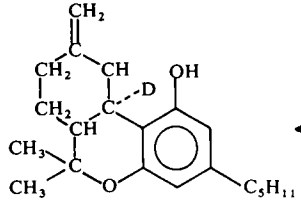
(258) Δ⁸—THC



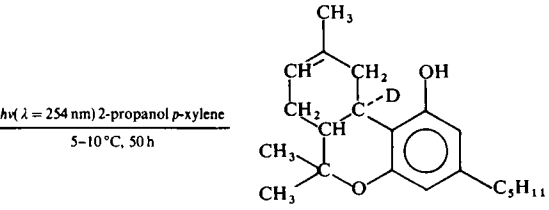
(92)

Quantitative deuteration at $C_{(2)}$ and $C_{(4)}$ of the phenolic ring was achieved[269] by reacting **257** under mild conditions with BF_3–Et_2O and treating the reaction mixture with 10% sodium carbonate in D_2O (equation 92). Using magnesium silicate (Florisil) and D_2O or H_2O it was possible to obtain **258** selectively labelled at the $C_{(2)}$ or $C_{(4)}$ ring carbons (equation 92). The H/D and D/H exchanges proceed much faster at $C_{(2)}$ than at $C_{(4)}$.

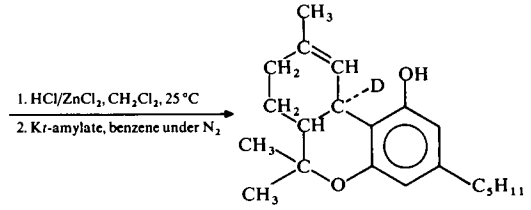
Deuterium label has been introduced regiospecifically into the C-ring of Δ^9-THC employing the HCl addition/elimination reaction (equation 93) used previously[274] for the conversion of Δ^8- to Δ^9-THC. Δ^9-THC deuterated at the $C_{(8)}$ position of the C ring was prepared by addition of DCl to the double bond of Δ^8-THC and subsequent elimination of HCl by potassium *t*-amylate. Deuterium has been introduced also at the $C_{(8)}$ and $C_{(10)}$ or at the $C_{(8)}$, $C_{(10)}$ and $C_{(11)}$ positions similarly, using DCl with Δ^9 or $\Delta^{9,11}$-THC (equation 94). UV irradiation of specifically labelled Δ^8-THC produced the correspondingly labelled $\Delta^{9,11}$-THC (**259b**).



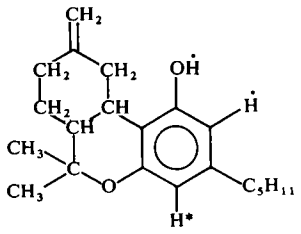
(**259b**) $\Delta^{9,11}$-THC, 30%



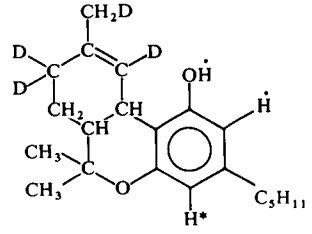
(**258b**) [10a^2H]-Δ^8-THC



(**257b**) [10-^{2}H]-Δ^9-THC (93)



(**259**)Ḣ = H or D

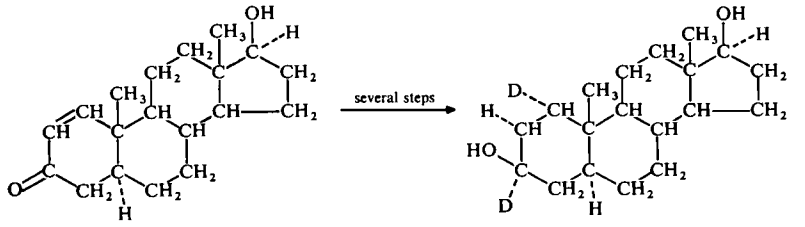


(**257c**) (94)

5. *Synthesis of deuteriated androstanediols*

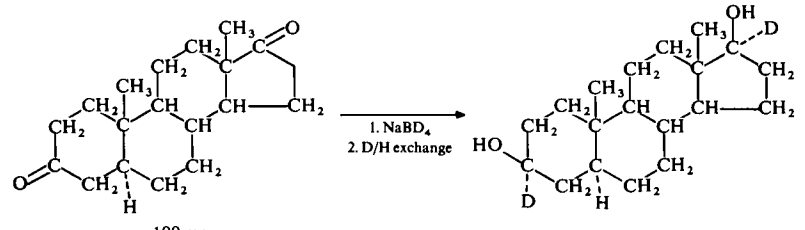
Six deuteriated androstanediols have been synthesized[275–277] for use in isotopic dilution-mass fragmentography as carriers or and as internal standards.

a. 1α,3α-$^2H_2$(5α)androstanediol-3β,17β (**260**) has been prepared in a multistep synthesis (equation 95).



40 mg (95)

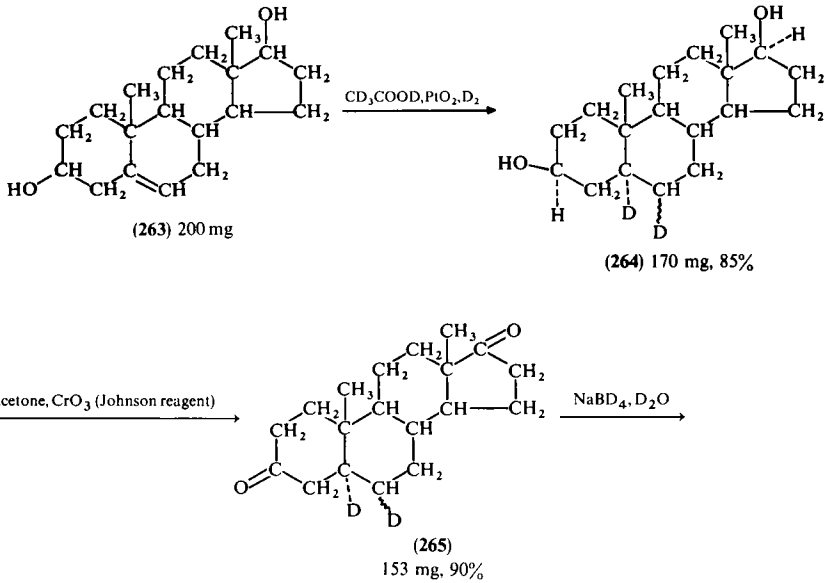
b. 3α,17α-$^2H_2$(5α)androstanediol-3β,17β (**261**) has been obtained by reduction of the corresponding dione-3,17 with sodium borodeuteride followed by D/H isotope exchange (equation 96).



100 mg (96)

(**261**) 75 mg (overall yield 75%)

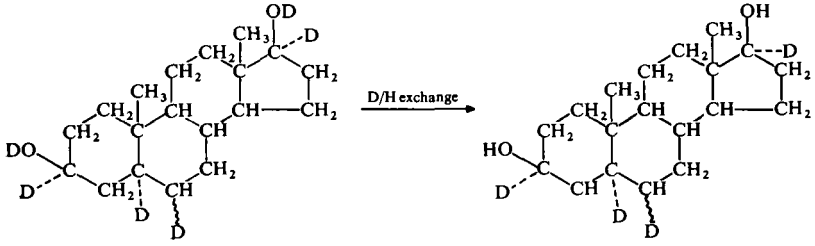
c. 3α,5α,6ξ,17α-$^2H_4$(5α)androstanediol-3β,17β (**262**) has been obtained in several steps from **263** via **264**, **265** and **266** (equation 97).



(**263**) 200 mg

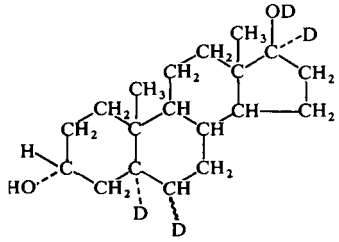
(**264**) 170 mg, 85%

(**265**)
153 mg, 90%

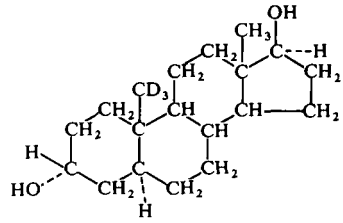


(266) (262) 124 mg, m.p. 158–167 °C, 62% overall yield (97)

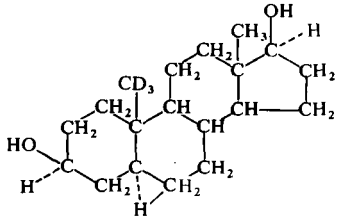
d. 5α,6ξ,17α-$^2H_3$(5α)androstanediol-3α,17β (**267**), 19-$^2H_3$(5α)androstanediol-3α,17β (**268**) and −3β,17β (**269**) have also been prepared[275]. The synthesis of **267** yielded a mixture of 5β,6ξ,17α-$^2H_3$(5β)androstanediol-3α,17β (**267a**), together with **267** in a 6:4 ratio.



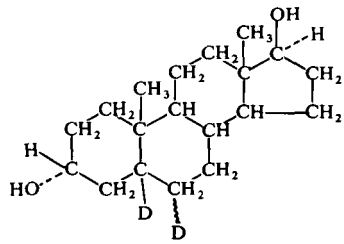
(267)



(268) 62%



(269)

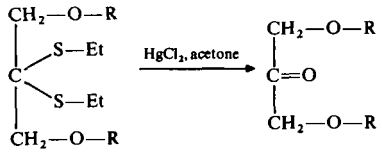


(267a) 93 mg

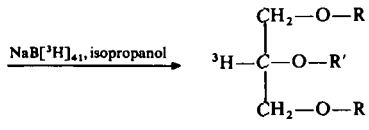
B. Syntheses and Uses of Tritium-labelled Compounds

1. Synthesis of polyunsaturated glyceryl alkyl ethers tritiated at $C_{(2)}$

[^{14}C]-labelled long-chain alkenyl ethers of glycerol were used as non-degradable model substances for studying the fate of lipoprotein triglyceride[278]. Polyunsaturated symmetrical trialkyl ethers, tritiated at the $C_{(2)}$ position, have been prepared[279,280] (equation 98).



(270) (271) m.p. 23 °C (98)



(272) R' = H, 0.74 mCi, 92.5% r.p.

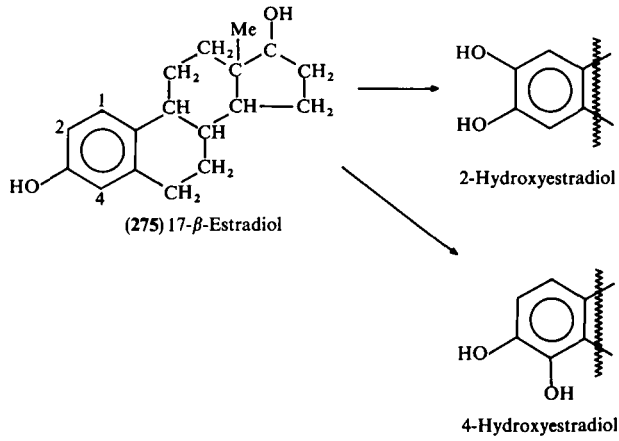
(273) R' = *cis*-9-octadecenyl

(274) R' = *cis*,cis-9,11-octadecadienyl

Di-*cis*-9-octadecenyloxyacetone diethyl mercaptal (**270**) was obtained from the dihydroxyacetone with *cis*-9-octadecenyl methane sulphonate[278]. This, treated with $HgCl_2$, yielded **271**, which was reduced to **272**. The latter has been etherified by *cis*-9-octadecenylmethane sulphonate yielding tris(*cis*-9'-octadecenyloxy)propane **273**. Esterification of **272** with *cis*,*cis*-9,11-octadecadienyl methane sulphonate produced 1,3-di-*cis*-9'-octadecenyloxy-2-*cis*,*cis*-9',11'-octadecadienyloxy-propane[2-^{3}H] (**274**).

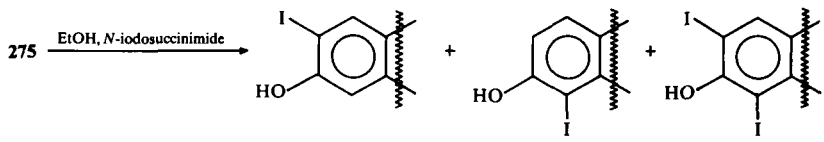
2. *Synthesis of [2-^{2}H]estradiol, [4-^{2}H]estradiol, [2-^{3}H]estradiol and [4-^{3}H]estradiol*

17-β-Estradiol (275) has been labelled[281] in the 2 or 4 position with tritium or deuterium for precise and fast indirect determinations of the biologically unstable catecholestrogens, which are the major metabolites of endogenous and exogenous estrogens in humans and experimental animals[282] (equation 99).



(275) 17-β-Estradiol

(99)



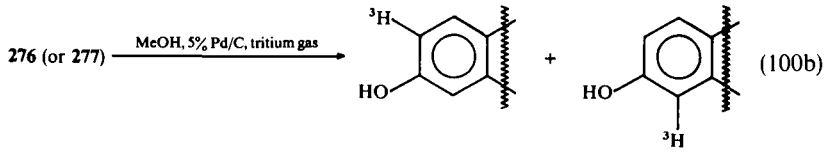
(276) 17% yield, m.p. 149 °C with decomposition

(277) 20% yield, m.p. 174 °C with decomposition

(278) discarded

(100a)

2- and 4-Iodoestradiols were prepared from **275** followed by chromatographic separation, when 2,4-di-iodoestradiol **278** was discarded. Reductive dehalogenation of **276** and **277** with tritium gas yielded [2-^{3}H]estradiol (**279**) and [4-^{3}H]estradiol (**280**) with greater than 99% radiochemical purities (equations 100a, b). [2-^{2}H]estradiol and [4-^{2}H]estradiol have been prepared similarly by reduction of corresponding iodo-compounds with deuterium gas.

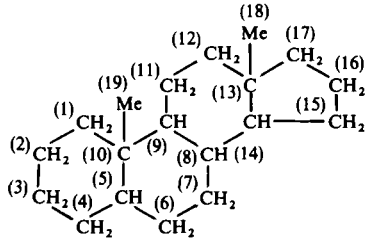


(100b)

(279) (280)

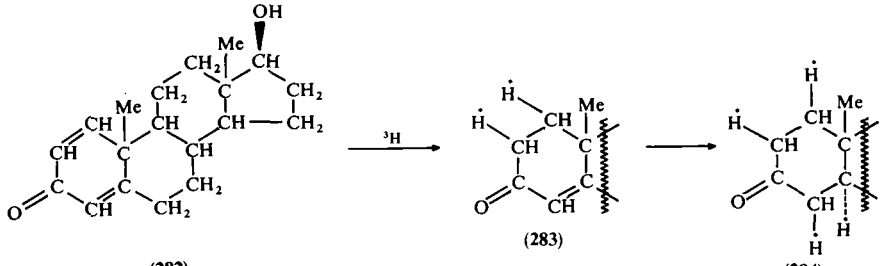
3. Labelling of steroids by tritium, activated by microwave discharge

Steroids, **281**, with rigid methyl groups at $C_{(18)}$ and $C_{(19)}$, an alkyl chain at $C_{(17)}$, hydroxyl or oxo groups at $C_{(3)}$, $C_{(11)}$, $C_{(17)}$, $C_{(20)}$ and a freely rotating hydroxyl group at $C_{(21)}$, are essential cell regulators. They have been tritium labelled in specific positions by catalytic hydrogenation of dehydro precursors, by catalytic dehalogenation of brominated steroids with tritium gas or by reduction of an oxo steroid with a reducing tritide[283]. They have been labelled also by exposure to tritium gas[283] or by catalytic exchange with tritiated water[284,285].

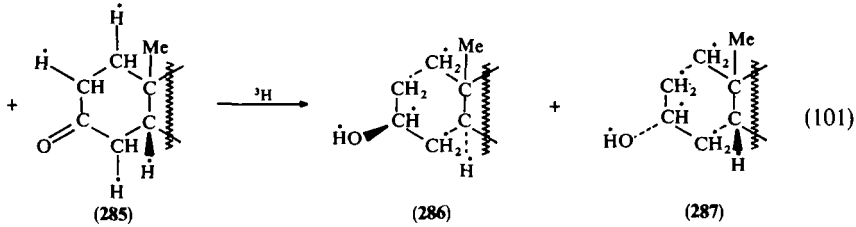


(**281**) Androstane

Detailed investigation of tritium labelling of steroids at −196 °C with tritium gas (freshly generated by heating uranium tritide to 350–400 °C and free of ^{3}He) activated by microwave discharge (100 W), creating a low-pressure plasma (containing electrons, ions, atoms and excited species) has been carried out by Tang and Peng[286]. Due to their stability the steroids are able to dissipate intramolecularly the excess energy received in



(**282**) (**283**) (**284**)



(285) (286) (287) (101)

the reaction with the activated tritium species without ring opening or other bond rupture. Hydroxy and oxo groups located at $C_{(3)}$, $C_{(11)}$ and $C_{(17)}$ are oxidized or reduced but not replaced by tritium. The sequence of reactions of activated tritium with isolated double bonds in dehydrotesterone is shown in equation 101.

282 = [^{3}H]dehydrotestosterone = [^{3}H]androstane-1,4-diene-17β-ol-3-one
283 = [^{3}H]androst-4-ene-17β-ol-3-one
284 = [^{3}H]5α-androstane-17β-ol-3-one
285 = [^{3}H]5β-androstane-17β-ol-3-one
286 = [^{3}H]5α-androstane-3β,17β-diol
287 = [^{3}H]5β-androstane-3α,17β-diol

The order of reactivity of C=C double bonds in steroids is $\Delta^1 > \Delta^4 > \Delta^5$. Saturation of the Δ^4 bond gives rise to 5α and 5β dihydro derivatives. The specific activity of the labelled by-product steroids can approach 29 Ci mmol^{-1}. Labelling of steroids by excited tritium depends not only on the functional groups present but also on the solvent and on the catalytic surface. The highest specific activity and the highest yield of labelled testosterone has been obtained in ethanol. The final products from the unsaturated steroids contain significant amounts of the labelled parents.

In the case of interaction of estrogens with activated tritium, the following labelled products have been isolated:

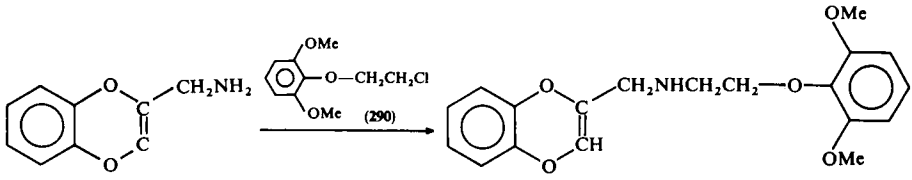
Irradiated steroid: *Estra-1,3,5(10)-triene-3-ol-17-one*
Labelled product: [^{3}H]parent (30% yield) and by-product: [^{3}H]5α-19-nor-androstane-3β-ol-17-one (46.9% yield).
Irradiated steroid: *Estra-1,3,5(10)-triene-3,17β-diol*
Labelled product: [^{3}H]parent (11.1% yield) and by-products: [^{3}H]5α-19-nor-Androstane-3β,17β-diol (33.8%), [^{3}H]5β-19-nor-Androstane-3β,17β-diol (29%) and [^{3}H)Estra-1,3,5(10)-triene-3-ol-17-one (26%).

The above and other studies indicate that steroid hormones (with the exception of 21-hydroxy steroids) can be readily tritium labelled with activated tritium. The method is especially useful for the tritium labelling of the steroids androstane, cholestane and pregnane, which are difficult to label by synthesis or by catalytic exchange[286].

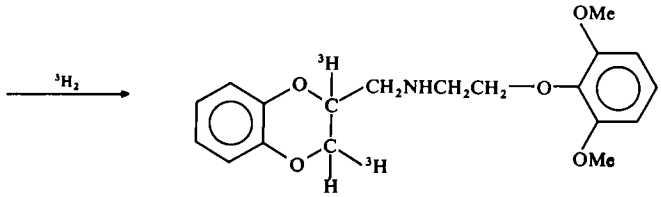
*4. Synthesis of tritium-labelled 2-N-[2,6-dimethoxyphenoxyethyl aminomethyl [2,3-^{3}H]-1,4-benzodioxane (**288**)*

This alpha adrenergic antagonist has been synthesized[287] by catalytic reduction of 2-[*N*-(2,6-dimethoxyphenoxyethyl)-aminomethyl]-1,4-benzodioxin (**289**) with tritium in various solvents and in the presence of various catalysts (equation 102). Saturation of the double bond in the presence of Pd/C catalyst is rapid, but is accompanied by H/T exchange with the solvent's protons. Radiochemical purity of the product **288** was about 52–67%. Use of $Cl(PPh_3)_3Rh$ in benzene as catalyst permitted one to obtain **288** with

the theoretical specific activity but in a slower reaction. No H/T exchange with benzene protons took place in agreement with previous observations[288]. **288** stored in MeOH was stable at −30 °C during 4 months, while at +4 °C the radiochemical purity decreased to 97% after 2 months.



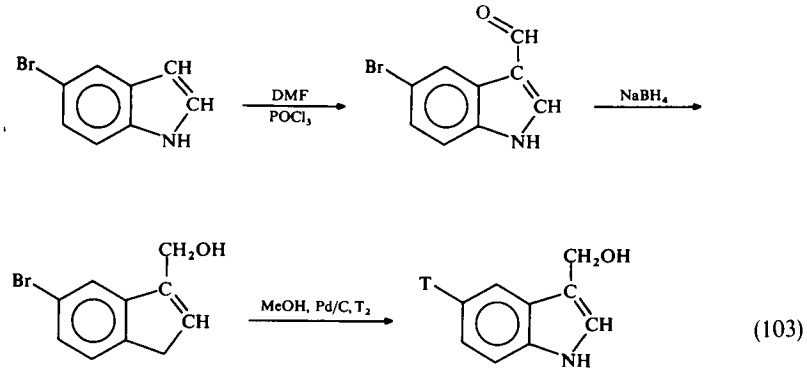
(289)
40% yield based on **290**



(288) (102)

5. Synthesis of 5-[^{3}H]-indole-3-carbinol

Indole-3-carbinol is a natural dietary anticarcinogen found as a glucosinolate[289] in cruciferous vegetables such as cabbage, cauliflower and broccoli. It inhibits tumor formation in rodents exposed to polycyclic aromatic hydrocarbons[290], and aflatoxin B_1-induced hepatocarcinogenesis in rainbow trout and rat[291]. Its tritium-labelled derivative, **291**, has been synthesized from 5-bromoindole[292–295] (equation 103). **291** is stable in 95% ethanol when stored under nitrogen at −20 °C protected from light, but turns orange if left at room temperature or if exposed to air.



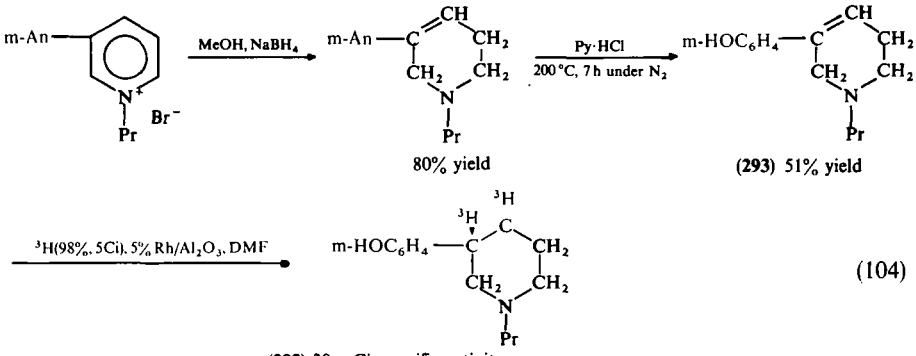
75%

(**291**) 85–90% yield
specific activity 21.14 Ci mmol^{-1}
99% radiochemical purity

(103)

*6. Synthesis of tritium-labelled (−)-3-PPP (**292**)*

This possible antipsychotic agent[296], (*S*)-3-(3-hydroxyphenyl)-*N*-propyl-[3,4-^{3}H]-piperidine (**292**), has been synthesized[297] by hydrogenation of compound **293** with tritium gas followed by resolution of the racemic mixture (equation 104). This has been done

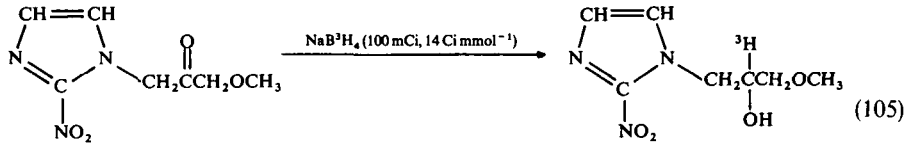


(104)

by adding the salt of (−)-3-PPP and the resolving agent[298] (+)-(*S*)-2,2-(1,1-binaphthyl)-phosphoric acid to a hot methanolic solution of tritium-labelled racemic 3-PPP product, followed by recrystallizations and silica gel chromatography. The optical purity of **292** was determined by HPLC using a chiral α_1-acid glycoprotein column[299]. ^{3}H NMR confirmed the exclusive incorporation of tritium in the 3 and 4 positions of the piperidine ring.

7. The synthesis of tritium-labelled misonidazole

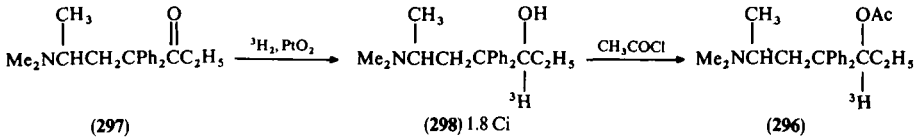
This compound, 1-(2-hydroxy-3-methoxypropyl)-2-nitro-1*H*-imidazole (**294**), is preferentially toxic to hypoxic cells[300] and mutagenic[301]. It has been tritium labelled[302] by NaB^3H_4 reduction of 1-(3-methoxy-2-oxopropyl)-2-nitro-1*H*-imidazole (**295**) and applied for metabolic studies (equation 105). The investigation of the stability of **294** at 37–100 °C and at pH 2.3–9.0 showed that it does not undergo visible ^{3}H-exchange under physiological conditions or in acidic or basic solutions, and is appropriate for metabolic studies.



(105)

8. Synthesis of tritiated 1-α-methadol and 1-α-acetylmethadol[^{3}H]

The drug 1-α-acetylmethadol (LAAM, **296**), which was found to have a longer time of action than methadone (**297**) itself[303], has been synthesized[304] by reduction of *d*-methadone with tritium on an Adams catalyst to **298** and acetylation of the latter (equation 106). *d*-Methadone has been isolated by crystallization of the ammonium



(297) (298) 1.8 Ci (296)

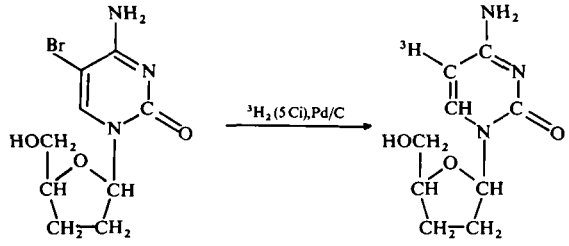
(106)

d-α-bromocamphor-π-sulphonate salt of *dl*-methadone. Specific activity of **296** and **298** as determined by MS was 20 Ci mmol^{-1}. ^{3}H NMR of **298** confirmed its 'α' configuration and showed that 68% of the tritium is located at the alcoholic carbon and 32% in the aromatic rings (introduced by H/T isotope exchange[305]).

9. *Synthesis of ^{3}H-labelled 2',3'-dideoxynucleosides of pharmacological interest*

Some 2',3'-dideoxynucleosides have shown promise[306] of activity against the HIV-1 virus associated with AIDS. These compounds have been tritium labelled[307]. [Pyrimidine-5-^{3}H]-2',3'-dideoxycytidine (**299**) has been prepared by catalytic dehalogenation[308] of 2',3'-dideoxy-5-bromocytidine (**300**) with tritium (equation 107).

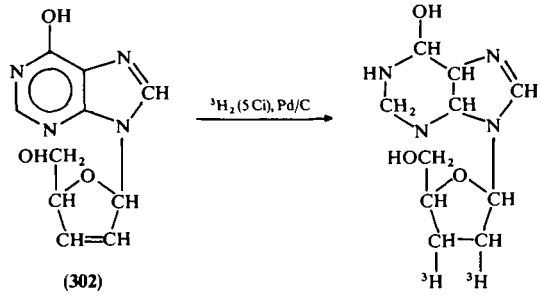
[Ribose 2,3-^{3}H]-2',3'-dideoxyinosine (**301**) has been prepared similarly from **302** (equation 108). [Adenine-8-^{3}H]-2',3'-dideoxyadenosine (**303**) has been prepared by



(300) (299)

(208 mCi, 98% pure by radio-TLC and —HPLC specific activity 25.2 Ci mmol^{-1})

(107)

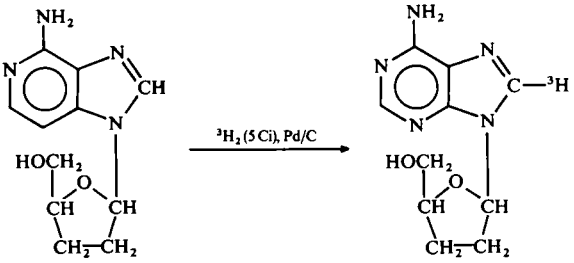


(302) (301) 152 mCi

(specific activity 31.6 Ci mmol^{-1}, > 98% of the total tritium in the dideoxyribose residue)

(108)

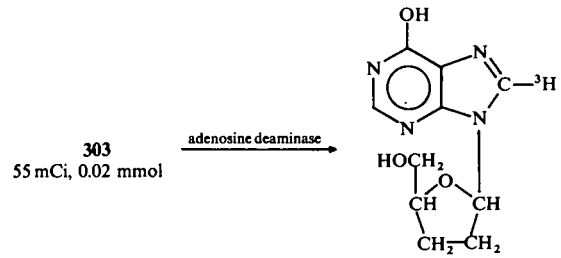
catalytic exchange with tritium gas[309] (equation 109). Acid hydrolysis showed 98% of the total tritium in the purine residue. T/H exchange in **303** in pH 7 phosphate buffer after 24 h at RT was found to be less than 1%.



(109)

(**303**)
specific activity 2.65 Ci mmol^{-1}

[Hypoxanthine-8-^{3}H]-2',3'-dideoxyinosine (**304**) has been prepared from **303** (equation 110).



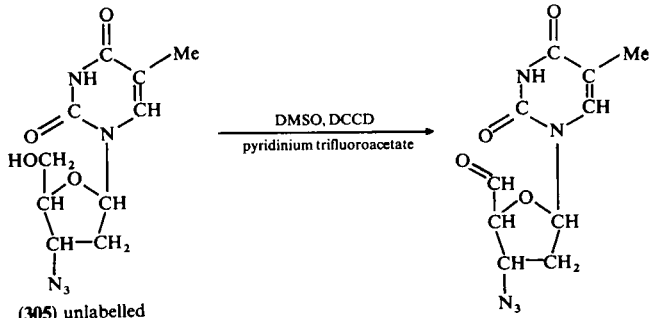
303
55 mCi, 0.02 mmol

(110)

(**304**) 52.7 mCi (95% yield)
98% pure by radio-TLC
(specific activity 2.61 Ci mmol^{-1})

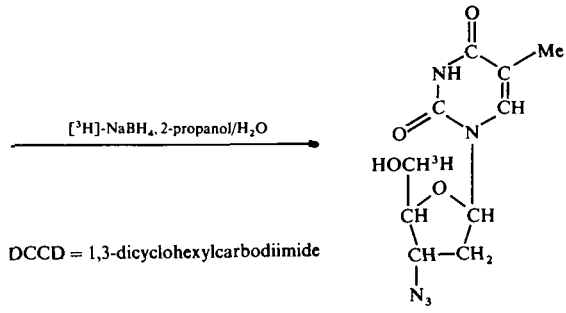
10. Synthesis of tritiated zidovudine

[5'-^{3}H]-3'-azido-3'-deoxythymidine (**305**), the antiviral agent (AZT or BW A509U) blocking infection of susceptible host cells *in vitro* by HIV, has been synthesized[310] by oxidation[311,312] of the unlabelled **305** to the 5'-aldehyde **306** followed by reduction with [^{3}H]-$NaBH_4$ (equation 111). Further radioimmunostudies with drug **305** are in progress[310].



(**305**) unlabelled

(**306**) 65%

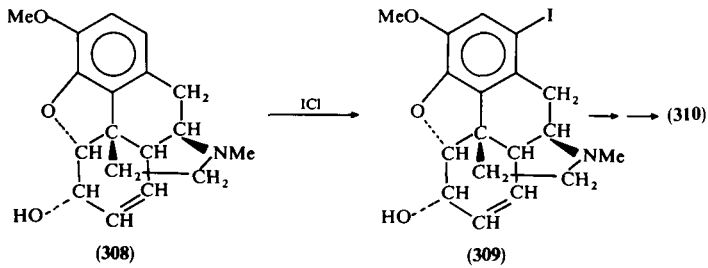


[5'-³H] (**305**)
(46% specific activity 14.0 Ci mmol^{-1}, chemical and radiochemical purity > 99%

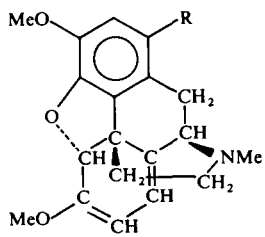
(111)

11. Synthesis of thebaine[1-³H]

Thebaine **307** linked to certain opiates found in mammalian tissue[313] has been tritium-labelled[314] at the $C_{(1)}$ position (quation 112). 1-Iodocodeine (**309**), prepared[315] from codeine (**308**), was converted to 1-iodothebaine (**310**) in 3 steps. Selective hydrogenolysis of the carbon–iodine bond in **310** with T_2 and Pd/C produced tritium-labelled **307** in about 80% yield. This synthetic route is radiochemically more efficient than the earlier methods[316].



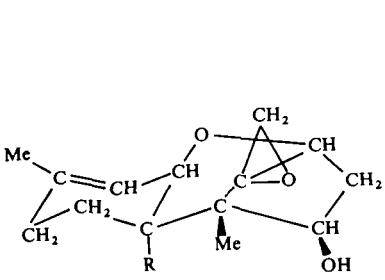
(112)



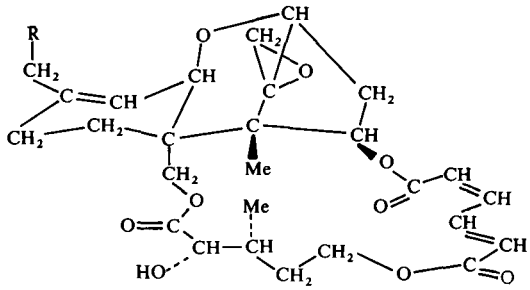
(**310**) R = I
(**307**) R = ³H (2.14 Ci specific activity 16 Ci mmol^{-1}, radiochemical purity > 97%

12. Synthesis of tritium-labelled verrucarol and verrucarin A

These mycotoxins are produced mainly by fungi belonging to the *Fusarium*, *Trichothecium*, *Myrothecium* and *Stachybotrys* families[317–319]. Two trichothecenes, [15-^{3}H]verrucarol (**312**) and [16-^{3}H]verrucarin A (**315**), have been synthesized (equations 113 and 114) with very high specific activity and purity for tracing these toxins and their metabolites in animal studies. **312** has been obtained[320] by oxidation of the unlabelled verrucarol **311** followed by reduction of the aldehyde **313** (equation 113). [16-^{3}H]Verrucarin (**315**) has been obtained by reduction of 16-mesyloxyverrucarin **317** (equation 114).



(**311**) R = $-CH_2OH$
(**312**) R = $-CH(^3H)OH$
(**313**) R = $-C(=O)H$



(**314**) R = H
(**315**) R = ^{3}H
(**316**) R = OH
(**317**) R = OSO_2Me

$$\mathbf{311} \xrightarrow{RuCl_2(Ph_3P)_3} \mathbf{313} \xrightarrow{[^3H]NaBH_4} \mathbf{312}\,(30\%\text{ yield}) \qquad (113)$$

specific activity 266 mCi mmol^{-1}

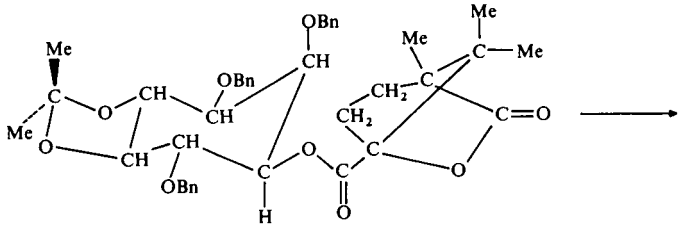
$$\mathbf{316} \xrightarrow{Et_3N,\,CH_2Cl_2,\,Me_2SO_2Cl} \mathbf{317} \xrightarrow[[^3H]NaBH_4]{\substack{CH_2Cl_2,\text{ sodium phosphate buffer,}\\ \text{hexadecyltributylphosphonium bromide}}} \mathbf{315}\,(4\%\text{ yield}) \qquad (114)$$

(based on the recovered radioactivity)
specific activity 130 mCi mmol^{-1}

13. Synthesis of tritium-labelled enantiomers of myo-inositol 1,4,5-triphosphate

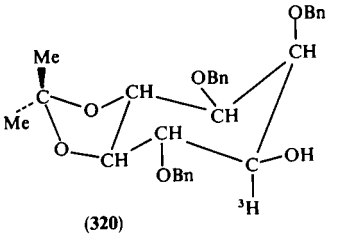
The synthetic route of D-myo-[1-^{3}H]-ins(1,4,5)P_3 (**318**) is given[321] in equation 115. The fully protected racemic inositol derivative[322,323] has been converted to a diastereomeric mixture of the (−)-ω-camphanate esters from which the precursor **319** has been isolated by HPLC. Basic hydrolysis of **319** followed by oxidation of 1-hydroxy-4,5-ketal tris benzyl ether **320** with DMSO–acetic anhydride[323] afforded the inosose **321**. The tritium-labelled equatorial alcohol **322** has been obtained by reduction of **321** with sodium borotritide[324]. Hydrolysis of the ketal group in **322** gave the tribenzyl ether **323** in 81% yield, and this in turn afforded the tritium-labelled perbenzylated ins(1,4,5)P_3 (**324**) in 34% yield. The final product, the triphosphate **318**, has been obtained by deprotecting **324** with a highly active Pd/C catalyst and hydrogen. To avoid the radiolytic decomposition of the high specific activity product **318**, the material was diluted to 0.5 mCi ml^{-1} for storage.

The enantiomeric L-myo-[^{3}H]-ins(1,4,5)P_3 ('ent-**318**') has been prepared in the same sequence of reactions starting from 'ent-319'.

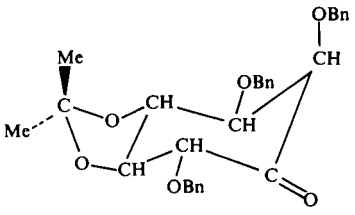


(319)

(Bn = benzyl)

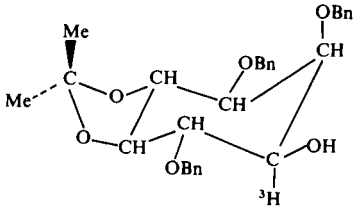


(320)



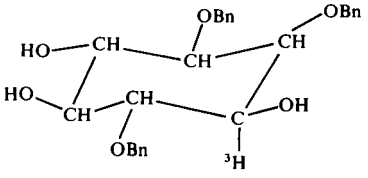
(321)

NaB^3H_4



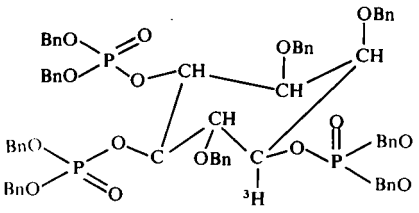
(322)

HCl/MeOH

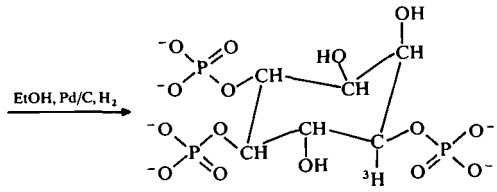


(323)

1. DMF, NaH
2. Tetrabenzylpyrophosphate



(324) colourless oil (34%)



(115)

(318) 30 mCi

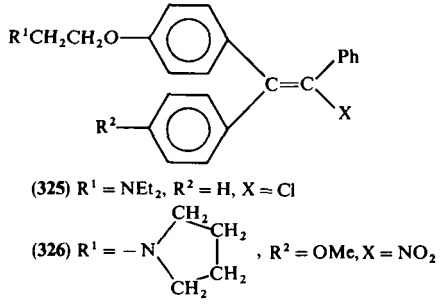
The enantiomers of the compound **318** play a leading role in the phosphoinositide pathway of interaction of external messengers with membrane receptors[325]. They are produced in this pathway by the action of a specific phospholipase C on phosphatidyl-inositol 4,5-bisphosphate[326].

Synthesis of labelled ins(1,4,5)P_3 have been carried out also in several other laboratories[327–332].

14. Preparation of tritium-labelled clomiphene and nitromiphene

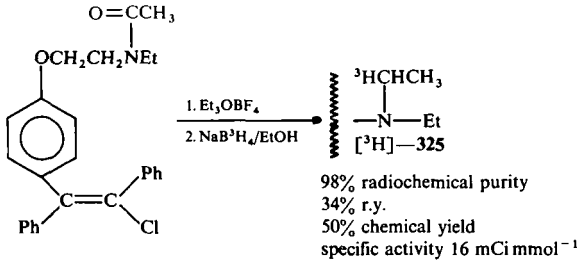
Two triarylethylene non-steroidal estrogen antagonists ('anti-estrogens'), clomiphene (**325**) and nitromiphene (**326**), have been tritium-labelled[333] for investigation of their metabolism. The synthesis has been carried out since a previous biotransformation study[334] of **325** revealed the production of metabolites with bioactivity equal to or greater than the parent compound[335] (equations 116 and 117).

A non-labelled metabolite **327** has been discovered[336] in the experiments *in vitro* with **326** ^{14}C-labelled at the carbon atom bearing the nitro group, besides an unidentified polar metabolite retaining the radiolabel.



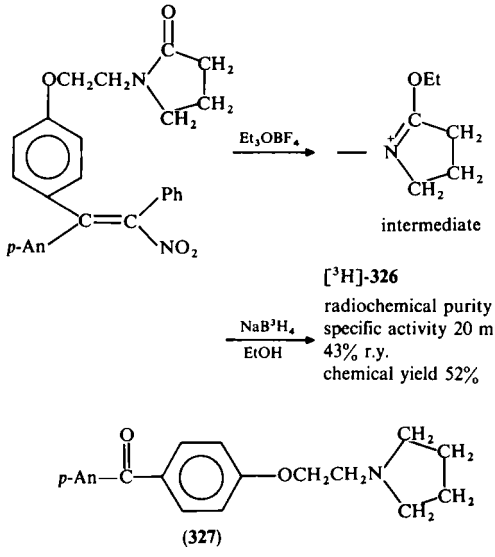
(325) $R^1 = NEt_2$, $R^2 = H$, X = Cl

(326) R^1 = , $R^2 = OMe$, $X = NO_2$



(116)

98% radiochemical purity
34% r.y.
50% chemical yield
specific activity 16 mCi mmol^{-1}



(117)

15. Iterative synthesis of polyethylene glycol oligomers radiolabelled with ^3H

Tritium-labelled homologous series of polyethylene glycols [$H(OCH_2CH_2)_nOH$, PEG, **328**] were needed as 'size standards' for probing the transport pathway of the intestinal epithelium[337,338] and to simplify and expedite sample analysis. The role of molecular size in the determination of intestinal absorption of orally administered drugs had to be resolved also. The synthesis of ^3H-PEG oligomers **328** has been carried out[339] by alkylation of the sodium anion of mono-tritylated ethylene glycol oligomers [$Ph_3C(OCH_2CH_2)_nOH$, $n = 1$–28], **329**, with *O*-tosyl-*O*-allyl-triethylene glycol or *O*-tosyl-*O*-allyl-pentaethylene glycol. Subsequent ozonolysis of the terminal group in **330** followed by reduction with $NaBH_4$ or $NaB[^3H]_4$ provided the next higher mono-tritylated [1-^1H] or [1-^3H] ethylene glycol oligomer **331**, which could be deprotected to the final glycol oligomer [1-^3H]-$H(OCH_2CH_2)_nOH$, **328**, $n = 4$–34, or used to carry on the iterative process (equation 118).

$$\underset{\textbf{(329)}}{Ph_3C(OCH_2CH_2)_nOH} \xrightarrow[TS(OCH_2CH_2)_5OCH_2CH=CH_2]{NaH} \underset{\textbf{(330)}}{Ph_3C(OCH_2CH_2)_{n+5}OCH_2CH=CH_2}$$

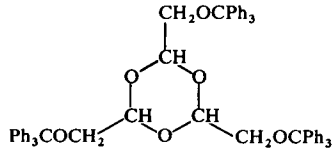
$$\xrightarrow[\text{2. EtOH, } Na_2CO_3, Me_2S, \; NaB[^3H]_4]{\text{1. THF, } Na_2CO_3, \text{ MeOH, } -78\,^\circ C, \text{ ozone, } N_2} \underset{\textbf{(331)}}{[1\text{-}^3H]Ph_3C(OCH_2CH_2)_{n+6}OH}$$

62–87% chemical yield

$$\xrightarrow{HCl, \text{ dioxane, MeOH}} \underset{\textbf{(328)}}{[1\text{-}^3H]H(OCH_2CH_2)_{n+6}OH} \qquad (118)$$

[1-^3H]PEG 97% radiochemical purity

The ozonolysis of the ditritylated compound $Ph_3COCH_2CH{=}CHCH_2OCPh_3$ has been carried out in the presence of sodium carbonate to avoid the formation of the trimer **332** (equation 119). **333** has been prepared as shown in equation 120.



(332)

$$Ph_3COCH_2CH{=}CHCH_2OCPh_3 \xrightarrow[\text{b. } NaBH_4,\ -78\,^{\circ}C \rightarrow 0\,^{\circ}C]{\text{a. } O_3,\ -78\,^{\circ}C,\ EtOH;\ Na_2CO_3,\ Me_2S} Ph_3COCH_2CH_2OH \quad (119)$$

$$H(OCH_2CH_2)_5OH \xrightarrow[\text{2. } p\text{-TsCl, } Et_3N,\ CH_2Cl_2,\ \text{dimethylaminopyridine}]{\text{1. a. NaH, THF, } N_2;\ \text{b. allyl bromide, reflux}} Ts(OCH_2CH_2)_5OCH_2CH{=}CH_2 \quad (120)$$

(333)

The yields and specific activities (in mCi mmol^{-1}) of different ^{3}H-alcohols and ^{3}H-polyethylene glycols **328′** obtained as shown in equation 121 using **330′** as the starting olefin are given in the table accompanying equation 121.

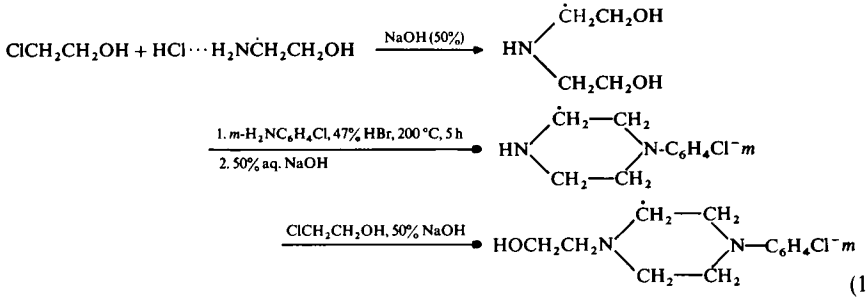
$n' = 3$	^{3}H-(**331′**) 99% yield	^{3}H-PEG (**328′**) 86% yield	specific activity 20.6 mCi mmol^{-1}
9	89	66	40.2
15	44	81	33.2
21	50	60	37.7
27	39	65	40.1
33	44	51	48.6

$$Ph_3C(OCH_2CH_2)_{n'}OCH_2CH{=}CH_2 \longrightarrow \underset{\textbf{(331′)}}{Ph_3C(OCH_2CH_2)_{(n'+1)}OH} \longrightarrow \underset{\textbf{(328′)}}{H(OCH_2CH_2)_{(n'+1)}OH} \quad (121)$$

16. Dual labelling of lobuprofen with tritium and carbon-14

Dual [^{3}H/^{14}C]-labelled lobuprofen, 2-[4-(3-chlorophenyl)-1-[2-^{14}C]piperazinyl]-ethyl 2-(4-isobutylphenyl)propionate (**334**) has been synthesized by esterification of 2-(4-isobutylphenyl[U-^{3}H])propionic acid with 2-[4-(3-chlorophenyl)-1-[2-^{14}C]piperazinyl]ethanol (**336**), to increase the analgesic activity of arylpropionic acid itself[340–342].

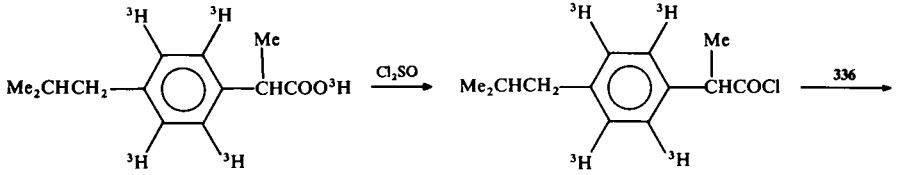
a. ^{14}C-labelled **336** has been prepared as shown in equation 122.

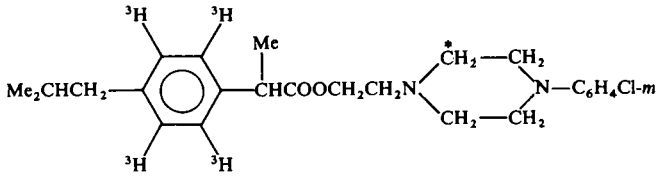


(**336**) specific activity 0.85 mCi mmol^{-1}
24% yield

(122)

b. $^{3}H/^{14}C$ *Lobuprofen* (**334**) has been obtained[340] according to the procedure indicated in equation 123. Total activity of **334** was 0.728 mCi for ^{3}H, 0.234 mCi for ^{14}C. Specific activity was 4.13 mCi mmol^{-1} for ^{3}H and 0.1327 mCi mmol^{-1} (4.91 MBq mmol^{-1}) for ^{14}C.





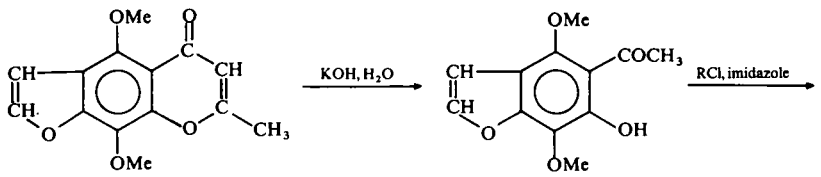
(123)

(**334**) radiochemical purity 98%
chemical purity 99.5%

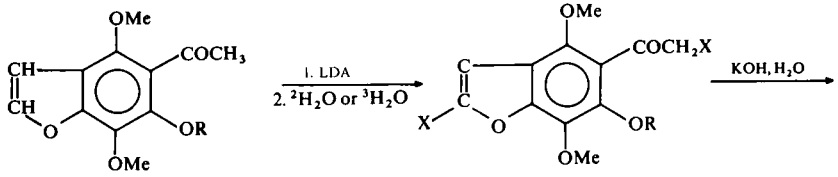
17. Synthesis of tritium, deuterium, ^{14}C- *and* ^{13}C*-labelled timefurone*

Timefurone (**337**), the methyl thioether analogue of khellin (**338**), is a naturally occurring furochromone isolated from *Ammi visnaga L.* which reduces LDL ('low density lipoprotein') and raises HDL ('high density lipoprotein') cholesterol levels in man[343,344]. It has been labelled[345] with tritium and deuterium at the $C_{(2)}$ position and with ^{14}C or ^{13}C at the $C_{(5)}$ position for biotransformation studies.

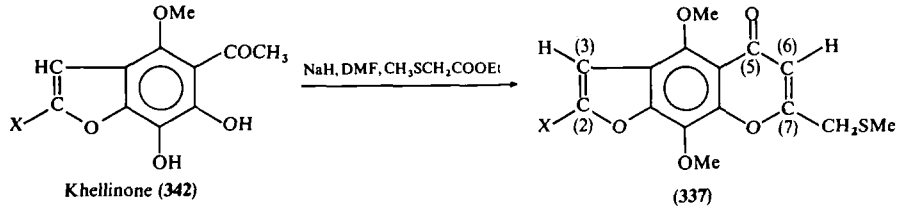
a. Tritium and deuterium labelled **337** have been prepared as shown in equation 124.



Khellin (**338**) (**340**)



(**339**) R = Me_2SiBu-*t* (**341**) X = ^{2}H or ^{3}H



Khellinone (342) (337)

(124)

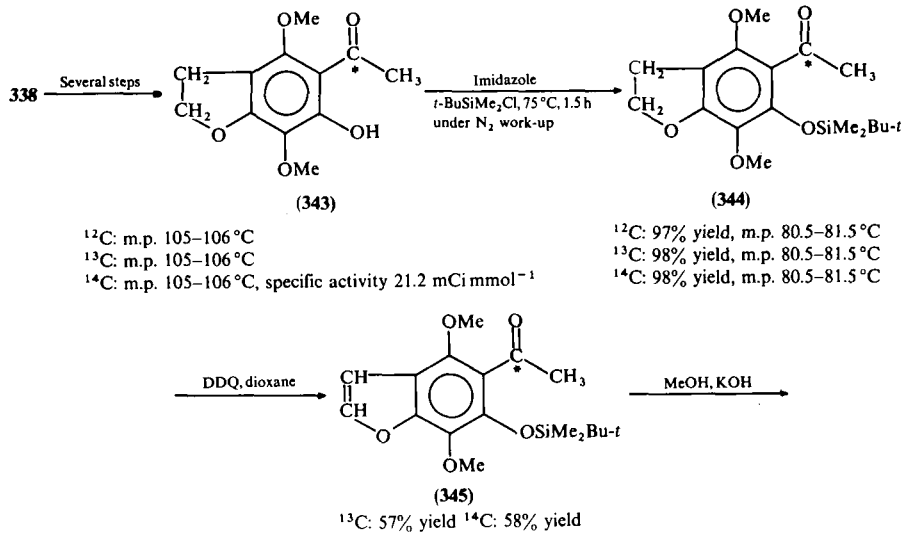
(342)(a) X = ^{2}H, 93%, 85% deuteriation at $C_{(2)}$
(b) X = ^{3}H, 95%, specific activity 103.2 μCi mg^{-1},
(337-^{3}H) X = ^{3}H, specific activity 80.2 μCi mg^{-1}
(337-^{2}H) X = ^{2}H, 71%

Treatment of **339** with LDA afforded a dilithium derivative which underwent deuteriation or tritiation both at $C_{(2)}$ and at the acetyl (methyl) carbon, as indicated in **341**, but in the subsequent step the CH_2D or CH_2T group underwent proton exchange and only the isotope at $C_{(2)}$ remained in the intermediate **342**. The latter was then converted into **337**-^{2}H or **337**-^{3}H.

The kinetics of D/H or T/H exchanges in **340** and **342** or in **337** have not been investigated *in vitro*, although it had been found that the label at $C_{(2)}$ is not exchangeable by subjecting khellinone either to acid or to basic treatment. However, when **337**-^{3}H has been orally and intravenously administered to rats, tritiated water was excreted in the urine indicating the metabolic instability of the label at $C_{(2)}$, which render **337** unsuitable for certain metabolic studies.

The synthesis of **337** labelled with ^{14}C in the metabolically stable $C_{(5)}$ position has therefore been carried out for conducting *in vivo* biotransformation studies with **337**.

b. ^{14}C- and ^{13}C-label had been introduced at the $C_{(5)}$ position of **337** according to equation 125 in a multistep synthesis, including oxidative degradation, reduction,



(343)

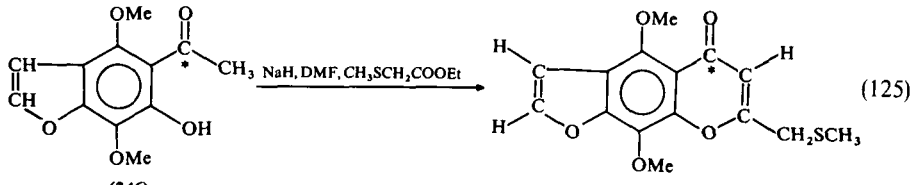
^{12}C: m.p. 105–106 °C
^{13}C: m.p. 105–106 °C
^{14}C: m.p. 105–106 °C, specific activity 21.2 mCi mmol^{-1}

(344)

^{12}C: 97% yield, m.p. 80.5–81.5 °C
^{13}C: 98% yield, m.p. 80.5–81.5 °C
^{14}C: 98% yield, m.p. 80.5–81.5 °C

(345)

^{13}C: 57% yield ^{14}C: 58% yield



(125)

(346)

^{13}C: 99% yield, m.p. 101.5–102.5 °C
^{14}C: 99% yield, m.p. 101.5–102.5 °C

(337—^{13}C) 70%, m.p. 150.5–152 °C
(337—^{14}C) 67.3% from **346**, m.p. 151–152 °C, total r.y. 33.8 mCi, specific activity 14.4 μCi mg^{-1}

decarboxylation, acylation, Fries rearrangement[346], treatment with DDQ, removal of the protecting silyl groups and, finally, condensation with ethyl methylthioacetate and cyclization to the ^{13}C- and ^{14}C-labelled products **337**.

V. DEUTERIUM, OXYGEN-18, CARBON-14 AND CARBON-13 TRACER AND NMR STUDIES OF THE MECHANISM OF CATALYTIC SYNTHESES OF ALCOHOLS AND HIGHER OXYGENATES FROM CO/H_2 AND CO_2/H_2O MIXTURES

The catalytic synthesis of alcohols from carbon monoxide and hydrogen has been frequently studied since the 1930s using alkalized zinc-chromium catalysts[347b,c], alkali-promoted Fischer–Tropsch catalysts[348], alkali-doped Cu/ZnO catalysts[349–365], group VIII promoted copper-based catalysts[366,367] and alkali-doped MoS_2 or alkali-doped Co/MoS_2 sulphur-resistant catalysts[364]. The mechanism of catalytic methanol synthesis and the mechanism of carbon–carbon bond formation in steps involving addition of one or more carbon atoms has been investigated using hydrogen, oxygen and carbon isotope labelling[351,352,359,364] and trapping of intermediates with amines and aldehydes.

A. Deuterium, Oxygen-18, Carbon-14 and Carbon-13 Studies of the Mechanism of Methanol Formation from Synthesis Gas

The reversible reactions given in equations 126–128 proceed simultaneously during industrial methanol synthesis employing the H_2/CO/CO_2 feed stream. A view has been expressed that these reactions may have a common intermediate. Formate or formyl intermediates have been suggested and identified by IR spectroscopy[368] in the water–gas shift reaction 126, as well as in the reaction of CO with H_2 and of CO_2 with H_2 over ZnO. A formyl intermediate from H_2/CO on co-adsorption on Cu/ZnO catalyst has been identified also by NMR[369a]. Originally, a hydroxycarbene [HC(OH)] route was proposed for its formation[369b], $CO + H_2 \rightarrow HC(OH)$, but it was rejected on thermodynamic grounds[349b]. Formyl groups may be formed directly from CO/H_2 or by hydrogenation of the formate (equations 127a, 127b and 128a). The formyl path is supported by ^{13}C experiments. Using a mixture of $^{13}C^{16}O$ and $^{12}C^{18}O$ over Rh/TiO_2 catalyst, $^{13}CH_3{}^{16}OH$ and $^{12}CH_3{}^{18}OH$ have been produced but not $^{13}CH_3{}^{18}OH$ and $^{12}CH_3{}^{16}OH$[369b]. The Cu/ZnO catalyst promotes the rapid scrambling of $^{13}C^{16}O$ and $^{12}C^{18}O$, accelerated by pre-adsorbed water pointing to the reversible formate mechanism (equations 127b and 128a). The path of equation 128a as a primary one under industrial conditions has been documented also in subsequent hydrogenations of $^{12}CO/^{14}CO_2$ and $^{14}CO/^{12}CO_2$ mixtures to methanol with the Cu/ZnO/Al_2O_3 catalyst[352b–e,373].

$$H_2O + CO \rightleftharpoons CO_2 + H_2$$
$$\Delta H_{600\,K} = -38.7\ \text{kJ mol}^{-1} \qquad (126)$$
$$\Delta G_{600\,K} = -16.5\ \text{kJ mol}^{-1}$$

$$2H_2 + CO \rightleftharpoons CH_3OH$$

$$\Delta H_{600\,K} = -100.46\,kJ\,mol^{-1} \quad (127)$$

$$\Delta G_{600\,K} = +45.36\,kJ\,mol^{-1}$$

$$3H_2 + CO_2 \rightleftharpoons CH_3OH + H_2O$$

$$\Delta H_{600\,K} = -61.59\,kJ\,mol^{-1} \quad (128)$$

$$\Delta G_{600\,K} = +61.80\,kJ\,mol^{-1}$$

$$CO + H^- \longrightarrow HCO^- \quad (127a)$$

$$CO + HO^- \longrightarrow HCOO^- \quad (127b)$$

$$CO_2 + H^- \longrightarrow HCOO^- \quad (128a)$$

The mechanistic relationship between methanol synthesis and the water–gas shift reaction has been studied with the use of $H_2{}^{18}O$ and D_2O. The yield of CH_3OH passes through a maximum (at low H_2O concentration) with increasing concentration of water in the inlet synthesis gas, while the concentration of CO_2 increases monotonously in the temperature interval 190–235 °C with increase of the water added to the synthesis gas ($H_2/CO = 70/30$ vol%) at 75 atm and with gas hourly space velocity of 6120 liters (STP) (kg catalyst)$^{-1}$ h^{-1} over a reduced Cu/ZnO (30/70) catalyst. The optimum concentration of water in the H_2/CO mixture depends on temperature.

Addition of $H_2{}^{18}O$ to the synthesis gas resulted in a much higher ^{18}O content in MeOH (and partly in the carbon dioxide) than in carbon monoxide. This indicates that water and carbon dioxide form a kinetically significant intermediate for incorporation of oxygen into methanol. The presence of $C^{18}O$ in the exit gas is in agreement with the reversible character of the reactions 126 and 127, but $H_2{}^{18}O$ is converted to the products at a faster rate than the exchange reaction. A 17.3% loss of ^{18}O during the exchange experiment is caused by isotopic exchange with surface ZnO.

The kinetic and mechanistic role of water has been studied also by adding D_2O to the H_2/CO synthesis gas stream and determining the distribution of deuterium in the exit gas products, when no $CHD_2O\overset{*}{H}$ or $CD_3O\overset{*}{H}$ ($\overset{*}{H}$ = H or D) has been found. The rates of formation of $CH_3O\overset{*}{H}$, $CH_2DO\overset{*}{H}$ ($\overset{*}{H}$ = H or D) and of HD over 2.45 g of Cu/ZnO 30/70 catalyst at 225 °C were equal to 63.0, 9.8 and 10.2 mmol h^{-1}, respectively. The H/D exchange between D_2O and H_2 or between D_2O and MeOH in the presence of the Cu/ZnO catalyst has not been investigated, but nevertheless the above kinetic results indicate a primary transfer of deuterium from D_2O to the resultant methanol via a reactive intermediate (equations 129a and b). Water is a source of hydrogen in the methyl group. Excess of water inhibits methanol formation by blocking the catalytic sites which activate the hydrogen required for the hydrogenation of the $DCOO^-$ intermediate common for both reactions 126 and 127. Reaction 126 is not retarded by the excess of water, because it requires the decomposition of the $DCOO^-$ intermediate only and activation of hydrogen is not necessary.

$$D_2O \longrightarrow OD^-_{(ads)} + D^+_{(ads)} \quad (129a)$$

$$OD^-_{(ads)} + CO \longrightarrow DCOO^-_{(ads)} \quad (129b)$$

$$DCOO^-_{(ads)} + 2H_2 \longrightarrow CH_2DOH + OH^-_{(ads)} \quad (129c)$$

No equilibration of the 50/50 $^{13}C^{16}O/^{12}C^{18}O$ mixture (at 274 torr) over pure ZnO has been observed, neither was any ^{18}O exchange between CO and ZnO found. In the course of the rather fast equilibration of a $^{13}C^{16}O/^{12}C^{18}O$ mixture over a Cu/ZnO catalyst pretreated with water, incorporation of ^{18}O into the catalyst took place. The intensity of the two hydroxyl overtone bands ($2\nu = 7205$ and 7278 cm^{-1}) sharply decreased,

indicating a reaction between the hydroxyl groups and carbon monoxide. Thus water has an evident effect on CO activation. The exchange reactions proceed via the associative mechanism of equations 130a and 130b:

$$HO^-\,(7205\,cm^{-1}) + CO \longrightarrow HCOO^- \tag{130a}$$

(fast exchange between CO and more reactive surface hydroxyl groups and fast scrambling of oxygen between $^{13}C^{16}O$ and $^{12}C^{18}O$)

$$HO^-\,(7278\,cm^{-1}) + CO \longrightarrow HCOO^- \tag{130b}$$

(slow exchange of oxygen between CO and the less reactive, slightly more strongly bound surface hydroxyl groups with a higher wave number, which is however still lower than that of reference hydroxyls on silica, equal to $7353\,cm^{-1}$)[370].

Weakening of the O—H bonds is associated with their reactivity toward CO. The associative mechanism of the isotope scrambling between carbon monoxide molecules is also supported by the lack of CO dissociation over copper mixed with oxides at room temperature. The dissociative scrambling of CO should be suppressed by hydroxylation of the catalyst surface[370].

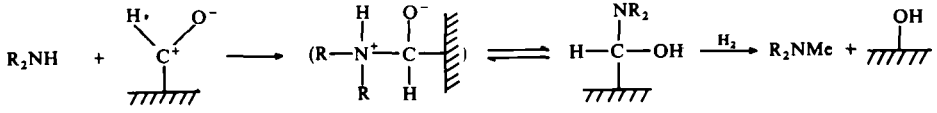
Diethylamine introduced into the inlet stream of H_2/CO (Cu/ZnO catalyst at 215 °C) was methylated rapidly to methyldiethylamine (equation 131):

$$Et_2NH + CO + 2H_2 \longrightarrow Et_2NMe + H_2O \tag{131}$$

The C_1 surface intermediate reacted also with propanal added to the H_2/CO synthesis gas, yielding 2-methyl-1-propanol (equation 132):

$$EtC\overset{O}{\underset{H}{<}} + CO + 3H_2 \longrightarrow Me_2CHCH_2OH + H_2O \tag{132}$$

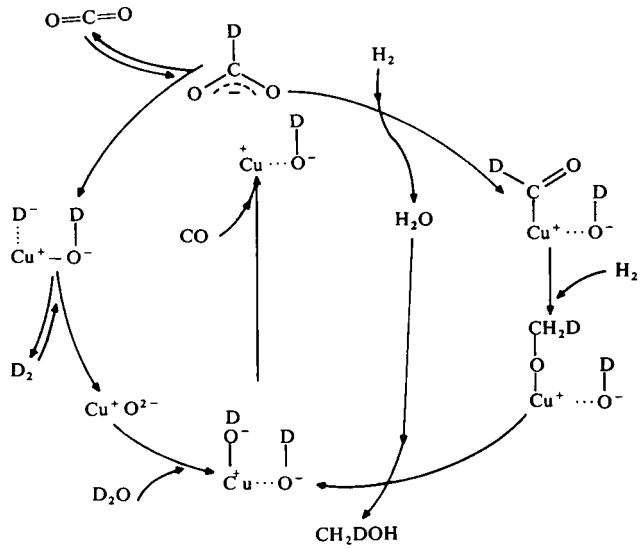
The amination of the surface intermediate competed with its hydrogenation to form methanol, but did not interfere with the water–gas reaction. This means that a C_1 intermediate (surface-bound formyl or hydroxycarbene) is produced in the subsequent step from the formate and reacts with amines[371] as shown in equation 133.



(133)

Admitting that the reactive hydroxyl species are linked to the copper species[372], albeit hydrogenation of CO_2 to methanol is occurring also, the scheme of equation 134 has been proposed as the mechanistic cycle for incorporation of water into methanol responsible for at least 65% of the methanol yield[351] from $CO/H_2 + H_2O$.

^{14}C-labelling experiments carried out at 250 °C under 52 atm, with the inlet gas consisting of 10% CO, 10% CO_2 and 80% H_2 using Cu/Zn/Al catalyst under typical plant conditions, showed[352] that almost all of the methanol was synthesized directly from [^{14}C]carbon dioxide and not from carbon monoxide. Reaction with carbon monoxide proceeds at a slow rate in the absence of carbon dioxide[374]. Formate species were found to co-exist both on the copper and on the zinc oxide components of the catalyst, the former being more active. Mobility of the —CHO group from oxygen to cation (equation 135) and its different reactivity depending on the 'anchor' (Cu^+, Zn^{2+}, etc.) has been suggested and discussed[375,376].



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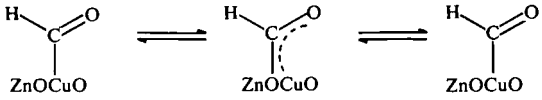


(135)

The mechanism of the formate formation[378] on the Cu/ZnO and CsOH doped Cu/ZnO catalysts has been investigated spectroscopically and theoretically[379]. Nucleophilic attack on CO by HO^- (equation 136) is followed by the intramolecular hydrogen transfer (equation 137) proceeding through a triangular transition state (T.S.) as shown on the MNDO energy diagram (Figure 1), which comprises also the structures of metalloformate **347** and formate **348.**

$$HO^- + CO \longrightarrow H\overset{\frown}{\underset{\frown}{-O-C-O}}^- \tag{136}$$

$$H\overset{\frown}{\underset{\frown}{-O-C-O}} \longrightarrow HCOO^- \tag{137}$$

Isotope effect studies of the transition state structure and of the isotopic exchanges in the $CO/H_2/CsOH/Cu/ZnO/HCOOCs$ system have not been carried out so far. Carbon-14 exchange and transport in the two, three and four component systems: '$^{14}CO_2$–CO-quartz walls', '$^{14}CO_2$–CO–NO_x(Ar, N_2, O_2)-quartz walls', '$^{14}CO_2$–CO–H_2' and 'CO_2–^{14}CO–H_2', and related ^{13}C kinetic isotope effects have been investigated[380–385].

The ion-specific promotion[355] of the Cu/ZnO catalysts for highly selective (89.9%) methanol synthesis is as Cs > Rb > K > Na > Li. The methanol yield passes through a flat maximum with increase of the cesium loading in the case of both Cu/ZnO and MoS_2 catalysts. This is in agreement with their bifunctional character owing to which activation of CO (proportional to $\theta_{(Cs)}$, i.e., the part of the Cu/ZnO surface covered with Cs) and the activation of hydrogen for the conversion of $HCOO^-$ to CH_3O^- (proportional to $(1 - \theta_{(Cs)}$, i.e., to the free Cu/ZnO surface)) must be balanced. New homogeneous catalysts

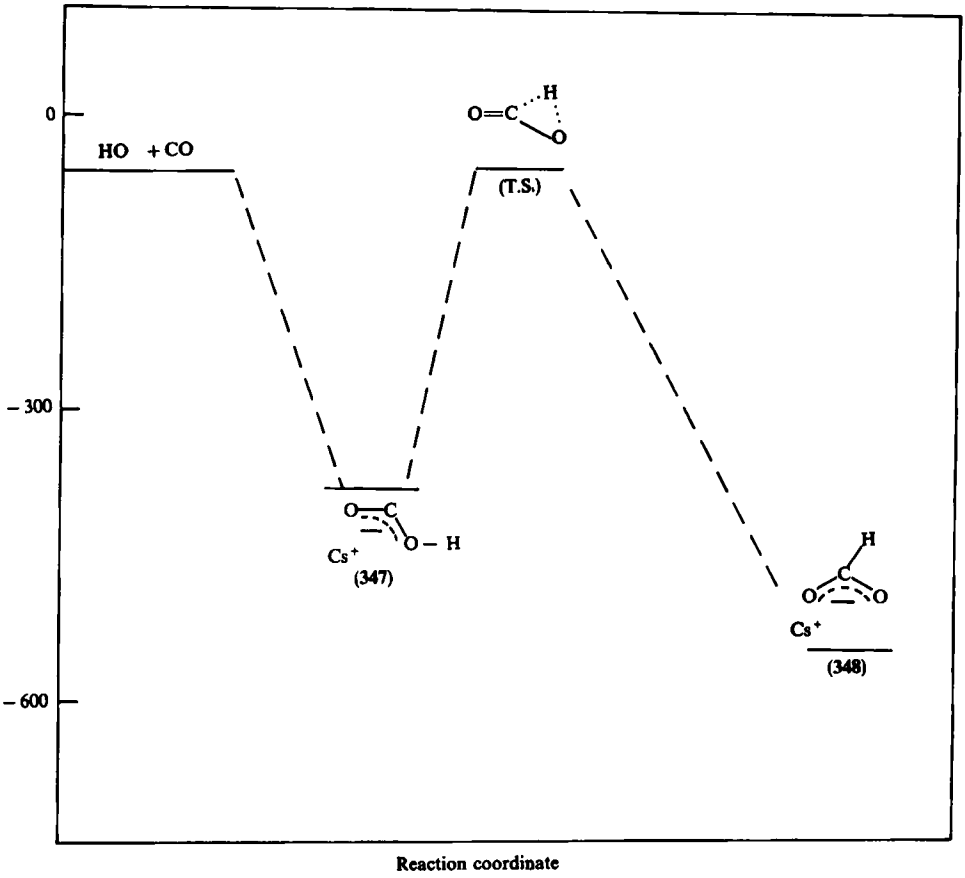
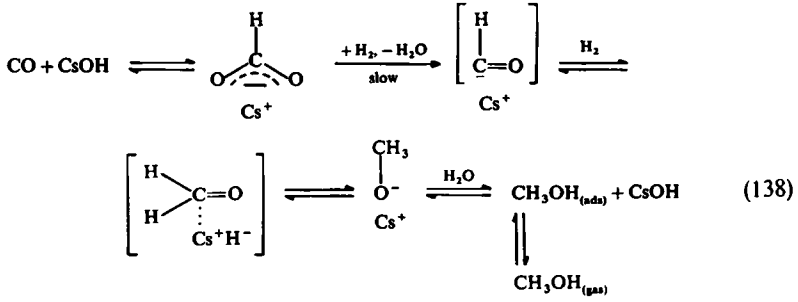


FIGURE 1. MNDO energy diagram for formate formation from carbon monoxide and hydroxide

(possessing bifunctional character) for MeOH synthesis consist of a Cu^+ compound and an alkali methoxide, when the nucleophilic attack, $MeO^- + CO \longrightarrow MeOCO^-$, is followed by hydrogenation of the metallocarboxylate with copper hydride, CuH. IR



(138)

studies of the role of Cs^+ in CO activation via association with its HO^- counterions led to the formulation of the scheme shown in equation 138 for the methanol synthesis[358]. However, the possibility of hydride association not with cesium but with a copper species or as a CuH moiety is not excluded. A dispersed Cu/ZnO catalyst for selective low-temperature (< 573 K), low pressure (< 10 kPa) is produced by calcination and reduction of the hydroxy carbonate, $(Cu_{0.3}Zn_{0.7})_5(OH)_6(CO_3)_2$.

High methanol productivity and stabilization of the catalyst against deactivation is achieved by surface doping of the Cu/ZnO catalyst with alkali metal, for instance in the form of cesium hydroxides or formates. For a H_2/CO ratio less than 1.0, the selectivity from > 98% methanol is shifted toward the synthesis of higher alcohols, especially 1-propanol and 2-methyl-1-propanol[363] (equation 139).

$$^{12}CH_3{}^{13}CH_2OH + {}^{12}CO/H_2 \longrightarrow {}^{13}CH_3{}^{12}CH_2{}^{12}CH_2OH \qquad (139)$$

Klier and coworkers investigated recently[362] the solid-state chemistry, morphology and stability of $Cs/Cu/ZnO/M_2O_3$ systems (where M = Al, Cr, Ga) for methanol synthesis to determine the causes of the long-lasting catalytic activity for M = Cr and severe deactivation for M = Al, Ga.

B. Isotopic Studies of the Mechanism of the Catalytic Synthesis of C_1–C_4 and Higher Alcohols

Besides the main reactions 126–128, other reactions which occur involve synthesis of methyl formate (equation 140):

$$2\,CO + 2\,H_2 \longrightarrow HCOOMe \qquad (140)$$

synthesis of saturated higher alcohols (equation 141):

$$n\,CO + 2n\,H_2 \longrightarrow C_nH_{2n+1}OH + (n-1)H_2O \qquad (141)$$

as well as formation of dehydrogenation products, aldehydes and ketones and also methyl and other esters (equation 142):

$$(n+1)CO + 2n\,H_2 \longrightarrow C_{n-1}H_{2n-1}COOMe + (n-1)H_2O \qquad (142)$$

and formation of dimethylether (equation 143):

$$2\,CH_3OH \longrightarrow CH_3OCH_3 + H_2O \qquad (143)$$

and of higher ethers and hydrocarbons, in quantities determined by the nature of the catalyst and the reaction conditions[348,349,359]. The higher alcohols and esters produced over methanol catalysts are used for conversion to aromatic gasoline or olefins over a zeolite class of acid catalysts[377].

1. The mechanism of methyl formate formation

It has been suggested[358] that the synthesis of methyl formate proceeds at the initial steps of higher oxygenate synthesis over Cs/Cu/ZnO catalyst and may involve one of more of five possible mechanisms (equations 144–148). The possible pathways are direct carbonylation of methanol (equation 144)[386–388]:

$$CH_3OH + CO \longrightarrow HCOOCH_3$$

$$\Delta G^\circ_{523} = +33{\cdot}4\ \text{kJ mol}^{-1}$$
$$\Delta H^\circ_{523} = -37{\cdot}77\ \text{kJ mol}^{-1} \qquad (144)$$
$$K_{eq\,523} = 4{\cdot}614 \times 10^{-4}$$

dehydrogenative coupling[389] of two methanol molecules (equation 145):

$$2\,MeOH \longrightarrow HCOOMe + 2H_2$$

$$\Delta G^\circ_{523} = +6{\cdot}62\,kJ\,mol^{-1}$$
$$\Delta H^\circ_{523} = +60{\cdot}46\,kJ\,mol^{-1} \qquad (145)$$
$$K_{eq\,523} = 2{\cdot}18 \times 10^{-1}$$

formaldehyde dimerization (Tischenko reaction):

$$2\,HCHO \longrightarrow HCOOCH_3$$

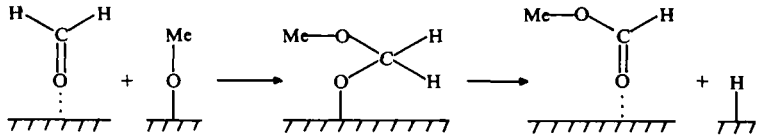
$$\Delta G^\circ_{523} = -46{\cdot}77\,kJ\,mol^{-1}$$
$$\Delta H^\circ_{523} = -116{\cdot}44\,kJ\,mol^{-1} \qquad (146)$$
$$K_{eq\,523} = 4{\cdot}69 \times 10^{4}$$

esterification of formic acid with methanol (equation 147):

$$HCOOH + MeOH \longrightarrow HCOOMe + H_2O$$

$$\Delta G^\circ_{523} = -13{\cdot}39\,kJ\,mol^{-1}$$
$$\Delta H^\circ_{523} = -9{\cdot}54\,kJ\,mol^{-1} \qquad (147)$$
$$K_{eq\,523} = 2{\cdot}147 \times 10^{1}$$

and finally a hemiacetal mechanism[355,390–393] with surface-bound species (equation 148):



The actual mechanism of the HCOOMe synthesis has been established by injecting isotopically labelled ^{13}C-enriched methanol into the synthesis gas and detecting the appearance of ^{13}C in the methyl group of methyl formate by ^{13}C NMR. The latter showed that the carbon monoxide reacted with the methanol as illustrated by equation 149:

$$\overset{*}{M}eOH + CO/H_2 \longrightarrow HC(=O)-O\overset{*}{M}e \qquad (149)$$

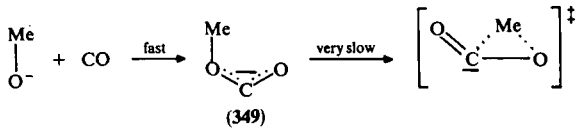
where * denotes ^{13}C enrichment

The carbonyl carbon in methyl formate originated from carbon monoxide and not from [^{14}C]methanol.

An additional mechanism (equation 150) has been proposed[358] for the Cs dopant on the Cu/ZnO catalyst.

$$CsOH + MeOH \underset{+H_2O}{\overset{-H_2O}{\rightleftharpoons}} \underset{Cs^+}{\overset{Me}{\overset{|}{O^-}}} \xrightarrow{CO} \underset{Cs^+}{\overset{Me}{\overset{|}{O}}}\!\!-\!\!\underset{|}{C}\!=\!O \underset{-H_2O}{\overset{+H_2O}{\rightleftharpoons}} HCOOMe + CsOH \qquad (150)$$

There is no activation barrier for the strongly exothermic facile nucleophilic attack on CO by the methoxide anion (equation 151) but an activation energy of 257 kJ mol^{-1} is required for the methyl transfer in the intermediate (**349**) leading to carbon–carbon bond formation[394]. Therefore, methyl formate is formed mainly by the more favourable hydrolytic pathway of equation 150, before the thermodynamically more stable acetate is obtained according to equation 151. The formation of HCOOMe by direct esterification of adsorbed formate by MeOH has been rejected due to considerable steric hindrance in equation 152:



(**349**) (151)

$$HCOO^- + \overset{*}{M}eOH \longrightarrow HCO\overset{*}{O}Me + HO^- \qquad (152)$$

The 'hemiacetal' route (equation 148) has also been rejected because isotopic equilibration between the adsorbed formaldehyde and [^{13}C]methanol should give methyl formate, ^{13}C-labelled both in the methyl and the carbonyl group contrary to the ^{13}C NMR results.

The gas-phase decomposition of $HCO_2{}^{14}CH_3$ in quartz vessels has been studied by Zieliński and Kamińska[407,408]. The decomposition of ^{14}C-labelled methyl formate in the presence of Cs/Cu/ZnO catalysts has not been investigated.

2. *The mechanism of catalytic production of ethanol*

Several pathways have been proposed for the catalytic synthesis of ethanol. These include direct synthesis from CO/H_2 (over Rh-supported catalysts)[395–397]:

$$2\,CO + 4\,H_2 \longrightarrow EtOH + H_2O \qquad (153)$$

homologation of methanol by CO/H_2 (in Fischer–Tropsch and other syntheses)[398–403]:

$$MeOH + CO + 2\,H_2 \longrightarrow EtOH + H_2O \qquad (154)$$

coupling of two methanol molecules (equation 155)[404]:

$$2\,MeOH \longrightarrow EtOH + H_2O \qquad (155)$$

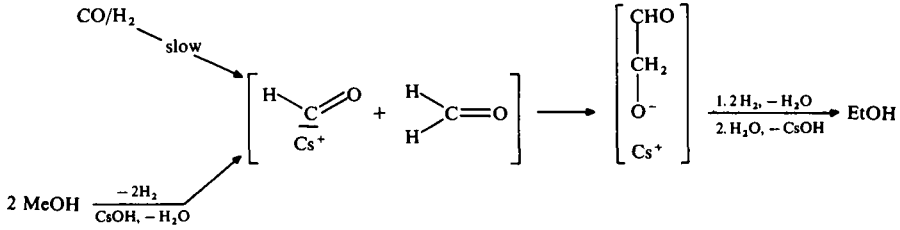
and the aldehyde coupling reaction[405] (equation 156):

$$2\,MeOH \xrightarrow{-2H_2} 2\,H_2CO \longrightarrow HOCH_2CHO \xrightarrow[-H_2O]{2H_2} EtOH \qquad (156)$$

Injection of $^{13}CH_2OH$ into the CO/H_2 synthesis gas stream[358] yielded doubly labelled ethanol over Cu/ZnO and Cs/Cu/ZnO catalysts (equation 157):

$$^{13}CH_3OH + CO/H_2 \xrightarrow[Cs/Cu/ZnO]{} {}^{13}CH_3{}^{13}CH_2OH\,(+CO/H_2) \qquad (157)$$

This result rules out the mechanisms of equations 153 and 154, but is consistent with dominance of the routes of equations 155 and 156 and with the aldehyde coupling reactions illustrated by equations 156 and 158. This mechanism involves a nucleophilic attack of an adsorbed formyl group on the electropositive carbon of an adsorbed formaldehyde molecule. Relatively low temperatures and high H_2/CO ratios are required to maintain the high methanol selectivity. The production of higher oxygenates becomes more significant as the temperature increases and the H_2/CO ratio decreases.

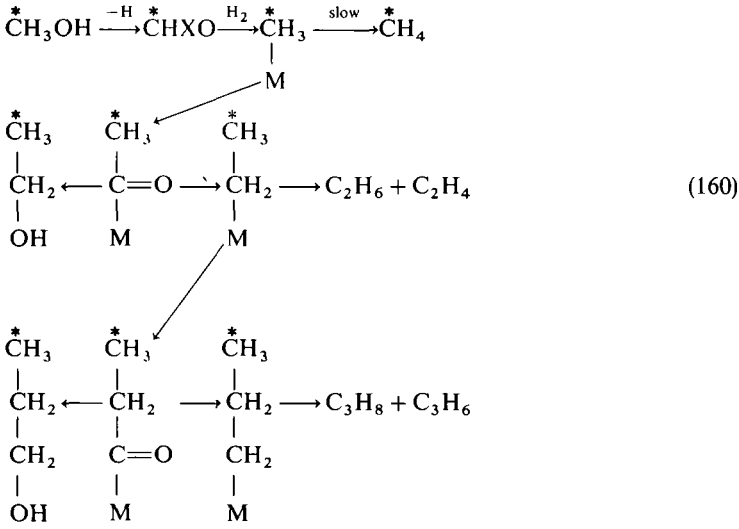


(158)

Injection of $^{13}CH_3OH$ yielded only β-labelled ethanol over Cs/MoS_2 and $Cs/Co/MoS_2$ catalysts as shown in equation 159:

$$^{13}CH_3OH + {}^{12}CO/H_2 \xrightarrow[Cs/(Co)/MoS_2]{} {}^{13}CH_3{}^{12}CH_2OH \qquad (159)$$

This last result indicates that carbon monoxide insertion is a feasible path for linear alcohol growth over MoS_2 catalysts as depicted in equation 160. The addition of cobalt to the catalyst enhanced the rate of the C_1–C_2 growth step and ethanol became the dominant product[406].



(160)

3. Mechanisms of higher alcohol and oxygenate synthesis

a. Synthesis of different isotopic 1-propanols. Isotopic tracer studies contributed greatly to the establishment of the mechanism of C—C bond formation in ethanol[355,359–361,363] over Cu/Zn and Cs/Cu/ZnO catalysts. Injection of isotopically labelled ethanol $CH_3{}^{13}CH_2OH$ (24% ^{13}C at $C_{(1)}$) or of $EtOH/{}^{13}CH_3OH$ (100% ^{13}C) mixtures into the continuous flow reactor operating at 523–583 K followed by ^{13}C NMR analysis of the ^{13}C enrichment in the products MeOH, EtOH, *n*-PrOH and $Me_2CHCHOH$ showed that over the non-doped Cu/ZnO catalyst the ^{13}C label from the $C_{(1)}$ carbon of EtOH incorporates preferentially into the $C_{(2)}$ carbon of 1-propanol and into the $C_{(2)}$ position of 2-methyl-1-propanol in the subsequent reaction steps (equation 161)[360]. This is in

agreement with the classical aldol condensation mechanism, followed by partial dehydration and hydrogenation of the product (equation 162).

$$CH_3{}^{13}CH_2OH + CH_3OH \xrightarrow[Cu/ZnO]{H_2/CO} CH_3{}^{13}CH_2CH_2OH \xrightarrow[Cu/ZnO]{CH_3O(H)} \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>{}^{13}CHCH_2OH \quad (161)$$

$$RCH_2{}^{13}CHO + \begin{matrix} H \\ H \end{matrix}\!\!>C=O \xrightarrow[+H_2]{-H_2O} \underset{\displaystyle Me}{RCH^{13}CHO} \xrightarrow{+H_2} \underset{\displaystyle Me}{RCH^{13}CH_2OH} \quad (162)$$

Contrary to the reaction path of equation 161, injection of $Me^{13}CH_2OH$ over Cs/Cu/ZnO catalyst produced at 573 K 1-propanol enriched primarily in the $C_{(3)}$ position by β-carbon addition (equation 163). The routes of equations 164 and 164a have been proposed[359,360] for the synthesis over the Cs/Cu/ZnO catalyst, where 'M' is the catalyst or H in the surface-bonded formaldehyde. Injection of unlabelled EtOH mixed with $^{13}CH_3OH$ provided $Et^{13}CH_2OH$ both over the non-doped and over the cesium-doped catalysts (equation 165).

$$CH_3{}^{13}CH_2O(H) + CH_3OH \xrightarrow[Cs/Cu/ZnO]{CO/H_2} {}^{13}CH_3CH_2CH_2OH \xrightarrow{MeO(H)} \begin{matrix} Me \\ {}^{13}CH_3 \end{matrix}\!\!>CHCH_2OH \quad (163)$$

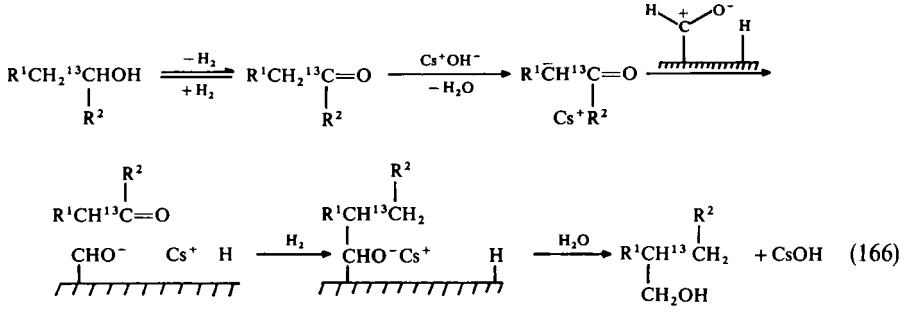
$$CH_3{}^{13}CH_2OH \underset{+H_2}{\overset{-H_2}{\rightleftharpoons}} CH_3{}^{13}CHO \underset{H^+}{\overset{-H^+}{\rightleftharpoons}} CH_2{=}{}^{13}CHO^- \xrightarrow[\beta\text{-addition}]{H_2CO}$$

$$[{}^-OCH_2CH_2{}^{13}CHO] \xrightarrow[-H_2O]{2H_2} {}^-OCH_2CH_2{}^{13}CH_3 \xrightarrow{H^+} HOCH_2CH_2{}^{13}CH_3 \quad (164)$$

$$RCH_2{}^{13}CHO + \begin{matrix} H \\ M \end{matrix}\!\!>C=O \xrightarrow[+H_2]{-MHO} \underset{\displaystyle CHO}{RCH^{13}CH_3} \xrightarrow{+H_2} \underset{\displaystyle CH_2OH}{RCH^{13}CH_3} \quad (164a)$$

$$EtOH + {}^{13}CH_3OH \xrightarrow[\text{or } Cs/Cu/ZnO,(CO/H_2)]{Cu/ZnO,(CO/H_2)} Et^{13}CH_2OH \quad (165)$$

The retention of oxygen of 'C_1' intermediate is probably caused by the strong bonding of the H_2CO^- group of the dioxygenated intermediate anion to the Cs^+ cations preventing hydrogenation of the free —CHO group to yield a ^{13}C methyl group as shown in equation 166.



(166)

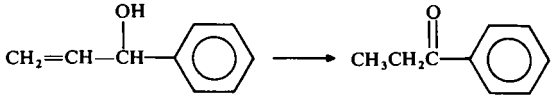
A more detailed discussion of the reaction pathways leading to formation of ^{13}C-enriched EtOH, *n*-PrOH, Me_2CHCH_2OH, *n*-butanol, (Me)(Et)CHOH and (Et)CH(Me)CH_2OH molecules over Cu/ZnO and over a Cs/Cu/ZnO catalyst, produced by injecting into the synthesis gas MeOH and EtOH enriched by ^{13}C in specific positions, as well as an analysis of routes leading to higher alcohols has been presented by Klier and coworkers[363]. A comparative study of higher alcohol and oxygenate syntheses over the industrial $Cs/Cu/ZnO/M_2O_3$ (M = Al, Cr) catalysts has also been published[361].

b. Synthesis of 1-propanol over alkali/MoS_2 and alkali/Co/MoS_2 catalysts. In this case the $C_2 \rightarrow C_3$ step is realized[359] by linear growth through CO insertion (equation 166a).

$$^{13}CH_3CH_2OH + CO/H_2 \xrightarrow[Cs/(Co)/MoS_2]{} {}^{13}CH_3CH_2CH_2OH \qquad (166a)$$

Earlier ^{14}C mechanistic studies of the catalytic syntheses of alcohols (and hydrocarbons) have been reviewed by Eidus[409], and by Derbentsev and Isagulyants[410]. The steam reforming of methane over nickel catalysts has been investigated with the use of D_2O[411].

c. Deuterium tracer and isotope effect study of the mechanism of double-bond migration in 3-functional substituted propenes in the presence of ruthenium tris(2,4-pentanedionate) has been carried out recently[412,413] (equation 166b).

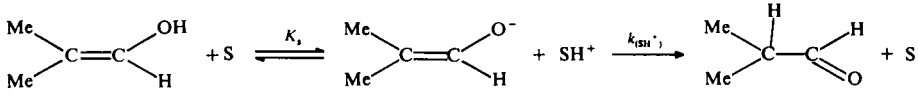


(166b)

Stable simple polyaryl-substituted enols have also been investigated with the use of deuterium[414] (equation 166c):

$$R^3R^2CH{-}C(=O){-}R^1 \underset{}{\overset{K_{Enol}}{\rightleftharpoons}} R^3R^2C{=}C(OH)R^1 \qquad (166c)$$

The large value of $(k_{(CH_3OH)}/k_{(CD_3OD)}) = (1.3 \pm 0.2) \times 10^{-4}/(5.3 \pm 0.5) \times 10^{-6}) = 24.5$, found in ketonization of 2-methylprop-1-en-1-ol in non-aqueous solvents at 27 °C, has been interpreted as supporting[415] the mechanism illustrated by equation 166d.



(166d)

The value 24.5 is considered as the product of the equilibrium isotope effect for the first step (K_S) and the kinetic isotope effect for the second step (k_{SH^+}), protonation of carbon. A relatively large value $k_{H_2O}/k_{D_2O} = 12$, observed in the ketonization of vinyl alcohol, has been interpreted similarly[416]. The possibility of tunnelling in the protonation of carbon has not been investigated. The primary deuterium isotope effect in the base-catalysed enolization of acetone has been described for a student laboratory experiment[417].

VI. ISOTOPE EFFECT STUDIES OF CHEMICAL REACTIONS

A. Deuterium, Carbon-14 and Oxygen-18 Isotope Effect Studies of Claisen Rearrangements

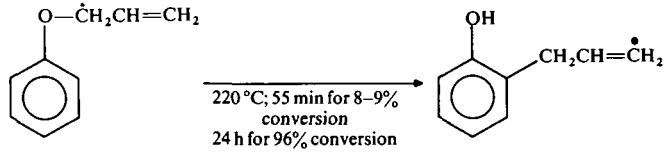
α-Dideuterio- and γ-dideuterio-allyl phenyl ethers[418], were obtained[419,420] as shown in equations 167 and 168. The values determined for the kinetic isotope effects (K.I.E.),

$(k_H/k^{\alpha}_{D_2}) = 1.18 \pm 0.02$ and $(k_H/k^{\gamma}_{D_2}) = 0.95 \pm 0.02$, respectively, in the temperature range 170–195 °C, led to the conclusion that, in the transition state of the claisen rearrangement, breaking of the C_α—O bond had proceeded to a greater extent than the forming of the C_γ—C_{ortho} bond. The bond orders of these bonds in the transition structure were calculated to be respectively 0.23–0.43 (for C_α—O) and 0.22–0.62 (for C_γ—C_{ortho}). The view has been expressed[421] that deuterium K.I.E. are incapable of throwing light on the synchronicity of such rearrangements and the discussion concerning the T.S. structures in sigmatropic rearrangements has been continued[422]. A single-temperature (220 °C) heavy-atom K.I.E. study of the rearrangement of allyl phenyl ether (equation 169), labelled severally with ^{18}O and with ^{14}C at α-C, γ-C and *ortho*-C, has therefore been carried out. The experimental ^{18}O-, ^{14}C- and ^{2}H-K.I.E. values were compared with the theoretical ones for these isotopes, calculated assuming different transition state struetures[423].

$$CH_2{=}CHCD_2Cl + PhOH \xrightarrow[\text{acetone}]{K_2CO_3} CH_2{=}CHCD_2OPh \qquad (167)$$

$$PhOCH_2CH_2CONMe_2 \xrightarrow{LiAlD_4} PhOCH_2CH_2CD_2NMe_2 \xrightarrow{MeI}$$

$$PhOCH_2CH_2CD_2NMe_3{}^+I^- \xrightarrow{Ag_2O} PhOCH_2CH{=}CD_2 \qquad (168)$$



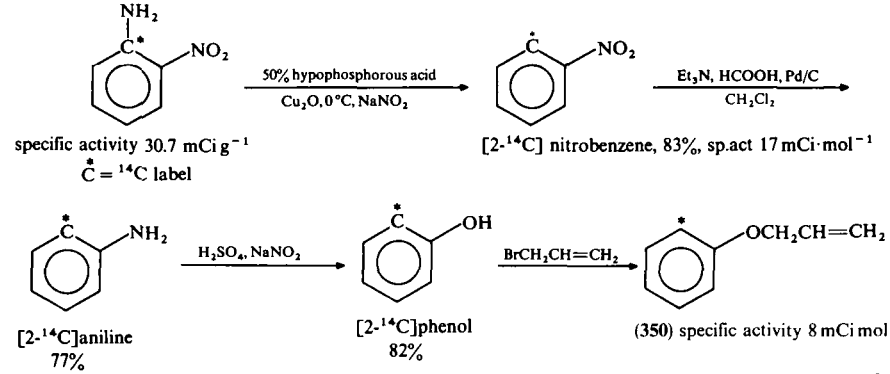
(350) (351) (169)

Allyl phenyl [^{18}O]ether was prepared by treating benzenediazonium tetrafluoroborate with $H_2{}^{18}O$ followed by reaction of the [^{18}O]phenol with allyl bromide (equation 170).

$$C_6H_5N_2{}^+BF_4{}^- \xrightarrow{H_2{}^{18}O} C_6H_5{}^{18}OH \xrightarrow[K_2CO_3]{BrCH_2CH=CH_2} C_6H_5{}^{18}OCH_2CH{=}CH_2 \qquad (170)$$

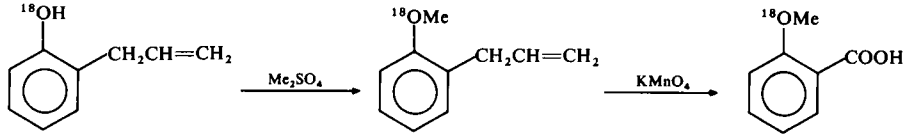
7.3% enriched with ^{18}O

Allyl [2-^{14}C]phenyl ether has been synthesized as shown in equation 171. [3-^{14}C]allyl phenyl ether ([α-^{14}C] **−350**) and [1-^{14}C]allyl phenyl ether ([γ-^{14}C] **−350**) have been prepared as described previously[424]. The degree of conversion was monitored by



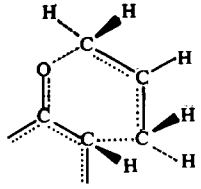
(171)

^{1}H NMR. Specific activity of [α-^{14}C]-, [γ-^{14}C]- and [2-^{14}C]-*ortho*-allylphenols has been determined after their conversion to the corresponding phenylurethanes. [^{18}O] concentrations in the [^{18}O]allylphenols have been determined by multiscan quadrupole mass spectrometry after their conversion to *o*-[^{18}O]methoxybenzoic acid, which has a substantial parent ion (equation 172).



(172)

Relative abundances of the ions *m/e* 152 and 154 have been measured. The average (from six determinations) experimental K.I.E. values for the thermal rearrangement of allyl phenyl ether to *o*-allylphenol at 220 °C in diphenyl ether were found to be 1.0297 ± 0.0016 for ^{18}O, 1.0306 ± 0.00432 for α-^{14}C, 1.0362 ± 0.0016 for γ-^{14}C and 1.0375 ± 0.0027 for [2-^{14}C]. The fact that the K.I.E. values are substantial for all four positions indicates that the Claisen rearrangement proceeds through a loose transition state of the type **352**.



(352)

The calculated ^{14}C K.I.E. values reproduced the experimentally measured ones by assuming that $n_{CO}/n_{CC} = 0.4/0.2$, were n_{CO} and n_{CC} are bond orders corresponding to the ether C_α–oxygen bond broken and to the new C_γ—C_{ortho} bond formed. The phenoxy and allylic fragments are rather loosely bound (total $n_{CO} + n_{CC} = 0.6$–0.7) in the T.S. The lack of knowledge of the temperature dependences of the measured heavy-atom K.I.E. values does not permit one to make decisive conclusions concerning the validity of the detailed calculational results. (According to the computations the ^{18}O and $^{14}C_\alpha$ K.I.E. values are caused chiefly by the positive value of the exponent, $(E_{heavy} - E_{light}) > O$, and should show normal temperature dependence, i.e., k_{12C}/k_{14C} should decrease with increase in the temperature. The $^{14}C_\gamma$ and $^{14}C_{ortho}$ isotope effects are determined by the Arrhenius pre-exponential factors, A_{12C}/A_{14C_γ} and $A_{12C}/A_{C_{ortho}}$, related to the motion of the effective mass along the reaction coordinate which is temperature independent). However, the final conclusion, that the completely synchronous rearrangement process (requiring the constancy of the total bond order to each atom) must be rejected, is probably correct.

Earlier isotopic studies of the Claisen rearrangement and of the gas-phase decomposition of allyl ethers have been reviewed elsewhere[122].

B. Isotope Effects and Tracer Studies of Oxidation and other Processes

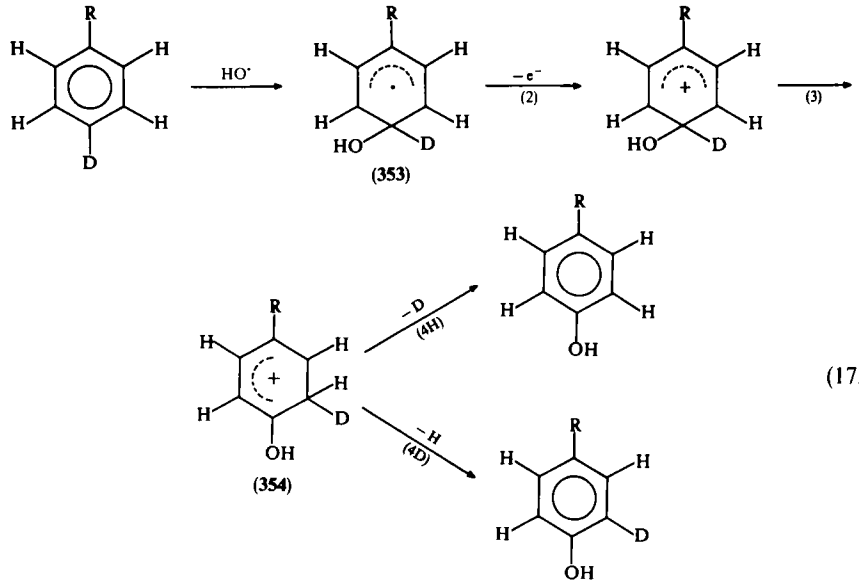
1. Studies of the mechanism of aromatic hydroxylation in Fenton and related reactions with the use of deuterium and oxygen-18

Toluene[4-^{2}H], anisole[4-^{2}H] and chlorobenzene[4-^{2}H], prepared by treating the corresponding Grignard reagents with D_2O, have been used[424] to study the one-electron

TABLE 1. NIH shifts in Fenton reactions with $Fe^{2+}/H_2O_2/Cu^{2+}$

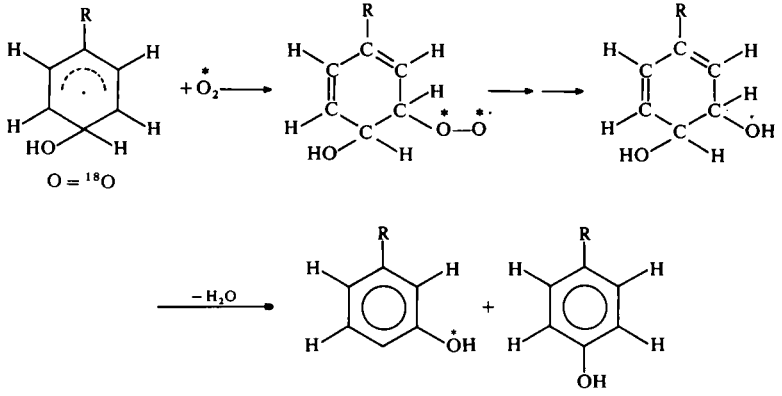
Substrate	Solvent	Product	Yield	(*o*:*m*:*p*)	NIH shift (%)
p-$MeOC_6H_4D$	H_2O	$MeOC_6H_4OH$	16	(87:2:11)	3.1
	90% MeCN	$MeOC_6H_4OH$	3	(98: < 1:1)	8
p-MeC_6H_4D	H_2O	MeC_6H_4OH	9	(56:16:28)	19.0
	90% MeCN	MeC_6H_4OH	12	(58:22:19)	48.2
p-ClC_6H_4D	H_2O	ClC_6H_4OH	2	(56:27:17)	22.8
	90% MeCN	ClC_6H_4OH	44	(57:22:21)	42.3
p-$MeCOC_6H_4D$	H_2O	$MeCOC_6H_4OH$	8	(33:42:25)	21.5
	90% MeCN	$MeCOC_6H_4OH$	9	(68:21:11)	45.7

oxidation and the NIH shift (rearrangement of hydrogen atom during enzymatic aromatic hydroxylations[425]). The NIH shift values given in Table 1 have been determined by GC/MS analyses of the products obtained with the Fenton reagent and with peroxydisulphate. The solvent-dependent shift values are substituent-dependent in the order: MeO ≪ Me, Cl, MeCO. Oxygen reduced the shift effectively and incorporated significantly into the *meta* position of the produced phenol in the case of toluene and anisole. Oxygen abstracts a hydrogen atom from the oxycyclohexadienyl radical intermediate **354** or adds to the product phenols with selective *meta* orientation. The likely mechanisms for the shift and for its reaction with oxygen are presented in equations 173 and 174.



(173)

The NIH shift depends on the efficiencies of the one-electron oxidation (step 2) and of the subsequent rearrangement (step 3), and also on the K.I.E. (k_H/k_D) for the deprotonation (steps 4) which is estimated to be in the range 1.7–3.0. The value $k_H/k_D = 1.72$ was obtained directly in the acid-catalysed dehydration of $PhCH(OH)CH_2D$ yielding styrene. The non-enzymic deprotonation of the toluene cation radical to form a benzyl radical in aqueous MeCN afforded $k_H/k_D \simeq 3.0$. The observed NIH shift of



(174)

50.8% for toluene suggests that formation of **354** proceeds in the case of toluene with 67–80% selectivity. The high NIH shifts in microbial and model P-450 hydroxylations under aerated conditions indicate that the one-electron oxidation is more efficient than H· abstraction by oxygen after formation of **353**.

2. Deuterium kinetic isotope effects in the oxidation of phenols by an oxo complex of ruthenium(IV)

Deuterium K.I.E. (k_H/k_D) in the oxidation of deuteriated phenol (C_6D_5OH) by $[(bpy)_2(py)Ru^{IV}(O)]^{2+}$ and by $[(bpy)_2(py)Ru^{III}(OH)]^{2+}$ to the corresponding quinone (bpy = 2,2'-bipyridine and py = pyridine) in acetonitrile were found[426] to be at 25 °C equal to

$$[1.9(\pm 0.4) \times 10^2\ M^{-1}s^{-1}/3.5(\pm 0.6) \times 10\ M^{-1}s^{-1}] = 5.43(\pm 0.2)$$

and

$$[4.0(\pm 0.4) \times 10/6.3(\pm 0.2)] = 6.35(\pm 0.4),$$

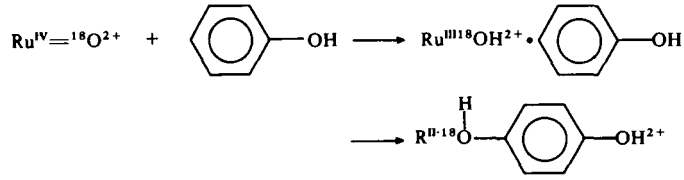
respectively. In the 14–36 °C temperature interval the thermodynamic parameters deduced from kinetic studies are: $\Delta H^{\ddagger} = 10.3(\pm 0.6)$ kcal mol^{-1} and $\Delta S^{\ddagger} = -14(\pm 2)$ e.u. for oxidation of C_6H_5OH with $Ru^{IV} = O^{2+}$ and $\Delta H^{\ddagger} = 10.8(\pm 1.2)$ and $\Delta S^{\ddagger} = -14(\pm 1)$ e.u. for oxidation of C_6D_5OH with $Ru^{IV} = O^{2+}$. The ratios of the second-order rate constants for the same two oxidations in H_2O at pH 7 are

$$[5.6(\pm 0.6) \times 10^2/4.8(\pm 0.4) \times 10^2] = 1.17(\pm 0.2)$$

at 25 °C. Oxidation of C_6H_5OD with $Ru^{IV} = O^{2+}$ in D_2O (pD 7) proceeds at 25 °C with $k = 1.9(\pm 0.2) \times 10^2$, $k_H/k_D = (5.6 \times 10^2/1.9 \times 10^2) = 2.95$.

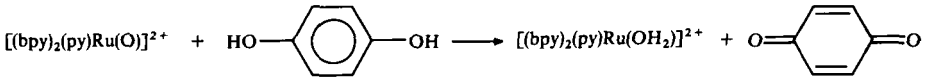
The k_H/k_D values for the oxidation of C_6H_5OH and C_6D_5OH with Ru^{III}—OH^{2+} in MeCN are $[4.0(\pm 0.4) \times 10/6.3(\pm 0.2)] = 6.3(\pm 0.4)$ at 25 °C. The corresponding values in H_2O (pH 7) are $[6.5(\pm 0.5) \times 10/5.5(\pm 0.5) \times 10] = 1.182$. Oxidation of C_6H_5OD with Ru^{III}—OH^{2+} in D_2O (pD 7) proceeds with $k = 9.5(\pm 0.2)\ M^{-1}s^{-1}$ and with $k_H/k_D = (6.5 \times 10/9.5) = 6.842$. The reaction is first order in both phenol and in $Ru^{IV}{=}O^{2+}$ or Ru^{III}—OH^{2+}, and proceeds via a Ru(II) complex $[(bpy)_2(py)Ru^{II}(p\text{-}HOC_6H_4OH)]^{2+}$. ^{18}O isotopic labelling showed that the transfer of the oxo group from $Ru^{IV}{=}O^{2+}$ to phenol is quantitative. Based on the above studies the mechanism given in equation 175 has been proposed for the oxidation of phenol by $Ru^{IV}{=}O^{2+}$ in MeCN.

The large C—H K.I.E. $k_{CH}/k_{CD} = 5.5$ in MeCN suggests a rate-limiting C—H bond breaking (H^+ loss) after the initial electrophilic attack. The fall of the CH/CD K.I.E.



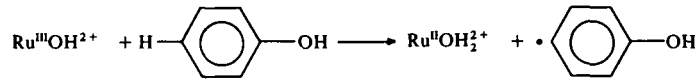
(175)

value in water to $k_H/k_D = 1.2$ at 25 °C suggests that here a change in mechanism takes place and initial electrophilic attack is rate limiting. H_2O acts as a base for the H^+ release from the C—H bond. The subsequent redox step (equation 176) is rapid both with free or with bound hydroquinone.



(176)

The lack of experimental data concerning the temperature dependence of the deuterium K.I.E. observed in the oxidation of C_6D_5OH with $Ru^{IV}{=}O^{2+}$ in acetonitrile does not allow one to assess the degree of tunnelling in this process involving hydrogen transfer from phenol to oxidant. Oxidation by $R^{III}—OH^{2+}$ proceeds via initial CH/H atom transfer in MeCN (equation 177) and by OH/H atom transfer in water. Equation 177 is followed by rapid migration of the hydroxylic proton to yield a phenoxy radical, which is attacked by a second $Ru^{III}—OH^{2+}$ species yielding hydroquinone, which is in turn oxidized rapidly to quinone (equations 178a and 178b).



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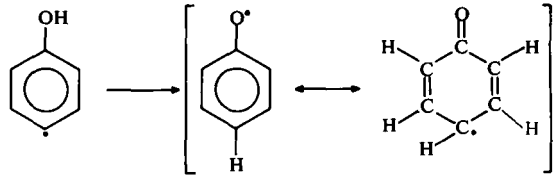
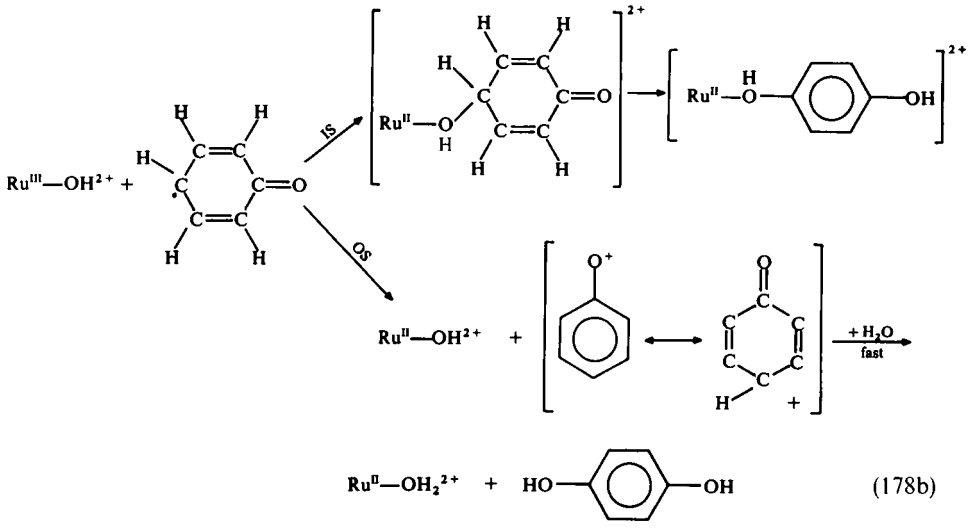


(178a)

3. Deuterium K.I.E. in the oxidation of formic acid by methyltributylammonium permanganate in methylene chloride solutions

Deuterium isotope effects in the non-catalytic oxidation of formic acid in methylene chloride at 25 °C by methyltributylammonium permanganate[428] have been found[429] to be 4.1 ± 0.2 (for HCOOH/DCOOH) and 1.34 ± 0.02 (for HCOOH/HCOOD)[430,431] and 10.7 ± 0.6 (for HCOOH/DCOOH) and 1.33 ± 0.05 (for HCOOH/HCOOD) in the case of reaction catalysed by MnO_2. These K.I.E. values have been accounted for by assuming that the catalytic reaction proceeds by way of equations 179 and 180 and the latter involves the rate-limiting cleavage of C—H/C—D bonds. The uncatalysed portion of the reaction is assumed to proceed as shown in equations 181 and 182, in agreement with previous theoretical studies[432] and with the observation that $[^{18}O]CO_2$ is formed



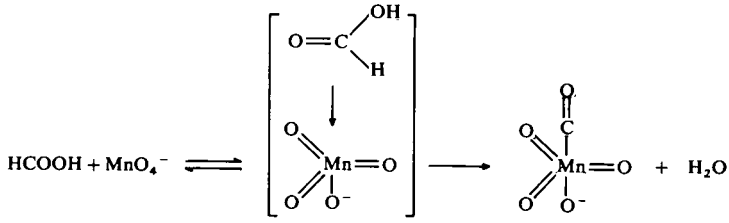
(178b)

IS denotes inner sphere[427] and OS denotes outer sphere

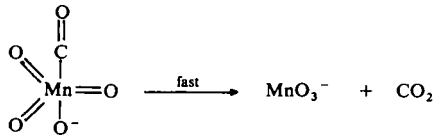
when [^{18}O]permanganate is used as the oxidant. The presence of water inhibits the rate of oxidation by competing with the reductant for a position in the coordination shell of MnO_2.

$$QMnO_4 + (MnO_2) \rightleftharpoons QMnO_4(MnO_2)_n \quad (179)$$

$$QMnO_4(MnO_2)_n + HCOOH \longrightarrow QMnO_3(MnO_2)_n + CO_2 + H_2O \quad (180)$$



(181)



(182)

4. Isotope effects in the oxidation of α-hydroxy acids

Practically no primary $^{13}C_{(1)}$ K.I.E. has been found[433]

$$(k_{^{12}C_{(1)}}/k_{^{13}C_{(1)}}) = 1.0011 \pm 0.0002 \text{ (pH 6.0, } T = 25\,^{\circ}\text{C)}$$

in the lactate oxidase catalysed decarboxylation of lactate (equation 183). This was interpreted as indicating the existence of an irreversible O_2-dependent step prior to the

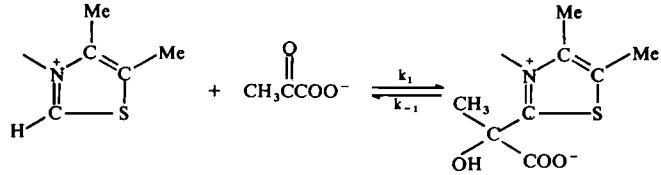
enzyme-catalysed decarboxylation.

$$CH_3CH(OH)^{13}COOH + O_2 \longrightarrow CH_3COOH + {}^{13}CO_2 + H_2O \qquad (183)$$

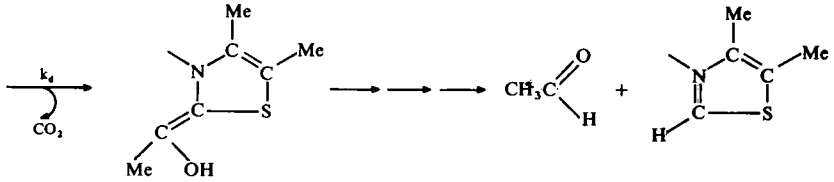
The reaction with O_2 (formation of a ternary enzyme–pyruvate–H_2O_2 complex) and the decarboxylation are consecutive reactions. This conclusion is supported by the ^{13}C K.I.E. for $^{13}C_{(2)}$ lactate in the same enzymic reaction, $k_{12C}/k_{13C} = 1.0048 \pm 0.0004$ (pH 6, $T = 25\,^{\circ}C$), which corresponds to the hydrogen transfer step from lactate to the enzyme preceding the subsequent oxidation and decarboxylation steps. The deuterium isotope effect for the same step ($k_H/k_D = 1.7$ at pH 7.0 and $T = 25\,^{\circ}C$)[434] indicates also that the dehydrogenation step is a partially rate-limiting step. The observed 1‰ fractionation of $^{13}C_{(1)}$ is the secondary isotope effect on the dehydrogenation step. The ^{13}C kinetic isotope effect at $C_{(1)}$ on the H_2O_2-catalysed *decarboxylation of pyruvate* (which is the model reaction for the enzyme reaction) was found to be dependent on pH: $k_{12C_{(1)}}/k_{13C_{(1)}}$ equals 1.0007 ± 0.0004 at pH 3.1, 1.0044 ± 0.0016 at pH 5.9, 1.0069 ± 0.0020 at pH 6.4 and 1.0283 ± 0.0014 at pH 10.0[433]. This dependence implies a change in the rate-determining step with increasing pH, from formation of the tetrahedral intermediate (k_1) to decarboxylation of this intermediate (k_3) in equation 184.

$$RCCOOH + H_2O_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \underset{OH}{\overset{OOH}{RCCOOH}} \xrightarrow{k_3} RCOOH + H_2O + CO_2 \qquad (184)$$

The attacking species is a H_2O_2 molecule below pH 3.8 and a HO_2^- anion above pH 3.8[435]. At pH 3 the first step is practically irreversible[436]. At pH 10 the decarboxylation becomes rate-limiting. The $^{13}C_{(1)}$ K.I.E. for pyruvate dehydrogenase reaction depends on the enzyme source and values of 1.009 and 1.024 were obtained with different samples[437]. A K.I.E. (k_{12C}/k_{13C}) of 1.05 has been obtained in the spontaneous decarboxylation of [2-(1-carboxy-1-hydroxyethyl)-3,4-dimethylthiazonium chloride], at 45.6 °C (pH 5 in H_2O, equation 185)[438]. This value compares with the value of 1.06 for divalent metal ion catalysed decarboxylation of oxaloacetic acid[439] and with values between 1.03 and 1.06 found for k_{12}/k_{13} in non-enzymic one-step decarboxylation reactions[440].



(185)



No primary deuterium K.I.E. was noticed in the oxidation of lactic, glycolic, mandelic and 2-hydroxy-2-methyl propanoic acid by sodium *N*-bromobenzenesulphonamide,

yielding the corresponding carbonyl compounds by oxidative decarboxylation[441,442]. The solvent isotope effect $k_{(H_2O)}/k_{(D_2O)}$ was 3.99. The problem of tritium, carbon-14 and carbon-13 kinetic isotope effects in the non-enzymic oxidative decarboxylation of lactic acid with MnO_2 in acidic medium is under current investigation[442a].

5. Deuterium study of the photooxidation of the secondary aliphatic alcohols

No significant primary H—D isotope effect has been found in the photooxidation of secondary aliphatic alcohols (*i*-PrOH[443], c-pentanol and c-butanol) carried out in aqueous suspensions of n-type semiconducting oxides ZnO and TiO_2. However, the comparison of the initial rates of Me_2CO production from oxygenated suspensions containing 0.02 M $(CH_3)_2CHOH$ and $(CD_3)_2CDOD$ in H_2O and D_2O demonstrated the existence of sizable H_2O/D_2O isotope effects (4.3 for the suspension containing ZnO and 2.8 for that containing TiO_2). A similar H_2O/D_2O effect was found for cyclobutanone formation from cyclobutanol. The conclusion has been reached that photogeneration of OH radicals from H_2O is the rate-determining step in the case of photooxidations of alcohols in oxygenated aqueous solutions.

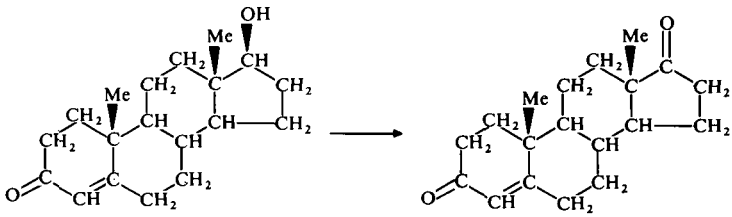
A deuterium isotope effect was found in the reactions of $\cdot CH_2OH$ radicals produced in glassy methanol at 77 K by cobalt-60 γ-irradiation using CH_3OH and CD_3OD. The reaction rate in the H-containing matrix was 1.8 times faster[444]. Reverse D isotope effects were observed in electron captures by methanol occurring at the 6.2- and 10.4-eV resonances[445].

The K.I.E. of $k_{(H)}/k_{(D)}$ was found to be about 1 below 393 K, < 1 from 393 to 1073 K, and > 1 above 1073 K for the gas-phase reactions of $OH + C_2H_2$ and $OH + C_2D_2$ at a total pressure of 1 atm in argon by using pulse radiolysis. The predominant reactions have been changing from additions at lower temperatures to H-atom abstractions at higher ones[446]. In the reaction of HO radicals with ethylene at 1 atm, a weak negative activation energy which is characteristic of the OH additions to the C=C bond has been found at < 560 K. At > 720 K a positive activation energy of 4–5 kcal mol^{-1} and both primary and secondary kinetic isotope effects have been observed. The high-temperature pathway has been attributed to H-abstraction from C_2H_4 by $\cdot OH$. The above temperature dependence was reproduced by theoretical calculations[446].

6. Deuterium isotope effect studies of cytochrome P-450-catalysed hydroxylations

a. The mechanism of androstenedione formation with essentially complete retention of deuterium from [16,16-$^2H_2$]testosterone and [16,16-$^2H_2$]epitestosterone (equation 186) catalysed by purified cytochrome P-450b has been investigated[447] and the dione formation via $C_{(16)}$-hydroxylation followed by loss of water and rearrangement has been ruled out. Kinetic studies utilizing [17-^{2}H]testosterone and [17-^{2}H]epitestosterone indicated that cleavage of the $C_{(17)}$ carbon–hydrogen bond is involved in a rate-determining step in the formation of androstenedione from both substrates. ^{18}O study of this reaction has also been carried out[447].

b. Cytochrome P-450-catalysed hydroxylation and carboxylic acid ester cleavage of



(186)

2,6-dimethyl-4-phenyl-3,5-pyridine dicarboxylic acid diethyl ester gave rise to the corresponding monoethyl ester and to 2-hydroxymethyl-6-methyl-4-phenyl-3,5-pyridinedicarboxylic acid diethyl ester. Experiments with ^2H and ^3H labels have been used[448] to determine a kinetic ^2H isotope effect of 15 for ethyl ester cleavage by rat liver P-$450_{PB-\beta}$. Rat liver microsomal systems showed kinetic ^2H and ^3H isotope effects of 8 and 11, respectively. Deuteration of the methyl group gave rise to a kinetic isotope effect of 7–11, but no increases have been observed in the rates of ester cleavage.

7. *Isotopic studies of dehydrations and decompositions*

a. The dehydration of alcohols (MeOH, EtOH, propan-2-ol) on hydride-forming rare-earth intermetallic compounds ($ErFe_2$, $DyFe_2$, Nd_2Co_7 and Sm_2Co_7) under mild conditions to carbon monoxide, acetaldehyde and acetone, respectively, simultaneously forming metal hydrides, has been claimed[449] by deuterium isotope experiments to proceed in the case of methanol and ethanol by a rate-limiting dissociation reaction on the activated alloy surfaces with subsequent migration of the liberated hydrogen to the underlying alloy phase.

b. The decomposition of methanol on Ni/SiO_2–MgO to carbon monoxide and hydrogen has been studied with the use of deuterium isotopic species[450]. CD_3OD decomposed more slowly than CH_3OH and CH_3OD. The difference in the activation energies of CD_3OD and the other two isotopic species was about 1 kcal mol^{-1}. Formaldehyde decomposed to CO and H_2 faster than methanol. The above results indicate that the rate-determining step involves the removal of H from the methoxy group.

c. Heavy atom (^{13}C, ^{18}O) kinetic isotope effects have been used to study the nature of the transition state in the gas-phase pyrolysis of β-propiolacetone at 230–319 °C and 30–272 torr in a static system[451]. The decomposition was first order and gave equal amounts of ethylene and carbon dioxide as the only products. Carbon-14 and carbon-13 kinetic isotope effects in the decarbonylation of lactic acid in concentrated and diluted sulphuric acid have been investigated in the temperature intervals 20–90–130 °C[451a,451b,c].

d. Thermostability of glucose oxidase. The thermal denaturation of glucose oxidase has been performed in a 97% D_2O medium. In this medium the enzyme was more stable and its half-life was 2.6-fold higher than in H_2O (at 60 °C)[452].

e. Kinetic isotope effects, structure–reactivity parameters and transition state structures in glycosidase catalysis have been reviewed[453]. α-Deuterium K.I.E. established that kinetically accessible glyceryl–enzyme intermediates are covalent rather than ionic. Proton donation to the leaving group gives rise to a solvent isotope effect in H_2O/D_2O.

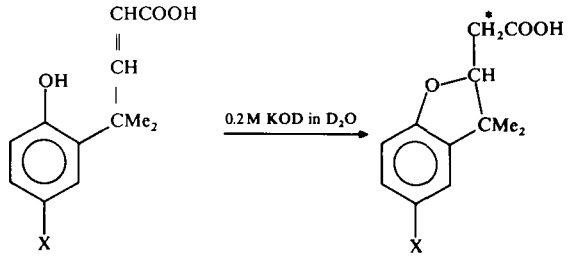
f. Isotopic studies of hydrolysis processes. A kinetic solvent isotope effect k_{H_2O}/k_{D_2O} of 2.2 ± 0.5 has been observed in the hydrolysis of 1-acetoxy-, 1-acetoxy-8-hydroxy- and 1,8-diacetoxynaphthalenes[454]. The position of bond cleavage in the acid-catalysed hydrolysis of sucrose carried out in the presence of $H_2{}^{18}O$ has been established utilizing the oxygen-18 isotope shift in carbon-13 nuclear magnetic resonance spectroscopy[455]. Fructosyl-O bond cleavage took place under the reaction conditions employed.

A deuterium isotope effect ($k_H/k_D = 2.3$) has been found in the new first-order decomposition pathway of *trans*-[Ru(CDO)(CO)(dppb)$_2$][SbF_6], where dppb = 1,2-bis(diphenylphosphino)benzene] to *trans*-[RuH(CO)(dppb)$_2$][SbF_6] and interpreted as caused by rate-determining concerted H migration and CO loss in a 6-coordinate complex[456].

8. *Isotopic studies of cyclizations and rearrangements*

a. The mechanism of cyclization of substituted 4-methyl-4-(2-hydroxyphenyl)pent-2-enoic acid derivatives (**355**) in water, proceeding by intramolecular nucleophilic addition of phenolate oxygen to double bonds activated by COO^- or COOH groups

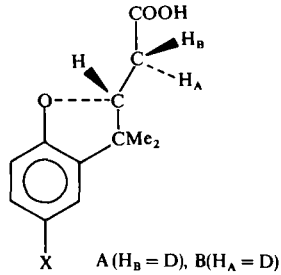
(equation 187) and catalysed by protonated amines, has been studied[457] by determining the (primary) solvent deuterium isotope effects. The value of k_{H_2O}/k_{D_2O} was found to be less than 2 for buffer acids at 39 °C, and about 5.4 for water. The rate constants for the exchange of the β-hydrogens of **356a** at 39 °C for deuterium were also determined.



(187)

(355a, b, c)
(a) X = H, **(b)** X = Br, **(c)** X = NO_2

(356) ≥ 90% monodeuterio diastereoisomer A
X = H, Br or NO_2



(356a)

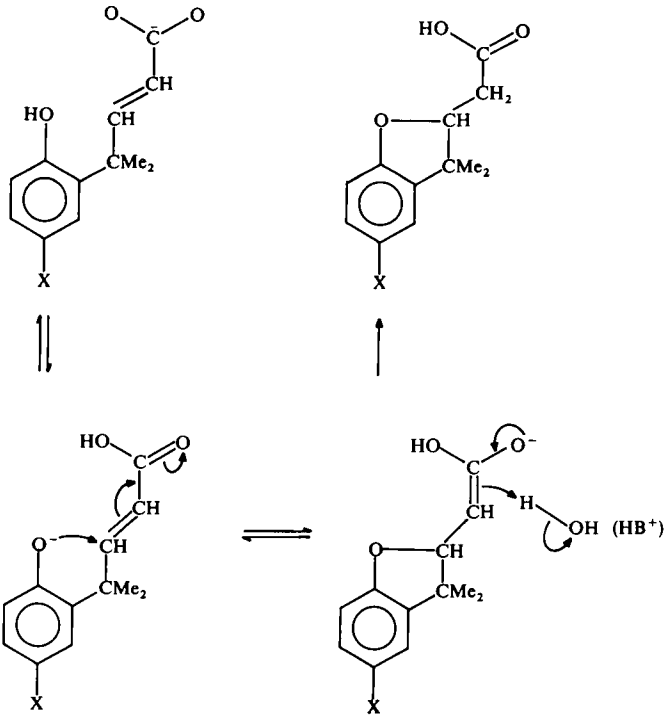
The ratio of monodeuterio diastereoisomers [A] to [B] after 6 days exchange of **356a** followed by ^{1}H NMR was as 13:1 (at 39 °C). Thus the exchange of the first proton of **356a** is ≳ 93% stereospecific. With **356c** in KOD/D_2O only the elimination product **355c** was formed, not accompanied by incorporation of deuterium. Rate-determining protonation of mono- or dianions of carboxylic acid enolates has been suggested as the most likely mechanism of these cycloadditions (equation 188).

b. 16β-Hydroxy-5α-androstan-17 one and its 16α-deuterio derivative (for numbering, see structure **281**) treated either with H_2SO_4 or with NaOH rearranged to the 17β-hydroxy-16-oxo isomer with the K.I.E. at the 16 position being equal to $(k_H/k_D) = 4.5$ or 3.0[458]. The product retained deuterium at C-17 to the extent of 16–65%. No significant loss of the isotope from the substrate was observed during the reaction. Further isotope-labelling experiments showed that an intramolecular 1,2-hydride shift is involved in the rearrangement.

Mass spectrometry of eight deuteriated analogues of prostaglandins has been studied[459] for choosing parent ion–daughter ion pairs monitoring prostaglandins in biological fluids by G.C./M.S. K.I.E. values have been determined in quenching of triplet anthanthrone by phenols in MeCN[460,461].

VII. ACKNOWLEDGEMENTS

We are obliged to Professor Kamil Klier for sending us reprints of his papers concerning ^{13}C isotope tracer reactions in oxygenate syntheses. One of us (M.Z.) also wishes to



(188)

thank Professor Judith A. McKenzie from ETH in Zürich for a kind invitation to her Stable Isotope Laboratory thus permitting the continuation of isotope effect studies with lactic acid as well as for introducting her to the investigation of carbon-isotope fractionation during aqueous photosynthesis[462]. Biomedical aspects of many of the described derivatives have been discussed with mgr. Halina Papiernik-Zielińska. We thank Dr. Riehard Kański for typing a substantial part of this chapter. Help given by Gregory Czarnota in the course of preparing the manuscript is also acknowledged. As before, most of the chapter has been written in our mother's house at Witeradow. We are grateful for her services. The work has been partially supported by the Faculty of Chemistry of Jagiellonian University and by the Department of Chemistry of Warsaw University.

VIII. REFERENCES

1. (a) R. C. Atkins and F. A. Carey, *Organic Chemistry*, Chap. 10, McGraw-Hill, Hamburg–New York, 1990.
(b) L. F. Fieser and Mary Fieser, *Organische Chemie.*, Chaps 8 and 22, Verlag Chemie, Weinheim, 1982.
(c) Mary Fieser, *Reagents for Organic Synthesis*, Wiley, New York, 1990.
(d) T. W. Graham Solomons, *Organic Chemistry*, fourth ed., Chap. 8, Wiley, Chichester, 1990.
(e) H. Hart, *Organische Chemie*, Chap. 7, VCH, Weinheim, 1989.
(f) F. Serratosa, *Organic Chemistry in Action*, Elsevier, Amsterdam, 1990, p. 237.
(g) A. Streitwiesser Jr. and C. H. Heathcock, *Introduction to Organic Chemistry*, third ed., Chap. 10, McMillan, New York, 1989.
(h) K. P. C. Vollhardt, *Organische Chemie*, Chaps 8 and 9, VCH, Weinheim, 1990.

2. (a) I. Pri-Bar and O. Buchman, *J. Labelled Compd. Radiopharm.*, **22**, 1227 (1985).
(b) R. Bombach, J. P. Stadelmann and J. Vogt, *Chem. Phys.*, **72**, 259 (1982).
3. J. Barber, *J. Labelled Compd. Radiopharm.*, **22**, 229 (1985).
4. A. P. Doerschuk, *J. Am. Chem. Soc.*, **73**, 821 (1951).
5. L. I. Gidez and M. L. Karnovsky, *J. Am. Chem. Soc.*, **74**, 2413 (1952).
6. J. Barber and J. Retey, in Reference 3.
7. E. C. Bate-Smith, *Phytochemistry*, **11**, 1153 (1972).
8. E. Haslam, *Recent Adv. Phytochem.*, **12**, 475 (1979).
9. P. Lesca, *Carcinogenesis*, **4**, 1651 (1984).
10. R. L. Chang, M.-T. Huang, A. W. Wood, C.-Q. Wong, H. L. Newmark, H. Yagi, J. M. Sawyer, D. M. Jerina and A. H. Conney, *Carcinogenesis*, **6**, 1127 (1985).
11. A. W. Wood, M. T. Huang, R. L. Chang, H. L. Newmark, R. E. Lehr, H. Yagi, J. M. Sayer, D. M. Jerina and A. H. Conney, *Proc. Natl. Acad. Sci. U.S.A.*, **79**, 5513 (1982).
12. J. M. Sawyer, H. Yagi, A. W. Wood, A. H. Conney and D. M. Jerina, *J. Am. Chem. Soc.*, **104**, 5562 (1982).
13. R. Dixit and B. Gold, *Proc. Natl. Acad. Sci. U.S.A.*, **83**, 8039 (1986).
14. A. R. Francis, T. K. Shetty and R. K. Bhattacharya, *Cancer Lett.*, **45**, 177 (1989).
15. D. H. Barch and C. C. Fox, *Cancer Res.*, **48**, 7088 (1988).
16. A. Dipple, R. C. Moschel and W. R. Hadgins, *Drug Metab. Rev.*, **13**, 249 (1982).
17. N. C. Mishra and B. Gold, *J. Labelled Compd. Radiopharm.*, **28**, 927 (1990).
18. R. W. Teel, R. M. Martin and R. Allahyari, *Cancer Lett.*, **36**, 203 (1987).
19. I. Kozak, L. Kronrad and M. Prochazka, *J. Labelled Compd. Radiopharm.*, **15**, 401 (1978).
20. S. D. Boyce, A. C. Barefoot and J. F. Hornig, *J. Labelled Compd. Radiopharm.*, **20**, 243 (1983).
21. T. M. Symons, T. A. Bellar, J. K. Carswell, J. DeMarco, K. L. Kropp, G. G. Robeck, D. R. Seeger, C. J. Slocum, B. L. Smith and A. A. Stevens, *J. Am. Water Works Assoc.*, **67**, 635 (1975).
22. J. J. Rook, *Water Treat. Exam.*, **23**, 234 (1974).
23. J. J. Rook, *J. Am. Water Works Assoc.*, **68**, 168 (1976).
24. R. F. Christman, J. D. Johnson, J. R. Haas, F. K. Pfaender, W. T. Liao, D. L. Norwood and H. J. Alexander, in *Water Chlorination: Environmental Impact and Health Effects*, Vol. 2 (Ed. R. L. Jolley), Ann Arbor Science Publishers, Ann Arbor, MI, 1978, pp. 15–28.
25. D. B. Babcock and P. C. Singer, *J. Am. Water Works Assoc.*, **71**, 149 (1979).
26. B. D. Quimby, M. F. Delaney, P. C. Uden and R. M. Barnes, *Anal. Chem.*, **52**, 259 (1980).
27. C. J. Moye, *Chem. Commun.*, 1966 (1967).
28. D. R. Britton, unpublished results cited in Reference 20, p. 251.
29. V. H. Savell, Jr., E. J. Valente and D. S. Eggleston, *J. Labelled Compd. Radiopharm.*, **27**, 641 (1988).
30. B. West, S. Preis, C. Schroeder and K. Link, *J. Am. Chem. Soc.*, **83**, 2676 (1961).
31. E. Valente, W. Porter, E. Lingafelter and W. Trager, *J. Med. Chem.*, **20**, 1489 (1977).
32. S. Urano, S. Nakano and M. Matsuo, *J. Labelled Compd. Radiopharm.*, **21**, 313 (1984).
33. (a) M. Zieliński and M. Kańska, in *The Chemistry of Quinonoid Compounds*, Vol. 2 (Eds. S. Patai and Z. Rappoport), Chap. 19, Wiley, Chichester, 1988, p. 1118.
(b) J. A. Juvick, M. A. Stevens and C. M. Rick, *HortScience*, **17**, 764 (1982).
(c) C. A. Elliger, *J. Labelled Compd. Radiopharm.*, **25**, 281 (1988).
(d) R. Jellema, E. T. Elema and M. Malingre, *J. Chromatogr.*, **210**, 121 (1981).
34. T. E. Walker and M. Goldblatt, *J. Labelled Compd. Radiopharm.*, **21**, 353 (1984).
35. S. Oae, R. Kiritani and W. Tagaki, *Bull. Chem. Soc. Jpn.*, **39**, 1961 (1966).
36. R. T. Morrison and R. N. Boyd, *Organic Chemistry*, 2nd ed., Allyn and Bacon, Inc., New York, 1966, p. 796.
37. M. E. Kurz and G. J. Johnson, *J. Org. Chem.*, **36**, 3184 (1971).
38. N. J. Lewis, S. Y. Gabhe and M. R. De LaMater, *J. Org. Chem.*, **42**, 1479 (1977).
39. A. A. Akhrem, M. L. Abeliovich and D. I. Metelitsa, *Doklady Akad. Nauk SSSR (Engl. Transl.)*, **213**, 909 (1973).
40. M. S. Kharasch and W. B. Reynolds, *J. Am. Chem. Soc.*, **65**, 501 (1943).
41. L. Klasinc and H. Güsten, *Z. Naturforsch.*, **27**, 1681 (1972).
42. K. B. Wiberg, *J. Am. Chem. Soc.*, **75**, 2665 (1953).
43. J. L. Borowitz, A. Raviv, P. Rona, D. Sadeh, D. Samuel and F. S. Klein, *J. Labelled Compd. Radiopharm.*, **1**, 259 (1965).
44. G. Puzo, K. H. Schram and J. M. McCloskey, *J. Org. Chem.*, **43**, 767 (1978).

45. L. P. Johnson, J. K. MacLeod, R. E. Summons and N. Hunt, *Anal. Biochem.*, **106**, 285 (1980).
46. M. Maeda and Y. Kawazoe, *Tetrahedron Lett.*, 1643 (1975).
47. R. Shapiro and R. S. Klein, *Biochemistry*, **6**, 3576 (1967).
48. J. A. Rabi and J. J. Fox, *J. Am. Chem. Soc.*, **95**, 1628 (1973).
49. G. Puzo, K. H. Schram and J. M. McCloskey, *Nucleic Acids Res.*, **41**, 2075 (1977).
50. H. Follmann and H. P. C. Hogenkamp, *J. Am. Chem. Soc.*, **92**, 671 (1970).
51. H. J. Schwandt, A. T. Wu, C. Finn and W. Sadee, *Nucleic Acid Chemistry*, Part 2 (Eds. L. B. Townsend and R. S. Tipson), Wiley–Interscience, New York, 1978, p. 901.
52. T. M. Woodcock, D. S. Martin, L. A. M. Damin, N. E. Kemeny and C. W. Young, *Cancer Res.*, **20**, 76 (1979).
53. K. H. Schram, S. Ratcliff and J. Neenan, *J. Labelled Compd. Radiopharm.*, **19**, 399 (1982).
54. S. B. Hassam, *J. Labelled Compd. Radiopharm.*, **22**, 1261 (1985).
55. D. L. Davis, *Rec. Adv. Tob. Sci.*, **2**, 80 (1976).
56. C. R. Enzell, *Rec. Adv. Tob. Sci.*, **2**, 32 (1976).
57. L. C. Berardi and L. A. Goldblatt, in *Toxic Constituents of Plant Foodstuffs* (Ed. I. E. Liener), Academic Press, New York, 1980, p. 183.
58. M. E. Mace, A. A. Bell and R. D. Stipanovic, *Phytopathology*, **64**, 1297 (1974).
59. R. Masciadri, W. Angst and D. Arigoni, *J. Chem. Soc., Chem. Commun.*, 1573 (1985).
60. R. D. Stipanovic, A. Stoessl, J. B. Stothers, D. W. Altman, A. A. Bell and P. Heinstein, *J. Chem. Soc., Chem. Commun.*, 100 (1986).
61. S. M. Wong, M. B. Slaytor, H. H. S. Fong, G. A. Cordell and N. R. Farnsworth, *Acta Pharm. Sinica*, **18**, 57 (1983).
62. M. G. Rojas, R. D. Stipanovic, H. J. Williams and S. B. Vinson, *J. Labelled Compd. Radiopharm.*, **27**, 995 (1989).
63. National Coordinating Group on Male Antifertility Agents (China), *Gynecol. Obstet. Invest.*, **10**, 163 (1979).
64. R. D. Stipanovic, H. J. Williams, D. P. Muehleisen and F. W. Plapp, Jr., *J. Labelled Compd. Radiopharm.*, **24**, 741 (1987).
65. S. J. Lu, Z. A. Ronai, M. H. Li and A. M. Jeffrey, *Carcinogenesis*, **9**, 1523 (1988).
66. S. J. Lu, M. H. Li and A. M. Jeffrey, *J. Labelled Compd. Radiopharm.*, **27**, 939 (1989).
67. K. Matsui and M. Ota, *Nippon Kagaku Zasshi*, **78**, 517 (1975).
68. A. K. Nadian, *J. Labelled Compd. Radiopharm.*, **21**, 307 (1984).
69. V. R. Shah, J. L. Bose and R. C. Shah, *J. Org. Chem.*, **25**, 677 (1960).
70. S. Tachikawa, M. Harada and H. Maeno, *Arch. Int. Pharmacodyn. Ther.*, **238**, 81 (1979).
71. H. Arima and K. Tamazawa, *J. Labelled Compd. Radiopharm.*, **22**, 1217 (1985).
72. D. Evans, D. Hart and P. Koelsch, *J. Am. Chem. Soc.*, **100**, 4593 (1978).
73. D. Evans, S. Tamis and D. Hart, *J. Am. Chem. Soc.*, **103**, 5813 (1981).
74. D. Boger and C. Brotherton, *J. Org. Chem.*, **50**, 3425 (1985).
75. R. Pontikis, N. H. Nam and H. Hoellinger, *J. Labelled Compd. Radiopharm.*, **27**, 927 (1989).
76. R. Dean and H. Rapoport, *J. Org. Chem.*, **43**, 2115 (1978).
77. H. Machida, A. Kuninaka and H. Yoshino, *Antimicrob. Agents Chemother.*, **21**, 358 (1982).
78. M. Kumagai, S. Sakata, T. Yamaguchi, K. Ikeda and H. Machida, *J. Labelled Compd. Radiopharm.*, **27**, 503 (1989).
79. C. Brown, J. Eustache, J. P. Frideling and B. Shroot, *J. Labelled Compd. Radiopharm.*, **21**, 973 (1984).
80. K. Müller, A. Retzow and W. Wiegrebe, *Arch. Pharm.*, **317**, 120 (1984).
81. F. Aubert, J.-P. Beaucourt and L. Pichat, *J. Labelled Compd. Radiopharm.*, **9**, 543 (1982).
82. A. Durand, L. G. Dring, R. Gomeni, C. Mas-Chamberlini and P. L. Morselli, *Br. J. Pharmacol.*, **69**, 310P (1980).
83. G. Bianchetti, J. Ganansia and P. L. Morselli, *J. Chromatogr.*, **176**, 134 (1979).
84. R. Fariello, C. L. Alicadri, E. Agabiti-Rosei, G. Romanelli, M. Castellano, L. Platto, S. Leto Di Priolo and G. Muiesan, *Clin. Sci.*, **61**, 465s (1981).
85. R. Fariello, C. L. Alcandri, E. Agabiti-Rosei, E. Boni, A. Zaninelli, M. L. Muiesan, G. Romanelli, M. Beschi, M. Castellano, A. Cinquegrana, P. Guarenti and G. Muiesan, *Clin. Trials J.*, **21**, 67 (1984).
86. D. Saunders and B. H. Warrington, *J. Labelled Compd. Radiopharm.*, **22**, 869 (1985).
87. T. Yoshioka, T. Fujita, T. Kanai, Y. Aizawa, T. Kurumada, K. Hasegawa and H. Horikoshi, *J. Med. Chem.*, **32**, 421 (1989).

88. T. Fujiwara, S. Yoshioka, T. Yoshioka, I. Ushiyama and H. Horikoshi, *Diabetes*, **37**, 1549 (1988).
89. T. Yoshioka, Y. Aizawa, T. Kanai, T. Fujita and K. Kawai, *J. Labelled Compd. Radiopharm.*, **28**, 911 (1990).
90. R. Deghenghi and G. Daneault, *Can. J. Chem.*, **38**, 1255 (1960).
91. S. Takatsuto and N. Ikekawa, *Chem. Pharm. Bull.*, **32**, 2001 (1984).
92. B. Pelc and E. Kodicek, *J. Chem. Soc., Perkin Trans.*, **1**, 2980 (1972).
93. S. Seo, T. Nagasaki, Y. Katsuyama, F. Matsubara, T. Sakata, M. Yoshioka and Y. Makisumi, *J. Labelled Compd. Radiopharm.*, **27**, 1383 (1989).
94. K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
95. M. G. Gillam, *J. Labelled Compd. Radiopharm.*, **27**, 1409 (1989).
96. J. H. Clark and D. K. Smith, *Tetrahedron Lett.*, **26**, 2233 (1985).
97. I. D. Entwistle, T. Gilkerson, R. A. W. Johnstone and R. P. Telford, *Tetrahedron*, **34**, 213 (1978).
98. M. G. Gillam, P. A. Harthoorn and A. N. Wright, in *Progress in Pesticide Biochemistry and Toxicology* (Eds. D. H. Hutson and T. R. Roberts), Vol. 4, Wiley, Chichester, 1985, pp. 261–355.
99. Y. Iimura, H. Sugimoto, Y. Tsuchiya, K. Higurashi, N. Karibe, A. Sasaki, S. Arahi, Y. Yamanishi, Y. Kawakami and K. Yamatsu, *Am. Chem. Soc. 196th National Meeting MEDI-101*, Los Angeles, California, September 25–30, 1988.
100. B. Hermans and P. Van Daele, *Ind. Chim. Belge*, **32**, 64 (1967).
101. Y. Iimura, M. Mishima and H. Sugimoto, *J. Labelled Compd. Radiopharm.*, **27**, 835 (1989).
102. R. Gamse, A. Molnared and F. Lembeck, *Life Sci.*, **25**, 629 (1979).
103. H. O. J. Collier, W. J. McDonald-Gibson and S. A. Saced, *Br. J. Pharmacol.*, **58**, 193 (1976).
104. R. S. Bodine and P.-L. Chien, *J. Labelled Compd. Radiopharm.*, **21**, 913 (1984).
105. M. Zielinski and M. Kańska in *The Chemistry of Quinonoid Compounds*, Vol. 2 (Eds. S. Patai and Z. Rappoport), Wiley, Chichester, 1988, 1155–1157.
106. L. Crombie, S. Dandegaonker and K. B. Simpson, *J. Chem. Soc.*, 1025 (1955).
107. C. Karlsson and E. Honkanen, *J. Labelled Compd. Radiopharm.*, **29**, 237 (1991).
108. V. Siglerova and K. Vereš, *J. Labelled Compd. Radiopharm.*, **27**, 509 (1989).
109. E. Hardegger and R. M. Montavou, *Helv. Chim. Acta*, **29**, 1199 (1946).
110. V. Soukupová, M. Černý and K. Vereš, *Radiochem. Radioanal. Lett.*, **18**, 107 (1974).
111. H. M. Garraffo and E. G. Gros, *J. Labelled Compd. Radiopharm.*, **19**, 149 (1982).
112. R. E. Marker, O. Kamm and E. L. Wittle, *J. Am. Chem. Soc.*, **59**, 1841 (1937).
113. A. M. Porto, F. E. Baralle and E. G. Gros, *J. Steroid Biochem.*, **3**, 11 (1972).
114. A. M. Porto and E. G. Gross, *J. Labelled Compounds*, **4**, 276 (1968).
115. K. Meyer, *Helv. Chim. Acta*, **29**, 1580 (1946).
116. R. E. Marker, *J. Am. Chem. Soc.*, **62**, 3350 (1940).
117. M. Kańska and A. Fry, *J. Am. Chem. Soc.*, **104**, 5512 (1982).
118. M. Kańska and A. Fry, *J. Am. Chem. Soc.*, **105**, 7666 (1983).
119. M. Kańska and A. Fry, *Tetrahedron Lett.*, **27**, 5063 (1986).
120. M. Zieliński and M. Kańska, in *The Chemistry of Sulphenic Acids and their Derivatives* (Ed. S. Patai), Chap. 14, Wiley, Chichester, 1990.
121. M. Zieliński and M. Kańska, in *The Chemistry of Quinonoid Compounds*, Vol. II (Eds. S. Patai and Z. Rappoport), Chap. 19, Wiley, Chichester, 1988, pp. 1167–1171.
122. M. Zieliński, in *Supplement E. The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues* (Ed. S. Patai), Chap. 10, Wiley, Chichester, 1980, pp. 379–448.
123. K. Nagren and B. Langström, *J. Labelled Compd. Radiopharm.*, **26**, 83 (1989).
124. M. Diksic, Y. L. Yamamoto and W. Feindel, *J. Labelled Compd. Radiopharm.*, **21**, 815 (1984).
125. M. A. Rosen, R. M. Jones, Y. Yano and T. F. Budinger, *J. Nucl. Med.*, **26**, 1424 (1985).
126. M. Diksic and D. Jolly, *J. Labelled Compd. Radiopharm.*, **23**, 987 (1986).
127. R. F. Friedland, C. A. Mathis, T. F. Buddinger, B. R. Moyer and M. Rosen, *J. Nucl. Med.*, **24**, 812 (1983).
128. S. Gauthier, M. Diksic, Y. L. Yamamoto, J. Tyler and W. Feindel, *J. Neurol. Sci.*, **12**, 215 (1985).
129. C. Halldin, J. Fowler, P. Bjurling, R. MacGregor, C. Arnott, A. Wolf and B. Langström, *J. Labelled Compd. Radiopharm.*, **23**, 1400 (1986).
130. C. F. Fowler and K. F. Tipton, *J. Pharm. Pharmacol*, **36**, 111 (1984).
131. C. Halldin, S. Stone-Elander, L. Farde, E. Ehrin, K.-J. Fasth, B. Långström and G. Sedvall, *J. Labelled Compd. Radiopharm.*, **23**, 1405 (1986).
132. K. K. Dean and K. J. Heald, *Science*, **189**, 805 (1975).

133. G. K. Mulholland, C. A. Otto, D. M. Jewett, M. R. Kilbourn, P. S. Sherman, R. A. Koeppe, K. A. Frey and D. E. Kuhl, *J. Labelled Compd. Radiopharm.*, **26**, 202 (1989).
134. G. K. Mulholland, S. A. Toorongian and D. M. Jewett, *J. Nucl. Med.*, **28**, 635p (1987).
135. B. Angelo, *Bull. Soc. Chim.*, **5**, 1710 (1969).
136. S. Selman and J. F. Eastham, *J. Org. Chem.*, **30**, 3804 (1965).
137. A. D. Bulat, Yu. Ia. Usaevich, B. Z. Askinazi and L. I. Vekshina, *Khim.-Farm. Zh.*, **11**, 86 (1977).
138. C. Prenant, L. Barré and C. Crouzel, *J. Labelled Compd. Radiopharm.*, **26**, 199 (1989).
139. M. Diksic and D. Jolly, *J. Labelled Compd. Radiopharm.*, **26**, 204 (1989).
140. M. Diksic and D. Jolly, *J. Labelled Compd. Radiopharm.*, **23**, 987 (1986).
141. R. F. Dannals, H. T. Ravert, A. A. Wilson, U. Scheffel, J. J. Frost and H. N. Wagner, Jr., *J. Labelled Compd. Radiopharm.*, **26**, 205 (1989).
142. G. L. Watkins, D. M. Jewett and M. R. Kilbourn, *J. Labelled Compd. Radiopharm.*, **26**, 80 (1989).
143. D. D. Dischino, M. J. Welch, M. R. Kilbourn and M. E. Raichle, *J. Nucl. Med.*, **24**, 1030 (1983).
144. M. M. Vora, T. E. Boothe, R. D. Finn, P. M. Smith and A. J. Gilson, *J. Labelled Compd. Radiopharm.*, **20**, 417 (1983).
145. C.-Y. Shine and A. P. Wolf, *J. Labelled Compd. Radiopharm.*, **22**, 171 (1985).
146. (a) C. Y. Shine and A. P. Wolf, *J. Nucl. Med.*, **22**, 58 (1981).
(b) T. Hara, T. Nozaki, T. Karasawa, M. Iio and R. Izuchi, *J. Labelled Compd. Radiopharm.*, **21**, 1213 (1984).
147. C.-Y. Shiue and A. P. Wolf, *J. Nucl. Med.*, **22**, P58 (1981).
148. T. Hara and T. Nozaki, *J. Labelled Compd. Radiopharm.*, **19**, 1630 (1982).
149. C. Halldin, K. O. Schoeps, S. Stone-Elander, B. Langström and J.-O. Thorell, *J. Nucl. Med.*, **28**, 636 (1987).
150. K. O. Schoeps, C. Halldin, J. O. Thorell, S. Stone-Elander, G. Blomquist and L. Widen, *J. Labelled Compd. Radiopharm.*, **26**, 86 (1989).
151. J. C. Sowden and H. O. L. Fisher, *J. Labelled Compd. Radiopharm.*, **26**, 86 (1989).
152. E. Ehrin, E. Westman, S. O. Nilsson and J. L. G. Nilsson, *J. Labelled Compd. Radiopharm.*, **17**, 453 (1980).
153. E. Ehrin, S. Stone-Erlander, J. L. G. Nilsson, M. Bergström, G. Blomqvist, T. Brismar, L. Eriksson, T. Grenz, P. Jansson, J. E. Litton, P. Malmborg, M. Ugglas and L. Widen, *J. Nucl. Med.*, **24**, 326 (1983).
154. G. Kloster, C. Müller-Plaz and P. Laufer, *J. Labelled Compd. Radiopharm.*, **18**, 855 (1981).
155. D. R. Turton, S. K. Sohanpal and V. W. Pike, *J. Labelled Compd. Radiopharm.*, **21**, 1211 (1984).
156. M. M. Vora, T. E. Boothe, R. D. Finn, P. M. Smith and A. J. Gilson, *J. Labelled Compd. Radiopharm.*, **20**, 417 (1983).
157. R. R. MacGregor, J. S. Fowler, A. P. Wolf, C. Y. Shine, R. E. Lade and C. N. Wan, *J. Nucl. Med.*, **22**, 800 (1981).
158. C. J. Pederson, *J. Am. Chem. Soc.*, **89**, 7017 (1967).
159. R. F. Dannals, B. Langstrom, J. J. Frost, H. T. Ravert, A. A. Wilson and H. N. Wagner, Jr., *J. Labelled Compd. Radiopharm.*, **23**, 1407 (1986).
160. C. Le Breton and C. Crouzel, *J. Labelled Compd. Radiopharm.*, **30**, 256 (1991).
161. F. Moimas, C. Angeli, G. Comisso, P. Zanon and E. Decorte, *Synthesis*, 509 (1985).
162. D. M. Wieland, K. C. Rosenspire, M. E. Van Dort, M. S. Haka, Y. W. Jung and D. L. Gildersleeve, *J. Labelled Compd. Radiopharm.*, **30**, 283 (1991).
163. (a) R. W. Fuller, H. D. Snoddy and K. W. Perry, *Biochem. Pharmacol.*, **30**, 2831 (1981).
(b) G. W. Kabalka, *Acc. Chem. Res.*, **17**, 215 (1984).
164. (a) J. Daly, J. K. Inscoe and J. Axelrod, *J. Med. Chem.*, **8**, 153 (1965).
(b) G. W. Kabalka, R. M. Lambrecht, M. Sajjad, J. S. Fowler, S. A. Kunda, G. W. McCollum and R. MacGregor, *Int. J. Appl. Radiat. Isot.*, **36**, 853 (1985).
165. M. S. Berridge, M. P. Franceschini, T. J. Tewson and K. L. Gould, *J. Nucl. Med.*, **27**, 834 (1986).
166. (a) K. Takahashi, M. Murakami, E. Hagami, H. Sasaki, Y. Kondo, S. Mizusawa, H. Nakamichi, H. Ida, S. Miura, K. Kamio, K. Uemura and T. Ido, *J. Labelled Compd. Radiopharm.*, **23**, 1111 (1986).
(b) E. Browne and R. B. Firestone, *Table of Radioactive Isotopes*, (Ed. V. S. Shirley), Wiley, Chichester, 1986.
167. G. W. Kabalka, J. F. Green and G. McCollum, *J. Labelled Compd. Radiopharm.*, **26**, 76 (1989).
168. B. Bauer and R. Wagner, *J. Labelled Compd. Radiopharm.*, **30**, 69 (1991).

169. J. R. Grierson and M. J. Adam, *J. Labelled Compd. Radiopharm.*, **23**, 1019 (1986).
170. P. A. Jerabek, D. D. Dischino, M. R. Kilbourn and M. J. Welch, *J. Labelled Compd. Radiopharm.*, **21**, 1234 (1984).
171. A. G. Beamon, W. Tautz and R. Duschinsky, *Antimicrob. Agents Chemother.*, 520 (1967).
172. J. D. Chapman, A. J. Franko and J. Sharplin, *Br. J. Cancer*, **43**, 546 (1981).
173. R. Chirakal, B. G. Sayer, G. Firnau and E. S. Garnett, *J. Labelled Compd. Radiopharm.*, **25**, 63 (1988).
174. K. L. Kirk, *J. Heterocycl. Chem.*, **13**, 1253 (1976).
175. R. Chirakal, G. Firnau and E. S. Garnett, *J. Nucl. Med.*, **27**, 417 (1986).
176. R. Chirakal, G. Firnau, G. Schrobilgen, J. McKay and E. S. Garnett, *Int. J. Appl. Radiat. Isot.*, **35**, 401 (1984).
177. S. C. Mislankar, D. L. Gildersleeve, D. M. Wieland, C. C. Massin, G. K. Mulholland and S. A. Toorongian, *J. Med. Chem.*, **31**, 362 (1988); *CA*, **108**, 74907 (1988).
178. D. M. Wieland, M. E. Van Dort and D. L. Gildersleeve, *J. Labelled Compd. Radiopharm.*, **26**, 207 (1989).
179. M. E. Phelps, *Celeb. Blood Flow Metab.*, **2**, 113 (1982).
180. H. Fukuda, *Eur. J. Nucl. Med.*, **7**, 294 (1982).
181. J. S. Fowler, R. R. MacGregor, A. P. Wolf, A. A. Farrell, K. I. Karlstrom and T. J. Ruth, *J. Nucl. Med.*, **22**, 376 (1981).
182. T. Takahashi, T. Ido, M. Shinohara, R. Iwata, H. Fukuda, T. Matsuzawa, M. Tada and H. Orui, *J. Labelled Compd. Radiopharm.*, **21**, 1215 (1984).
183. (a) T. Haradahira, M. Maeda, H. Omae and M. Kojima, *J. Labelled Compd. Radiopharm.*, **21**, 1218 (1984).
    (b) F. Oberdorfer, B.-C. Traving, W. Maier-Borst and W. E. Hull, *J. Labelled Compd. Radiopharm.*, **25**, 465 (1988).
184. D. Keppler, J. Fauler, T. Gasser, A. Holstege, K. Leube, C. Schulz-Holstege and G. Weckbecker, *Adv. Enzyme Regul.*, **23**, 61 (1985).
185. G. M. Clark and W. L. McGuire, *Breast Cancer Res. Treat.*, **3**, 157 (1983).
186. S. J. Brandes and J. A. Katzenellenbogen, *J. Labelled Compd. Radiopharm.*, **23**, 1395 (1986).
187. C. Y. Shine, M. Watanabe, A. P. Wolf, J. S. Fowler and P. Salvadori, *J. Labelled Compd. Radiopharm.*, **21**, 533 (1984).
188. H. Ali and J. E. van Lier, *J. Labelled Compd. Radiopharm.*, **23**, 1417 (1986).
189. T. J. Tewson, M. S. Berridge, M. Soderlind and M. Vaidya, *J. Labelled Compd. Radiopharm.*, **23**, 1413 (1986).
190. A. Lin, K. E. Carlson, J. A. Katzenellenbogen, H. F. VanBrocklin, C. J. Mathias and M. J. Welch, *J. Labelled Compd. Radiopharm.*, **30**, 434 (1991).
191. C. Lemaire, M. Guillaume, A. Plenevaux, R. Cantineau, P. Damhaut, L. Christiaens, *J. Labelled Compd. Radiopharm.*, **30**, 134 (1991).
192. G. Kloster, P. Laufer and G. Stöcklin, *J. Labelled Compd. Radiopharm.*, **20**, 391 (1983).
193. R. Weinreich, Z. B. Alfassi, G. Blessing and G. Stöcklin, *Nucl. Med. Suppl.*, **17**, 202 (1980).
194. G. Blessing, R. Weinreich, S. M. Quaim and G. Stöcklin, *Int. J. Appl. Radiat isot.*, **33**, 333 (1982).
195. H. Michael, H. Rosezin, H. Apelt, G. Blessing, J. Knieper and S. M. Qaim, *Int. J. Appl. Radiat. Isot.*, **32**, 581 (1981).
196. O. T. DeJesus, W. L. Woolverton, G. J. C. Van Moffaert, M. D. Cooper and A. M. Friedman, *J. Labelled Compd. Radiopharm.*, **23**, 1403 (1986).
197. A. M. Friedman, O. T. DeJesus, R. J. Dinerstein, L. I. Goldberg and G. J. C. Moffaert, *Eur. J. Pharmacol.*, **108**, 327 (1985).
198. R. F. Martin and W. A. Haseltine, *Science*, **213**, 896 (1981).
199. A. I. Kassis, S. J. Adelstein, C. Haydock, K. S. R. Sastry, K. D. McElvany and M. J. Welch, *Radiat. Res.*, **90**, 362 (1982).
200. R. C. Mease, E. R. DeSombre, A. Hughes, A. M. Friedman and R. H. Seevers, *J. Labelled Compd. Radiopharm.*, **23**, 1397 (1986).
201. W. L. McGuire, *Proc. Soc. Exp. Biol. Med.*, **162**, 22 (1979).
202. H. Maas and W. Jonat, *J. Steroid Biochem.*, **19**, 833 (1983).
203. G. Stocklin, *Int. J. Appl. Radiat. Isot.*, **28**, 131 (1977).
204. C. C. Huang and A. M. Friedman, in *Radiotracers for Medical Applications*, Vol. 1 (Ed. G. V. S. Rayudu), Chap. 6, CRS Press, Boca Raton, FL, 1983.

205. R. E. Gibson, W. C. Eckelman, B. E. Francis, H. A. O'Brien, Jr., J. K. Mazaitis, D. S. Wilbur and R. C. Reba, *Int. J. Nucl. Med. Biol.*, **9**, 245 (1982).
206. J. A. Katzenellenbogen, K. D. McElvany, S. G. Senderoff, K. E. Carlson, S. W. Landvatter and M. J. Welch, *J. Nucl. Med.*, **23**, 411 (1982).
207. J. A. Katzenellenbogen, S. G. Senderoff, K. D. McElvany, H. A. O'Brien, Jr. and M. J. Welch, *J. Nucl. Med.*, **22**, 42 (1981).
208. S. W. Landvatter, J. A. Katzenellenbogen, K. D. McElvany and M. J. Welch, *J. Med. Chem.*, **25**, 1307 (1982).
209. J. A. Spicer, D. F. Preston, R. J. Baranczuk, E. Harvey, M. M. Guffey, D. C. Bradshaw and R. G. Robinson, *J. Nucl. Med.*, **20**, 761 (1979).
210. M. D. Hylarides, A. A. Leon, F. A. Mettler, Jr. and D. S. Wilbur, *J. Org. Chem.*, **49**, 2744 (1984).
211. H. Hofmeister, H. Laurent, P. E. Schulze and R. Weichert, *Tetrahedron*, **42**, 3575 (1986).
212. R. N. Hanson, H. El-Wakil and F. Murphy, *J. Labelled Compd. Radiopharm.*, **27**, 615 (1989).
213. J. Berger, NM/MIRD Pamphlet No. 7, *J. Nucl. Med., Suppl. No. 5.*, in Reference 215.
214. K. H. Worms and H. Blum, *Z. Anorg. Allg. Chem.*, **457**, 209 (1979).
215. M. Eisenhut, B. Kimmig, B. Bubeck, D. M. Taylor and K. zum Winkel, *J. Labelled Compd. Radiopharm.*, **21**, 1092 (1984).
216. J. Ahern, New England Nuclear, Boston, M. A. (quoted in Reference 217).
217. B. J. Agha, G. A. Garbolas, K. Wets and G. A. Digenis, *J. Labelled Compd. Radiopharm.*, **21**, 821 (1984).
218. H. Buttar, *Toxicology Lett.*, **13**, 211 (1982).
219. A. Rothman, *J. Chromatogr.*, **253**, 283 (1982).
220. E. Taylor, F. Kiezzle, R. Robey and A. McKillop, *J. Am. Chem. Soc.*, **92**, 2175 (1970).
221. C. A. Mathis, S. M. Moerlein, Y. Yano, A. T. Shulgin, R. N. Hanson and H. F. Kung, *J. Labelled Compd. Radiopharm.*, **23**, 1258 (1986).
222. R. N. Hanson, *Int. J. Nucl. Med. Biol.*, **12**, 315 (1985).
223. R. J. Flanagan, V. V. Somayaji and L. I. Wiebe, *J. Labelled Compd. Radiopharm.*, **23**, 1419 (1986).
224. R. J. Flanagan, V. V. Somayaji and L. I. Wiebe, *J. Labelled Compd. Radiopharm.*, **23**, 1421 (1986).
225. R. J. Flanagan, F. P. Charleson, E. I. Synnes, L. I. Wiebe, Y. X. Theriault and T. K. Nakashima, *Can. J. Chem.*, **63**, 2853 (1985).
226. T. Arunachalam, C. Longoope and E. Caspi, *J. Biol. Chem.*, **254**, 5900 (1979).
227. T. H. Wasserman, J. Stetz and T. L. Philips, *Cancer Clin. Trials*, **4**, 7 (1981).
228. J. R. Mercer, L. I. Wiebe and J. D. Chapman, *J. Labelled Compd. Radiopharm.*, **26**, 107 (1989).
229. R. B. Hochberg, *Science*, **205**, 1138 (1979).
230. R. Bucourt, M. Vignan, V. Torelli, H. Richard-Foy, C. Geynet, C. Secco-Millet, G. Redeuilh and E. E. Baulieu, *J. Biol. Chem.*, **253**, 8221 (1978).
231. J. N. DaSilva and J. E. van Lier, *J. Labelled Compd. Radiopharm.*, **23**, 1414 (1986).
232. A. Ali, J. Rousseau, M. A. Ghaffari and J. E. van Lier, *J. Labelled Compd. Radiopharm.*, **26**, 102 (1989).
233. H. Hofmeister, H. Laurent, P. E. Schulze and R. Wiechert, *Tetrahedron*, **42**, 3575 (1986).
234. R. M. Hoyte, W. Rosner, I. S. Johnson, J. Zieliński and R. B. Hochberg, *J. Med. Chem.*, **28**, 1695 (1985).
235. R. N. Hanson, F. Murphy, M. Choshal and C. Rosenthal, *J. Labelled Compd. Radiopharm.*, **26**, 111 (1989).
236. J. P. Raynaud and T. Ujasoo, in *Innovative Approaches in Drug Research* (Ed. A. F. Harns), Elsevier, Amsterdam, 1986, pp. 47–72.
237. R. N. Hanson, C. Rosenthal, M. Ghoshal, F. Murphy, R. E. Gibson, V. Sood and R. C. Reba, *J. Labelled Compd. Radiopharm.*, **26**, 105 (1989).
238. J. S. Baran, *J. Med. Chem.*, **10**, 1188 (1967).
239. G. Teutsch, A. Belanger, D. Philbert and C. Tournemine, *Steroids*, **39**, 607 (1982).
240. T. J. Lampidis, S. D. Bernal, I. C. Summerhayes and L. B. Chen, *Ann. N.Y. Acad. Sci.*, **397**, 299 (1982).
241. B. M. Kinsey, A. I. Kassis, F. Fayad, W. W. Layne and S. J. Adelstein, *J. Labelled Compd. Radiopharm.*, **23**, 1257 (1986).
242. (a) M. J. Weiss, M. J. Weiner and D. R. Elmalch, *J. Labelled Compd. Radiopharm.*, **26**, 109 (1989).

(b) M. P. Kung and H. F. Kung, *J. Labelled Compd. Radiopharm.*, **27**, 691 (1989).
243. S. M. Moerlein, W. Beyer and G. Stocklin, *J. Chem. Soc. Perkin Trans. 1*, 779 (1988).
244. S. M. Moerlein, K. R. Wade, C. J. Mathias and M. J. Welch, *J. Nucl. Med.*, **29**, 929 (1988).
245. R. M. Baldwin and T. W. Lin, *J. Radioanal. Chem.*, **65**, 163 (1981).
246. J. Quivy, M. Zeicher, A. Delcorde, P. Henrot, M. Deblaton, R. Pirotte, A. Verbist and J. Frühling, *J. Labelled Compd. Radiopharm.*, **30**, 442 (1991).
247. M K. Dewanjee, M. Tago, R. D. Ellefsen and M. P. Kaye, *J. Labelled Compd. Radiopharm.*, **21**, 1095 (1984).
248. M. M. Goodman, K. R. Ambrose, K. H. Neff and F. F. Knapp, Jr., *J. Labelled Compd. Radiopharm.*, **23**, 1252 (1986).
249. J. Mertens, J. Eersels, W. Vanryckeghem and M. S. Robbins, *J. Labelled Compd. Radiopharm.*, **23**, 1255 (1986).
250. U. S. Occupational Safety and Health Administration—*Fed. Register*, **43**, 11514 (1978).
251. U. S. Environmental Protection Agency—*Fed. Register*, **42**, 48026 (1977).
252. M. I. Prival, E. C. McCoy, B. Butterand and H. S. Rosencrantz, *Science*, **195**, 76 (1977).
253. W. M. Kluwe, *Toxicol. Appl. Pharmacol.*, **59**, 84 (1981).
254. J. G. Omichinski and S. D. Nelson, *J. Labelled Compd. Radiopharm.*, **25**, 263 (1988).
255. W. M. Kluwe, *Toxicology*, **27**, 287 (1983).
256. B. Prager, P. Jacobsen, P. Schmidt and D. Stern (Eds.), *Beilsteins Hadbuch der Organischen Chemie*, 4th ed., Vol. syst. No. **10**, Springer, Berlin, 1978, p. 111.
257. S. D. Nelson, J. G. Omichinsky, L. Iyer, E. Dybin, W. P. Gordon and E. J. Soderlund, *Biochem. Biophys. Res. Commun.*, **121**, 213 (1984).
258. K. D. McMichael, *J. Am. Chem. Soc.*, **89**, 2943 (1967).
259. Y. Ueno, in *Mycotoxins in Human and Animal Health* (Eds. J. V. Rodricks, C. W. Hesseltine and M. A. Mehlman), Pathox Publishers Inc., Park Forest South, IL, 1977, p. 189.
260. D. P. Michaud, B. L. Karger and P. Vouros, *J. Labelled Compd. Radiopharm.*, **25**, 345 (1988).
261. J. L. Neumeyer, S. Lal and R. J. Baldessarini, in *Apomorphine and other Dopaminomimetics*, Vol. 1—*Basic Pharmacology* (Eds. G. L. Gessa and G. L. Corsini), Raven Press, New York, 1981, pp. 1–17.
262. J. L. Neumeyer, H. M. Abdel-Maksoud, T. M. Trainor, P. Vouros and P. J. Davis, *Biomed. Environ. Mass Spectrom.*, **13**, 223 (1986).
263. R. Gottlied and J. L. Neumeyer, *J. Am. Chem. Soc.*, **98**, 7108 (1976).
264. Y. Gao, T. M. Trainor, P. Vouros and J. L. Neumeyer, *J. Labelled Compd. Radiopharm.*, **25**, 293 (1988).
265. J. Z. Ginos, A. Lamonte, G. C. Cotzias, A. K. Bose and R. J. Bramsilla, *J. Am. Chem. Soc.*, **95**, 2991 (1973).
266. W. H. Soine, J. E. Hudson, B. A. Shoulders and R. V. Smith, *J. Pharm. Sci.*, **9**, 1040 (1980).
267. W. H. Soine, P. Salgo and R. V. Smith, *J. Labelled Compd. Radiopharm.*, **16**, 597 (1979).
268. (a) F. E. Granchelli, C. N. Filer, A. H. Soloway and J. L. Neumeyer, *J. Org. Chem.*, **45**, 2275 (1980).
(b) A. Makriyannis and S. W. Fesik, *Mol. Pharmacol.*, **27**, 624 (1985).
(c) A. Makriyannis, D. J. Siminovitch, S. K. Das Gupta and R. G. Griffin, *Biochim. Biophys. Acta*, **859**, 49 (1986).
269. A. R. Banijamali, N. Abou-Taleb and C. J. Van der Schfy, *J. Labelled Compd. Radiopharm.*, **25**, 73 (1988).
270. M. L. Timmons, C. G. Pitt and M. E. Wall, *Tetrahedron Lett.*, 3129 (1969).
271. J. L. G. Nilsson, I. M. Nilsson and S. Agurell, *Acta Chem. Scand.*, **23**, 2209 (1969).
272. S. Burstein and R. Mechoulam, *J. Am. Chem. Soc.*, **90**, 2420 (1968).
273. H. Hoellinger, N. H. Nam, J. F. Decauchereux and L. Pichat, *J. Labelled Compd. Radiopharm.*, **13**, 401 (1977).
274. R. Mechoulam, P. Braun and Y. Gaoni, *J. Am. Chem. Soc.*, **94**, 6159 (1972).
275. F. Jacolot, F. Berthou, D. Picart, J. Y. Le Gall and H. H. Floch, *J. Labelled Compd. Radiopharm.*, **19**, 553 (1982).
276. C. Djerassi and J. Gutzwiller, *J. Am. Chem. Soc.*, **88**, 4537 (1966).
277. L. Tobes and L. J. Throop, in *Organic Reactions in Steroid Chemistry* (Eds. J. Fried and J. A. Edwards), Van Nostrand Reinhold Co., New York, 1972, pp. 147–151.
278. F. Paltauf and F. Spener, *Chem. Phys. Lipids*, **2**, 168 (1968).
279. P. J. Barry and B. M. Craig, *Can. J. Chem.*, **33**, 716 (1955).

280. G. Halperin, *J. Labelled Compd. Radiopharm.*, **20**, 269 (1983).
281. D. J. Porubek, M. J. Namkung, M. R. Juchan and S. D. Nelson, *J. Labelled Compd. Radiopharm.*, **21**, 703 (1984).
282. P. Ball, H. P. Gelbke and R. J. Knuppen, *J. Clin. Endocrinol Metab.*, **40**, 406 (1975).
283. E. A. Evans, *Tritium and its Compounds*, 2nd ed., Butterworth, London, 1974, pp. 60, 264, 303, 384.
284. J. L. Garnett and J. H. O'Keefe, *J. Labelled Compd. Radiopharm.*, **11**, 177 (1975).
285. R. A. Brooks, M. A. Long and L. A. Garnett, *J. Labelled Compd. Radiopharm.*, **19**, 659 (1982).
286. G. Z. Tang and C. T. Peng, *J. Labelled Compd. Radiopharm.*, **25**, 585 (1988).
287. G. Guillaumet and G. Coudert, *J. Labelled Compd. Radiopharm.*, **21**, 161 (1984).
288. J. F. Biellman and M. Liesenfel, *Bull. Soc. Chim. France*, 4029 (1966).
289. R. McDanell, A. E. M. McLean, A. B. Hanley, R. K. Heaney and G. R. Fenwick, *Food Chem. Toxicol.*, **26**, 59 (1988).
290. L. W. Wattenberg and W. D. Loub, *Cancer Res.*, 1410 (1978).
291. J. E. Nixon, J. D. Hendriks, N. E. Pawlowski, C. B. Pereira, R. O. Sinnhuber and G. S. Bailey, *Carcinogenesis*, **5**, 615 (1984).
292. R. H. Dashwood, L. Uyetake, A. T. Fong, J. D. Hendriks and G. S. Bailey, *J. Labelled Compd. Radiopharm.*, **27**, 901 (1989).
293. W. E. Noland and C. Reich, *J. Org. Chem.*, **32**, 828 (1967).
294. P. N. James and H. R. Snyder, *Org. Synth.*, **39**, 30 (1959).
295. R. M. Silverstein, E. E. Ryshiewicz and S. W. Chaikin, *J. Am. Chem. Soc.*, **76**, 4485 (1954).
296. S. Hjorth, A. Garlsson, D. Clark, K. Svensson, H. Wikström, D. Sanchez, P. Lindberg, U. Hacksell, L.-E. Arvindsson, A. Johansson and J. L. G. Nilsson, *Psychopharmacology*, **81**, 89 (1983).
297. Thorberg, L. Johansson and L. Gawell and Ch. Sahlberg, *J. Labelled Compd. Radiopharm.*, **23**, 927 (1986).
298. W. Arnold, J. J. Daly, R. Imhof and E. Kyburz, *Tetrahedron Lett.*, **24**, 343 (1983).
299. J. Hermansson, *Chromatogr.*, **298**, 67 (1984).
300. J. L. Foster, *Int. J. Radiat. Oncol. Biol. Phys.*, **4**, 157 (1978).
301. J. B. Chin, D. L. K. Sheinin and A. L. Rauth, *Mutation Res.*, **58**, 1 (1978).
302. J. L. Born and B. R. Smith, *J. Labelled Compd. Radiopharm.*, **20**, 429 (1983).
303. J. D. Blaine, P. Renault, G. L. Levine and J. A. Whysner, *Ann. N.Y. Acad. Sci.*, **311**, 214 (1978).
304. D.-C. Thang, N.-H. Nam, R. Pontikis and L. Pichat, *J. Labelled Compd. Radiopharm.*, **19**, 619 (1982).
305. E. A. Evans, H. C. Sheppard, J. C. Turner and D. C. Warrell, *J. Labelled Compd.*, **10**, 569 (1974).
306. R. Dagani, 'The Quest for Therapy', *Chem. Eng. News*, **65**, 41 (1987).
307. G. F. Taylor and J. A. Kepler, *J. Labelled Compd. Radiopharm.*, **27**, 683 (1989).
308. A. Matsuda, H. Inoue and T. Ueda, *Chem. Pharm. Bull.*, **26**, 2340 (1978).
309. E. A. Evans, H. C. Sheppard, J. C. Turner and D. C. Warrell, *J. Labelled Compd. Radiopharm.*, **10**, 569 (1974).
310. J. A. Hill and G. A. Freeman, *J. Labelled Compd. Radiopharm.*, **25**, 277 (1988).
311. K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661 (1965).
312. J. Herscovici and K. Antonakis, *J. Chem. Soc., Chem. Commun.*, 561 (1980).
313. S. J. Patterson, L. E. Robson and H. W. Kosterlitz, *Br. Med. Bull.*, **39**, 31 (1983).
314. S. C. Choudhry, L. Serico, J. Cupano, D. H. Malarek and A. A. Liebman, *J. Labelled Compd. Radiopharm.*, **27**, 1403 (1989).
315. A. A. Liebman, D. H. Malarek, J. F. Blount, N. R. Nelson and C. M. Delaney, *J. Org. Chem.*, **43**, 737 (1978).
316. H. Rapoport, C. H. Lovell, H. R. Reist and M. E. Warren, *J. Am. Chem. Soc.*, **89**, 1942 (1967).
317. Y. Ueno, *Trichothecenes—Chemical, Biological and Toxicological Aspects*, Elsevier, New York, 1983.
318. Z. Joffe, *Fusarium Species—Their Biology and Toxicology*, Wiley, New York, 1986.
319. B. B. Jarvis and C. S. Yatawara, *J. Org. Chem.*, **51**, 2906 (1986).
320. B. Yagen and B. B. Jarvis, *J. Labelled Compd. Radiopharm.*, **27**, 675 (1989).
321. J. F. Marecek and G. D. Prestwich, *J. Labelled Compd. Radiopharm.*, **27**, 917 (1989).
322. J. Gigg, R. Gigg, S. Payne and R. Conant, *Carbohydr. Res.*, **142**, 132 (1985).
323. J. Gigg, R. Gigg, S. Payne and R. Conant, *J. Chem. Soc., Perkin Trans. 1*, 1757 (1987).
324. M. F. Boehm and G. D. Prestwich, *Tetrahedron Lett.*, **29**, 5217 (1988).

325. M. J. Berridge, *Annu. Rev. Biochem.*, **56**, 159 (1987).
326. M. J. Berridge and R. F. Irvine, *Nature*, **312**, 315 (1984).
327. J. P. Vacca, S. J. de Solms and J. R. Huff, *J. Am. Chem. Soc.*, **109**, 3478 (1987).
328. Y. Watanabe, M. Mitani and S. Ozaki, *Chem. Lett.*, 123 (1987).
329. C. B. Reese and J. G. Ward, *Tetrahedron Lett.*, **28**, 2309 (1987).
330. J. L. Meek, F. Davidson and F. W. Hobbs, *J. Am. Chem. Soc.*, **110**, 2317 (1988).
331. A. M. Cooke, B. V. L. Potter and R. Gigg, *Tetrahedron Lett.*, **28**, 2305 (1987).
332. C. E. Dreef, R. J. Tuinman, C. J. J. Elie, G. A. vander Marel and J. H. van Boom, *Red. Trav. Chim. Pays-Bas*, **107**, 395 (1987).
333. P. C. Ruenitz and J. R. Bagley, *J. Labelled Compd. Radiopharm.*, **21**, 857 (1984).
334. P. C. Ruenitz, *Drug Metab. Dispos.*, **9**, 456 (1981).
335. P. C. Ruenitz, J. R. Bagley and C. M. Mokler, *Biochem. Pharmacol.*, **32**, 2941 (1983).
336. P. C. Ruenitz and J. R. Bagley, *J. Labelled Compd. Radiopharm.*, **20**, 1113 (1983).
337. J. R. Rapenheimer and K. Z. Reiss, *J. Membr. Biol.*, **100**, 123 (1987).
338. C. Tagesson, P. A. Anderson, T. Anderson, T. Bolin, M. Kallberg and R. Sjodahl, *Scand. J. Gastroenterol.*, **18**, 481 (1983).
339. J. F. Dellaria, Jr., J. F. Denissen, F. A. Kerdesky, R. G. Maki, D. J. Hoffman and H. N. Nellans, *J. Labelled Compd. Radiopharm.*, **27**, 1437 (1989).
340. J. Santamaria, P. Rivera, M. Esteban, J. L. Martin and J. M. Carretero, *J. Labelled Compd. Radiopharm.*, **25**, 287 (1988).
341. P. Manoury, A. Dumas, H. Najer, D. Branceni, M. Prouteau and F. M. Lefebre-Borg, *J. Med. Chem.*, **22**, 554 (1979).
342. V. Rovei, M. Broquaire, G. Tedeschi, J. J. Thebault, J. P. Sauvanet and J. Larrivaud, *Therapie*, **35**, 551 (1980).
343. A. M. Gotto, Jr., *Atheroscler. Rev.*, **4**, 17 (1979).
344. C. Harvengt and J. P. Desagon, *Int. J. Clin. Pharmacol. Res.*, **3**, 363 (1983).
345. R. S. P. Hsi, R. B. Gammill and E. G. Daniels, *J. Labelled Compd. Radiopharm.*, **22**, 1273 (1985).
346. J. Diago-Meseguer, A. L. Palomo-Coll, J. R. Fernandez-Lizarbe and A. Zugaza-Bilbona, *Synthesis*, 547 (1980).
347. (a) G. Natta, U. Colombo and I. Pasquon, in *Catalysis*, Vol. 5 (Ed. P. H. Emmett), Reinhold, New York, 1957, p. 131.
    (b) G. Natta, in *Catalysis*, Vol. 3 (Ed. P. H. Emmett), Reinhold, New York, 1955, p. 349.
    (c) H. H. Kung, *Catal. Rev. Sci. Eng.*, **22**, 235 (1980).
348. R. B. Anderson, J. Feldman and H. H. Storch, *Ind. Eng. Chem.*, **44**, 2418 (1952).
349. (a) K. J. Smith and R. B. Anderson, *J. Catal.*, **85**, 428 (1984).
    (b) K. Klier, *Adv. Catal.*, **31**, 243 (1982).
350. G. Vedage and K. Klier, *J. Catal.*, **77**, 558 (1982).
351. G. A. Vedage, R. Pitchai, R. G. Herman and K. Klier, in *Proc. 8th Int. Cong. Catal., Vol 2, II-47-58, West Berlin, 1984*, Dechema, Frankfurt-am-Main, 1984.
352. (a) P. J. Denny and I. C. I. Bilingham, in Reference 351, p. VI-19.
    (b) A. Y. Rozovskii, G. I. Lin, L. G. Liberov, E. V. Sliminskii, S. M. Loktev, Y. B. Kagan and A. N. Basshkirov, *Kinet. Katal.*, **18**, 691 (1977).
    (c) G. C. Chinchen, P. J. Denny, D. G. Parker, M. S. Spencer and A. D. Whan, *Appl. Catal.*, **30**, 333 (1987).
    (d) G. C. Chinchen, P. J. Denny, D. G. Parker, G. D. Short, M. S. Spencer, K. C. Waugh and D. A. Whan, *Prepr., Div. Fuel Chem. Am. Chem. Soc.*, **29**, 178 (1984).
    (e) G. C. Chinchen, K. C. Waugh and D. A. Whan, *Appl. Catal.*, **25**, 101 (1986).
353. G. A. Vedage, R. G. Herman and K. Klier, *J. Catal.*, **95**, 423 (1985).
354. G. E. Parris and K. Klier, *J. Catal.*, **97**, 374 (1986).
355. G. A. Vedage, P. B. Himelfarb, G. W. Simmons and K. Klier, *ACS Symp. Ser.*, **279**, 295 (1985).
356. G. E. Parris and K. Klier, *J. Catal.*, **97**, 374 (1986).
357. J. Nunan, K. Klier, Ch.-W. Young, P. B. Himelfarb, R. G. Herman, K. Klier, C. E. Bogdan and G. W. Simmons, *Inorg. Chem.*, **28**, 3868 (1989).
358. J. G. Nunan, C. E. Bogdan, K. Klier, K. J. Smith, C.-W. Young and R. G. Herman, *J. Catal.*, **113**, 410 (1988).
359. K. Klier, R. G. Herman, J. G. Nunan, K. J. Smith, C. E. Bogdan, C.-W. Young and J. G. Santiesteban, in *Methane Conversion* (Eds. D. M. Bibby, C. D. Chang, R. F. Howe and S. Yurchak), Elsevier, Amsterdam, 1988, pp. 109–125.

360. J. G. Nunan, C. E. Bogdan, R. G. Herman and K. Klier, *Catal. Lett.*, 49 (1989).
361. J. G. Nunan, R. G. Herman and K. Klier, *J. Catal.*, **116**, 222 (1989).
362. J. G. Nunan, P. B. Himelfarb, R. G. Herman, K. Klier, C. E. Bogdan and G. W. Simmons, *Inorg. Chem.*, **28**, 3868 (1989).
363. J. G. Nunan, C. E. Bogdan, K. Klier, K. J. Smith, C.-W. Young and R. G. Herman, *J. Catal.*, **116**, 195 (1989).
364. (a) J. G. Santiesteban, C. E. Bogdan, R. G. Herman and K. Klier, *Mechanism of C_1–C_4 Alcohol Synthesis over Alkali/MoS_2 and Alkali/Co/MsO_2 Catalysts*, Lectures presented by Kamil Klier, Faculty of Chemistry, Jagellonian University, Cracow, 1990.
(b) R. R. Stevens, Eur. Pat. Appl. 85 109214.8 (July 23, 1985), assigned to Dow Chemical Co.
365. J. Haber, *The Mechanisms of Interactions of Hydrocarbons with Active Catalytic Centres*, 23rd Annual Polish Colloq. on Catalysis, Cracow, 1991-02-05, Plenary Lecture and Annual Polish Chem. Soc. Meeting, Sept. 4, 1991, Plenary Lecture W2.
366. P. Courty, O. Durand, E. Freund and A. Sugier, *J. Mol. Catal.*, **17**, 241 (1982).
367. J. A. Sibilia, J. M. Dominguez, R. G. Herman and K. Klier, Prepr., *Div. Fuel. Chem., Am. Chem. Soc.*, **29**, 261 (1984).
368. (a) A. Ueno, T. Onishi and K. Tamaru, *Trans. Faraday Soc.*, **66**, 756 (1970).
(b) J. F. Edwards and G. L. Schrader, *J. Phys. Chem.*, **89**, 782 (1985).
369. (a) J. Saussey, J. C. Lavalley, J. Lamotte and T. Rais, *Chem. Commun.*, 278 (1982); see also Reference 369b.
(b) A. Takeuchi and J. R. Katzer, *J. Phys. Chem.*, **85**, 937 (1981).
370. K. Klier, J. H. Shen and A. C. Zettlemoyer, *J. Phys. Chem.*, **77**, 1458 (1973).
371. J. March, *Advanced Organic Chemistry*, 2nd ed., McGraw-Hill, New York, 1977, p. 819.
372. J. B. Bulko, R. G. Herman, K. Klier and W. G. Simmons, *J. Phys. Chem.*, **83**, 3118 (1979).
373. V. D. Kuznetsov, F. S. Shub and M. I. Temkin, *Kinet. Katal.*, **23**, 932 (1982).
374. K. Klier, reply to P. J. Denny, published in Reference 351, pp. VI, 19–20.
375. V. Ponec, in Reference 347, p. VI, 20 (remarks on lecture by K. Klier).
376. K. C. Waugh, in Reference 347, p. VI, 21 (remarks on lecture by K. Klier).
377. C. D. Chang and A. J. Silvestri, *J. Catal.*, **47**, 249 (1977).
378. G. Thomas, *Ann. Chim.*, **6**, 367 (1951).
379. C. E. Bogdan, Ph. D. Dissertation, Department of Chemistry, Lehigh University, Bethlehem, PA, 1988.
380. M. Zieliński, A. Wawer and A. Tabaka, *Nukleonika*, **15**, 165 (1970).
381. M. Zieliński, *Nukleonika*, **16**, 191 (1971).
382. M. Zieliński and A. Wawer, *Rocz. Chem.*, **46**, 315 (1972).
383. A. Wawer and M. Zieliński, *Nukleonika*, **23**, 903 (1978).
384. A. Wawer, Ph. D. Dissertation, Department of Chemistry, Warsaw University, Warsaw, 1975.
385. A. Wawer and M. Zieliński, *Polish J. Chem.*, **55**, 147 (1981).
386. J. C. Gjaldbaek, *Acta Chim. Scand.*, **2**, 683 (1948).
387. A. Aguilo and T. Horlenko, *Hydrocarbon Proc.*, **59**, 120 (1980).
388. S. P. Tonner, D. L. Trimm and M. S. Wainwright, *J. Mol. Catal.*, **18**, 215 (1983).
389. N. W. Cant, S. P. Tonner, L. D. Trimm and M. S. Wainwright, *J. Catal.*, **91**, 197 (1985).
390. K. Takahashi, N. Takezawa and H. Kobayashi, *Chem. Lett.*, 7, 106 (1983).
391. B. Denise and R. P. A. Sneeden, C_1 *Mol. Chem.*, **1**, 307 (1985); B. Denise and R. P. A. Sneeden, *React. Kinet. Catal. Lett.*, **26**, 265 (1984); *Chem. Abstr.* **102**, 120666t (1985).
392. L. L. Mueller and G. L. Griffin, *J. Catal.*, **105**, 352 (1987).
393. P. A. Sorum and O. T. Onsager, in Reference 351, Vol. 2, p. 233.
394. K. Klier, D. Zeroka and D. Bybell, 189th National Meeting of the American Chemical Society, Miami Beach, FL, Abstract No. COLL-0033, April, 1985.
395. A. Takeuchi and J. R. Katzer, *J. Phys. Chem.*, **86**, 2438 (1982).
396. A. Takeuchi, J. R. Katzer and R. W. Crecely, *J. Catal.*, **82**, 474 (1983).
397. S. Kagami, S. Naito, Y. Kikuzono and K. Tamaru, *J. Chem. Soc., Chem. Commun.*, 256 (1983).
398. I. Wender, S. Friedman, W. A. Steiner and R. B. Anderson, *Chem. Ind.*, 1694 (1958).
399. H. Pichler and H. Schulz, *Chem.-Ing.-Tech.*, **42**, 1162 (1970).
400. G. Henrici-Olivé and S. Olivé, *Angew. Chem., Int. Ed. Engl.*, **15**, 136 (1976).
401. W. M. H. Sachtler, in Reference 351, Vol. 1, p. 151.
402. F. Fischer, *Ind. Eng. Chem.*, **17**, 576 (1925).
403. T. J. Mazanec, *J. Catal.*, **98**, 115 (1986).

404. G. D. Graves, *Ind. Eng. Chem.*, **23**, 1381 (1931).
405. J. R. Fox, F. A. Pesa and B. S. Curatolo, *J. Catal.*, **90**, 127 (1984).
406. J. G. Santiesteban, C. E. Bogdan, R. G. Herman and K. Klier, *Proc. 9th Int. Cong. Catal.* (Eds. M. J. Phillips and M. Ternan), Vol. 2, Chem. Inst. Canada, 1988, pp. 561–568.
407. M. Zieliński, in *The Chemistry of Carboxylic Acids and Esters* (Ed. S. Patai), Chap. 10, Interscience, London, 1969.
408. M. Kamińska, Master Thesis, Warsaw University, Warsaw, 1967.
409. Ia. T. Eidus, *Usp. Khim.*, **36**, 824 (1967).
410. Yu. I. Derbentsev and G. V. Isagulyants, *Usp. Khim.*, **38**, 1579 (1969).
411. J. R. H. Ross, M. C. F. Steel and A. Zeini-Isfahami, in *Symposium on the Mechanism of Hydrocarbon Reactions*, 5–7 June, 1973, Siofok, Hungary (Eds. F. Marta and D. Kallo), Akademiai Kiado, Budapest, 1975, pp. 201–214.
412. S. Krompiec and J. Suwiński, *Polish J. Chem.*, **64**, 505 (1990).
413. S. Krompiec, Annual Meeting of the Polish Chem. Soc., Cracow, September 4–7, 1991, Poster No. 43 in Z1.
414. Z. Rappoport, *Organic Chemistry Lecture R1*, Annual Meeting of The Polish Chem. Soc., Cracow, September 5, 1991.
415. Ch. S. Chin, S. Y. Lee, J. Park and S. Kim, *J. Am. Chem. Soc.*, **110**, 8244 (1988).
416. B. Capon and C. Zucco, *J. Am. Chem. Soc.*, **104**, 7567 (1982).
417. J. Henderson, *J. Chem. Educ.*, **65**, 349 (1988).
418. K. D. McMichael and G. L. Korver, *J. Am. Chem. Soc.*, **101**, 2746 (1979).
419. H. Schmid and K. Schmid, *Helv. Chim. Acta*, **35**, 1879 (1952).
420. J. P. Ryan and P. R. O'Connor, *J. Am. Chem. Soc.*, **74**, 5866 (1952).
421. M. J. S. Dewar and E. F. Healy, *J. Am. Chem. Soc.*, **106**, 7127 (1984).
422. J. J. Gajewski, in *Isotopes in Organic Chemistry*, Vol. 2 (Eds. E. Buncel and C. C. Lee), Elsevier, New York, 1987, pp. 115–176.
423. L. Kupczyk-Subotkowska, W. H. Saunders, Jr. and H. J. Shine, *J. Am. Chem. Soc.*, **110**, 7153 (1988).
424. T. Kurata, Y. Watanabe, M. Katoch and Y. Sawaki, *J. Am. Chem. Soc.*, **110**, 7472 (1988).
425. T. Matsuura, *Tetrahedron*, **33**, 2869 (1977).
426. W. K. Seok and T. J. Meyer, *J. Am. Chem. Soc.*, **110**, 7358 (1988).
427. A. R. Forrester and R. H. Thompson, *J. Chem. Soc.*, 1844 (1966).
428. D. G. Lee, *J. Org. Chem.*, **49**, 4509 (1984).
429. D. G. Lee and J. F. Perez-Benito, *J. Org. Chem.*, **53**, 5725 (1988).
430. D. G. Lee, in *Oxidation in Organic Chemistry*, Part D, Academic Press, New York, 1982, p. 151.
431. D. G. Lee and J. F. Perez-Benito, *Can. J. Chem.*, **63**, 1275 (1985).
432. A. K. Rappe and W. A. Goddard, *J. Am. Chem. Soc.*, **104**, 3287 (1982).
433. E. Melzer and H. L. Schmidt, *Biochem. J.*, **252**, 913 (1988).
434. C. Walsh, O. Lockridge, V. Massey and R. Abeles, *J. Biol. Chem.*, **248**, 7049 (1973).
435. G. A. Hamilton, *Prog. Bioorg. Chem.*, **1**, 83 (1971).
436. M. H. O'Leary, *Methods Enzymol.*, **64**, 83 (1980).
437. E. Melzer and H. L. Schmidt, *J. Biol. Chem.*, **262**, 8159 (1987).
438. F. Jordan, D. J. Kuo and E. U. Monse, *J. Am. Chem. Soc.*, **100**, 2872 (1978).
439. S. Seltzer, G. A. Hamilton and F. H. Westheimer, *J. Am. Chem. Soc.*, **81**, 4018 (1959).
440. M. H. O'Leary, *Bioorg. Chem.*, **1**, 259 (1977).
441. A. Mathur, V. Sharma and K. K. Banerji, *Indian J. Chem., Sect. A*, **27A**, 123 (1988); *Chem. Abstr.*, **109**, 210366u (1988).
442. A. Mathur and K. K. Banerji, *J. Chem. Soc., Perkin Trans. 2*, 1645 (1987).
(a) M. Zieliński, *Zesz. Nauk. Uniw. Jagiellon.* (*Universitatis Jagellonicae Acta Chimica*), **34**, 227 (1991).
443. J. Cunningham and S. Srijaranai, *J. Photochem. Photobiol.*, **43**, 329 (1988).
444. E. L. Zapadinskii and V. A. Tolkachev, *Khim Vys. Energ.*, **22**, 305 (1988).
445. I. I. Furlei, E. A. Burmistrov, A. S. Vorob'ev and G. A. Tolstikov, *Dokl. Akad. Nauk and SSSR*, **299**, 1442 (1988).
446. A. Liu, W. A. Mulac and C. D. Jonah, *J. Phys. Chem.*, **92**, 3828, 5942 (1988).
447. A. W. Wood, D. C. Swinney, P. E. Thomas and D. E. Ryan, *J. Biol. Chem.*, **263**, 17322 (1988).
448. F. P. Guengerich, L. A. Peterson and R. H. Boecker, *J. Biol. Chem.*, **263**, 8176 (1988).

449. H. Imamura, S. Kasahara, T. Takaida and S. Tsuchiya, *J. Chem. Soc., Faraday Trans. 1*, **84**, 765 (1988).
450. M. Akiyoshi and H. Hattori, *Sekiyu Gakkaishi*, **31**, 239 (1988); *Chem. Abstr.*, **109**, 229988v (1988).
451. J. M. Santiuste Bernejo, *Afinidad*, **44**, 427 (1987); *Chem. Abstr.*, **109**, 54176z (1988).
(a) M. Zieliński, G. Czarnota and Halina Papiernika-Zielińska, in *IXth National Meeting of The Polish Society for Radiation Research, Cracow, April 2–3, 1992* Institute of Nuclear Physics, Cracow, 1992, p. 84.
(b) M. Zieliński, G. Czarnota and Halina Papiernik-Zielińska, *J. Radioanal. Nucl. Chem., Articles*, **159**, 305 (1992).
(c) M. Zieliński, H. Papiernik-Zielińska and G. Czarnota, paper presented during the Annual Meeting of the Polish Chemical Society in Bialystok, September 1992.
452. W. N. Ye, D. Combes and P. Monsan, *Enzyme Microb. Technol.*, **10**, 498 (1988).
453. A. C. Elliott, B. F. Li, C. A. J. Morton, J. D. Pownall, T. Selwood, M. L. Sinnott, I. J. L. Souchard and A. K. Stuart-Tilley, *J. Mol. Catal.*, **47**, 255 (1988); *Chem. Abstr.*, **109**, 207156v (1988).
454. F. Hilbert and K. J. Spiers, *J. Chem. Soc., Perkin Trans. 2*, 571 (1988).
455. T. L. Mega and R. L. Van Etten, *J. Am. Chem. Soc.*, **110**, 6372 (1988).
456. D. S. Barratt and D. J. Cole-Hamilton, *J. Chem. Soc., Dalton Trans.*, 2683 (1987).
457. L. Amyes and A. J. Kirby, *J. Am. Chem. Soc.*, **110**, 6505 (1988).
458. N. Numazawa, M. Nagaoka and A. Mutsumi, *Chem. Pharm. Bull.*, **35**, 4673 (1987); *Chem. Abstr.*, **109**, 129425r (1988).
459. R. J. Strife and J. R. Simms, *Anal. Chem.*, **60**, 1800 (1988).
460. A. B. Belyev, V. A. Kuz'min and P. P. Levin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1007 (1988).
461. M. Zieliński and M. Kańska, in Reference 33a, pp. 1145–1146.
462. D. J. Hollander and J. A. McKenzie, *Geology*, **19**, 929 (1991).

CHAPTER 11

Epoxidation and hydroxylation

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Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

ABBREVIATIONS

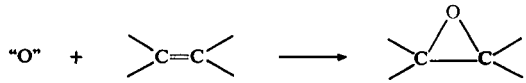
DCHT	dicyclohexyl tartrate	MMPP	magnesium monoperoxyphthalate
DCTA	dicyclohexyl tartramide	MTPP	metallo tetraphenylporphyrin
de	diastereomeric excess	PA	peroxycarboxylic acid
DET	diethyl tartrate	TPP	tetraphenylporphyrin
DIPT	diisopropyl tartrate		

I. INTRODUCTION

Epoxidation and hydroxylation are important and fundamental reactions in organic chemistry and have been studied extensively. The two functionalizations possess a common feature in that oxygen atoms are inserted.

Usually it is not easy to introduce directly dioxygen molecules (i.e. $^3O_2$) in reactions 1 and 2. Dioxygen is reduced into hydrogen peroxide, which is in turn activated by introducing appropriate substituents. A typical example is peroxycarboxylic acid, RCO_3H, which shows enhanced electrophilicity owing to the strongly electron-attracting acyl

group. An alternative important activation method is the utilization of metallic catalysts forming metallo peroxides (MOOR) or exo metal (M=O) as an active species. In these cases asymmetric oxidations are anticipated since the reactions involve a possible contact interaction with substrate molecules in the coordination field of the metallic catalysts. Such reactions will be discussed in detail in the following sections.



(1)

(2)

Nucleophilic oxygen transfers by ROO^- to electron-deficient olefins are another relevant type of reaction. Here again, asymmetric induction is anticipated because the oxidation involves a contact interaction between base-catalysts and substrates. On the contrary, in radical hydroxylations and epoxidations, stereospecific O-transfers are not possible because of the intermediacy of planar radicals.

Cytochrome P-450 model reactions have recently been studied extensively. Metallo porphyrins (P—M) are oxidized into high valent oxo metallo compounds (P—M=O) which in turn transfer an oxygen atom to various substrates (equation 3). An important feature of these model systems is that they often lead to an asymmetric oxygenation. The oxidants usually used are peroxyacids (RCO_3H), iodosylarenes (ArIO), hypochlorite ion (ClO^-) and sometimes dioxygen (O_2).

$$P—M \xrightarrow{\text{oxidant}} P—M{=}O \longrightarrow O\text{-transfer} \qquad (3)$$

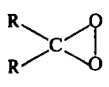
A large number of studies have been conducted on the epoxidation and hydroxylation of organic compounds, and these have been reviewed repeatedly. The present chapter summarizes recent developments in the epoxidation of C—C double bonds and the hydroxylation of C—H bonds. Interest is focussed on regioselectivities and on asymmetric oxidations. Topics on heterogeneous catalyses are not included.

II. EPOXIDATION

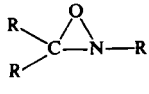
A. Introduction

Epoxidations of olefins are important synthetic and industrial reactions. Electrophilic epoxidations by peroxyacids have been applied repeatedly and reviewed extensively[1]. Various types of electron-attracting groups were tested in order to elevate the electrophilicity of hydrogen peroxide[2]. For example, peroxycarbonic acids were developed as neutral epoxidizing reagents not producing acids.

Three-membered peroxides, dioxiranes (**1**) and oxaziridines (**2**), are recently developed remarkable oxidants. The latter are easily obtained by peroxide oxidation of imines and have been applied for asymmetric O-transfers. Dioxirans (**1**) are formed *in situ* by the reaction of ketones with monoperoxy sulfate ions. The chemistry and characterization of dioxiranes was pioneered by the group of R. W. Murray[3]. The high strain energy



(1)

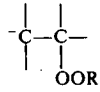


(2)

involved leads to enhanced reactivity, and hence to a neutral epoxidation at low temperatures suitable for the preparation of unstable epoxides.

Radical epoxidations by proxy radicals, ROO·, are long known side reactions in the autoxidation of olefins. Epoxide formation by the cyclization of the adduct radical (**3**) becomes a major reaction when an acylperoxy radical (RCO_3·) is used. Here, the stereospecificity is lost because of the involvement of radical **3**, affording more stable *trans*-epoxides predominantly. The same is true for the nucleophilic epoxidation of electron-deficient olefins with the peroxide anion ROO^-, where a similar adduct (**4**) is involved. In this case, however, an asymmetric epoxidation is possible in the presence of appropriate asymmetric catalysts.

(3)



(4)

Recently, much interest has been centred on metal-catalyzed asymmetric epoxidations. The pioneering work was done by Katsuki and Sharpless on Ti-catalyzed asymmetric epoxidation of allylic alcohols (see Section II.F.5). A recent topic is the asymmetric epoxidation of unfunctionalized olefins. Stereoselective epoxidations have been reported by biomimetic systems such as metalloporphyrins[4]. An enantiomeric excess of 80% has been attained by using sophisticated porphyrins.

The mechanisms and scope of various types of epoxidations are reviewed in the following sections, focussing on stereoselective epoxidations.

B. Electrophilic Epoxidations by Peroxyacids

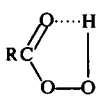
1. Mechanism of epoxidation by peroxycarboxylic acids

The epoxidation of olefins by peroxycarboxylic acids (PA) is quite important and has been reviewed repeatedly[1]. The characteristic features of epoxidations with PAs are such that the epoxidations are accelerated (a) by increasing electron density in C—C double bonds and (b) electron-attracting groups on PAs. The epoxidation rates are significantly reduced by intermolecular hydrogen bonds with coordinating solvents such as ethers. The scale of relative reactivity (R = alkyl)[1a]

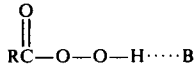
$$\underset{1}{CH_2{=}CH_2} < \underset{25}{RCH{=}CH_2} < \underset{60}{PhCH{=}CH_2} < \underset{500}{RCH{=}CHR} < \underset{600}{R_2C{=}CR_2}$$

is important for the prediction of product selectivities.

The intramolecular hydrogen bonding of RCO_3H (**5**) was evidenced by its IR,[5] dipole moments[6] and microwave analyses[7]. In coordinating solvents, peroxycarboxylic acids exist as the complex **6** with intermolecular hydrogen bonding[8]. Thus, the transition picture **7** (equation 4) has been widely accepted. Kinetic isotope effect studies suggested that the transition state (**7**) is somewhat unsymmetrical[9]. Solvent effects in the PA epoxidations are significant, e.g. the epoxidation rates in ether or ethyl acetate are

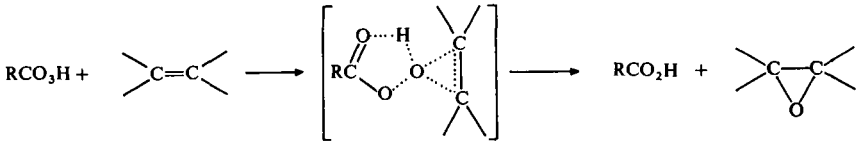


(5)



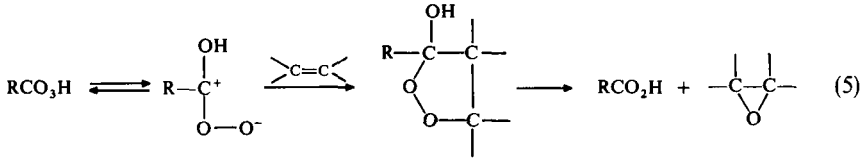
(6)

approximately one-tenth of those in benzene or chloroform. The much slower epoxidation with PAs with intermolecular H-bonding (**6**) is suggestive of the importance of cyclic transition state **7**. When coordinating groups are available in olefins, their intermolecular hydrogen bonding with PA leads to a *syn*-selective epoxidation[10] (see Section II.B.3).



(7) (4)

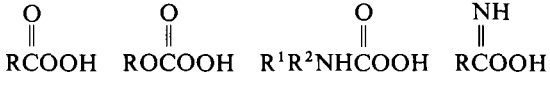
As an alternative pathway for epoxidation, a 1,3-dipolar mechanism, was proposed where PA reacts as a 1,3-dipolar reagent[11] (**8**, equation 5). However, the relative reactivity of various olefins[12] and the absence of steric retardation for substituted PAs[13] are against the 1,3-dipolar mechanism. The simple picture of equation 4 can explain all the experimental results.



(8) (9) (5)

2. Epoxidations by various peroxyacids

Since hydrogen peroxide is not sufficiently electrophilic to epoxidize olefins directly, its reactivity must be enhanced by introducing electron-attracting groups as shown in peroxyacids **10–13.**



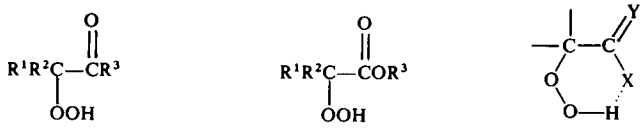
(10) **(11)** **(12)** **(13)**

Peroxycarboxylic acids (**10**) have been used widely and their electrophilic reactivity is enhanced by the electron-attracting acyl group. PAs are synthesized by the acid-catalyzed reaction of RCO_2H[14] or the base-catalyzed reaction of RCOCl with hydrogen peroxide[15]. The most widely used PA in laboratories has been *meta*-chloroperoxybenzoic acid (MCPBA), but its commercial manufacture is planned to be stopped owing to its hazardous nature. It is said that magnesium monoperoxyphthalate (MMPP)[16] could be handled safely and reacts in a similar way as MCPBA.

Epoxides are sensitive to acid-catalyzed ring-opening reactions and hence sodium carbonate or phosphate buffers are sometimes added to neutralize the carboxylic acid formed.[17] In case of peroxycarbonic (**11**)[18] and peroxycarbamic acids (**12**)[19], neutral epoxidations are possible because no acids form. The most useful adaptation of the activation principle was accomplished by Payne[20]. Thus, the epoxidations by peroxycarboimidic acid (**13**) *in situ* formed from nitriles (usually solvent acetonitrile) and hydrogen peroxide are quite safe and useful since, under weakly alkaline conditions, the oxidations are conducted without accumulation of peroxide **13**[20,21]. The imido peroxyacids **13** epoxidize olefins electrophilically like **10**[21], and are suitable also for

large-scale preparations[22]. When trichloroacetonitrile is used, the epoxidation proceeds under neutral conditions (i.e. pH ~7)[23]. The reaction of the Vilsmeier reagent with hydrogen peroxide is reported to yield imidonium peroxides, $R_2N^+{=}CH(OOH)$, which are able to epoxidate olefins at low temperatures[24].

α-Hydroperoxyketones (**14**) and esters (**15**) are easily obtained by base-catalyzed autoxidation. In these the electron-attracting groups are separated by one-carbon atom from the —OOH group. Olefins are epoxidized on gentle heating with α-hydroperoxyketones, esters, nitriles and amides[25]. The intramolecular hydrogen bonding shown in the general structure **16** was evidenced by the fact that the epoxidation rates were not dependent on solvents[19b]. A similar intramolecular H-bonding was reported in the epoxidation with α-azo hydroperoxides[26].



(14) (15) (16)

The electrophilic reactivities of various hydroperoxides range over many orders of magnitude from hydrogen peroxide to peroxycarboxylic acid, as exemplified for the oxidation of sulfide (equation 6)[27].

$$t\text{-BuOOH} < \text{HOOH} < \underset{\text{OOH}}{\text{Ph}_2\text{CCO}_2\text{Me}} < \underset{\text{OOH}}{\text{Ph}_2\text{CC}{\equiv}\text{N}} < \text{ArCO}_3\text{H} \qquad (6)$$

0.41 1.00 2.3×10^2 6.2×10^2 5.3×10^6

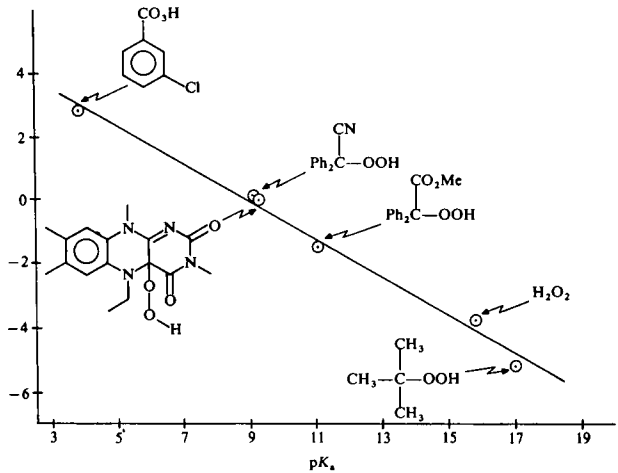
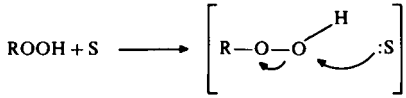


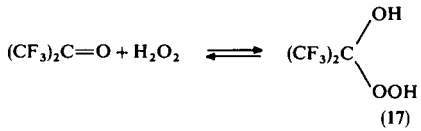
FIGURE 1. Plot of log of second-order rate constants for the sulfoxidation of thioxane (k_a) by ROOH species vs the pK_a of the corresponding ROH. Solvents were *t*-BuOH for rates and water for the pK_a values at 30 °C. Reprinted with permission from T. C. Bruice, J. B. Noar, S. S. Ball and U. V. Venkataram, *J. Am. Chem. Soc.*, **105**, 2452 (1983). Copyright (1983) American Chemical Society

The relative rates of ROOHs are correlated satisfactorily with the pK_a values of the corresponding ROHs (Figure 1). This suggests that the S_N2 reaction on the peroxy oxygen is controlled by the departing ability of RO^- (equation 7). It is interesting to note that 4*a*-hydroperoxylumiflavin, a model peroxide in monooxygenases, also satisfies the correlation in Figure 1.



(7)

Peroxyhemiacetal (**17**; equation 8) as an adduct of hexafluoroacetone and hydrogen peroxide is an effective epoxidizing agent[28]. The epoxidation of olefins proceeds in the presence of a catalytic amount of ketone under neutral conditions.

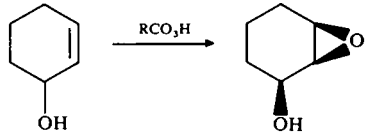


(17)

(8)

3. *Stereoselective epoxidation by peroxyacids*

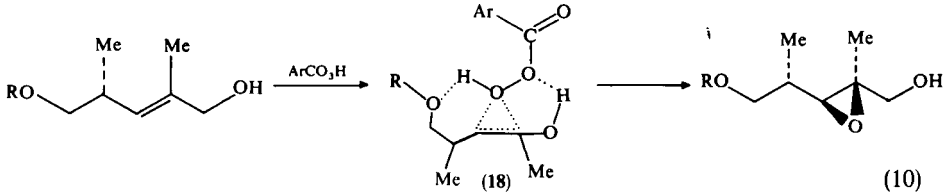
Peroxycarboxylic acids exist as the intramolecular H-bonded form (**5**), as noted in the previous section, in non-coordinating solvents and as the intermolecular H-bonded form (**6**) in coordinating solvents such as ethers. When a coordinating group is present in an olefin, a directed epoxidation could be attained. A typical example is the *syn*-epoxidation of cyclic allyl alcohols (equation 9)[10,29].



(9)

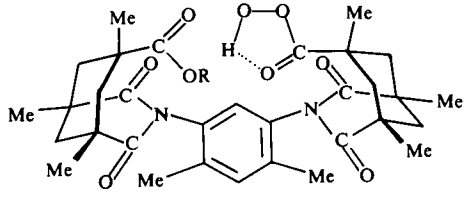
Selective formations of *syn*-epoxides are also known for olefins having amide[30], carbamate[31] and acetal groups[32]. However, only low *syn*-selectivity has been reported for olefinic esters[33] and for some allylic alcohols[34]. The importance of H-bonding as the directing effect for *syn*-epoxidations is exemplified by the fact that the *syn*:*anti* ratios for the CF_3CO_3H epoxidation of cyclohexenyl silylether changed from 4.5:1 in dichloromethane to 1:7.5 in THF[35]. The more stable *anti*-epoxide became a predominant product in the oxidation with the hydrogen-bonded complex of CF_3CO_3H and THF.

It is interesting to note here that a cooperative hydrogen-bonding effect was observed in the epoxidation of acyclic allylic alcohols[36]. A highly selective epoxidation could be realized via cooperative H-bonding (**18**) as shown in equation 10.



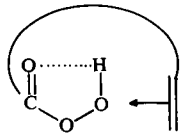
(10)

The steric effect of substituents on olefins is usually small since PA epoxidations proceed by transferring the outer peroxidic oxygen as pictured as **7** in equation 4. For example, rate ratios for *cis*- and *trans*-olefins are close to unit, i.e. only 1.1–2.2. Rebeck and coworkers synthesized highly crowded peroxyacids (**19**) and compared their epoxidation rates[37]. The resulting *cis/trans* ratios for the epoxidation of 2-octenes were 1.2, 5.6 and 7.7 for MCPBA, **19** (R = Me) and **19** (R = Et), respectively, suggesting a high ratio for the C-shaped peroxyacid **19**. These results indicate that a stereoselective epoxidation is possible by using a highly crowded peroxyacid.



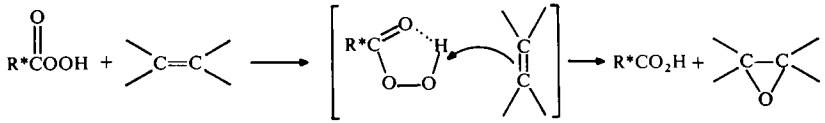
(19)

A selective epoxidation of peroxyarachidonic acid was shown to proceed intramolecularly, via a large-ring transition state as pictured in **20**[38].

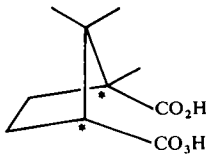


(20)

Attempted asymmetric epoxidations (equation 11) using optically active peroxyacids (**21**) were unsuccessful (i.e. <5% ee)[39]. Inspection of the transition state (**22**) for the epoxidation shows that a high asymmetric induction in epoxides cannot be expected because of the absence of any contact interaction between the chiral R* group and olefin molecules[29a,39]. For example, the epoxidation of styrene with (+) monoperoxycamphoric acid (**23**) resulted in only 4.4% ee[40].



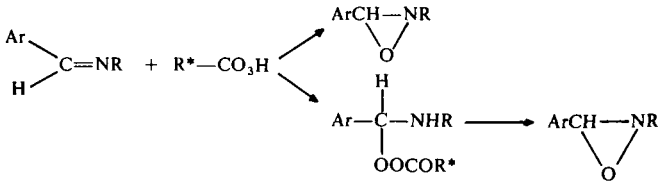
(21) (22) (11)



(23)

In contrast, rather high enantiomeric excess values could be obtained in the oxidation of imines by peroxyacids. Optically active oxaziridines were prepared in up to 60% ee yield

by using the peroxyacid **23**[41]. The high asymmetric induction could not be explained by the one-step mechanism (equation 12a), but is indicative of the two-step mechanism of equation 12b involving separate addition and cyclization steps. In the latter mechanism, a contact interaction becomes possible between the asymmetric center R* and the central carbon atom. An earlier kinetic study on oxaziridine formation also supported the two-step mechanism[42].



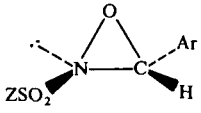
(12a)

(12b)

C. Epoxidations with Oxaziridines and Dioxiranes

1. Epoxidations by oxaziridines

Davis and coworkers showed that sulfonyloxaziridines (**24**) are useful neutral oxidizing reagents and are easily obtained by the epoxidation of sulfonimines with peroxyacids or monoperoxy sulfate ($KHSO_5$, oxone)[43].



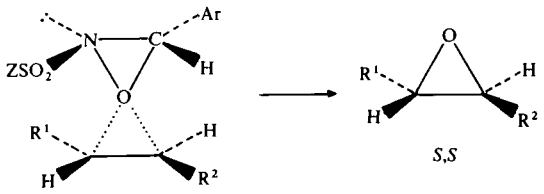
(24)

Their formation and reactivity have been reviewed recently[44]. The oxidizing ability of the oxaziridine is enhanced by the strongly electron-attracting sulfonyl group, transferring the oxygen atom to substrates. The epoxidation is accelerated by electron-attracting groups in Ar and Z, affording a positive Hammett ρ-value of $+1.0$[45].

The most interesting feature of oxaziridines is that they are suitable for stereoselective O-transfers[46]. The selective oxidation is due to the rigid stereochemistry of three-membered oxazirane rings. Either a planar (**25**) or a spiro transition state (**26**) is conceivable for the epoxidation with **24** (equations 13 and 14).

After examining the selectivity of olefin epoxidations with several optical active oxaziridines (**24**), Davis and colloborators concluded that the planar transition state as shown in equation 13 is operative[47]. *Ab initio* calculations for simple model reactions also indicated that the planar transition state is more probable[48].

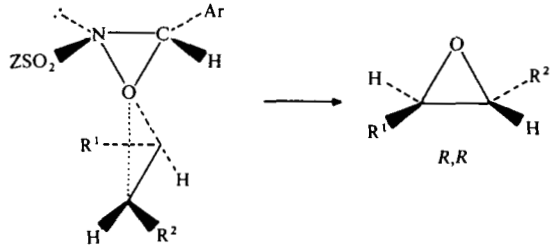
The transition state **25** is of a more tight structure in comparison to the case of peroxyacids (equation 11). The olefin substituents R^1 and R^2 are situated in close proximity



(25), planar

S,S

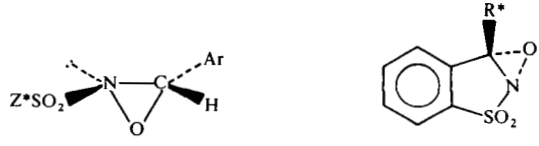
(13)



(26), spiro

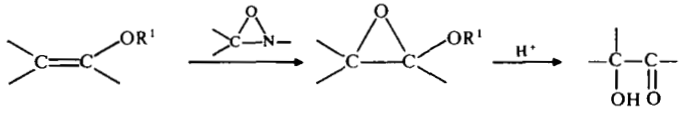
R,R (14)

to the two asymmetric centers of oxaziridine. Indeed, many successful cases of asymmetric epoxidations with oxaziridines have been reported. For example, the epoxidation of β-methylstyrene with **27**[49] and **28**[47b] afforded the asymmetric epoxide in 65 and 61% ee, respectively. These % ee values are rather high for unfunctionalized olefins. Further improvement in the structure of oxaziridines may lead to a practical asymmetric epoxidation.



(−)-(*S,S*)-(27) (28)

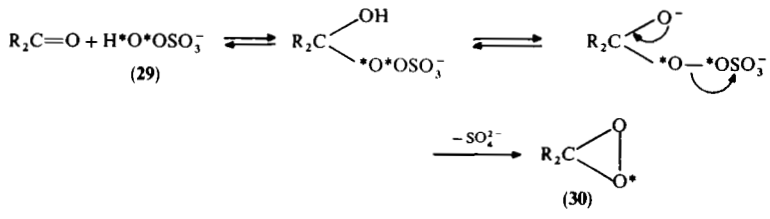
The epoxidation of enol ethers followed by acid-catalyzed transformation into α-hydroxy ketones (equation 15) is a useful synthetic method[50]. The formation of asymmetric α-hydroxy ketones via the asymmetric epoxidation will be described in Section III.B.2.



(15)

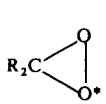
2. Epoxidations by dioxiranes

The chemistry of dioxiranes has been developed in the last decade and has been reviewed by prominent authors[3,51], so we will outline it only briefly. Dioxirane chemistry was started by a careful observation of Montgomery that the decomposition of the caroate ion (HSO_5^-) was accelerated by the addition of acetone in neutral aqueous solutions[52]. The dioxirane intermediates were proposed, since added substrates were oxidized and a scrambled oxygen (O=M*) was produced from doubly-labeled caroate (**29**, equations



(29) (30) (16)

16 and 17a)[53]. Since then, the caroate–ketone system was shown to be quite useful for the oxygenation of olefins, sulfur and nitrogen compounds and other hydrocarbons[54]. The pathway of equation 17b was evidenced by the fact that the resulting ^{18}O content in substrates was just the half (i.e. */2) of $^{18}O\%$ in the starting caroate[55].



(30)

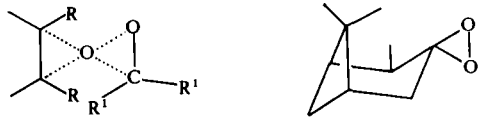
$$\xrightarrow{HSO_5^-} R_2CO + O{=}O^* \qquad (17a)$$

$$\xrightarrow{S:} R_2C{=}O + S{=}O^{*/2} \qquad (17b)$$

The breakthrough in dioxirane chemisty was achieved by Murray and Jeyaraman by distilling the dioxirane solutions and demonstrating their potent reactivity[56]. Dimethyldioxirane in acetone was a yellow compound absorbing ultraviolet light at 335 nm and oxidized olefins to produce epoxides in over 90% yield. Later, the spectral characterizations for various dioxiranes were reported[57].

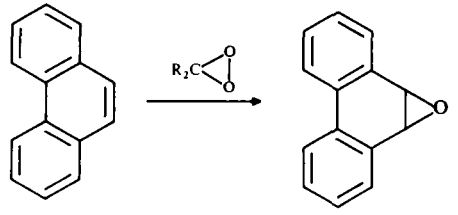
Dioxiranes epoxidize olefins stereospecifically and electrophilically as shown by the epoxide stereochemistry and by the Hammett's substituent effect of $\rho = -0.90$ for substituted styrenes[58]. A significantly large steric effect was observed in the epoxidation of aliphatic olefins; the rate ratios for *cis*- and *trans*-olefins were *ca* 10 in contrast to the peroxyacid case (i.e. 1–2). this large effect reflects a repulsive interaction between the olefin and dioxirane substituents in the transition state (**31**). An asymmetric epoxidation has also been attempted using chiral ketons. For example, the attempted induction with chiral dioxirane **32** was only 9–12.5% ee[59]. This indicates that the interaction of the chiral group with the olefins is too weak to induce significant asymmetry.

Since dioxiranes are neutral oxidants and possess high reactivity, they are conveniently used for the preparation of unstable epoxides. Thus, arene oxides were prepared easily[56,60]. Methyl(trifluoromethyl)-dioxirane is a potent oxidant and epoxidizes phenanthrene smoothly at $-20\,^{\circ}C$ affording the 9,10-oxide[61], see equation 18. Allenes could be converted to acid-sensitive spiro epoxides[62]. The formation (equation 19) of allene monoepoxide (**33**) and diepoxide (**34**) could be easily controlled by the stoichiometric amount of dioxirane. The epoxides **33** and **34** are useful synthetic intermediates.

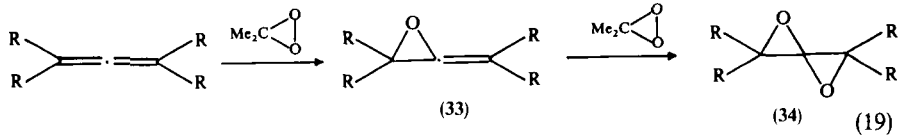


(31)

(32)



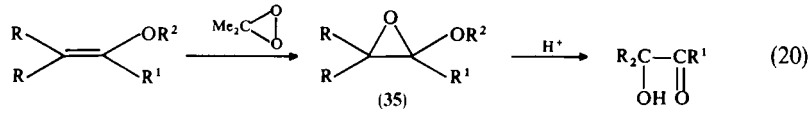
(18)



(33) (34)

(19)

The epoxidations of enol ethers[63a,b] and silyl enol ethers [63b,c] are also successful by using dioxiranes. The isolation of enol epoxides is quite easy and can be carried out by the evaporation of the solvent acetone. In the case of silyl enols ($R^2 = SiR_3$), the corresponding epoxides (**35**; equation 20) are easily converted to α-silyloxy ketones as a useful synthetic intermediate.



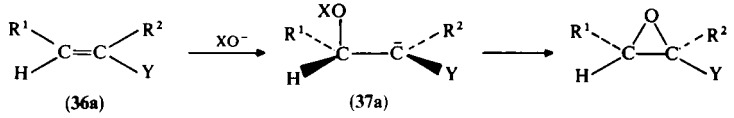
(20)

The oxidizing ability of dioxiranes is high enough to epoxidize directly electron-deficient olefins such as α,β-unsaturated esters[56,64]. Here, it is obvious that dioxiranes epoxidize the olefins electrophilically since electron-donating groups accelerated the epoxidation, i.e. $\rho = -1.53$ for substituted cinnamates[65]. The potent oxidizing ability of dioxiranes is due to the strain energy of the three-membered peroxide[56]. Considering the high oxidizing power of dioxiranes, their application for syntheses will increase probably significantly in the future.

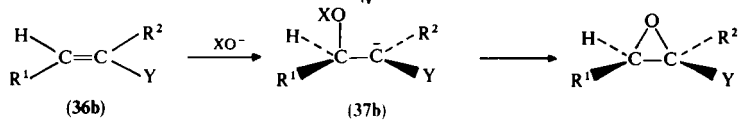
D. Nucleophilic Epoxidations

1. *Nucleophilic epoxidations*

The reaction of hydroperoxide ions with electron-deficient olefins (**36**, Y = COR, CO_2R, CN, etc.) is known as the alkaline or nucleophilic epoxidation (or the Weitz–Scheffer epoxidation)[67]. In the case of alkaline hydrogen peroxide (X = OH), the equilibria between the Michael adduct **37a** and **37b** are established and *trans*-epoxides are obtained stereo-selectively via the intramolecular cyclization of the more stable conformer **37b** (equation 21a and 21b).



(21a)



(21b)

Stereospecific epoxidation would result if the cyclization of **37** were faster than the isomerization between **37a** and **37b**. Such cases have been found with hypochlorite (X = Cl)[68] and peroxycarboxylate anions (X = RCO)[69], the stereospecificity being higher with the former. A detailed theoretical study on these nucleophilic epoxidations has been reported[70]. The paper states that the stereospecificity becomes higher (a) with increasing nucleofugacity (i.e. leaving group ability) of X, (b) with increasing hyperconjugation ability of COX and (c) with decreasing electron-attracting ability of Y.

Typical alkaline epoxidations are conducted with hydrogen peroxide or sodium hypochlorite in the presence of sodium or potassium hydroxide in water or aqueous methanol[71]; among those used are Amberlyst 15[72], perborate salts[73], and alumina support[74]. The hydrogen peroxide epoxidation of α,β-unsaturated acids catalyzed by tungstate at pH 5–7

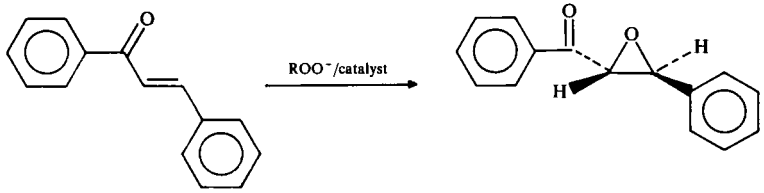
was shown to be an electrophilic reaction because of the accelerating effect of alkyl groups[75]. The epoxidation of fluoroolefins is conveniently done with hypohalite ions[76]. Exceptionally stable fluoro-α-lactones have been synthesized by the ClO^- oxidation of perfluoroketenes (equation 22)[77].

$$R_2C{=}C{=}O \xrightarrow{ClO^-} R_2C(O)C{=}O \qquad (22)$$

The nucleophilic oxidation of ketenes by iodosobenzene yields, via α-lactones, polyesters[78].

2. *Asymmetric epoxidations*

The pioneering work on asymmetric epoxidations by Wynberg's group was done by applying optically active phase-transfer catalysts[79]. Chalcone was epoxidized in 48% ee by utilizing the alkaloid catalyst **38**; see equation 23. Later, many catalysts were developed for nucleophilic epoxidations. Thus, the use of cyclodextrins resulted in only 11% ee[80], but poly-*L*-alanines[81] and poly-*L*-leucine[82] were good catalysts affording epoxides up to 96 and 92% ee, respectively. The best result of 99% ee has been reported for the case of polymer-supported polyamino acids[83]. Employing these catalysts, practically pure 2*R*,3*S*-epoxides were synthesized conveniently since the products were easily separated from the polymer-supported catalysts.



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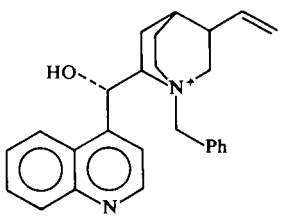


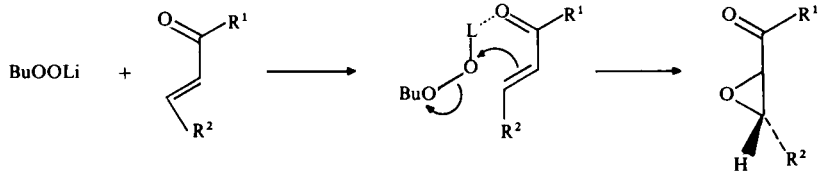
(38)

The asymmetric Weitz–Scheffer epoxidation of naphthoquinones has been extensively studied using various phase-transfer catalysts[84]. In the epoxidation with bovine serum albumine catalyst, the reaction with *t*-BuOOH afforded a higher ee% than with HOOH[85a]. The asymmetric induction was dependent on solvents,[85b] the best result being 100% ee[85c].

In these epoxidations under phase-transfer conditions, the asymmetric induction is apparently due to the contact interaction between the catalyst and the Michael adduct. The asymmetric epoxidations are not always general but are significantly dependent on the substrate structures; e.g., a small structural change might result in a large decrease in ee%.

An interesting attempt is the epoxidation with lithium *t*-butyl peroxide under anhydrous conditions, when α,β-unsaturated esters and sulfones are epoxidized in a stereo- and

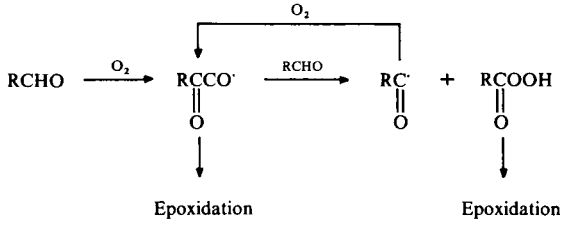
regiospecific manner[86]. When esters of chiral alcohols were oxidized by *t*-BuOOLi, the corresponding epoxides were obtained in 65% diastereomeric excess (de)[86b]. In these cases the contact coordination of the Li ion with the carbonyl oxygen is the origin of asymmetric induction (equation 24).



(24)

E. Radical Epoxidations

The autoxidations of olefins are long known to be accompanied by C—C bond scissions and epoxidations[87]. The co-autoxidation of aldehydes and olefins is also known to result in epoxidation of the olefin by peroxyacid and acylperoxy radicals ($RCO_3^{\cdot}$) as shown in equation 25[88]. Later, it was reported that the photooxidation of diketones under oxygen results in an efficient *trans*-epoxidation[89]. Since the relative reactivities of these substrates are different from those of peroxyacids, the photoepoxidation may be applied as a selective synthetic method[90]. Details of this photoepoxidation were studied and acylperoxy radicals were shown to be key intermediates (equation 26)[91]. Here, olefins were epoxidized electrophilically since Hammett's ρ-value for substituted styrene was -1.0 (vs σ^+) and practically identical with the value for $PhCO_3H$ epoxidation ($\rho = -0.96$ vs σ^+)[92]. The importance of polar transition state **39** is deduced from the negative ρ-value. It is interesting to note that the addition of $RCO_3^{\cdot}$ to styrenes is 10^5-fold faster than that of *t*-BuOO$^{\cdot}$, which is explicable by the polar effect such as shown in **39**.



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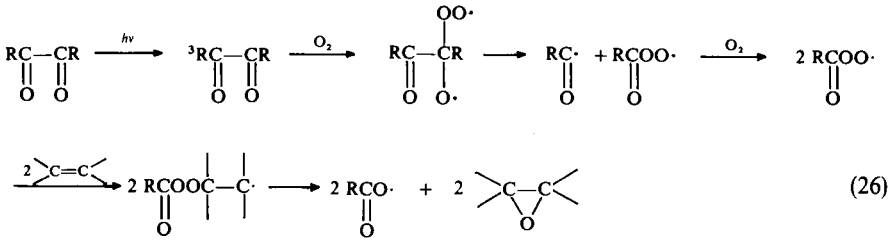
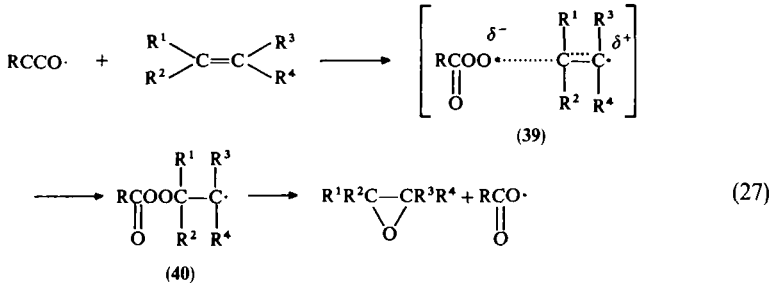


(26)

TABLE 1. Relative rates for the epoxidation of olefins

Substrate	$PhCO_3H$[92]	$MeCO_3\cdot$[92]	Me_2C(O)O[58]
$PhCH{=}CH_2$	0.14	0.13	0.45
$PhMeC{=}CH_2$	1.00	1.00	
trans-PhCH=CHMe	1.59	1.80	1.00
$PhMeC{=}CMe_2$	20.2	1.32	
trans-PhCH=CHPh	0.064	0.64	0.15
1-Octene	0.13	0.006	0.10
Cyclohexene	2.79	0.09	1.65
1-Methylcyclohexene	13.6	0.96	4.6
1,2-Dimethylcyclohexene	63.2	1.69	5.9
Ph_2S	1900	<0.01	
Ph_2SO	23	<0.01	



(39)

(40)

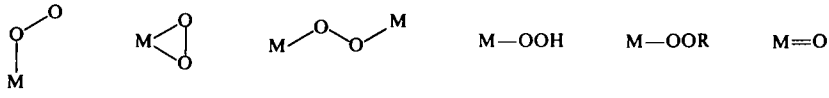
(27)

The radical epoxidation by acylperoxy radicals is roughly parallel with the PA epoxidation (Table 1). A small difference is in the effect of alkyl groups. In the radical epoxidation the accelerating effect by the second methyl group is negligibly small. This can be understood by the unimportance of the R^1 and R^2 groups in the stabilization of adduct radical **40** (equation 27). The intermediacy of adduct radical **40** explains the predominant formation of more stable *trans*-epoxides. For example, the radical epoxidation of *cis*-PhCH=CHR afforded epoxides of *cis*:*trans* ratios of 97:3 and 100:0 for R = Me and Ph, respectively[93]. The *trans* % of epoxides from *cis*-olefins may be a good indicator for radical epoxidations.

It is interesting to compare the relative reactivities of various substrates in Table 1. The epoxidation rates by PA are proportional to the π-electron densities of the olefins. The epoxidation rates of aliphatic olefins by acylperoxy radicals are relatively lower than those by PA. The radical oxidants are not reactive towards sulfides and sulfoxides, which are, however, easily oxidized by PAs. The reactivities by dioxirane are rather constant, suggesting near saturation rates reflecting its high oxidizing power

F. Metal-catalyzed Epoxidations

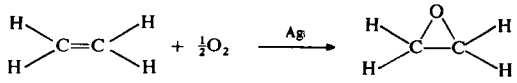
The metal-catalyzed epoxidations of olefins are important synthetic reactions and have been reviewed repeatedly[29,94–96]. Key intermediates relevant for epoxidations are various types of peroxo metal complexes (**41–45**) and oxo metals (**46**). Detailed discussions on these complexes are not included in this section, and only their reactivities are outlined briefly.



Superoxo (41) Peroxo (42) μ-Peroxo (43) Hydroperoxo (44) Alkylperoxo (45) Oxo (46)

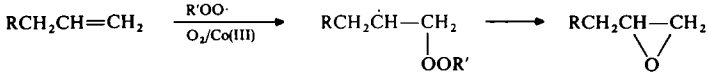
1. Epoxidations by molecular oxygen

Direct utilization of molecular oxygen is an ideal epoxidizing system. Such systems are, however, rather few. One successful process is the heterogeneous Ag-catalyzed epoxidation of ethylene[97]; see equation 28. This reaction is an important industrial process and has been studied extensively. A tracer study using dideuterioethylene revealed no retention of stereochemistry in the resulting epoxide[98]. This seems to suggest a radical-type epoxidation by AgOO· radical, but an intervention of a peroxo (**42**) or exo complex (**46**) cannot be excluded. A mechanistic conclusion was difficult although theoretical calculations have been reported[99]. The selectivity for ethylene oxide increased up to over 80% by adding moderators such as chlorine and alkali metals. This epoxidation method is applicable to styrene[100] and nonbornene[101] not having active β-hydrogens, but not for other simple olefins.



(28)

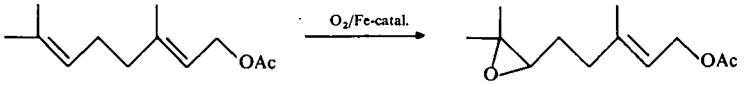
In the metal-catalyzed autoxidations of olefins, epoxides are often obtained as a by-product. Sometimes, the radical epoxidation by peroxy radicals becomes a major reaction, for example, in the olefin autoxidation catalyzed by $Co(acac)_3$[102a] and Co-naphthenate[102b]. The autoxidative epoxidation was accelerated by the radical initiator AIBN and was retarded by hydroquinone, suggesting a radical epoxidation. The epoxide formation is accomplished by the radical cyclization of **47** (equation 29), which is competitive with the alternate addition of oxygen leading to polyoxide formation.



(29)

(47)

A cluster ion, $Fe_3O(piv)_6L_3^+$, is an effective catalyst for the epoxidation of diolefins such as geraniols (equation 30)[103]. The regioselectivity for this epoxidation was the same as in the PA case. Other examples are the Ru(III)-catalyzed epoxidations of cyclohexene[104] and cholesterol esters[105].

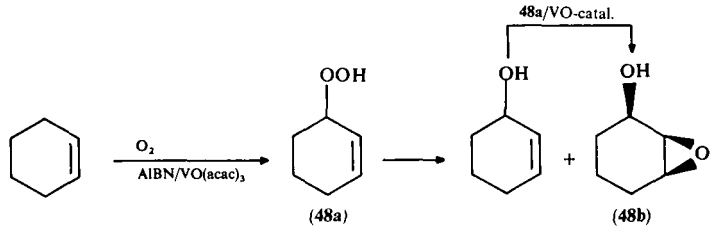


(30)

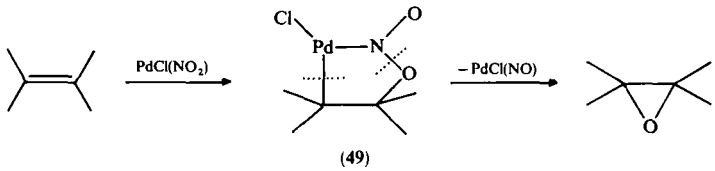
Vanadium catalysts are of a specific nature. Thus, the catalyzed autoxidation of cyclohexene yielded cyclohexenol as shown in equation (31)[106]. The predominant formation of *syn*-epoxy alcohol (**48a**) is due to the specific nature of vanadium catalyst to coordinate to alcohols.

In the ideal case for dioxygen epoxidations both oxygen atoms should be utilized for epoxide formation. Such an attempt has been reported by applying a palladium nitro complex[107], when the oxygen atom of the nitro ligand is transferred to the olefins via a

metalla-cyclopentane (**49**). The combination of reactions 32 and 33 results in the utilization of both oxygen atoms of dioxygen.



(31)

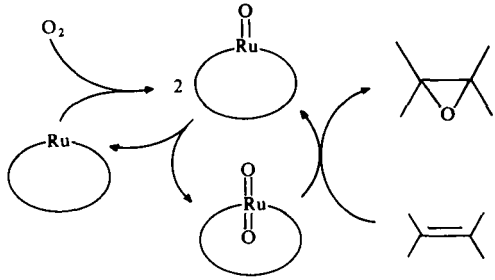


(49)

(32)

$$PdCl(NO)L_2 \xrightarrow{O_2} PdCl(NO_2)L_2 \qquad (33)$$

The metallo tetraphenylporphyrin (MTPP)-catalyzed epoxidation using oxygen has been studied as a cytochrome P-450 model reaction. An earlier attempt was made via reductive activation of oxygen based on the Pd-catalyzed reaction of O_2 and H_2[108]. The oxygen activation was achieved by a disproportionation of an oxo ruthenium(IV) complex to yield a active dioxo Ru(VI) complex (Scheme 1). The catalytic activity was thought to be due to the *ortho* buttressing of the bulky tetramesitylporphyrinate ligand. Another aerobic epoxidation has been developed using manganese complexs of naphthoquinone mono-oximes, the maximum turnover being 260[109b]. Aerobic epoxidations are efficiently catalyzed by microorganisms and enzymes[110].

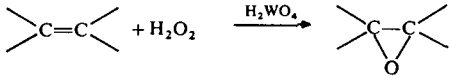


SCHEME 1. Aerobic epoxidation with ruthenium porphyrin catalysis[109a]

2. *Epoxidations by hydrogen peroxide*

Hydrogen peroxide is a mild oxidant and the olefin epoxidations are possible with it only when appropriate catalysts are applied[111]. For example, the oxidation of allyl alcohol with aqueous hydrogen peroxide in the presence of tungstic acid yields the corresponding olefins in 40–50% yields (equation 34). The catalytic epoxidation proceeds via the formation of peroxytungstic acid (**50**; equation 35). Similarly, metal catalysts such

as Mo, V, Pd, B, As, etc. are effective in the H_2O_2 oxidation. Aqueous conditions are not appropriate for epoxidations since epoxides are prone to acid-catalyzed hydrolysis.

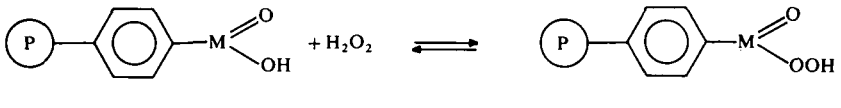


(34)

(35)

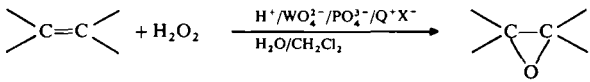
(50)

Polymer-anchored catalysts are conveniently separated from the reaction mixture after catalyzed H_2O_2 epoxidation (equation 36). Systems involving As[112], Se[113] and Te[114] have been reported as being effective for olefin epoxidations.

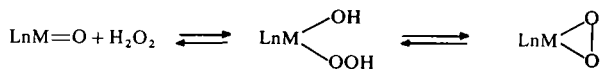


(36)

A practical olefin epoxidation has been developed using tungstate–phosphate catalysts under phase-transfer conditions[115]. The active epoxidizing species is the diperoxotungstophosphate ion, and the phase-transfer catalyst is alkylammonium salt (Q^+X^-); see equation 37. The two-phase system prevents the hydrolysis of the produced epoxides. Use of Mo- or W-based heteropolyacids under similar conditions leads to more efficient epoxidation by reducing the acid-catalyzed epoxide decomposition[116]. The formation of a peroxo complex (**51**; equation 38) was suggested as the active epoxidizing agent formed from the heteropolyacids.



(37)



(38)

(Ln = ligand)

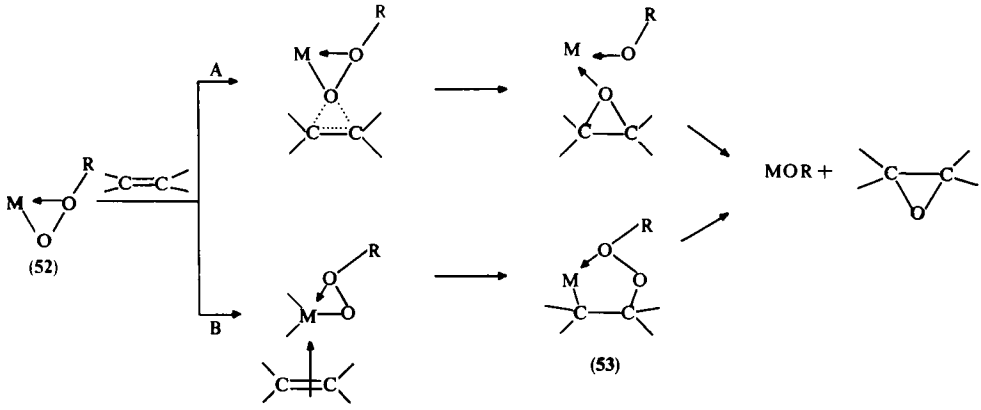
(51)

3. *Epoxidations by hydroperoxides and other oxidants*

Olefin epoxidations with alkyl hydroperoxides catalyzed by metal complexes, e.g. Mo, V and Ti, are the most important industrial process for the manufacture of propylene oxide (the Halcon process)[117]. Despite intensitive studies[94–96], the detailed epoxidation mechanism has not been clarified. In view of the quite high selectivity and stereospecificity, it is generally accepted that the epoxidations proceed via a heterolytic rather than a homolytic mechanism.

Two alternative pathways, A and B in Scheme 2, each involving a *metal alkyl peroxidic complex* (**52**), have been proposed. Mechanism A involves an electrophilic O-transfer to

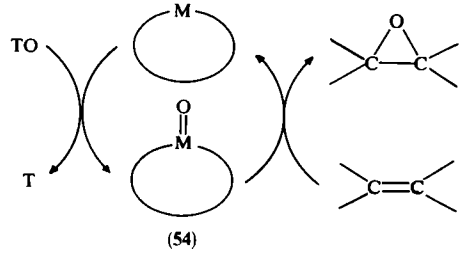
olefins just like the 'butterfly' epoxidation by peroxyacids[118]. Mechanism B involves a five-membered *dioxametallocyclopentane* (**53**), i.e. it occurs via a pseudo-cyclic peroxymetalation[119]. For the particular case of vanadium, the alkylperoxy complexes were isolated, and pathway B was supported by the fact that the relative rates were correlated with the coordinating tendency of olefins[120]. The operating pathway seems, however, to change by changing metals, ligands and solvents.



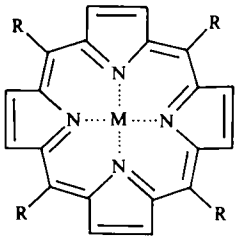
SCHEME 2. Epoxidation mechanisms via a metal alkyl peroxidic complex

The epoxide selectivities were increased by adding pyridine in the MoO_2(acac)-catalyzed epoxidation with *t*-BuOOH[121]. The stereochemistry of epoxidation of methylenecyclohexane derivatives by $Mo(CO)_6$/*t*-BuOOH was different from that of peroxyacid oxidation, and the oxygen atom was transferred from the less hindered open direction[122].

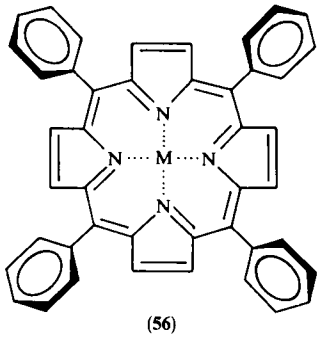
The second type of catalytic reaction (Scheme 3) is the epoxidation involving *metallo oxo intermediates* (**54**). This type of reaction has been extensively studied after the pioneering study by Groves and coworkers on iron porphyrin complexes[123]. The metallo complexes of Fe, Co, Cr, Mn, Ru, etc., having porphyrin ligands, have been mostly studied[4,124]. Porphyrin ligands (**55**) are planar and can possess several redox states of the central metallic ions and hence oxo metals. Effective O-transfers have been established via metallo oxo complexes using iodosobenzene [123a], sodium hypochlorite[125], peroxyacids[123], hydroperoxides[126] and amine *N*-oxides[127] as the terminal oxidant, with iodosobenzene, PhIO, as a mild oxidant, being used most frequently.



SCHEME 3. Epoxidation via metallo oxo intermediate. TO = terminal oxidant

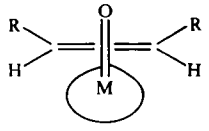


(55)

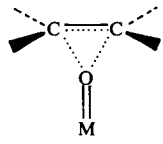


(56)
Tetraphenylporphyrin

Stereoselective and stereospecific epoxidations could be attained by Fe(TPP)Cl/PhIO[123,128]. The less hindered *cis*-stilbene was oxidized fifteen times faster than the *trans*-isomer, while the *cis*/*trans* rate ratio for stilbene was close to unity for peroxy acid epoxidation. The rate ratios of *cis* ≫ *trans* for many olefins suggest the epoxidation by Fe(TPP)Cl/PhIO is sensitive to the steric effect of olefin substituents. The significant steric effect may be well explained by the side-on approach (**57**), rather than by an open-course transition state (**58**)[128].

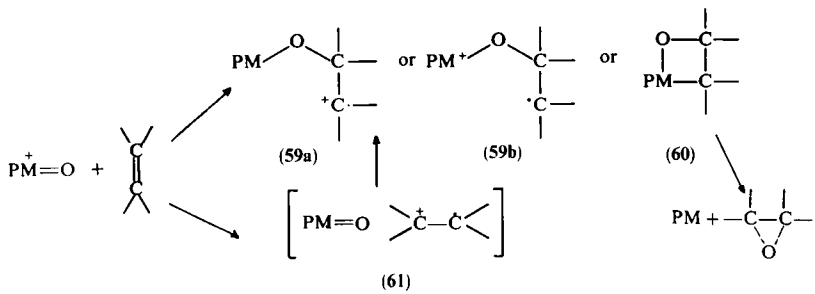


(57)



(58)

Examination of metals and ligands revealed various features of metallo porphyrine-catalyzed epoxidations. When M = Mn(III), the stereospecificity of epoxidation decreased considerably; e.g. *cis*-*β*-methylstyrene yielded the corresponding *trans*-epoxide as the major product, accompanying C—C scission[129]. Sometimes, the epoxidation was accompanied by rearrangements and isomerizations suggestive of a one-electron transfer from olefins to oxo metals[130] and the relative epoxidation rates were correlated, contrary to the peroxy acid oxidation, with ionizing potentials of olefins[130b]. These facts clearly indicate an intervention of one-electron transfer during the epoxidation. A likely mechanism is shown in Scheme 4. The observed cationic rearrangements[130a] may be explained by **59a**. The predominant formation of *trans*-epoxides results from the free C—C rotation in intermediates **59a** or **59b**[129]; the C—C scission in the presence of oxygen is explicable by the oxygen addition to **59b**[129b].

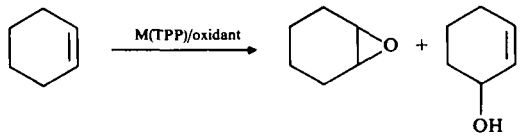


(59a) (59b) (60) (61)

SCHEME 4. Detailed epoxidation mechanism via oxo metals

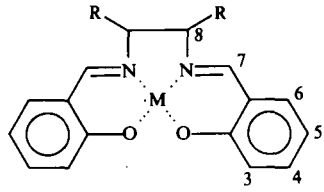
The involvement or importance of one-electron transfer (**61**), adduct formation (i.e. **59a** or **59b**) or metallocycle (**60**) may depend on the kinds of metals, olefins and axial ligands. A reversible formation of two intermediates, metallocycle **60** and a π-complex between Fe = O and olefin, has been suggested in the epoxidation with Fe(TPP)Cl/MCPBA[131]. Mechanisms involving these intermediates were analyzed by theoretical calculations[132].

The allylic hydroxylation of olefins is one of the side reactions in olefin epoxidations with metallo porphyrins and oxidants.The ratios of epoxidation and hydroxylation by (TPP)M = O depend on metals and ligands. For example, the allylic hydroxylation of cyclohexene with manganese porphyrins is much more efficient than that of iron cases[129,133]. The importance of axial ligands is exemplified in the epoxidation with Mn(TPP)OAc/NaOCl. That is, the formation of *cis,trans*-isomerized epoxides was reduced by the addition of pyridine as an axial ligand[134a], and the epoxide yields were considerably increased by the presence of intermolecularly anchored axial ligand[134b].



(39)

A serious weak point for the metallo porphyrin-catalyzed epoxidation is the oxidation of the porphyrin rings themselves, resulting in low turnovers. The rings may be moderately stabilized by introducing sterically bulky groups and/or electron-withdrawing (e.g. F or Cl) groups[135]. A convenient system for scale-up is the epoxidation with MTPPs bearing electron-attracting substituents under two-phase conditions using aqueous sodium hypochlorite or hydrogen peroxide as the terminal oxidant[136]. The reported high turnover of 200,000 for manganese(III) porphyrin with 2,6-difluorophenyl groups could be regarded as a practical epoxidation system[137]. An attempt at stabilizing Mn(III) porphyrin was to bind the catalyst with colloidal anion-exchange particles[128].

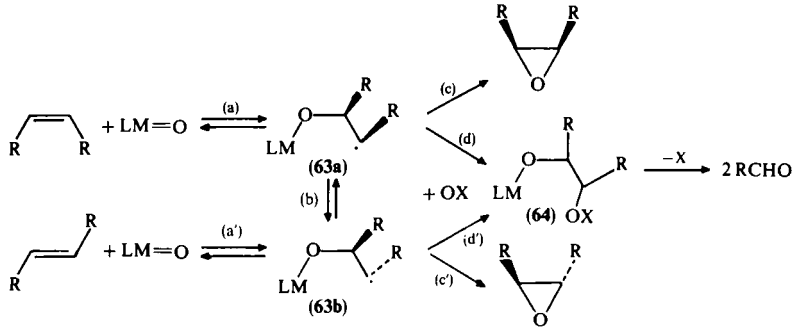


(62)

Salen complexes (**62**) are another choice since salen [i.e. *N,N'*-ethylene-bis(salicylideneaminate)] ligands are more stable and soluble than porphyrin catalysts. The reaction of cyclohexene with Mn(III) (salen)/*t*-BuOOH afforded only cyclohexene oxide in the presence of radical inhibitors[139]. When PhIO was used at the terminal oxidant, stereospecific epoxidations could be attained[140]. The relative rates of olefins were nearly constant, reflecting the high reactivity of the (salen) Mn = O species.

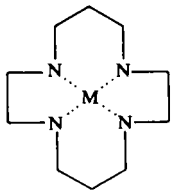
Similar results were obtained for the case of Co(II)(salen) [**62**, M = Co(II)]; stereospecific epoxidation resulted with iodosobenzene as the terminal oxidant while the epoxidation with *t*-butyl hydroperoxide was accompanied by a radical reaction[141]. The activity of Cr(III)(salen)/PhIO was elevated significantly, with some C—C scission, by adding pyridine-*N*-oxide as the axial ligand[142]. The kinetic study on this system revealed that the addition of olefins to Cr = O (step a in Scheme 5) is rate-determining. The observed stereospecific epoxidation indicated that the interconversion between **63a** and **63b** is quite

slow. In the case of Ni(II)(salen)/NaOCl under phase-transfer conditions, *cis*- and *trans*-olefins yielded *trans*-epoxides only, i.e. a stereoselective *trans* epoxidation[143]. This means that the equilibrium between **63a** and **63b** is established and shifted to the more stable *trans* adduct **63b**. The accompanying reaction was the C—C scission (path d in Scheme 5) in below 10%.



SCHEME 5. Epoxidation and C—C scission by LM=O

The nickel(II) cyclam complex [**65**, M = Ni(II)] is likewise active as the catalyst for PhIO epoxidations[144]. The substituent effect of $\rho = -0.82$ (σ^+) for substituted styrenes indicated an electrophilic attack of LNi=O on olefins. Thus, the interconversion between **63a** and **63b** was operating moderately since *cis*-stilbene yielded *cis*- and *trans*-stilbene oxides in 1:1 ratio. A ^{18}O-tracer study indicated that C—C scission occurred after the addition of oxygen to the adduct radical **63**. These results show that the interconversion between **63a** and **63b** is dependent on the nature of the central metals.



(65)

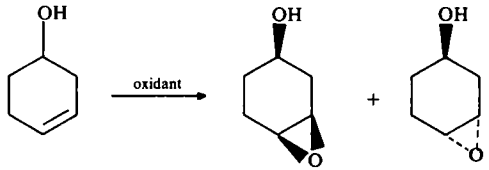
It is of interest that olefin epoxidations are also possible with only Cu(II) and PhIO in the absence of porphyrin or salen ligands[145a]. The active species here is of a radical nature since *cis*-stilbene yielded *cis*- and *trans*-epoxides (*ca* 3:4 ratio) and the cyclohexene epoxidation was accompanied by allylic hydroxylation. In the PhIO oxidation catalyzed by binuclear cupper complexes involving tetrapyridyldiamines, *cis*-stilbene was converted to *trans*-stilbene oxide and benzaldehyde[145b]. The formation of isomerized epoxide and C—C cleavage products suggested again an intervention of active oxidizing species of radical nature. Valentine and collaborators[146] have reported that the PhIO epoxidation is also catalyzed by an Al(III)(TPP) catalyst with no higher valence state. These facts indicate the presence of an active oxidizing species like **66**, the central atom acting only as a Lewis acid. Further detailed study is needed to clarify the active species in these interesting oxygen-transfers.

L—Al(III)—O—I^+—Ph

(66)

4. Stereoselective epoxidations of allyl alcohols

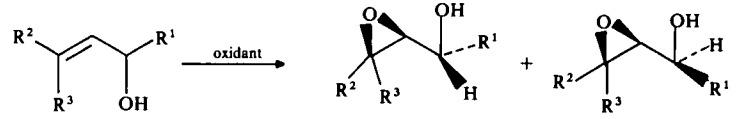
Developing stereoselective reactions is one of the central targets of recent organic syntheses. Metal-catalyzed epoxidations play a significant role in this field. A typical example is the stereoselective epoxidations of allyl and homoallyl alcohols. Thus, the *syn*-epoxidation of cyclohexen-4-ol is possible by the molybdenum- or vanadium-catalyzed oxidation (equation 39)[147]. The $VO(acac)_2$-catalyzed oxidations exhibit a high HO-directed regioselectivity as observed in the epoxidation of geraniol and linalool[147]. The high *syn*-selectivity of the vanadium catalyst is due to the strong coordination of the hydroxyl group[29a].



(39)

$PhCO_3H$	60%	40%
$Mo(CO)_6$/*t*-BuOOH	98%	2%
$VO(acac)_2$/*t*-BuOOH	98%	2%

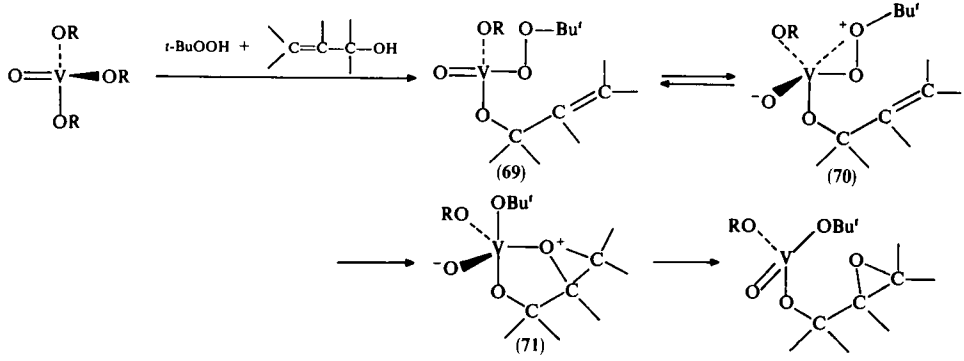
Constrasted selectivities are often observed between peroxyacid and metal-catalyzed systems in the oxidation of acyclic allyl alcohols (**67**; equation 40). Table 2 lists stereoselective epoxidations of acyclic allyl alcohols by various oxidants. A high *erythro*-selectivity has been found when $R^2 = R^3 = H$ and R^1 = alkyl in the oxidation with VO $(acac)_2$/*t*-BuOOH. When R^3 = alkyl, high *threo*-selectivities were observed for MCPBA[147] and $Al(OBu)_3$/*t*-BuOOH[148]. The epoxidation with a monoperoxo molybdenium complex showed a significant *erythro*-selectivity[149].



(67) (68a), *threo* (68b) *erythro*

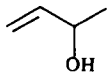
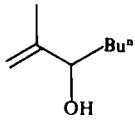
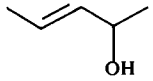
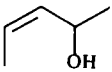
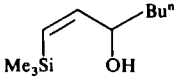
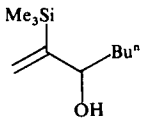
(40)

The vanadate-catalyzed *syn*-epoxidation of allyl alcohols is thought to proceed according to Scheme 6[29a]. The first step is the exchange of the alkoxy group yielding a peroxy

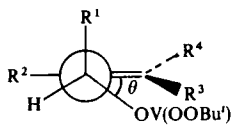


SCHEME 6. Vanadate-catalyzed epoxidation of allyl alcohol

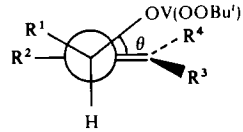
TABLE 2. Stereoselective epoxidation of acyclic allyl alcohols

Substrate	Ratio of *threo*:*erythro*			
	$VO(acac)_2/BuOOH$[147]	MCPBA[147]	$Al(OBu)_3/BuOOH$[148]	$L_2Mo(O)(O_2)$[149]
	20:80	60:40	42:58	7:93
	2:98	41:59	13:87	6:94
	29:71	64:36	64:36	27:73
	71:29	95:5	99:1	49:51
	92:8[150]	87:13[150]		
	1:99[150]	39:61[150]		

complex (**69**) with *t*-butylperoxy and allyloxy ligands; this step was evidenced by an inhibiting effect of added alcohols. The next step is the intramolecular epoxidation via **70** and **71**. The stereochemistry of epoxides is determined by the relative stability of the stereoisomers **70** or **71**. *Erythro*-epoxy-alcohols are formed from conformer **72** (i.e. dihedral angle $\theta \sim 50°$), where the oxygen atom is transferred from the bottom side. On the other hand, the *threo*-isomer is produced from conformer **73** where steric repulsion between the R^1 and R^2 groups is significant. The observed high *erythro*-selectivity when R^1 = alkyl is well understood since conformer **72** is more stable than **73**.

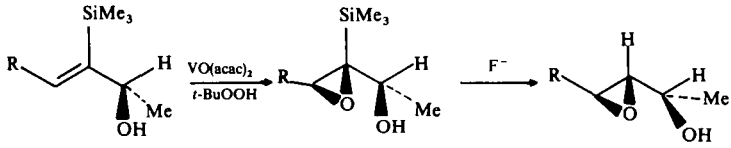


(72)



(73)

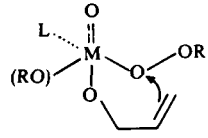
The energy difference between **72** and **73** becomes considerably large by substituting bulky trimethylsilyl group, leading to a high selectivity[150]. Since the Me_3Si group is easily converted by F^- into H, the reaction of equation 41 is quite useful, the *erythro*-selectivity being as high as 99%.



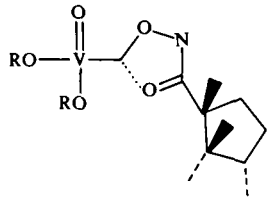
(41)

5. The Sharpless–Katsuki epoxidation

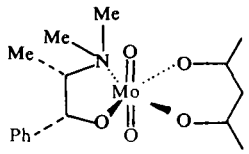
The key step in the metal-catalyzed epoxidation of allyl alcohols is, as mentioned above, the intramolecular O-transfer in the coordinated complex (**74**). Hence, it is quite natural that an asymmetric epoxidation could be expected when asymmetric ligands are introduced. The initial attempt was the successful asymmetric epoxidation (in up to ~30% ee) by using chiral catalysts such as **75**[151] and **76**[152].



(74)

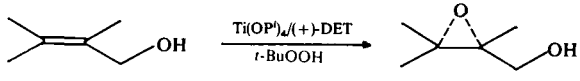


(75)

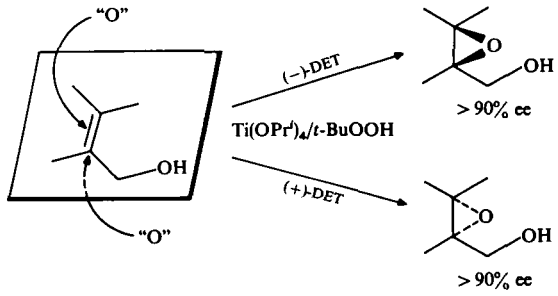


(76)

In 1980, Sharpless and Katsuki reported the first practical asymmetric epoxidation using a complex of titanium tetraisopropoxide and diethyl tartarate (DET)[153]; see equation 42. Almost all olefins tested yielded epoxides of >90% ee as listed in Table 3. The sense of asymmetric induction is determined by the stereochemistry of the tartarates and is not dependent on the substrate structures. As shown in Scheme 7, the O-transfer is below the molecular plane of alcohols when (+)-DET is used, and the epoxidation with (−)-DET catalyst is from the top side. The experienced sense of the asymmetric induction in Scheme 7 is quite general and selective (i.e. >90% ee); a few exceptions involve *cis*-allyl alcohols having bulky substituents.

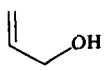
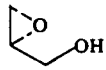
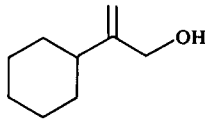
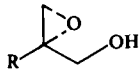
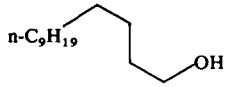
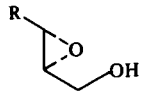
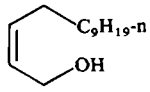
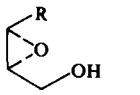
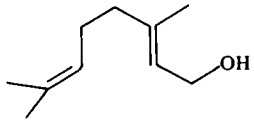
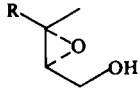
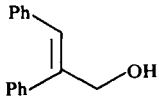
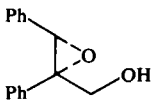


(42)



SCHEME 7. The Sharpless–Katsuki asymmetric epoxidation. Partly reprinted with permission from T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980). Copyright (1980) American Chemical Society

TABLE 3. Asymmetric epoxidation of allylic alcohols with *t*-BuOOH catalyzed by $Ti(OPr^i)_4$ and (+)-DET[a]

Allylic alcohols	Epoxy alcohols	Yield (%)	ee (%)	Configuration
		98	89	2*S*
		81	>95	2*S*
		79	>95	2*S*,3*S*
		82	90	2*S*, 3*R*
		77	95	2*S*,3*S*
		87	>95	2*S*,3*S*

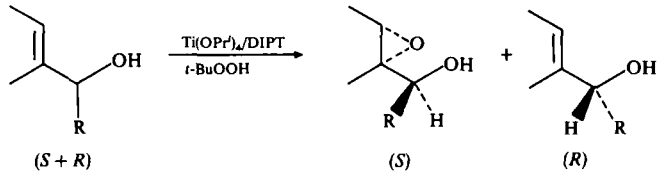
[a]Reprinted with permission from T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980). Copyright (1980) American Chemical Society.

The Sharpless–Katsuki asymmetric epoxidations are quite useful and have been reviewed[154]. The asymmetric epoxidation is not influenced by functional groups such as ethers, esters, nitriles, ketones, acetals and oxazolines.

Since the presence of water reduces the optical yields significantly, the crude *t*-butyl hydroperoxide should be dehydrated by azeotropic distillation[155]. Weak points of the epoxidation are that a stoichiometric amount of $Ti(OPr^i)_4$-DET catalyst is needed and that some of the epoxides are decomposed by acid catalysis exerted by the Ti complex[156]. In order to overcome these points the Ti catalyst should be used catalytically. Indeed Sharpless and coworkers[157] found that the epoxidation proceeds catalytically (i.e. 5–10% Ti catalyst) in the presence of 3 A or 4 A molecular sieves (zeolites), when asymmetric epoxidation of twenty allyl alcohols proceeded successfully in the high optical yields of 90–95% ee. This catalytic epoxidation using molecular sieves is quite practical, since the produced epoxides could be used *in situ* for the next transformations[158]. An attempt to use a titanium-pillared monmorillonite catalyst is reported[159].

Facile *kinetic resolution* is possible by the Sharpless–Katsuki epoxidation of secondary allylic alcohols[160]. This method is based on the large difference in epoxidation rates between enantiomers of the starting allylic alcohol. As shown in equation 43, the kinetic resolution is useful since the asymmetric epoxy alcohols and epoxides could be obtained simultaneously.

Some examples are listed in Table 4. In most cases the recovered allylic alcohols are practically pure, i.e. >95% ee.

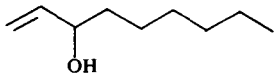
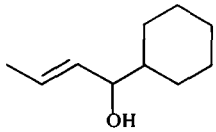
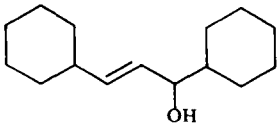
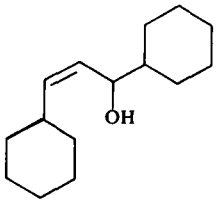
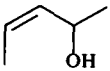
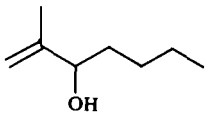


(43)

(S + R) (S) (R)

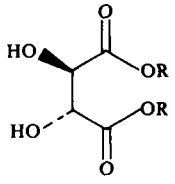
DIPT = Diisopropyl tartarate

TABLE 4. Kinetic resolution of racemic allylic alcohols[a]

Allylic alcohol	Relative rate[b] k_{fast}/k_{slow}	Unreacted alcohol[c] Configuration	% ee	Epoxy alcohol Erythro:threo
	83	*R*	>96	99:1
	104	*R*	>96	97:3
	—	*R*	>96	97:3
	—	*S*	~10	2:98
	~20	*R*	91	81:19
	138	*R*	>96	98:2

[a]Reprinted with permission from V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda and K. B. Sharpless, *J. Am. Chem. Soc.*, **103**, 6237 (1981). Copyright (1981) American Chemical Society.
[b]Relative rates of *S* or *R* enantiomers.
[c]The yields of recovered allylic alcohols ranged from 30–45%; the maximum yield in a kinetic resolution is 50%.

An ideal kinetic resolution is realized when the rates for the fast (k_f) and slow reactions (k_s) are different infinitively, e.g. $k_f/k_s = \infty$ as the case of enzyme reactions. In such a case a 50% conversion results in a 100% pure kinetic resolution. The dependence of the enantiomeric excess on the relative rates is shown in Figure 2. When k_f/k_s is 100, a 55% conversion suggests a practically pure resolution. The resolutions in Table 4 were carried out using 0.6 equivalent of *t*-BuOOH and yielded practically pure starting olefins and epoxy alcohols when the k_f/k_s values are *ca* 100[160]. It is interesting to note that the utilization of (+)-DIPT afforded *S*-allyl alcohols and (−)-DIPT yielded *R*-isomers. The kinetic resolution becomes a catalytic reaction in the presence of molecular sieves[157b]. The substituent effect of tartarate esters in the kinetic resolution has been studied. Superior results were obtained with diisopropyl (DIPT, **77b**) and dicyclohexyl tartarate (DCHT, **77c**) in the stoichiometric resolution, and DCHT was slightly better than DIPT in the catalytic resolution[157]. The diethyl (DET) or dimethyl esters were much less efficient.



(a) R = Et; DET
(b) R = *i* − Pr; DIPT
(c) R = cyclohexyl; DCHT

(77)

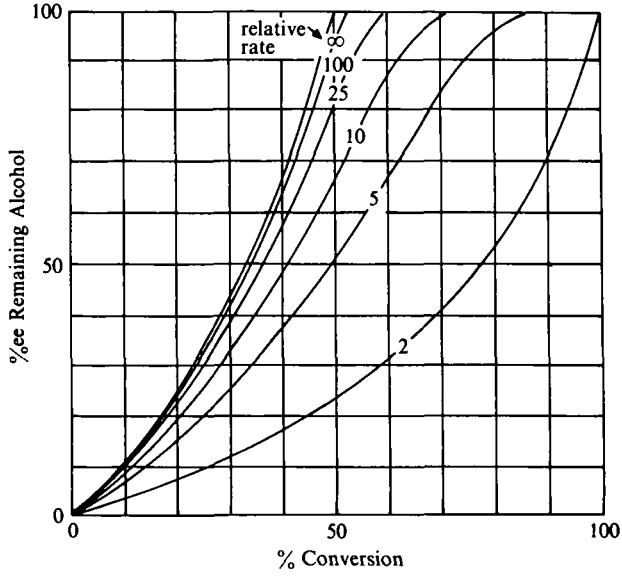
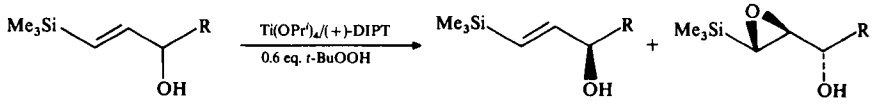


FIGURE 2. Dependence of enanthiomeric excess on relative rates. Reprinted with permission from V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda and K. B. Scharpless, *J. Am. Chem. Soc.*, **103**, 6237 (1981). Copyright (1981) American Chemical Society

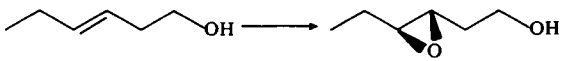
The kinetic resolution is useful since *R*- and *S*-allyl alcohols could be easily obtained by choosing (+) or (−) tartrates. A review article is available[161]. The introduction of the bulky trimethylsilyl group may result in the increased k_f/k_s ratios leading to successful resolutions. In fact, a simultaneous resolution of allyl and epoxy alcohols becomes practical, i.e. >99% ee, by introducing a Me_3Si group (equation 44)[162]. The k_f/k_s values in these cases are as high as 700[163]. The modified resolution has been applied for the preparation of synthetic intermediates[164].



(44)

Another type of kinetic resolution is possible for 4-substituted allyl alcohols. For example, a kinetic resolution of 4-phenyl-*cis*-3-penten-1-ol afforded the corresponding (*S*) allyl alcohol in 95% ee[165]. The *trans*-pentenol, however, gave the (*R*) isomer is only 6% ee.

The asymmetric epoxidation of acyclic homoallyl alcohols is likewise possible, although not so successful. For example, the oxidation of 3-hexen-1-ol with $Ti(OPr^i)_4$/(+)-DET afforded the corresponding epoxy alcohol in moderate optical yield of 50% ee[166]; attempted resolutions of six homoallyl alcohols resulted in 22–55% ee. The low enantioselectivity for homoallyl alcohols is comprehensible because of the incoorporation of one more methylene group in comparison to the allyl alcohols. Katsuki and coworkers reported that an improved result could be obtained with other metallo complexes of Zr, Hf and Ta possessing longer M—O bonds than that of Ti—O[167]. For example, the reaction of equation 45 with $Zr(OPr^n)_4$/DCTA yielded epoxy alcohol in 72% ee. The best result of 74% ee was obtained by using trityl hydroperoxide in the $Ti(OPr^i)_4$/(−)-DET-catalyzed epoxidation of trishomoallylic alcohol[168].

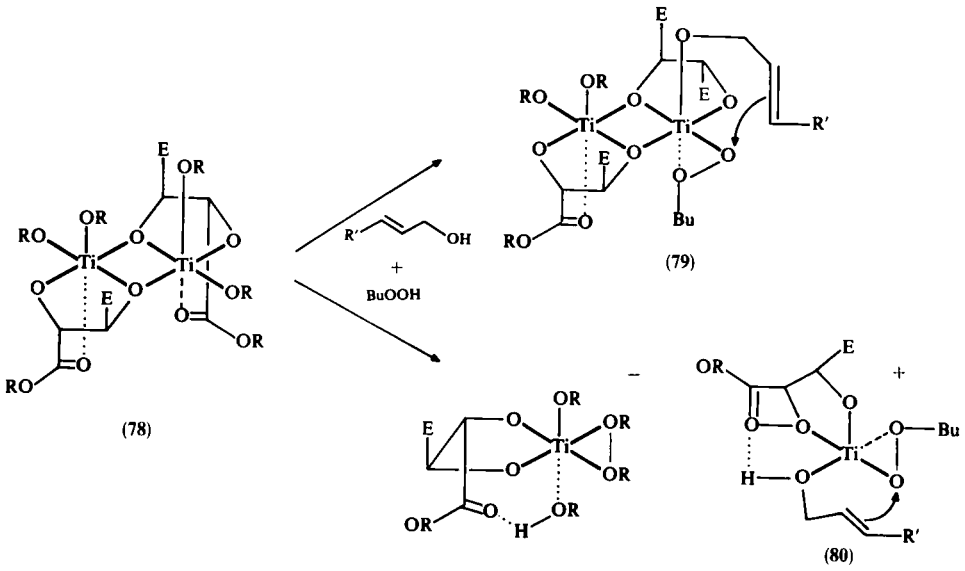


(45)

As described above, the Sharpless–Katsuki asymmetric epoxidation is quite useful for many synthetic applications. As to the mechanism of asymmetric induction, Sharpless and collaborators isolated a dinuclear dimer complex (**78**) from the mixture of $Ti(OPr^i)_4$, DET and PhCON(OH)Ph, and proposed that the asymmetric epoxidation is via a dinuclear complex such as **78** in Scheme 8[154a,169]. But the situation is more complex, since a NMR study revealed that the complex structures are different from that of crystals[170]. Cory[171] proposed that the active species may be the monomeric complex where allylic alcohols are coordinated with Ti and with ligands by hydrogen-bonding (**80** in Scheme 8). A mechanistic conclusion from the experimental evidence seems to be difficult at present. A frontier orbital analysis for the active epoxidizing species is also reported[172].

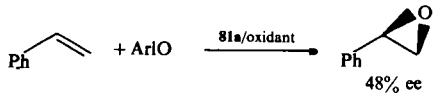
6. *Asymmetric epoxidations of unfunctionalized olefins*

The asymmetric epoxidations of unfunctionalized olefins without coordinating groups such as hydroxyl are difficult but very interesting. The metallo porphyrine-catalyzed epoxidation by Groves and Myers is the pioneering work in the field of asymmetric epoxidations involving M=O species (equation 46)[173]. This asymmetric induction is due to the steric repulsion between *meso*-substituted binaphthyl rings and approaching olefin

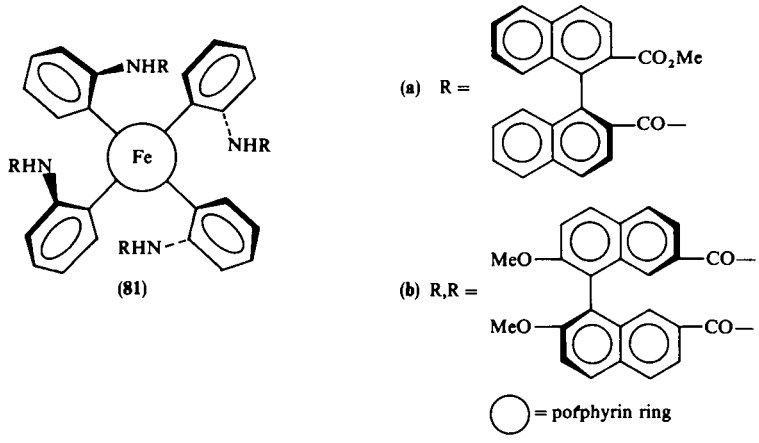


SCHEME 8. Mechanism of the Sharpless–Katsuki epoxidation; $E = CO_2R$

molecules. The oxidation of styrene with catalyst **81a** afforded (*R*)-(+)-styrene oxide in 48% ee, while yielding 20% ee from 1-octene. These ee yields were not always high, but the report suggested a good route for the following metal-catalyzed asymmetric epoxidations.



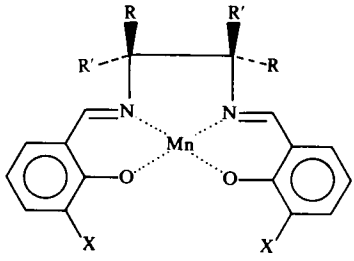
(46)



Since then, various types of substituents on the *meso* position of phorphyrin rings have been developed. Thus, *p*-chlorostyrene was epoxidized in 50% ee with a 'basket-handled'

catalyst involving *L*-phenylalanine[174]. Use of a 'twin-coronet type' complex bearing four binaphtyl groups epoxidized-*o*-nitrostyrene in 80% ee maximally[175]. Utilization of the 'vaulted' porphyrin (**81b**) bearing binaphthoyl groups resulted in asymmetric epoxidation with 20–70% ee depending on the olefin structures, the highest being 72% ee for *cis*-*β*-methylstyrene[176]. In this case, the epoxidation with Mn(III) porphyrins gave only 6–36% ee. A common weak point of these metallo porphyrin-catalyzed epoxidations is the decrease in optical yields with increasing conversion. That is, a development of tough catalysts is essential. In this respect, a 'chiral wall' porphyrin catalyst bearing four binaphthyl groups might be a tough catalyst with over 200 turnovers when applied in the NaOCl epoxidation under two-phase conditions[177].

More promising results have been obtained in the catalyzed asymmetric epoxidations using chiral salen complexes. Katsuki and collaborators[178] succeeded in the asymmetric epoxidation with manganese salen complexes (**82**), the maximum being 72% ee for *cis*-*β*-methylstyrene using PhIO and **82d** [X = (*S*)-3-(1-phenyl propyl)]. Jacobsen's group[179] reported independently that more simple catalysts, e.g. **82a–c**, afforded higher asymmetric inductions. As listed in Table 5, the asymmetric epoxidation with **82** and PhIO is quite excellent, the maximum being 93%ee for cyclohexanone ketal. The 84% ee for *cis*-*β*-methyl-styrene is rather high, and also significant is the 48% ee for the epoxidation of *trans*-stilbene in which it has been regarded as difficult to induce an asymmetry.



(82)

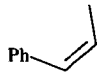
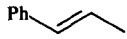
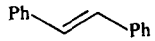
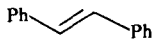
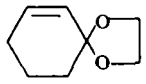
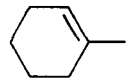
(a) (*S*,*S*); R = Ph, R' = H, X = H
(b) (*R*,*R*); R = H, R' = Ph, X = H
(c) (*R*,*R*); R = H, R' = Ph, X = *t*-Bu
(d) R = H, R' = Ph, X = PhCH(Et)

The successful asymmetric epoxidation by using salen manganese catalyst (**82**) is probably due to the existence of an asymmetric center close to the central metal ion. When olefin molecules are approaching the central Mn(V)=O from a side-on direction, a double stereo control operates by the two bulky groups (*t*-Bu or Ph) on the salen ring. The advantage of this catalytic system is that the stereochemistry of the resulting epoxides could be controlled easily by changing the substituents, R and R', on the salen complex **82**.

Recently, Jacobsen and coworkers reported a practical asymmetric epoxidation by conducting the oxidation with NaOCl under two-phase conditions[180]. Thus, the asymmetric epoxidation of *cis*-methylstyrene could be carried out in 86% ee using commercial bleach and an easily prepared chiral Mn(III) salen complex. Most probably in near future, a practically pure asymmetric epoxidation will be developed using manganese salen complexes.

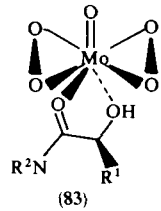
The asymmetric epoxidations of unfunctionalized olefins with oxo metal complexes were, as mentioned above, successful. However, the asymmetric epoxidations with metal–peroxide complexes were not always fruitful. For example, the epoxidation of squalene with MoO_2(acac)/(+)-DIPT/*t*-BuOOH gave the corresponding epoxide of only 14%ee[181]. The use of a molybdenim diperoxide complex containing an asymmetrical ligand (**83a**) afforded epoxides in 5–35%ee[182]. The initial asymmetric yield in the epoxidation of *trans*-2-butene was as high as 55% ee with catalyst **83c** bearing a bidentate ligand[183]. An interesting phenomena was observed, namely that the co-addition of

TABLE 5. Asymmetric epoxidation of representative olefins using chiral (salen)manganese complex (**82**)[a]

Olefin	Catalyst	Yield (%)	ee%	Configuration
	**82c**	73	84	1*R*,2*S*-
	**82a**	93	20	1*S*,2*S*
	**82c**	75	57	*R*-
	**82a**	63	33	*S*,*S*-
	**82d**[178b]	95	48	1*R*,2*R*
	**82c**	52	93	—
	**82c**	50	59	1*R*,2*S*

[a]Oxidant: PhIO; catalyst 1–8 mol%. Reprinted with permission from W. Zhang, J. L. Loebach, S. R. Wilson and E. N. Jacobsen, *J. Am. Chem. Soc.*, **112**, 2801 (1990). Copyright (1990) American Chemical Society.

2*S*,3*S*-1,2-butanediol resulted in the formation of *R*-epoxide in 93.2% ee, while the use of 2*R*,3*R*-diol yielded the *S*-epoxide in 89.8% ee. These apparently excellent results were, after detailed study, shown to be due to kinetic resolution of the produced epoxides. Further studies are needed to develop a practical catalytic system.



(**83**)

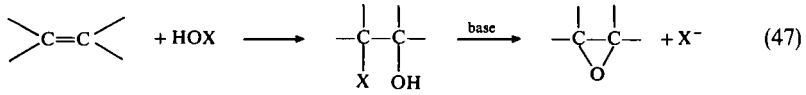
(a) $R = R^1 = Me$
(b) $R^2 = (CH_2)_5$, $R' = Me$
(c) $R = Me$, $R^1 = PhCH_2$

G. Miscellaneous Epoxidations

1. *Electrochemical epoxidations*

The epoxide synthesis by the base-catalyzed reaction of halohydrins (equation 47) is a classical synthetic reaction. If the halide ion, X^-, is oxidized electrochemically (equation 48), the halogen species will be utilized repeatedly according to equation 47. Such electrochemical epoxidations have been realized and are well known. Industrial

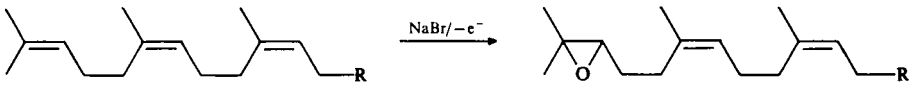
interest in electrochemical epoxidations has been focussed on the production of ethylene and propylene oxides in aqueous sodium chloride or bromide solutions[184]. The selectivity for propylene oxide was reported to be as high as 97% in the indirect propylene epoxidation using a bipolar trickle tower[185]. The current efficiency for the Br^--mediated epoxidation of 1-hexene was *ca* 65% in an undivided parallel-plate reactor[186]. Use of alternating current is also possible but with lower current efficiencies, e.g. 22% for the propylene epoxidation with NaBr[187]. Electrochemical epoxidations of various olefins have been accomplished to afford epoxides in 60–80% yields in wet DMF solutions containing a quaternary ammonium bromide on an anion-exchange resin (i.e. $P\text{-}NR_3^+/Br^-$)[188].



(47)

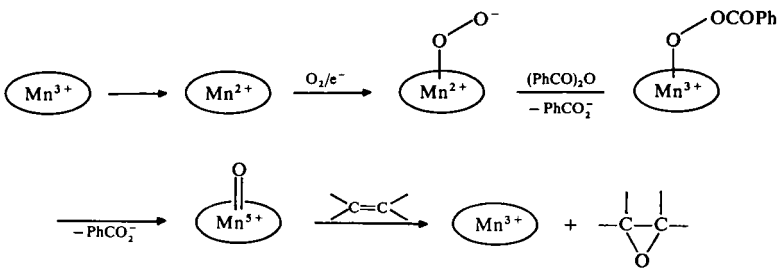
$$X^- + H_2O \xrightarrow{-e} HOX \qquad (48)$$

ω-Epoxidations could be realized when polyisoprenoids were oxidized electrochemically in the presence of NaBr in MeCN–THF–H_2O[189]; see equation 49. The electrochemical epoxidation of 4-cyclohexene-1,2-carboxylate was studied in detail in aqueous acetonitrile[190]. The epoxide yield was almost quantitative, i.e. 97%, by the electrolysis with low (i.e. <0.05 M) concentration of Br^-; major products were the dibromide with over 1.5 M Br^- and the bromohydrin under acidic conditions.



(49)

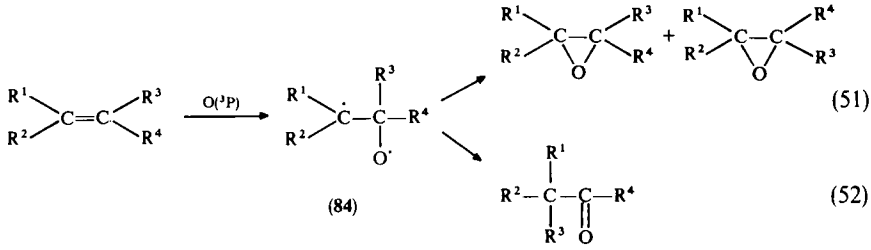
Utilization of metallo porphyrins as electrochemical mediators (or catalysts) is a new field of electrochemical epoxidations. For example, Cr(IV)(TPP) was converted to the active oxo complex, O=Cr(V)(TPP), capable of epoxidizing olefins[191]. An interesting system is the reaction of Mn(TPP)Cl bearing 1-methylimidazole as an axial base in the presence of benzoic anhydride and oxygen (equation 50)[192]. The reduction of Mn^{3+} induces the addition of oxygen, and the following benzoylation yields the metallo oxo species (Mn=O) leading to olefin epoxidations. The total Faradaic efficiency was 56% for cyclooctene oxide[192a]. Similar electrochemical epoxidations are possible with Fe(III)(TPP)[193] and Mn(III)(salen) complexes[194].



(50)

2. Epoxidation by active oxygen species

a. Oxygen atom. The Hg-sensitized photolysis of nitrous oxide yields a triplet oxygen atom in the state (^3P). The gase-phase reaction of $O(^3P)$ with olefins afforded epoxides and rearranged ketones as illustrated in equations 51 and 52[195]. Isomeric epoxides are formed via adduct **84**; thus *cis*- and *trans*-epoxides were obtained in 1:1 ratio from the reaction of *cis*-2-butene. The relative reactivity of methyl-substituted olefins is in the order of tetra- > tri- > dimethyl > unsubstituted ethylene, suggesting an electrophilic nature of the oxygen atom[196].

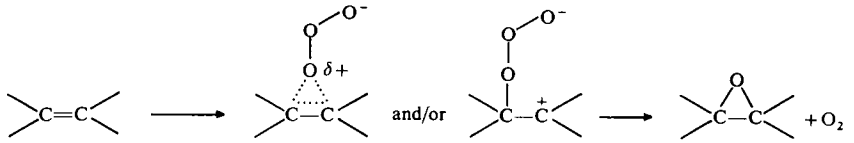


(51)

(52)

Oxygen atom in solutions is produced *in situ* by the photolysis of amine N-oxides, e.g. pyridine N-oxide[197]. Styrene was oxidized to styrene oxide and acetophenone in 15:1 ratio, and cyclohexene yielded cyclohexene oxide, cyclohexanone and 1,2-diol in a ratio of 5:1:1. These results suggest that the oxygen atom is not an efficient epoxidizing agent.

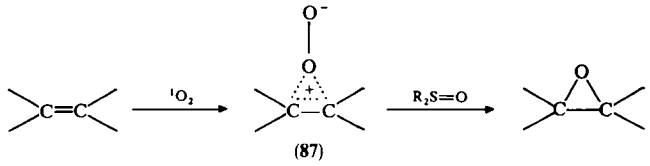
b. Ozone. Epoxides are by-products in the ozonolysis of olefins, but they become a major product especially in the case of hindered olefins. For example, epoxide yields were 60 and 90% from the ozonolysis of adamantylidene and dineopentyl-*t*-butylethylene, respectively[198]. These epoxidations are stereospecific since *Z*- and *E*-olefins afforded the corresponding *Z*- and *E*-epoxides[199]. The epoxidation of hindered olefins was thought to proceed via a σ-complex with ozone (**85**) in equation 53[200]. On the other hand, dipolar intermediates such as **86** were assumed for unhindered olefins because the epoxidation produced *cis-trans*-isomerized epoxides and was dependent on solvents[198]. Thus, the relative importance of the two intermediates **85** and **86** may be changed by olefin structures and solvents.



(53)

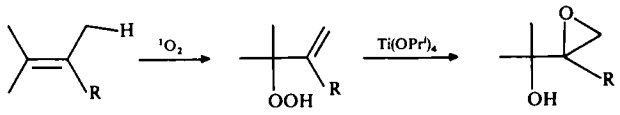
c. Singlet oxygen. The ene reaction of olefins with singlet oxygen ($^1O_2$) to yield allylic hydroperoxides has been studied extensively[201]. Sometimes epoxides are formed as a by-product. The intervention of a perepoxide intermediate (**87**; equation 54) has been indicated by trapping experiments[202].

Adam and coworkers developed an elegant one-pot synthesis (equation 55) of epoxy alcohols by the combination of the ene reaction of $^1O_2$ and the Ti-catalyzed intramolecular epoxidation[203]. By this method many synthetically useful epoxy alcohols could be easily prepared in 60–80% yields. For example, cyclohexene was converted to *cis*-2,3-epoxy-

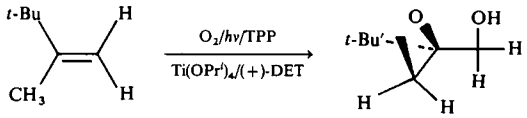


(87) (54)

cyclohexanol in 91% yield. The Sharpless–Katsuki asymmetric catalysis leads to a one-pot asymmetric synthesis of epoxy alcohols directly from olefins[203]. For example, the $^1O_2$ oxidation of 2-*t*-butylpropene in the presence of $Ti(OPr^i)_4$/(+)-DET yielded (*S*)-epoxy alcohol (**88**) of 72% ee in 79% yield (equation 56).

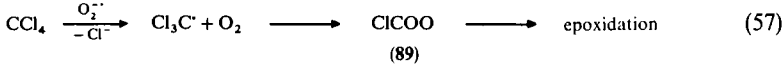


(55)



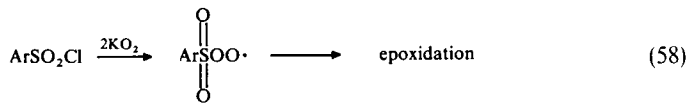
(*S*)-(**88**) (56)

d. Superoxide. Superoxide, $O_2^{-\cdot}$, is not a potent oxidant by itself[204] but is activated by appropriate additives. For example, the oxidation of malonic esters with $O_2^{-\cdot}/O_2$ yielded the corresponding hydroperoxide anion which is capable of epoxidizing enones[205]. The reaction (equation 57) with carbon tetrachloride yielded peroxy radicals (**89**) which epoxidize olefins[206]. The intervention of radical epoxidation was evidenced by the fact that *cis*-stilbene yielded *trans*-stilbene oxides predominantly.



(89) (57)

Similarly, olefins are epoxidized by sulfonylperoxy species formed in the reaction of potassium superoxide and arylsulfonyl chloride[207]; see equation 58. This method is suitable for the preparation of acid-sensitive epoxides, e.g. pyrene oxide, because of the neutral and low-temperature conditions[207].



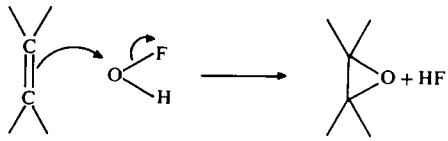
(58)

e. Hypohalites. Hypohalites may react as an active oxygen species. One example is the observation of epoxide formation in the NaOCl oxidation of olefins under phase transfer conditions[208]. A radical epoxidation with ClO· was suggested since *cis*-alkenes yielded *trans*-epoxides predominantly.

The epoxidation with elemental fluorine is an interesting system. Epoxides are obtained simply by introducing fluorine gas into olefin solutions in MeCN–water (9:1)[209]. The epoxidation (equation 59) was fast and efficient at 0 °C. It is interesting to note that

α,β-unsaturated ketones and esters were epoxidized facilely in a full stereospecific manner. These results indicate an epoxidation mechanism as shown in equation 60. The strongly electron-attracting effect of F makes possible an electrophilic epoxidation, just as in the case of peroxyacids.

$$F_2 + H_2O/MeCN \xrightarrow[-10\,^\circ C]{} HOF\cdot MeCN \xrightarrow[0\,^\circ C]{\text{olefin}} \text{epoxidation} \tag{59}$$

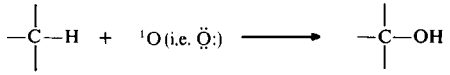


(60)

III. HYDROXYLATION

A. Introduction

Hydroxylations of C—H bonds are often the first step for the functionalization of organic compounds, but have not been so throughly studied as epoxidations since the substitution or insertion of an oxygen atom into C—H bonds is not easy, and the applied reagents have to be strongly electrophilic oxidants or radical species. C—H hydroxylations are classified into two reaction types.



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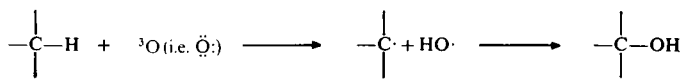
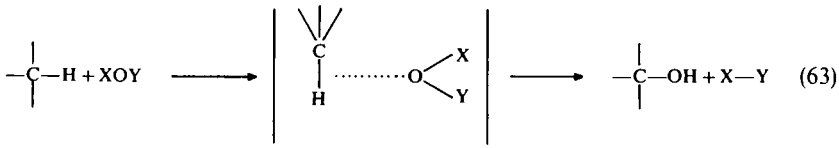


(62)

The first type is the insertion of a singlet oxygen atom (^1O) into C—H bonds (equation 61). In many cases oxygen atoms are transferred from electrophilic oxidants XOY via **90** as shown in equation 63; the oxidants are peroxyacids, oxaziridines and dioxiranes. In these O-transfers oxygen atoms are inserted into C—H bonds and hence the stereochemistry of substrates is retained.

The second type is the hydroxylation by triplet oxygen atom (^3O) and involves, as shown in equation 62, radical intermediates via hydrogen atom abstraction. These radical hydroxylations are observed in autoxidations and peroxide reactions and the substrate stereochemistries are not retained because of the involvement of radical intermediates.



(63)

(90)

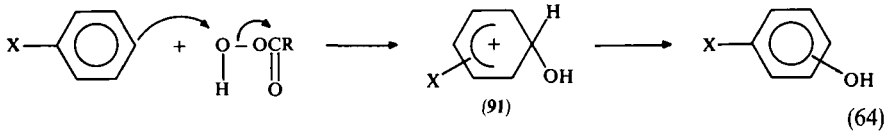
Metal-catalyzed hydroxylations have been developed extensively[210] and are classified into two types, the oxo metal (M=O) and the metal–peroxide catalyses. Metalloporphyrin

catalyses are also studied extensively as a bio-mimetic reaction[4]. Radiolytic hydroxylations are radical reactions via hydroxyl radical and have been reviewed[211]. Here we give only outlines and recent developments pertaining to the hydroxylations of C—H bonds so as to avoid overlapping with the above reviews. Dihydroxylations of olefins are not included in this chapter.

B. Electrophilic Hydroxylations by Peroxides and Other Oxidants

1. *Hydroxylations by peroxyacids and related oxidants*

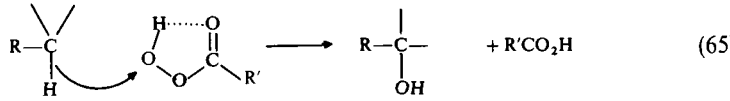
Aromatic rings are hydroxylated by peroxyacids (PA); for example, the hydroxylation of mesitylene was attained by either an uncatalyzed or a BF_3-catalyzed reaction of peroxytrifuluoroacetic acid[212]. Cationic intermediates (**91**; equation 64) are involved since the NIH shift was observed[213]. The hydroxylations are faster for arenes with electron-donating substituents, yielding *o*- and *p*-oriented hydroxylated products. In the preparative hydroxylation of phenol with peroxyacetic acid (60 °C in acetic acid), catechol and hydroquinone were obtained in 45 and 35% yields, respectively, based on the PA[214]. Since the hydroxylated products are more reactive than the starting arenes, the resulting phenols are prone to be further oxidized by PAs. Thus, the MCPBA oxidation of *p*-cymene yielded the corresponding quinones[215].



(64)

Aliphatic C—H bonds are also hydroxylated by PAs. The electrophilic nature of the hydroxylation was demonstrated by the fact that the oxidation of methylcyclohexene with CF_3CO_3H afforded the tertiary and secondary alcohols in 71 and 29% yields, respectively, the tertiary C—H bond being over twenty times more reactive than the secondary one[216]. Later, the hydroxylation of aliphatic C—H bonds by PAs was studied extensively[217] and applied to organic syntheses[218]. The hydroxylation with PA is quite useful because tertiary C—H bonds are selectively hydroxylated according to the reactivity order of tertiary ≫ secondary ≫ primary C—H bonds[216].

The detailed study by Schneider and Müller has revealed that the hydroxylation with PAs proceeds with high regioselectivity and retention of stereochemistry[219]. The electrophilic nature of the PA hydroxylation was shown by Hammett's correlation of $\rho^* = -2.2$ for alkanes and $\rho = +0.63$ for peroxybenzoic acids. These data together with the kinetic isotope effect of $k_H/k_D = 2.2$ for methylcyclohexane pointed to an electrophilic O-insertion into C—H σ-bonds as shown in equation 65. The relative rates for tertiary and secondary C—H bonds towards peroxybenzoic acids are as high 90–500, leading to highly selective hydroxylations of tertiary C—H bonds. This is true when the radical decomposition of PAs (see Section III.C.1) is not involved.

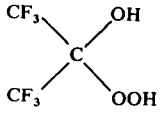


(65)

The hydroxylation with persulfonic acids is likewise of electrophilic nature as evidenced by Hammett's ρ value of -4.48 for the hydroxylation of substituted benzenes with

decanepersulfonic acid[220]. Aliphatic C—H bonds are also hydroxylated by persulfonic acids[221].

A quite high NIH shift of over 50% has been observed in the aromatic hydroxylation by the hydroperoxy ketal (**92**) obtained from hexafluoroacetone and hydrogen peroxide[222]. This suggests an involvement of cationic intermediates such as **91**. Another interesting reaction is the hydroxylation with fluorine in actonitrile[223]. Hypohalite (**93**) has been suggested as the key oxidizing species in the stereospecific hydroxylation of tertiary C—H bonds, e.g. *cis*-decaline afforded *cis*-9-decalol in over 80% yield. The hypofluorous acid (**93**) is formed from F_2 and the moisture present, since the addition of $H_2{}^{18}O$ resulted in ^{18}O-transfer to C—H bonds. In both the cases of **92** and **93**, the electrophilicity of the oxygen atom is enhanced by the strongly electron-attracting fluorine group.



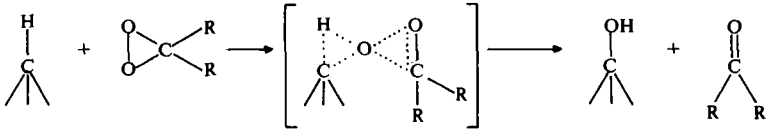
(92)

FOH

(93)

2. Hydroxylation by dioxiranes and oxaziridines

A surprising feature in the chemistry of dioxiranes is the facile O-insertion in C—H bonds[3,51]. Tertiary C—H bonds are selectively hydroxylated by dimethyldioxirane (**94**, R = Me); e.g. adamantane afforded 1-adamantanol selectively and *cis*-decaline yielded *cis*-9-decalol with retention of stereochemistry. These facts suggest transition state **95** for the stereospecific hydroxylation. The σ-electrons in the C—H bond attack the electrophilic peroxy oxygen in the dioxirane. This picture fits the reported kinetic isotope effect of $k_H/k_D = 4.97$[224].

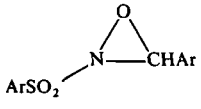


(66)

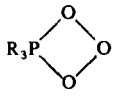
(94) (95)

The reactivity of methyl(trifluoromethyl)dioxirane (**94**, R,R = Me, CF_3) is considerably enhanced and, using it, secondary C—H bonds are easily hydroxylated[225]. This oxidant is 7000 times more reactive than dimethyldioxirane and converts adamantane into adamantane-1,3,5,7-tetraol[226]. The oxidation of alcohols to ketones is also possible[227]. The stereospecific hydroxylations by dioxiranes may be applied for various organic syntheses, taking in account the reactivity order of tertiary > secondary > primary C—H bonds.

On the other hand, the reactivity of oxaziridines is not sufficient for the hydroxylation of C—H bonds. For example, anisol was hydroxylated in only 12% yield by using oxaziridine (**96**) with a strongly electron-attracting sulfonyl group[228]. The oxidation of



(96)

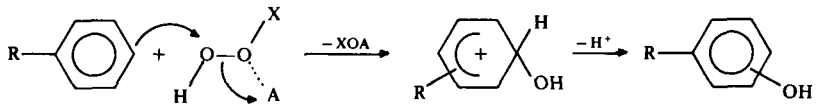


(97)

ketone enolates with the optically active oxaziridine **96** yielded α-hydroxy ketones enantioselectively (>96% ee)[229]. Silyl enol ethers were oxidized to α-hydroxyketones by phosphite ozonide (**97**)[230].

3. *Acid-catalyzed hydroxylations using peroxides*

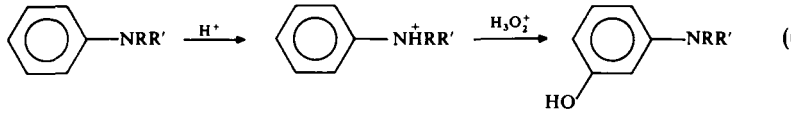
Since direct oxyfunctionalizations of C—H bonds are usually difficult with hydrogen peroxide or its derivatives, acid catalyses have long been applied as an activation method. Hydroxylation of aromatic substrates were especially throughly studied. Hart and coworkers[212,231] reported the BF_3-catalyzed hydroxylation of polymethylbenzenes with CF_3CO_3H. Kurz and collaborators[232] reported the ring hydroxylation of aromatics by $AlCl_3/H_2O_2$ in moderate yields, e.g. 70 and 40% yields for anisol and toluene. These substances are *o,p*-directing and the electrophilicity of the peroxide derivative XOOH is increased by the coordination of the acid catalyst A as depicted by **98** in equation 67.



(**98**) (67)

Olah's group[233] reported *o*- and *p*-hydroxylations with super acids and H_2O_2, which involves the reaction of protonated hydrogen peroxide ($H_3O_2^+$ or HO^+). The use of the inexpensive HF/BF_3 catalyst was reported to be preferable, product distributions being the same[234]. The CF_3CO_2H-catalyzed reaction of bis(trimethylsilyl)peroxide[235], $Me_3SiOOSiMe_3$, is a safe, smooth and convenient method for the oxidation of arenes to phenols[236].

Jacquesy and coworkers applied the super acid/H_2O_2 systems to phenols and their ethers, leading to *m-hydroxylations*[237]. Thus, in the hydroxylation with $HF{\cdot}SbF_5/H_2O_2$ the electrophilic attack of $H_3O_2^+$ (or HO^+) on O-protonated phenols yielded *m*-hydroxylated products predominantly. The reaction of naphthols resulted in hydroxylation on the nonphenolic ring, suggesting again predominant O-protonation[237]. The *m*-direction in the hydroxylation of anilines[238] is due to the complete protonation on the amino groups (equation 68). Similar *m*-hydroxylations were applied to various anilines and indoles.

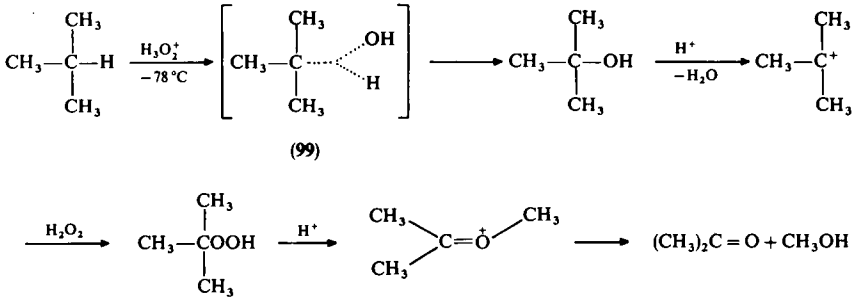


(68)

These acid-catalyzed hydroxylations are not applicable for aliphatic substrates, since the hydroxylated products are more reactive than the starting compounds and hence oxidized further[239]. For example, the reaction of isobutane with H_2O_2/magic acid ($HSO_3F/SbF_5/FSO_2Cl$) gave initially insertion of a hydroxyl cation into the C—H bond via transition state **99**, but yielded acetone ultimately by oxidation of the produced alcohol as shown in equation 69[240]. The oxidation with ozone/magic acid involves an interesting reaction of O_3H^+, but cannot be used for C—H hydroxylations since the products are ketones[241].

4. *Base-catalyzed hydroxylations via enolates*

Base-catalyzed hydroxylations are another choice when direct oxygenations are difficult. It is long known that carbanions are formed and react facilely with oxygen in base-



(99)

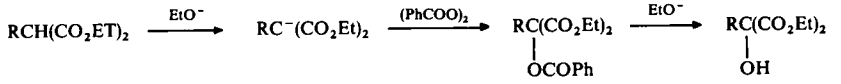
(69)

catalyzed autoxidations[242]. The reaction of carbanions with oxygen is very fast (e.g. $k_2 = 10^9\,M^{-1}s^{-1}$ for triphenylmethide ion in DMSO)[243] and usually the rate- determining step is the formation of carbanions, i.e. equation 70. However, the selectivities for alcohols are relatively low, yielding various oxygenated products. Useful base-catalyzed hydroxylations are the oxygenations of carbanions or enolates with oxidants such as peroxides or oxaziridines as described below.

$$RH + B^- \xrightarrow{\text{slow}} R:^- + BH \tag{70}$$

$$R:^- + O_2 \xrightarrow{\text{fast}} ROO^- \longrightarrow \longrightarrow ROH + \text{others} \tag{71}$$

α-Hydroxylations of ketones and esters have been studied extensively. The first typical reaction is the α-hydroxylation of malonic esters via the benzoyloxylation with benzoyl peroxide (equation 72)[244]. α-Hydroxylations of ketones may be attained by either the direct oxygenation of enolate anions (**100**) *in situ* formed by a base-catalyzed reaction (equation 73a) or by oxidation after converting them to silyl enol ethers (**101**, equation 73b). The oxidation of enol ethers with peroxyacids[245] and $PhIO/BF_3 \cdot Et_2O/H_2O$[246] afforded α-hydroxyketones in good yields (60–80%). Enolate ions were oxidized directly with PhIO to α-hydroxyketones[247a] and esters[247b]. Utilization of bis(trimethylsilyl)-peroxide resulted in somewhat lower yields (i.e. 30–60%)[248].



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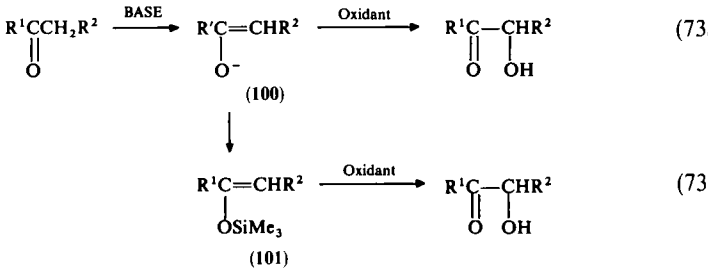


(73a)

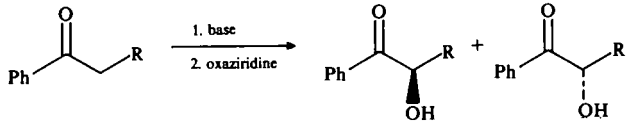
(73b)

(100)

(101)

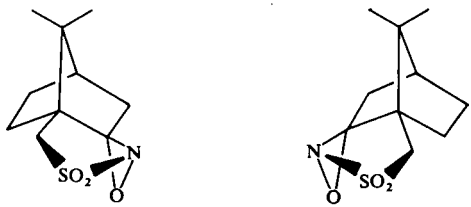
Asymmetric α-hydroxylation of ketones could be achieved by using chiral oxaziridines as oxidants for lithium or sodium enolates[249]; see equation 74. Use of oxaziridine (+)-(**102**) afforded *S*-α-hydroxyketones and (−)-(**103**) yielded the *R*-isomers. When sodium

bis(trimethylsilyl)amide was used as a base, the asymmetric induction was as high as 95% ee[249]. The origin of the induction was reported to be due to nonbonded steric interactions. A diastereoselective hydroxylation was reported for the base-catalyzed reaction of L-pyroglutamate ester[250]. The oxaziridine oxidation of enolates from optically active hydrazones afforded an α-hydroxylation of ketones with high enantioselectivity of >96% ee[251]. All these methods require stoichiometric amounts of optically active reagents and do not constitute a practical synthesis. A notable exception is the catalytic α-hydroxylation, as reported by Shioiri and coworkers using dioxygen under phase-transfer conditions[252] (equation 75) when *R*- and *S*-α-hydroxyketones could be obtained in up to 74% ee. The addition of phosphite is essential for the reduction of produced hydroperoxides to α-ketols. Apparently, the asymmetric induction is achieved in the enolization step catalyzed by chiral catalysts.

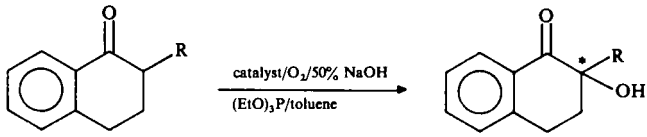


(74)

(*R*) (*S*)



(+)-(**102**) (−)-(**103**)



(75)

5. Hydroxylation via organometallic compounds

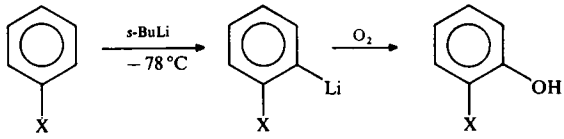
It is well known that hydroxylations are often observed in the autoxidations of organometallic compounds (equation 76)[253]. Hydroxylations of organometallic compounds are also attained by the benzoyloxylation with benzoyl peroxide followed by hydrolysis[254]. Another route for the preparation of phenols in good yields (i.e. 39–98%) is via electrophilic oxygenation with silyl peroxide, followed by hydrolysis (equation 77)[255]. Nitrobenzene is also reactive as the oxygenating agent[256].

$$RMgX \xrightarrow{O_2} ROH + \text{others} \tag{76}$$

$$RX \xrightarrow{BuLi} RLi \xrightarrow{Me_3SiOOSiMe_3} ROSiMe_3 \xrightarrow[MeOH]{HCl} ROH \tag{77}$$

Air oxidation of organo copper compounds (RCu) usually leads to the formation of dimers (R-R), but phenol formation becomes the predominant reaction when RCu bears

an *o*-alkoxy group[257]. A directed *o*-hydroxylation has been attained by means of the selective *ortho*-lithiation of aromatic substrates[258]. The one-pot hydroxylation (equation 78) yielded *o*-phenols, when $X = CONMe_2$ or OMe, in 37–50% yields. Similarly, *ortho*-hydroxylations have been reported for the case of $X = CHO$[259a], $CH_2NHCOBu^t$[259b] and OMe[259c].

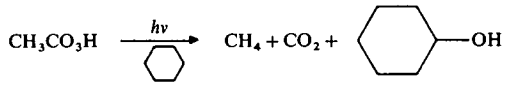


(78)

C. Radical Hydroxylations

1. Radical hydroxylations by peroxyacids

Autoxidations of hydrocarbons yield the corresponding alcohols, but the product mixtures include also ketones and carboxylic acids. A preparative radical hydroxylation is the reaction with peroxyacids, such as the formation of cyclohexanol in 90% yield from cyclohexane and peroxyacetic acid (equation 79)[260]. The photolysis induced the radical decomposition of peroxyacetic acid and the methane formation suggests hydrogen atom abstraction by methyl radicals. On the other hand, the photolysis of peroxyacetic acid in toluene yielded complex mixtures of products resulting from ring methylation and side-chain hydroxylation[261].



(79)

Lefort and coworkers systematically studied radical hydroxylations with peroxyacids[262]. Various radicals were produced by the thermolysis of several PAs and their reactivities were examined. The reaction scheme is outlined in equations 80–84.

$$RCO_3H \longrightarrow RCO_2\cdot + HO\cdot \tag{80}$$

$$RCO_2\cdot \longrightarrow R\cdot + CO_2 \tag{81}$$

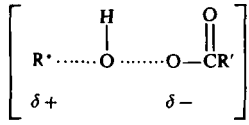
$$R\cdot + SH \longrightarrow RH + S\cdot \tag{82}$$

$$S\cdot(\text{or } R\cdot) + \underset{\displaystyle H}{\overset{|}{O}}\!-\!OCOR \longrightarrow SOH(\text{or } ROH) + RCO_2\cdot \tag{83}$$

$$X\cdot + H\!-\!OOCOR \longrightarrow X\cdot + RCO_3\cdot \tag{84}$$

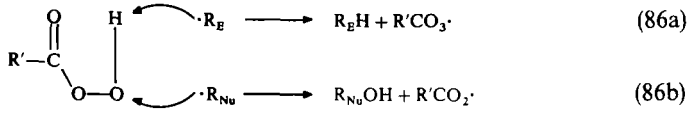
The decarboxylation of aliphatic carboxy radicals (equation 81) is very fast. The hydrogen atom abstraction from substrate SH produces radical S·, which is in turn hydroxylated via an S_H2 reaction on the peroxy oxygen of PA. It is interesting to note that more nucleophilic radicals react faster with the peroxy oxygen of PA; i.e. the relative reactivity of equation 83 is in the decreasing order of tertiary > secondary > primary radicals. For example, the relative reactivity of alkyl radicals ($R = n\text{-}C_{10}H_{21}$) is shown in equation 85. These relative reactivities of radicals with PA are correlated with their ionization potentials and are explained by the importance of the polar effect pictured in **104**[262].

$$\underset{100}{R\dot{C}Me_2} > \underset{11}{R\dot{C}HMe} > \underset{0.4}{R\dot{C}HCl} > \underset{0.016}{R\dot{C}H_2} \tag{85}$$



(104)

The predominant reaction of electrophilic radicals such as HO·, ROO· and CH_3· is hydrogen atom abstractions from substrate SH or from PAs (equation 84). Thus, the generation of these electrophilic radicals leads to the hydroxylation of SH[263]. The reactions of various radicals with PAs are rationalized by the schematic equations 86a and 86b. It should be noted here that the radical hydroxylation of C—H bonds, in contrast to the case of non-radical hydroxylation (Section III.B.1), affords alcohols without retention. For example, *cis*-decaline was oxygenated to a mixture of *cis*- and *trans*-9-decalols[264]. The S_H2 reaction on the peroxy oxygen of alkyl hydroperoxides (i.e. ROOH in place of PA in equation 83) is 150–200 fold slower than that of PAs, while the hydrogen abstraction of ROOH (cf. equation 84) is 50–100 fold faster than that of PA[265]. In other words, the departing ability of RO groups is much less in comparison to the RCO_2 group. Accordingly, there is no occurrence of radical hydroxylations with hydroperoxides.



(86a)

(86b)

2. Hydroxylations by hydroxyl and related radicals

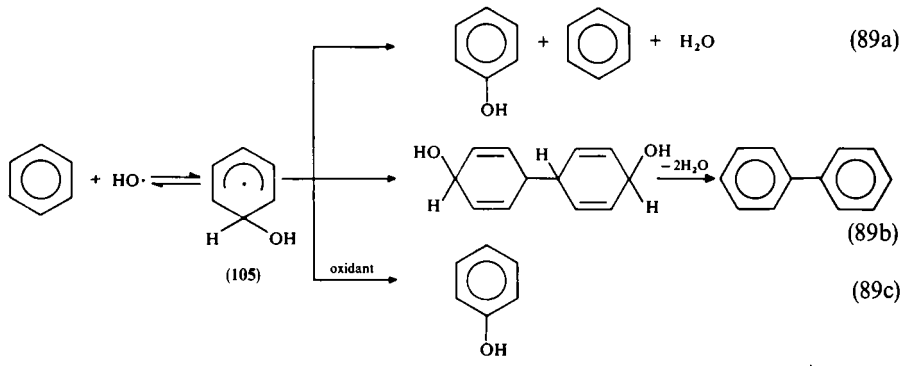
a. Formation and reaction of hydroxyl radical. The reactive hydroxyl radicals are able to abstract hydrogen atoms and add to double bonds. They are produced by the radiolysis of water (equation 87) or the reduction of hydrogen peroxide (equation 88). Reactions of hydroxyl radicals by radiolysis[266a,c], the Fenton reactions [266b] and the oxidation of intermediary cyclohexadienyl radicals[266c] have been reviewed. In the present section we will briefly summarize recent advances.

$$H_2O \rightsquigarrow H_2O^{+}\cdot \xrightarrow{H_2O} H_3O^{+} + HO\cdot \tag{87}$$

$$H_2O_2 + Fe_2^{+} \longrightarrow Fe^{3+} + HO^{-} + HO\cdot \tag{88}$$

The hydroxylation of aromatic substrates has been studied repeatedly. This reaction is based on the facile addition of hydroxyl radical to aromatic rings. For example, the addition to benzene yields the cyclohexadienyl radical (**105**), which disproportionates to afford phenol (equation 89a) or dimerizes to biphenyl (equation 89b). The addition rates of hydroxyl radical to substituted benzenes are in the narrow range of (0.3–1) × $10^{10}\,M^{-1}s^{-1}$, the substituent effect being quite small[267]. The addition of oxidants like Fe^{3+}, Cu^{2+} or O_2 leads to the formation of phenols (equation 89c)[266b,c] when the resulting *o*:*m*:*p* ratios are dependent somewhat on the oxidants[268].

Hamilton and coworkers reported that hydroxylation yields were significantly increased by adding catechol to the Fenton (i.e. H_2O_2/Fe^{2+}) system[269]. In this modified system the active species is derived from the iron–catechol complex **106** (equation 90). The yields of phenols were also improved by adding quinones (e.g. 40% based on

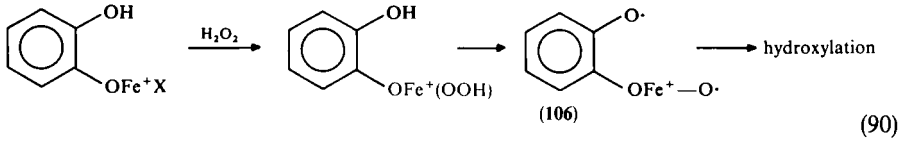


(89a)

(89b)

(89c)

H_2O_2)[270] and, more remarkably, up to 80% by the addition of one-electron transfer agents such as phenylenediamines or phenothiazines[271]. The quite high yields suggest an active species like **106** rather than free hydroxyl radicals. The remarkable *cis*-hydroxylation of cyclohexanol as reported by Groves and van Der Pury also indicated a similar active species[272].



(90)

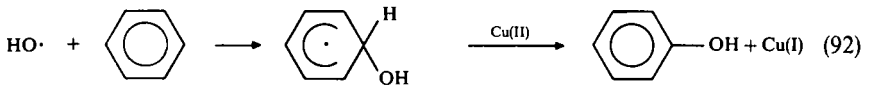
b. Catalyzed hydroxylations utilizing oxygen. The Udenfriend system uses the mixture Fe^{2+}/EDTA/O_2/ascorbic acid in order to utilize molecular oxygen. EDTA coordinates with iron ion, and ascorbate is consumed to reduce dioxygen to hydrogen peroxide[266a,273]. Thus, the point here is the reductive activation of oxygen. Recently it was reported that the addition of flavin (i.e. Fe^{3+}/ascorbate/flavin/O_2) resulted in up to 68% hydroxylation of aromatic substrates[274].

Other modifications of the Udenfriend system are the arene hydroxylation with Ru(III)/EDTA/ascorbate/O_2[275] and the selective *ortho* hydroxylation (e.g. over 70%) of anisol simply with Fe^{2+}/O_2[276]. The hydroxylation by phenazine methosulfate/nicotinamide/O_2 is intriguing in that the phenazine reduces dioxygen as a redox catalyst[277].

The reaction with Cu(I)/O_2 is another hydroxylating system utilizing oxygen[278]. The catalytic reaction proceeds as outlined in equations 91 and 92. A detailed ^{18}O-tracer study revealed that the reaction of cyclohexadienyl radical with oxygen proceeds either through hydrogen atom abstraction (equation 93a) or by addition and elimination (equation 93b)[279,280].

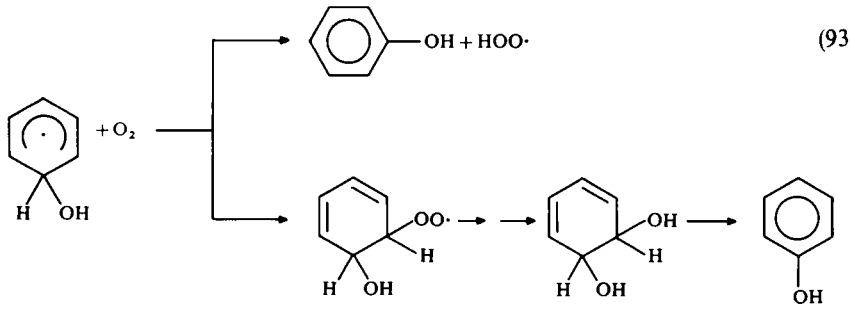
$$\text{Cu(I)} + \tfrac{1}{2}O_2 \longrightarrow \text{Cu(II)} + \tfrac{1}{2}H_2O_2 \qquad (91a)$$

$$\text{Cu(I)} + H_2O_2 \longrightarrow \text{Cu(II)} + \text{HO}\cdot \qquad (91b)$$



(92)

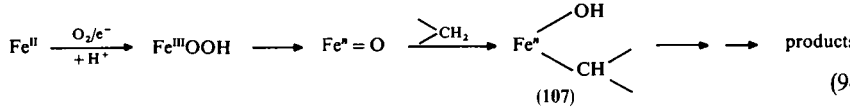
c. Hydroxylations of aliphatic C—H bonds. The oxidant composed of iron powder/O_2/RCO_2H/ pyridine, called *the Gif system*, is suitable for oxidations of aliphatic



(93a)

(93b)

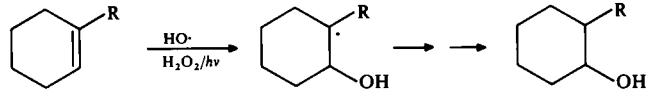
substrate[281]. The most characteristic point is the relative reactivity of secondary ≫ tertiary > primary C—H bonds. In fact, adamantane and methylcyclohexane did not afford tertiary alcohols. A working hypothesis involves insertion of iron into C—H bonds as depicted in **107** (equation 94).[282] Products are alcohols and ketones, and the system could be applied for a variety of organic syntheses as reviewed recently[283]. A modified system of Fe complex/Zn powder/AcOH/2,2'-bipyridine/H_2O_2 resulted in the similar reactivity of C—H bonds affording alcohols only[284].



(107)

(94)

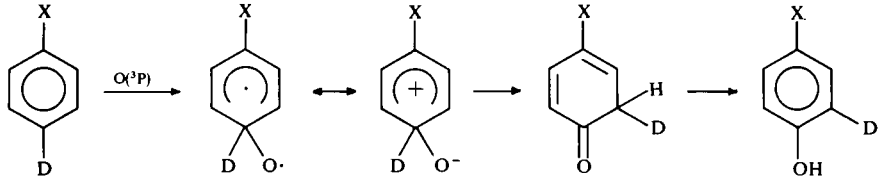
Tertiary C—H bonds were preferentially hydroxylated by irradiating a mixture of the substrates with H_2O_2 or peroxyacetic acid[285]. Secondary alcohols could be obtained from the reaction of hydroxyl radicals with cycloalkenes as shown in equation 95[286].



(95)

3. *Hydroxylations with oxygen atom*

Oxygen atoms (^3P) in the liquid phase are produced by microwave discharge of O_2 or by γ radiolysis of CO_2. Reactions of O(^3P) atoms with arenes lead to phenols. The electrophilic nature of oxygen atom was shown by the negative ρ-value of -1.6 (σ^+) for substituted benzenes[287]. The NIH shift, as shown in equation 96, was in the range of 48–55%, which is close to those of microsome oxidations[287b].



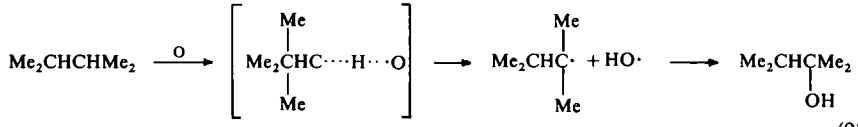
(108a) (108b)

(96)

These results were considered to suggest the importance of the dipolar structure **108b**. The diradical intermediate (**108a**) was also shown to be important since *o*-xylene afforded *o*-cresol (62%) by demethylation via this intermediate[288]. The slowness of the cyclization of **108** to yield an epoxide is explicable on the basis of the triplet nature of the diradical.

An alternative method for oxygen atom production is the photolysis of pyridine *N*-oxides[289a], by which benzenes are converted to phenols. The NIH shift values for *p*-D-anisol increased in polar solvents[290] which may indicate the increased importance of the dipolar **108b**. 3-Methylpyridazine 2-oxide has also been utilized as the oxygen source. When the *N*-oxide of pteridine derivatives was used the O-transfer changed to a sensitized oxygenation involving one-electron transfer[291].

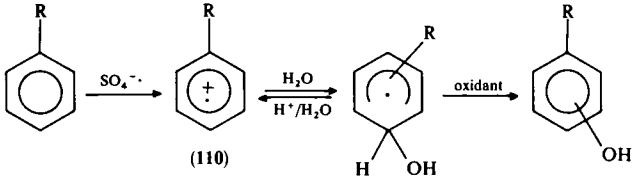
The hydroxylation of aliphatic C—H bonds has been less fully studied, but the steric effect was shown to be less important in the reaction of oxygen atoms with 2,3-dimethylbutane[292]. The small steric effect may be explained by the linear transition state (**109**; equation 97).



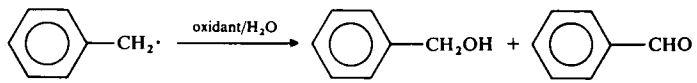
(97)

4. Hydroxylations by one-electron oxidation

The decomposition of peroxydisulfate, $S_2O_8^{2-}$, yields the sulfate radical $SO_4^{-\cdot}$,which is a potent one-electron oxidant for many organic substrates[293]. For example, the reaction of $S_2O_8^{2-}/Cu^{2+}$ in the presence of arenes yields phenols via the cation radical (**110**) and the dienyl radical (**111**) (equation 98a), phenol was obtained in 64% yield from benzene[294]. When side chains are present, e.g. R = CH_3, their oxygenation (equation 98b) proceeds competitively.



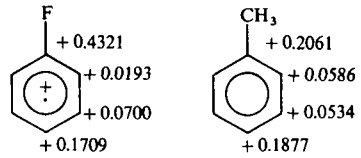
(98a)



(98b)

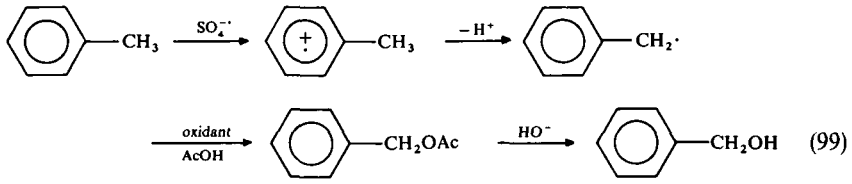
The hydroxylation of benzenes by $SO_4^{-\cdot}$ was accelerated by electron-donating groups, the ρ-value being -2.3 (σ^+)[295]. The isomer ratios in phenols are determined by the nucleophilic addition of water to the cation radical **110**, which in turn depends on the cationic charge distribution in **110**. The reaction of fluorobenzene yielded *o*-, *m*- and *p*-fluorophenol and phenol in the ratio of 5:trace:60:35, with phenol being formed by an

ipso attack[296]. Toluene afforded cresols in the ratio of *o*:*m*:*p* = 41:3:56 without *ipso* substitution. These product ratio are in line with calculated distributions of positive charges (INDO method) as shown in **112** and **113**. The absence of *ipso* substitution for toluene reflects the very low departing ability of the methyl group. These product ratios are different from the case of Fenton oxidation (e.g. *o*:*m*:*p* = 57:18:25 for cresols from toluene) where product distributions are determined by the reactivity of arenes towards the hydroyl radical.



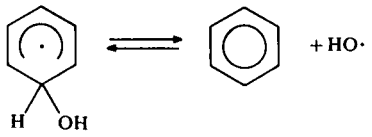
(112) (113)

The ring hydroxylation (equation 98a) and the side-chain oxygenation (equation 98b) are competitive reactions. The reaction in acetic acid results predominantly in side-chain acetoxylation (equation 99),[297] since the addition to the cation radical is slowed down in acetic acid. The ρ-value for substituted toluenes was -1.9 (σ^+), supporting the importance of one-electron oxidation[297a].



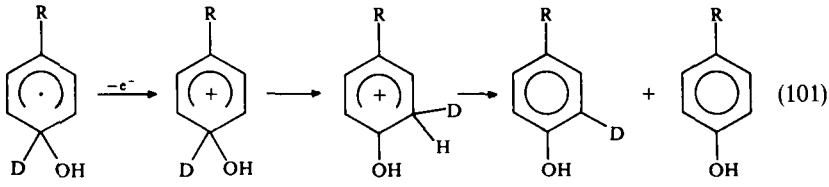
(99)

The formation of hydroxyl radicals from the dienyl radical (**111**) was suggested from the fact that nitrobenzene was hydroxylated during the reaction of $SO_4^{-\cdot}$ and benzene[298]. This indicates a reversible addition–elimination between benzene and hydroxyl radical (equation 100).



(100)

The NIH shift (i.e. the rearrangement of hydrogen atoms observed during enzymatic aromatic hydroxylations[299]) was originally explained by arene oxide intermediates, but not all results were compatible with this mechanism[300]. The NIH shift in the Fenton hydroxylation was shown to be considerably high (e.g. 30–40%) in dry acetonitrile[301].



(114) (115) (101)

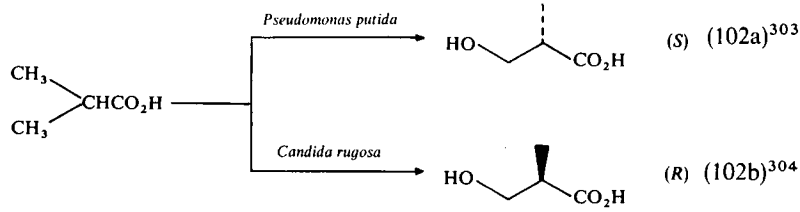
Detailed study on the oxidants revealed that the NIH shifts are high (i.e. 40–50%), even in aqueous solutions, in the presence of one-electron oxidants such as Cu^{2+}, Fe^{3+} and quinones[280]. These facts mean that the one-electron oxidation of **114** to **115** is the key step in the NIH shift (equation 101). The presence of oxygen reduced the shift remarkably by abstracting a deuterium atom from **114**, not affording cation **115**.

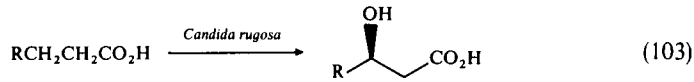
D. Metal-catalyzed Hydroxylations

1. Features of biochemical hydroxylations

A number of biochemical processes are known for hydroxylating aliphatic and aromatic C—H bonds[302]. Stereospecific hydroxylations of specific C—H bonds are of particular interest. For example, in the biological hydroxylation of isolactic acid *R*- and *S*-3-hydroxy-2-methylpropionic acid could be obtained by choosing different fungi. These hydroxy acids have two functional groups near to the asymmetric center and are useful starting materials.

The most characteristic feature of biochemical oxygenations is the *ω-hydroxylation*; that is, hydrocarbons are hydroxylated at the terminal methyl groups[305]. Examples are the hydroxylation of equation 102 and the ω-hydroxylation of di-isopropylbenzene yielding the (*R*,*R*)-dihydroxy compound[306]. Enantioselective β-hydroxylations of carboxylic acids are also possible by choosing fungi. The reaction of equation 103 afforded (*R*)-β-hydroxy acids with high selectivities, e.g. R = Me (95% ee), Et (93% ee), and Pr (96% ee)[307].





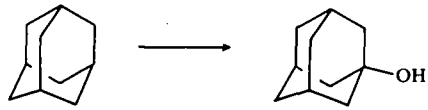
Many biological hydroxylations of aliphatic C—H bonds proceed with retention of configuration[308]. Thus, ω-hydroxylation of octane by rat liver microsomes, believed to involve a ferryl ion (Fe^{5+}=O) intermediate, was shown to proceed with retention[309]. Stereoselective hydroxylations have been obtained for benzylic[310] and allylic oxygenations[311] using dopamine β-mono oxygenase catalyst.

Details of these biological hydroxylations are outside the scope of this chapter, although they are the target of current synthetic organic studies.

2. Direct hydroxylations by metallic oxidants

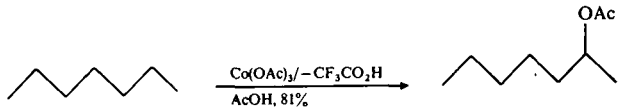
Oxygenations of alkane C—H bonds are possible only with potent oxidants such as chromic acid or permanganate. The former oxidant is known to be selective for tertiary C—H bonds, the relative reactivity of primary:secondary:tertiary C—H bonds being 1:65:3500[312]. Thus, tertiary alcohols could be obtained by chromic acid oxidation

of adamantane and of decaline[313]; see equation 104. Benzyltrimethylammonium permanganate is soluble in organic solvents and oxidizes methylcyclohexane to 1-methylcyclohexanol in good yield[314].



(104)

The hydroxylation of secondary C—H bonds is usually difficult since the produced alcohols are easily oxidized to ketones. α-Hydroxylations of ketones are sometimes possible, e.g. by using thallic sulfate[315]. A well-known reaction is the selective 2-acetoxylation of alkanes by $Co(OAc)_3/CF_3CO_2H$ in acetic acid[316] (equation 105). The involvement of alkyl radical intermediates was evidenced by the formation of 2-heptyl chloride in the presence of carbon tetrachloride. The high reactivity of C—H bonds of the penultimate (i.e. $\omega - 1$) carbon is well recognized in many cases.

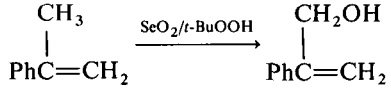


(105)

3. Hydroxylations by metallic catalysts and oxidants

The oxidations with stoichiometric amounts of metallic oxidants are not advisable owing to high costs, problems of treatment and waste chemicals. Therefore, catalyzed oxygenations have been throughly studied and reviewed frequently[94,317]. In the following the outline of these processes and recent advances are briefly summarized.

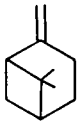
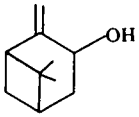
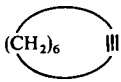
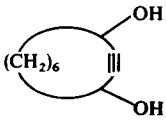
a. Hydroxylations of activated C—H bonds. Selenium dioxide has long been known as a selective hydroxylation reagent for allylic or activated C—H bonds, problems here being the separation of colloidal selenium and the formation of organoselenium compounds. These were prevented by using (equation 106) SeO_2-catalyzed *t*-BuOOH oxidation[318]. These oxidations are convenient for the conversion of olefins to allyl alcohols[319] and acenaphthenes to diols[320]. Use of selenium dioxide on silica gel resulted in the selective hydroxylation of the α-methyl group of cyclic olefins.[321] Table 6 lists several examples of α-hydroxylations occurring through catalyzed oxidation with *t*-butyl hydroperoxide.



(106)

Acyloxylations are equivalent to hydroxylations owing to the facile hydrolysis of acetates to alcohols. Useful acetoxylation reagents of activated C—H bonds are peresters in the presence of metallic catalysts such as cuprous bromide[324], taking place by a chain reaction as shown in equations 107–109. The peroxyesters are decomposed by Cu(I), yielding *t*-butoxy radicals (equation 107). The latter abstracts a hydrogen atom from active C—H bonds, usually from an allylic or α-hydrogen of ethers (equation 108). The third step is the oxidative ligand transfer from the cupric complex (equation 109). In this manner, cyclohexene afforded 3-acetoxycyclohexene in good yields[325]. Since the acyloxylation involves allylic radical intermediates, the isomerization of double bonds

TABLE 6. Hydroxylations of aliphatic C—H bonds

Substrate	Conditions	Product (% yield)	Reference
1-Decene	t-BuOOH/SeO_2/CH_2Cl_2	3-Hydroxy-1-decene (61%)	322
1-Decyne	t-BuOOH/SeO_2/CH_2Cl_2	3-Hydroxy-1-decyne (48%)	322
Cyclohexane	t-BuOOH/$Cr(acac)_2$/108 °C	Cyclohexanol (22%) Cyclohexanone (42%)	323
	t-BuOOH/SeO_2/C_6H_{12}		318
	t-BuOOH/SeO_2/CH_2Cl_2		320

is inevitable. Thus, the major products from terminal olefins are 3-acetoxy-1-olefins as shown in equation 110[328].

$$R'CO_3Bu^t + Cu(I) \longrightarrow t\text{-}BuO\cdot + Cu(II)(OCOR') \quad (107)$$

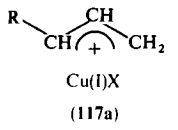
$$t\text{-}BuO\cdot + RH \longrightarrow t\text{-}BuOH + R\cdot \quad (108)$$

$$R\cdot + Cu(II)(OCOR) \longrightarrow ROCOR' + Cu(I) \quad (109)$$

$$RCH_2CH{=}CH_2 + R'CO_3Bu^t \xrightarrow[AcOH]{CuX} \underset{\displaystyle OAc}{RCHCH{=}CH_2} + \underset{\displaystyle OAc}{RCH{=}CHCH_2} \quad (110)$$

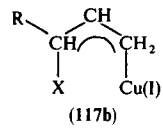
(116a) **(116b)**

The product-determining step is the reaction of intermediate allyl radicals with Cu(II)X. It is not easy to conclude whether the reaction of allyl radicals with Cu(II)X occurs via one-electron transfer (**117a**) or a ligand transfer (**117b**). The situation may be changed by the kinds of ligand X. For example, the ratios **116a**:**116b** for the acyloxylation of butenes in acetic acid were 9:1 with CuOAc but 3:7 $CuCl$[326a]. The predominant formation of thermodynamically unstable 3-acetoxy olefins (**116a**) could be explained by the intramolecular acyl transfer in the copper complex (**118**)[327]; see equation 111.

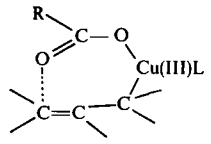


Cu(I)X

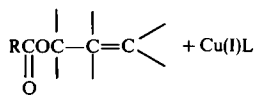
(117a)



(117b)



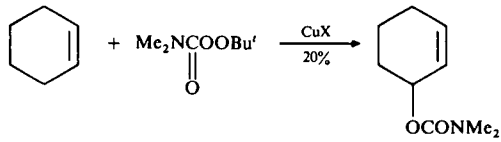
(118)



(119a)

(111)

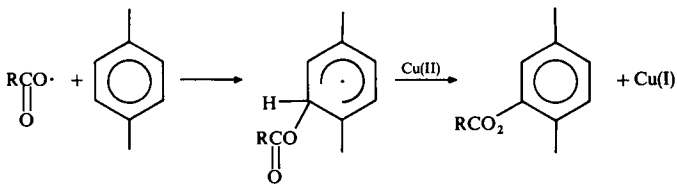
The same reaction of bicyclo[3.2.1]octene-2[328] and β-pinene[329] resulted in the selective *exo*-acyloxylation. α-Acyloxylations of ethers were studied extensively[324,330]. Acyloxylations with copper salts and peroxyesters took place with propargylic C—H bonds[331] and β-lactam rings[332]. α-Amidoxylation could be attained by using peroxyamidates as shown in equation 112[333].



(112)

b. Hydroxylations of arenes. Catalyzed hydroxylations of arenes such as the Fenton and related reactions were already mentioned in Section III.C.2.a. These reactions proceed via the reaction of hydroxyl radical or via the one-electron oxidation as observed with $S_2O_8^{2-}/Fe^{2+}/Cu^{2+}$[334]. Several examples of arene hydroxylations are listed in Table 7. The product ratios are sometimes changed because the produced phenols are further oxidized. In this respect, acetoxylated products are stable and suitable as preparative reactions. Such acyloxylations are attained by the reaction of diacyl peroxides and copper catalyst (equations 113 and 114). For example, the oxygenation of *p*-xylene with benzoyl peroxide and $CuCl_2$ afforded the corresponding benzoate in good yields[335]. Utilization of $(i\text{-PrOCO})_2/CuCl_2$) afforded the corresponding carbonates[336,337] in over 80% for arenes with electron-donating groups. A few examples are listed in Table 7.

(113)



(114)

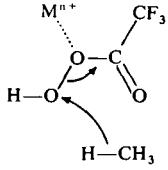
TABLE 7. Hydroxylation and acyloxylation of aromatic compounds

Substrate	Conditions	Product (% yield)	*o*:*m*:*p*	Reference
(A) Hydroxylation				
Toluene	$H_2O_2/AlCl_3$	Cresol (40%)	60:8:32	232
Toluene	H_2O_2/superacid[a]	Cresol	71:6:23	233
PhCl	H_2O_2/superacid	Chlorophenol	28:7:65	233
Toluene	$MeSiOOSiMe_3/CF_3SO_3H$	Cresol (88%)	63:10:27	236
PhCl	$MeSiOOSiMe_3/CF_3SO_3H$	Chlorophenol (71%)	34:10:56	236
Toluene	$S_2O_8^{2-}/Fe^{2+}/Cu^{2+}$	Cresol (81%)	63:3:33	334
PhCl	$S_2O_8^{2-}/Fe^{2+}/Cu^{2+}$	Chlorophenol (50%)	19:3:78	294
(B) Acyloxylation				
Toluene	$(PhCOO)_2/CuCl_2$	Benzoate (38%)	56:18:26	336
Toluene	$(i\text{-PrOCO}_2)_2/CuCl_2$	Carbonate (85%)	56:18:26	336
Naphthalene	$(i\text{-PrOCO}_2)_2/CuCl_2$	Carbonate (89%)	$\alpha:\beta = 92:8$	337

[a] Superacid: HSO_3F–FSO_2Cl; −78 °C.

c. Hydroxylations of unactivated C—H bonds. Hydroxylations of unactivated C—H bonds are most difficult and need a strongly electrophilic oxidant or radical species. Activation of methane C—H bonds is a challenging problem, and was attempted (equation 115) by hydroxylation with a H_2O_2 and ruthenium complex[338a] or by Pd(III)-catalyzed H_2O_2 oxidation in trifluoroacetic anhydride[338b]. The latter reaction is explained to be due to the increased electrophilicity of the peroxyacid owing to the coordination with the Pd-catalyst.

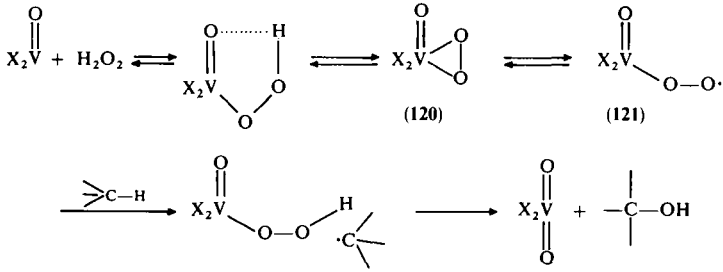
$$CH_4 + H_2O_2 \longrightarrow CH_3OH \tag{115}$$



(119)

The second type of activation is the hydroxylation of C—H bonds by means of metal oxo complexes[339]. The previously mentioned Gif system is assumed to be a selective hydroxylation via Fe=O intermediate[340]. Details will be discussed in Section III.D.4.

The third type is the radical hydroxylation of C—H bonds. Mimoun and collaborators reported that vanadium(V) peroxo complexes, composed of V_2O_5, picolinic acid and H_2O_2 are the active hydroxylating agent for C—H bonds[341]. The active species with X = picolinate is reported to be the diradical **121** rather than the peroxo form (**120**), based on the fact that *cis*-decaline afforded *cis*- and *trans*-decalin-9-ol; see equation 116.



(120) (121)

(116)

Cobalt-catalyzed autoxidation of hydrocarbons represent one of the large-scale applications of homogeneous catalyses. In these processes, the key steps are the homolytic decomposition of *in situ* formed hydroperoxides and the following hydrogen abstraction by the metaloxy radical (**122**)[342]; see equation 117. The radical nature was again evidenced by the major formation of *trans*-decaline-9-ol from *cis*-decaline. Chromium peroxo complexes were shown to hydroxylate hydrocarbons similarly in a homolytic way[343].

$$L(RCO_2)CO^{III}—OOBu^t \longrightarrow L(RCO_2)CO^{III} + t\text{-}BuOO\cdot \tag{117a}$$

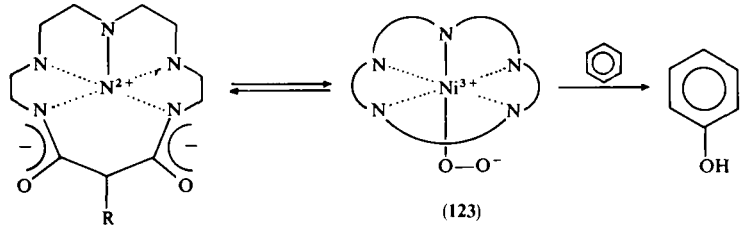
$$L(RCO_2)CO^{III}—OOBu^t \longrightarrow L(RCO_2)CO^{III}—O\cdot + t\text{-}BuO\cdot \tag{117b}$$

(**122**)

d. Hydroxylations using oxygen. The direct utilization of molecular oxygen is an ideal method for hydroxylations but is not easy to carry out. Some attempts are described below.

It is well known that feme irons form stable diamagnetic complexes with oxygen. Kimura and coworkers[344] found that NI(II) complexes of some dioxomacrocyclic ligands form stable dioxygen adducts and are able to transfer oxygen atoms to arenes, e.g. toluene was hydroxylated to yield *o*- and *p*-cresols. The reaction was reported to proceed via the oxygen complex (**123**) as shown in equation 118, but the intervention of oxenoid (Ni=O) species is also likely. This interesting system was reported to accompany the oxidation of ligands[345]. Further studies are needed to understand this oxygenation catalysis.

ω-Hydroxylases are remarkable in their ability to hydroxylate regioselectively the terminal methyl group of unactivated alkanes. An inorganic mimic of such hydroxylases has been studied by using a geolite system containing Pd(0) and Fe(II) in oxygen/hydrogen atmosphere[346]. Hydrogen peroxide was produced from hydrogen and oxygen and its reaction with Fe(II) resulted in C—H hydroxylations via a hydroxyl radical or via Fe=O. The relative reactivity of octane/cyclohexane was as high as >190 and the primary/tertiary reactivity ratio was relatively high, i.e. 0.67, partially mimicking ω-hydroxylases. A more selective terminal hydroxylation has been attained using PhIO and *t*-butylphthalocyaninate iron(II) catalyst in super cages of NaY-type geolite[347].

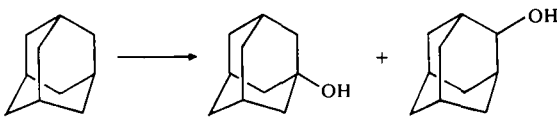


(123) (118)

Binuclear iron complexes are a highly interesting catalytic system because methane monooxygenase is known to involve such an iron site. In this respect, Moro-oka and colloborators reported a quite effective μ-oxo binuclear iron complex (**124**, HBPZ = hydro-tris-1-pyrazolylborate and Hfacac = hexafluoroacetylacetone) for dioxygen hydroxylation of alkanes[348]. A catalytic system composed of **124**, CF_3CO_2H and Zn powder was effective for the hydroxylation of a variety of alkanes and arenes. Benzene and toluene were hydroxylated to yield phenol, *o*- and *p*-cresol, turnovers being 12.1, 6.7 and 2.7, respectively. Using this sytem n-pentane afforded 2-pentanol and adamantane yielded the 1-alcohol predominantly (equation 119)[348a]. The preferential tertiary C—H hydroxylation is in sharp contrast with the Gif system selectively oxidizing secondary C—H bonds. A binuclear iron complex was indicated as a plausible catalyst in the hydroxylation of cyclohexane with a Fe(II)–aminosilane complex on silica gel[349].

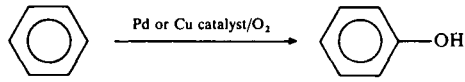
Fe(HBPZ)(Hfacac)OFe(HBPZ)(Hfacac)

(124)



(119)

Aerobic hydroxylations of arenes are important industrial processes and have been studied extensively. The hydroxylation of benzene was effected by CuCuI/O_2[350a], CuCl/O_2[350b] and Pd(OAc)-1,10-phenanthroline/O_2/CO (equation 120)[351].

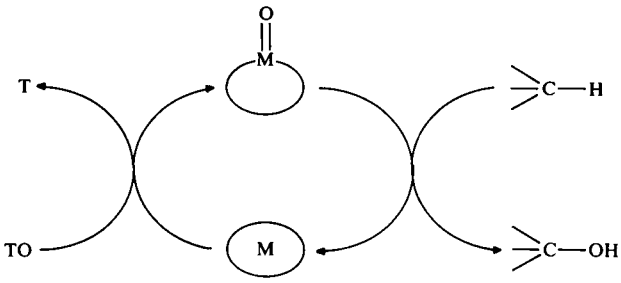


(120)

Effective *ortho* hydroxylations of phenols were possible with $CuCl/O_2$[352]. Some of these conversions might attain industrial importance.

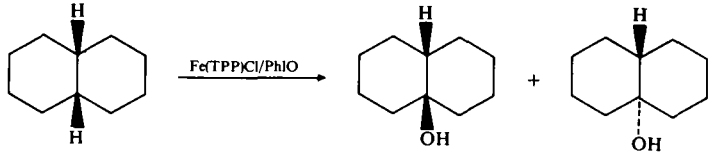
4. Hydroxylations by P-450 model systems

Cytochrome P-450 model reactions[4,353] recently became important subjects. The outline of the catalyses is shown in Scheme 9; oxidants are PhIO, ClO^- or peroxyacids.



SCHEME 9. Hydroxylation of C—H bonds by a P-450 model reaction catalyzed by metallo porphyrins

The Fe(TPP)Cl-catalyzed oxidation of cyclohexane with PhIO afforded cyclohexanol and cyclohexanone in 31 and 6%, respectively[354]. The same oxidation of *cis*-decaline resulted in *cis*-hydroxylation accompanying the *trans*-alcohol (equation 121). The retentive *cis*-alcohol formation was explained by the fast O-transfer in the radical intermediate (**127**)[354b]. Similarly, the hydroxylation of allylic C—H bonds accompanies allylic rearrangement in 20–40% yield[355]. These results support the two-step mechanism involving a radical hydrogen atom abstraction and the recombination as shown in Scheme 10.

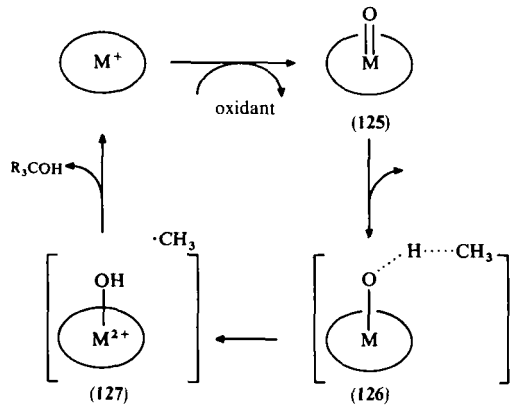


(121)

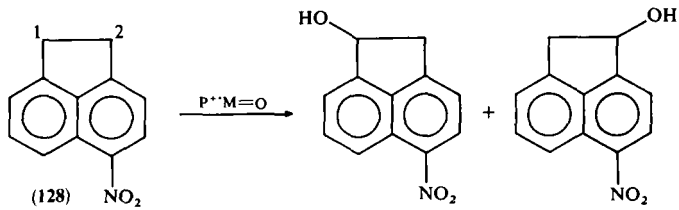
Two pathways conceivable for the hydrogen atom abstraction by oxo metal complexes are the direct radical abstraction (equation 122a) and the alternative one-electron oxidative hydroxylation (equation 122b). To differentiate between the two pathways, the regioselective hydroxylation of 5-nitroacenaphthene (**128**; equation 123) has been studied, i.e. C-1 hydroxylation for pathway 122a and C-2 hydroxylation for pathway 122b[356]. The 1-/2-alcohol ratios with M = Cr, Fe and Mn(TPP) increased in the order of $Mn < Fe < Cr$ and hence the electrophilicity was shown to be in the order of $Mn^V{=}O < Fe^V{=}O < Cr^V{=}O$. The reaction with *o*-xylene was likewise concluded to be a radical hydrogen atom abstraction[357].

$$(P^{+\cdot})M{=}O + RH \longrightarrow PM{-}OH + R\cdot \qquad (122a)$$

$$(P^{+\cdot})M{=}O + RH \longrightarrow PM{=}O + RH^{+\cdot} \longrightarrow PM{-}OH + R\cdot \qquad (122b)$$



SCHEME 10. Hydroxylation of C—H bond by metallo porphyrins.



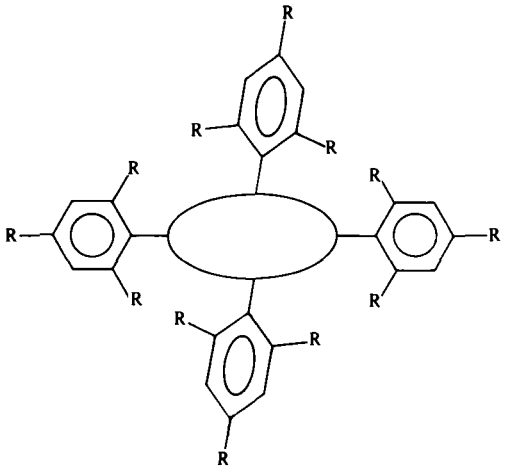
(123)

In the C—H hydroxylation by Fe(TPPs), most effective was the oxidation with perhalogenated porphyrins (e.g. F_5Cl_5-substituted) and PhIO[358]. In other words, the radical nature of Fe=O increased by introducing electronegative halogens. Even with the most reactive catalyst, $(F_5Cl_8TPP)Fe$, the secondary C—H bond of heptane was about 1500-fold less reactive than the double bond of *cyclooctene*.

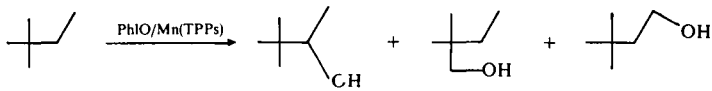
The hydroxylation of alkane C—H bonds with Mn(TPPs) in dichloromethane–water was accelerated by bases and lipophilic carboxylic acids, the maximal turnover being $125\,min^{-1}$[359]. Somewhat effective catalysis systems for alkane hydroxylations are cationic Mn(*meso*-tetra-*N*-methylpyridinyl)porphyrin on silica support[360a] and montmorillonite[360b].

Sterically hindered manganese porphyrins have been used to catalyze a shape-selective alkane hydroxylation. Increasing steric constraints resulted in increased production of primary alcohols[361]. In the Mn(TPPs)(OAs)-catalyzed PhIO hydroxylation, the primary/secondary alcohol ratios were 0.034, 0.05 and 0.59 for TPPs (**129**) with R = H, OMe and Ph, respectively. The product ratios for the hydroxylation of 2,2-dimethylbutane with PhIO/Mn(TPPs) (**130**) are shown in equation 124. The hydroxylation with the less hindered **130a** (R = H) afforded predominantly the secondary alcohol [i.e. (ω-1)-hydroxylation], while the reaction with hindered porphyrin **130c** (R = Ph) resulted in the 4-C—H hydroxylation (i.e. ω-hydroxylation). Thus, ω- and (ω-1)-hydroxylations could be controlled by choosing the substituents on porphyrins.

Various iron and manganese porphyrins were compared as catalysts for the hydroxylation of anisol by H_2O_2 or PhIO. Whereas all iron porphyrins gave low hydroxylation yields, Mn(III)-*meso*-tetraarylporphyrins bearing halogen substituents (e.g. Cl_8Br_8-substituted) gave up to 70% yields based on the oxidants, for the *para*-



(129)



(124)

130a(R = H)	91	9	< 1
130b(R = MeO)	85	11	3
130c(R = Ph)	25	6	69

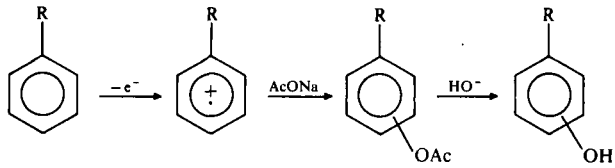
hydroxylation of anisol[362]. The same catalyzed oxidation in the presence of imidazol was also successfully applied for the 9,10-epoxidation of phenanthrene.

E. Miscellaneous Hydroxylations

1. Electrochemical hydroxylations

Functionalizations by electrooxidations have been reviewed repeatedly[363]. Only the outlines of electrochemical hydroxylations are symmarized here.

a. Direct electrochemical reactions. The direct one-electron oxidations of aromatic substrates are usually facile and the reaction in AcONa/AcOH affords acetoxylated products which are equivalent to hydroxylations (equation 125). For example, 1,4-dimethoxybenzene resulted in 68% 2-acetoxylation[364] and anisol afforded 70% yield of acetoxylated product ($o:p = 1:1$)[365]. Higher yields were obtained in the reaction with CF_3CO_2Na in CF_3CO_2H[366]. Electrooxidations in aqueous solutions are not appropriate for arene hydroxylations because the produced phenols are further oxidized to quinones.

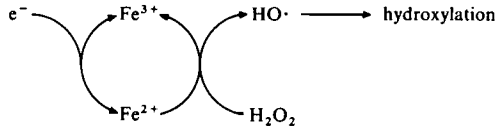


(125)

Direct oxidations of alkanes are usually difficult, but adamantane could be oxidized at around 2.5 V Ag/Ag^{+}[367]. The electrooxidation at 1.8 V in CF_3CO_2H–$(CF_3CO)_2O$ in the presence of Bu_4NBF_4 afforded 1-hydroxyadamantane in 83% yield, while the oxidation at 2.3 V gave 1,3-dihydroxyadamantane in 70% yield. The first step of this functionalization is the deprotonation of the adamantane cation radical.

b. Indirect electrochemical reactions. Indirect electrochemical hydroxylations are the reactions via activated catalysts or mediators generated by electrochemical reactions. For example, hydroxyl radicals were often assumed in the anodic oxidation using lead dioxide electrodes in water. In fact, a detailed study on the anodic hydroxylation of benzene concluded the formation and reaction of hydroxyl radicals on the PbO_2 electrode surface[368].

The electrochemical reduction of oxygen to hydrogen peroxide is quite easy and hence the addition of Fe(II)[369] and Cu(I) ions[370] results in the realization of *the electrochemical Fenton reaction.* Phenols could be obtained by the reaction of hydroxyl radicals from the redox catalyst and hydrogen peroxide. Since the metal ion is reduced electrochemically, the metallic catalyst is recycled repeatedly as shown in equation 126. A practical aspect of the electrochemical hydroxylation with Fe^{2+}/H_2O_2 has been tested[371]. Phenol yields by a batch process were rather low because of further oxidation, but the current yields by a continuous process were increased up to 70% by extracting the phenolate ion.



(126)

In the Udenfriend system (Fe^{3+}/EDTA/ascorbate/O_2) substitution of ascorbate with electrochemical reduction results in the electrochemical Udenfriend hydroxylation[372], when, e.g., hydroxylation of phenol yielded dihydroxybenzenes in 30% yield[372a].

Electrochemical reduction of oxygen in the presence of Mn(III)(TPP)Cl/imidazol/AcOH produced Mn=O resulting in hydroxylations and epoxidations (equation 127)[373]. The current efficiencies of hydroxylations were rather low, e.g. 7.5 and 3% for cyclooctane and adamantane, respectively, while the efficiency for epoxidations was as high as 50%. The oxygenations of C—H bonds are much more difficult than double-bond epoxidations.

$$Mn^{III} \xrightarrow{e^-/O_2} Mn^{II} \leftarrow OO \xrightarrow{e^-} Mn^{III}—OO^- \xrightarrow{H^+} Mn^{III}OOH$$

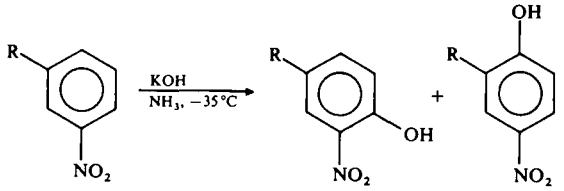
$$\xrightarrow[-H_2O]{H^+} Mn^{V}{=}O \xrightarrow{RH} ROH + Mn^{III} \qquad (127)$$

A direct electrochemical oxidation of iron fluoroporphyrin, $Fe(TPP)^{2-}$, was reported to yield $Fe^{V}{=}O$ leading to C—H hydroxylations[374]. The turnover number was, however, only 10.

2. *Nucleophilic hydroxylations*

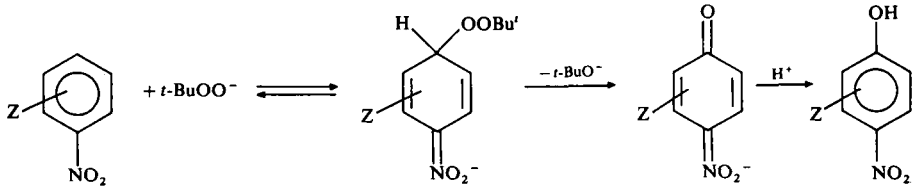
Hydroxylations by nucleophiles are possible in the case of nitroaromatics. Thus, *o*- and *p*-nitrophenols could be obtained by the reaction of nitrobenzenes with potassium hydroxide (equation 128)[375]. The substitution proceeds via an anionic σ-complex between the nitrobenzenes and the hydroxide ion. The reaction of 2,4-dinitrochlorobenzene in

DMSO–water was followed by NMR spectroscopy[376]. It was found that a Meisenheimer complex was first formed and then the chlorine atom was substituted by a hydroxyl group.

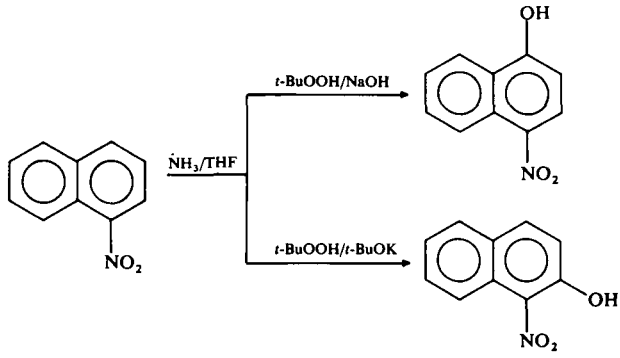


(128)

The hydroxylation of nitroarenes is also possible with hydroperoxide ions (ROO^-)[377,378]; see equation (129). Thus, nitrobenzenes with *t*-BuOOK/NH_3 afforded *p*-nitrophenols in 45–96% yields[377]. Another interesting result is the control of the reaction route by reaction conditions as shown in equations 130a and 130b. The difference is due to the limited solubility of NaOH in liquid ammonia. While a high concentration of strong base favors 2-hydroxylation, (equation 130b), the lower base concentration results in the kinetically-controlled orientation, i.e. 4-hydroxylation (equation 130a).



(129)



(130a)

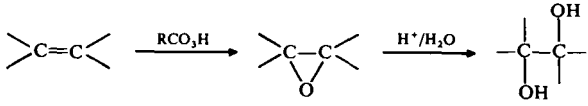
(130b)

3. *Dihydroxylations*

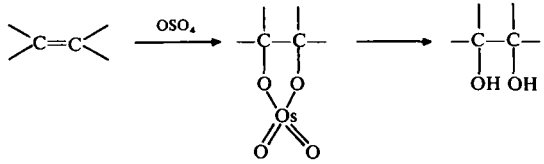
The dihydroxylation of olefins is one of the fundamental organic transformations. In this section only a few important aspects are summarized since details are described in the Chapter by M. Barbok in this volume.

Trans-dihydroxylations of olefins are easily attained by acid-catalyzed ring-opening of epoxides (equation 131). On the other hand, *cis*-dihydroxylations are carried out using oxidants such as potassium permanganate and osmium tetroxide[379]. The oxidation with OsO_4 (equation 132) is catalyzed by tertiary amines such as pyridine and quinuclidine,

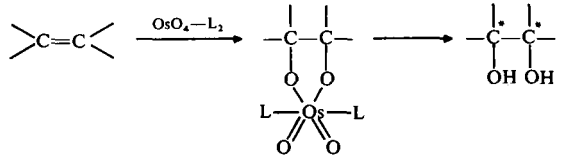
and hence the use of chiral amines results in asymmetric hydroxylations (equation 133). High yields (i.e. over 90% ee) of asymmetric induction have been reported using alkaloid derivatives[380] and diamines[381]. Catalytic reactions are more practical than the stoichiometric ones. Sharpless and coworkers reported an efficient catalytic asymmetric dihydroxylation up to 90% ee[382].



(131)



(132)



(133)

IV. CONCLUSION

Epoxidations and hydroxylations are very often the first step for functionalizations of organic compounds. Remarkable advances have occurred in the last decade. These include the asymmetric epoxidation by Sharpless and Katsuki, oxidations with dioxiranes and the asymmetric oxygenations of unfunctionalized alkenes and alkanes.. Structures and reactivities of active oxygen species have been clarified considerably, and various methods were developed to control their reactivities.

It is to be expected that practically pure asymmetric epoxidations and hydroxylations as catalytic processes will be attained in the next decade. Utilizations of dioxygen as a terminal oxidant will also be a target of intensive studies.

V. ACKNOWLEDGMENT

The author acknowledges Mr. Morio Inaishi for his helpful assistance in the preparation of the manuscript.

VI. REFERENCES

1. (a) D. Swern, *Organic Peroxides*, Vol. 2 (Ed. D. Swern), Wiley–Interscience, New York, 1971, p. 355.
   (b) V. G. Dryuk, *Tetrahedron*, **32**, 2855 (1976).
   (c) B. Plesničar, in *The Chemistry of Peroxides* (Ed. S. Patai), Wiley–Interscience, Chichester, 1983, p. 521.
   (d) G. Bouillon, C. Lick and K. Schank in Reference 1c, p. 287.
2. J. Robeck, Jr., *Heterocycles*, **15**, 1 (1981).
3. R. W. Murray, *Chem. Rev.*, **89**, 1187 (1989).

4. P. W. White, *Bioorg. Chem.*, **18**, 440 (1990).
5. D. Swern, L. P. Witnauer, C. R. Eddy and W. E. Parker, *J. Am. Chem. Soc.*, **77**, 5537 (1955).
6. O. Exner and B. Plesničar, *Collect. Czech. Chem. Commun.*, **43**, 3079 (1978).
7. M. Oldani, T. K. Ha and A. Baulder, *J. Am. Chem. Soc.*, **105**, 360 (1983).
8. B. Plesničar, V. Menart, M. Hodoscek, J. Koller, F. Kovacic and J. Skerjanc, *J. Chem. Soc., Perkin Trans. 2*, 1397 (1986).
9. R. P. Hanzlik and G. O. Schearer, *J. Am. Chem. Soc.*, **97**, 5231 (1975).
10. (a) G. Berti, *Top. Stereochem.*, **7**, 93 (1973).
    (b) T. Itoh, K. Jitsukawa, K. Kaneda and S. Teranishi, *J. Am. Chem. Soc.*, **101**, 159 (1979).
11. H. Kwart and D. H. Hoffman, *J. Org. Chem.*, **31**, 419 (1966).
12. K. D. Bingham, G. D. Meakins and G. H. Witham, *Chem. Commun.*, 445 (1966).
13. H.-J. Schneider, N. Becker and K. Philippi, *Chem. Ber.*, **114**, 1562 (1981).
14. (a) Y. Sawaki and Y. Ogata, *Tetrahedron*, **21**, 3381 (1965).
    (b) L. S. Silbert, E. Siegel and D. Swern, *Organic Synthesis*, Collect. Vol. 5, 904 (1973).
15. (a) Y. Ogata and Y. Sawaki, *Tetrahedron*, **23**, 3327 (1967).
    (b) R. M. McDonald, R. N. Steppel and J. E. Dorsey, *Org. Synth.*, **50**, 15 (1970).
16. P. Brougham, M. S. Cooper, D. A. Cummerson, H. Heaney and N. Thompson, *Synthesis*, 1015 (1987).
17. (a) N. C. Jang, W. Chiang, D. Leonov, I. Bilyk and B. Kim, *J. Org. Chem.*, **43**, 3425 (1978).
    (b) M. Imuta and H. Ziffer, *J. Org. Chem.*, **44**, 1351 (1979).
18. (a) R. D. Bach, M. W. Klein, R. A. Rynz and J. W. Holubka, *J. Org. Chem.*, **44**, 2569 (1979).
    (b) Y. Tsunokawa, S. Iwasaki and S. Okuda, *Tetrahedron Lett.*, **23**, 2113 (1982).
19. (a) N. Matsumura, N. Sonoda and T. Tsutsumi, *Tetrahedron Lett.*, 2029 (1970).
    (b) J. Rebek, R. McCready, S. Wolf and A. Mossman, *J. Org. Chem.*, **44**, 1485 (1979).
20. (a) G. B. Payne, P. H. Deming and P. H. Williams, *J. Org. Chem.*, **26**, 659 (1961).
    (b) G. B. Payne, *Tetrahedron*, **18**, 763 (1962).
21. Y. Ogata and Y. Sawaki, *Tetrahedron*, **20**, 2065 (1964).
    (b) Y. Ogata and Y. Sawaki, *Bull. Chem. Soc. Jpn.*, **38**, 194 (1965).
    (c) R. G. Carlson, N. S. Behn and C. Cowles, *J. Org. Chem.*, **36**, 3832 (1971).
22. R. D. Bach and J. W. Knight, *Org. Synth.*, **60**, 63 (1981.
23. L. A. Arias, S. Adkins, C. J. Nagel and R. D. Bach, *J. Org. Chem.*, **48**, 888 (1983).
24. (a) J. P. Dulcère and J. Rodriguez, *Tetrahedron Lett.*, **23**, 1887 (1982).
    (b) J. Rodriguez and J. P. Dulcère, *J. Org. Chem.*, **56**, 469 (1991).
25. (a) J. R. Rebek, Jr., R. McCready and R. Wolak, *J. Chem. Soc., Chem. Commun.*, 705 (1980).
    (b) J. Rebek, Jr., and R. McCready, *J. Am. Chem. Soc.*, **102**, 5602 (1980).
26. A. L. Baumstark, *Bioorg. Chem.*, **14**, 326 (1986).
27. T. C. Bruice, J. B. Noar, S. S. Ball and U. V. Venkataram, *J. Am. Chem. Soc.*, **105**, 2452 (1983).
28. (a) R. P. Heggs and B. Granem, *J. Am. Chem. Soc.*, **101**, 2484 (1979).
    (b) A. J. Biloski, R. P. Heggs and B. Ganem, *Synthesis*, 810 (1980).
29. (a) K. B. Sharpless and T. R. Verhoeven, *Aldrichimia Acta*, **12**, 63 (1979).
    (b) A. Pfenninger, *Synthesis*, 89 (1985).
    (c) A. S. Rao, S. K. Paknikar and J. G. Kirtang, *Tetrahedron*, **39**, 2323 (1983).
30. For example, G. Lukacs and D. K. Fukushima, *J. Org. Chem.*, **34**, 2707 (1969).
31. P. Kočovsky and I. Starý, *J. Org. Chem.*, **55**, 3236 (1990).
32. I. Honda, A. Ori and G. Tsuchihashi, *Chem. Lett.*, 1417 (1986).
33. P. Chamberlain, M. C. Roberts and G. H. Whitham, *J. Chem. Soc.*, (*B*), 1374 (1970).
34. For example, I. V. Ekhato, J. V. Silverton, and C. H. Robinson, *J. Org. Chem.*, **53**, 2180 (1988).
35. B. A. McKittrick and B. Ganem, *Tetrahedron Lett.*, **26**, 4895 (1985).
36. M. R. Johnson and Y. Kishi, *Tetrahedron Lett.*, 4347 (1979).
37. (a) J. Rebek, Jr., L. Marshall, R. Wolak and J. McManis, *J. Am. Chem. Soc.*, **106**, 1170 (1984).
    (b) J. Rebek, Jr., L. Marshall, J. McManis and R. Wolak, *J. Org. Chem.*, **51**, 1649 (1986).
38. E. J. Corey, H. Niwa and J. R. Falk, *J. Am. Chem. Soc.*, **101**, 1586 (1979).
39. J. D. Morrison and H. S. Mosher, *Asymmetric Organic Reactions*, Prentice-Hall, New Jersey, 1971, p. 258.
40. R. C. Ewins, H. B. Henbest and M. A. McKervey, *Chem. Commun.*, 1085 (1967).
41. W. H. Pirke and P. L. Rinaldi, *J. Org. Chem.*, **43**, 4475 (1978).
42. Y. Ogata and Y. Sawaki, *J. Am. Chem. Soc.*, **95**, 4687, 4692 (1973).

43. F. A. Davis and O. D. Stringer, *J. Org. Chem.*, **47**, 1774 (1982).
44. F. A. Davis and A. C. Sheppard, *Tetrahedron*, **54**, 5703 (1989).
45. F. A. Davis, J. M. Billmers, D. J. Gosciniak, J. C. Towson and R. D. Bach, *J. Org. Chem.*, **51**, 4240 (1986).
46. F. A. Davis and R. H. Jenkins, Jr., in *Asymmetric Synthesis* (Eds. J. D. Merrison and J. W. Scott), Vol. IV, Academic Press, New York, 1984, p. 322.
47. (a) F. A. Davis, M. E. Harakal and S. B. Awad, *J. Am. Chem. Soc.*, **105**, 3123 (1983).
    (b) F. A. Davis, R. ThimmaReddy, J. P. McCauley, Jr., R. M. Przeslawski, M. E. Harakal and P. J. Carroll, *J. Org. Chem.*, **56**, 809 (1991).
48. R. D. Bach and G. J. Wolber, *J. Am. Chem. Soc.*, **106**, 1410 (1984).
49. F. A. Davis and S. Chatlopadhyay, *Tetrahedron Lett.*, **27**, 5079 (1986).
50. (a) F. A. Davis, L. C. Vishwakarma, J. G. Billmers and J. Finn, *J. Org. Chem.*, **49**, 3241 (1984).
    (b) F. A. Davis and A. C. Sheppard, *J. Org. Chem.*, **52**, 954 (1987).
51. W. Adam, R. Curci and J. O. Edwards, *Acc. Chem. Res.*, **22**, 205 (1989).
52. R. E. Montgomery, *J. Am. Chem. Soc.*, **96**, 7820 (1974).
53. J. O. Edwards, R. H. Pater, R. Curci and F. DiFuria, *Photochem. Photobiol.*, **30**, 63 (1979).
54. (a) R. Curci, M. Fiorentino, L. Troisi, J. O. Edwards and R. H. Pater, *J. Org. Chem.*, **45**, 4758 (1980).
    (b) A. R. Gallopo and J. O. Edwards, *J. Org. Chem.*, **46**, 1684 (1981).
55. Y. Sawaki and S. Ishikawa, unpublished results.
56. R. W. Murray and R. Jeyaraman, *J. Org. Chem.*, **50**, 284 (1985).
57. (a) L. Cassidei, M. Fiorentino, R. Mello, O. Sciacovelli and R. Curci, *J. Org. Chem.*, **52**, 699 (1987).
    (b) W. Adam, Y. Y. Chan, D. Cremer, J. Gauss, O. Schentzow and M. Schneidler, *J. Org. Chem.*, **52**, 746 (1987).
58. (a) A. L. Baumstark and C. J. McCloskey, *Tetrahedron Lett.*, **29**, 3311 (1987).
    (b) A. L. Baumstark and P. C. Vasquez, *J. Org. Chem.*, **53**, 3437 (1988).
59. R. Curci, M. Fiorentino and M. R. Serio, *J. Chem. Soc., Chem. Commun.*, 155 (1984).
60. R. Jeyaraman and R. W. Murray, *J. Am. Chem. Soc.*, **106**, 2462 (1984).
61. (a) R. Mello, M. Fiorentino, O. Sciacovelli and R. Curci, *J. Org. Chem.*, **53**, 3890 (1988).
    (b) R. Mello, F. Ciminale, M. Fiorentino, C. Fusco, T. Prencipe and R. Curci, *Tetrahedron Lett.*, **31**, 6097 (1990).
62. (a) J. K. Crandal, G. E. Salazar and R. J. Watkins, *J. Am. Chem. Soc.*, **109**, 4338 (1987).
    (b) J. K. Crandal, D. J. Batal, D. P. Sobesta and F. Lin, *J. Org. Chem.*, **56**, 1153 (1991).
63. (a) L. Troisi, L. Cassidei, L. Lopez, R. Mello and R. Curci, *Tetrahedron Lett.*, **30**, 257 (1989).
    (b) W. Adam, L. Hadjiarapoglou and X. Wang, *Tetrahedron Lett.*, **30**, 6497 (1989).
    (c) H. K. Chenault and S. J. Danishefsky, *J. Org. Chem.*, **54**, 4249 (1989).
64. (a) W. Adam, L. Hadjiarapoglou and B. Nestler, *Tetrahedron Lett.*, **31**, 331 (1990).
    (b) W. Adam, L. Hadjiarapoglou and A. Fed, *Chem. Ber.*, **124**, 227 (1991).
65. R. W. Muray and D. L. Shiang, *J. Chem. Soc., Perkin Trans. 2*, 349 (1990).
66. P. Politzer, R. Bar-Adon and R. S. Miller, *J. Phys. Chem.*, **91**, 3191 (1987).
67. S. Patai and Z. Rappoport in *The Chemistry of Alkenes* (Ed. S. Patai), Wiley–Interscience, London, 1964, p. 512.
68. J. R. Doherty, D. D. Keane, K. G. Karathe, W. I. O'Sallivan, E. M. Philbin, R. M. Simons and P. C. Teague, *Tetrahedron Lett.*, 441 (1968).
69. R. Curci and F. DiFuria, *Tetrahedron Lett.*, 4085 (1974).
70. Y. Apeloig, M. Karni and Z. Rappoport, *J. Am. Chem. Soc.*, **105**, 2784 (1983).
71. For example, (a) S. Hrycko, P. Morand, F. L. Lee and E. J. Gabe, *J. Org. Chem.*, **53**, 1515 (1988).
    (b) A. A. M. Huwen-Claasen, A. J. H. Klunder and B. Zwanenburg, *Tetrahedron*, **45**, 7134 (1989).
    (c) S. Sugiyama, S. Ohigashi, R. Sawa and H. Hayashi, *Bull. Chem. Soc., Jpn.*, **62**, 3202 (1989).
72. C. W. Jefford, G. Bernardinelli, J. C. Rossier, S. Kohmoto and J. Boukouvalas, *Tetrahedron Lett.*, **26**, 615 (1985).
73. K. L. Reed, J. T. Gupton and T. L. Solarz, *Synth. Commun.*, **19**, 3579 (1989).
74. A. Foucaud and M. Bakouetila, *Synthesis*, 854 (1987).
75. K. S. Kirshenbaum and K. B. Sharpless, *J. Org. Chem.*, **50**, 1979 (1985).
76. (a) M. R. Bryce, R. D. Chambers and J. R. Kirk, *J. Chem. Soc., Perkin Trans. 1*, 1391 (1984).

(b) P. L. Coe, A. W. Mott and J. C. Tatlow, *J. Fluorine Chem.*, **30**, 297 (1985).
77. P. L. Coe, A. Sellars, J. C. Tatlow, G. Whittakar and H. C. Fielding. *J. Chem. Soc., Chem. Commun.*, 362 (1982).
78. R. M. Moriarty, S. C. Gupta, H. Hu, D. R. Berenschot and K. B. White, *J. Am. Chem. Soc.*, **103**, 686 (1981).
79. H. Wynberg, and B. Greijdanus, *J. Chem. Soc., Chem. Commun.*, **427** (1978).
80. S. Banfi, S. Colonna and S. Juliá, *Synth. Commun.*, **13**, 1049 (1983).
81. S. Juliá, J. Guaixer, J. Masana, J. Rocas, S. Colonna, R. Annunziata and H. Molinari, *J. Chem. Soc., Perkin Trans. 1*, 1317 (1982).
82. P. W. Baures, D. S. Eggleston, J. R. Flisak, K. Gombatz, I. Lantos, W. Mendelson and J. J. Remich, *Tetrahedron Lett.*, **31**, 6501 (1990).
83. S. Itsuno, M. Sakakura and K. Ito, *J. Org. Chem.*, **55**, 6047 (1990).
84. H. Pluim and H. Wynberg, *J. Org. Chem.*, **45**, 2498 (1980).
85. (a) S. Colonna and A. Manfredi, *Tetrahedron Lett.*, **27**, 387 (1986).
(b) S. Colonna, A. Manfredi and M. Spadoni, *Tetrahedron Lett.*, **28**, 1577 (1987).
(c) S. Colonna, N. Gaggero and A. Manfredi, *Tetrahedron*, **44**, 5167 (1988).
86. (a) C. Clark, P. Hermans, O. Meth-Cohn, C. Moore, H. C. Taljaad, and G. van Vuuren, *J. Chem. Soc., Chem. Commun.*, 1387 (1986).
(b) O. Meth-Cohn, C. Moore and H. C. Taljaad, *J. Chem. Soc., Perkin Trans. 1*, 2663 (1988).
87. F. R. Mayo, *Acc. Chem. Res.*, **1**, 193 (1968).
88. (a) E. Niki and Y. Kamiya, *Bull. Chem. Soc., Jpn.*, **40**, 583 (1967).
(b) F. Tsuchiya and I. Ikawa, *Can. J. Chem.*, **47**, 3191 (1969).
89. N. Shimizu and P. D. Bartlett, *J. Am. Chem. Soc.*, **98**, 4193 (1976).
90. G. Büchi, K. W. Fowler and A. M. Nadzan, *J. Am. Chem. Soc.*, **104**, 544 (1982).
91. Y. Sawaki and C. S. Foote, *J. Org. Chem.*, **48**, 4934 (1983).
92. Y. Sawaki and Y. Ogata, *J. Org. Chem.*, **49**, 3344 (1984).
93. Y. Sawaki and Y. Ogata, *J. Am. Chem. Soc.*, **103**, 2049 (1981).
94. R. A. Sheldon and J. K. Kochi, *Metal-Catalyzed Oxidation of Organic Compounds*, Chap. 9, Academic Press, New York, 1981.
95. H. Mimoun, *J. Mol. Catal.*, **7**, 1 (1980).
96. K. A. Jørgensen, *Chem. Rev.*, **89**, 431 (1989).
97. (a) W. M. H. Satchler, C. Backx and R. A. van Santen, *Catal. Rev.*, **23**, 127 (1981).
(b) R. A. van Santen and H. P. C. E. Kuipers, *Adv. Catal.*, **35**, 265 (1987).
98. (a) A. L. Larrabee and R. L. Kuczkowski, *J. Catal.*, **52**, 72 (1978).
(b) N. W. Cant and W. K. Hall, *J. Catal.*, **52**, 81 (1978).
99. (a) E. A. Carter and W. A. Goddard, III, *J. Catal.*, **112**, 80 (1988).
(b) P. J. van der Hoek, E. J. Baerends and R. A. van Santen, *J. Phys. Chem.*, **93**, 6469 (1989).
(c) K. A. Jørgensen and R. Hoffmann, *J. Phys. Chem.*, **94**, 3046 (1990).
100. Y. Murakami and K. Tanaka, *Nippon Kagaku Kaishi*, **11**, 1603 (1977).
101. J. T. Roberts and R. J. Madix, *J. Am. Chem. Soc.*, **110**, 8540 (1988).
102. (a) R. Budnik and J. K. Kochi, *J. Org. Chem.*, **41**, 1384 (1976).
(b) S. C. Sethi, A. D. Natu and M. S. Wadia, *Heterocycles*, **18**, 221 (1982).
103. S. Ito, K. Inoue and M. Matsumoto, *J. Am. Chem. Soc.*, **104**, 6450 (1982).
104. (a) M. M. T. Khan and A. P. Rao, *J. Mol. Catal.*, **39**, 331 (1987).
(b) M. M. T. Khan, A. P. Rao and R. S. Shukla, *J. Mol. Catal.*, **49**, 299 (1989).
105. J. C. Marchon and R. Ramasseull, *Synthesis*, 389 (1989).
106. K. Kaneda, K. Jitsukawa, T. Itoh and S. Teranishi, *J. Org. Chem.*, **45**, 3004 (1980).
107. (a) M. A, Andrews and C.-W.F. Cheng, *J. Am. Chem. Soc.*, **104**, 4268 (1982).
(b) A. Heumann, F. Chauret, B. Waegell, *Tetrahedron Lett.*, **23**, 2767 (1982).
(c) M. A. Andrew, T. C.-T. Chang, C.-W. F. Cheng, T. J. Emge, K. P. Kelly and T. F. Koetzle, *J. Am. Chem. Soc.*, **106**, 5913 (1984).
(d) S. E. Diamond, F. Mares, A. Szalkiemicz, D. A. Muccigrosso and J. P. Solar, *J. Am. Chem. Soc.*, **104**, 4266 (1982).
108. (a) I. Tabushi and A. Yazaki, *J. Am. Chem. Soc.*, **103**, 7371 (1981).
(b) I. Tabushi and K. Morimitsu, *J. Am. Chem. Soc.*, **106**, 6871 (1984).
109. (a) J. T. Groves and R. Quinn, *J. Am. Chem. Soc.*, **107**, 5790 (1985).
(b) D. Baluch, J. Charalambous and L. B. Haines, *J. Chem. Soc., Chem. Commun.*, 1178 (1988).

110. G. S. Fonken and R. A. Johnson, *Chemical Oxidations with Microorganisms*, Marcel Dekker, New York, 1972.
111. J. P. Schirmann and S. Y. Delavarenne, *Hydrogen Peroxide in Organic Chemistry*, Chap. 2, Documentation Ind., Paris, 1979.
112. S. Jacobson, F. Mares and P. Zambri, *J. Am. Chem. Soc.*, **101**, 6946 (1979).
113. R. T. Taylor and H. A. Flood, *J. Org. Chem.*, **48**, 5160 (1983).
114. W. F. Brill, *J. Org. Chem.*, **51**, 1149 (1986).
115. (a) C. Venturello, E. Alneri and M. Ricci, *J. Org. Chem.*, **48**, 3831 (1983).
(b) C. Venturello and M. Ricci, *J. Org. Chem.*, **51**, 1599 (1986).
(c) C. Venturello and R. D'Aloisio, *J. Org. Chem.*, **53**, 1553 (1988).
116. (a) Y. Matoba, H. Inoue, J. Akagi, T. Okabayashi, Y. Ishii and M. Ogawa, *Synth. Commun.*, **14**, 865 (1984).
(b) Y. Ishii, K. Yamawaki, T. Ura, H. Yamada, T. Yoshida and M. Ogawa, *J. Org. Chem.*, **53**, 3587 (1988).
117. R. Landau, G. A. Sullivan and D. Brown, *Chemtech*, 602 (1979).
118. (a) A. O. Chong and K. B. Sharpless, *J. Org. Chem.*, **42**, 1587 (1977).
(b) H. J. Ledon, P. Durbut and F. Varescon, *J. Am. Chem. Soc.*, **103**, 3601 (1981).
119. (a) H. Mimoun, *J. Mol. Catal.*, **7**, 1 (1980).
(b) H. Mimoun, *Angew. Chem., Int. Ed. Engl.*, **21**, 734 (1982).
120. H. Mimoun, M. Mignard, P. Brechot and L. Saussine, *J. Am. Chem. Soc.*, **108**, 3711 (1986).
121. H. Ota, K. Matsukawa and T. Endo, *Tetrahedron Lett.*, **29**, 2843 (1988).
122. S. J. Danishefsky and N. Mantlo, *J. Am. Chem. Soc.*, **110**, 8129 (1988).
123. (a) J. T. Groves, T. E. Nemo and R. S. Myers, *J. Am. Chem. Soc.*, **101**, 1032 (1979).
(b) J. T. Groves, R. C. Haushalter, M. Nakamura, T. E. Nemo and B. J. Evans, *J. Am. Chem. Soc.*, **103**, 2884 (1981).
124. (a) F. P. Guengerich and T. L. Macdonald, *Acc. Chem. Res.*, **17**, 9 (1984).
(b) T. J. McMurry and J. T. Groves in *Cytochrome P-450, Structure, Mechanism and Biochemistry* (Ed. P. R. Ortiz de Montellano), Plenum Press, New York, 1986, p. 1.
125. B. Meunier, E. Guilmet, M.-E. de Carvalho and R. Poilblanc, *J. Am. Chem. Soc.*, **106**, 6668 (1984).
126. (a) H. J. Lodon, P. Durbut and F. Varescon, *J. Am. Chem. Soc.*, **103**, 3601 (1981).
(b) G.-X. He and T. C. Bruice, *J. Am. Chem. Soc.*, **113**, 2747 (1991).
127. C. M. Dicken, F.-L. Lu, M. W. Nee and T. C. Bruice, *J. Am. Chem. Soc.*, **107**, 5776 (1985).
128. (a) J. T. Groves and T. E. Nemo, *J. Am. Chem. Soc.*, **105**, 5786 (1983).
(b) J. R. Lindsay Smith and P. R. Sleath, *J. Chem. Soc., Perkin Trans. 2*, 1009 (1982).
129. (a) J. P. Collman, J. I. Brauman, B. Meunier, T. Hayashi, T. Kodadek and S. A. Raybuck, *J. Am. Chem. Soc.*, **107**, 2000 (185).
(b) J. T. Groves and M. K. Stern, *J. Am. Chem. Soc.*, **110**, 8628 (1988).
130. (a) T. G. Traylor and A. R. Mikoztal, *J. Am. Chem. Soc.*, **109**, 2770 (1987).
(b) T. G. Traylor and F. Xu, *J. Am. Chem. Soc.*, **110**, 1953 (1988).
131. J. T. Groves and Y. Watanabe, *J. Am. Chem. Soc.*, **108**, 507 (1986).
132. (a) A. Sevin and M. Fontecave, *J. Am. Chem. Soc.*, **108**, 3266 (1986).
(b) K. A. Jørgensen, *J. Am. Chem. Soc.*, **109**, 698 (1987).
(c) T. R. Cundari and D. S. Drago, *Inorg. Chem.*, **29**, 487 (1990).
133. D. Mansuy, J. Loclaire, M. Fontecave and P. Dansette, *Tetrahedron*, **40**, 2847 (1984).
134. (a) For example, E. Guilmet and B. Meunier, *New. J. Chem.*, **6**, 511 (1982).
(b) F. Montanari, M. Penso, S. Quici and P. Biganò, *J. Org. Chem.*, **50**, 4888 (1985).
135. P. S. Traylor, D. Dolphin and T. G. Traylor, *J. Chem. Soc., Chem. Commun.*, 279 (1984).
136. (a) S. Banfi, F. Montanari and S. Quici, *J. Org. Chem.*, **53**, 2863 (1988).
(b) F. Montanari, S. Banfi and S. Quici, *Pure Appl. Chem.*, **61**, 1631 (1989).
137. E. Takahashi, H. Amatsu, T. K. Miyamoto and Y. Saeaki, *Nippon Kagaku Kaishi*, 480 (1988).
138. H. Turk and W. T. Ford, *J. Org. Chem.*, **56**, 1253 (1991).
139. K. Srinivasan, S. Perrier and J. K. Kochi, *J. Mol. Catal.*, **36**, 297 (1986).
140. K. Srinivasan, P. Michaud and J. K. Kochi, *J. Am. Chem. Soc.*, **108**, 2309 (1986).
141. J. D. Koola and J. K. Kochi, *J. Org. Chem.*, **52**, 4545 (1987).
142. E. G. Samsel, K. Srinivasan and J. K. Kochi, *J. Am. Chem. Soc.*, **107**, 7606 (1985).
143. H. Yoon and C. J. Burrows, *J. Am. Chem. Soc.*, **110**, 4087 (1988).

144. J. F. Kinneary, J. S. Albert and C. J. Burrows, *J. Am. Chem. Soc.*, **110**, 6124 (1988).
145. (a) C. C. Franklin, R. B. VanAtta, A. Fan Tai and J. S. Valentine, *J. Am. Chem. Soc.*, **106**, 814 (1984).
(b) A. Fan Tai, L. D. Margerum and J. S. Valentine, *J. Am. Chem. Soc.*, **108**, 5006 (1986).
146. (a) W. Nam and J. S. Valentine, *J. Am. Chem. Soc.*, **112**, 4977 (1990).
(b) Y. Yang, F. Diederich and J. S. Valentine, *J. Am. Chem. Soc.*, **112**, 7826 (1990).
147. K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973).
148. K. Takai, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, **21**, 1657 (1980); *Bull. Chem. Soc. Jpn.*, **56**, 3791(1983).
149. H. Tomioka, K. Takai, H. Oshima and H. Nozaki, *Tetrahedron Lett.*, **21**, 2843 (1980).
150. H. Tomioka, T. Suzuki, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, **23**, 3387 (1982).
151. R. C. Michaelson, R. E. Palermo and K. B. Sharpless, *J. Am. Chem. Soc.*, **99**, 1990 (1977).
152. S. Yamada, T. Mashiko and S. Terashima, *J. Am. Chem. Soc.*, **99**, 1988 (1977).
153. T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980).
154. (a) M. G. Finn and K. B. Sharpless, in *Asymmetric Synthesis* (Ed. J. D. Morrison), Vol. 5, Chap. 8, Academic Press, New York, 1985, p. 247.
(b) C. H. Behren and K. B. Sharplss, *Aldrichimica Acta*, **16**, 67 (1983).
(c) A. Pfenninger, *Synthesis*, 89 (1986).
155. J. G. Hill, B. E. Rossiter and K. B. Sharpless, *J. Org. Chem.*, **48**, 3607 (1983).
156. (a) T. Katsuki, *Tetrahedron Lett.*, **25**, 2821 (1984).
(b) M. Caron and K. B. Sharpless, *J. Org. Chem.*, **50**, 1557 (1985).
157. (a) R. M. Hanson and K. B. Sharpless, *J. Org. Chem.*, **51**, 1922 (1986).
(b) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune and K. B. Sharpless, *J. Am. Chem. Soc.*, **109**, 5765 (1987).
158. J. M. Klunder, S. Y. Ko and K. B. Sharpless, *J. Org. Chem.*, **51**, 3710 (1986).
159. B. M. Choudary, V. L. K. Valli and A. D. Prasad, *J. Chem. Soc., Chem. Commun.*, 1186 (1990).
160. V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikada and K. B. Sharpless, *J. Am. Chem. Soc.*, **103**, 6237 (1981).
161. B. E. Rossiter in *Asymmetric Synthesis* (Ed. J. D. Morrison), Vol. 5, Academic Press, New York, 1985, p. 193.
162. (a) Y. Kitano, T. Matsumoto and F. Sato, *J. Chem. Soc., Chem., Commun.*, 1323, (1986).
(b) Y. Kitano, T. Matsumoto, Y. Takeda and F. Sato, *J. Chem. Soc., Chem. Commun.*, 1732 (1986).
163. P. R. Carlier, W. S. Mungall, G. Schröder and K. B. Sharpless, *J. Am. Chem. Soc.*, **110**, 2978 (1988).
164. (a) M. Kusakabe, H. Kato and F. Sato, *Chem. Lett.*, 2163 (1987).
(b) Y. Kitano, T. Matsumoto and F. Sato, *Tetrahedron*, **44**, 4073 (1988).
165. K. B. Sharpless, C. H. Behrens, T. Katsuki, A. W. M. Lee, V. S. Martin, M. Takatani, S. M. Viti, F. J. Walker and S. S. Woodard, *Pure Appl. Chem.*, **55**, 589 (1983).
166. B. E. Rossiter and K. B. Sharpless, *J. Org. Chem.*, **49**, 3707 (1984).
167. S. Ikegami, T. Katsuki and M. Yamagushi, *Chem. Lett.*, **83**, (1987).
168. E. J. Corey and D.-C. Ha, *Tetrahedron Lett.*, **29**, 3171 (1988).
169. (a) I. D. Williams, S. F. Pederson, K. B. Sharpless and S. L. Lippard, *J. Am. Chem. Soc.*, **106**, 6430 (1984).
(b) D. R. Carlier and K. B. Sharpless, *J. Org. Chem.*, **54**, 4016 (1989).
(c) C. J. Burns, C. A. Martin and K. B. Sharpless, *J. Org. Chem.*, **54**, 2826 (1989).
170. P. G. Potvin, P. C. C. Kwang and M. A. Brook, *J. Chem. Soc., Chem., Commun.*, 773 (1988).
171. E. J. Corey, *J. Org. Chem.*, **55**, 1963 (1990).
172. K. A. Jørgensen, R. A. Wheeler and R. Hoffmann, *J. Am. Chem. Soc.*, **109**, 3240 (1987).
173. J. T. Groves and R. S. Myers, *J. Am. Chem. Soc.*, **105**, 5791 (1983).
174. D. Mansuy, P. Batteioni, J.-P. Renaud and P. Guerin, *J. Chem., Soc.,.Chem. Commun.*, 155 (1985).
175. Y. Naruta, F. Tani and K. Maruyama, *Chem. Lett.*, 1269 (1989).
176. J. T. Groves and P. Viski, *J. Org. Chem.*, **55**, 3628 (1990).
177. S. O'Malley and T. Kodadek, *J. Am. Chem. Soc.*, **111**, 9116 (1989).
178. (a) R. Irie, K. Noda, Y. Ito, N. Matsumoto and T. Katsuki, *Tetrahedron Lett.*, **31**, 7345 (1990).
(b) R. Irie, K. Noda, Y. Ito and T. Katsuki, *Tetrahedron Lett.*, **32**, 1055 (1991).
179. W. Zhang, J. L. Loebach, S. R. Wilson and E. N. Jacobsen, *J. Am. Chem. Soc.*, **112**, 2801 (1990).

180. W. Zhang and E. N. Jacobsen, *J. Org. Chem.*, **56**, 2296 (1991).
181. K. Tani, M. Hanafusa and S. Otsuka, *Tetrahedron Lett.*, 3017 (1979).
182. H. B. Kagan, M. Mimoun, C. Mark and V. Schurig, *Angew. Chem., Int. Ed. Engl.*, **18**, 485 (1979).
183. V. Schurig, H. Hinter, U. Leyrer, C. Mark, P. Pitchen and H. B. Kagan, *J. Organomet. Chem.*, **370**, 81 (1889).
184. (a) N. L. Weinberg, in *Technique of Electroorganic Synthesis* (Ed. M. M. Baizer), Marcel Dekker, New York, 1973, p. 821.
(b) K. G. Ellis and R. E. W. Jansson, *Chem. Ind (London)*, 864 (1980).
185. K. G. Ellis and R. E. W. Jansson, *J. Appl. Electrochem.*, **13**, 651 (1983).
186. R. C. Alkire and J. Kohler, *J. Appl. Electrochem.*, **18**, 405 (1988).
187. R. C. Alkire and J. E. Tsai, *J. Electrochem. Soc.*, **129**, 1157 (1982).
188. J. Yoshida, J. Hashimoto and N. Kawabata, *J. Org. Chem.*, **47**, 3575 (1982).
189. (a) S. Torii, K. Uneyama and S. Matsunami, *J. Org. Chem.*, **45**, 6 (1980).
(b) I. M. Avrutov and N. Y. Grigoréva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 224 (1985); *Chem. Abstr.*, **102**, 204120 (1985).
(c) S. Torii, H. Tanaka and T. Inokuchi, *Top. Curr. Chem.*, **148**, 153 (1988).
190. S. Torii, K. Uneyama, H. Tanaka, T. Yamataka, T. Yasuda, M. Ono and Y. Kohmoto, *J. Org. Chem.*, **46**, 3312 (1981).
191. S. E. Creager and R. W. Murray, *Inorg. Chem.*, **24**, 3824 (1985).
192. (a) S. E. Creager, S. A. Raybuck and R. W. Murray, *J. Am. Chem. Soc.*, **108**, 4225 (1986).
(b) H. Nishihara, K. Pressprich, R. W. Murray, and J. P. Collman, *Inorg. Chem.*, **29**, 1000 (1990).
193. F. Ojima, N. Kobayashi and T. Osa, *Bull. Chem. Soc. Jpn.*, **63**, 1374 (1990).
194. C. P. Horwitz, S. E. Creager and R. W. Murray, *Inorg. Chem.*, **29**, 1006 (1990).
195. R. Klain and M. D. Scheer, *J. Phys. Chem.*, **73**, 597, 1598 (1969).
196. J. J. Haval, *J. Am. Chem. Soc.*, **96**, 536 (1976).
197. T. Tsuchiya, H. Arai and H. Igeta, *Tetrahedron Lett.*, 2747 (1969).
198. P. S. Bailey, *Ozonation in Organic Chemistry*, Vol. 1, Chaps, XI and X, Academic Press, New York, 1978.
199. R. W. Murray and A. Suzui, *J. Am. Chem. Soc.*, **95**, 3343 (1973).
200. P. S. Bailey, H. H. Hwang and C.-Y. Chiang, *J. Org. Chem.*, **50**, 231 (1985).
201. A. A. Frimer (Ed.), *Singlet Oxygen*, CRC Press, Boca Raton, Fl., 1985.
202. A. P. Schaap, S. G. Rechter, G. R. Faler and S. R. Villasenor, *J. Am. Chem. Soc.*, **105**, 1691 (1983).
203. (a) W. Adam, A. Griesbeck and E. Staab, *Tetrahedron Lett.*, **27**, 2839 (1986).
(b) W. Adam, M. Braun, A. Griesbeck, V. Lucchini, E. Staab and B. Will, *J. Am. Chem. Soc.*, **111**, 203 (1989).
204. D. T. Sawyer and J. S. Valentine, *Acc. Chem. Res.*, **14**, 393 (1981).
205. M. Sagawara and M. M. Baizer, *Tetrahedron Lett.*, **24**, 2223 (1983); *J. Org. Chem.*, **48**, 4931 (1983).
206. H. Yamamoto, T. Mashino, T. Nagano and M. Hirobe, *J. Am. Chem. Soc.*, **108**, 539 (1986).
207. (a) Y. H. Kim and B. C. Chung, *J. Org. Chem*, **48** 1562 (1983).
(b) H. K. Lee, K. S. Kim, J. C. Kim and Y. H. Kim, *Chem. Lett.*, **561** (1988).
208. H. E. Fonouni, S. Krishnan, D. G. Kuhn and G. A. Hamilton, *J. Am. Chem. Soc.*, **105**, 7672 (1983).
209. (a) S. Rozen and M. Kol, *J. Org. Chem.*, **55**, 5155 (1990).
(b) M. H. Hung, B. E. Smart, A. E. Feiring and S. Rozen, *J. Org. Chem.*, **56**, 3187 (1991).
210. (a) A. E. Shilov, *Activation of Saturated Hydrocarbon by Transition Metal Compounds*, Chap. 5, Reidel, Dordrecht, 1984.
(b) H. Mimoun, in *The Chemistry of Peroxides* (Ed. S. Patai), Wiley Chichester, 1983, p. 463.
(c) C. L. Hill, *Activation and Functionalization of Alkanes*, Wiley–Interscience, New York, 1989.
211. (a) D. F. Sangster, in *The Chemistry of the Hydroxyl Group* (Ed. S. Patai), Chap. 3, Wiley, London, 1971.
(b) M. K. Eberhardt, *Reviews on Heteroatom Chemistry* (Ed. S. Oae), Vol. 4, Myu, Tokyo, 1991, p. 1.
212. H. Hart, *Acc. Chem. Res.*, **4**, 337 (1971).
213. D. Jerina, J. Daly, W. Landis, B. Witkop and S. Undenfriend, *J. Am. Chem. Soc.*, **89**, 3347 (1967).
214. T. Tsuchiya, M. Andoh and J. Iwamura, *Nippon Kagaku Kaishi*, 370 (1979).
215. Y. Asakawa, R. Matsuda, M. Tori and M. Sano, *J. Org. Chem.*, **53**, 5453 (1988).

216. U. Frommer and V. Ullrich, *Z. Naturforsch*, **26B**, 322 (1971).
217. (a) W. Müller and H.-J. Schneider, *Angew. Chem., Int. Ed. Engl.*, **18**, 407 (1979).
(b) H.-J. Schneider, N. Becker and K. Phillipi, *Chem. Ber.*, **114**, 1562 (1981).
218. (a) M. Tori, M. Sano and Y. Asakawa, *Bull. Chem. Soc. Jpn.*, **58**, 2669 (1985).
(b) M. Tori, R. Matsuda and Y. Asakawa, *Tetrahedron*, **42**, 1275 (1986).
219. H. J. Schneider and W. Müller, *J. Org. Chem.*, **50**, 4609 (1985).
220. R. L. Safiullin, L. R. Enikeeva and V. D. Komissarov, *Kinet. Katal.*, **30**, 1040 (1989).
221. R. L. Safiullin, R. N. Zaripov, V. D. Komissarov and G. A. Tolstikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 973 (1989); *Chem. Abstr.*, **111**, 232, 125h (1989).
222. S. Kojo and K. Fukanishi, *Chem. Lett.*, 1707 (1983).
223. S. Rozen, M. Brand and M. Kol, *J. Am. Chem. Soc.*, **111**, 8325 (1989).
224. R. W. Murray, R. Jeyaraman and L. Mohan, *J. Am. Chem. Soc.*, **108**, 2470 (1986).
225. R. Mello, M. Fiorentino, O. Sciacovelli and R. Curci, *J. Org. Chem.*, **53**, 3890 (1988).
226. R. Mello, L. Cassidei, M. Fiorentino, C. Fusco and R. Curci, *Tetrahedron Lett.*, **31**, 3067 (1990).
227. R. Mello, L. Cassidei, M. Fiorentino, C. Fusco, W. Hümmer, V. Jäger and R. Curci, *J. Am. Chem. Soc.*, **113**, 2205 (1991).
228. F. A. Davis, N. F. Abdul-Malik and L. A. Jenkins, *J. Org. Chem.*, **48**, 5128 (1983).
229. F. A. Davis and B. C. Chen, *Tetrahedron Lett.*, **31**, 6823 (1990).
230. C. Iwata, Y. Takemoto, A. Nakamura and T. Imanishi, *Tetrahedron Lett.*, **26**, 3227 (1985).
231. (a) H. Hart and C. A. Buehler, *J. Am. Chem. Soc.*, **85**, 2177 (1963).
(b) H. Hart and C. A. Buehler, *J. Org Chem.*, **29**, 2397 (1964).
232. M. E. Kurz and G. Johnson, *J. Org. Chem.*, **36**, 3184 (1971).
233. G. A. Olah and R. Ohnishi, *J. Org. Chem.*, **43**, 865 (1978).
234. G. A. Olah, A. P. Fung and T. Keumi, *J. Org. Chem.*, **46**, 4305 (1981).
235. M. Taddei and A. Ricci, *Synthesis*, 633 (1986).
236. G. A. Olah and T. D. Ernst, *J. Org. Chem.*, **54**, 1204 (1989).
237. (a) J. P. Gesson, J. C. Jacquesy and M. P. Jouannetaud, *Chem. Commun.*, 1128 (1980).
(b) J. P. Gesson, J. C. Jacquesy and M. P. Jouannetaud, *New. J. Chem.*, **6**, 477 (1982).
(c) J. C. Jacquesy, M. P. Jouannetaud and G. Morellet, *Tetrahedron Lett.*, **24**, 3099 (1983).
(d) C. Bevier, H. Carreyre, J. C. Jacquesy and M. P. Jouannetaud, *New. J. Chem.*, **14**, 283 (1990).
238. (a) C. Berrier, J. C. Jacquesy, M. P. Jouannetaud and A. Renoux, *Tetrahedron Lett.*, **27**, 4565 (1986).
(b) J. C. Jacquesy, M. P. Jouannetaud, G. Morellet and Y. Vidal, *Bull. Soc. Chim. Fr.*, 625 (1986).
(c) C. Berrier, J. C. Jacquesy, M. P. Jouannetaud and A. Renoux, *New. J. Chem.*, **11**, 611 (1987).
239. G. A. Olah, G. K. S. Prakash and J. Sommer, *Superacids*, Wiley, New York, 1985, p. 311.
240. G. A. Olah, N. Yoneda and D. G. Parker, *J. Am. Chem. Soc.*, **99**, 483 (1977).
241. G. A. Olah, N. Yoneda and D. G. Parker, *J. Am. Chem. Soc.*, **98**, 5261 (1976).
242. G. Sosnovsky and E. H. Zaret, *Organic Peroxides* (Ed. D. Swern), Vol. I, Wiley–Interscience, New York, 1970, p. 517.
243. G. A. Russell and A. G. Bemis. *J. Am. Chem. Soc.*, **88**, 5491 (1966).
244. S. O. Lawesson, C. Frisell, D. Z. Denny and D. B. Denney, *Tetrahedron*, **19**, 1229 (1963).
245. R. Z. Andriamialisoa, N. Langlois and Y. Langlois, *Tetrahedron Lett.*, **26**, 3563 (1985).
246. R. M. Moriarty, M. P. Duncan and O. Prakash, *J. Chem. Soc., Perkin Trans. 1*, 1781 (1987).
247. (a) R. M. Moriarty, H. Hu and S. C. Gupta, *Tetrahedron Lett.*, **22**, 1283 (1981).
(b) R. M. Moriarty and H. Hu, *Tetrahedron Lett.*, **22**, 2747 (1981).
248. M. Pohmakotr and C. Winotai, *Synth. Commun.*, **18**, 2141 (1988).
249. F. A. Davis and M. S. Haque, *J. Org. Chem.*, **51**, 4083 (1986).
250. T. Ohta, A. Hosoi and S. Nozoe, *Tetrahedron Lett.*, **29**, 329 (1988).
251. D. Enders and V. Bhushan, *Tetrahedron Lett.*, **29**, 2437 (1988).
252. M. Masui, A. Ando and T. Shioiri, *Tetrahedron Lett.*, **23**, 2835 (1988).
253. (a) G. Sosnowski and J. H. Brown, *Chem. Rev.*, **66**, 529 (1966).
(b) T. G. Brilkina and V. A. Shushunov, *Reactions of Organometallic Compounds with Oxygen and Peroxides*, Iliffe Books Ltd., London, 1969.
254. S. O. Lewesson and N. C. Yang, *J. Am. Chem. Soc.*, **81**, 4231 (1959).
255. M. Taddei and A. Ricci, *Synth. Commun.*, 633 (1985).
256. A. K. Sinhababu and R. T. Borchardt, *J. Org. Chem.*, **48**, 1941 (1983).
257. G. J. Lambert, R. P. Duffley, H. C. Dalzell and R. K. Razdan, *J. Org. Chem.*, **47**, 3350 (1982).
258. K. A. Parker and K. A. Koziski, *J. Org. Chem.*, **52**, 674 (1987).

259. (a) J. Einhorn, J.-L. Luche and P. Demerseman, *J. Chem. Soc., Chem. Commun.*, 1350 (1988).
(b) G. Simig and M. Schlosser, *Tetrahedron Lett.*, **29**, 4277 (1988).
(c) R. C. Cambie, P. I. Higgs, P. S. Rutledge and P. D. Woodgate, *J. Organomet. Chem.*, **384**, C6 (1990).
260. D. L. Heywood, B. Phillips and H. A. Stansburg, Jr., *J. Org. Chem.*, **26**, 281 (1961).
261. Y. Ogata and K. Tomizawa, *J. Org. Chem.*, **43**, 261 (1978).
262. D. Lefort, J. Fossey, M. Gruselle, J. Y. Nedelec and J. Sorba, *Tetrahedron*, **41**, 4237 (1985).
263. (a) J. Fossey and D. Lefort, *Tetrahedron*, **36**, 1023 (1980).
(b) J. Sorba, J. Fossey, J. Y. Nedelec and D. Lefort, *Tetrahedron*, **35**, 1509 (1979).
264. J. Fossey, D. Lefort, M. Massoudi, J. Y. Nedelec and J. Sorba, *Can. J. Chem.*, **63**, 678 (1985).
265. V. V. Lipes, *Kinet. Katal.*, **27**, 1046 (1986).
266. (a) D. F. Sangster, in *The Chemistry of the Hydroxyl Group* (Ed. S. Patai), Chap. 3, Wiley, London, 1971.
(b) C. Walling, *Acc. Chem., Res.*, **8**, 125 (1975).
(c) M. K. Eberhardt, in *Reviews in Heteroatom Chemistry*, (Ed. S. Oae), Myu, Tokyo, Vol. 4, p. 1 (1991).
267. P. Neta and L. M. Dorfman, in *Radiation Chemistry*, Vol. 1 (Ed. E. J. Hart), *Adv. Chem. Ser.*, **81**, 222 (1968).
268. (a) C. Walling and R. A. Johnson, *J. Am. Chem. Soc.*, **97**, 363 (1975).
(b) M. K. Eberhardt and M. I. Martinez, *J. Phys. Chem.*, **79**, 1917 (1975).
(c) N. V. Raghavan and S. Steenken, *J. Am. Chem. Soc.*, **102**, 3495 (1980).
269. G. A. Hamilton, J. P. Friedman and P. H. Campbell, *J. Am. Chem. Soc.*, **88**, 5266, 5269 (1966).
270. S. Tamagaki, K. Suzuki, H. Okamoto and W. Tagaki, *Tetrahedron Lett.*, **24**, 4847 (1983).
271. S. Tamagaki, M. Sasaki and W. Tagaki, *Bull. Chem. Soc. Jpn.*, **62**, 153 (1989).
272. J. T. Groves and M. Van Der Puy, *J. Am. Chem. Soc.*, **98**, 5290 (1976).
273. S. Undenfriend, C. T. Clark, J. Axelrod and B. Brodie, *J. Biol. Chem.*, **208**, 731 (1954).
274. S. Tamagaki, M. Sasaki and W. Tagaki, *Bull. Chem. Soc. Jpn.*, **62**, 159 (1989).
275. M. M. T. Khan and R. S. Shukla, *J. Mol. Catal.*, **45**, 25 (1988).
276. (a) T. Miura, K. Shibata, K. Adachi, T. Sawaya and M. Kimura, *Chem. Pharm. Bull.*, **31**, 100 (1983).
(b) U. Jingjit, C. Bouchoule, J. M. Maissant, P. Canesson and M. Blanchard, *J. Mol. Catal.*, **27**, 373 (1984).
277. H. W. Richter, M. A. Fetrow, R. E. Lewis and W. H. Waddell, *J. Am. Chem. Soc.*, **104**, 1666 (1982).
278. (a) M. K. Eberhardt, R. Colina and K. Soto, *J. Org. Chem.*, **53**, 1074 (1988).
(b) S. Ito, T. Yamazaki, H. Okada, S. Okino and K. Sasaki, *J. Chem. Soc., Perkin Trans. 2*, 285 (1988).
279. N. Narita and T. Tezuka, *J. Am. Chem. Soc.*, **104**, 7316 (1982).
280. T. Kurata, Y. Watanabe, M. Katoh and Y. Sawaki, *J. Am. Chem. Soc.*, **110**, 7472 (1988).
281. (a) D. H. R. Barton, M. J. Gastiger, W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 41 (1983).
(b) D. H. R. Barton, J. Boivin, W. B. Motherwell, N. Ozbalik, K. M. Schwartzentruber and K. Jankowski, *New J. Chem.*, **10**, 387 (1986).
282. D. H. R. Barton, J. Boivin, N. Ozbalik and K. M. Schwartzentruber, *Tetrahedron Lett.*, **26**, 447 (1985).
283. D. H. R. Barton and N. Ozbalik, Reference 210c, p. 281.
284. W. Nam and J. S. Valentine, *New J. Chem.*, **13**, 677 (1989).
285. S. N. Sharma, H. R. Sonawane and S. Dev, *Tetrahedron*, **41**, 2483 (1985).
286. H. R. Sonawane, B. S. Nanjundiah and R. G. Kelkar, *Tetrahedron*, **42**, 6673 (1986).
287. (a) A. Hori, H. Matsumoto, S. Takamuku and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 16 (1978).
(b) S. Takamuku, H. Matsumoto, A. Hori and H. Sakurai, *J. Am. Chem. Soc.*, **102**, 1441 (1980).
288. E. Zadok and Y. Mazur, *Tetrahedron Lett.*, **21**, 4955 (1980).
289. (a) T. Tsuchiya, H. Arai and H. Igeta, *Tetrahedron Lett.*, 2747 (1969).
(b) T. Tsuchiya, H. Arai and H. Igeta, *Tetrahedron Lett.*, 2213 (1970).
290. Y. Ogawa, S. Iwasaki and S. Okuda, *Tetrahedron Lett.*, **22**, 3637 (1981).
291. M. Sako, S. Ohara, K. Shimada, K. Hirota and Y. Maki, *J. Chem. Soc., Perkin Trans. 1*, 863 (1990).
292. E. Zadok and Y. Mazur, *Angew. Chem.*, **94**, 311 (1982).

293. Review: F. Minisci, A. Citterio and C. Giordano, *Acc. Chem. Res.*, **16**, 27 (1983).
294. C. Walling, D. M. Camaioni and S. S. Kim, *J. Am. Chem. Soc.*, **100**, 4814 (1978).
295. P. Neta, V. Madhavan, H. Zemel and R. W. Fessenden, *J. Am. Chem. Soc.*, **99**, 163 (1977).
296. M. K. Eberhardt, *J. Org. Chem.*, **42**, 832 (1977).
297. (a) L. Jönsson and L.-G. Wistrand, *J. Chem. Soc., Perkin Trans. 1*, 669 (1979).
(b) C. Walling, C. Zhao and G. M. El-Taliawi, *J. Org. Chem.*, **48**, 4910 (1983).
(c) A. Belli, C. Gordano, and A. Citterio, *Synthesis*, 477 (1980).
298. M. K. Eberhardt, G. A. Martinez, J. I. Rivera and A. Fuentes-Aponte, *J. Am. Chem. Soc.*, **104**, 7069 (1982).
299. (a) D. M. Jerina and W. J. Daly, *Science*, **185**, 573 (1974).
(b) G. A. Hamilton, in *Molecular Mechanism of Oxygen Activation* (Ed., O. Hayaishi), Academic Press, New York, 1974, p. 405.
300. (a) B. D. Preston, J. A. Miller and E. C. Miller, *J. Biol. Chem.*, **258**, 8304 (1983).
(b) R. P. Hazlik, K. Hogberg and C. M. Judson, *Biochemistry*, **23**, 3048 (1984).
301. L. Castle, J. R. Lindsay Smith and G. V. Buxton, *J. Mol. Catal.*, **7**, 235 (1980).
302. R. A. Sheldon and J. K. Kochi, Reference 94, p. 215.
303. C. T. Goodhue and J. R. Schaeffer, *Biotech. Bioeng.*, **13**, 203 (1971).
304. J. Hasegawa, M. Ogura, S. Hamaguchi, M. Shimazaki, H. Kawaharada and K. Watanabe, *J. Ferment. Technol.*, **59**, 203 (1981).
305. S. W. May, *Enzyme Microb. Tech.*, **1**, 15 (1979).
306. R. A. Johnson, C. M. Hall, W. C. Krueger and H. C. Murray, *Bioorg. Chem.*, **2**, 99 (1973).
307. J. Hasagawa, W. Ogura, H. Kanema, H. Kawaharada and K. Watanabe, *J. Ferment. Tech.*, **61**, 37 (1984).
308. K. R. Hanson and I. A. Rose, *Acc. Chem. Res.*, **8**, 1 (1975).
309. A. G. Katopodis, H. A. Smith, Jr. and S. W. May, *J. Am. Chem. Soc.*, **110**, 897 (1988).
310. K. B. Taylor, *J. Biol. Chem.*, **249**, 454 (1974).
311. S. R. Sirimanne and S. W. May, *J. Am. Chem. Soc.*, **110**, 7560 (1988).
312. K. B. Wiberg and G. Foster, *J. Am. Chem. Soc.*, **83**, 423 (1961).
313. R. C. Bingham and P. v. R. Schleyer, *J. Org. Chem.*, **36**, 1198 (1971).
314. H.-J. Schmidt and H. J. Schäfer, *Angew. Chem., Int. Ed. Engl.*, **18**, 68 (1979).
315. M. Pechal and M. Strasak, *J. Pract. Chem.*, **326**, 374 (1984).
316. J. Hanotier, P. Camerman, H. Hanotier-Bridoux and P. de Radzitsky, *J. Chem. Soc., Perkin Trans., 2*, 2247 (1972).
317. H. Mimoun, in *The Chemistry of Peroxides* (Ed., S. Patai), Wiley, Chichester, 1983, p. 463.
318. M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, **99**, 5526 (1977).
319. M. Haruna, and K. Ito, *J. Chem. Soc., Chem. Commun.*, 483 (1981).
320. B. Chabaud and K. B. Sharpless, *J. Org. Chem.*, **44**, 4202 (1979).
321. B. R. Chhabra, K. Hayano, T. Ohtsuka, H. Shirahama and T. Matsumoto, *Chem. Lett.*, 1703 (1981).
322. W. Berends and J. Konings, *Recl. Trav. Chem. Pays-Bas*, **74**, 1365 (1955).
323. J. G. Zajacek and L. J. Carr, *German Offen.*, 2,400,322 (1974); *Chem. Abstr.*, **81**, 104855 (1974).
324. D. J. Rawlinson and G. Sosnowsky, *Synthesis*, 1 (1972).
325. K. Pederson, P. Jakobsen and S.-O. Lawesson, *Org. Synth.*, Coll. Vol. 5, 70 (1973).
326. (a) J. K. Kochi, *J. Am. Chem. Soc.*, **84**, 774 (1962).
(b) C. Walling and A. A. Zavitsas, *J. Am. Chem. Soc.*, **85**, 2084 (1963).
327. A. L. J. Beckwith and A. A. Zavitsas, *J. Am. Chem. Soc.*, **108**, 8230 (1986).
328. H. L. Goering and U. Mayer, *J. Am. Chem. Soc.*, **86**, 3753 (1964).
329. J. J. Villenave, H. Francois and R. Lalande, *Bull. Soc. Chim. Fr.*, 599 (1970).
330. G. Sosnowsky and S.-O. Lawesson, *Angew. Chem.*, **76**, 218 (1964).
331. H. Kropf, R. Schroeder and R. Fölsing, *Synthesis*, 894 (1977).
332. H. Matsumura, T. Yano, M. Ueyama, K. Tori and W. Nagata, *J. Chem. Soc., Chem. Commun.*, 485 (1979).
333. D. J. Rawlinson, M. Konieczny and G. Sosnowsky, *Z. Naturforsch.*, **34B**, 76 (1979).
334. M. K. Eberhardt, *J. Org. Chem.*, **42**, 832 (1977).
335. C. G. Reid and P. Kovacic, *J. Org. Chem.*, **34**, 3308 (1969).
336. P. Kovacic, C. G. Reid and M. J. Brittain, *J. Org. Chem.*, **35**, 2152 (1970).
337. M. E. Kurz and P. Kovacic, *J. Org. Chem.*, **33**, 1950 (1968).

338. (a) A. S. Goldstein and R. S. Drago, *J. Chem. Soc.*, Chem. Commun., 21 (1991).
(b) L.-C. Kao, A. C. Hutson and A. Sen. *J. Am. Chem. Soc.*, **113**, 700 (1991).
339. R. H. Holm, *Chem. Rev.*, **87**, 1401 (1987).
340. D. H. R. Barton, F. Halley, N. Ozbalik, M. Schmitt, E. Young and G. Balavoine, *J. Am. Chem. Soc.*, **111**, 7144 (1989).
341. H. Mimoun, L. Saussine, E. Daire, M. Postel, J. Fischer and R. Weiss, *J. Am. Chem. Soc.*, **105**, 3101 (1983).
342. L. Saussine, E. Brazi, A. Robine, H. Mimoun, J. Fischer and R. Weiss, *J. Am. Chem. Soc.*, **107**, 3534 (1985).
343. E. Daire, H. Mimoun and L. Saussine, *New J. Chem.*, **8**, 271 (1984).
344. (a) E. Kimura, A. Sakonaka, R. Machida and M. Kodama, *J. Am. Chem. Soc.*, **104**, 4255 (1982).
(b) E. Kimura and R. Machida, *J. Chem. Soc., Chem., Commun.*, **499** (1984).
345. D. Chen, R. J.Motekaitis and A. E. Martell, *Inorg. Chem.*, **30**, 1396 (1991).
346. N. Herron and C. A. Tolman, *J. Am. Chem. Soc.*, **109**, 2837 (1987).
347. T. Kimura, A. Fukuoka and M. Ichikawa, *Shokubai*, **31**, 357 (1989).
348. (a) N. Kitajima, M. Ito, H. Fukui and Y. Moro-oka, *J. Chem. Soc., Chem. Commun.*, 102 (1991).
(b) N. Kitajima, H. Fukui and Y. Moro-oka, *J. Chem. Soc., Chem. Commun.*, 485 (1988).
349. Y. Kurusu and D. C. Neckers, *J. Org. Chem.*, **56**, 1981 (1991).
350. (a) J. Van Gent, A. A. Wismeijer, A. W. P. G. Peters Rit and H. Van Bekkum, *Tetrahedron Lett.*, **27**, 1059 (1986).
(b) A. Kunai, S. Hata, S. Ito and K. Sasaki, *J. Org. Chem.*, **51**, 3471 (1986).
351. (a) T. Jintoku, H. Taniguchi and Y. Fujiwara, *Chem. Lett.*, 1865 (1987).
(b) T. Jintoku, K. Takaki, Y. Fujiwara, Y. Fuchita and K. Hiraki, *Bull. Chem. Soc. Jpn.*, **63**, 438 (1990).
352. (a) P. Capdevielle and M. Maumy, *Tetrahedron Lett.*, **23**, 1577 (1982).
(b) O. Reinaud, P. Capdevielle and M. Maumy, *Synthesis*, 612 (1990).
353. (a) P. R. Ortiz de Montellano, *Cytochrome P450: Structure, Mechanism and Biochemistry*, Plenum Press, New York, 1986.
(b) J. H. Dawson and M. Sono, *Chem. Rev.*, **87**, 1255 (1987).
354. (a) J. T. Groves and T. E. Nemo, *J. Am. Chem. Soc.*, **105**, 6243 (1983).
(b) J. T. Groves and P. Viski, *J. Am. Chem. Soc.*, **111**, 8537 (1989).
355. J. T. Groves and D. V. Subramanian, *J. Am. Chem. Soc.*, **106**, 2177 (1984).
356. R. K. Khanna, J. S. Sutherlin and D. Lindsey, *J. Org. Chem.*, **55**, 6233 (1990).
357. E. Baciocchi, M. Crescenzi and O. Lanzalunga, *J. Chem. Soc., Chem. Commun.*, 687 (1990).
358. J. F. Bartoli, O. Brigaud, P. Battioni and D. Mansuy, *J. Chem. Soc., Chem. Commun.*, 440 (1991).
359. S. Banfi, A. Maiocchi, A. Moggi, F. Montanari and S. Quici, *J. Chem. Soc., Chem. Commun.*, 1794 (1990).
360. (a) P. Battioni, J.-P. Lallier, L. Barloy and D. Mansuy. *J. Chem. Soc., Chem. Commun.*, 1149 (1989).
(b) L. Barloy, P. Battioni and D. Mansuy, *J. Chem. Soc., Chem., Commun.*, 1365 (1990).
361. (a) K. S. Suslick, B. Cook and M. Fox, *J. Chem. Soc., Chem. Commun.*, 580 (1985).
(b) B. R. Cook, T. J. Reinert and K. S. Suslick, *J. Am. Chem. Soc.*, **108**, 7281 (1986).
362. M.-N. Carrier, C. Scheer, P. Gouvine, J.-F. Bartori, P. Battioni and D. Mansuy, *Tetrahedron Lett.*, **31**, 6645 (1990).
363. (a) H. Lund and M. M. Baizer, *Organic Electrochemistry*, Marcel Dekker, New York, 1991.
(b) S. Torii, *Electroorganic Syntheses*, Part I, Kodansha and VCH, Tokyo, 1985.
364. K. Yoshida, M. Shigi, T. Kanbe and T. Fueno, *J. Org. Chem.*, **40**, 3805 (1975).
365. M. A. Hatter, *Ger. Offen.*, 2,756,588 (1978).
366. Y. H. So and L. L. Miller, *Synthesis*, 468 (1978).
367. A. Bewick, G. J. Edwards, S. R. Jones and J. M. Mellor, *Tetrahedron Lett.*, 631 (1976).
368. B. Fleszar and J. Ploszynska, *Electrochim. Acta*, **30**, 31 (1985).
369. T. Matsue, M. Fujihira and T. Osa, *J. Electrochem. Soc.*, **128**, 2565 (1981).
370. B. Fleszar and A. Sobkwiak, *Electrochem. Acta*, **26**, 1699 (1981).
371. T. Tzedakis, A. Savall and M. J. Clifton, *J. Appl. Electrochem.*, **19**, 911 (1989).
372. (a) J. M. Maissant, C. Bouchoule, P. Canesson and M. Blanchard, *J. Mol. Catal.*, **18**, 189 (1983).
(b) M. Blanchard, C. Bouchoule, G. Djaneye-Boundjou and P. Canesson, *Tetrahedron Lett.*, **29**, 2177 (1988).

373. P. Loduc, P. Battioni, J. F. Bartoli and D. Mansuy, *Tetrahedron Lett.*, **29**, 205 (1988).
374. A. Nanthakumar and H. M. Goff, *J. Am. Chem. Soc.*, **112**, 4047 (1990).
375. (a) E. V. Malykhin, A. A. Shtark and V. D. Shteingarts, *Zh. Org Khim.*, **18**, 1898 (1982).
(b) E. V. Malykhin, G. A. Kobsnichenko and V. D. Shteingarts, *Zh. Org. Khim.*, **22**, 806 (1986).
376. R. Bacaloglu, A. Blaskó, C. Bunton, E. Dorwin, F. Ortega and C. Zucco, *J. Am. Chem. Soc.*, **113**, 238 (1991).
377. M. Makosza and K. Sienkiewicz, *J. Org. Chem.*, **55**, 4979 (1990).
378. G. Mattersteig, W. Pritzkov and V. Voeckel, *J. Prakt. Chem.*, **332**, 569 (1990).
379. W. J. Mijs and C. R. H. I. de Jonge, *Organic Syntheses by Oxidation with Metal Compounds*, Plenum Press, New York, 1986.
380. (a) S. G. Hentges and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 4263 (1980).
(b) J. S. Svendsen, I. Marko, E. N. Jacobsen, C. P. Rao, S. Bott and K. B. Sharpless, *J. Org. Chem.*, **54**, 2263 (1989).
381. K. Tomioka, M. Nakajima and K. Koga, *J. Am., Chem. Soc.*, **109**, 6213 (1987).
382. E. N. Jacobsen, I. Marko, W. S. Mungall, G. Schroder and K. B. Sharpless, *J. Am. Chem. Soc.*, **110**, 1968 (1988).

CHAPTER **12**

Hydroxymethylation via radical intermediates

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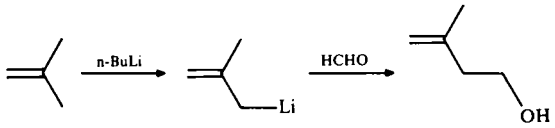
Suppliment E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

I. GENERAL INTRODUCTION

The hydroxymethyl group is one of the most useful substituents for organic synthesis and therefore the development of efficient and selective hydroxymethylation procedures is of importance. Among these the use of lithium reagents is one of the most convenient methods. Thus, the reaction of n-butyllithium with a compound having an active hydrogen atom affords a lithium derivative[1], which leads to an alcohol upon treatment with formaldehyde[2].



(1)

Our aim in this chapter is to summarize hydroxymethylations via radical intermediates which have been reported mainly in the last decade. In general, synthetic chemists are somewhat prejudiced against reactions via radical intermediates because of their low selectivity, and this has discouraged them also from developing hydroxymethylation methods via radical intermediates. However, Minisci and his coworkers have proved that regioselective substitution reactions of heteroaromatics are induced efficiently by several kinds of radical initiators[3]. Recently, furthermore, highly efficient regioselective hydroxymethylations of unsaturated compounds were performed by radical cyclization–desilylation processes[4,5]. In the fields of photochemistry and radiation chemistry, formation of a hydroxymethyl radical is a common reaction, and our recent results show that efficient synthetic reactions can be carried out by photochemical[6] and radiation chemical processes[7]. We hope that the present chapter will enable synthetic chemists to recognize the usefulness of radical intermediates in hydroxymethylations.

II. HYDROXYMETHYL RADICALS

A. Generation of Hydroxymethyl Radicals

1. Radical initiators

It is well known that electrophilic free radicals readily abstract an α-hydrogen of an alcohol to generate a hydroxyalkyl radical. Several kinds of free-radical sources, such as Fenton's reagent (Fe^{2+}—H_2O_2), its analogue (Ti^{3+}—H_2O_2), *t*-butyl hydroperoxide, hydroxylamine-*O*-sulfonic acid, ammonium peroxydisulfate, etc., have been applied to this purpose. Thermal and redox decomposition of these radical sources initially produces electrophilic radicals, such as ·OH, NH_3^+ and SO_4^-. Using alcohols, they afford a hydroxyalkyl radical in high efficiency by hydrogen abstraction from the alcohol and the resulting hydroxyalkyl radical can be used for synthetic reactions. The rate constants

for these species with methanol have been determined by pulse radiolysis[8]: ·OH, 8.8×10^8; $SO_4^{-\cdot}$, $3.2 \times 10^6\ M^{-1}\ s^{-1}$.

$$H_2O_2 \xrightarrow{Fe^{2+}\ Fe^{3+}} \cdot OH + OH^- \quad (2)$$

$$\cdot OH \xrightarrow{CH_3OH} \cdot CH_2OH + H_2O \quad (3)$$

2. Radiation chemical processes

The primary process for the γ-radiolysis of a methanol solution is the ionization of methanol producing the radical cation of methanol and a solvated electron. These primary species are transformed into hydroxymethyl radicals by the reactions 5 and 6 and in to the radical anions of the solute (S) by the attachment of solvated electrons, respectively. The radical anion thus formed is rapidly protonated to give a neutral free radical of the substrate. The cross recombination of the resulting species (·CH_2OH and HS·) will lead to the formation of hydroxymethylation products. Even when one-electron reduction of the substrate is not expected, we can use the radiation chemical process as the source of hydroxymethyl radicals to initiate further addition reactions.

$$CH_3OH \xrightarrow{\gamma\text{-ray}} CH_3OH^{+\cdot} + e_s^- \quad (4)$$

$$CH_3OH^{+\cdot} + CH_3OH \longrightarrow CH_3OH_2^+ + CH_3O\cdot \quad (5)$$

$$CH_3O\cdot + CH_3OH \longrightarrow CH_3OH + \cdot CH_2OH \quad (6)$$

$$S + e_s^- \longrightarrow S^{-\cdot} \quad (7)$$

$$S^{-\cdot} + H^+ \longrightarrow HS\cdot \quad (8)$$

$$HS\cdot + \cdot CH_2OH \longrightarrow HSCH_2OH \quad (9)$$

(S = unsaturated substrate)

3. Photochemical processes

The most characteristic property of photochemical reactions is selective energy deposition to a substrate in contrast to radiation chemical processes, and the reactivity of a photoexcited state depends highly on the multiplicity. In general, the photoexcited triplet state of carbonyl compounds abstracts hydrogen atom from alcohols. This process leads to the formation of a hydroxylalkylation product by coupling of initial radical pairs[9] while the efficiency is not high in the case of methanol. On the other hand, the photoexcited singlet state frequently shows ionic character and is subject to an efficient 'polar addition' of methanol affording a methoxyl derivative[10]. The facts suggest that hydroxymethylation by the use of photoexcited states is limited for the triplet state which is produced by either direct excitation or by sensitization.

$$S \xrightarrow{h\nu} {}^1S^* \quad (S = \text{phenylnorbornene, etc.}) \quad (10)$$

$${}^1S^* + CH_3OH \longrightarrow HSOCH_3 \quad (11)$$

$$S \xrightarrow{h\nu} {}^1S^* \quad (S = \text{cyclopentenone, etc.}) \quad (12)$$

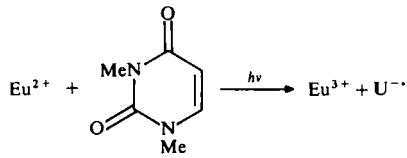
$$^1S^* \longrightarrow {}^3S^* \tag{13}$$

$$^3S^* + CH_3OH \longrightarrow HS\cdot + \cdot CH_2OH \tag{14}$$

$$HS\cdot + \cdot CH_2OH \longrightarrow HSCH_2OH \tag{15}$$

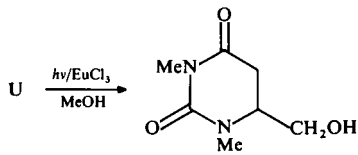
Of particular importance is the photochemical electron transfer reaction which leads to the formation of radical cations of methanol and radical anions of the substrate. The reaction paths to the hydroxymethylation products after the initial active species formed are similar to those of the radiation chemical process described above. However, in the case of the photochemical method, the efficiency of hydroxymethylation can be significantly enhanced by use of photoredox catalysts as shown in the following example[6].

$$Eu^{3+} + CH_3OH \xrightarrow{h\nu} Eu^{2+} + CH_3OH^{+\cdot} \tag{16}$$



(U) (17)

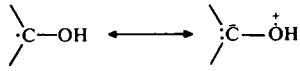
The overall reaction affords the 5,6-dihydro-hydroxymethyl derivative in 95% yield.



(18)

B. Properties of Hydroxymethyl Radicals

α-Hydroxyalkyl radicals have strong nucleophilic character, which can be presumed from their highly negative redox potentials and from their low pK_a values[11]. These physical parameters for the hydroxyalkyl radicals $\cdot CH_2OH$, $CH_3\dot{C}HOH$ and $(CH_3)_2\dot{C}OH$ have been determined to be: redox potentials[12] −0.73, −0.93 and −1.05[13] V; pK_a[14] 10.7, 11.6 and 12.2, respectively. These nucleophilic properties of α-hydroxyalkyl radicals are attributable to the resonance stabilization of ionic structures as shown in reaction 19[11].



(19)

The nucleophilic character of the hydroxyalkyl radical is important for the efficient hydroxyalkylation. However, the nucleophilic character of the radical intermediates is correlated with the highly negative redox potentials which make an electron transfer from the radicals to an electron acceptor (A) preferable[15]. Since the latter reaction is undesirable for hydroxyalkylation, efficient electron acceptors must be eliminated from the reaction system. The rate constants of reaction 20 were measured with various electron acceptors, such as Rhodamine B, NAD^+, 9,10-anthraquinone-2-sulfonate, etc.[13].

Especially, α-hydroxy-*t*-alkyl radicals with highly negative redox potentials mainly undergo the electron transfer reaction and the yield of hydroxyalkylation becomes extremely low[11].

$$\cdot CH_2OH + A \xrightarrow{SET} HCHO + H^+ + A^{-\cdot} \quad (A = \text{oxidant}) \tag{20}$$

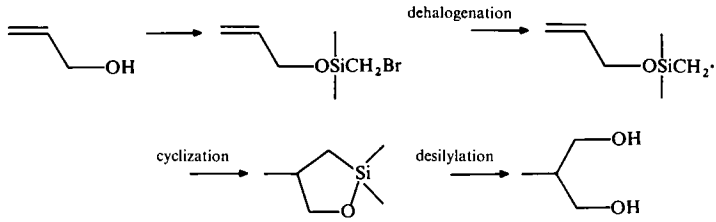
III. HYDROXYMETHYLATION VIA RADICAL INTERMEDIATES

A. Hydroxymethylation via Radical Cyclization–Desilylation

One of the most important recent developments in hydroxymethylation is the radical cyclization–desilylation process. A (bromomethyl)dimethylsilyl ether, which is produced by a reaction of an unsaturated alcohol with (bromomethyl)dimethylchlorosilane, affords a cyclic silyl ether via radical cyclization. Successive oxidation of the resulting ether induces desilylation to afford a diol product in a high yield.

This reaction was reported by Itoh and coworkers[4] and independently by Stork and Kahn at almost the same time[5]. Various groups have developed synthetic applications of this reaction, and the results were published in over a dozen papers[4,5,16–25].

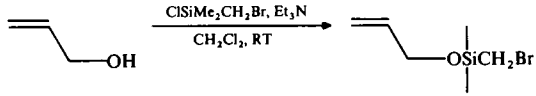
The most important feature of this reaction is the highly regioselective intramolecular radical addition to unsaturated functional groups. In almost all substrates, a 3-oxa-2-silahexenyl radical results in a 5-*exo* addition similarly to the cyclization of a 5-hexenyl radical. However, in some cases, other modes of cyclization (6-*endo*[4,20,21], 6-*exo*[22] and 7-*endo*[22]) take place competitively or predominantly. The treatment of the resulting cyclic silyl ether gives a diol in a high yield. In this section, we summarize the recent progress in the cyclization–desilylation process.



(21)

1. General procedure

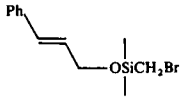
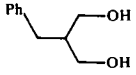
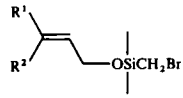
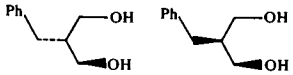
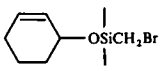
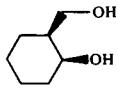
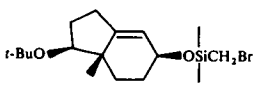
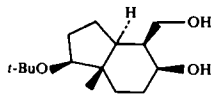
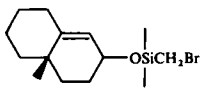
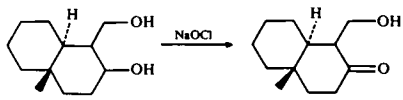
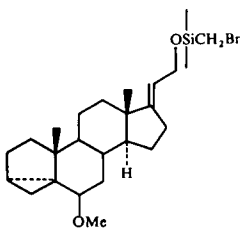
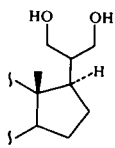
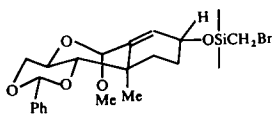
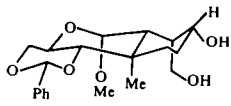
a. Preparation of bromomethyldimethylsilyl ether from alcohol. The key intermediate of this reaction, the bromomethyldimethylsilyl ether, is easily prepared under mild conditions. Reactions of a parent unsaturated alcohol with (bromomethyl)chlorodimethylsilane in dichloromethane proceeds even at room temperature in the presence of triethylamine[17].



(22)

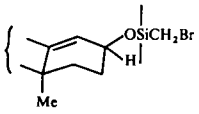
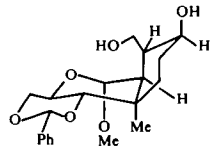
b. Dehalogenation and successive cyclization. Elimination of Br atom from the ether to induce radical cyclization is achieved by treatment with Bu_3SnH and a catalytic

TABLE 1. Selective 5-*exo* cyclization

Bromide	Procedure[a]	Product and yield[b] (ratio)	Reference
 (1)	A	 85%(100)	4
 (2a) $R^1 = H$, $R^2 = Ph$ (2b) $R^1 = Ph$, $R^2 = H$	A	 85% (84) (16) 94% (100) (0)	4
 (3)	A	 75%(100)	4
 (4)	B	 88%(100)	5, 19
 (5)	B		5
 (6)	C	 77% 78%	16 17
 (7a)	D	 64%	18

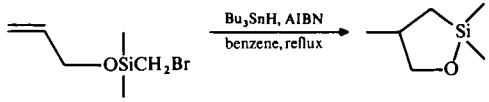
(*continued*)

TABLE 1. (*continued*)

Silyl ether	Procedure[a]	Product and yield[b] (ratio)	Reference
 (**7b**)	D	 73% (yield of siloxane)	18

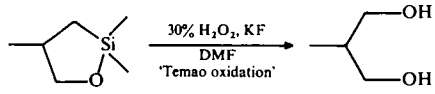
[a]*Method A.* To a solution of the ether (2 mmol) in 36 mL of benzene was added dropwise a mixture of Bu_3SnH (1.2–1.5 mmol) and AIBN (0.03 mmol) in 4 mL of benzene at reflux over a 2 h period followed by heating for an additional 1–2 h. The reaction can be carried out in 0.025–0.05 M solution. After evaporation of the benzene, the residual oil was treated with 1.2 mL of 30% H_2O_2 in 5 mL of DMF and KF (10 mmol) at 60 °C for 7–8 h. After the usual workup, purification was achieved by column chromatography (Merck 7719, ether–hexane).
Method B. Refluxing of the ether in benzene with 1.5 equiv Bu_3SnH and 1/20 equiv AIBN gave a cyclization product which was oxidized by KF/DMF/30% H_2O_2.
Method C. To a solution of the ether (1.9 mmol) in 3 mL benzene at reflux temperature were added Bu_3SnH (1.0 mmol) and AIBN (0.04 mmol) in 1.8 mL benzene during 1.5 h. The mixture was refluxed for an additional 2.5 h, and the solvent was evaporated. The residue was dissolved in DMF containing KF (29.3 mmol) and 1.2 mL 30% H_2O_2, and the mixture was heated at 80–85 °C for 3 days. Workup and chromatography of the crude product on SiO_2 (hexanes–acetone).
Method D. Detailed experimental procedure was not described; cyclization, Bu_3SnH and AIBN; oxidation, H_2O_2 and KF.
[b]Isolated yields.

amount of AIBN. The resulting α-silyl radical leads to regio- and stereoselective cyclization, which is a very useful reaction to construct skeletons of natural products. Thus, the stereoelectronic and steric factors governing the reactions of α-silyl radicals have been studied in detail. The regio- and stereoselective cyclization of various kinds of silyl ethers will be discussed in the following section.



(23)

c. Desilylation of siloxane. Tamao–Kumada oxidation has been applied to the reaction of siloxane. The novel oxidative cleavage of the Si—C bond induces the transformation of the siloxane into the corresponding diol[26].

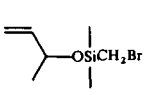
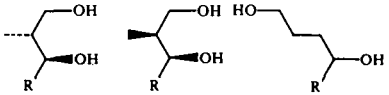
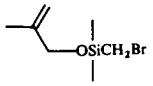
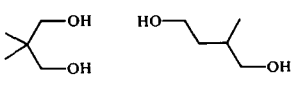
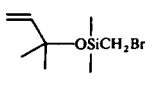
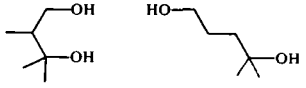


(24)

2. Mechanistic consideration of the cyclization

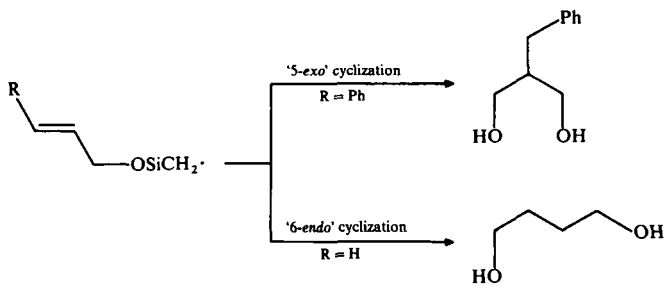
a. Selective 5-exo cyclization. It has been reported that 2-silahexenyl radical shows preferential 6-*endo* cyclization[27]. On the other hand, a number of aliphatic 3-oxa-2-silahexenyl radicals cyclize predominantly in the 5-*exo* mode as shown in Table 1. A

TABLE 2. Competitive 5-*exo* and 6-*endo* cyclization

Silyl ether	Procedure[a]	Product and yield[b] (ratio)	Reference
			4
(8a) R = Me	E	95% (69) (15) (16)	
(8b) R = *i*-Pr	E	90% (82) (−0) (18)	
(8c) R = *t*-Bu	E	91% (71) (0) (29)	
(8d) R = CH=CH$_2$	E	85% (61) (11) (28)	
(8e) R = Ph	A	88% (54) (5) (41)	
	E		4
(9)		52% (35) (65)	
	E		4
(10)		83% (91) (9)	

[a]*Method E.* Cyclization was similar to method A. Successive oxidation was carried out in 3 mL of MeOH and 3 mL of THF and Na_2CO_3 (2 mmol) at reflux for 5 h.
Method A. See Table 1.
[b]Isolated yields.

terminal bulky phenyl group of a nonrigid simple olefin (**1**, **2**) leads to selective 5-*exo* cyclization. However, a bulky group of the allylic position (**8**) and methyl group of the vinyl position (**9**) induces a competitive cyclization between the 5-*exo* and 6-*endo* modes (Table 2)[4]. Steric effects of the 1-substituent on the allylic skeleton contribute to the preferable formation of 2,3-*threo*-1,3-*diol*. Thus, the intramolecular cyclization of the radical proceeds stereoselectively to give the parent siloxane, that is, *trans*-3,4-disubstituted 1-sila-2-oxacyclopentane[4]. Reactions of rigid cyclic olefins (**3**, **4**, **5**, **7**) lead to a *cis*-diol formation via a *cis*-fused bicyclic ring system. These examples demonstrate that the selective *trans* addition to a cyclic olefin gives a thermodynamically less stable ring system[4,5,18,19].

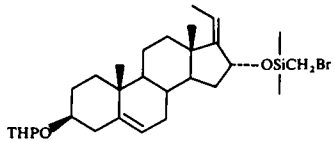
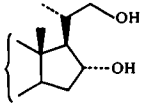
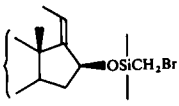
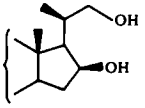
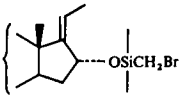
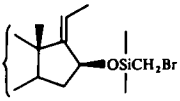
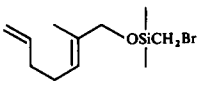
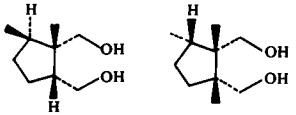


(25)

b. Competition between 5-exo and 6-endo cyclization. The 5-*exo* mode cyclization predominates, but the 6-*endo* mode can also be observed for allylic systems without terminal functionality (**8**, **9**, **10**) to give a noticeable amount of 1,4-diols[4].

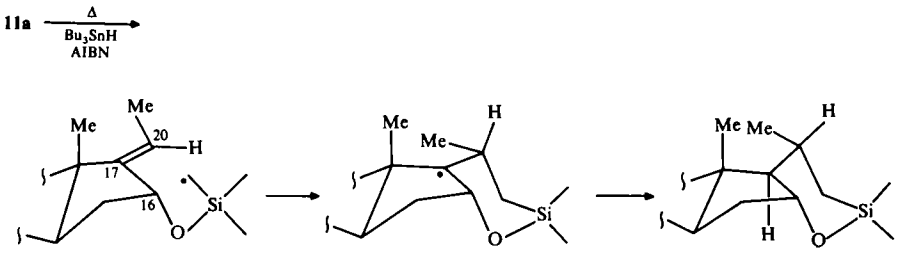
c. Selective 6-endo cyclization. Selective 6-*endo* cyclization in a rigid ring system is applied to construct side chains of physiologically significant 22-hydroxylated steroids[20]. Treatment of the four conformationally rigid, stereoisomeric bromosilyl ethers **11a–d** with Bu_3SnH and AIBN was carried out (Table 3). The *E*-allylic ethers, **11a** and **11b**,

TABLE 3. Selective 6-*endo* cyclization

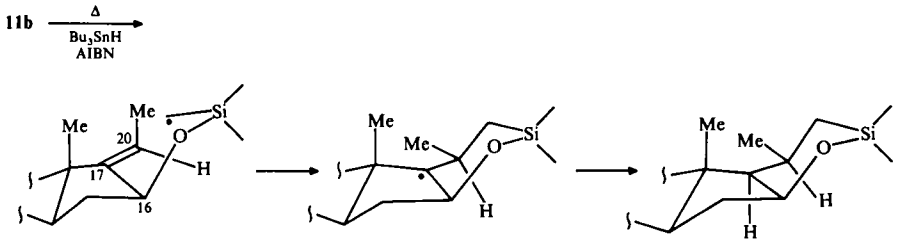
Silyl ether	Procedure[a]	Product and yield[b] (ratio)	Reference
 **(11a)**	F	 66%	20
 **(11b)**	F	 59%	20
 **(11c)**	F	no reaction	20
 **(11d)**	F	no reaction	20
 **(12)**	G	 40%[c] (1) (2)	21

[a] *Method F.* Cyclization was carried out by treatment of the ether with 1.5 equiv Bu_3SnH at reflux in benzene in the presence of a catalytic amount of AIBN for 10 h. Successive oxidation was carried out in methanol and THF (1:1) with 30% H_2O_2 (excess) and $KHCO_3$ (1.3 equiv) at reflux temperature for 16 h.
Method G. Cyclization was carried out by treatment of the ether with 1.5 equiv Bu_3SnH at 80 °C in benzene in the presence of a catalytic amount of AIBN. Successive oxidation was carried out in DMF with 30% H_2O_2 and KF at 60 °C. Cyclization was also tried by electrolysis; −1.2 V (*vs* SCE) in 0.2 M $LiClO_4$/DMF, vitamin B_{12a} (cat 12 mol%), VIS light; total yield of the ethers was only 6%.
[b] Isolated yields.
[c] Yield of the cyclic ether.

afforded *cis*- and *trans*-cyclic ethers, respectively. In contrast, the *Z*-allylic ethers, **11c**, and **11d**, did not yield a cyclized product. The result indicates that the *Z*-methyl group at $C_{(20)}$ obstructs radical cyclization with 6-*endo* mode. The cyclization process generates two chiral centers at the $C_{(17)}$ and $C_{(20)}$ positions. The chirality at $C_{(20)}$ directly depended on the chirality of the parent 16-hydroxy derivatives. On the other hand, both **11a** and **11b** yielded the 17α-H products selectively. Apparently these 16-hydroxy derivatives preclude formation of the alternative 17β-H products. This clear-cut stereoselective generation of two chiral centers at $C_{(17)}$ snd $C_{(20)}$ from both **11a** and **11b** indicates that the chirality was cleanly 'transmitted' from the stereodirecting $C_{(16)}$ α-bromo silyl ether group during free-radical-mediated cyclization.



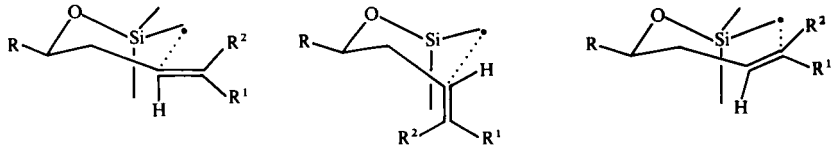
(26)



(27)

Selective 6-*endo* cyclization was also observed in the reaction of (bromodimethyl)silyl ethers of primary terpenoid alcohols[21]. The silyl ether **12** afforded products in the 6-*endo* mode by treatment with Bu_3SnH/AIBN or by electrolysis upon photoirradiation with a photoredox catalyst, that is, vitamin B_{12}. The exclusive formation of cyclopentane derivatives was ascribed to a concerted 6-*endo* → *cis*-5-*exo* 'tandem' cyclization.

d. Alternative 6-exo or 7-endo cyclizations. Dehalogenation in a 6-heptenyl system gives an alternative 6-*exo* or 7-*endo* cyclization, which is controlled only by methyl substitution at the olefin terminus as shows in Table 4[22]. The complete selectivity is rationalized in terns of the relative stabilities of the three transition states **A** (6-*exo-syn*), **B** (6-*exo-anti*) and **C** (7-*endo*). The radicals with a terminal methyl group (in the cases of **13b** and **13c**) led to selective 6-*exo-syn* cyclization. The result suggests that the methyl group at the terminal olefinic carbon inhibits 6-*exo-anti* and 7-*endo* cyclization with considerable steric hindrance in the transition state of **B** and **C**. In contrast, 7-*endo* cyclization of the radicals without methyl substitution (in the case of **13a**) indicates apparent relative stability of the transition state **C** over **A** or **B**.

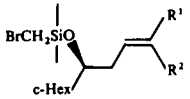
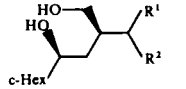
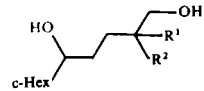
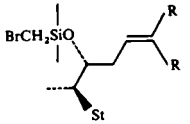
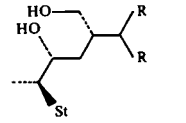
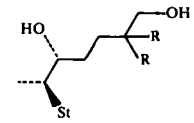
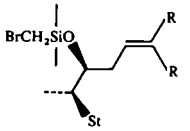
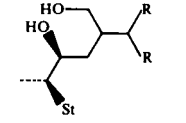
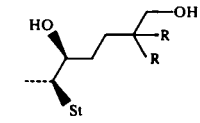


(A) 6-*exo-syn* (B) 6-*exo-anti* (C) 7-*endo*

The high degree of regio- and stereocontrol demonstrated in this novel type of free-radical-mediated chirality transmission process in a nonrigid, acyclic system suggests the suitability of this approach as a general method for the hydroxy-directed 1,3-asymmetric induction at an sp^2 center[22]. The stereoselective 6-*exo* α-silyl radical cyclization in combination with the subsequent oxidative cleavage allows convenient access to 1,4-diols with branched chains[22].

e. Selective 5-exo cyclization of alkyne systems. Cyclization of α-silyl-alkynyl radical has also been reported[23–25]. Selective formation of 1,3-diols as shows in Table 5 indicates

TABLE 4. Alternative 6-*exo* and 7-*endo* cyclization[22]

Silyl ether	Procedure[a]	Product and yield[b] (ratio)	
	H		
(13a) $R^1 = R^2 = H$		85%	87%
(13b) $R^1 = H$, $R^2 = Me$		83%	
(13c) $R^1 = R^2 = Me$			
	H		
(14a)[c] R = H		0%	80%
(14b)[c] R = Me		87%	0%
	H		
(15a)[c] R = H			80%
(15b)[c] R = Me		85%	

[a] *Method H.* Cyclization was carried out with Bu_3SnH generated *in situ* from a catalytic amount of Bu_3SnCl and an excess of $NaB(CN)H_3$ in refluxing *t*-BuOH for 12–16 h in the presence of a catalytic amount of AIBN. Successive oxidation of the cyclic ether was carried out by treatment with excess 30% $H_2O_2/KHCO_3$ in refluxing THF/MeOH for 2–3 h.

[b] Isolated yields.

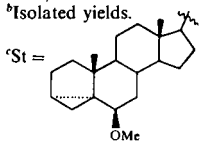
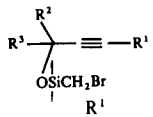
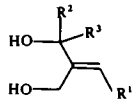
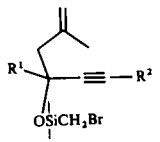
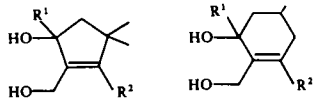
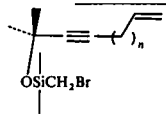
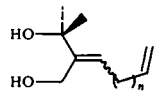
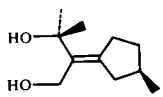
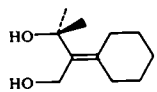
[c] St = 

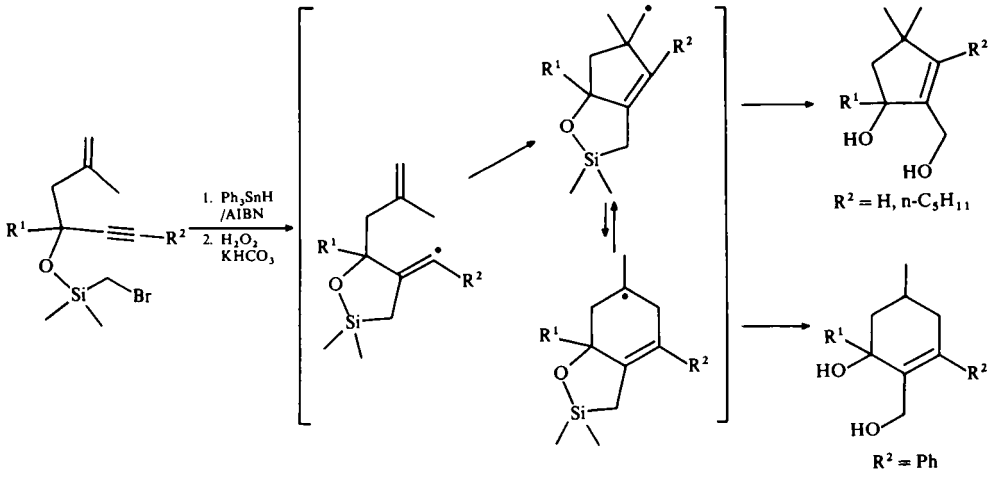
TABLE 5. Selective 5-*exo* cyclization of alkyne systems

Silyl ether	Procedure[a]	Product and yield[b] (ratio)	Reference
	I		23
R^1 R^2 R^3			
(16a) H n-C_5H_{11} H		77%	
(16b) n-C_8H_{17} H H		62	
(16c) H Me Me		69%	
(16d) n-C_4H_9 Bu H		65%	
	I		25
R^1 R^2			
(17a) H n-C_5H_{11}		79% 90 10	
(17b) H H		65% 100 0	
(17c) n-C_5H_{11} H		75% 100 0	
(17d) Ph H		80% 42 58	
		**18a, b, d** 	25
n		70% E/Z = 80/20	
(18a) 1			
(18b) 2			
(18c) 3		**18c**  	
(18d) 4		89% 5 95	

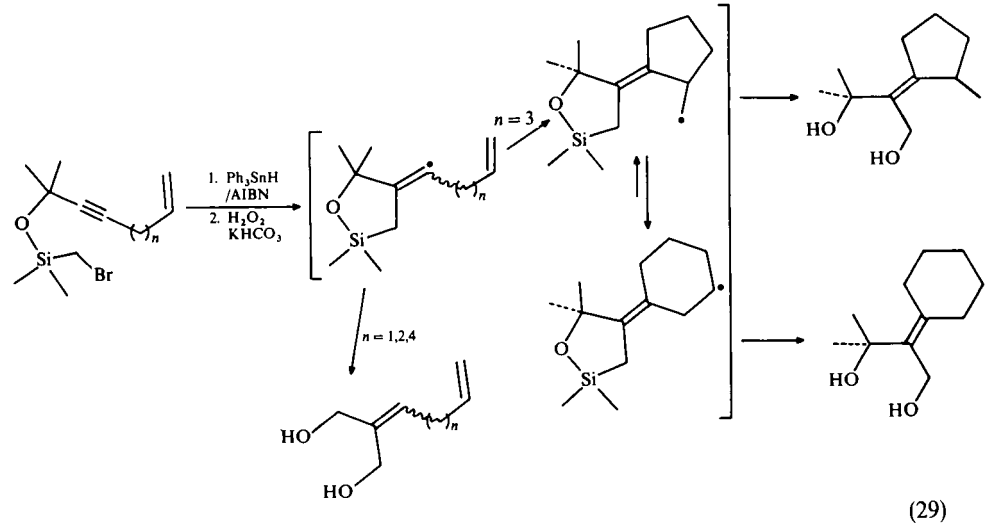
[a] *Method I.* Cyclization was carried out by slow addition of Ph_3SnH (1.1 equiv) and a catalytic amount of AIBN to the ether (0.025 M) in refluxing benzene. Successive oxidation was carried out by 30% H_2O_2 and $KHCO_3$ in THF/MeOH 1/1. The resulting diols were isolated by flash chromatography over silica gel.
[b] Isolated yields.

that all alkynyl radicals cyclized regioselectively in the 5-*exo* mode. However, in the cases of **17** and **18c**, efficient intramolecular trapping of the exocyclic vinyl radicals afforded cyclic products. The mode of the successive cyclization seems to be controlled by the stability of the vinyl radical. Thus, the terminal phenyl group (**17d**) enables the radical to cyclize in the 6-*endo* mode (58%) competitively to the 5-*exo* mode (42%)[25].

Radical cyclization of the substrates with an olefinic side chain of various lengths ($n = 1, 2, 3, 4$) afforded cyclic products only from the substrate where $n = 3$, and the rearranged *endo*-product was preferentially (95%) observed. The product distribution is



(28)



(29)

ascribed to the stability of the 6-*endo* radical produced by intramolecular radical trapping[25].

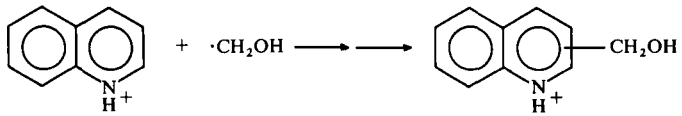
B. Hydroxymethylation of Heteroaromatics by Free-radical Sources

The electron-deficient nature of heteroaromatics is remarkably enhanced by protonation, and the protonated heteroaromatics became very reactive with nucleophilic reagents. From this viewpoint, the substitution reaction of heteroaromatics by nucleophilic carbon-centered free radicals in acidic conditions has been developed by Minisci and coworkers[3,28]. Several kinds of nucleophilic radicals, such as alkyl, acyl, α-oxylakyl,

aminocarbonyl and α-amidoalkyl radicals, have been applied to the substitution reaction[28]. For hydroxymethylation, thermal[28] or redox decomposition[11,28,29] of a radical source in methanol gives a primary electrophilic radical such as ·OH. This primary radical does not directly attach heteroaromatics but reacts with methanol to produce a hydroxymethyl radical, which in turn reacts with protonated heteroaromatics as shown in equation 30–32.

$$H_2O_2 \xrightarrow{Cr^{2+}} 2\cdot OH \tag{30}$$

$$CH_3OH + \cdot OH \longrightarrow \cdot CH_2OH + H_2O \tag{31}$$



(32)

Efficient regioselective substitution of protonated heteroaromatics by hydroxymethyl radicals makes this reaction highly attractive as a general method for functionalizing heteroaromatic bases. This system needs no special apparatus such as irradiation sources mentioned in the later sections. It is clear that the efficient generation of hydroxymethyl radicals is a key point for this system, and many radical sources have been investigated. In this section, we describe the recent progress of hydroxymethylation of heteroaromatics by free-radical sources.

1. Reaction efficiencies of free-radical sources

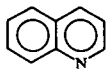
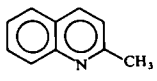
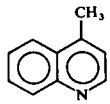
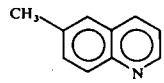
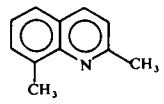
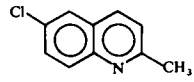
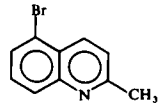
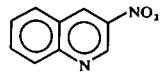
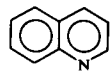
Radical sources used by Minisci's group are hydrogen peroxide, *t*-butyl hydroperoxide, ammonium peroxydisulfate, sodium perborate and peroxydicarbonate[3,28]. Palmer and McIntyre reported similar hydroxymethylation of quinoline derivatives by use of hydroxylamine-*O*-sulfonic acid (HOSA) in 1968[30]. Redox decomposition of HOSA was recently applied by Minisci's group[11] and the details will be discussed in the following section. The results of hydroxymethylation of these free-radical sources are summarized in Table 6.

There are noticeable differences in the conversions of quinoline, and ammonium peroxydisulfate generally gave good results. The yields of hydroxymethylation based on the conversion are generally quantitative and not dependant on the free-radical source. The substitution was observed to proceed selectively at the 2- and 4-positions of quinoline. In the reaction of unsubstituted quinoline, a mixture of 2- and 4-hydroxymethyl derivatives is obtained, and the ratio reported by Minisci's group[3] is 1:1 and the ratio by Palmer and McIntyre[30] is 55:25. At higher conversion, 2,4-dihydroxymethyl derivatives were also obtained, and the first hydroxymethyl group does not appreciably affect the reactivity of the heteroaromatic derivative[3].

Decomposition of a free-radical source in ethanol or isopropyl alcohol is supposed to induce formation of the corresponding hydroxyalkyl radicals. However, the reaction in ethanol gave the substitution product with a considerably lower yield than in methanol, and isopropyl alcohol did not give a substitution product[3]. This is consistent with the fact that *t*-hydroxyalkyl radicals are easily oxidized to the corresponding ketones as described in Section II.

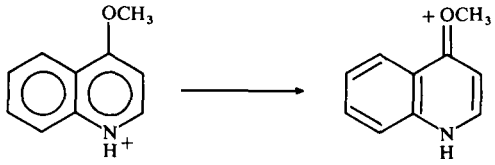
The quantitative analysis of relative reaction rates for 4-substituted quinolines was carried out for a dioxanyl radical which provides a 2-substitution product efficiently[3]. The relative rates were as follows: OMe, 0.12; Me, 0.75; H, 1; Cl, 2.7; COOEt, 7.1; CN 22. The remarkably low reactivity of 4-methoxyquinoline is explained by a reduced

TABLE 6. Hydroxymethylation of heteroaromatics by free-radical sources

Substrate	Radical source	Ratio[a]	Product	Yield[b] (%)	Ratio	Reference
	$(NH_4)_2S_2O_8$	1:0.2	2- and 4-CH_2OH	40[c]	8:2	3
	$(NH_4)_2S_2O_8$	1:2	2- and 4-CH_2OH	53	1:1	3
	t-BuOOH + Fe^{2+}	1:0.3	2- and 4-CH_2OH	23[c]	1:1	3
	$H_2O_2 + Cr^{2+}$	1:2	2- and 4-CH_2OH	27	—	3
	H_2NOSO_3H	1:3	2- and 4-CH_2OH	35	2:1	30
	$(NH_4)_2S_2O_8$	1:2	4-CH_2OH	86		3
	$NaBO_3$	1:2	4-CH_2OH	60		3
	Perkadox 26[d]	1:1	4-CH_2OH	45		3
	H_2NOSO_3H	1:3	4-CH_2OH	34		30
	$(NH_4)_2S_2O_8$	1:1	2-CH_2OH	43		3
	H_2NOSO_3H	1:3	2-CH_2OH	52		30
	H_2NOSO_3H	1:3	2- and 4-CH_2OH	—	2:1	30
	H_2NOSO_3H	1:3	2-CH_2OH	46		30
	H_2NOSO_3H	1:3	2-CH_2OH	57		30
	H_2NOSO_3H	1:3	2-CH_2OH	39		30
	H_2NOSO_3H	1:3	no reaction			30
	$(NH_4)_2S_2O_8$	1:2	1-CH_2OH	31		3

[a]Ratio of substrate and radical source.
[b]Yields are based on substrate used.
[c]Yield based on radical source.
[d]Bis(4-butylcyclohexyl)peroxydicarbonate.

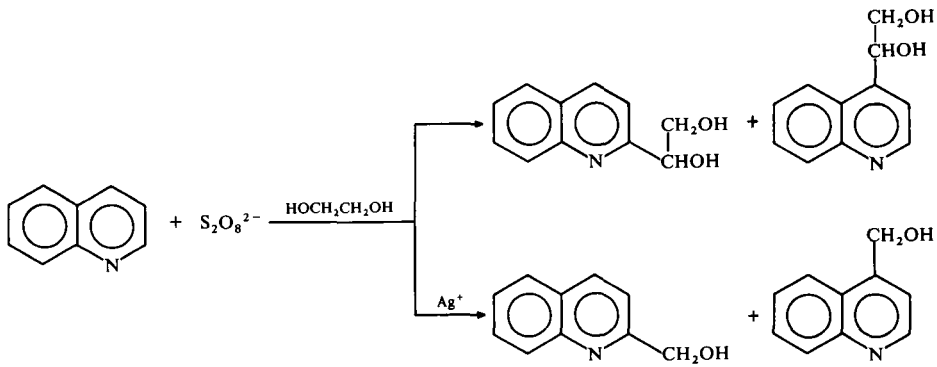
positive charge density at the reactive site due to a direct interaction to the protonated aza-group with a methoxyl substituent resulting in a 'quinonoid' form. Thus, the electron-accepting capacity of the heteroaromatic ring in the rate-determining step of the reaction is reduced.



(33)

2. Extended systems for hydroxymethylation of heteroarenes

The radical-induced hydroxymethylation of heteroaromatics has been extended by use of a redox reaction of metal ions[11,31]. The reaction of quinoline with ethylene glycol was initiated by peroxydisulphate, which results in 2- and 4-substitution of quinoline. In the presence of silver salts the main products of the reaction were again 2- and 4-hydroxymethyl derivatives[31].



(34)

In this reaction system, the key intermediate is an alkoxy radical ($HOCH_2CH_2O\cdot$) produced by oxidation of ethylene glycol by Ag^{2+}. Successive degradation of the alkoxy radical gives a hydroxymethyl radical. The redox processes indicated in equations 35–38 show that catalytic amounts of silver salts are effective for the production of hydroxymethyl radical.

$$S_2O_8^{2-} + Ag^+ \longrightarrow SO_4^{2-} + SO_4^{-\cdot} + Ag^{2+} \quad (35)$$

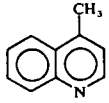
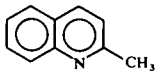
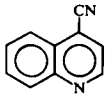
$$SO_4^{-\cdot} + Ag^+ \longrightarrow SO_4^{2-} + Ag^{2+} \quad (36)$$

$$HOCH_2CH_2OH + Ag^{2+} \longrightarrow HOCH_2CH_2O\cdot + H^+ + Ag^+ \quad (37)$$

$$HOCH_2CH_2O\cdot \longrightarrow \cdot CH_2OH + HCHO \quad (38)$$

Another extension of the hydroxymethylation is also achieved by redox reaction of a metal ion, in which degradation of hydroxylamine-*O*-sulfonic acid (HOSA) by a redox-chain mechanism results in an efficient hydroxymethylation of quinoline derivatives[11]. HOSA has been reported to induce a free-radical hydroxymethylation of quinoline, and

TABLE 7. Hydroxymethylation of quinolines by redox decomposition of HOSA (hydroxylamine-*O*-sulfonic acid)

Base	$FeSO_4$ (mmol)	Base/HOSA/H_2SO_4 (mmol)	$MeOH/H_2O$ (mL)	T (°C)	Product	Yield[a] (%)	Reference
	0.12	4: 4:4	8:4	20	2-CH_2OH	43	11
	4	4: 4:4	20:15	20	2-CH_2OH	41	11
	0	4:12:4	10:0	64	no reaction		11
	0	4:12:4	15:0.7	60	2-CH_2OH	57	11
	0	4:12:0	10:0	64	2-CH_2OH	18	11
	0	4:12:0	10:0	64	2-CH_2OH	52	30
	0	4:12:0	10:0	64	4-CH_2OH	34	30
	0.12	4: 4:4	8:4	20	4-CH_2OH	17	11
	0.12	4:12:4	8:4	20	4-CH_2OH	50	11
	1.2	4:12:4	8:4	20	4-CH_2OH	61	11
	1.2[b]	4:12:4	8:4	20	4-CH_2OH	68	11
	0.12	4: 4:4	4:2	20	2-CH_2OH	28	11

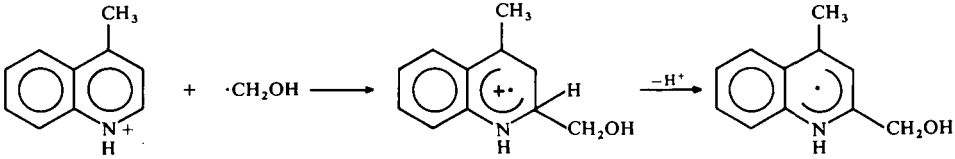
[a]Yields are based on the substrate.
[b]Reaction was carried out in the presence of iron powder (1.2 mmol).

the authors mentioned the absence of a significant effect of Fe^{2+} ion[30]. In a recent reinvestigation of this reaction system[11], however, an apparent positive effect of Fe^{2+} ion was observed as shown in Table 7. Without Fe^{2+} ion, the reaction efficiency depended highly on the temperature, acidity of the medium and the amount of water. The conversion increased with increasing temperature, and no appreciable reaction took place at temperatures lower than 50 °C. However, the presence of Fe^{2+} considerably enhanced the efficiency and hydroxymethylation took place even at 20 °C, and the exothermic reaction was completed in a few minutes. Furthermore, when ferrous sulfate was used in the presence of iron powder, in order to minimize the ratio Fe^{3+}/Fe^{2+}, a very high yield of hydroxymethylation was obtained.

Initiation

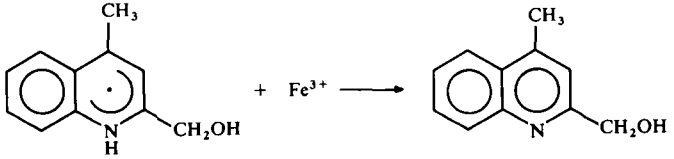
$$^{+}NH_3OSO_3^{-} + Fe^{2+} \longrightarrow NH_3^{+\cdot} + Fe^{3+} + SO_4^{2-} \quad (39)$$

$$NH_3^{+\cdot} + CH_3OH \longrightarrow NH_4^{+} + \cdot CH_2OH \quad (40)$$



(41)

Propagation



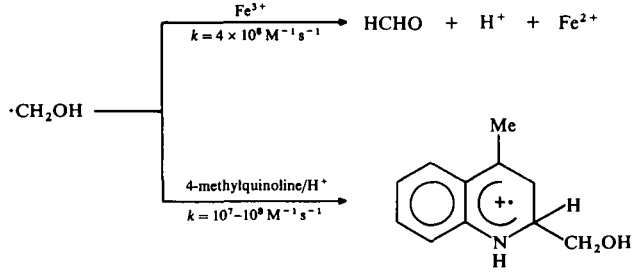
(42)

Termination $$NH_3^{+\cdot} + Fe^{2+} \longrightarrow NH_3 + Fe^{3+} \quad (43)$$

Although no mechanistic investigation was carried out, it is clear that the Fe^{2+}/Fe^{3+} redox system catalyzes the substitution. In the absence of Fe^{2+}, the reaction is observed only at high temperatures, and the low efficiency is attributed to the decomposition rate of HOSA and to ionic side reactions. Hydrolysis of HOSA to yield hydroxyammonium cation and hydrogen sulfate anion, neither of which are efficient for the substitution, is not negligible above 25 °C, and this reaction decreases the efficiency of the substitution[11].

$$NH_3^+OSO_3^- + H_2O \longrightarrow NH_3OH + HSO_4^- \quad (44)$$

In the presence of Fe^{3+}, oxidation of hydroxyalkyl radical by Fe^{3+} may compete with the substitution as described in Section II. In fact, hydroxyethylation became inefficient and no substitution was observed with isopropyl alcohol. However, the oxidation of hydroxymethyl radical is not predominant and can be reduced by the design of reaction conditions[11]. The estimated oxidation rate constant of the hydroxymethyl radical by Fe^{3+} is about $4 \times 10^8\ M^{-1}\ s^{-1}$, while the addition rate constant to protonated 4-methylquinoline is supposed to be in the range of 10^7–$10^8\ M^{-1}\ s^{-1}$.

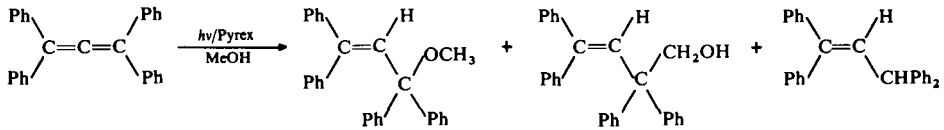


(45)

C. Photochemical Hydroxymethylation

1. *Hydroxymethylation via photochemical hydrogen abstraction*

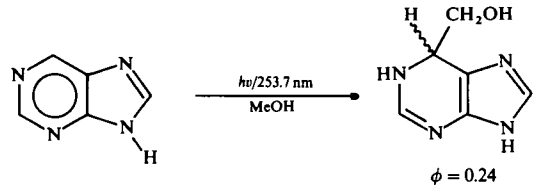
Photoirradiation of unsaturated substrates in methanol results in hydroxymethylation via hydrogen abstraction from methanol by the photoexcited triplet state as described in Section II, but the yield is not satisfactory. The main reason is the inefficient hydrogen abstraction from methanol, which is considerably slower than in ethano and isopropyl alcohol. Thus, even if hydroxymethylation is observed in a photoreaction of an unsaturated substrate, it is often only a minor reaction and the main reaction is methoxylation via the photoexcited singlet state. A typical example is photoaddition of methanol to cumulene. The product ratio of the methoxyl, hydroxymethyl and dihydro derivatives was 10:1:1, respectively[32].



10 mM total yield > 95%

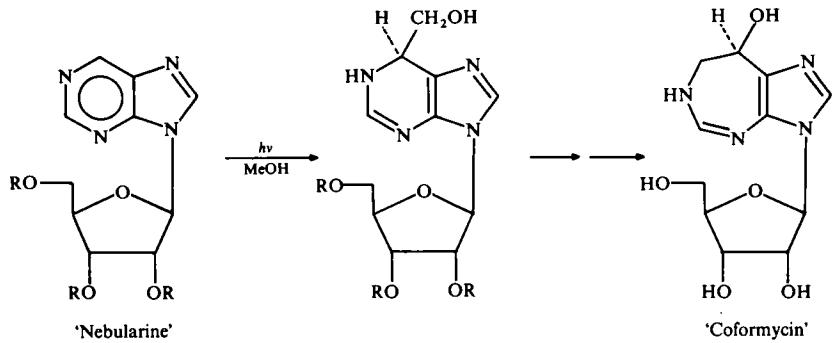
(46)

The number of papers dealing with hydroxymethylation via photoexcited states of a substrate[33-35] is much less than that of the photochemical methoxylation via singlet states. However, efficient hydroxymethylation via the photoexcited state of a substrate has been observed in the case of ribofuranosylpurine for the synthesis of Coformycin[36]. In the earlier studies of photochemical reactions of nucleic acid components, photoaddition of alcohols to purine ring resulting in hydroxyalkylation at $N_{(1)}$ position has been reported[37].



(47)

Extension of this reaction to nucleosides has been carried out in connection with the synthesis of Coformycin, which is an inhibitor of adenosine deaminase. Evans and Wolfenden reported that photoirradiation of 9-(β-D-ribofuranosyl)purine (Nebularine) in methanol gives three hydroxymethylation products, two 6-diastereomers of 1,6-dihydro-6-(hydroxymethyl)nebularine and the oxidatively aromatized 6-(hydroxymethyl)nebularine[38]. Umezawa and his coworkers found that photoreaction of 2',3',5'-tri-*O*-acetylnebularine gave a 1,6-dihydro-6-(hydroxymethyl) adduct in a very high efficiency (96% yield), and the hydroxymethylation product was considered to be free from isomeric impurities[39,40]. The resulting hydroxymethyl derivative was easily converted to Coformycin[39,40]. However, their reinvestigation in 1983 shows that Nebularine gave the same three major products found originally by Evans and Wolfenden[38]. The X-ray diffraction of the major intermediate product indicates the structure of 1,6-dihydro-6-(*S*)-(hydroxymethyl)-9-(β-D-ribofuranosyl)purine[41].



(48)

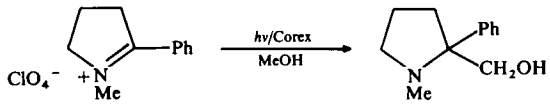
In contrast, more recent results reported by Robbins and his coworkers show that this photohydroxymethylation has no significant stereoselectivity[36]. In any event, these studies indicate that direct photolysis of the substrates can induce efficient hydroxymethylations from the synthesis of natural products.

2. *Hydroxymethylation via photochemical oxidation of methanol*

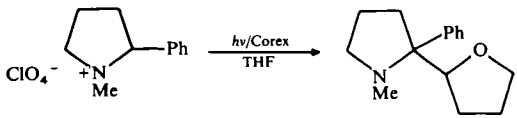
One-electron oxidation of methanol by photoredox reaction provides a hydroxymethyl radical in high efficiency as described in Section II. Thus, efficient hydroxymethylation

is expected for a photoredox reaction which is considerably more efficient than the reaction via hydrogen abstraction. This section is concerned with one-electron oxidation of methanol by photoredox reaction and successive hydroxymethylation of a substrate.

a. Reaction of directly photoexcited substrate. There are only few, but noticeable, examples of photochemical hydroxymethylation via direct electron transfer from solvent to a photoexcited substrate[42,43]. 2-Phenyl and 2-isobutenyl-1-pyrrolinium salts afforded solvent adducts upon photoirradiation in alcohols or ethers which have active α-hydrogens and low ionization potentials[42]. The fluorescence of 2-phenyl-1-pyrrolinium perchlorate is efficiently quenched by the solvents which is consistent with the product formation. The deuterium isotope effects on the fluorescence quenching by methanol, k_qCH_3OH/k_qCD_3OH and k_qCH_3OH/k_qCH_3OD, were 1.15 and 1.36, respectively. These values suggest a fluorescence quenching pathway via electron transfer and successive proton transfer reactions, both of which contribute to the overall rate[42].

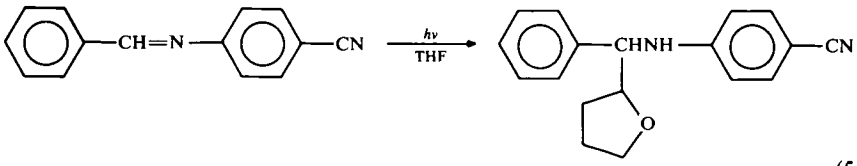


43% $\phi = 0.011$ (49)



42% $\phi = 0.015$ (50)

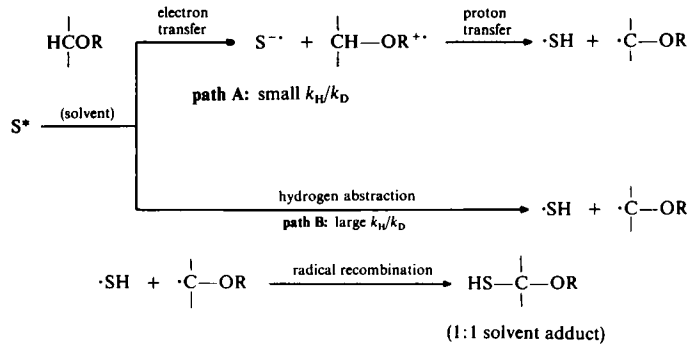
Recently, similar photochemical solvent additions to 4'-cyano-benzylideneaniline (CBA) via the electron transfer process has been reported. Photoirradiation of CBA in tetrahydrofuran or other electron-donating solvents gave solvent adducts regioselectively, and the mechanism was confirmed by deutrium isotope effects on the product formation[43].



44% (51)

In both cases, photoexcitation of a substrate induces electron transfer from a solvent molecule to the photoexcited substrate resulting in a radical–ion pair, which affords a solvent adduct via proton transfer and successive coupling of the radicals. The difficult problem to prove the electron transfer mechanism (path A) is to overcome another reaction mechanism such as hydrogen abstraction by the excited state (path B) leading to the same result. Determination of deuterium isotope effects on the fluorescence quenching and on the product formation is a useful method to overcome the possibility of hydrogen abstraction[42,43], which is familiar for the photochemical reaction of nitrogen-containing substrates[44].

$$S \xrightarrow{h\nu} S^* \quad (S = \text{unsaturated substrate}) \tag{52}$$

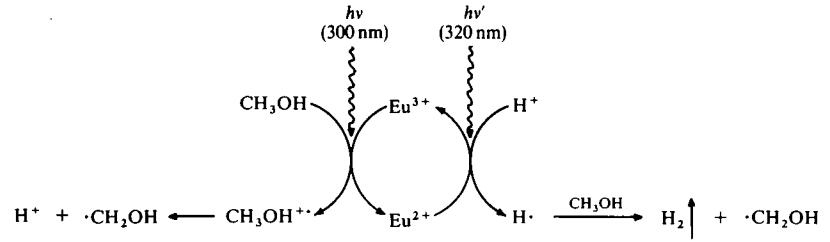


(53)

(54)

b. Eu^{3+}/Eu^{2+} photoredox reaction in methanol. Many kinds of photoredox catalysts, including organometalic compounds, have been applied to solar energy conversion systems. However, the redox properties of these catalysts are not suitable for synthetic reactions, and further search for novel photoredox catalysts has been required. Rare-earth ions are characterized by excellent fluorescence properties[45], and the quenching of the fluorescence by organic substrates may often induce electron transfer reactions. In fact, photochemical electron transfer reactions of Eu^{3+} leading to the oxidation of aromatic hydrocarbons[46], simple ligands[47] and water[48] have been reported. However, these reactions were not very useful as synthetic routes.

A methanol solution of $EuCl_3$ shows an absorption spectrum with maxima at 230 nm and 275 nm, and the latter band was assigned to a charge transfer (CT) band between methanol and Eu^{3+}. Photoirradiation of the CT band induced evolution of hydrogen gas and simultaneous formation of a new absorption band[49] around 320 nm which was assigned to Eu^{2+}. The fact indicates that a photoredox cycle of Eu^{3+}/Eu^{2+} is operative by photoirradiation of Eu^{3+} in methanol. Evolution of hydrogen gas is attributable to the reduction of a proton by Eu^{2+}, and the resulting hydrogen atom abstracts a hydrogen atom from methanol to afford a hydrogen molecule and a hydroxymethyl radical. The following ion–molecule reaction also provides a hydroxymethyl radical as described in Section II. Formation of ethylene glycol and formaldehyde indicates that the hydroxymethyl radical is quenched by both recombination and oxidation. The turn-over number of the catalyst for the hydrogen evolution was more than 1000, which demonstrates the high efficiency of the photoredox catalyst.



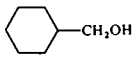
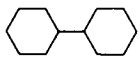
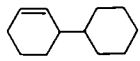
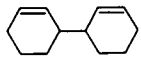
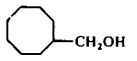
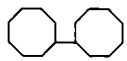
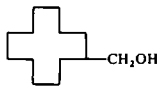
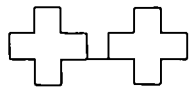
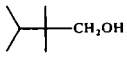
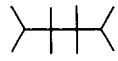
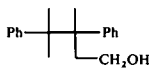
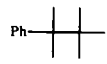
(55)

$$2 \cdot CH_2OH \longrightarrow HOCH_2CH_2OH \tag{56}$$

$$2 \cdot CH_2OH \longrightarrow HCHO + CH_3OH \tag{57}$$

$$\cdot CH_2OH + Eu^{3+} \longrightarrow HCHO + Eu^{2+} + H^+ \tag{58}$$

TABLE 8. Reaction of alkenes by the Eu^{3+}/Eu^{2+} photoredox system in MeOH[a]

Alkene	Conc. (mM)	Conv. (%)	Product and yield (%)[b]			
						
	100	71	49	22	16	2
	500	49	3	7	15	15
						
	100	78	52	25		
	500	50	8	31		
						
	100	64	42	36		
	500	43	7	61		
						
	100	81	37	4	26	
	500	50	13	7		
						
	50	100	24	50		

[a]Irradiation conditions: $[EuCl_3 \cdot 6H_2O] = 5$ mM, under Ar atmosphere, high-pressure mercury lamp + Pyrex filter, 8 h.
[b]Based on conversion.
[c]Irradiation time: 3 h.

The Eu^{3+}/Eu^{2+} photoredox reaction in the presence of a simple alkene afforded products of hydroxymethylation and dimerization with noticeable amounts of hydrogen gas[49] as shown in Table 8. The ratio of the products and yield of hydrogen gas depended on the concentration of alkene. Hydroxymethylation and hydrogen evolution were predominant under dilute conditions. On the other hand, dimer formation was predominant under high concentrations. These facts indicate that a hydrogen atom reacts competitively with methanol and alkene leading to a hydrogen molecule and primary radicals, such as hydroxymethyl radicals and alkyl radicals. These primary radicals undergo successive reactions resulting in formation of the final products. In contrast, reaction of an aryl-substituted alkene gave a dimeric product predominantly without hydrogen evolution[50]. The product distribution is supposed to depend on the reactivity of the alkene with hydrogen atoms on the one hand and with hydroxymethyl radicals, on the other, and on the stability of the resulting primary radicals[49,50].

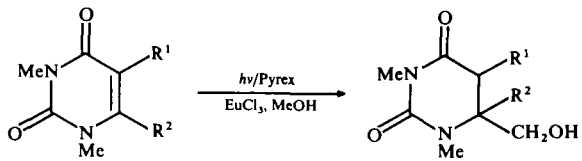
The redox potential of Eu^{2+} in the ground and the photoexcited states were estimated to be -0.43 V[51] and -2.4 V[52] (Vs NHE), respectively. The highly negative redox

TABLE 9. Reaction of 1,3-dimethyluracil and its derivatives by the Eu^{3+}/Eu^{2+} photoredox system in MeOH[a]

Substrate		Conc.	Irrad.	Conv.	Yield[b]
R^1	R^2	(mM)	time (h)	(%)	(%)
H	H	20	3	100	84
		100	6	89	98
		200	8	66	95
CH_3	H	100	5	88	91[c]
F	H	100	5	64	78[c]
Cl	H	50	5	71	57[c]
			12	100	32 (35)[d]
H	CH_3	100	5	8	40

[a]Irradiation conditions: $[EuCl_3 \cdot 6H_2O] = 10$ mM, high-pressure mercury lamp + Pyrex filter, under Ar atmosphere.
[b]Based on conversion.
[c]Mixture of diastereomers.
[d]Yield of a dehalogenation product (1,3-dimethyl-5-hydro-6-hydroxymethyluracil).

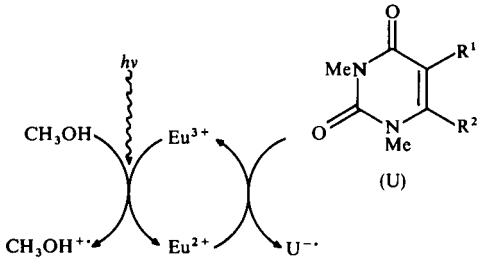
potential of $*Eu^{2+}$ (photoexcited states of Eu^{2+}) is expected to induce one-electron reduction of a substrate. 1,3-Dimethyluracil has a much more positive redox potential than the simple alkenes, which showed only radical reactions. The Eu^{3+}/Eu^{2+} photoredox reaction in the presence of 1,3-dimethyluracil afforded a 6-hydroxymethyl-5,6-dihydro derivative in a quantitative yield. Other uracil derivatives also afforded similar methanol adducts regioselectively as shown in Table 9[6].



(59)

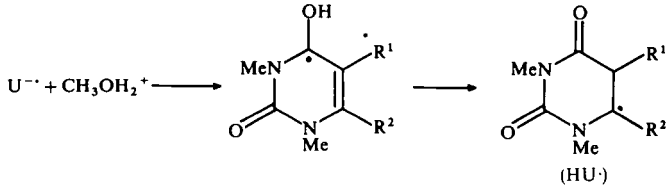
The regioselectivity of this reaction was explained by a mechanism involving one-electron reduction of uracil by photoexcited Eu^{2+}, in which protonation of the resulting radical anion leads regioselectively to the 6-yl radical. Efficient fluorescence quenching of Eu^{2+} by uracil derivatives was observed, the rate of which depended strongly on the substituent at the 5-position (Cl, $2.0 \times 10^9\ M^{-1}\ s^{-1}$; H, $7.4 \times 10^8\ M^{-1}\ s^{-1}$; CH_3, $3.2 \times 10^8\ M^{-1}\ s^{-1}$). The fact indicates that the fluorescence quenching proceeds via electron transfer from $*Eu^{2+}$ to uracil derivatives[53]. Deutrium isotope effects supported regioselective formation of the 6-yl radical via the radical anion. When a CH_3OD solution of 1,3-dimethylthymine and $EuCl_3$ was irradiated to about 50% conversion, the incorporation of a deuterium atom into the hydroxymethyl derivative was observed by MS to be 99% and the deuterium was found preferentially at the 5-position by NMR. On the other hand, the deuterium incorporation in the recovered thymine was negligibly small (less than 3%). These facts indicate that an alcoholic proton adds selectively to the 5-position, preferably via the radical anion (equation 62) because such a high regioselectivity cannot be reasonably explained by a free-radical addition to the C=C double bond of uracil derivatives. When 1,3,6-trimethyluracil was irradiated in CH_3OD in the presence of $EuCl_3$ for 40 h, about 50% incorporation of a deuterium atom in the 5-position of the recovered trimethyluracil was observed. No deuterium incorporation was detected after 24 h in the dark. Thus, the very low reactivity of 1,3,6-trimethyluracil can be

explained by the fact that the trimethyluracil-6-yl radical does not readily recombine with a hydroxymethyl radical to give the hydroxymethyl derivative due to the steric hindrance of the 6-methyl group. The radical mainly undergoes deprotonation to recover trimethyluracil, which causes the deuterium incorporation.

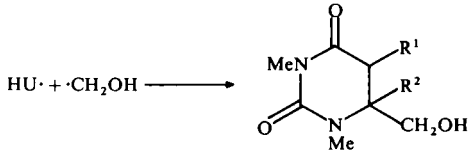


(60)

$$CH_3OH^{+\cdot} \xrightarrow{CH_3OH} \cdot CH_2OH + CH_3OH_2^{+} \tag{61}$$



(62)

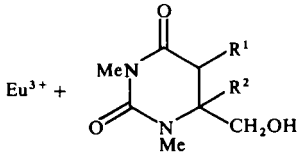


(63)

It is noticeable that dimeric products were not observed even in trace amounts. This fact suggests the presence of an interaction between Eu^{3+} and uracil in the dark, leading to the 'long-range' electron transfer mechanism (equation 64) described by Sato and coworkers[54].

$$[CH_3OH\cdots Eu^{3+}\cdots U] \xrightarrow{h\nu} [CH_3OH^{+\cdot}\cdots {}^{*}Eu^{2+}\cdots U] \longrightarrow$$

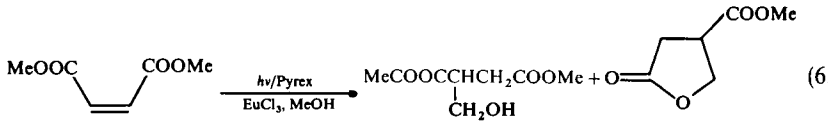
$$\xrightarrow{H^+} [\cdot CH_2OH\cdots Eu^{3+}\cdots U^{-\cdot}] \longrightarrow [\cdot CH_2OH\cdots Eu^{3+}\cdots HU\cdot] \longrightarrow$$



(64)

The Eu^{3+}/Eu^{2+} photoredox reaction in the presence of dimethyl maleate afforded a hydroxymethylation product and its lactone in high yields. However, dimethyl maleate

quenched the fluorescence of $*Eu^{2+}$ with a considerably lower rate constant than those of the uracils. The fact suggests that the reaction of dimethyl maleate is initiated by addition of a hydroxymethyl radical, and the resulting radical is reduced by Eu^{2+} in the dark to give a carbanion which affords the hydroxymethyl derivative by protonation[55].



(65)

As described above, the Eu^{3+}/Eu^{2+} photoredox reaction in methanol is of importance as an efficient hydroxymethylation method of unsaturated substrates. Note that the reaction mechanism is highly dependent on the reduction potentials of the substrates.

D. Radiation-induced Hydroxymethylation

1. Hydroxymethylation of substituted pyridinium ions

Generation of hydroxymethyl radicals by free-radical sources has been applied to substitution of heteroaromatics as described in Section III.B. Sugimori's group has applied the radiation process to the substitution of pyridine derivatives, such as pyridinecarboxylates[56,57], pyridinecarboxamides[58] and pyridinecarbonitriles[59]. In the cases of pyridinecarboxylate and pyridinecarboxamide, γ-ray irradiation in acidic methanol resulted in the substitution by a methyl or a hydroxymethyl group, and the reactivity

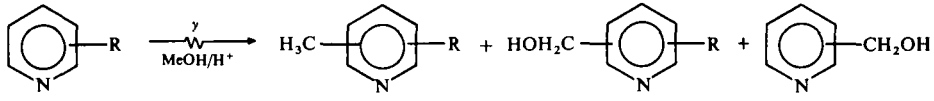
TABLE 10. Reaction of pyridinium derivatives induced by γ-ray irradiation in MeOH

Substrate	Substitution product	*G* value
Methyl 2-pyridinecarboxylate	4-Me	1.29
	4,6-diMe	0.10
	4-Me-6-CH_2OH	0.16
Methyl 3-pyridinecarboxylate	6-Me	0.58
	4-Me	0.21
	4,6-diMe	0.31
Methyl 4-pyridinecarboxylate	2-Me	0.16
	2-CH_2OH	0.23
2-Pyridinecarboxamide	4-Me	0.55
	4-Me-6-CH_2OH	0.28
3-Pyridinecarboxamide	4-Me	0.26
	6-Me	0.97
4-Pyridinecarboxamide	2-CH_2OH	0.22
2-Pyridinecarbonitrile	4-Me	0.86
	2-CH_2OH-pyridine[a]	0.15[b]
3-Pyridinecarbonitrile	4-Me	1.27
	5-Me	1.15
	5-CH_2OH	0.06[b]
4-Pyridinecarbonitrile	2-Me	1.60
	4-CH_2OH-pyridine[a]	0.37[b]

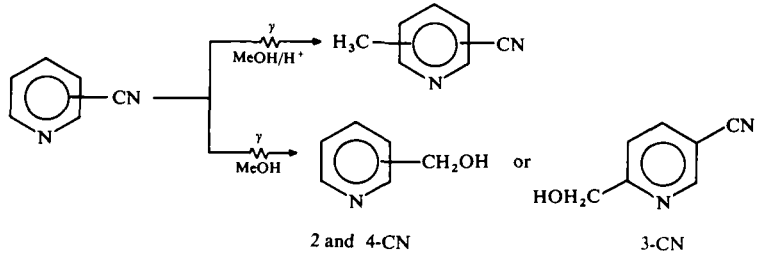
[a]A hydroxymethyl pyridine was produced by substitution of a cyano group.
[b]Irradiation in the absence of sulfuric acid.

depended upon the position of the substituent as shown in Table 10. In general, the product distribution shows considerably higher efficiency of methylation than hydroxymethylation. The similarities of the reactions of pyridinecarboxylates and pyridinecarboxamides suggest that the mechanism for the esters should be parallel to that of the amides[58]. The predominant methylation is inconsistent with the yields of $\cdot CH_2OH$ and $\cdot CH_3$ as shown by the G values, 2.7 and 0.2, respectively[60]. Thus, the hydroxymethyl radical was presumed to be the common active species both for methylation and for hydroxymethylation[56,58].

In contrast, γ-ray irradiation of 2- and 4-pyridine carbonitriles in acidic methanol afforded only methylation products. The methylation in the presence of sulfuric acid can be explained by a mechanism initiated by an electron transfer from the hydroxymethyl radical to the protonated pyridine carbonitriles[59]. On the other hand, substitution of a cyano group by a hydroxymethyl group was observed in the absence of sulfuric acid. The reactions under argon are similar to those under N_2O, with respect to the products and their yields. The fact indicates that both the solvated electron and the hydroxymethyl radical should play a role in the substitution reactions[59].



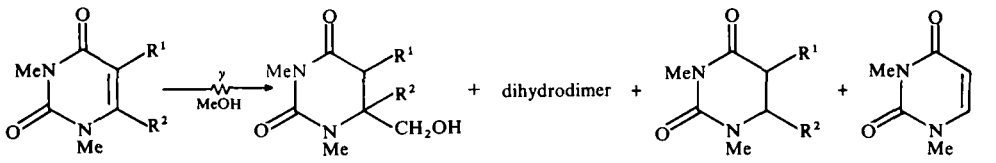
R = $COOCH_3$, $CONH_2$ (66)



(67)

2. Hydroxymethylation of 1,3-dimethyluracils

As described in Section II, the primary process for the γ-radiolysis of methanol solutions is an ionization of the methanol producing radical cations of methanol and solvated electrons. These primary species are transformed into hydroxymethyl radicals and the radical anions of the substrate. Thus, γ-radiolysis of uracil derivatives in methanol provides a quite similar reaction system to that of the photoredox reaction of Eu^{3+}/Eu^{2+}



(R^1 = Br, R^2 = H)

(68)

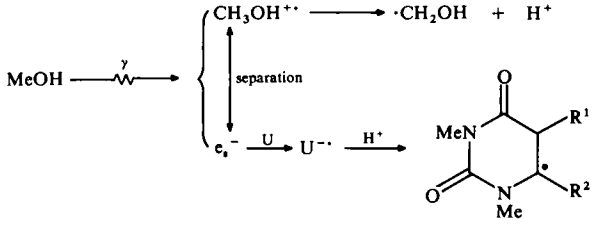
TABLE 11. Reaction of 1,3-dimethyluracil and its derivatives induced by γ-ray irradiation in MeOH[a] (See equation 68)

Substrate		Conv.		Product yield (%)[b]	(G-value)[c]	
R^1	R^2	(%)	5-H-6-CH_2OH	dihydrodimer	5,6-diH	dehalogenation[d]
H	H	76	77(6.6)	2(0.1)	0	—
CH_3	H	46	47(2.4)	11(0.6)	7(0.4)	—
H	CH_3	12	80(1.1)	0	20(0.3)	—
F	H	72	28(2.3)	23(0.9)	0	0
Cl	H	63	22(1.6)	34(1.2)	0	trace
Br	H	48	3(0.2)	0	0	24(1.3)

[a]Irradiation conditions; [1] = 0.1 M, Ar saturated, RT, Dose = 0.1 MGy.
[b]Based on conversion.
[c]G-value is a radiation yield (molecular amount at 100 ev).
[d]Dehalogenation of a halouracil resulted in formation of 1,3-dimethyluracil.

and might become an alternative method for the regioselective hydroxymethylation which was achieved by the photochemical reactions as described in Section IIIC. It has been shown that γ-ray irradiation of 1,3-dimethyluracil in methanol induces regioselective hydroxymethylation at the 6-position[7]. The formation of a dihydro dimer was also observed as a minor product, though the structure was not specified. Other derivatives also undergo similar reactions as shown in Table 11.

The regioselective formation of hydroxymethyl derivatives is reasonably explained by the mechanism via a radical anion which is similar to that of the Eu^{3+}/Eu^{2+} photoredox reaction[6]. Regioselective hydroxymethylation takes place in an almost quantitative yield in the photoredox reactions, while in the γ-radiolysis the yield of the main product is lower and formations of dimer and dihydro products are also, observed, especially in the cases of 5-substituted derivatives. These different behaviors in the two systems may be explained by the different spatial distributions of the primary active species initially produced. γ-Ray irradiation of methanol induces ionization of methanol with a very high energy, which leads to solvation of the ejected electron at a place far from the methanol radical cation. Accordingly, the relatively long distance between a hydroxymethyl radical and uracil radical anion leads to homo-coupling of the radicals, resulting in the dimer products. On the other hand, in the photoredox reaction, Eu^{3+} catalyzes the electron transfer from methanol to the uracil, and the methanol radical cation and the uracil radical anion are expected to be formed as a geminate pair. Therefore, the very efficient following reactions between the geminate pair provide the selective hydroxymethylation without dimer formation.

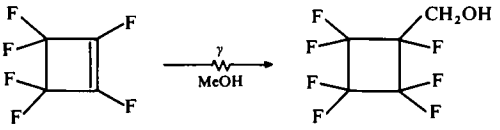


(69)

3. *Hydroxymethylation of haloalkenes*

In the early studies of radiation chemistry, it was reported that γ-ray irradiation of haloalkenes in methanol leads to hydroxymethylation[61–64]. Especially, the reaction of

perfluoroalkenes afforded hydroxymethylation product[61,62] with noticeably high efficiency.



84.7% (70)

$$CF_3CF{=}CF_2 \xrightarrow[MeOH]{\gamma} CF_3CHFCF_2CH_2OH \quad (71)$$

76.1%

IV. CONCLUSION

In this chapter, we have summarized the recent development of hydroxymethylation via radical intermediates. The hydroxymethyl radical has strong nucleophilicity and highly negative redox potential. The former promotes hydroxymethylation, while the latter leads to decay of the radical. The bilateral character requires a sophisticated reaction system for an efficient hydroxymethylation, which is achieved by the use of a redox reagent. Novel photoredox catalysts should be explored for synthetic purpose. Both inorganic and organic semiconductors, as well as hybrid catalysts by combination of a photoredox catalyst with various enzymes, will probably be of importance. The cyclization–desilylation process has possibilities of wide applications to the field of fine-chemical synthesis with excellent regio- and stereoselectivity. The radiation chemical process needs an expensive irradiation facility, which restricts wide application to synthetic reactions at present. However, for large-scale reactors in chemical industries, electron accelerators will supply convenient reaction systems.

Finally, we hope that development of the studies on hydroxymethyl radical and its alternates will induce further progress of synthetic reactions via various radical intermediates.

V. REFERENCES

1. B. J. Wakefield, *The Chemistry of Organolithium Compounds*, Pergamon, Oxford, 1978.
2. B. M. Trost and R. A. Kunz, *J. Am. Chem. Soc.*, **97**, 7152 (1975); S. R. Abrams, D. D. Nucciarone and W. Steck, *Can. J. Chem.*, **61**, 1073 (1983); Y. Gaoni, *Tetrahedron Lett.*, **23**, 5219 (1982); Y. Gaoni and A. Tomazic, *J. Org. Chem.*, **50**, 2984 (1985).
3. W. Buratti, G. P. Gardini, F. Minisci, F. Bertini, R. Galli and M. Perchinunno, *Tetrahedron*, **27**, 3655 (1971).
4. H. Nishiyama, T. Kitajima, M. Matsumoto and K. Itoh, *J. Org. Chem.*, **49**, 2298 (1984).
5. G. Stork and M. Kahn, *J. Am. Chem. Soc.*, **107**, 500 (1985).
6. A. Ishida, S. Toki and S. Takamuku, *J. Chem. Soc., Chem. Commun.*, 1481 (1985).
7. A. Ishida, S. Toki and S. Takamuku, *Radiat. Phys. Chem.*, **27**, 165 (1986).
8. C. E. Adams, J. W. Boag and B. D. Michael, *Trans. Faraday Soc.*, **61**, 492 (1965); H. Eibenberger, S. Steenken, P. O'Neill and D. Schulte-Frohlinde, *J. Phys. Chem.*, **82**, 749 (1978).
9. P. De Mayo, J.-P. Pete and M. Tchir, *Can. J. Chem.*, **46**, 2535 (1968); D. Pfau and M. Vilkas, *Compt. Rend.*, **254**, 1817 (1962).
10. P. J. Kropp, *J. Am. Chem. Soc.*, **95**, 4610 (1973).
11. A. Citterio, A. Gentile, F. Minisci, M. Serravalle and S. Ventura, *Tetrahedron*, **41**, 617 (1985).

12. J. Lilie, G. Beck and A. Henglein, *Ber. Bunsenges. Phys. Chem.*, **75**, 458 (1971).
13. P. S. Rao and E. Hayon, *J. Am. Chem. Soc.*, **96**, 1287 (1974).
14. K. D. Asmus, A. Henglein, A. Wigger and G. Beck, *Ber. Bunsenges. Phys. Chem.*, **70**, 756 (1966); G. P. Laroff and R. W. Fessenden, *J. Phys. Chem.*, **73**, 3794 (1969).
15. S. N. Bhattacharya and P. C. Mandal, *J. Chem. Soc., Faraday Trans. 1*, **82**, 2103 (1986); M. Venturi, S. Emmi, P. G. Fuochi and Q. G. Mulazzani, *J. Phys. Chem.*, **84**, 2160 (1980); D. W. Johnson and G. A. Salmon, *J. Chem. Soc., Faraday Trans. 1*, **73**, 256 (1977) and **75**, 446 (1979); M. Freiberg, W. A. Mulac, K. H. Schmidt and D. Meyerstein, *J. Chem. Soc., Faraday Trans. 1*, **76**, 1838 (1980); E. Papaconstantinou, *J. Chem. Soc., Faraday Trans 1*, **78**, 2769 (1982), John E. Packer, J. Moenig and B. C. Dobson, *Aust. J. Chem.*, **34**, 1433 (1981).
16. A. Kurek-Tyrlik and J. Wicha, *Tetrahedron Lett.*, **29**, 4001 (1988).
17. A. Kurèk-Tyrlik, J. Wicha and A. Zarechi, *J. Org. Chem.*, **55**, 3484 (1990).
18. R. V. Bonnert, M. J. Davies, J. Howarth and P. R. Jenkins, *J. Chem. Soc., Chem. Commun.*, 148 (1990).
19. G. Stork and J. Sofia, *J. Am. Chem. Soc.*, **108**, 6826 (1986).
20. M. Koreeda and I. A. George, *J. Am. Chem. Soc.*, **108**, 8098 (1986).
21. E. R. Lee, I. Lakomy, P. Bigler and R. Scheffold, *Helv. Chim. Acta*, **74**, 146 (1991).
22. M. Koreeda and L. G. Hamann, *J. Am. Chem. Soc.*, **112**, 8175 (1990).
23. E. Magnol and M. Malacria, *Tetrahedron. Lett.*, **27**, 2255 (1986).
24. G. Agnel, M. Malacria, *Synthesis*, 687 (1989).
25. M. Journet, E. Magnol, G. Agnel and M. Malacria, *Tetrahedron Lett.*, **31**, 4445 (1990).
26. K. Tamao, N. Ishida, T. Tanaka and M. Kumada, *Organometallics*, **2**, 1694 (1983); K. Tamao, N. Ishida and M. Kumada, *J. Org. Chem.*, **48**, 2120 (1983).
27. J. W. Wilt, *J. Am. Chem. Soc.*, **103**, 5251 (1981); *Tetrahedron*, **41**, 3979 (1985); A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron Lett.*, **26**, 373 (1985).
28. F. Minisci, *Synthesis*, 1 (1973.
29. A. Citterio, A. Gentile, F. Minisci, M. Serravalle and S. Ventura, *J. Chem. Soc., Chem. Commun.*, 916 (1983).
30. M. H. Palmer and P. S. MuIntyre, *Tetrahedron Lett.*, 2147 (1968).
31. T. Caronna, A. Citterio, L. Grossi, F. Minisci and K. Ogawa, *Tetrahedron*, **32**, 2741 (1976).
32. M. W. Klett and R. P. Johnson, *Tetrahedron Lett.*, **24**, 1107 (1983).
33. K. Yamada, H. Shosenji, S. Fukunaga and K. Hirahara, *Bull. Chem. Soc. Jpn.*, **49**, 3701 (1976).
34. A. Sugimori, T. Furihata, S. Mikayama, M. Yoshida and Y. Nakanishi, *Bull. Chem. Soc. Jpn.*, **55**, 2906 (1982).
35. M. Ogata and K. Kano, *J. Chem. Soc., Chem. Commun.*, 1176 (1967).
36. D. K. Buffel, C. McGuigan and M. J. Robbins, *J. Org. Chem.*, **50**, 2664 (1985).
37. H. Linschitz and J. S. Connolly, *J. Am. Chem. Soc.*, **90**, 2979 (1968); J. S. Connolly and H. Linschitz, *Photochem. Photobiol.*, **7**, 791 (1968).
38. B. Evans and R. Wolfenden, *J. Am. Chem. Soc.*, **92**, 4751 (1970).
39. M. Ohno, N. Yagisawa, S. Shibahara, S. Kondo, K. Maeda and H. Umezawa, *J. Am. Chem. Soc.*, **96**, 4326 (1974).
40. M. Shimazaki, S. Kondo, K. Maeda, M. Ohno and H. Umezawa, *J. Antibiot.*, **32**, 537 (1979).
41. M. Shimazaki, H. Nakamura, Y. Iitaka and M. Ohno, *Chem. Pharm. Bull.*, **31**, 3104 (1983).
42. J. Stavinoha, E. Bay, A. Leone and P. S. Mariano, *Tetrahedron Lett.*, **21**, 3455 (1980).
43. A. Ishida, D. Sugita and S. Takamuku, *J. Photochem. Photobioi., A, Photochem.*, in press.
44. D. G. Whitten and Y. J. Lee, *J. Am. Chem. Soc.*, **94**, 9142 (1972).
45. G. Blasse, in *Luminescence of Inorganic Solids* (Ed. R. D. Bartolo), Plenum Press, New York, 1978, 457.
46. G. Levin, *J. Phys. Chem.*, **82**, 1584 (1978); N. Sabattini, M. T. Indelli, M. T. Gandolfi and V. Balzani, *J. Phys. Chem.*, **86**, 3585 (1982).
47. N. Azuma, A. Matsumoto and J. Shiokawa, *Polyhedron*, **2**, 63 (1983).
48. Y. Haas, G. Stein and M. Tomkiewicz, *J. Phys. Chem.*, **74**, 2558 (1970).
49. A. Ishida, S. Toki and S. Takamuku, *Chem. Lett.*, 893 (1985).
50. A. Ishida, S. Yamashita, S. Toki and S. Takamuku, *Bull. Chem. Soc. Jpn.*, **59**, 1195 (1986).
51. M. Chou, C. Creutz and N. Sutin, *J. Am. Chem. Soc.*, **99**, 5615 (1977).
52. C. Creutz, *Inorg. Chem.*, **17**, 1046 (1978).
53. A. Ishida, S. Toki and S. Takamuku, *Chem. Lett.*, 117 (1986).

54. T. Sato, H. Kaneko and S. Yamaguchi, *J. Org. Chem.*, **45**, 3378 (1980).
55. A. Ishida, S. Yamashita and S. Takamuku, *Bull. Chem. Soc. Jpn.*, **61**, 2229 (1988).
56. K. Nakamura, T. Sugiyama, T. Suzuki and A. Sugimori, *Chem. Lett.*, 1203 (1977).
57. K. Nakamura, Y. Morita, T. Suzuki, T. Sugiyama and A. Sugimori, *Bull. Chem. Soc. Jpn.*, **52**, 488 (1979).
58. A. Sugimori, M. Nishijima and H. Itoh, *Bull. Chem. Soc. Jpn.*, **55**, 3055 (1982).
59. A. Sugimori, S. Mori, K. Maeda and M. Nishijima, *Chem. Lett.*, 769 (1984).
60. J. W. T. Spinks and R. J. Woods, *An Introduction to Radiation Chemistry*, 2nd ed., Wiley, New York, 1976, p. 415.
61. H. Muramatsu, S. Moriguchi and K. Inukai, *J. Org. Chem.*, **31**, 1306 (1966).
62. H. Muramatsu, K. Inukai and T. Ueda, *Bull. Chem. Soc. Jpn.*, **40**, 903 (1967).
63. H. Muramatsu, *J. Org. Chem.*, **27**, 2325 (1962).
64. T. Yumoto and T. Matsuda, *Nippon Kagaku Kaishi*, 369 (1972).

CHAPTER 13

Ozonolysis

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Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

I. INTRODUCTION

A. Preface

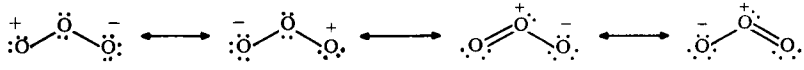
The present chapter, which deals with ozonolysis of organic molecules, is included in this volume as all intermediates and most of the initial products of ozonation of organic compounds contain peroxidic moieties. This subject was not covered in previous volumes of this series. The chapter covers cases where 'lysis' occurs, involving double or triple bonds. Ozonation of single bonds was discussed in detail in a previous volume[1] and will not be dealt with here. Ozonation of polymers is a subject which deserves a separate chapter and is not included in this review.

Water purification, although it often includes ozonolysis of organic materials, also lies beyond the scope of this chapter. The same is true for pulping and bleaching of wood by ozone, and for the interaction of organic materials in the ozone layer and other environmental problems which involve ozone.

A comprehensive review about ozonation in organic chemistry was provided by Bailey in two volumes[2] published in 1978 and 1982.

B. The Nature of the Ozone Molecule

The structure of the ozone molecule can be described as a resonance hybrid of four canonical forms (**1**–**4**). Each oxygen atom is sp^2-hybridized and the entire molecule is enclosed by a π-cloud containing four electrons. It has an angular structure. The obtuse angle and the oxygen–oxygen bond lengths were established by a microwave spectrum and were found to be 116° 45′ and 1.278 Å, respectively[3a]. The existence of a cyclic isomer of ozone in low concentration was also suggested[3b]. A ground-state diradical structure for ozone was concluded by *ab initio* calculations using generalized valence-bond and configuration interaction methods[3c]. Ozone is a reactive gas, which is able to function as an electrophile[4], a nucleophile[5], a 1,3-dipole[6] and a diradical[7]. In fact, most of the mechanistic studies on ozonolysis point at the 1,3-dipolar and electrophilic properties or a combination of both as the main explanation of the initial attack of ozone[6,8].



(1) (2) (3) (4)

C. Ozonation Techniques

1. Source of ozone

Ozone is generally produced as a mixture of ozone and oxygen, generated by electric discharge of oxygen. The techniques involved in its generation were summarized in the early reviews by Long[9] and Bailey[10] and other practical books[11]. There are several types of commercially available 'ozonators' for this purpose. An alternative way of producing ozone and its use in ozonolysis were described[12] by Mazur and coworkers, and consist of microwave discharge of oxygen.

2. Gas–liquid phase ozonation

Most of the ozonations are carried out by this method. The ozone–oxygen mixture is passed through a solution of the substrate, usually at low temperatures. The nature of the solvent has an important effect on the reaction. The solvents used in ozonolysis

are divided into two categories: participating and nonparticipating solvents. The former tend to react with the intermediate products of ozonation and thus bring about different products. The various nonparticipating solvents affect the rate of reaction, the selectivity and the stereochemistry of the products. These effects are discussed in the relevant sections. Ozonations in super acids, like magic acid ($FSO_3 + SbF_6$), lead to oxidation of alkanes[13a], alcohols, aldehydes and ketones[13b]. However, these are beyond the scope of this chapter.

3. *Liquid phase ozonation*

For kinetic studies, previously prepared solutions of ozone in CCl_4, or other chlorinated solvents, were introduced to solutions of substrates[8]. Recently, fluorinated hydrocarbons were used as efficient solvents for O_3 in ozonolysis of organic compounds[14].

4. *Gas phase ozonation*

Schönbein, who was the first chemist to carry out ozonolysis, did it in the gase phase[15]. The present major interest in gas phase reactivity of ozone stems from the realization that the ozone layer which protects the globe from UV light is being destroyed by reaction with organic vapors. Gas phase ozonolyses of olefins, acetylenes and other organic compounds are studied intensively due to their industrial interest, as well as in mechanistic studies. The differences in kinetics and product compositions between the gas phase and liquid phase ozonolysis are discussed in the following sections.

5. *Solid–gas phase ozonation*

The reaction of gaseous ozone with solid organic compounds has been studied in limited cases[16]. The ozonolysis of *trans*-stilbene was faster than that of some of its bulky derivatives, which were slow and incomplete[16].

6. *Dry ozonation*

a. Ozonation on silica gel. This procedure involves the preadsorption of the substrate on silica gel followed by adsorption of ozone at $-78\,^{\circ}C$ and allowance of time for the mixture to react as it warms slowly to room temperature. The technique was first reported[17] in 1975 by Mazur's group. This procedure is especially suitable for the oxidation of alkanes. It is very regioselective and the selectivity can be controlled by choosing the proper concentration of the substrate. It is also free from any competition with solvents. An excellent review on this subject was given in a previous volume[1].

b. Ozonation on polyethylene. A recent development is the ozonolysis of olefins adsorbed on polyethylene[18]. This procedure afforded selective ozonolysis and the isolation of products which were not accessible by ozonolysis in solution[18,19].

c. Oxidation of alkanes with O_3 on MgO was described[20] in 1980.

7. *Miscellaneous techniques*

Ozonolysis under chemiluminescence mimetic conditions has been carried both in micellar and in homogeneous conditions[21]. The influence of ultrasound on the reaction path of alkene ozonolysis has also been investigated[22].

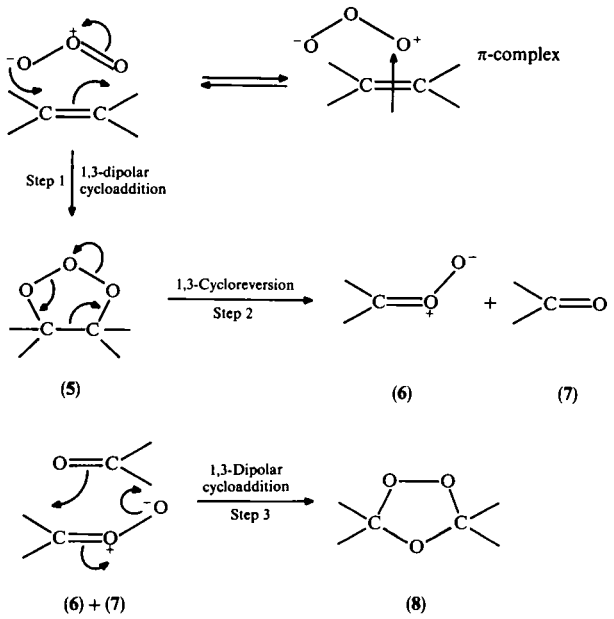
II. OZONOLYSIS OF OLEFINIC COMPOUNDS

A. Mechanism and Intermediates

An excellent historical perspective of the mechanism of ozonolysis of olefins is presented in Bailey's first volume[2]. A more recent review of the mechanism of olefin ozonolysis by Kuczkowski can be found in Padwa's outstanding book on 1,3-dipolar cycloaddition[23]. In the present chapter, only more recent concepts of the mechanism are discussed, with only a short survey of history.

The reaction of ozone with ethylene which was discovered by Schönbein[15] in 1868 as well as the works of Harries[24a], Staudinger[24b], Riech[25] and Briner[26] and collaborators showed that ozonolysis of olefinic compounds leads to the cleavage of the double bond, yielding aldehydes, ketones, peroxidic products and occasionally carboxylic acids. A major contribution to the understanding of the mechanism was made by Criegee, who predicted the formation of an initial peroxidic adduct which was named later 'primary ozonide' or 'molozonide' (**5**) and which decomposes to an aldehyde or ketone (**7**) and a carbonyl oxide (**6**)[27]. The carbonyl oxide (**6**) and the aldehyde or ketone (**7**) recombine to a more stable product, i.e. the ozonide or 'final ozonide' (**8**). The latter is sometimes called 'secondary ozonide'.

Refinements of Criegee's mechanism were made by Bauld and Bailey and their coworkers[28], as well as by Kuczkowski and his group[29]. Based on Huisgen's classification of ozone as a typical 1,3-dipole[6], a cycloaddition of ozone to the double bond was postulated. The present-day concept of the mechanism, in nonparticipating solvents, involves two stages of symmetry-allowed 1,3-dipolar cycloaddition and a cycloreversion reaction as shown in Scheme 1. The mechanisms of the particular stages and the formation of side products are described in the following sections.

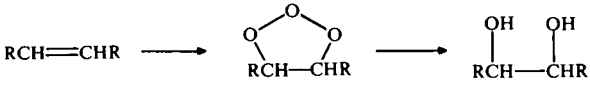


SCHEME 1. The three basic steps of Criegee's mechanism

1. Ozone attack on carbon–carbon double bond. Formation of primary ozonide

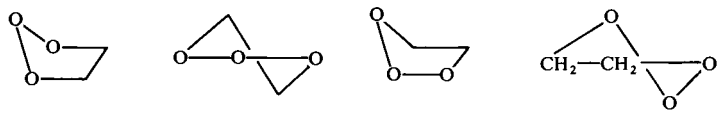
Although several authors[30] believe that π-complexes of olefins with ozone precede ozone attack, there is no real evidence for such complexes. However, π-complexes of ozone have been reported with several olefins at low temperatures[31]. On the other hand, the formation and structure of the primary ozonide (**5**) is well established.

a. Structure of primary ozonide. The primary ozonides are stable enough at low temperatures to be observed spectroscopically *in situ* for hours. Early evidence[32] for their existence and their structure as 1,2,3-trioxolanes was obtained by their reduction to glycols (**9**). It was found that such diols were obtained only in the case of *trans*- and 1-alkenes, leading to the conclusion that *cis* primary ozonides are less stable or do not form. However, IR experiments at −175 °C showed the existence of primary ozonides, derived from *cis*-1,2-diisopropylethylene and *cis*-1-hexene as well[33], with IR bands at 690, 970 and 1100 cm^{-1}. Low-temperature NMR studies of ozonolysis reaction mixtures of *trans*-1,2-di-*t*-butylethylene showed[34] only 2 singlets for the *t*-butyl group as well as for the methine protons. This proved that the primary ozonide has a symmetrical structure, consistent with a 1,2,3-trioxolane structure. Later, NMR studies also established the difference in stability between the *cis* and *trans* primary ozonides[35]. The absorptions of the methine protons of primary ozonides derived from *trans*- and *cis*-2-butene were at 4.12 and 4.52 ppm, respectively.



(9)

Theoretical calculations, using *ab initio* MO calculations, concerning the most stable conformer, showed[36] that a symmetrical O-envelope is the most probable structure (**10**). However, the barriers to pseudorotation to the other two conformers, **11** and **12** (see Scheme 2) are low. In another report[37], using MC-SCF calculations, the half-chair conformer (**13**) was claimed to predominate.



(10) (11) (12) (13)

SCHEME 2

A major contribution to the elucidation of the structure and stereochemistry of the primary ozonide, produced in the gas phase from ethylene and ozone, was supplied recently[38] by Gillies and Suenram and their coworkers. The existence as well as the conformation were studied by microwave techniques and were determined unequivocally. The observed lowest-energy conformation oxygen envelope of ethylene primary ozonide with a C_s symmetry is shown in Figure 1. By these techniques they could also estimate the dipole moment of the ethylene primary ozonide to be 3.43*D*. By utilizing *cis*- and *trans*-CHD=CHD they could also show the stereospecifity of the ozone addition. More recent[39] theoretical calculations using SCF, MP2 and MPH levels of theory were in excellent agreement with the results obtained by the microwave study. Similar results

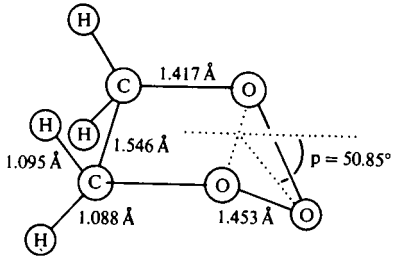


FIGURE 1. The lowest-energy gas-phase conformation of ethylene primary ozonide, from microwave study. Reprinted with permission from Gillies *et al.*, *J. Am. Chem. Soc.*, **110**, 7991.[38] Copyright (1988) American Chemical Society

were obtained by AM1 calculations for primary ozonides derived from ethylene and also *cis*- and *trans*-2-butene[40].

b. Mechanism of formation of primary ozonides. Ozone has the electronic structure described by in-plane σ orbitals and an out-of-plane π-system which contains 4 electrons. An alkene has a π-orbital with 2 electrons, consequently it reacts with the 4-π-system in a $\pi 4s + \pi 2s$ cycloaddition process. This is illustrated in Figure 2 and considered a ground-state allowed process by Woodward–Hofmann's rules. It is analogous to the cycloaddition of an allyl anion with alkenes, even though theoretical work indicated that the electron distribution in the ground state of ozone, when unsolvated, is such that it is better described as a singlet diradical[41]. Kinetic studies show, however, that the electrophilic nature of O_3 is also expressed in the rate of formation of the initial product. Electron-donating groups on the 1,3-dipolarophile, e.g. the olefinic double bond, increase the rate of ozone attack, whereas electron-attracting substituents decrease it[8,42]. The reactions were found to be of the second order, i.e. first order for each reactant[8]. These facts were explained by Huisgen who suggested[6] that 'concerted addition' should not be taken to mean that the two new σ bonds in the transition state form simultaneously to the same degree. Rather, the electrophilic oxygen of the ozone is more strongly bonded in the transition state than the nucleophilic oxygen, i.e. there is a semipolar transition state (**14**); see equation 1. This is in agreement with the observation[43] that an increase in the dielectric constant of the solvent brings about a slight increase in the rate constant.

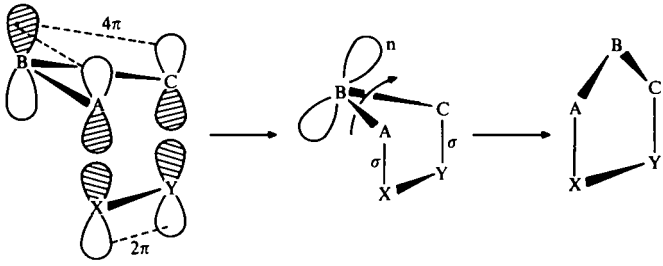
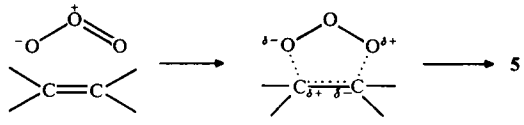
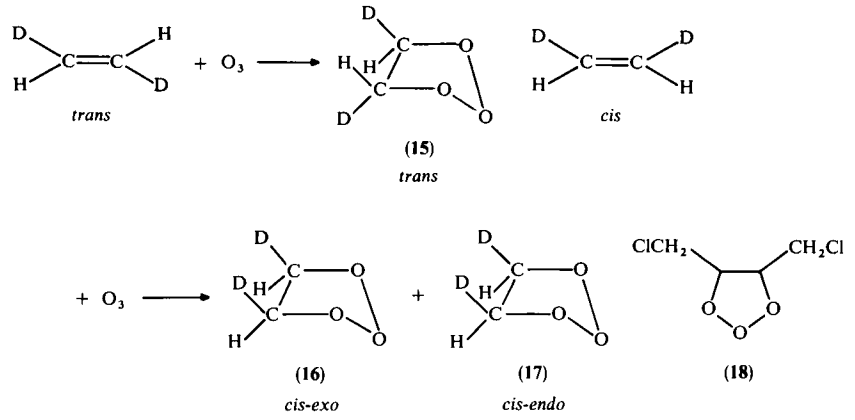


FIGURE 2. Orbital diagram of the *supra, supra* addition of a 4π and 2π system to produce a five-membered ring. Reprinted with permission from R. P. Lattimer, R. L. Kuczkowski, and C. W. Gillies, *J. Am. Chem.* Soc., **96**, 348. Copyright (1974) American Chemical Society



(14) (1)

Ozonolysis of olefins, similar to other concerted cycloadditions, has a highly negative entropy and low enthalpy requirements[8]. The strongest evidence for a concerted reaction is stereochemical. Figure 2 illustrates the 'exaggerated envelope' conformation which is the expected geometry of the transition state. Therefore, a concerted cycloaddition of ozone and alkene will result in retention of the alkene configuration in the primary ozonide. The stereospecificity of the addition is generally determined by analysis of the stable decomposition products, mostly by stereochemical analysis of the final ozonides. Direct evidence came recently from the microwave study of the reaction of isomerically pure *trans*- and *cis*-1,2-dideuteroethylenes[38a]. Ozone adds in the gas phase to the *trans* isomer stereospecifically to give exclusively the *trans* primary ozonide (**15**); see Scheme 3. Similarly, *cis*-1,2-dideuteroethylene reacted with ozone to give *cis,endo* and *cis,exo* primary ozonides, **16** and **17** respectively.



SCHEME 3

Additional evidence for the concertedness of the cycloaddition of ozone to alkenes was provided[44] by Choi and Kuczkowski who determined the kinetic isotope effect by using α and β deuterated styrenes ($PhCD{=}CH_2$ and $PhCH{=}CD_2$, respectively). They observed an inverse kinetic secondary isotope effect (KSIE, $k_H/k_D \approx 0.88$) at both ends of the double bond.

A relatively stable primary ozonide was reported[45] having chloromethylene substituents (**18**). It was resistant to attack of deuterated methanol — even at relatively high temperatures (−10 °C), and reacted with methanol quite slowly even at 24 °C. The authors claim that it was produced by a nonconcerted cycloaddition of ozone to 1,3-dichloro-2-butene. Presentation of the frontier molecular orbital interactions between ozone and alkenes is shown in Figure 3. It is described[46] as a LUMO controlled reaction in which the LUMO of the 1,3-dipole and the alkene's HOMO are the closest and have the strongest interaction. Substituent effects that lower the LU of the dipolar molecule or raise the alkene's HO energy will accelerate this LUMO-controlled reaction.

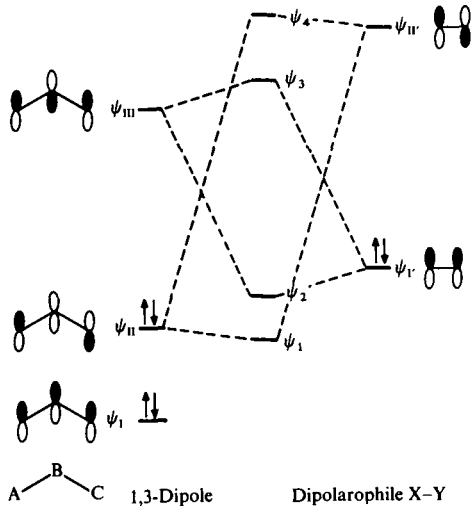
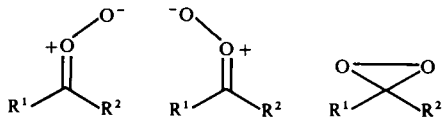


FIGURE 3. HOMO–LUMO interaction scheme for ABC (1,3-dipole) with XY (dipolarophile). The relative order of the orbitals approximates those for ozone and ethylene. From Reference 23

2. Cleavage of primary ozonide. Formation and structure of carbonyl oxide

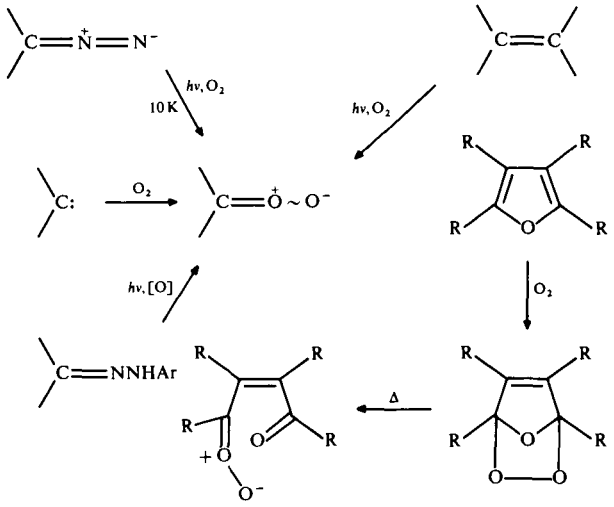
As shown in Scheme 1, the primary ozonide decomposes to a carbonyl compound (aldehyede or ketone) and a fraction that has a COO group which was named carbonyl oxide and which was originally proposed by Criegee.

a. Nature of carbonyl oxide. In order to account for the stereochemistry of the final ozonides (**8**), Bauld and Bailey and their coworkers suggested[28] that the carbonyl oxide exists in two configurations, e.g. *syn* and *anti* (**6A** and **6B**, $R^1 = H$, respectively). Later, calculations actually showed that a barrier to rotation exists in carbonyl oxide, which is large enough to provide for the existence of *syn* and *anti* isomers. Cremer reports[47] that this barrier is 32–41 kcal mol^{-1}. Both Cremer[47] and Hull[48] find that the *syn* isomer is much more stable, in agreement with some experimental interpretations[49]. They also showed that a dioxirane structure (**19**) should be more stable than a carbonyl oxide. However, there is a considerable barrier to conversion, especially in liquid phase ozonolysis, although in certain cases a dioxirane was detected by microwave spectroscopy[50].



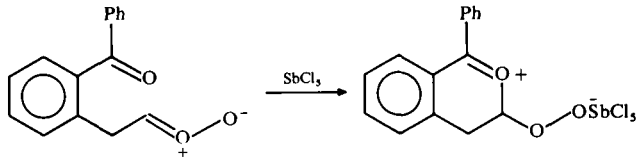
(6A) (6B) (19)

While the evidence for a carbonyl oxide intermediate in ozonolysis is overwhelming, it was never isolated or detected spectroscopically in the course of an ozonolysis.



SCHEME 4. Alternative routes, other than ozonolysis, to carbonyl oxides

However, it was produced by several alternative routes and also studied spectroscopically. In two recent reviews[51,52] the methods for the preparation of carbonyl oxides and its spectroscopic studies are discussed. Alternative routes to carbonyl oxides are shown in Scheme 4. Stable $SbCl_5$ complexes of carbonyl oxide (**20**) could be precipitated in CCl_4. They were too labile to be purified but spectroscopic data have been reported[53a].

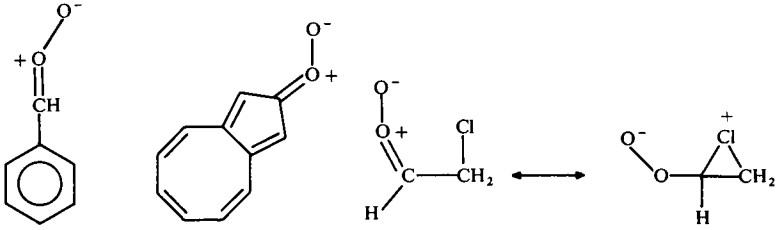


(**20**)

To date, the electronic structure of carbonyl oxide is still a subject for debate. Quite a few important reactions of carbonyl oxides, such as 1,3-dipolar cycloaddition and addition to alcohols, may be explained by terms of the zwitterionic structure (**6**). Some of the empirical calculations postulate a zwitterionic character[53b] while *ab initio*[54] and other empirical calculations[55] predict a diradical ground state. Cremer tries to describe[47] the carbonyl oxide as being a composite of both a 1,3-singlet diradical and a zwitterion. He concedes that substituents and solvents can lead to a dominance of zwitterionic character.

Carbonyl oxide is isoelectronic with ozone, and it is a bent triatomic species. Theoretical calculations which were mentioned above are against equilibration between *syn* and *anti* isomers. Equilibration is expected to proceed either by inversion (either at the carbon or at the oxygen) or through a cyclic dioxirane (**19**). The inversion processes is claimed to be quite energetic and the isomerization through the cyclic dioxirane was excluded experimentally by ^{18}O labelling of one of the oxygens, as no scrambling of ^{18}O occurred. However, in many cases where it was difficult to explain the stereochemistry of the final ozonides, occasional equilibrations between *syn* and *anti* carbonyl oxide were suggested depending on the substituents, solvents or temperatures[49,56].

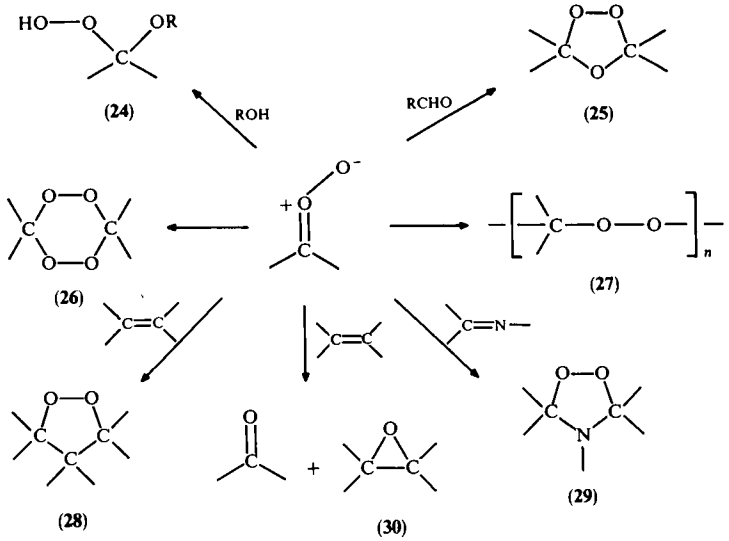
Since carbonyl oxides are unstable at moderate temperatures, spectroscopic studies were carried out with matrix cage techniques. The $\pi \rightarrow \pi^*$ transition is the strongest in the UV/VIS spectrum and is between 378 and 582 nm. There is excellent agreement between theory and experiment[57]. The colors of carbonyl oxides in a matrix range from yellow for **21** to blue for **22**.



(21) (22) (23)

A characteristic feature of the IR spectrum is its intense bands between 890 and 1050 cm^{-1} which are assigned to O—O. Weak bands between 550 and 740 cm^{-1} were assigned to an O—O deformation vibration[58]. Using matrix isolation techniques, it was also possible to determine the dipole moments for several carbonyl oxides.

A relatively stable carbonyl oxide was reported[45], suggesting a very low reactivity explained by neighboring halogen participation (**23**). Generally, carbonyl oxides have a very short lifetime, long enough, however, to leave the solvent cage and undergo various reactions with nucleophiles and 1,3-dipolarophiles besides the aldehyde, which is formed and usually recombines with the carbonyl oxide to form the final ozonide. Carbonyl oxides react quantitatively with methanol to give α-methoxyhydroperoxide (**24**, R = Me). They react with externally added aldehydes to form cross ozonides (**25**), dimerize to diperoxides (1,2,4,5-tetroxanes, **26**) and polymerize to cyclic and linear polyperoxides (**27**). In some cases they were reported to react with alkenes to form the 1,3-dipolar cycloadducts



(24) (25) (26) (27) (28) (29) (30)

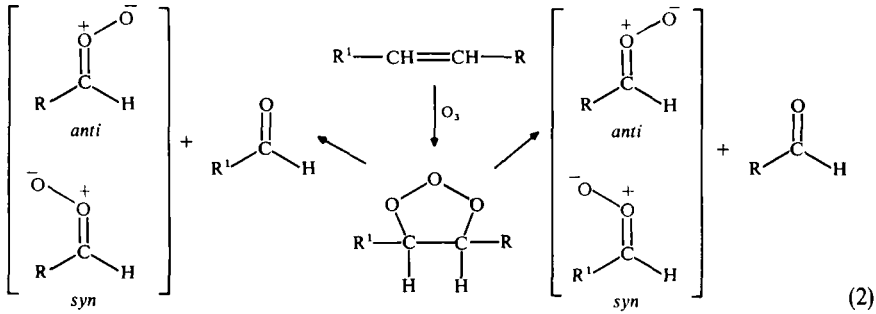
(1,2-dioxolanes, **28**)[59]. The following relative dipolarophilicities towards carbonyl oxides were inferred:

$$RCH{=}O > RCH{=}\underset{\displaystyle OR}{\underset{|}{CH}} > RC{=}\underset{\displaystyle OR}{\underset{|}{O}} > RC{=}\underset{\displaystyle R}{\underset{|}{O}}$$

Cycloaddition of carbonyl oxide to C=N double bond was recently reported, yielding **29**[59b].

Carbonyl oxides are oxidizing agents which can react with double bonds to form epoxides (**30**). Specific products derived via carbonyl oxides and their synthetic utilization are discussed in other sections.

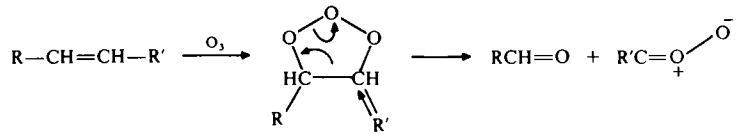
b. Cleavage of primary ozonide. The cleavage of the primary ozonide (**5**) to a carbonyl compound and a carbonyl oxide (**6**) is a cycloreversion reaction, i.e. the reverse of the cycloaddition described in Figure 2. Both the C—C σ bond and the C—O bonds are cleaved apparently by a symmetry-allowed (3 + 2) thermal electrocyclic process. Two modes of fragmentation are possible when the alkene is unsymmetrically substituted, leading to different carbonyl oxides (equation 2). Moreover, if the substituents on the carbonyl oxide are not identical, *syn* and *anti* stereoisomers, may form. In general, then, the ozonation of an alkene can lead up to four different carbonyl oxide intermediates and two carbonyl compounds, depending on both the regio- and stereoselectivity of the decomposition of the primary ozonide.



(2)

Many investigations have focussed on the regioselectivity of primary ozonide cleavage. Early studies were summarized in Bailey's book[2] as well as in Kuczkowski's review[23]. Most of them involved ozonolysis of alkenes in the presence of methanol. Under these conditions, the carbonyl oxide is intercepted to form the easily detectable 2-methoxy hydroperoxide (**24**, R = Me). The most extensive studies were those carried out by Fliszàr and coworkers[60] in the late 1960s and were discussed in detail in the reviews mentioned above[2,23]. More recent publications on this matter include those of Griesbaum[61], Kuczkowski[59,62], Bunnelle[63] and others[64,65]. The results indicate that in most cases a reasonable prediction of the preferred direction of primary ozonide cleavage can be based on the inductive effects of the alkene substituents. Thus, electron-donating groups tend to be incorporated into the carbonyl oxide fragment and electron-withdrawing groups turn up mainly in the carbonyl compound. Accordingly, for instance, 1-alkenes were found to lead to an excess of the substituted carbonyl oxide, while allyl bromide shows the opposite regioselectivity. The flow of electrons in the cleavage of the 1,2,3-trioxolane ring under the influence of electron-donating and electron-attracting groups are shown in equations 3 and 4, respectively. A noteworthy exception was found

for *trans* dialkylethylenes where the carbonyl oxides were formed predominantly with less branched alkyls (e.g. Me > Et > *i*-Pr > *t*-Bu). The use of substituent inductive effect alone to predict the cleavage of the 1,2,3-trioxolane ring is certainly not sufficient and conformational effects must be considered. The difference in energy in propene, for instance, between the two pathways is very small (< 1 kcal mol^{-1}) and the ratio between the two isomers, **31** and **32**, is about 7:4 (equation 5).



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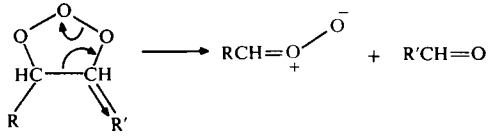

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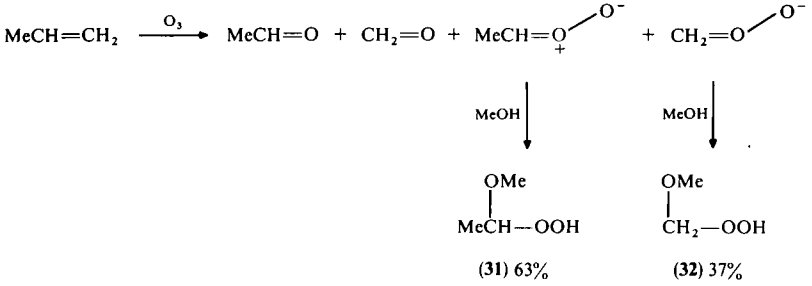
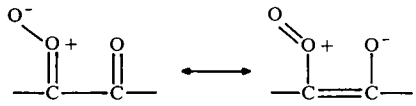


(5)

Fliszàr and coworkers[60] have observed that the ozonolysis of α,β-unsaturated carbonyl compounds gave keto carbonyl oxides, not as would have been predicted by the inductive effect of the carbonyl groups. Their argument was that the carbonyl oxide is stabilized by resonance, as shown in **33** (equation 6). However, more recent studies[61] showed that the keto carbonyl oxides are unstable and, by following the reaction using NMR at low temperatures, it was found that α,β-unsaturated ketones decompose in a regioselective way, in line with the electron-attracting character of the carbonyl group, as shown for methyl vinyl ketone (equation 7).



(6)

(33)

$$CH_2{=}CHCOMe \xrightarrow{O_2,\,MeOH} MeCOCH{=}O + MeOCH_2OOH \qquad (7)$$

The understanding of the stereochemistry of the primary ozonide cleavage is very important for making predictions about the structures of both the carbonyl oxides and the final ozonides. Two groups have developed models which account for the transfer

of stereochemistry via the Criegee mechanism[28,29,49]. Detailed computational study provided additional refinements and some new insights[66,67]. Kuczkowski's group suggested[29], based on an O-envelope structure for the primary ozonide, that there are two different transition states, e.g. two different decomposition routes (Figure 4). Pathway I will orient a substituent pseudoaxially to the envelope's main base and transform to a *syn* carbonyl oxide. Pathway II will orient the substituent pseudoequatorially and lead to the *anti* isomer. The preferred cleavage pathway for a given substituted alkene will depend on the relative energies of the two transition states. These, in turn, depend on the interactions between the various substituents on the two carbons in the transition state.

The second approach[49] to the stereochemistry of this cleavage assumes a C—C twist chair conformation, adopting the principle of least motion. Thus, the developement of the *syn* and *anti* carbonyl oxides, which is shown in Figure 5, involves two rules. First, equatorial substituents are preferentially converted into *anti* and axial substituents into *syn* carbonyl oxides, respectively. Second, equatorial substituents are incorporated into a carbonyl oxide in preference to axial substituents, except for the primary ozonide from *trans* alkenes with bulky groups.

The predictions from both approaches are essentially the same and they are generally in agreement with the observed results for the final ozonides, summarized in Table 1.

The rate of the primary ozonide decomposition obeys first-order kinetics and indicates that the energy of activation for the decomposition is not very large. The energy of activation for hexene in ether, for instance, was found to be 6.9 kcal mol^{-1} [33]. The first-order kinetics and the low activation energies seem reasonable for a symmetry-allowed concerted breakdown of an unstable 1,2,3-trioxalane, in reversion of the process shown in Figure 2.

Differences in the *cis/trans* ratios of the final ozonides were observed, depending on the rate of the warm-up of the reaction mixtures. These differences are consistent in numerous cases. The surprising observation that *trans*-1,2-diisopropylethylene gave more *cis* isomer on slow warm-up led Bailey and Ferrell[49] to argue that the warm-up rate influences the primary ozonide cleavage step by affecting the establishment of equilibria

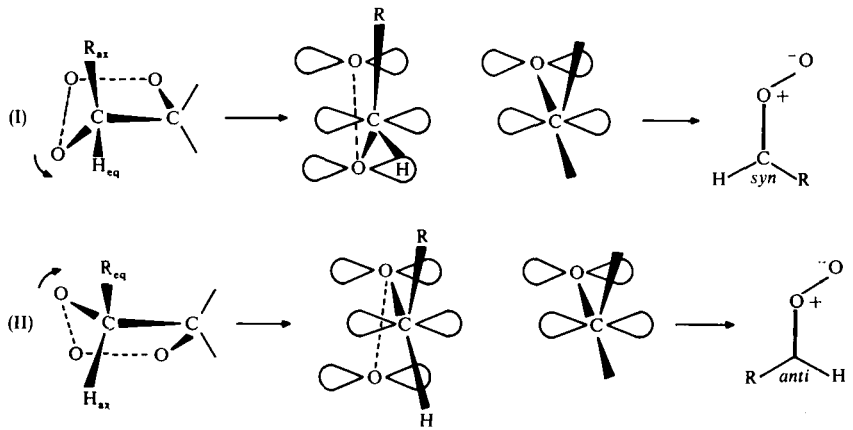


FIGURE 4. Cycloreversion cleavage of the primary ozonide to give *syn* or *anti* carbonyl oxide and a carbonyl species. Reprinted with permission from R. P. Lattimer, R. L. Kuczkowski, and C. W. Gillies, *J. Am. Chem. Soc.*, **96**, 348. Copyright (1974) American Chemical Society

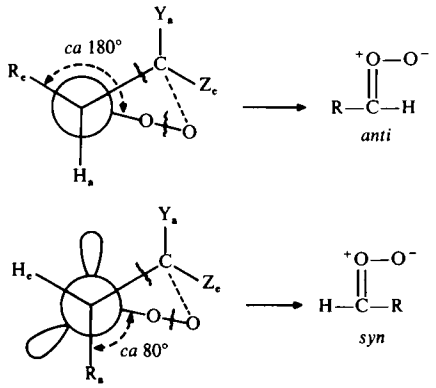


FIGURE 5. The development of *syn* and *anti* carbonyl oxides from the C—C half-chair conformation of the primary ozonide. Copyright (1978) American Chemical Society

TABLE 1. Predicted stereochemical course of normal and cross-ozonide formation as a symmetry-allowed 1,3-dipolar cycloreversion and cycloaddition[a]

Olefin configuration	Primary ozonide configuration	Primary ozonide conformation[b]	Carbonyl oxide configuration	Final ozonide configuration[c]
1-Alkane		Equatorial	*anti*	
trans-Alkene	*trans*	Axial	*syn*	*trans*
cis-Alkene	*cis*	Equatorial	*anti*	*cis*
cis-Alkene	*cis*	Axial	*syn*	*trans*

[a]Reprinted in part with permission from R. P. Lattimer et al., *J. Am. Chem. Soc.*, **96**, 348. Copyright (1974) American Chemical Society.
[b]Oxygen envelope or C—C twist transition state. *Axial* or *equatorial* refers to the position of the R group in the incipient carbonyl oxide.
[c]Predominant.

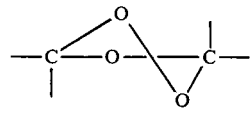
between its various conformers. Thus slow warm-up enhances cleavage of conformers with equatorial substituents and produces more *anti* carbonyl oxide. However, contribution from *syn–anti* equilibration of the carbonyl oxide on slow warm-up cannot be excluded.

3. *Formation and structure of final ozonide*

It is accepted that the formation of the final ozonide (**8**) is by a 1,3-dipolar cycloaddition of the carbonyl oxide (**6**) with a carbonyl group, generally that of the aldehyde or the ketone which is formed during the cleavage of the primary ozonide. Since the carbonyl oxide is isoelectronic with ozone and the π system of a carbonyl group is isoelectronic with the alkene double bond, the interaction between the 1,3-dipolar carbonyl oxide and the carbonyl compound can be visualized the same way as for the initial attack of ozone on the double bond (Figure 2). In frontier molecular orbital terms, it must be described again as a LUMO controlled reaction, where the carbonyl oxide LUMO and the carbonyl group HOMO have the strongest interaction (Figure 3).

This recombination of the two fragments of the primary ozonide takes place more readily when an aldehyde is involved, rather than a ketone, and the stereochemistry of the product is controlled in general by the short-lived carbonyl oxide. Some of the final ozonides are regarded unstable and 'explosive', however, since 1962[68] it has become a common practice to purify and isolate them although they are still considered very explosive. Isomers are separated by chromatographic methods[28]. Ozonides have absorptions in the IR region in the range of 1113–1015 cm^{-1}, bands that are thought[68] to be C—O vibrational frequencies. IR spectra have been used to distinguish between *cis* and *trans* isomeric species (1360–1325 cm^{-1} for *trans* and 855–820 cm^{-1} for *cis*). NMR signals for protons attached to the 1,2,4-trioxolane ring were reported[69] in the range of δ 4.87–6.20, with a general trend of *cis* ozonides to absorb at a slightly lower field.

The unambiguous stereochemistry of several ozonides could be determined either by microwave spectroscopy[29] or indirectly by the differential reactivity of *cis* (*meso*) and *trans* (racemic) ozonides with optically active reagents[70]. Experimental as well as *ab initio* calculations confirmed the oxygen–oxygen half-chair conformation (**34**) for ozonides.



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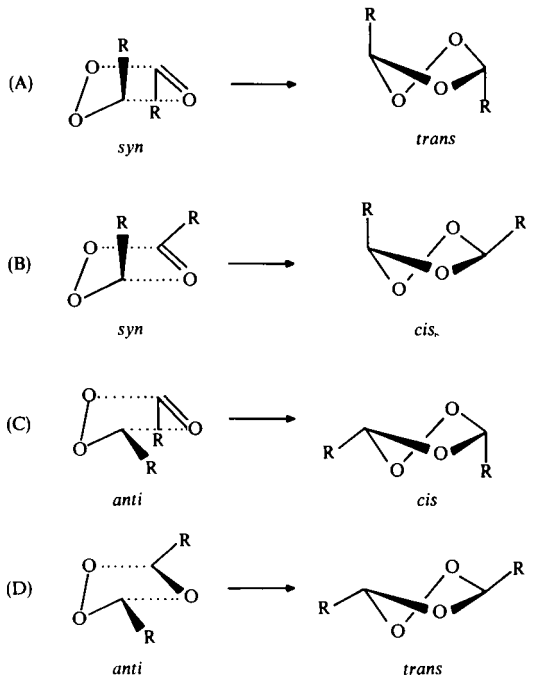
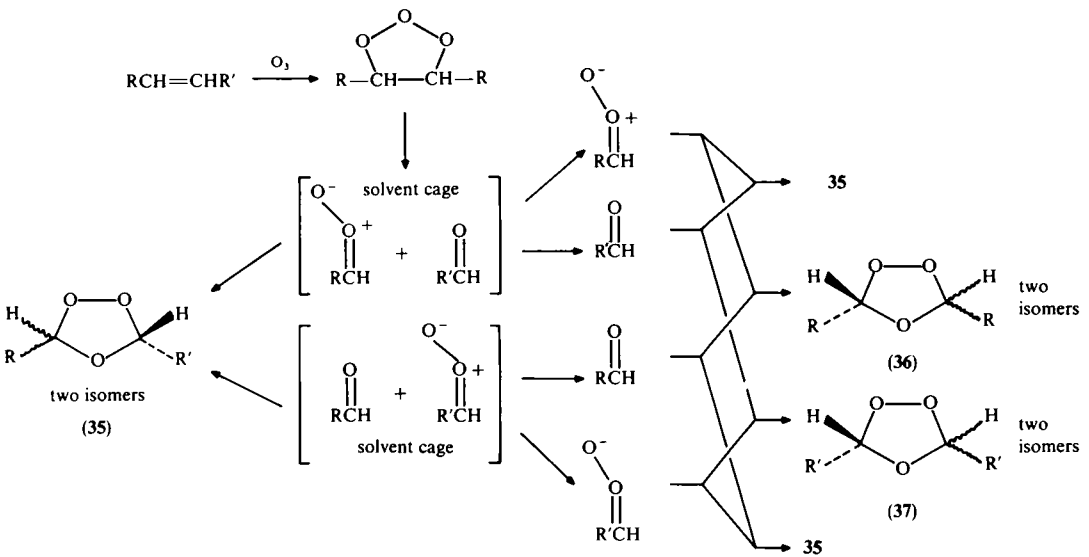


FIGURE 6. Oxygen envelope conformations illustrating *syn* and *anti* carbonyl oxides and carbonyls forming final ozonides



SCHEME 5. Solvent cage effect on the final ozonide structure

Although there are several theories to rationalize the stereochemistry of final ozonides, including a biradical mechanism, the most consistent with experimental observations is the concerted cycloaddition → cycloreversion → cycloaddition mechanism. One analysis, based on experimental observation[49] and calculations[71], is presented in Figure 6.

Figure 6 is useful for discussing 1,3-interactions between carbonyl oxides and aldehyde substituents. For a cycloaddition involving a *syn* carbonyl oxide, either R vs H (A) or R vs R (B) interaction occurs. For the *anti* isomer, either H vs H (C) or R vs H (D) interaction is evident. With increasing bulkiness, the transition states B and C will become less favored. Thus, in agreement with predictions summarized in Table 1, *syn* and *anti* carbonyl oxides produce *trans* and *cis* ozonides, respectively.

In the predictions made in Table 1 there is a lack of consideration of dipole–dipole and electronic interactions in the recombination process. The specific influence of fluorine, as a π donor and σ acceptor, on the stereochemistry of the final ozonide was investigated by RHF and other *ab initio* calculations[71b]. One should also consider the possibility of *syn–anti* equilibration of the carbonyl oxide as well as the conformational changes in the primary ozonide during slow warm-up which were discussed in the previous section.

Temperature as well as polarity of the solvent influence the total yield, the stereochemistry and rate of formation of ozonides. This is frequently attributed to the change in the solvent cage effect, since ozonides are formed from the two decomposition products of the primary ozonide (Scheme 5). At higher temperature and higher solvent polarity the caged species can diffuse faster and react with other species present in the solution.

4. Normal and cross ozonides

An ozonide that has identical substituents with those of the parent alkene is generally named 'normal ozonide' as, for instance, ozonide **35** in Scheme 5. It was mentioned above that the regioselectivity of the primary ozonide cleavage is in most cases not absolute and cross ozonides are formed when unsymmetrical alkenes are treated with ozone. Ozonides **36** and **37** are examples of symmetrical cross ozonides. The isolation of the latter, either after ozonolysis of unsymmetrical olefins or by ozonolysis of mixtures of olefins, served during the 1960s as evidence for the Criegee mechanism. One of the first examples[72] was the ozonolysis of methyl oleate, where all six possible ozonides were formed, corresponding to **35–37** (*cis* and *trans* for each structure). The relative yields of the normal and cross ozonides provide information about the solvent cage effect. The cross ozonide yields are increased by polar solvents, where this effect is minimized. They are also increased by higher alkene concentrations and temperatures. It has been shown[73] that in polar solvents up to 90% of the ozonide formation occurs outside the solvent cage. A model was described for the increase in cross-ozonide fraction on changing the solvent (equations 8 and 9),

$$\frac{\text{cross-fraction (solvent, } \varepsilon')}{\text{cross-fraction (solvent, } \varepsilon)} = \exp(-\Delta E/RT) \tag{8}$$

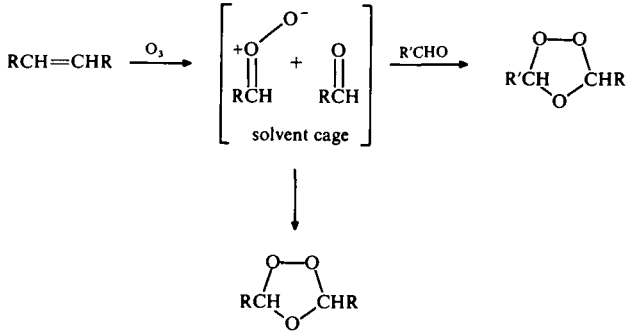
$$\Delta E = 2\mu_{CO}\cdot\mu_{C}\cdot r^{-3}(1/\varepsilon' - 1/\varepsilon) \tag{9}$$

where μ_{CO} and μ_{C} are the dipole moments of the carbonyl oxide and carbonyl compound, respectively, r refers to the size of the solvent cage while ε and ε' are the dielectric constants of the two solvents, respectively. From this model one can probably estimate the dipole moment of a carbonyl oxide.

5. Aldehyde and ketone insertion

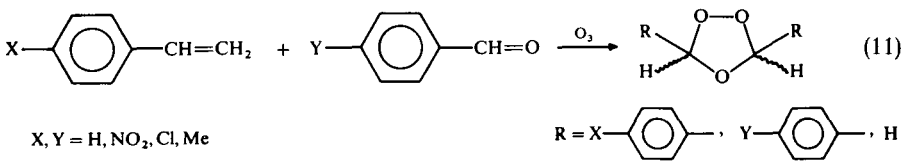
An aldehyde or ketone added to the ozonolysis reaction mixture is incorporated into the final ozonide. The latter 'cross' ozonide formation gave credence to the formulation

of the Criegee mechanism. Its production involves the emergence of the carbonyl oxide from the solvent cage as shown in equation 10.



(10)

Studying the products and rates of reactions in ozonolysis of mixtures of *p*-substituted styrenes in the presence of *p*-substituted benzaldehydes[73b] (equation 11) gave more information about the electronic effect on cross ozonide formation. It was shown that electron-withdrawing groups increased cross ozonide formation by enhancing the dipolar character of the carbonyl oxide and the dipolarophilicity of the aldehyde. The substituent also influences the direction of cleavage of the primary ozonide and the solvent cage effect [$k_{stilbene}/k_{ethylene}$ had a slope (ρ) of +1.4]. The mechanism of ozonolysis of 1,1-dideuterated ethylene in acetaldehyde was investigated[74]. The kinetic model which was described included a quantitative estimation of the kinetic secondary isotope effect for the carbonyl oxide, the relative dipolarophilicity of CH_2O and CH_3CHO and the cage effect.[74].



(11)

For as yet unknown reasons, introduction of a large excess of aldehyde could not be used for quantitative trapping of carbonyl oxides. This and other problems concerning aldehyde insertion were thoroughly investigated. A summary of this investigation is given in earlier reviews[2,23].

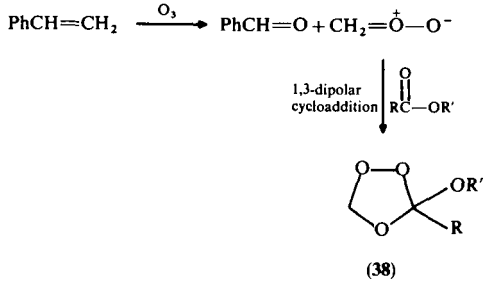
Added aldehydes incorporate into the final ozonide much more readily than ketones. In general, except for recent results[19b] on ozonolysis carried out with polyethylene, tetrasubstituted ethylenes do not yield a final ozonide.

6. *Insertion of esters*

Ozonolysis of styrene in esters of formic, acetic and propionic acids resulted in the formation of 5–10% alkoxy ozonides (**38**)[74]; see equation 12.

7. *Mechanistic differences between solvent ozonolysis and gas phase ozonolysis*

It appears likely from rate constants and activation energies that the initial cycloaddition of ozone to olefins is a similar process both in the gas phase and in the



(12)

(38)

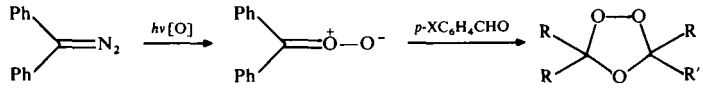
condensed phase[75]. The final products, however, do differ. It is apparent that the solvent provides stabilization of the intermediates and transition states leading to the formation of ozonides, and also holds the cleavage fragments of the primary ozonide in close proximity (solvent cage effect). It is still unclear whether the primary ozonide observed by microwave spectroscopy[38] was formed in the gas phase or in a condensed phase on the surface of the cell walls. Ozonolysis of ethylene in the gas phase leads mostly to nonozonide products, yielding mainly formic acid, CO_2, carbon monoxide and formaldehyde, while in the condensed phase it gives the final ozonide (50–80%)[73a]. It therefore seems that after the formation of the primary ozonide, the mechanism in the gas phase is different than that in the liquid phase. There have been several proposals for the gas phase mechanism, among them one involving free radicals[76].

8. *Ozonolysis on polyethylene*

In this novel technique[18], there is probably extra stabilization of the Criegee intermediates since it leads to higher yields of ozonides and to ozonides which have not been accessible by ozonolysis in solution. Impressive results have been published in recent years by Griesbaum's group about ozonolysis products on polyethylene. It seems that the solid matrix provides enchanced proximity for the fragments to recombine, even better than solvents. These recent reports are discussed in the relevant sections.

9. *Alternative sources for final ozonides*

a. From carbonyl oxides prepared by routes other than ozonolysis. Recently, Murray and Morgan[77] studied the mechanism of the cycloaddition of nonozone sources of carbonyl oxide (equation 13) with *p*-substituted aromatic aldehydes and compared the Hammett relationship to ozonide formation in ozonolysis. The results were consistent with a 1,3-dipolar cycloaddition mechanism. The electronic effects on the rate of ozonide formation were similar with carbonyl oxides from both sources. The ρ values were rather close, +0.48 and +0.76 for the photolytic and ozonolytic reactions, respectively[77].

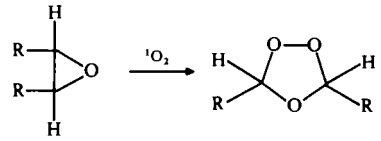


(13)

R = Ph, X-C_6H_4, H
X = OMe, *t*-Bu, Me, Cl, F

b. Addition of singlet oxygen to epoxides and to furan. Although this is a non-ozonolytic method, it is pertinent to mention it, because the ozonides which are obtained

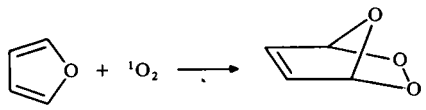
provide evidence for ozonide structure[78a] and sometimes they were easier to isolate. Thus electron transfer photooxygenation of naphthyl epoxide (equation 14) gave a crystalline ozonide (**39**), the stereochemistry of which was assigned by X-ray crystallography[78b]. The cycloaddition of singlet oxygen to furan (equation 15) gave the ozonide (**40**), which is the product would be derived from a hypothetical cyclobutadiene[78c].



(14)

(**39**)

R = 1- or 2-Naphthyl



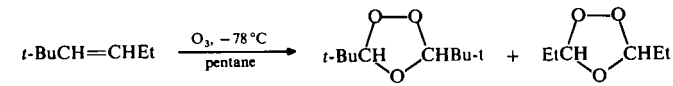
(15)

(**40**)

B. General Pattern of Products Derived from Ozonolysis of Alkenes

1. Final ozonides and products derived from them

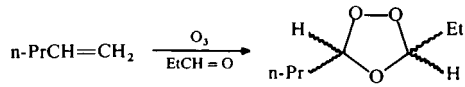
The structure and formation of the final ozonides (also referred to as secondary ozonides) were discussed in the previous section. According to the model, which is summarized in Table 1, the preferred stereoisomer for a *trans* alkene should have a *trans* configuration. Experimentally, it was found that the *trans/cis* ratio depends on the size of the substituents, i.e. the predominance of *trans* configuration increases with substituent bulk. For cross ozonides, these predictions are not always correct[79] as shown in equation 16.



(16)

cis/trans ratio: 38:62 68:32

The *cis/trans* ratio for the ozonides derived from *cis* alkenes with large substituents (*t*-Bu, *i*-Pr) is in favor of the *cis* configuration. In *cis* alkenes with small groups (Me) the

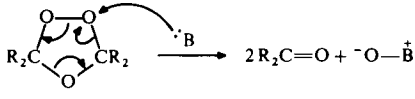


(17)

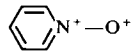
Concentration of propanal	*cis/trans* ratio
0.25 M	72:28
1.0 M	59:41
2.0 M	58:42

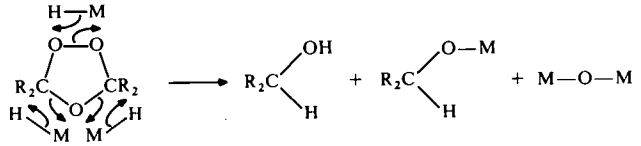
ratio is in favor of the *trans* configuration. The ethyl group falls between the two extremes. In ozonides formed by ozonolysis of 1-alkene, stereoisomers are possible only in the cross ozonides, which are very rarely formed. The preferred configuration in these final ozonides is the *cis*, and the *cis–trans* ratio decreases with the concentration of the foreign aldehyde as shown[69a] for 1-pentene in the presence of propanal (equation 17). The final ozonides are generally not the target of ozonolysis processes, but they are usually transformed into various types of products by procedures which are discussed below.

a. Reduction of ozonides. Mild reducing agents will generally bring about the cleavage of the ozonide to two carbonylic fractions. In the case of ozonolysis of symmetric olefins, a single carbonyl compound is formed. If unsymmetric olefins are involved, a mixture of carbonyl compounds is obtained. The most commonly used agents for this conversion are $(CH_3)_2S$ and Ph_3P and sometimes other nucleophilic agents might do the same (equation 18). The reduction can be described as a nucleophilic displacement resulting in the elimination of an oxygen atom and cleavage of the 1,2,4-trioxolane ring. Other reducing agents can lead to the formation of alcohols (e.g. $LiAlH_4$ or other metal hydrides) by a probable mechanism shown in equation 19.



(18)

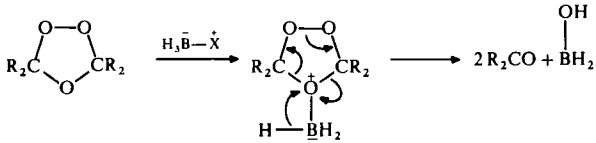
B	$\overset{+}{B}—O^-$
Me_2S	$Me_2\overset{+}{S}—O$
Ph_3P	$Ph_3\overset{+}{P}—O^-$
	



(19)

M = Metal

Borane reduction is viewed[80] as an electrophilic initial attack of borane on one of the oxygens of the ozonide (equation 20). Carles and Fliszàr have illustrated[69b], using triphenylphosphine and ^{18}O-labelled ozonide, that the oxygen which is displaced comes from the peroxidic bond and predominantly from the oxygen which is closer to the carbon bearing the more electron-attracting group. They suggested an initial attack on the least hindered side and a cyclic intermediate (**41**; see equation 21). Catalytic hydrogenation[81] and reduction with formic acid[82] have been reported.



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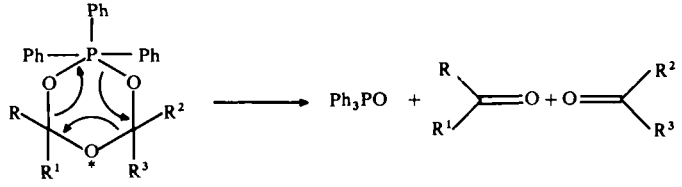
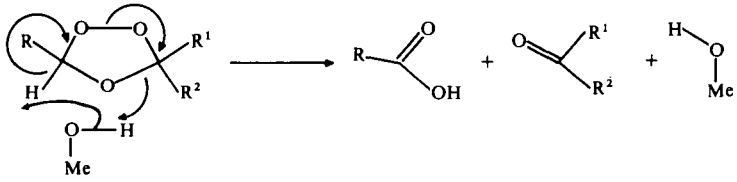
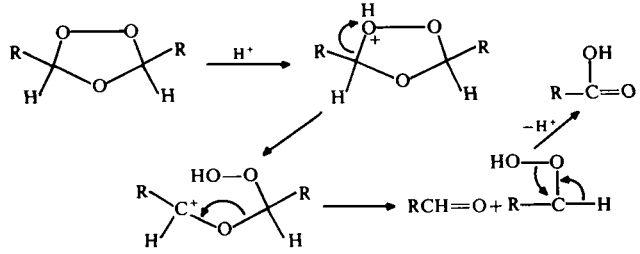


(41) $\overset{*}{O}=^{18}O$

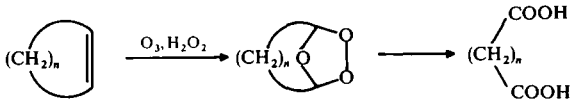
(a) $R = R^1 = R^2 = H$, $R^3 = Ph$
(b) $R = Me$, $R^2 = Ph$, $R^1 = R^3 = H$

b. Acid/base catalyzed decomposition of ozonides. Criegee and Korber[83] proposed a mechanism which involves acid/base catalysis for the formation of a carboxylic acid along with the ketone or aldehyde in the presence of methanol (equation 22). Another mechanism was proposed[84] for the acid-catalyzed decomposition of 1-hexene ozonide which led to a carboxylic acid (equation 23).



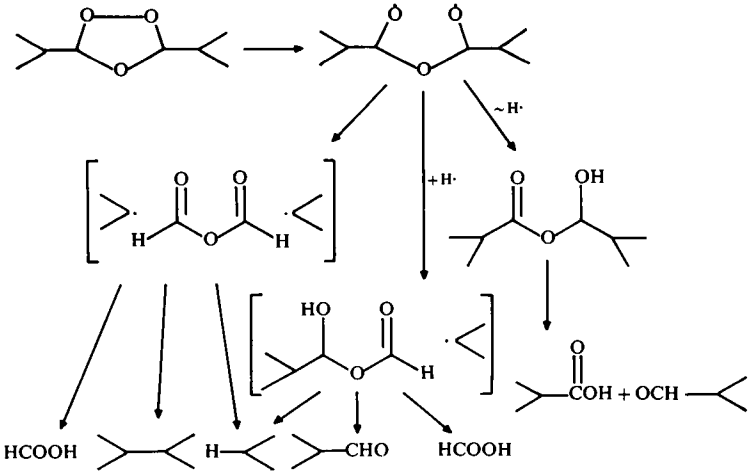


c. Oxidative cleavage of ozonides. Ozonation in the presence of hydrogen peroxide leads to the formation of carboxylic acids. Cycloolefins were heated with ozone in the presence of HOOH and the products were dicarboxylic acids[85] (equation 24).



d. Thermal and photolytic decomposition of ozonides. Most of the published work concerning thermal and photolytic decompositions point to a homolytic cleavage of the 1,2,4-trioxolane ring. The products pattern by both photolytic and thermal decompositions are generally similar. The proposed mechanism in the cases of diisopropyl

ozonide and cyclopentyl ozonide is shown in equations 25 and 26, respectively[86]. Both *cis* and *trans* diisopropylethylene ozonides gave the same products. The synthesis of unstable cyclobutadiene derivative **43** was evidenced by isolation of its dimer **44** in the photolysis of the ozonide **42** (equation 27)[87]. A similar mechanism has been proposed



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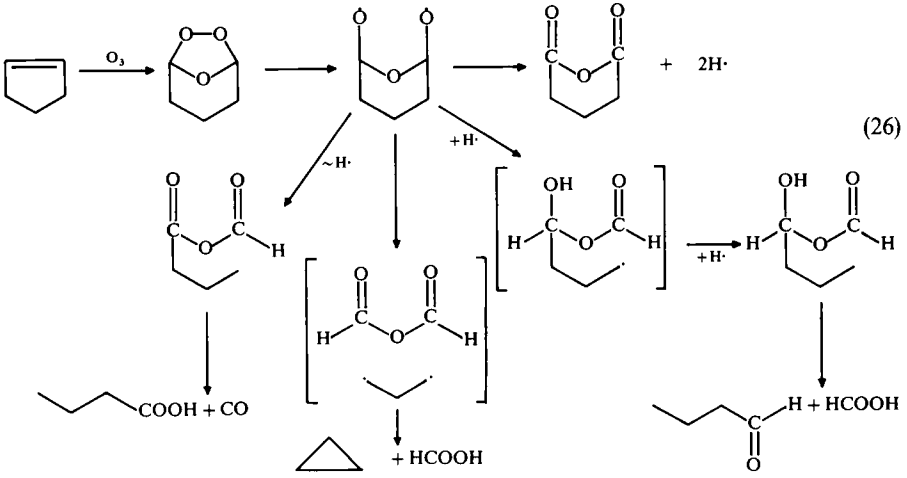

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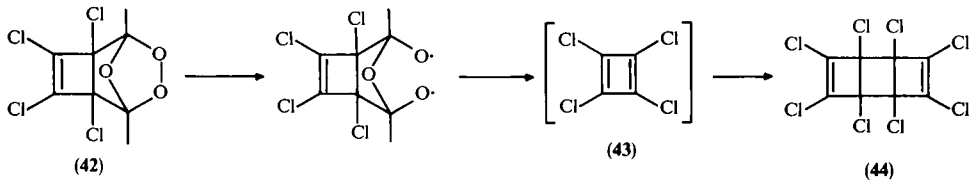

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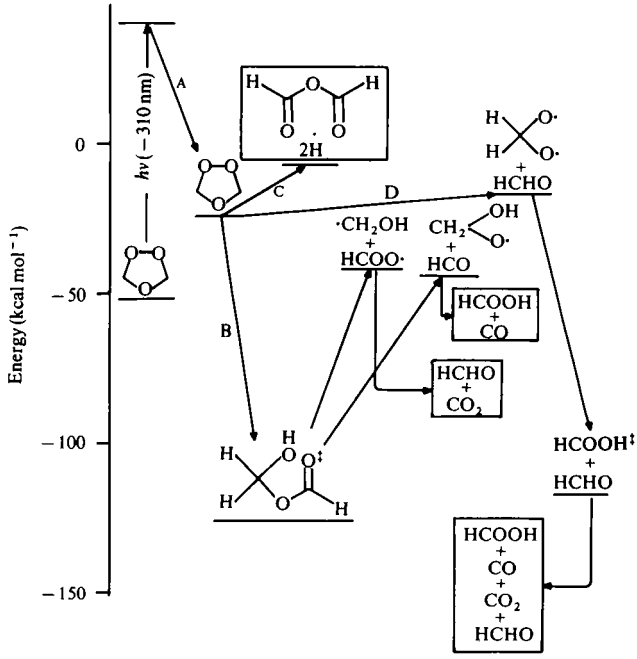
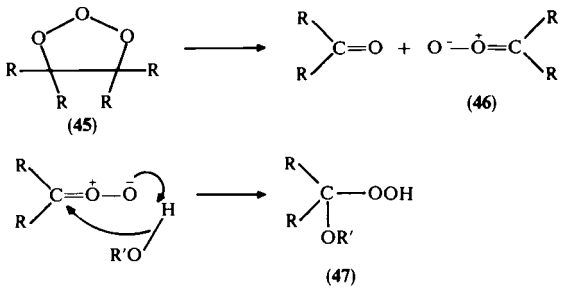


FIGURE 7. Energy diagram of the photolysis of ethene ozonide. Reproduced from Reference 88 by permission of the Chemical Society of Japan

for the gas phase photolysis of simple ozonides, derived from ethylene, propylene, 2-butene and isobutene[88]. An energy diagram of the photolysis of ethene ozonide was suggested as shown in Figure 7. The double β-scission process (path C), which is a major path in the liquid phase[86], is about 4–13% in the gas phase[88].

2. α-Oxyalkyl hydroperoxides and other products derived from carbonyl oxide

a. α-Alkoxyalkyl hydroperoxides. When ozonolysis is carried out in the presence of an alcohol α-alkoxyalkyl, hydroperoxides (**47**) are formed (equation 28). It was shown that they are produced from the intermediate carbonyl oxide (**46**) rather than by direct



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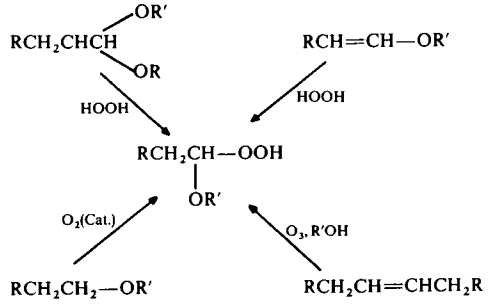
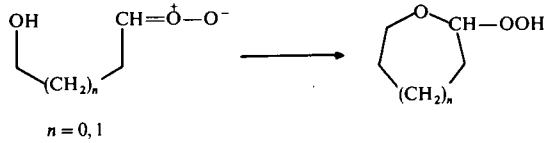


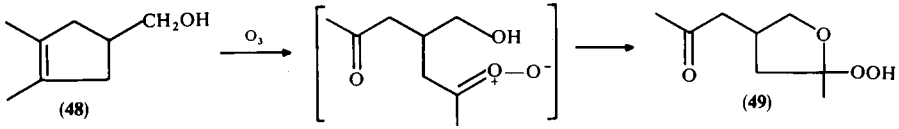
SCHEME 6

attack of the alcohol on the primary ozonide (**45**). These products are relatively stable, isolable and are produced in good yields. As mentioned above, they are used to trap quantitatively the intermediate carbonyl oxide. They were characterized by IR, NMR and chemical reactivity[89]. α-Alkoxyalkyl hydroperoxides are well known and have been prepared by other routes, e.g. oxidation or treatment of ethers[90], vinyl ethers[91] or acetals[92] with hydrogen peroxide (Scheme 6). Cyclic alkoxyalkyl hydroperoxides are formed upon ozonolysis of unsaturated alcohols. However, it was suggested[93] that these products could also be formed by direct intramolecular decomposition of the primary ozonide (equation 29).

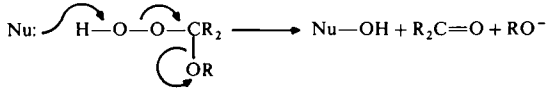


(29)

A competition between an alcohol group and an acetyl group (formed in the ozonolysis of alcohol (**48**) for the carbonyl oxide was tested[94]. The sole product observed was the cyclic hydroperoxide (**49**).



b. Decomposition of α-alkoxyalkyl hydroperoxides. By mild reduction (Ph_3P, CH_3SCH_3) and upon nucleophilic displacement, α-alkoxyalkyl hydroperoxides yield either aldehydes or ketones, depending on the substituents (equation 30). In the presence of a base (e.g. tertiary amines) or in the presence of DMSO, they yield esters[95] by the mechanism shown in equation 31 in the cases where a hydrogen is present on the alkyl group.



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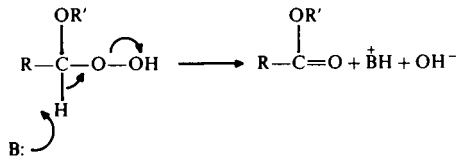
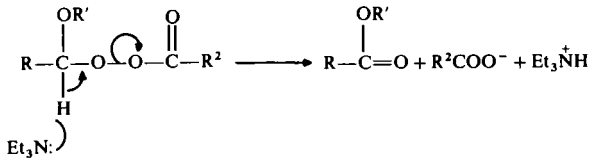


(31)

Acylation prior to base application results in better yields, since an acyloxy group is a better leaving group than a hydroxide (equation 32)[96]. α-Alkoxyalkyl hydroperoxides can undergo hydrolysis to the corresponding aldehydes or ketones together with hydrogen peroxide (equation 33)[97]. They can combine with a carbonyl group either inter-[98] or intramolecularly[99] as shown in the propenylpulegol derivative (**50**).



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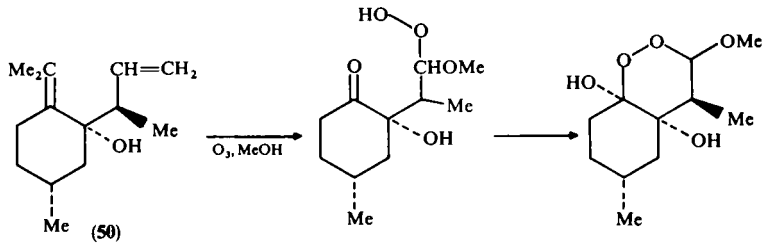
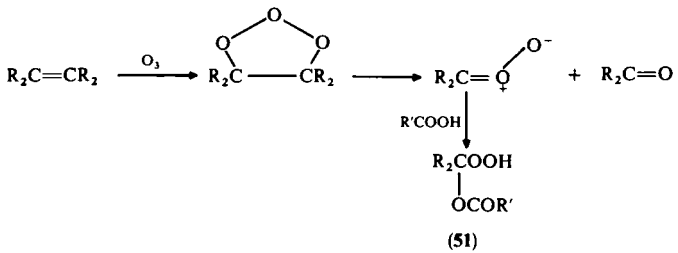
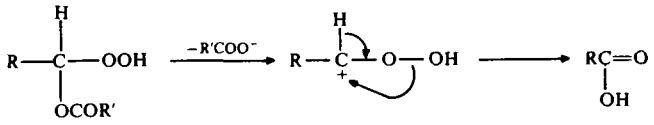


(**50**)

c. Acyloxyalkyl hydroperoxides. Ozonolysis in the presence of a carboxylic acid brings about the formation of an acyloxyalkyl hydroperoxide (**51**), similar to the formation of the alkyloxy derivative. The acyloxy derivatives can be reduced to aldehydes, and upon elimination of carboxylic acid they may be converted to acids (equation 34). A peroxide (**52**) was formed by interaction of the acyloxyalkyl hydroperoxide with the aldehydic fraction in the ozonolysis of *cis*-9-octadecene in the presence of acetic acid[100].



(**51**)



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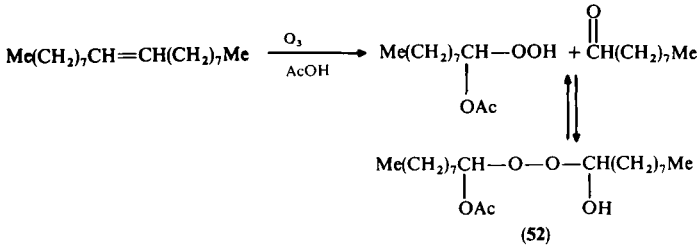
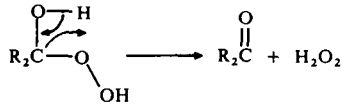


(52)

d. α-Hydroxyalkyl hydroperoxides. α-Hydroxyalkyl hydroperoxides are formed when the ozonolysis is carried out in the presence of water. They are unstable compounds which can lose hydrogen peroxide and yield ketones or aldehydes (equation 35)[101]. They were also reported to rearrange to carboxylic acids (equation 36)[102] or convert into dihydroxy dialkyl peroxides (equation 37)[103].



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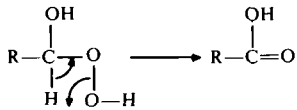
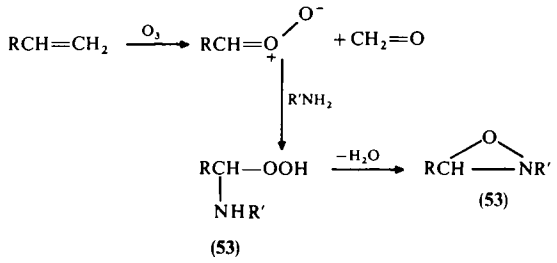


(36)

(37)

e. Products of amozonolysis. The ozonolysis in the presence of ammonia and amines was called by Fremery and Fields[104] 'amozonolysis'. The amino hydroperoxides which are formed by addition of the amine to the carbonyl oxide (equation 38) are unstable intermediates which tend to either cyclize to oxaziridines (**53**) or polymerize[105]. The formation of 3,4-dioxazolidines was reported as well (equation 39)[106]. Ozonolysis of cyclopentadiene in the presence of ammonia resulted in a considerable amount of pyridine, which is the product of reductive amination[106]. The 2-pentadial (**54**) is formed by the reduction of the carbonyl oxide group, leading to pyridine (equation 40). Ozonolysis of cyclic olefins, followed by reduction with $Na(CN)BH_3$ and treatment with primary amines, gave rise to cyclic amines[107] (equation 41). The aza crown ether (**55**) was similarly prepared from 2,5-dihydrofuran and *N,N'*-diphenylethylenediamine (equation 42)[107].



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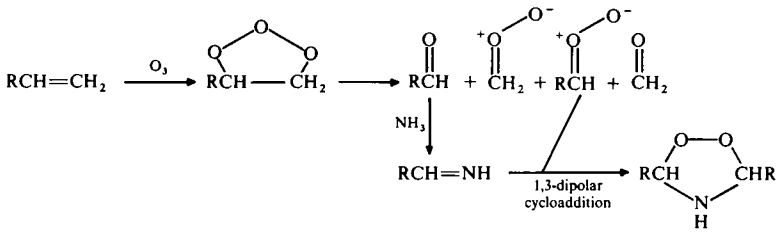

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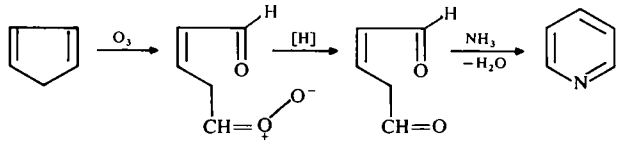

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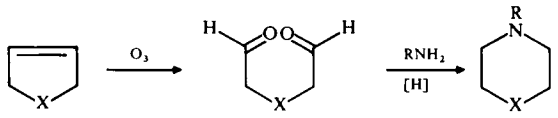

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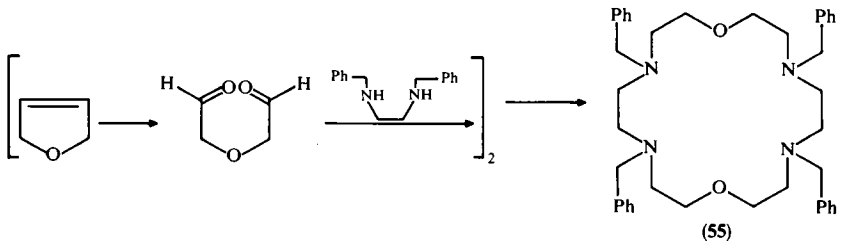
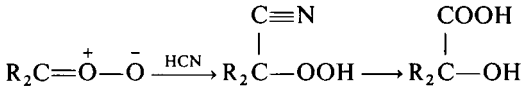


(42)

f. Products of cyanozonolysis. This term was introduced by Fields[108] who studied the ozonolysis of alkenes in the presence of hydrogen cyanide. The cyano hydroperoxides are again unstable and tend to decompose to hydroxy acids (**56**; equation 43). Cyclooctene was thus transformed into 2,9-dihydroxysebacic acid (**57**; equation 44) and indene into the lactone **58** (equation 45).



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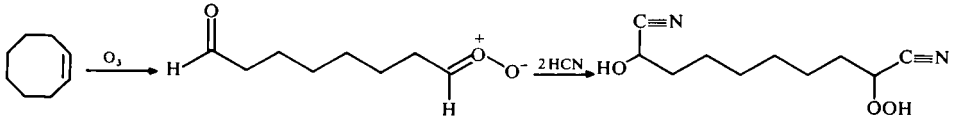

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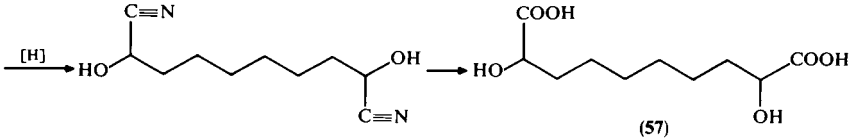

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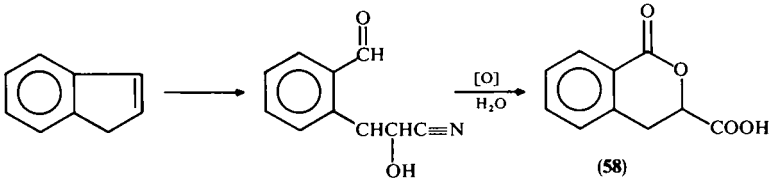
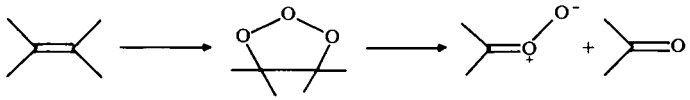


(45)

(58)

g. Diperoxides. Ketone diperoxides (**59**) are the major products in the ozonolysis of tetrasubstituted olefins[109] in nonparticipating solvents, and are side products in other cases. Because of decreased 1,3-dipolarophilic character of the ketones which are formed in the ozonolysis of tetrasubstituted alkenes, they fail to recombine with the carbonyl oxide and the latter undergoes a 3 + 3 cycloaddition to form the diperoxide. This is probably a nonconcerted $n4 + n4$ symmetry-forbidden cycloaddition (equation 46). Diperoxides are stable, high melting compounds which were shown to exist in the chair conformation[110]. The pyrolysis and photolysis of ketone diperoxides can lead to ketones (equation 47)[111]. The photolysis of cyclohexanone diperoxide resulted in the formation of macrocyclic compounds (Scheme 7)[112].



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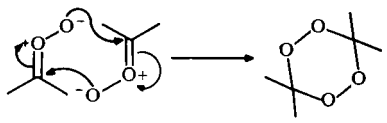

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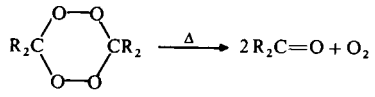

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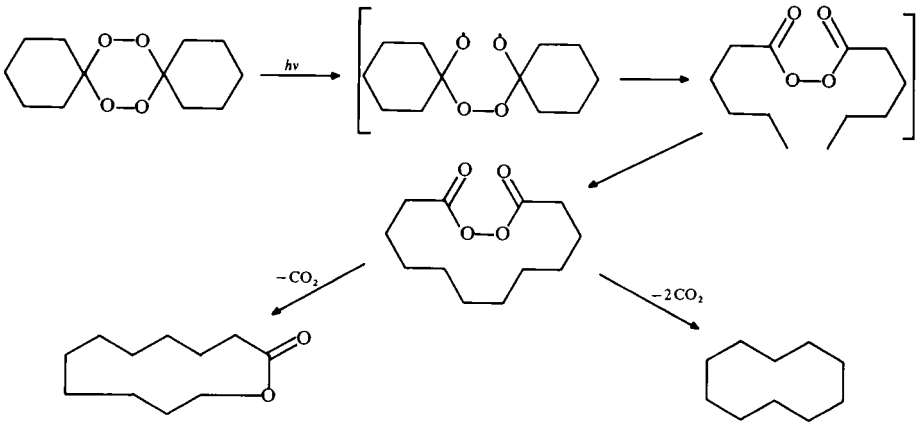
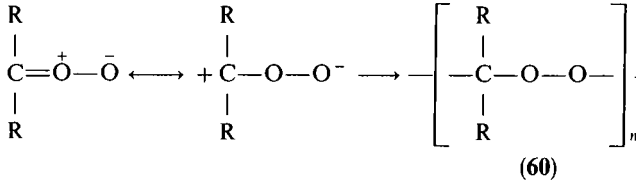


SCHEME 7. Photolysis of cyclohexane diperoxide

3. *Peroxidic oligomers and polymers*

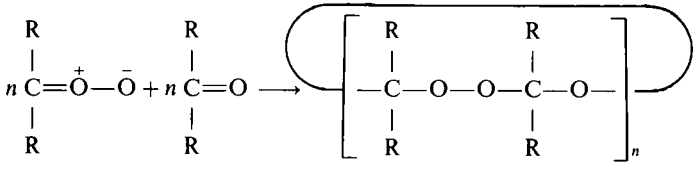
Ozonolysis of olefins in nonparticipating solvents gives rise, to some extent, to polymeric products.

Criegee proposed that polymeric and oligomeric peroxides from tetrasubstituted ethylenes were polymers of the carbonyl oxide zwitterion (equation 48)[113]. Other authors have shown[114] that the oligomers are co-oligomers (mainly cyclic) of carbonyl oxides and carbonyl compounds (aldehydes or ketones). Such an oligomer will have alternative ether and peroxide linkages, as shown in structure **61** (equation 49). Greenwood and Rubinstein[115] believe that the oligomer structure is irregular, e.g. a random combination of structures **60** and **61** (i.e. **62**). Their structure is based on NMR and IR spectra. They



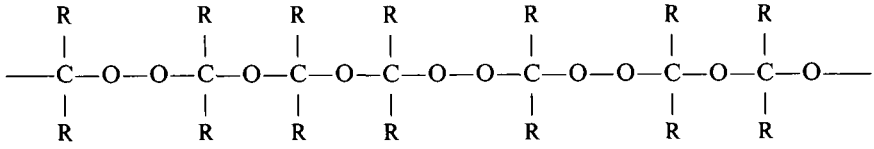
(48)

(60)



(49)

(61)

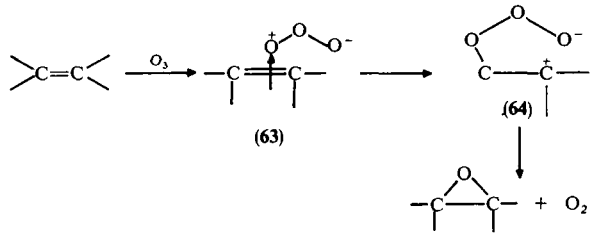


(62)

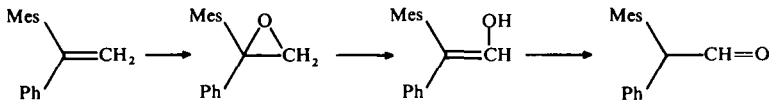
also suggested that they were open-chain oligomers with trioxy linkages present occasionally. Criegee and Lohaus[109] reported a highly explosive cyclic trimer of acetone carbonyl oxide and also a carbonyl oxide polymer, alongside with the formation of a diperoxide.

4. Epoxides

a. Direct epoxidation by ozone. Olefins with bulky groups were shown to undergo, to a large extent, epoxidation at the double bond[116]. The mechanism which was proposed[116] consists of the electrophilic attack of a terminal oxygen in the ozone molecule to form intermediate **64** (equation 50). It was also assumed that the π-complex (**63**) precedes this attack. Ring closure to epoxide occurs with the formation of molecular oxygen. The epoxides which are formed sometimes[116] rearrange spontaneously to carbonyl compounds (equation 51). The molecular oxygen which is formed was later shown to be singlet oxygen[117]. The amount of partial cleavage, e.g. epoxide formation, increases with the bulkiness of the substituents around the double bond. The epoxide formation is stereospecific; *cis* and *trans* isomers of 1-naphthyl-1-phenyl-1-propene gave as major products their respective *cis* and *trans* epoxides, uncontaminated with the other isomer (equation 52)[118]. Stereoselectivity was also observed[119] in the ozonolytic epoxidation of cyclic alkenes. Thus alkene **65** yielded the β-epoxide exclusively (equation 53). Other methods of epoxidation lead to both α and β isomers.



(63) (64) (50)



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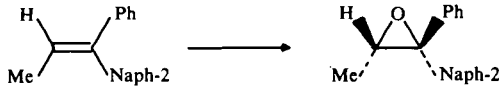

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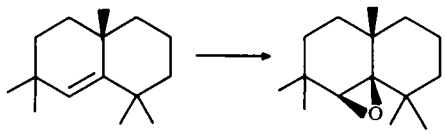
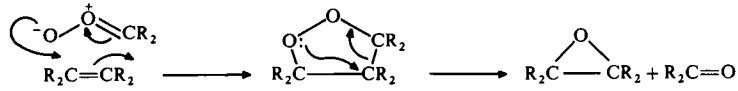


(65) β-epoxide (53)

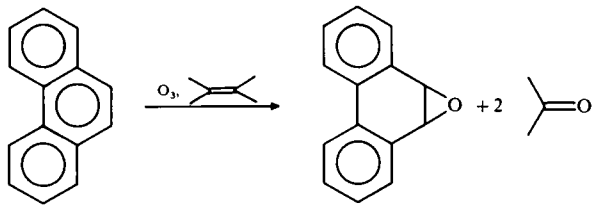
b. Indirect epoxidation. Some of the peroxidic products of ozonolysis can epoxidize the double bond of an olefin. The peracids which are by-products of ozonolysis are sometimes responsible for small amounts of epoxides present in ozonolysis of alkenes. It was shown by both calculation[48,120] and experiment[121] that the intermediate carbonyl oxide is an epoxidizing agent. Carbonyl oxides which were prepared by nonozonolytic routes were shown to epoxidize double bonds[121]. At the present time it is assumed that epoxides are formed both by direct electrophilic attack of ozone and by carbonyl oxide. Gillies[122] suggested a mechanism in which a 1,3-dipolar cycloaddition is again involved (equation 54).



(66) (67) (54)

Ab initio calculations[120] show that in the reaction of $CH_2{=}O^+{-}O^-$ with ethylene it transfers oxygen to give formaldehyde and ethylene oxide. The calculated transition state energies of the epoxidation are 4–8 kcal mol^{-1}, comparable to activation energies of cycloaddition reactions which are encountered in the ozonolysis of alkenes. Cremer proposed[120] a mechanism similar to that described in equation 54. The preferred collision mode is rationalized on the basis of FMO interactions in which formaldehyde carbonyl oxide ($CH_2{=}O^+{-}O^-$) adds to ethylene, yielding 1,2-dioxolane (**66**, R = H). The energy requirements for this path are similar to those for expoxidation. The 1,2-dioxolane ring decomposes immediately giving, among other products, oxirane (**67**, R = H).

Ozonolysis of 2,3-dimethyl-2-butene in the presence of phenanthrene at low temperatures resulted in epoxidation of the phenanthrene (equation 55)[123]. The epoxidation was probably brought about by the acetone carbonyl oxide which was formed and other ozone-derived oxidants. Formation of an epoxide hydroperoxide by intramolecular addition of α-hydroxy group to carbonyl oxide was described recently[124] and will be discussed in the following section.



(55)

C. Ozonolysis of Particular Types of Olefins

In some reviews[2,10,125] products which did not fit into the general pattern discussed above were termed 'abnormal' or 'anomalous', whether they were major products or

side products of ozonolysis. However, these 'abnormal' reactions can be general be predicted by considering the structure and functional groups of the particular compound. The ozonolysis of such structures will also be discussed in the following subsections.

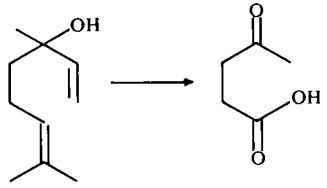
1. Ozonolysis of allyl alcohols, allyl ethers and allyl amines

Young and his coworkers[126] studied the ozonolysis of allyl alcohols and ethers and estimated the amount of acid formed by cleavage at the allylic carbon. It ranged from about 23% in 2-buten-1-ol to 60% in cinnamyl alcohol (equation 56).

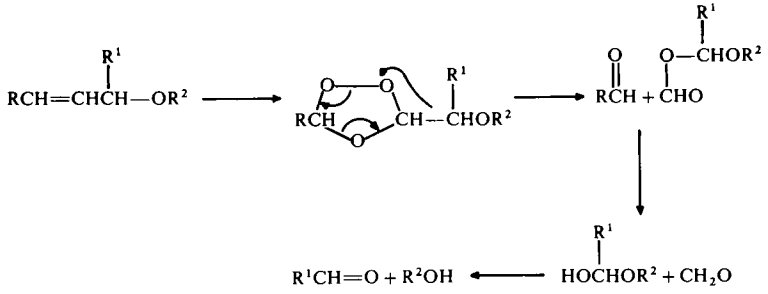
$$\mathrm{RCH{=}CHCH_2OH} \xrightarrow[2.\ \mathrm{HOH}]{1.\ \mathrm{O_3}} \mathrm{RCH{=}O + HCOOH + CH_2{=}O} \qquad (56)$$

R = Me, Ph

Vlad and Souček[127] were surprised to obtain levulinic acid (**69**) upon ozonolysis of linalool (**68**). The mechanism which was proposed for this frequently occurring reaction involves a rearrangement of the final ozonide (equation 57)[2].



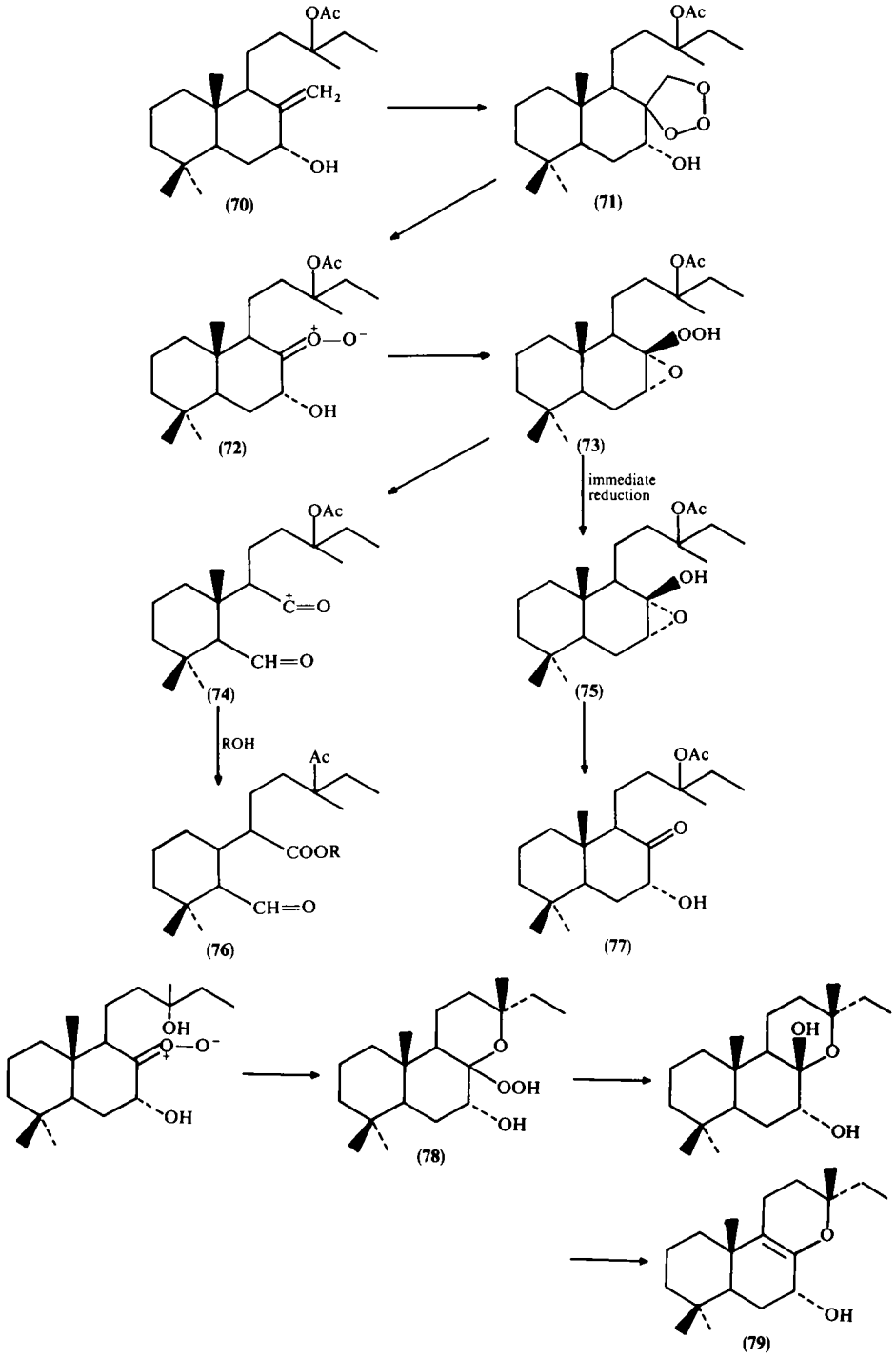
(**68**) (**69**)

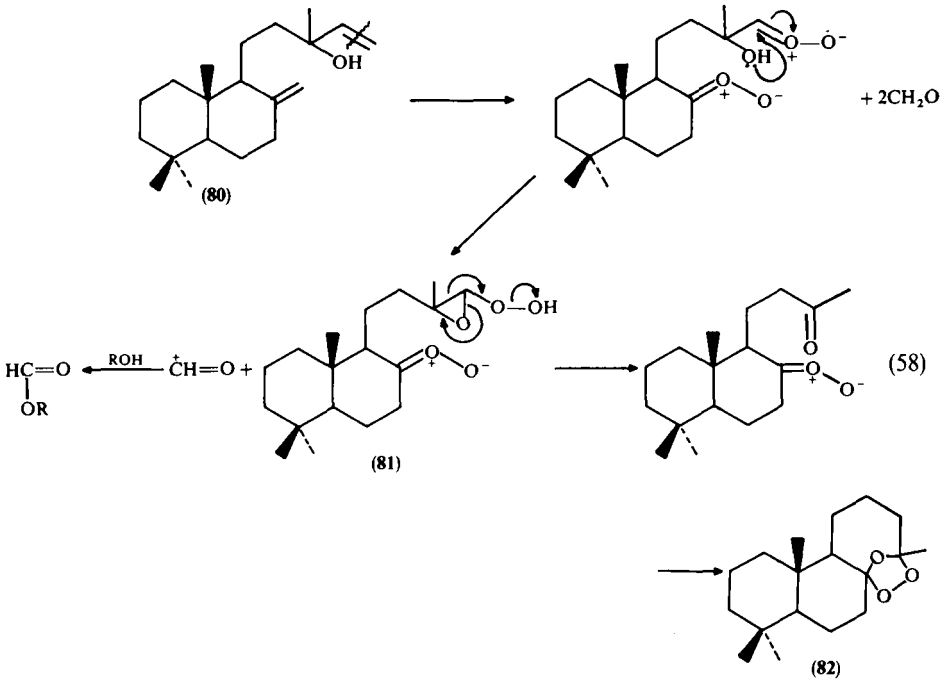


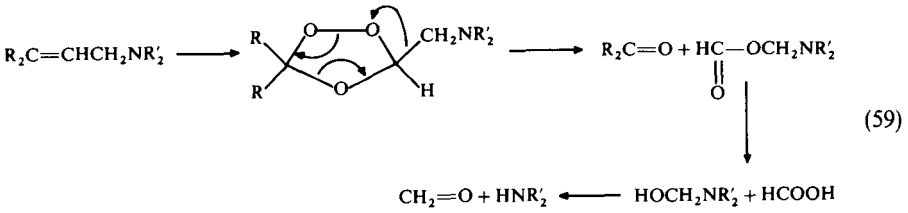
(57)

Recently[124], a different mechanism was suggested which is based on the study of the ozonolysis of allylic hydroxy olefins derived from manool (**70**). This mechanism involves the formation of an epoxy hydroperoxide (**73**) by intramolecular addition. Long reaction times resulted in the formation of the acylium intermediate (**74**) which is trapped by either intra- or intermolecular nucleophilic attack. Evidence for the formation of the epoxy hydroperoxide was afforded by the immediate reaction (by triethylphosphite) to the hydroxy epoxide (**75**), which rearranged to the hydroxy ketone (**77**). When the side-chain hydroxyl group was not protected, it gave a six-membered cyclic alkoxy hydroperoxide (**78**) which, after reduction, lost a molecule of water yielding **79**.

The manool derivative (**80**) with the allylic hydroxyl group in the side chain gave, by treatment with ozone, the intramolecular ozonide (**82**)[128]. The formation of **82** (equation 58) was explained by formation of an epoxy hydroperoxide as an intermediate


OAc
CH2
OH
(70)
OAc
O
O
O
OH
(71)
OAc
O—O⁻
OH
(72)
OAc
OOH
O
(73)
immediate reduction
OAc
C=O
CH=O
(74)
OAc
OH
O
(75)
ROH
Ac
COOR
CH=O
(76)
OAc
O
OH
(77)
OH
O—O⁻
OH
O
OOH
OH
(78)
OH
O
OH
O
OH
(79)

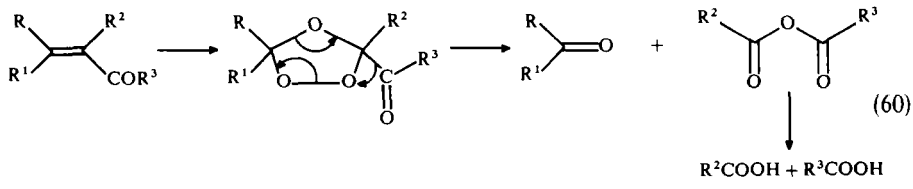


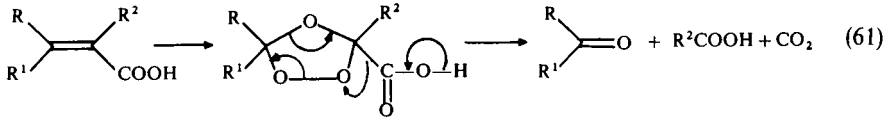


(**81**). Allyl amines decompose upon treatment with ozone to give high yields of formic acid, as shown in equation 59.

2. *Ozonolysis of α,β-unsaturated carbonyl compounds*

The presence of a carbonyl or a carboxyl group near the double bond brings about 'anomalous' types of products. Very often, by letting the reaction mixture decompose over a period of several days, acid anhydrides and carbon dioxide are formed. This subject was discussed and summarized in several reviews[2,10,125]. The accepted

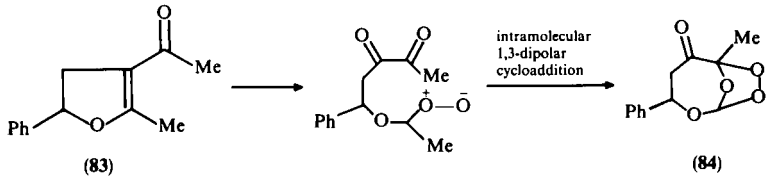




(61)

mechanism is that of Barton and Seoane[128], and is shown in equations 60 and 61. Similar results were observed in cyclic ketones such as indenone and naphthoquinone derivatives[2,10,125].

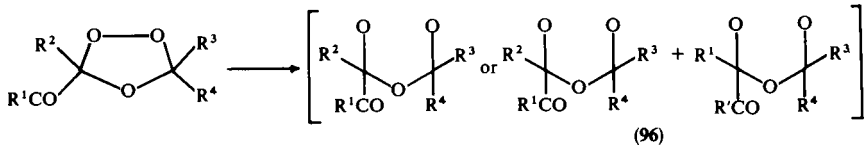
Bunnelle and coworkers reported[129] a very stable ozonide (**84**) from the ozonolysis of the cyclic vinyl ether (**83**), which is also an α,β-unsaturated carbonyl compound. They called this an 'anomalous' ozonide, but it is not a product of rearrangement but rather an intramolecular cross ozonide, formed by the insertion of the side-chain carbonyl group (equation 62).

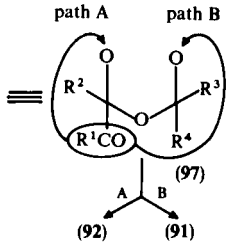


(62)

The unexpected stability of this ozonide was attributed to the electron enrichment by the etheric moiety. The 1,2,4-trioxolene ring survived reduction and other manipulations. Its structure was established by NMR and X-ray techniques.

Except for this cross ozonide (**84**) and until very recently, α-oxo-ozonides were not isolated. However, Griesbaum and coworkers reported[19c] the isolation of several α-oxo-ozonides, mostly by ozonolysis on polyethylene and some in pentane. They prepared the 2,4-dinitrophenylhydrazone (DNPH) derivatives (**94**) of these ozonides which were found to be very stable[19c]. Acyclic α-oxo-alkenes gave isolable ozonides (Scheme 8). In addition to anhydrides (**91**), products of 1,3-acyl migration were identified (**92**). The authors propose an intermediate, **96**, in which the peroxidic bond was cleaved, enabling the acyl group to migrate to each one of the exposed oxygens. Intermediate **96** is suggested to be either of a diradical or ionic character (equation 63). Griesbaum and coworkers[19e] also isolated the α-diozonides (**93**) which are formed by 1,3-dipolar





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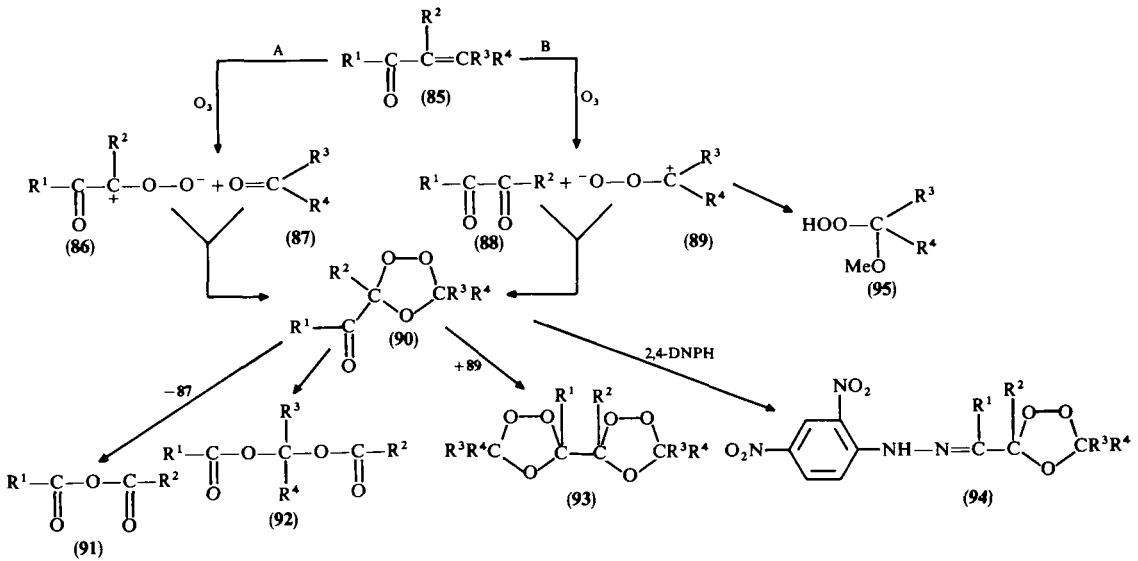
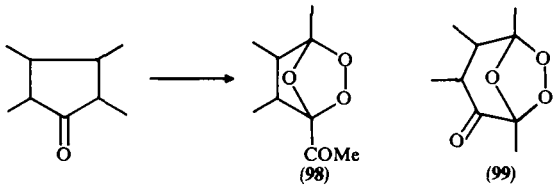


	a	b	c	d	e	f	g	h	i
R^1	CH_3	CH_3	*t*Bu	CH_3	CH_3	CH_3	H	H	H
R^2	H	CH_3	*t*Bu	H	H	CH_3	H	CH_3	CH_3
R^3	H	H	H	H	CH_3	CH_3	CH_3	H	CH_3
R^4	H	H	H	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3

SCHEME 8. Ozonolysis of α,β-unsaturated olefins



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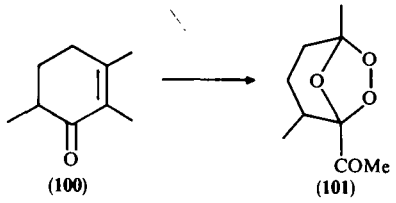
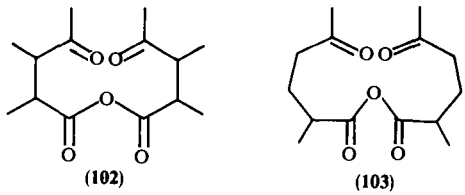
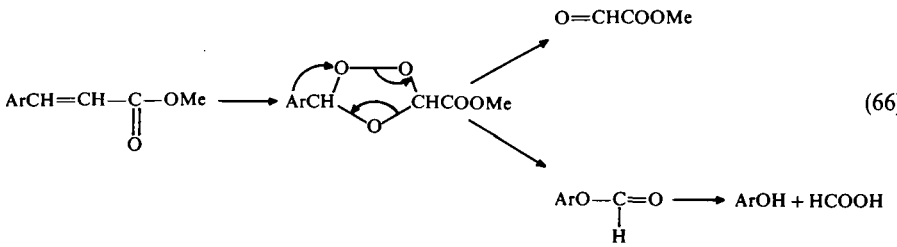


(65)

cycloaddition of the intermediate carbonyl oxide (**89**) with the carbonyl groups of the α-oxo-ozonide (**90**). They also isolated two isomeric ozonides in the ozonolysis of cyclopentanone. One is the 'normal' ozonide **99** (equation 64) and the other is the intramolecular insertion product (**98**). The cyclohexenone derivative (**100**) gave (equation 65) only the 'abnormal' acetyl cyclopentanone ozonide (**101**).





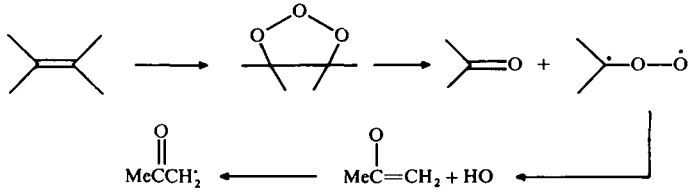
(66)

On decomposition the cyclic ozonides **98** and **101** gave migration products as well as the disproportionation products **102** and **103**, respectively. In ozonolysis of cinnamic acid esters, the migrating group is not the carbomethoxy group but rather the aromatic ring (equation 66). Kolsaker and Bailey conducted a detailed study[130] of cinnamic esters and similar compounds. They propose a mechanism for the phenol formation which involves rearrangement in the oxyalkyl hydroperoxide intermediates (equation 67).

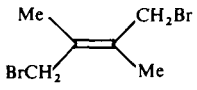
(67)

3. Ozonolysis of tetraalkylated ethylenes

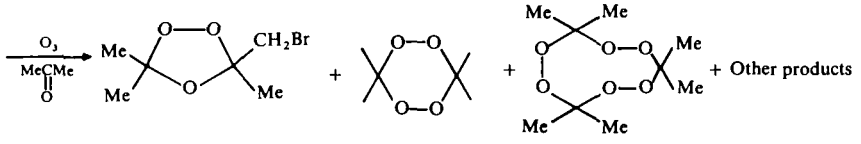
The major products of ozonolysis of 2,3-dimethyl-2-butene and other tetrasubstituted ethylenes in nonparticipating solvents, as mentioned in Section II.B.2.g, are diperoxides. A careful study of the ozonolysis of tetramethylethylene in the gas phase[131] by FTIR showed that the Criegee intermediate $M_2C—O—O$ biradical, which is the equivalent of carbonyl oxide, is formed. However, it fails to give any ozonide but rather decomposes through an acetonyl radical (equation 68). In solution, the ozonolysis proceeds in the same way only until the carbonyl oxide is formed. The latter fails to recombine to the final ozonide and, in the absence of any other trapping agent, it prefers to dimerize to a diperoxide (see Section II.B.2.g) or to polymerize (Section II.B.3). There are three cases in which final ozonides could be observed upon ozonolysis in solution. One case includes the ozonides of cyclobutene and cyclopentene with substituents at positions 1 and 2. This case was discussed in earlier reviews[10]. The second case concerns olefinic compounds that are activated by electron-withdrawing groups like in **104**[132], and which yield, upon ozonolysis, ketones. The 1,3-dipolarophilic character of acetone and other ketones is much decreased as compared to aldehydes and they leave the solvent cage before they recombine. Therefore, by carrying out the ozonolysis in acetone as a solvent Murray and coworkers[133] found some evidence for the insertion of acetone into the final ozonide (equation 69).



(68)



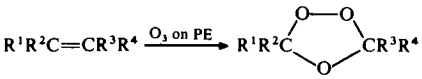
(104)



(69)

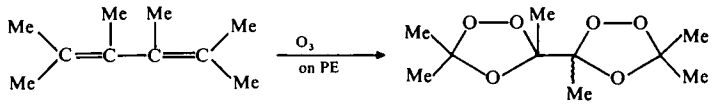
Very recently[18,19b], Griesbaum and his coworkers overcame this problem by carrying out the ozonolysis on polyethylene. It seems that the solid matrix provides enhanced proximity for the fragments to recombine. The isolation and complete characterization of four tetrasubstituted ozonides (equation 70) and the diozonide of a hexasubstituted diene (**105**; equation 71) were reported[19b]. Only in the case of tetramethylethylene were there traces of diperoxide and triperoxide.

The diozonide **105** underwent thermal decomposition to yield the diacetyl oxyperoxide (**107**) and the lactone **106** (Scheme 9).



(70)

(a) $R^1 = R^2 = R^3 = R^4 = Me$
(b) $R^1 = R^2 = Me$, $R^3 = R^4 = Et$
(c) $R^1 = R^3 = Me$, $R^2 = R^4 = Ph$
(d) $R^1 = R^2 = Me$, $R^3 = R^4 = Ph$



(71)

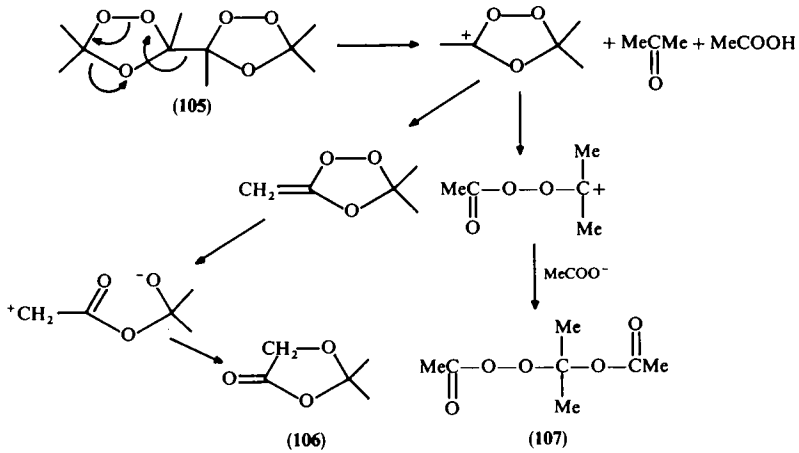
(105)

Cycloalkylidenecycloalkanes are also tetrasubstituted ethylenes, and their ozonolysis was studied by Griesbaum and his group[19b]. Symmetrical and unsymmetrical cycloalkylidenecycloalkanes (**108**) afforded spiro-1,2,4-trioxolanes (**109**), which had not been isolated before. Their thermal decomposition gave cyclic ketones (**110**) and lactones (**111**), whereby photolysis afforded macrocyclic anhydrides (**112**); see Scheme 10.

4. Ozonolysis of cycloalkenes

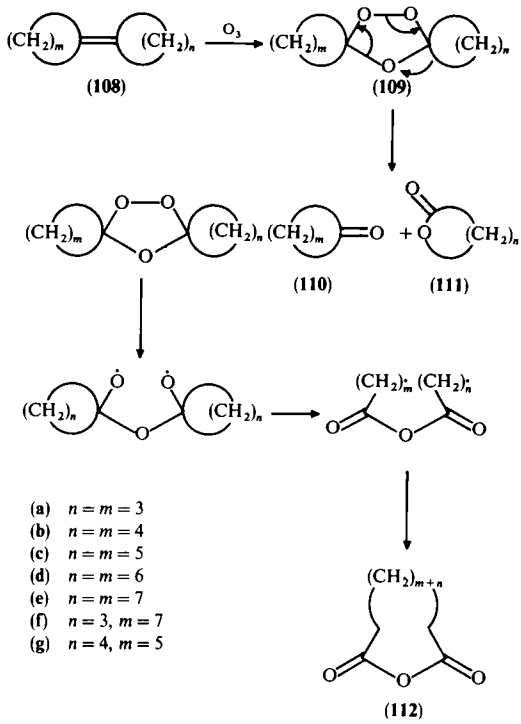
Cyclobutene and cyclopentene derivatives react with ozone similarly to acyclic olefins. The produced cyclic ozonides were isolated and identified[2]. The carbonyl oxide and the carbonyl intermediates are in close proximity and interact to yield stable six- and seven-membered ring ozonides, respectively (equations 72 and 73). These ozonides were, as mentioned in the previous section, the first isolated tetrasubstituted ozonides.

Ozonolyses of 1-methylcyclobutene and 1-methylcyclopentene in methanol were studied recently[134b]. In each case all possible methoxyhydroperoxides were obtained (**113** and **114**) as well as the peroxyhemiacetals (**117** and **118**). 1-Methylcyclobutene gave, in addition, the hydroperoxy tetrahydrofurans **115** and **116** (Scheme 11).

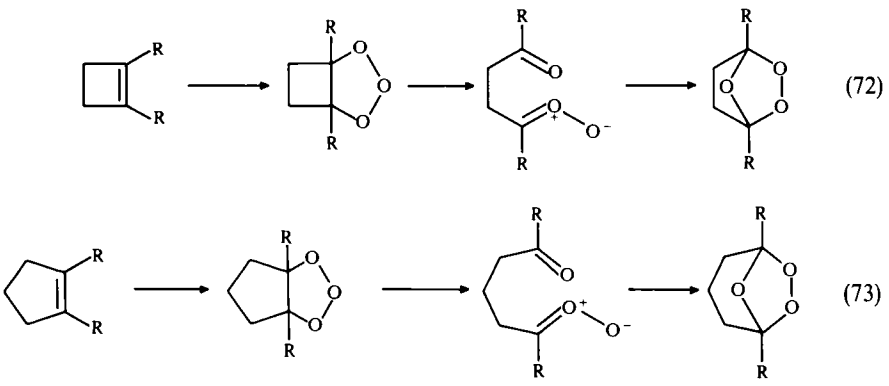


(105) (106) (107)

SCHEME 9

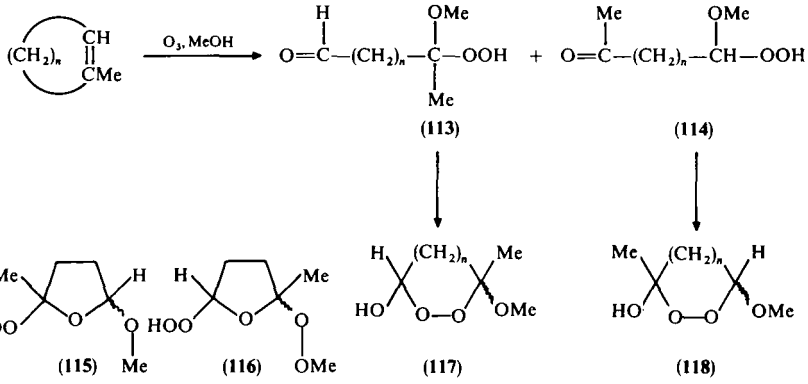


SCHEME 10

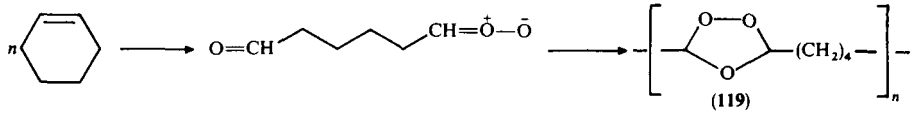


Early reports on ozonolysis of cyclohexene and its derivatives indicate the formation of peroxidic polymers. Cyclohexene was reported[134] to yield a polymer which contained successive ozonide rings (**119**; equation 74).

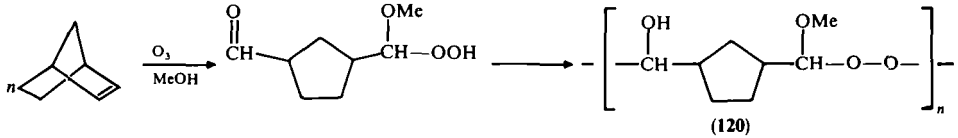
The structure suggested[135] for the polymer which was obtained by the ozonolysis of norbornylene in methanol is that of a polyperacetal (**120**; equation 75). Gas-phase



SCHEME 11

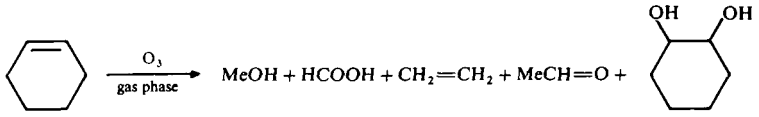


(74)



(75)

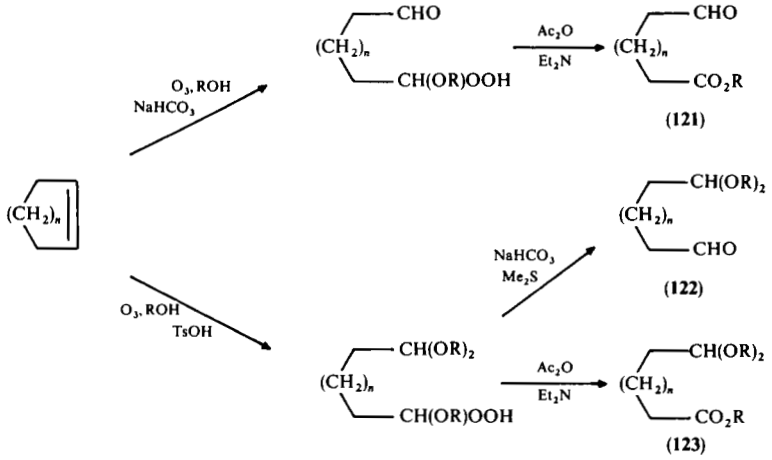
ozonolysis of cyclohexene gave a mixture of formic acid, methanol, acetaldehyde, ethylene and 1,2-cyclohexanediol (equation 76)[136].



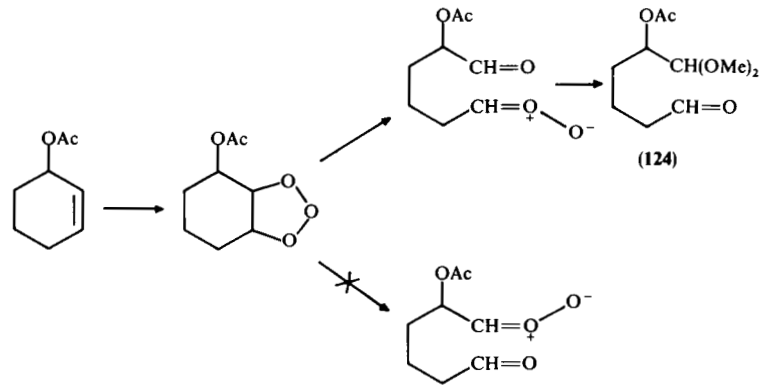
(76)

A simple modification of ozonolytic workup procedures for cyclic olefins[96] gave rise to a useful synthetic application. The ozonolysis was carried out at −78 °C in CH_2Cl_2–alcohol either buffered with $NaHCO_3$ or by using *p*-toluenesulfonic acid (Scheme 12). These were followed either by dehydration or reduction, leading to a variety of products with differentiated terminal functionalities (**121**–**123**). This was applied to several cyclic olefins and results are summarized in Table 2.

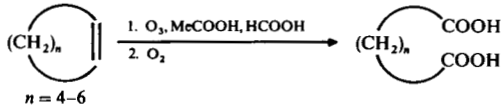
The influence of an acetoxy group on the regioselectivity of the cleavage of the primary ozonide of substituted cyclohexene was reported[96]. The sole product observed in ozonolysis and workup of 3-acetoxycyclohexene was **124**, indicating the regioselectivity induced by the acetoxy group.



SCHEME 12

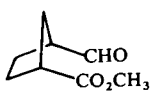
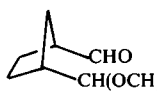
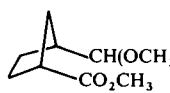


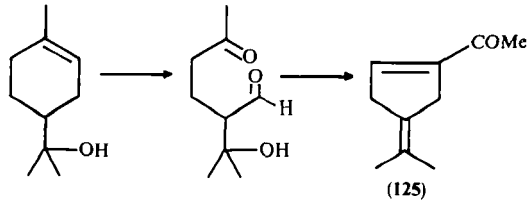
A practical method for the preparation of α,ω-dicarboxylic acids from cycloolefins was described[137] by ozonolysis in acetic–formic acid mixture, followed by oxidation with oxygen (equation 77). The ozonolysis of α-terpineol followed by steam distillation in the presence of acids gave the cyclopentyl ketone (**125**)[138]; see equation 78. The same group reported[139] an intramolecular oxygen transfer upon ozonolysis of a diphenylcyclopentene derivative (**126**) to give **127** (equation 79). In the presence of methanol it gave the hemiperacetal (**128**). Structures were elucidated by X-ray techniques.



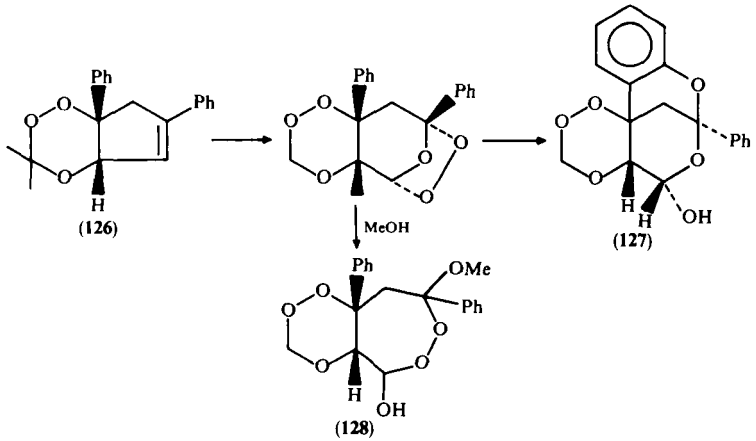
(77)

TABLE 2. Ozonolysis of cyclic alkenes in methanol

Alkene	Alcohol	Aldehyde-ester	Yield (%)	Acetal-aldehyde	Yield (%)	Acetal-ester	Yield (%)
Cyclohexene	MeOH	$MeO_2C(CH_2)_4CHO$	96	$(MeO)_2CH(CH_2)_4CHO$	93	$(MeO)_2CH(CH_2)_4CO_2Me$	83
Cyclohexene	*t*-BuOH	$t\text{-}BuO_2C(CH_2)_4CHO$	91	—		—	
Cyclopentene	MeOH	$MeO_2C(CH_2)_3CHO$[12]	47	$(MeO)_2CH(CH_2)_3CHO$	48	$(MeO)_2CH(CH_2)_3CO_2Me$	72
Cycloheptene	MeOH	$MeO_2C(CH_2)_5CHO$	93	$(MeO)_2CH(CH_2)_5CHO$	95	$(MeO)_2CH(CH_2)_5CO_2Me$	100
Cyclododecene	MeOH	$MeO_2C(CH_2)_{10}CHO$	94	$(MeO)_2CH(CH_2)_{10}CHO$	95	$(MeO)_2CH(CH_2)_{10}CO_2Me$	83
Norbornylene	MeOH		90		90		92

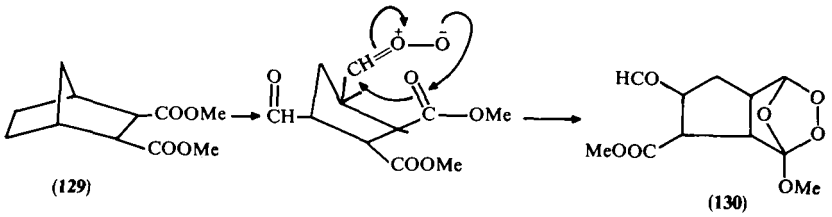


(125) (78)

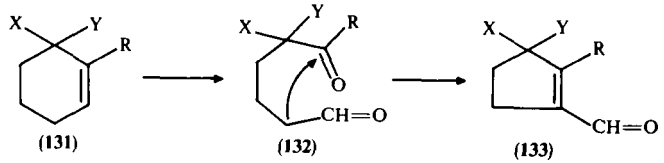


(79)

There are numerous reports from the group of Odinokov and Tolstikov on the use of cycloolefins in the synthesis of natural products by means of ozonolysis. In one of the reports[140] an intramolecular insertion of an ester group occurred upon ozonolysis of 3,4-dicarbomethoxynorbornylene (**129**) resulting in the methoxy ozonide (**130**); see equation 80. Ring contraction was reported[141] by ozonolysis and workup of cyclohexene derivatives to cyclopentene carboxaldehyde (**133**). This is the result of an intramolecular



(80)

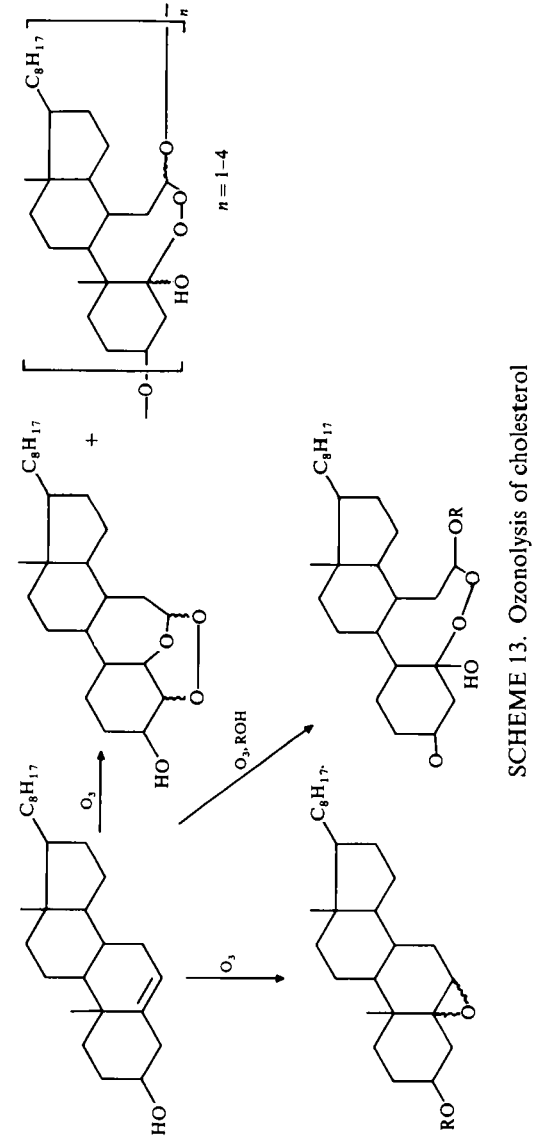


(81)

R = H, Me, Et, OEt

(a) X, Y =

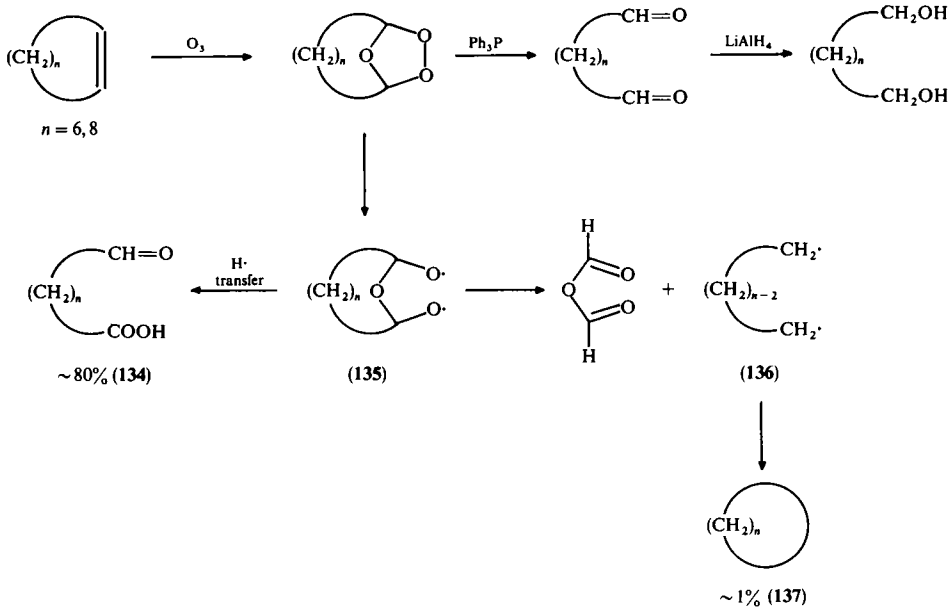
(b) X = H, Y = Me



SCHEME 13. Ozonolysis of cholesterol

Claisen–Schmidt condensation of the intermediate dicarbonyl open-chain derivative **132** (equation 81). A recent work on the ozonolysis of cholesterol[142] is summarized in Scheme 13.

In the works on cycloolefins with larger than six-membered rings which were discussed above, it was impossible or there was no attempt to isolate ozonides. Recently[19b], the ozonolyses of cyclooctene, cyclodecene and norbornene on polyethylene were reported to produce isolable ozonides. Their thermal and reductive decompositions were studied as well (Scheme 14). These results were rationalized by homolytic cleavage of the peroxide upon heating. The diradical **135**, which is formed, undergoes either an intramolecular hydrogen transfer to yield **134** or it may split off formic anhydride to yield the cycloalkane (**137**) via the diradical **136**. A diradical was also suggested[19b] in the case of the norbornene ozonide decomposition (Scheme 15).



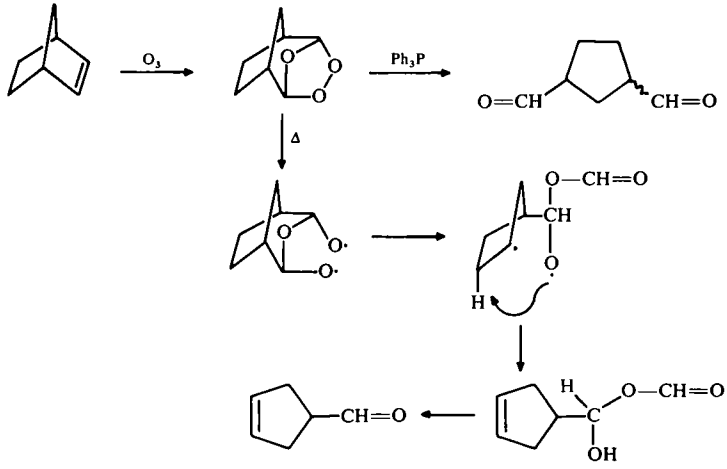
SCHEME 14

The ozonolysis of indene and its derivatives, which can be considered as cyclic olefins, was studied by several groups and is discussed in Section II.C.7.

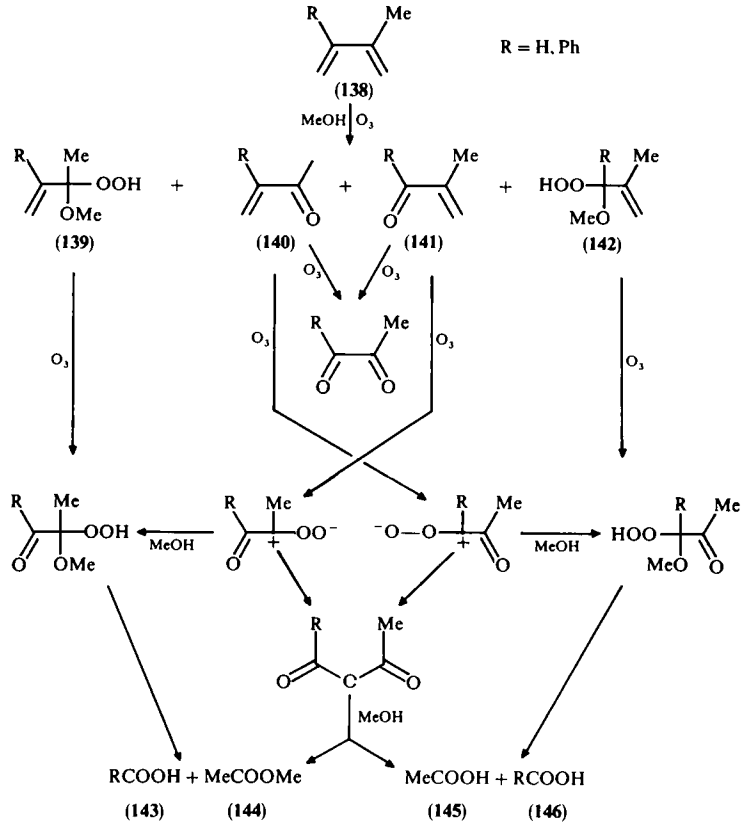
5. *Ozonolysis of dienes*

The ozonolyses of acyclic 1,3-butadiene derivatives have been extensively studied[18,19a,143]. In methanol[143], subsequent reactions of the primary cleavage products afforded products of secondary cleavage (Scheme 16). Some of the products arose from cleavage of both the double bonds and the single bonds of the diene system (**138**). The mode of formation of the abnormal cleavage products (**143–146**) was elucidated by the ozonolysis of the α,β-unsaturated intermediates (**139–142**).

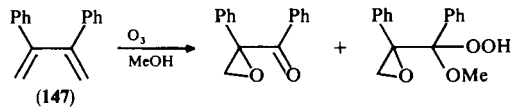
Ozonolysis of both 2,3-diphenylbutadiene (**147**) and of 2,3,4,5-tetramethyl-2,5-hexadiene (**148**) gave products in which one of the double bonds of the diene has been



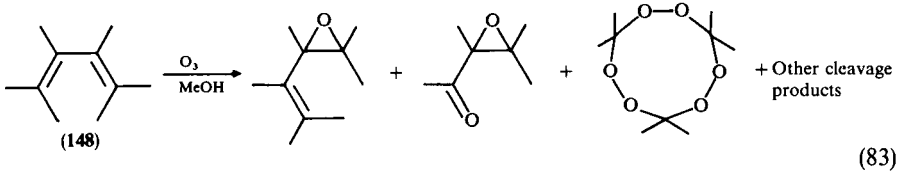
SCHEME 15



SCHEME 16

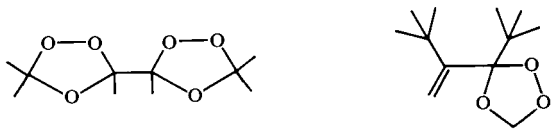


(147) (82)



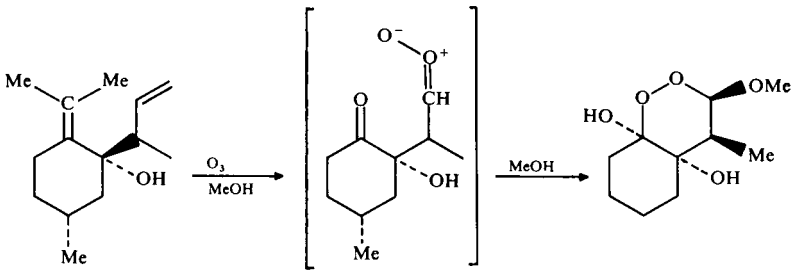
(148) (83)

epoxidized (equations 82 and 83)[143]. Ozonolysis of these 1,3-butadiene derivatives on polyethylene was investigated as well[18,19a], when it was possible to isolate both mono- and diozonides, **149** and **150**, which were found to be relatively stable.



(149) (150)

Many natural products contain nonconjugated double bonds. Studies of these compounds showed in several cases lack of selectivity[144]. In other cases, intramolecular interactions in the intermediates occur as in the case of 1-methyl-2-propenylpulegal (equation 84). Selective ozonation of one bond in a diene system is often needed in synthesis. A convenient method was reported[145] using various colored dyes as internal end-point indicators. The useful dyes and some results of selective ozonolysis are shown in Tables 3 and 4, respectively. Other attempts to ozonize dienes selectively consisted of either using ozone solutions, or using only one equivalent of ozone or by careful control of the time and flow of ozone (see the following section)[146–149].

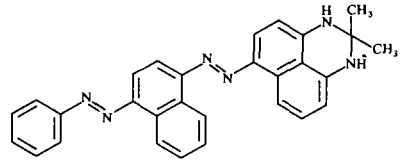


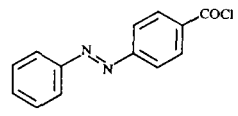
(84)

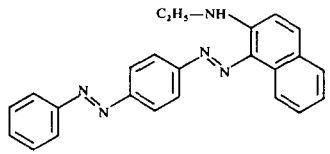
6. *Stepwise ozonolysis of cycloalkadienes*

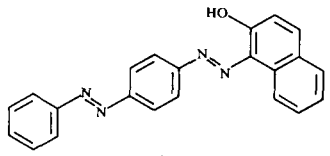
a. Conjugated cyclodienes. With molecules containing more than one olefinic linkage in the same ring, ozonolysis often occurs with remarkable selectivity. In the ozonolysis of cyclopentadiene in the presence of ammonia, the monoozonolysis product is trapped (Section II.B.2.e) to form pyridine[106]. In small rings intramolecular trapping also occurs;

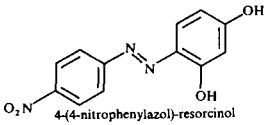
TABLE 3. Dyes used as end-pont indicators of ozonation. Reproduced from Reference 145 by permission of George Thieme Verlag

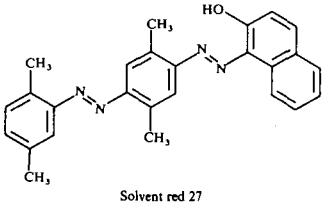


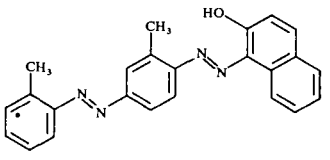








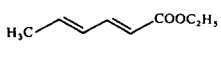
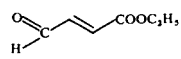
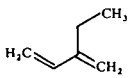
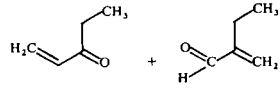
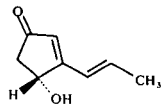
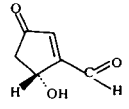
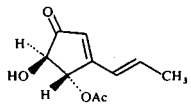
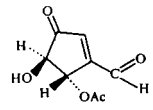
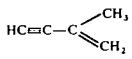
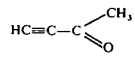
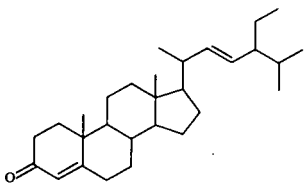
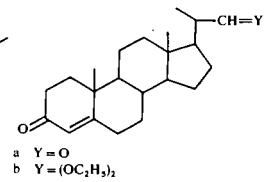


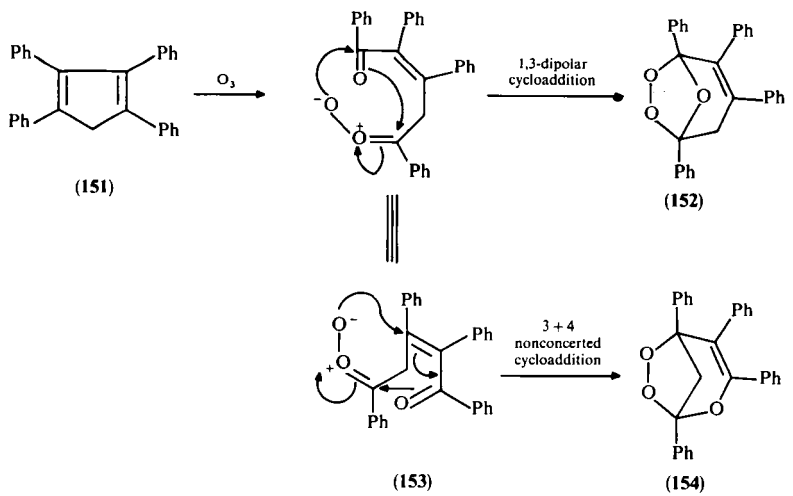


thus upon ozonolysis of 1,2,3,4-tetraphenylcyclopentadiene (**151**)[148] two products resulted from intramolecular trapping of the intermediate 5-oxopent-3-ene-1-carbonyl oxide (**153**). The ozonide **152** was formed by 1,3-dipolar cycloaddition, while the dihydropyran derivative **154** was formed by intramolecular, 3 + 4 cycloaddition (equation 85), probably in a nonconcerted process. A more systematic study on the stepwise ozonolysis of conjugated cyclohexadiene and cyclooctadiene was carried out by Hudlicky and his coworkers[149]. The control was carried out by adding a saturated solution of ozone in dichloromethane dropwise at −78 °C. The ozonolysis was followed immediately by reduction with dimethyl sulfide and the products were dicarbonyl olefins (equations 86–88). They found that the conjugated cyclodienes could be ozonized quantitatively in a stepwise manner. In substituted cyclodienes, the dicarbonyl compounds which were obtained were those derived from the ozone attack at the more substituted olefinic site.

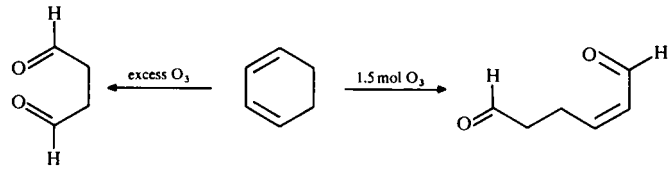
The stepwise ozonolysis of 1,3-cyclooctadiene was also reported by Schreiber and Meyers at about the same time[150], in their synthesis of the macrolide antibiotic (+)-brefeldin C.

TABLE 4. Ozonation of dienes using dyes as internal end-points indicators. Reproduced from Reference 145 by permission of George Thieme Verlag

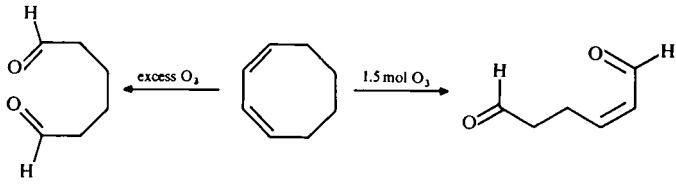
Educt	Products	Dye and solvent	Yield (%)
		Solvent red 19; ethanol	85
		Solvent red 19; methanol	64
		Solvent red 19; ethanol	90
		Solvent red 19; ethanol	85
		Solvent red 23; methanol/ether (1/1)	64
	 a Y = O b Y = $(OC_2H_5)_2$	Solvent red 23; dichloromethane/ethanol (2/1)	85



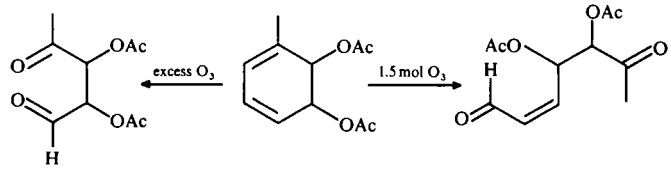
(85)



(86)

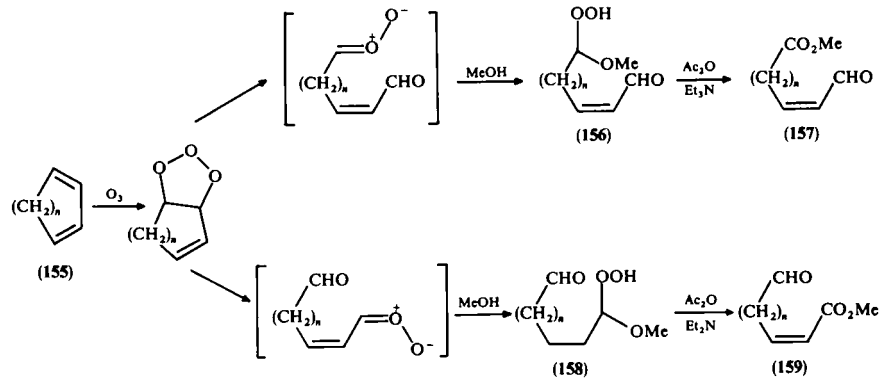


(87)



(88)

Where there is cleavage of one double bond in a conjugated cyclic system, there are two possibilities for the decomposition of the primary ozonide. One will result in a carbonyl oxide group conjugated to the remaining double bond and the other in an α,β-unsaturated aldehyde system. This regioselectivity was systematically studied recently by Wang and Zvilichovsky[151]. The ozonolysis was controlled by using Sudan Red 7B as an internal indicator (see Section II.C.5) and carried out at $-78\,^{\circ}C$ in methylene chloride containing 2–3 equivalents of methanol and buffered with sodium bicarbonate. The regioselectivity was determined by converting the methoxy hydroperoxide group with acetic anhydride and triethylamine into an ester group. Carrying out analytical scale reactions in $CDCl_3$ permitted the study of the regioselectivity also by NMR of the crude reaction mixture. The products and selectivity are summarized in Scheme 17 and



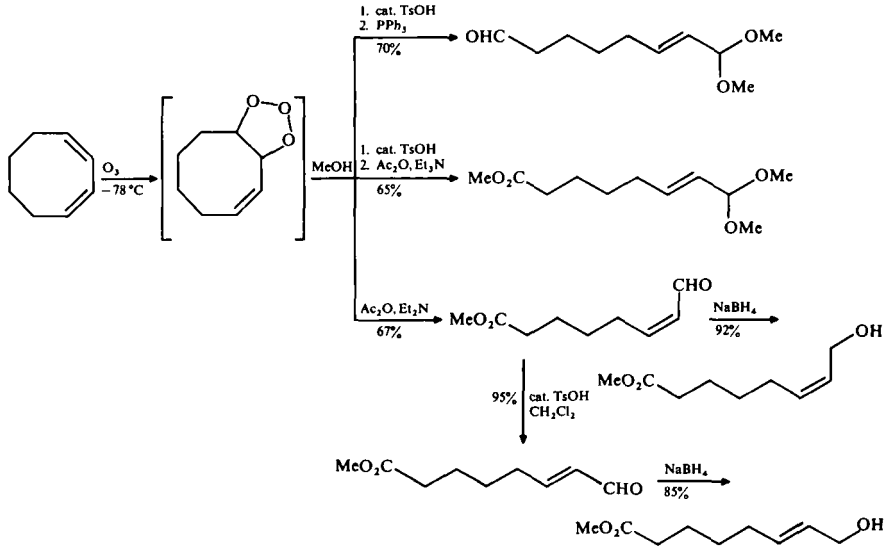
SCHEME 17

TABLE 5. Ratios of isomers[a] in the ozonolysis of 1,3 cyclic dienes (**155**)

Compound	Ratio **157**:**159**	Yield (%)[b]
(a) $n = 4$	15:1	71
(b) $n = 3$	5:1	65
(c) $n = 2$	1:8	50

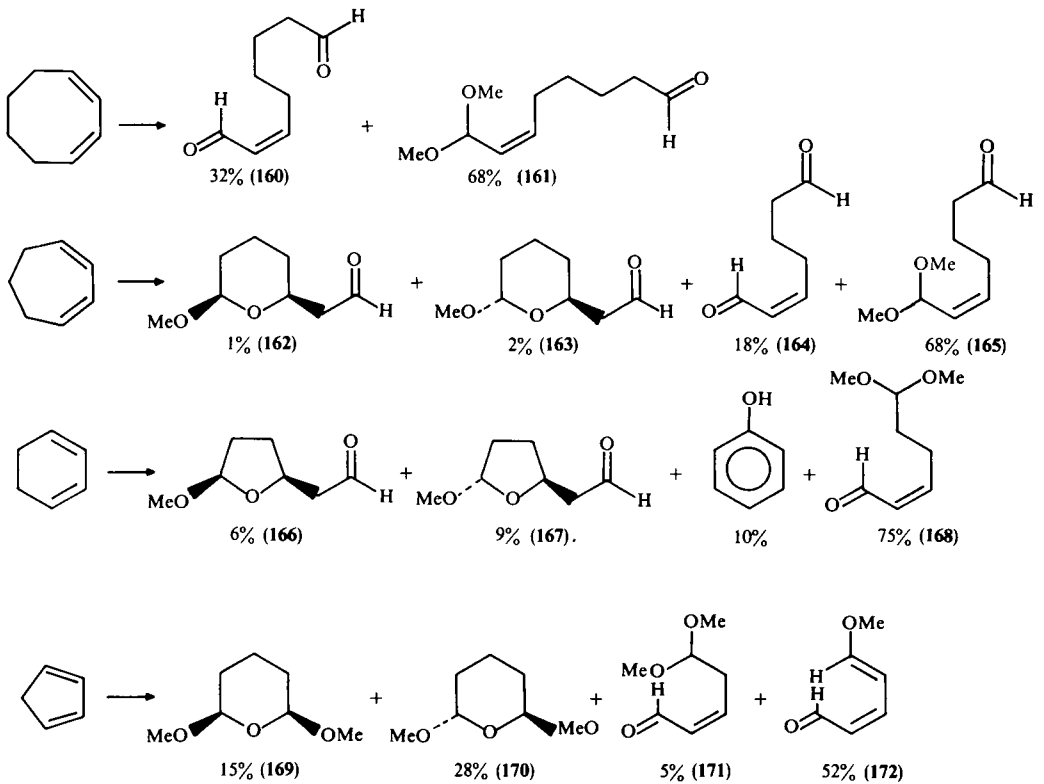
[a]The ratios were determined by ^{1}H NMR analysis on the crude products.
[b]Isolated combined yields.

Table 5. It is interesting to note that in the larger rings, such as cycloheptadiene and cyclooctadiene, **157** is the predominant product. This selectivity is in agreement with the more negative inductive effect of an unsaturated group as compared to an alkyl group, but it decreases 3-fold with the decrease in size of the ring. In the smaller ring, e.g. cyclohexadiene, the reverse selectivity was shown[151]. The absence of regioselectivity in open-chain dienes was shown by ozonolysis of *trans–cis*-6,8-tetradecadiene under the same conditions[151]. The preparation of a variety of useful synthetic intermediates by the stepwise ozonolysis of 1,3-cyclooctadiene and by choice of workup procedures is shown in Scheme 18.



SCHEME 18

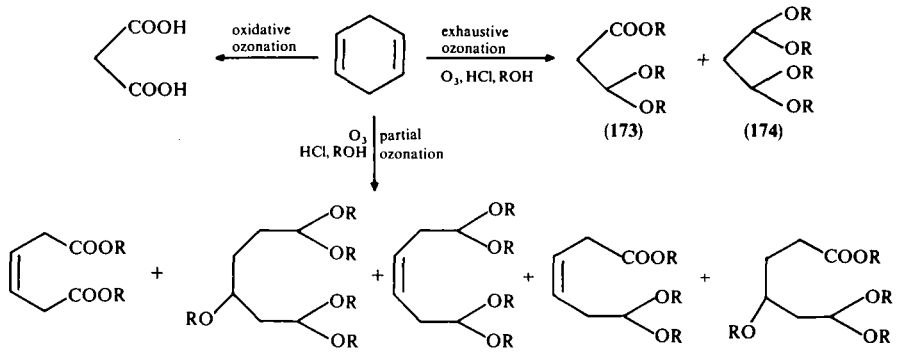
Shortly after this report, Griesbaum, Jung and Mertens reported[152] the partial ozonolysis of C_5–C_8 1,3-cyclodienes in pure methanol, followed by reduction with Me_2S. The stepwise ozonolysis was controlled by the careful addition of 0.7 equivalents of O_3. Along with some heterocyclic products, the major products were open-chain unsaturated


32% (160)
68% (161)
1% (162)
2% (163)
18% (164)
68% (165)
6% (166)
9% (167).
10%
75% (168)
15% (169)
28% (170)
5% (171)
52% (172)

SCHEME 19

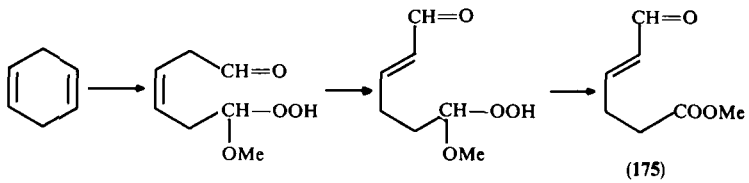
dialdehydes and acetals (Scheme 19). In light of the previously mentioned study[151] it is possible to explain the formation of these compounds: (a) In the absence of buffer in these experiments, some acids which were formed upon addition of ozone to methanol have catalyzed the formation of acetals of the aldehydic group which is formed initially as the primary ozonide is cleaved. (b) The free aldehydic group is that which is formed by the reduction of the carbonyl oxide. (c) Considering (a) and (b) a perfect correlation with results in the previous study is demonstrated. In 1,3-cyclooctadiene the major product is **161** where the double bond is close to the acetal (68–100%). The 32% of **160** can result from both selectivities. The same is true for that derived from 1,3-cycloheptadiene (**164** + **165**, 86%). 1,3-Cyclohexadiene gave 75% of **168** which is the product of the reverse regioselectivity, e.g. the acetal which was derived from the initially formed aldehyde is remote from the double bond. The major achievement of this study[152] is its success in isolating and identifying products from ozonolysis of 1,3-cyclopentadiene. In this case, the initially formed aldehyde gives an enol ether (**172**) as well as the acetal (**171**). Both products amount to 57% yield, showing that the regioselectivity in the 1,3-cycloreversion of the primary ozonide of the five-membered diene is similar to that in the six-membered cyclodiene. The cyclic products **169** and **170** could result from either regioselectivity.

b. Nonconjugated cyclodienes. Mittelbach and coworkers recently studied[153] the complete and partial ozonolysis of 1,4-cyclohexadiene. They studied both oxidative and acid catalyzed ozonolyses. The products which were identified are summarized in Scheme 20.



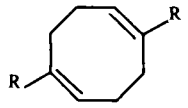
SCHEME 20

Exhaustive ozonolysis of 1,4-cyclohexadiene rings was described by Kirkemo and White[154]. Partial ozonolysis of 1,4-cyclohexadiene in CH_2Cl_2–MeOH containing $NaHCO_3$ was reported by Odinokov and coworkers to yield, after elimination and isomerization, the α,β-unsaturated aldehyde ester **175** (equation 89)[155]. In their pursuit of the synthesis of natural pheromones, the same group reported also the partial and

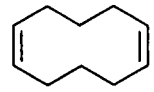


(89)

exhaustive ozonolysis of 1,5-cyclooctadiene (**176**)[156], 1,5-dimethyl-1,5-cyclooctadiene (**177**)[157] and (2,2)-1,6-cyclodecadiene (**179**)[158].

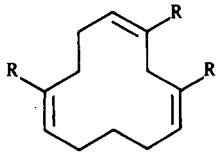


(**176**) R = H
(**177**) R = Me

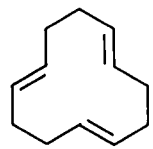


(**178**)

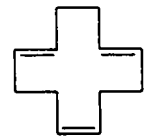
Odinokov and coworkers[159,160] also studied the ozonolysis of isomers and derivatives of cyclododecatriene (**179–182**).



(**179**) R = H
(**180**) R = Me



(**181**)



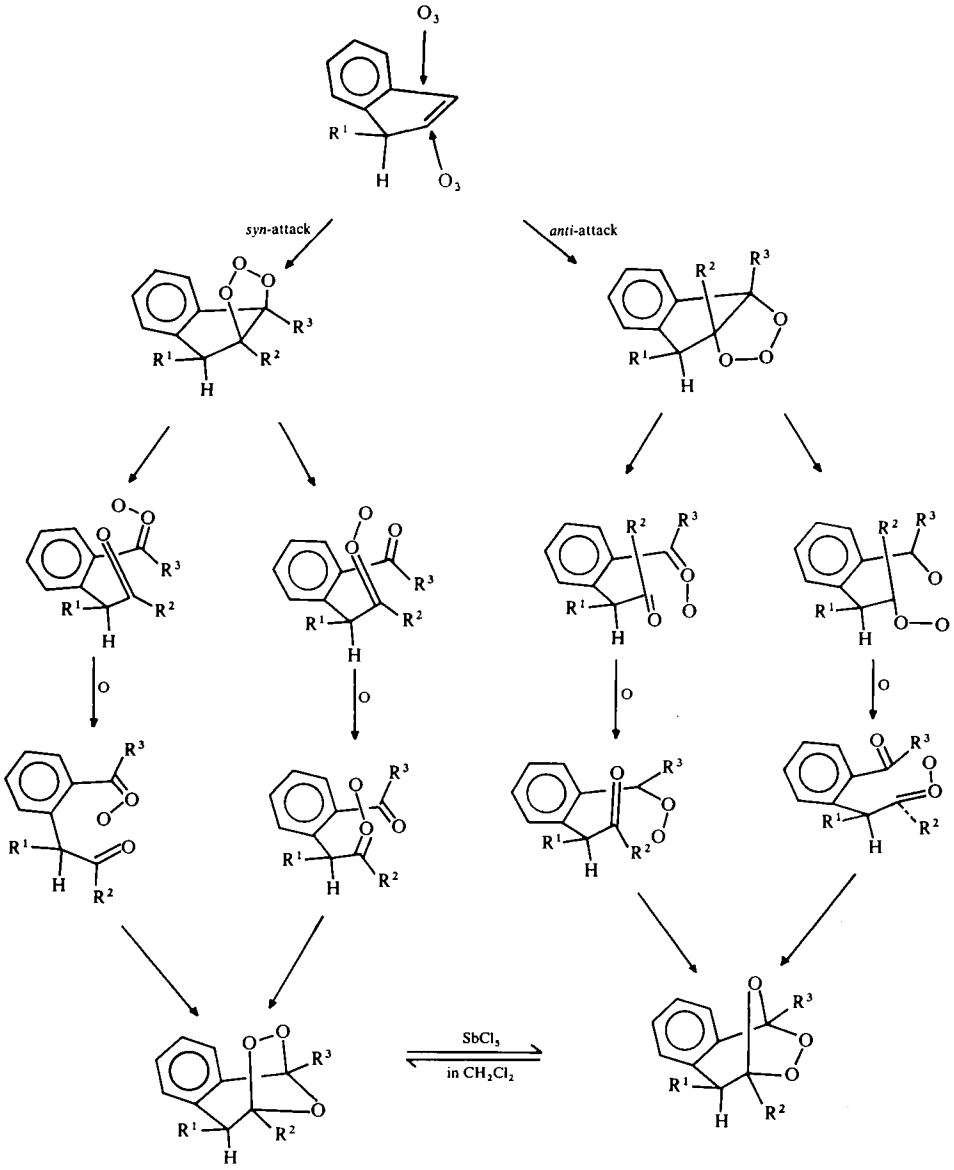
(**182**)

7. Ozonolysis of indene, acenaphthylene and their derivatives

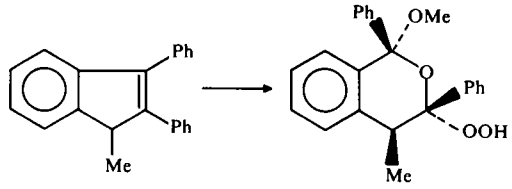
The groups of Nojima and Kusabayashi and of McCullough have been studying for the last few years the ozonolysis of 1-substituted indenes and the substituent effects on the structure of the products[161–166]. Ozonides of indene derivatives were also prepared earlier[167]. The bicyclic ozonides are usually obtained as a mixture of *exo* and *endo* isomers[163]. Nojima McCullough and coworkers have ozonized 29 differently 1,2,3-substituted indenes in CCl_4 and have isolated almost that number of pairs of *exo–endo* isomers[163]. Since the *exo/endo* ratio was found to show little dependence on the relative isomer stability or the substituent electronic effect, the results were discussed in terms of the direction of approach of the ozone to the indene substrate. The routes to the *endo* and *exo* isomers are shown in Scheme 21. In most of the cases the *exo* isomer was the predominant one. The proportion of the *exo* isomers increased with the bulk of the 1-substituent. When the substituent at position 1 was a *t*-butyl group, only the *exo* isomer was obtained. In aprotic solvents the *exo/endo* ratio was solvent-independent while protic solvents exerted a significant influence[165]. The ozonolysis of 1-methyl-2,3-diphenylindene (**183**) in methanol at −70 °C afforded an unusual methanol participated product (**184**) whereas at 20 °C it gave the expected *endo* and *exo* ozonides[165,166].

The ozonide *exo/endo* ratios increased with the decrease of the reaction temperature[165]. The exception was the ozonolysis of **185** and **186**, in which the reverse trend was observed.

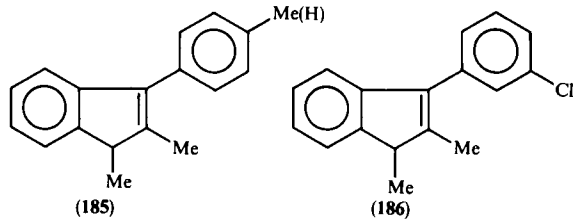
A remarkable effect of the method of generation of the carbonyl oxide intermediate on the products of ozonolysis was observed by comparison of products obtained on ozonolysis of 1-substituted 2,3-diphenyl indenes (**187**) to those obtained from *o*-(1-substituted-2-phenyl-3-methoxy-2-propenyl) benzophenones (**190**)[161]. Both groups of compounds should react through common carbonyl oxide intermediates, however, upon ozonolysis in $MeOH + CH_2Cl_2$ at −70 °C, they afforded different stereochemical isomers, **188** and **189**, respectively. On ozonolysis of **190** (Scheme 22) in aprotic solvents (CCl_4, MeCN) no ozonides were isolated while **191** were obtained from **187**. In protic solvents ($AcOH–CH_2Cl_2$ and $CF_3CH_2OH–CH_2Cl_2$), the indene derivatives (**187**) gave predominantly the *exo* ozonides (**191**), whereas the *endo* isomer (**192**) was obtained exclusively from the ozonolysis of the benzophenone derivatives (**190**)[161].


O3
R1
H
O3
syn-attack
anti-attack
R2
R3
O
O-O
SbCl5
in CH2Cl2
endo-ozonide
exo-ozonide

SCHEME 21



(183) (184)



(185) (186)

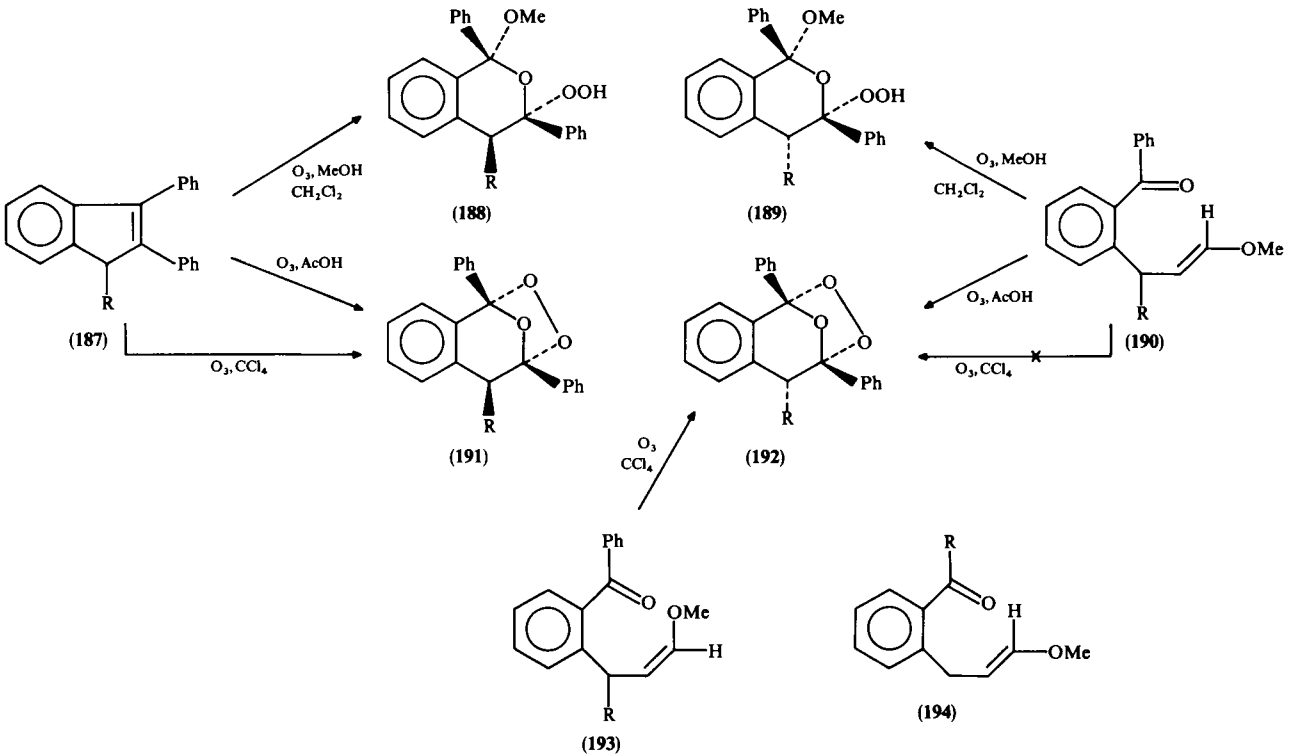
A comparison between the *Z*-benzophenone derivative (**193**) and its *E*-stereoisomer (**190**), carried out recently[162], showed that the *Z*-benzophenone derivative behaved upon ozonolysis as the indene derivative (**187**), e.g. yielding an ozonide in CCl_4 and MeCN and the isolated ozonide had the *exo* structure.

Acenaphthylene (**195**), as would be expected, reacted with ozone exclusively at the cyclopentene ring[168]. The ozonolysis of 1-methylacenaphthylene (**196**) and acenaphthylene (**195**) in CCl_4, MeCN, AcOH and trifluroethanol revealed that the ozonide yield was much higher in protic solvents than in aprotic ones[169]. Such assistance by the protic solvents in ozonide formation was not observed in 1-phenylacenaphthylene (**197**). Acenaphthylene and its derivatives gave, upon ozonolysis in methanol, similarly to what had been obtained from indene derivatives[166], the naphthopyran derivatives (**198**)[169]. Ozonation of 1,2-dichloroacenaphthylene in nonparticipating solvents[170] resulted in the isolation of two stable isomeric substances which were claimed to be the primary ozonide (**199**) and the final ozonide (**200**).

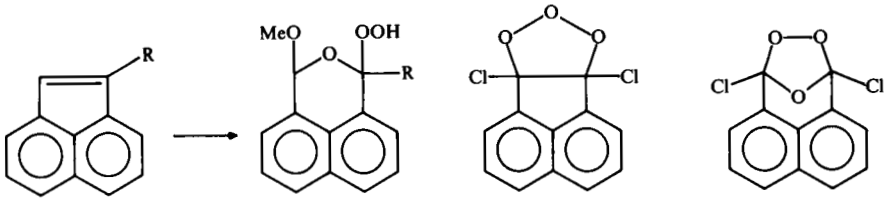
8. *Ozonolysis of haloalkenes*

From reports in the literature it became evident that halogen substituents in vinylic positions impart a relative resistance to ozone to the corresponding double bonds. A rate study of ozone with mono-, di-, tri- and tetrachloroethylenes revealed that the rates decreased drastically in the above order, ethylene being approximately 25,000 times more reactive than tetrachloroethylene[8]. Similar results were obtained by a Russian group[42]. Absolute rates of reaction were derived in several temperatures in CCl_4 by a stopped flow technique[171], when the activation parameters range from $E_a = 11$ kcal mol^{-1} for tetrachloroethylene to 2.4 kcal mol^{-1} for 1-hexene. Some of the rate constants reported[171] are (k = L mol^{-1} s^{-1}): $Cl_2C{=}CHCl$ (2.1), *cis*-ClCH=CHCl (21.3), *trans*-ClCH=CHCl (590), allyl chloride (11,700), 1-hexene (110,000).

Ozonolyses of fluoro and difluoro ethylene were reported to be exceptional and more similar to alkenes[122]. Cremer did a theoretical study on fluoroalkenes which indicated that all the steps, from the formation of the primary ozonide to the final ozonide, are exothermic[71b].


Ph
OMe
OOH
Ph
R
(188)
(189)
(187)
O_3, MeOH
CH_2Cl_2
O_3, AcOH
O_3, CCl_4
(191)
(192)
(190)
O_3
CCl_4
(193)
(194)

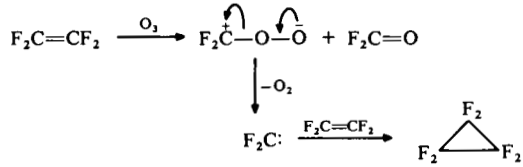
SCHEME 22



(195) R = H
(196) R = Me
(197) R = Ph

(198) (199) (200)

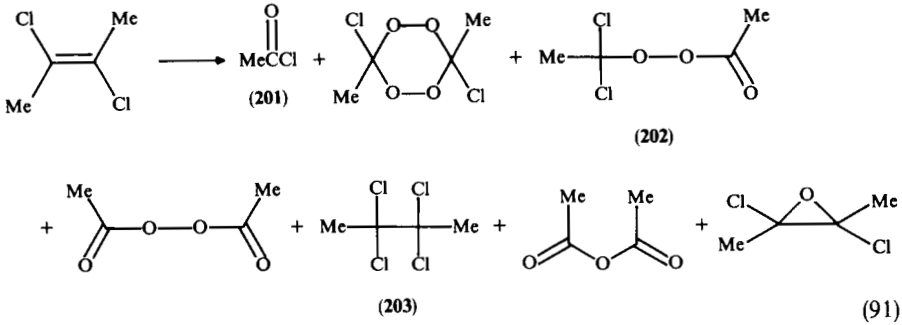
In the ozonolysis of tetrafluoroethylene, a small amount of hexafluorocyclopropane was observed[172]. The route proposed for this abnormal product is shown in equation 90.



(90)

Gas-phase ozonolysis of vinyl chloride led to formaldehyde and chlorodioxirane as the major products identified by matrix IR and MW spectroscopy[173].

The ozonolysis of *trans*-2,3-dibromo- and dichlorobutene in nonparticipating solvents was investigated by Griesbaum[174,175]. The products which were identified in the case of the dichloro derivative are shown in equation 91.

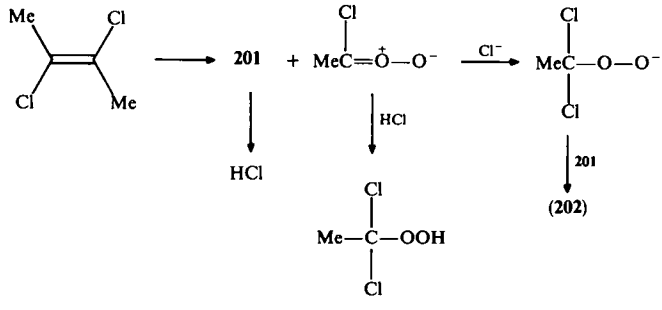


(201) (202) (203)

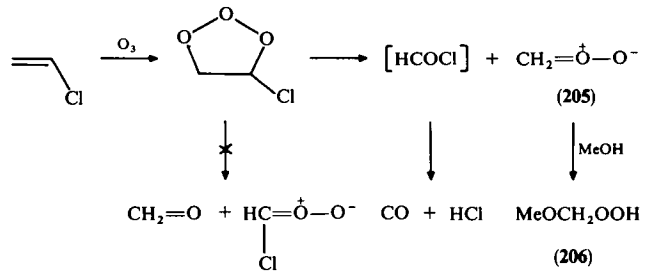
(91)

The formation of tetrachlorobutane (**203**) is probably the result of the formation of Cl_2 by oxidation of HCl, which is in turn produced from acetyl chloride (**201**) by traces of water. The best explanation for the formation of the dichloro peroxide (**202**) was given by Gaeb and Turner[176], as shown in equation 92. Higher yields of **202** were obtained upon the addition of chloride anion (as $R_4N^+Cl^-$) to the ozonolysis reaction mixture. On addition of excess HCl a good yield of the dichloro hydroperoxide (**204**) was observed[176].

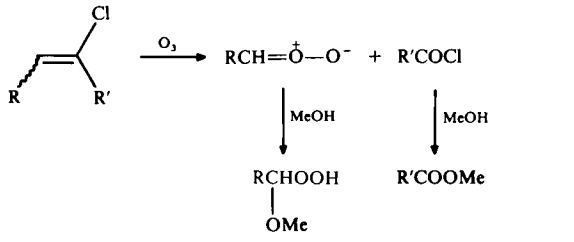
Ozonolysis of vinyl chloride[177] and other monochloro-substituted[178] olefins in methanol was studied by Griesbaum and coworkers (equations 93 and 94). The fact most worthwhile mentioning is that the vinyl chloride derived primary ozonide is cleaved exclusively in one direction, leading only to the unsubstituted carbonyl oxide (**205**, equation 93). Therefore, the major product isolated upon the ozonolysis of vinyl chloride in methanol is the highly explosive methoxymethyl hydroperoxide (**206**).



(92)



(93)

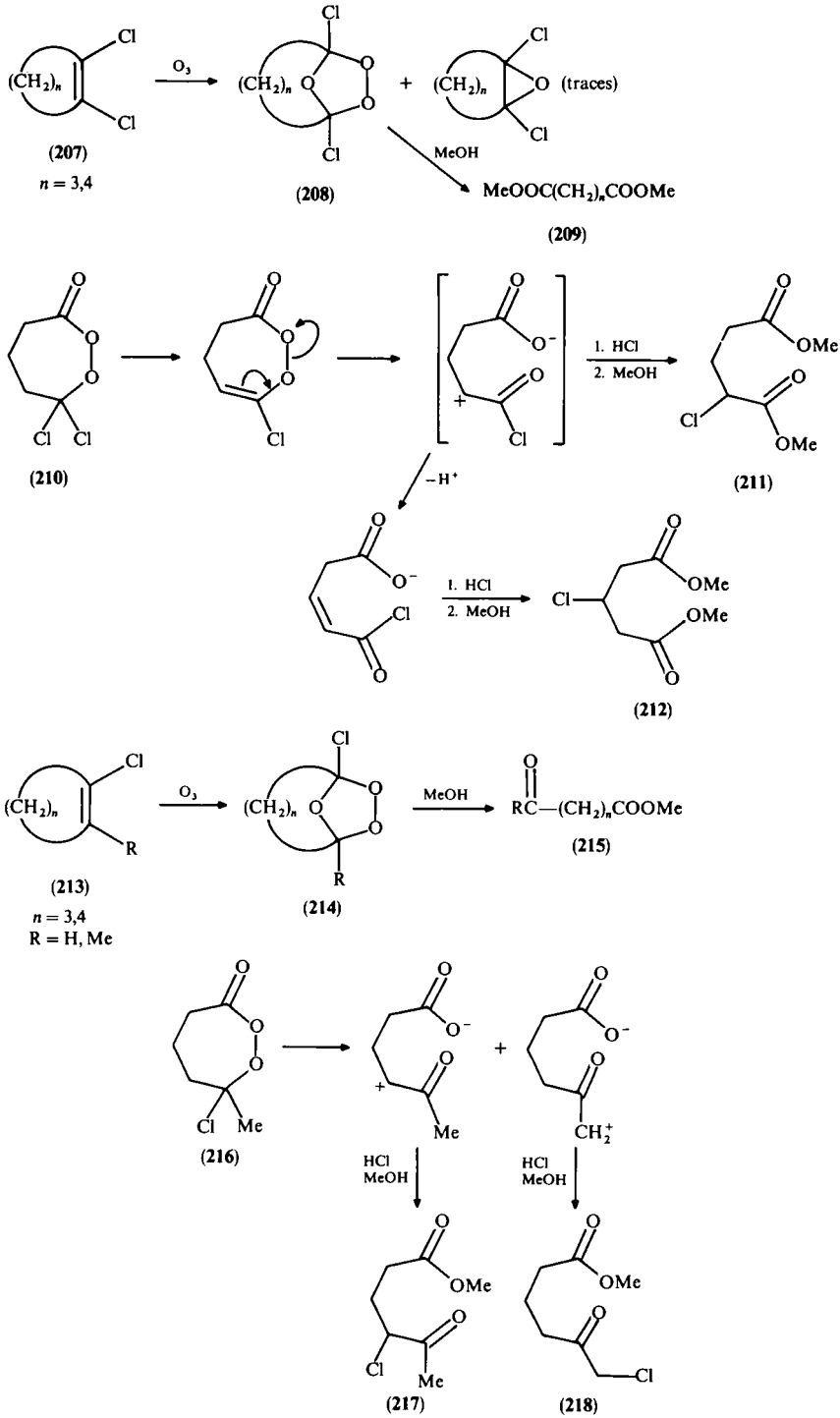


(94)

By studying the ozonolysis of cyclic mono- (**213**) and dichloroolefins (**207**) on polyethylene[177] it was possible to isolate the bicyclic ozonides **214** and **208**, respectively. Their thermal decomposition in $CDCl_3$–methanol mixtures at 60 °C resulted in open-chain esters some of which had a chlorine substituent (**211**, **212** and **217**). The route to these chloro esters, shown in Scheme 23, involves elimination and addition of HCl. The intermediates **210** and **216** are formed by a mechanism similar to the formation of **202** in the ozonolysis of dichlorobutene (equation 92).

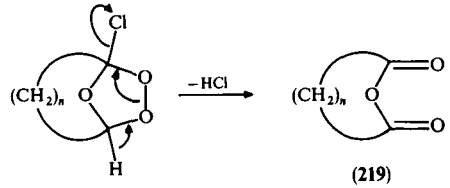
When in **213**, R = H the cyclic anhydride **219** was obtained, probably formed by elimination of HCl (equation 95).

Because of the decrease in reactivity of the double bond substituted with a halogen, it was possible to isolate the monoozonides of monochlorosubstituted dienes (equations 96 and 97)[178]. It was shown[45] that a chlorine in the allylic position has a stabilizing effect on the primary ozonide and on the carbonyl oxide intermediate. This is probably due to the participation of the neighboring chlorine in the positive charge distribution, as shown in structure **220**. It was also reported[45] that the composition of the mixture of the primary ozonides formed were the same upon ozonolysis of both *cis*- and

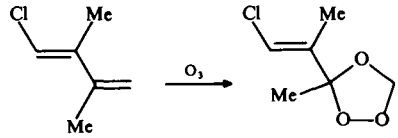


SCHEME 23

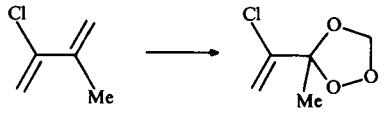
trans-1,4-dichloro-2-butene, leading to the conclusion that the addition of ozone was in two steps rather than in a concerted mechanism (equation 98).



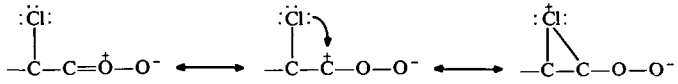
(219) (95)



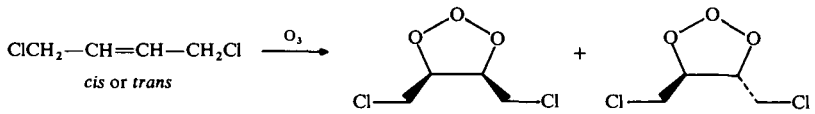
(96)



(97)

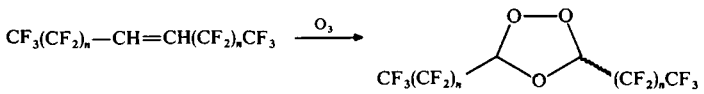


(220)



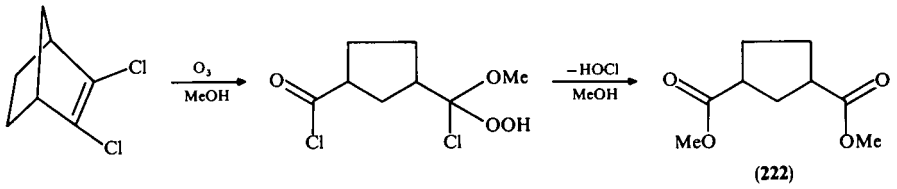
(98)

Unusually stable final ozonides derived from perfluorinated olefins, of the general formula **221**, were reported[179] to be generated by heating with ozone (equation 99). The rates of formation of the fluorinated ozonides (**221**) were about 1×10^{10} slower than for the nonfluorinated analogs.



(221) (99)

Dichloronorbornene afforded upon ozonolysis in methanol the cyclopentane diester (**222**, equation 100)[180].

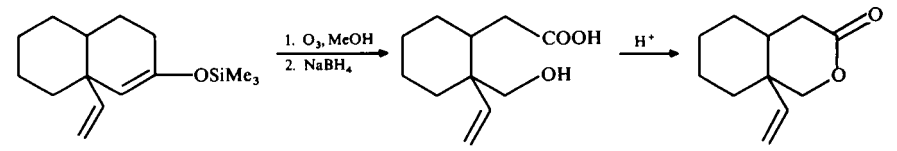


(222)

(100)

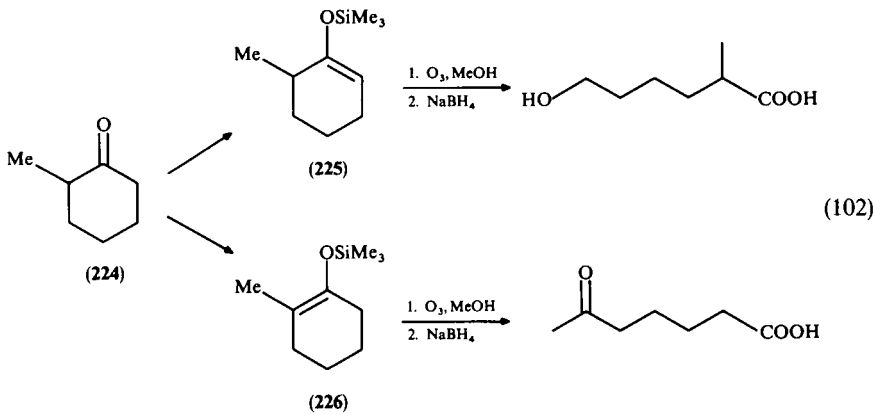
9. Ozonolysis of enolates and vinyl ethers

A very useful synthetic operation involves ozonation of enolates. The general procedure is by transforming the ketones or aldehydes to the corresponding trialkylsilyl derivatives. The double bond in silyloxalkenes is more reactive towards ozone than most other double bonds. Thus the trimethylsilyl enolate bond in **223** (equation 101) could be selectively ozonized[181]. In the case of 2-methylcyclohexanone (**224**) both the kinetic enolate (**225**) and the thermodynamic product (**226**) were prepared and ozonized to yield different doubly functionalized products (equation 102)[181].



(223)

(101)



(225)

(224)

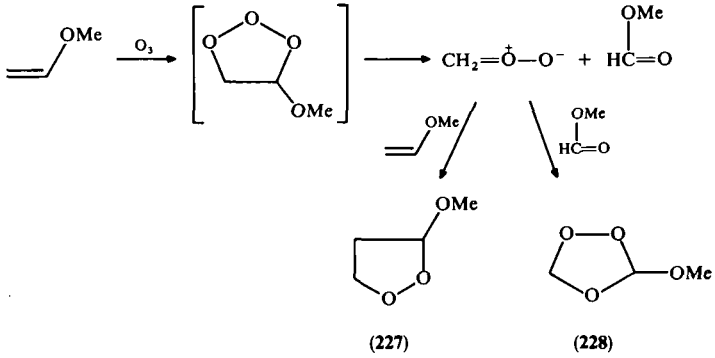
(226)

(102)

Methyl vinyl ether has an electron-rich double bond which is also a reactive dipolarophile. Therefore, in the ozonolysis of methyl vinyl ether, Kuczkowski and Kuel[182] observed the formation of 3-methoxy-1,2-dioxalane (**227**) as the major product (68%), while only about 9% of the ozonide (**228**) was obtained (equation 103).

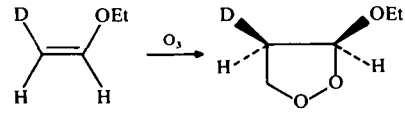
From additional trapping experiments[62] the following relative dipolarophilicities toward carbonyl oxide were inferred: aldehydes > enol > ethers > esters > ketones. Ozonolysis of stereo-labeled ethyl vinyl ethers (**229** and **231**) gave ethoxy 1,2-dioxolanes (**230** and **232**) with retention of the alkene configuration (equations 104 and 105). This

observation was claimed to be the first example where stereospecificity, implying concertedness, was directly observed for the cycloaddition of a carbonyl oxide.



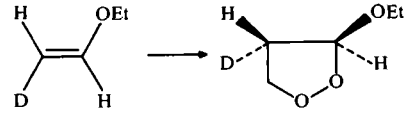
(103)

(227) (228)



(104)

(229) (230)



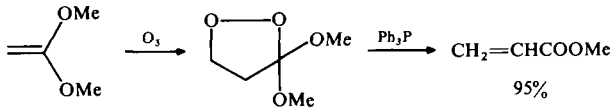
(105)

(231) (232)

The stereochemistry at the carbon derived from the carbonyl oxide component was investigated[59a] by studying the ozonolysis of (*E*)- and (*Z*)-1-ethoxypropene. The results were consistent with the Criegee mechanism. The two alkenes produce different relative amounts of the *syn* and *anti* carbonyl oxide which recombine with the dipolarophiles at different rates[59a].

Vinyl acetate reacts similarly to methyl vinyl ether[184] yielding on ozonolysis 51% 3-acetoxy-1,2-dioxolane and 34% 3-acetoxy-1,2,4-trioxolane.

Ozonolysis of 1,1-dimethoxyethene (**233**) gave also a 1,3-dipolar cycloaddition of the carbonyl oxide with the starting reactive alkene to give 68% of 3,3-dimethoxy-1,2-dioxolane (**234**)[183]; see equation 106.



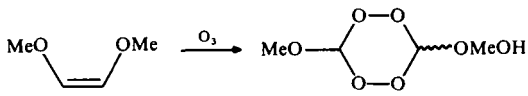
(106)

(233) (234)

It is interesting to note that Ph_3P reacted with **234** to form methyl acrylate in 95% yield.

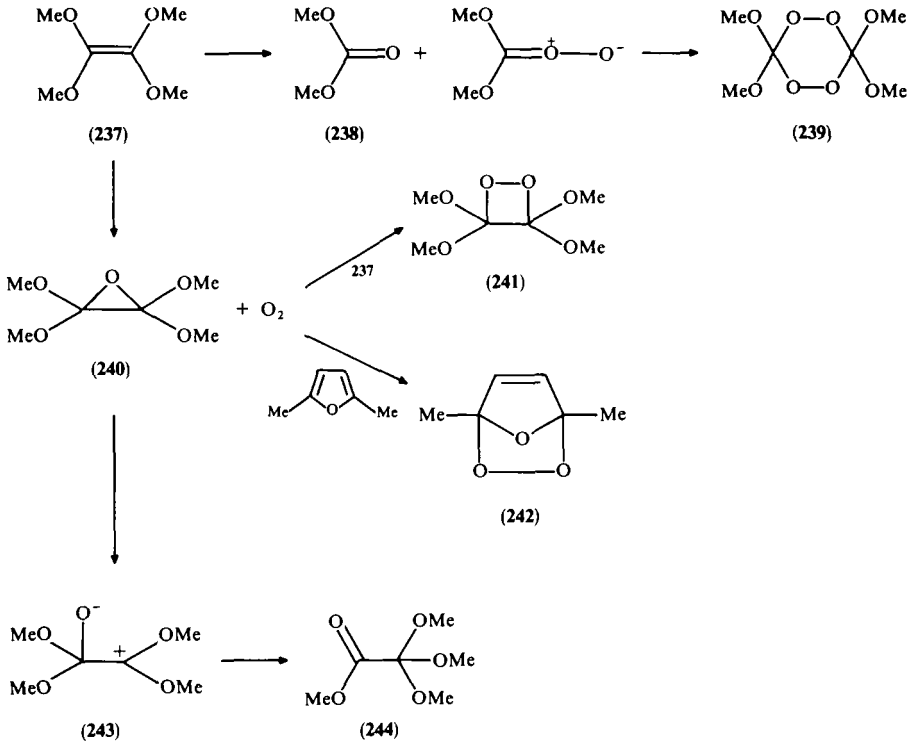
In the ozonolysis of (*Z*)-1,2-dimethoxyethane (**235**) it was not possible to observe the formation of a dioxalane derivative, instead, 15% of the diperoxide (**236**) which was

formed by a 3 + 3 dimerization of the intermediate carbonyl oxide were isolated[183] (equation 107).



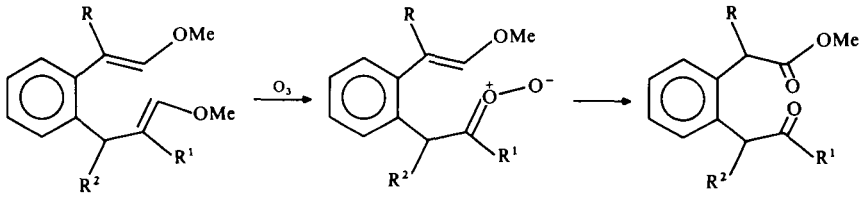
(235) (236) (107)

Ozonolysis of tetramethoxyethene (**237**)[184] produced 20–40% dimethyl carbonate, 35–60% methyl trimethoxyacetate and 20–35% dioxethane (**241**), depending on the solvent, temperature and concentration of the alkenes. It was shown that singlet oxygen is formed and reacts with **237** to yield the dioxethane **241**. The singlet oxygen was also trapped by 2,5-dimethylfuran. A competing radical chain oxidation was also proposed[185] to account for both the products and the stereochemistry of the ozonolysis of **237** (Scheme 24). The ozonolysis of several vinyl ether derivatives on polyethylene was reported[19c] to yield fair yields of the corresponding ozonides. These could not be observed on ozonolysis in solution.



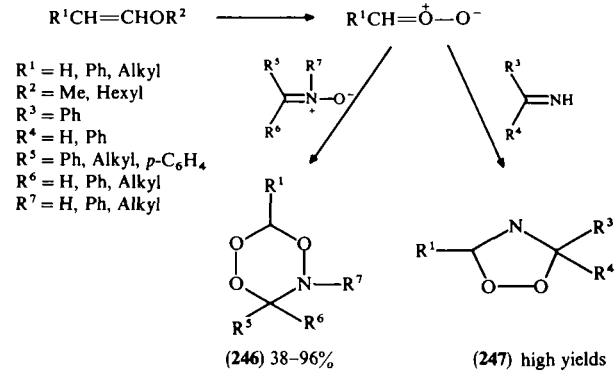
SCHEME 24

Evidence for intramolecular oxygen transfer from a carbonyl oxide moiety to a methoxyvinyl group was afforded by the study of the ozonolysis of the dimethoxy diene system **245**[185] (equation 108).



(245) (a) $R = R^1 = Ph$, $R^2 = H$
(b) $R = Me$, $R^1 = Ph$, $R^2 = H$
(c) $R^1 = R = Ph$, $R^2 = Me$ (108)

The regioselectivity of the ozonolysis of vinyl ethers, leading to a single carbonyl oxide, was utilized by Nojima, McCullough and their coworkers to study the cycloaddition of carbonyl oxides to imines and nitrones[186,187]. The carbonyl oxides underwent 3 + 2 cycloaddition with imines to yield 1,2,4-dioxazolidines (**247**) and a 3 + 3 cycloaddition with nitrones to yield 1,2,4,5-trioxaziranes (**246**); see Scheme 25.



(246) 38–96% (247) high yields

SCHEME 25

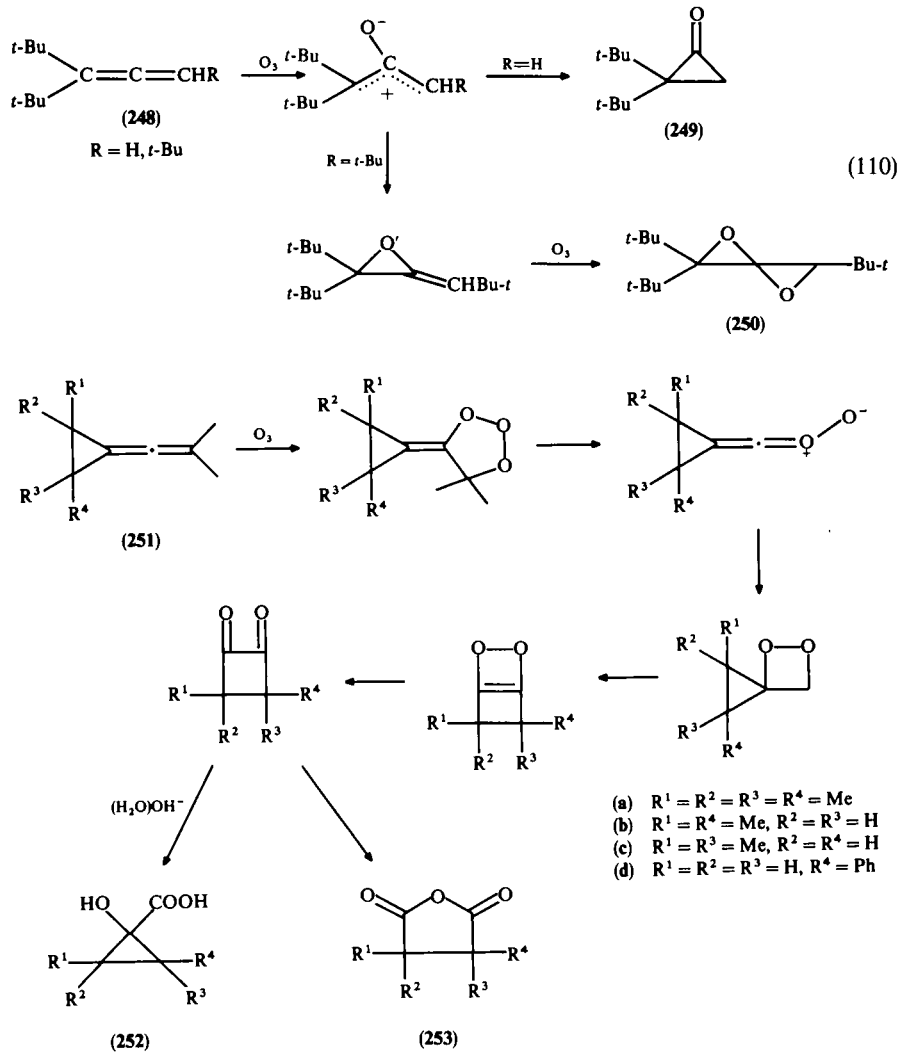
10. Ozonolysis of allenes, alkylidene and alkenylidenecyclopropanes and alkylidenecyclobutanes

Kolsaker and his coworkers ozonized mono-, di-(1,1), tri- and tetraalkyl allenes. They found that only 1 mol equivalent of ozone reacted. Carbon monoxide was evolved in all cases and the major products were the expected aldehydes or ketones, plus small amounts of carboxylic acids (equation 109)[188].

$$\rangle{=}\cdot{=}\langle + O_3 \rightarrow \rangle{=}O + CO + O{=}\langle \qquad (109)$$

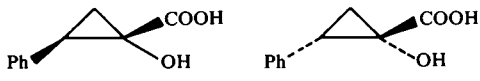
Sterically hindered allenes react by transfer of a single oxygen to form also allene epoxides and cyclopropanones (**249**) as, for example, di- and tri-*t*-butylallene in equation 110[189]. Hartzler[190] as well as Crandall and Schuster[191] studied the ozonolysis of the cyclopropenylallene (**251**). The rearrangement products and the proposed route of their formation are shown in Scheme 26.

In cases where the substituents were different, as in **251b** and **251c**, the succinic anhydride derivative **253** which was isolated showed a retention of configuration. The phenyl alkenylidene derivative **251d** gave both stereoisomers **254** and **255**.



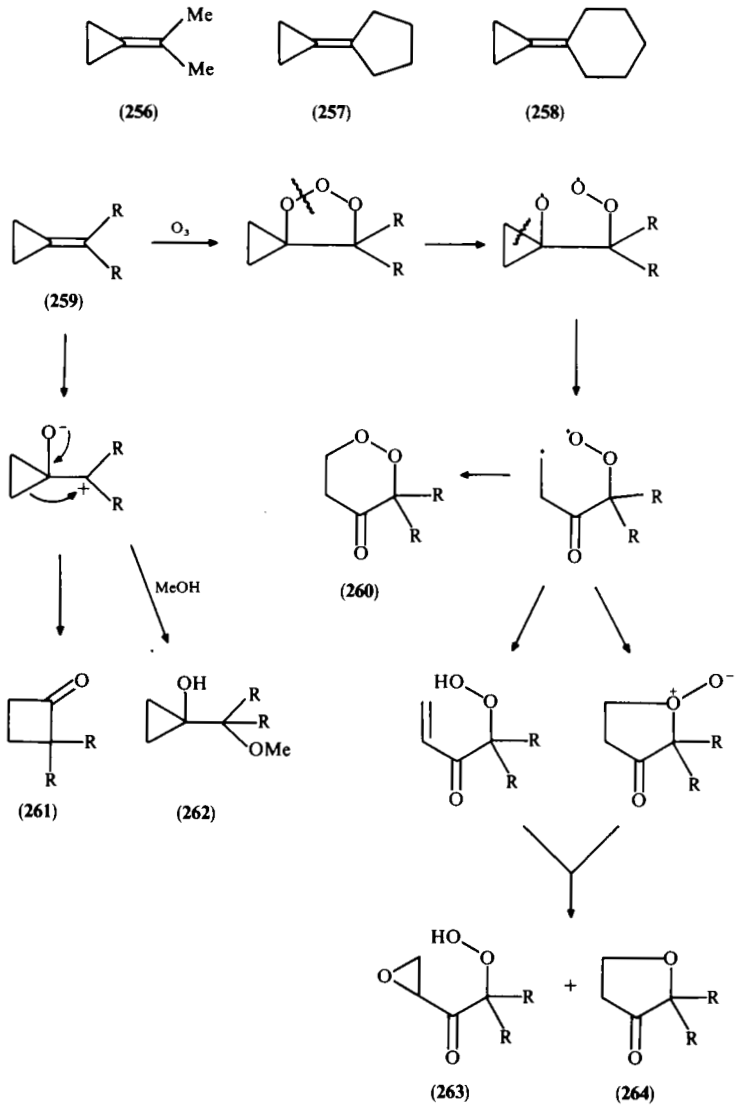
(110)

SCHEME 26



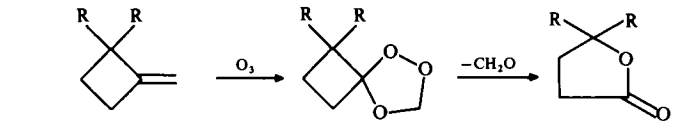
The ozonolysis of alkylidene cycloalkanes (**256–258**) was investigated by de Boer and his group[192]. Almost none of the products contained a cyclopropyl moiety. The mechanism which was proposed for the formation of the unexpected products is shown in Scheme 27. In nearly all cases, the main product was the cyclic oxaketone **264**. Products

were isolated by gas chromatography and their structure determined by IR, NMR and MS, and in the case of **262** where R,R was a cyclohexane ring, by an X-ray technique.



SCHEME 27

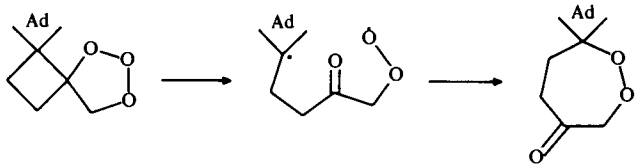
In a similar study[193] of methylene cyclobutane (**265a**) and its adamantyl derivative (**265b**), a major product was γ-butyrolactone (**266**) together with some of the conventional cyclobutanone product (equation 111). The adamantyl derivative gave also 45% yield of the seven-membered ring peroxide **267**, probably by a homolytic mechanism (equation 112)[193].



(265) (266) (111)

(a) R = H

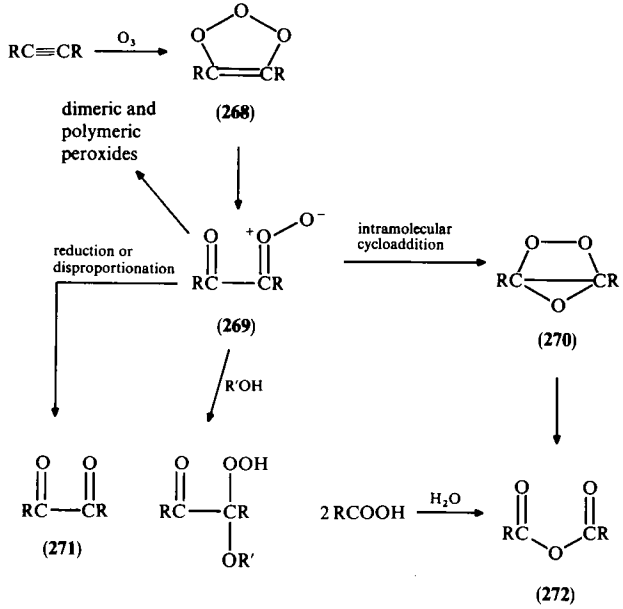
(b) R,R = (Ad)



(267) (112)

III. OZONOLYSIS OF ACETYLENES

Ozonation of acetylene and other alkynes has been discussed in previous reviews and articles[2,9,194]. A triple bond is much less reactive towards ozonolysis than a double bond. This was shown kinetically[42,195] and by studying the ozonolysis of compounds having both a triple and a double bond[196]. It is accepted that the mechanism of the



SCHEME 28

initial attack of ozone on a triple bond in the liquid phase is analogous to that proposed by Criegee for a double bond. A 1,3-dipolar cycloaddition was proposed, based on the structure of the products and on kinetic measurements in solvents of different polarities[116] and with different substituents[197]. The 1,3-dipolar cycloaddition of ozone to the triple bond should yield the intermediate trioxolene ring (**268**; Scheme 28). Evidence for the existence of such an intermediate and of a carbonyl oxide **269** was reported by Keay and Hamilton[198]. The thermal production of a 1,2-dicarbonyl compound (**271**) even in the absence of strong reducing agents was regarded as a clue for the intermediacy of the carbonyl oxide[199]. Concerning the mechanism of the formation of large amounts of anhydrides (**272**) in the ozonolysis of acetylenic compounds, Jackson and Hull[199] suggested that it might involve an intermediate of ozonide structure (**270**). As evidence for this route, they reported the observance of chemiluminescence during the decomposition of their relatively stable carbonyl oxide, in the presence of fluorescents such as 9,10-diphenylanthracene.

Miller and coworkers made a kinetic study on the ozonation of a series of propargyl compounds in CH_2Cl_2. They found the reaction to be clearly first order in regard to both ozone and the alkyne. There was a slight increase in the relative rates of ozonation as substituent G was varied (equation 113)[197].

$$\underset{\textbf{(273)}}{CH{\equiv}CCH_2G} \xrightarrow{O_3} \text{Ozonolysis products} \qquad (113)$$

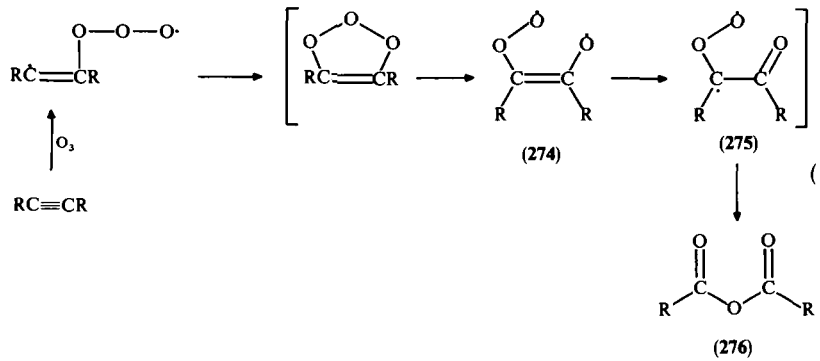
G:	Cl	Br	OCOMe	OH	NMe_2	$(CH_2)_6Me$
Relative rates:	1.0	1.3	1.7	5.5	8.5	16.6

For propargyl acetate (**273**, $G = OCOCH_3$), the rate constants change only slightly with the polarity of the solvent (equation 114).

$$CH{\equiv}CCH_2OCOCH_3 \xrightarrow{O_3,\,\text{solvent(S)}} \text{Ozonolysis products} \qquad (114)$$

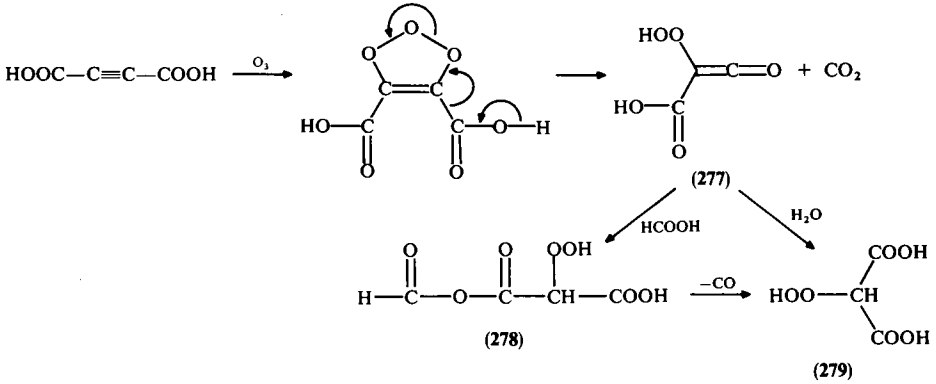
Solvent (S):	AcOH	AcOMe	3:1 AcOH	1:1AcOH	1:3 AcOH	HOH
Rate constants			HOH	HOH	HOH	
$k(M^{-1}s^{-1})$:	74 ± 7	104 ± 40	168 ± 3	270 ± 47	264 ± 18	218 ± 8

The mechanism proposed by De More for the gas-phase ozonation of acetylenes is outlined in equation 115. The mechanism involves a very short-lived diradical (**274**) and its rearrangement to diradical **275**, the major reaction product being the corresponding anhydride (**276**)[200]. Ozonation of acetylenedicarboxylic acid in concentrated formic acid



(115)

afforded hydroperoxymalonic acid (**279**)[201]. The proposed mechanism is shown in equation 116 and involves the intermediate ketene **277**, which can either react with water or formic acid to produce **279** or **278**, respectively. The hydroperoxyanhydride (**278**) can lose CO to produce hydroperoxymalonic acid (**279**).



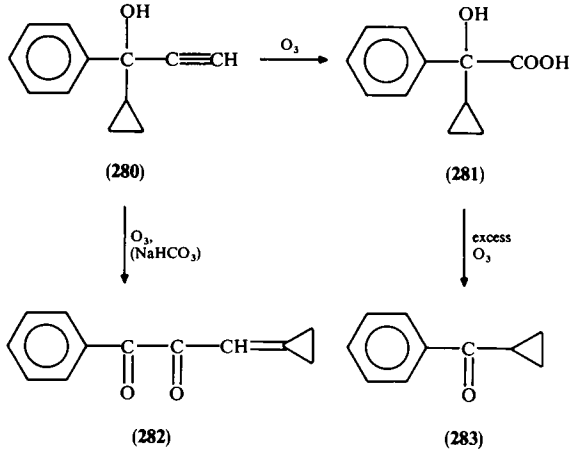
(116)

The ozonation of acetylenic ethers followed by reductive work-up gave α-keto esters[202] as shown in equation 117.

$$RC{\equiv}COR' \xrightarrow[2.\,[H]]{1.\,O_3} RCOCOOR' \qquad (117)$$

While the triple bond is less reactive towards ozone than a double bond, it reacts faster than a benzene ring (see Section IV.A).

Under controlled conditions acetylenic alcohols like **280** (equation 118) can be converted to glycolic acid (**281**). With excess ozone or in the presence of bicarbonate, ketone **283** and diketone **282** are produced, respectively[203]. The formation of **282** is very difficult to accept, both because the transformation cannot be explained and because of the unexpected stability of the new double bond towards ozone.



(118)

IV. OZONOLYSIS OF AROMATIC COMPOUNDS

A. Ozonolysis of Benzene and Its Derivatives

Historical discussions of ozonation of benzene and other aromatic compounds can be found in earlier publications[2,9,10,24].

Benzene is much less reactive towards ozone than an olefinic double bond. Quantitative studies[195] on the reaction of ozone with compounds possessing both aromatic and olefinic moieties show that the ozone absorption is usually quantitative until the olefinic bond has reacted entirely, after which it is much slower. The values obtained for the second-order rate constants establish the reactivity order: olefinic double bond > acetylenic triple bone > benzene bonds, and in terms of rate constants the comparison of the following 3 compounds is illustrative:

Compound	$PhCH{=}CH_2$	$PhC{\equiv}CH$	$PhCH_2CH_3$
$k(l\,mol^{-1}\,s^{-1})$	3.1×10^5	60	0.25

Table 6 shows the rate relationships for various substituted benzene derivatives as reported by Andrews and coworkers[204].

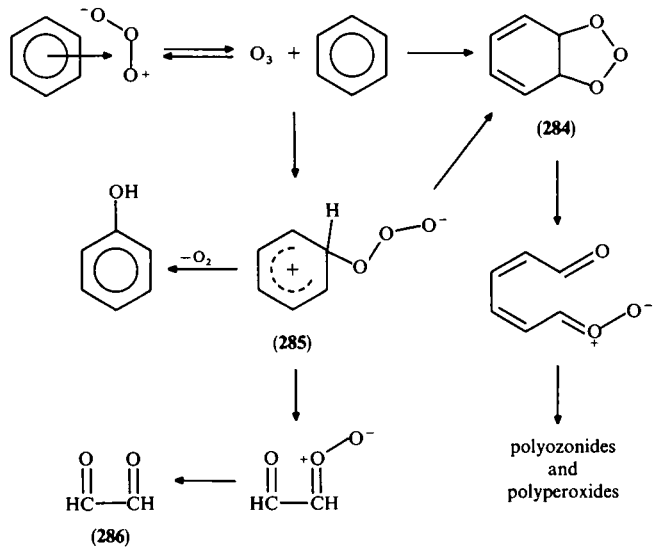
The rates appear to increase with increasing alkyl group substitution, but decrease with the bulk of the alkyl groups. Substitution with electron-withdrawing groups reduces the rate of interaction with ozone.[205].

The ozonolysis of benzene is catalyzed by Lewis acids. This fact, together with the observation that electron-donating groups enhance ozone attack, suggest an electrophilic attack of ozone. Therefore, many authors conclude that the formation of the primary ozonide involves two steps, as shown in Scheme 29. Benzene and its derivatives give at very low temperatures colored π-complexes[117]. However, there is no proof that these are precursors of ozone attack, which usually occurs at higher temperatures.

The major product of exhaustive ozonolysis of benzene followed by reduction of the peroxidic products is glyoxal (**286**). The latter is an important industrial product which can be synthesized in high yields by ozonolysis of benzene. On ozonolysis of benzene at elevated temperatures, some phenol is detected, which may arise from the initial zwitterion intermediate (**285**) as shown in Scheme 29.

TABLE 6. Relative rates of ozonolysis of alkylbenzenes

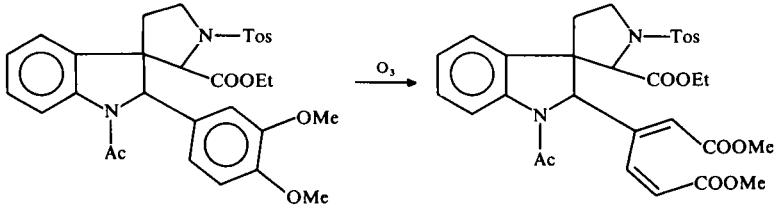
Benzene derivative	Relative rate	Benzene derivative	Relative rate
Benzene	1.0	Mesitylene	150
Toluene	5.9	1,3,5-Triethylbenzene	143
Ethylbenzene	12.1		
Isopropylbenzene	12.5	1,3,5-Tri-*t*-butylbenzene	11.8
t-Butylbenzene	2.5		
p-Xylene	33.9	Durene	382
o-Xylene	29.3	Pentamethylbenzene	1786
m-Xylene	27.9	Pentaethylbenzene	375
m-Diethylbenzene	38.2	Hexamethylbenzene	8750
m-Diisopropylbenzene	35.7	Hexaethylbenzene	120
p-Di-*t*-butylbenzene	5.6		



SCHEME 29

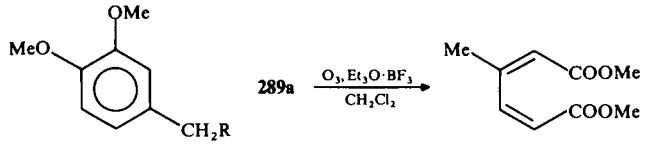
Ozonolysis of benzene in the gas phase appears to differ little from the liquid-phase ozonation[206].

A stepwise and selective ozonolysis could be carried out in 1,2-dimethoxybenzene derivatives. The classical example is in Woodward's synthesis of strychnine[207]. Only the activated dimethoxy-substituted ring in **287** was attacked by ozone, and in that only the bond which was bearing the two methoxy groups (equation 119).



(287) (288) (119)

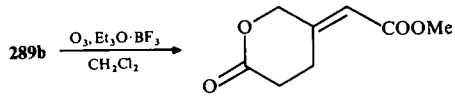
This principle was elaborated and further studied[208a]. Ozonolysis of the toluene derivatives (**289**), carried out in CH_2Cl_2 in the presence of $BF_3 \cdot Et_2O$, led to a selective cleavage at the disubstituted bond yielding products **290** and **291**, respectively



(289) (a) R = H
(b) R = OH

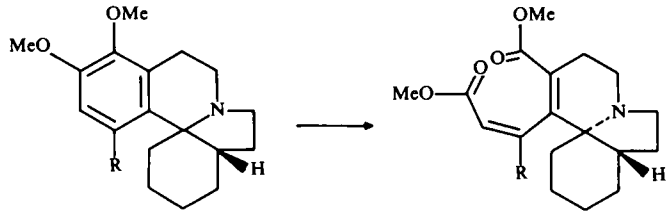
(290) (120)

(equations 120 and 121). Similar ozonolysis of erythrinan derivatives (**292**) afforded high yields of secoerythrinans (**293**)[208a]; see equation 122.



(121)

(291)

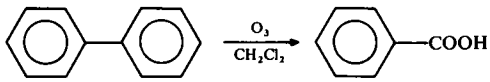


(122)

(292) (a) R = H
(b) R = OMe

(293)

Ozonolysis of biphenyl in chloroform brings about the destruction of one ring, resulting in 86% yield of benzoic acid (equation 123)[208b]. Analogous results were observed in the three isomers of terphenyl.



(123)

B. Ozonolysis of Phenols

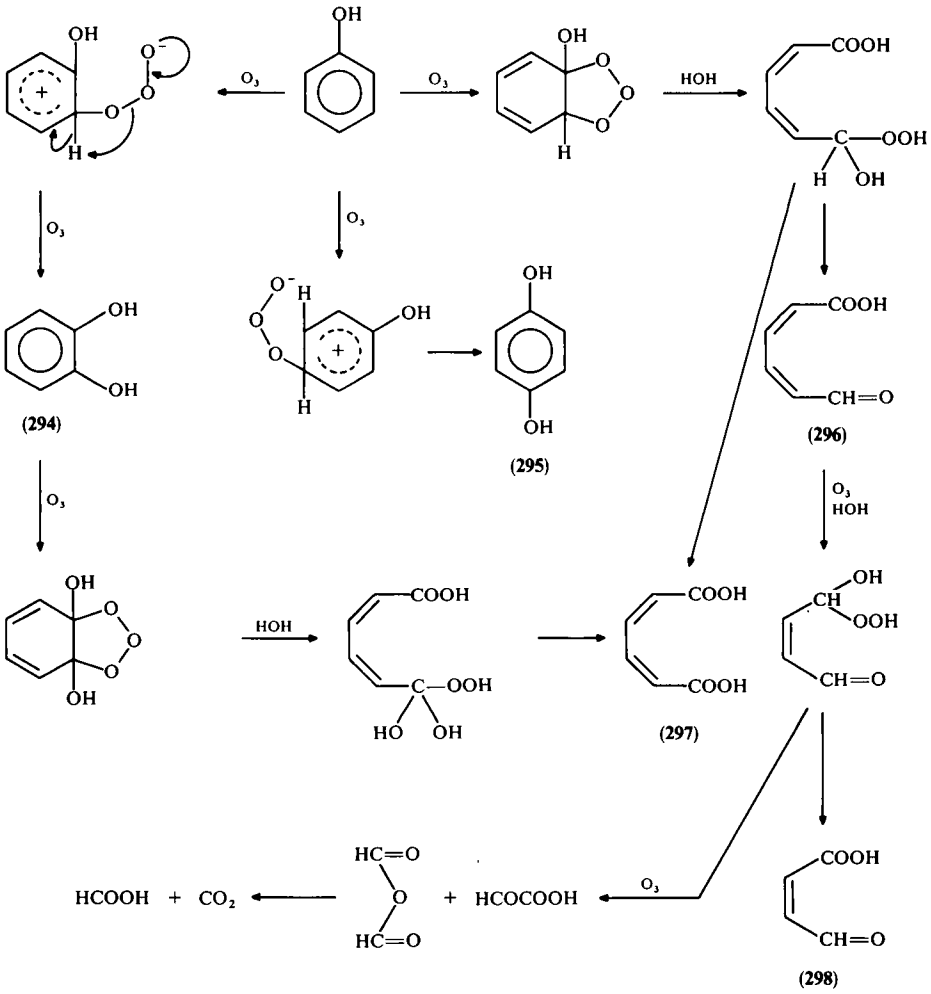
There is considerable interest in the ozonation of phenols because of need to purify waste water containing such substances[209–212]. Exhaustive ozonolysis results in small molecules like carbon dioxide, formic acid, glyoxal and oxalic acid. More careful ozonolysis leads to the formation of catechol (**294**), hydroquinone (**295**), muconic acid (**297**), muconic monoaldehyde (**296**), maleic monoaldehyde (**298**) as well as some of the small molecules mentioned above. The possible paths proposed for the formation of these products are shown in Scheme 30.

The tendency of phenols to be cleaved by ozone was applied to the modifications of natural products[213]. Ozonolysis of phenolic hydroabietic acid derivatives in methanol resulted in the formation of five-membered lactones (equations 124–126).

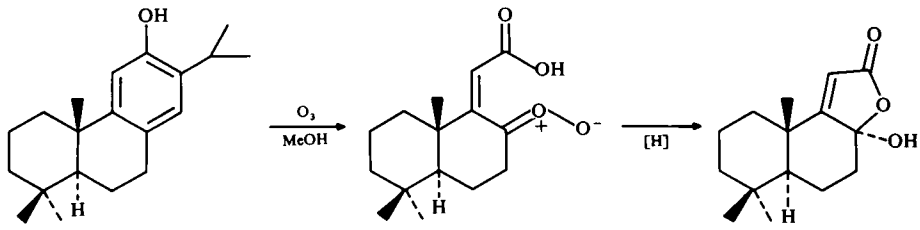
C. Ozonolysis of Naphthalene and Polycyclic Aromatic Compounds

For some of the most common polycyclic compounds, the order of rate of reaction with ozone is anthracene > pyrene > phenanthrene > naphthalene > benzene[213]. Generally, condensed aromatic compounds are more reactive than benzene but less reactive than olefins. The site of initial attack is at the double bond of lowest bond localization energy which is not always the site of electrophilic attack[214]. The latter fact supports the idea of a 1,3-dipolar cycloaddition rather than an electrophilic attack of the ozone.

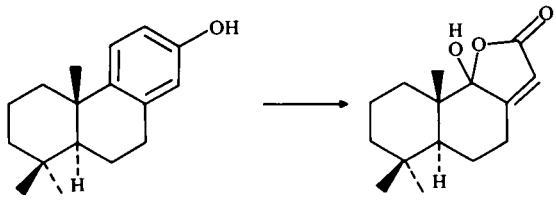
The ozonolysis of naphthalene in methanol gave a considerable yield of the peracetal **300** (Scheme 31) and glyoxal derivatives, along with some decomposition products.



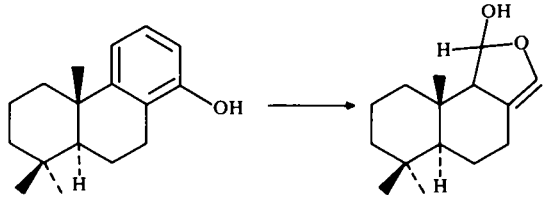
SCHEME 30



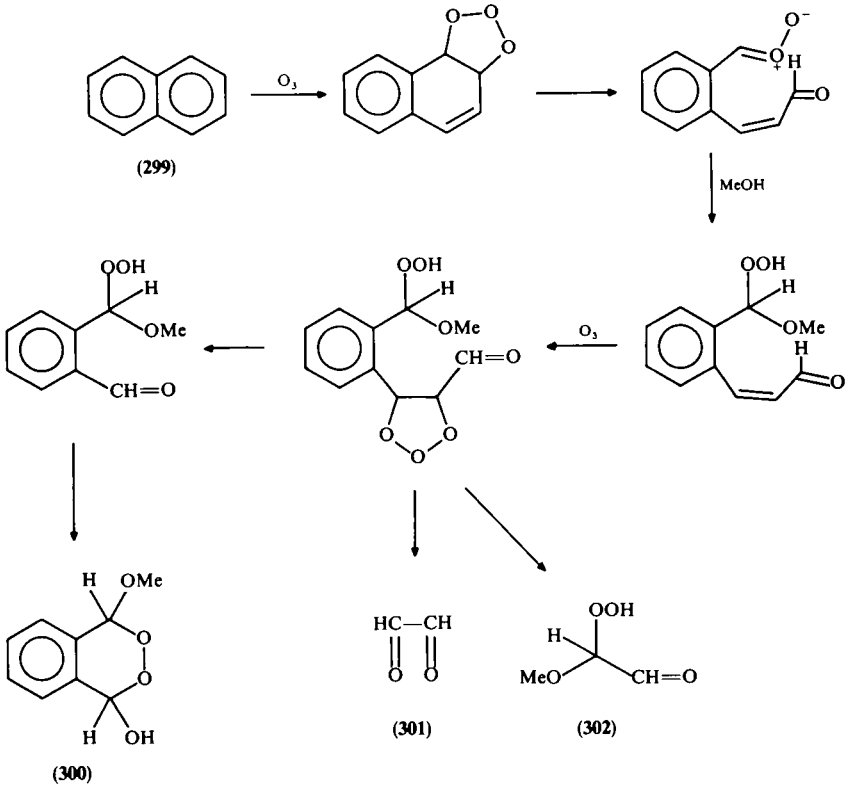
(124)



(125)

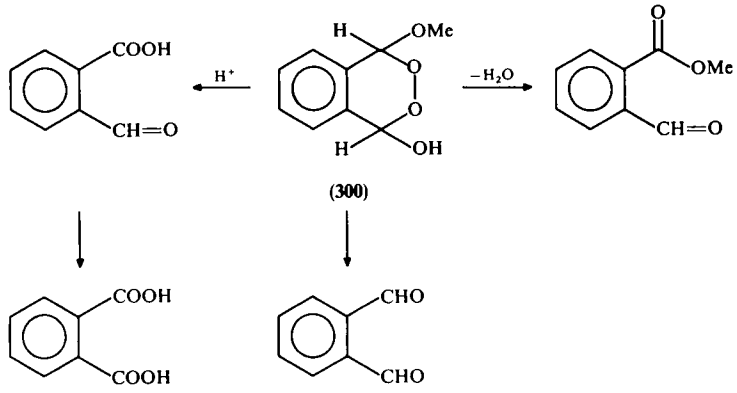


(126)



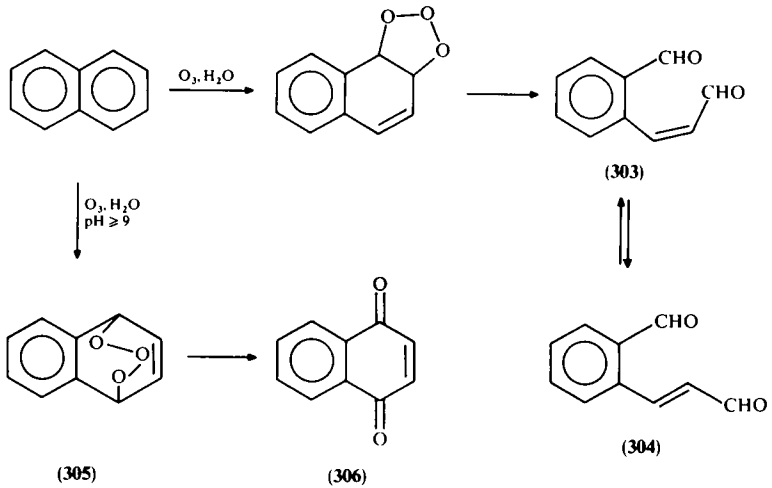
SCHEME 31

Naphthalene reacted with two moles of ozone, as shown in Scheme 31, and products of monoozonolysis could not be detected[215–217]. The site of attack was always the 1,2-bond in the unsubstituted ring, unless the substituents were OH or OR, which lead to attack near these groups. The major product (**300**) could be transformed to phthalaldehydic acid, phthalaldehyde and phthalic acid and its monoester (equation 127).



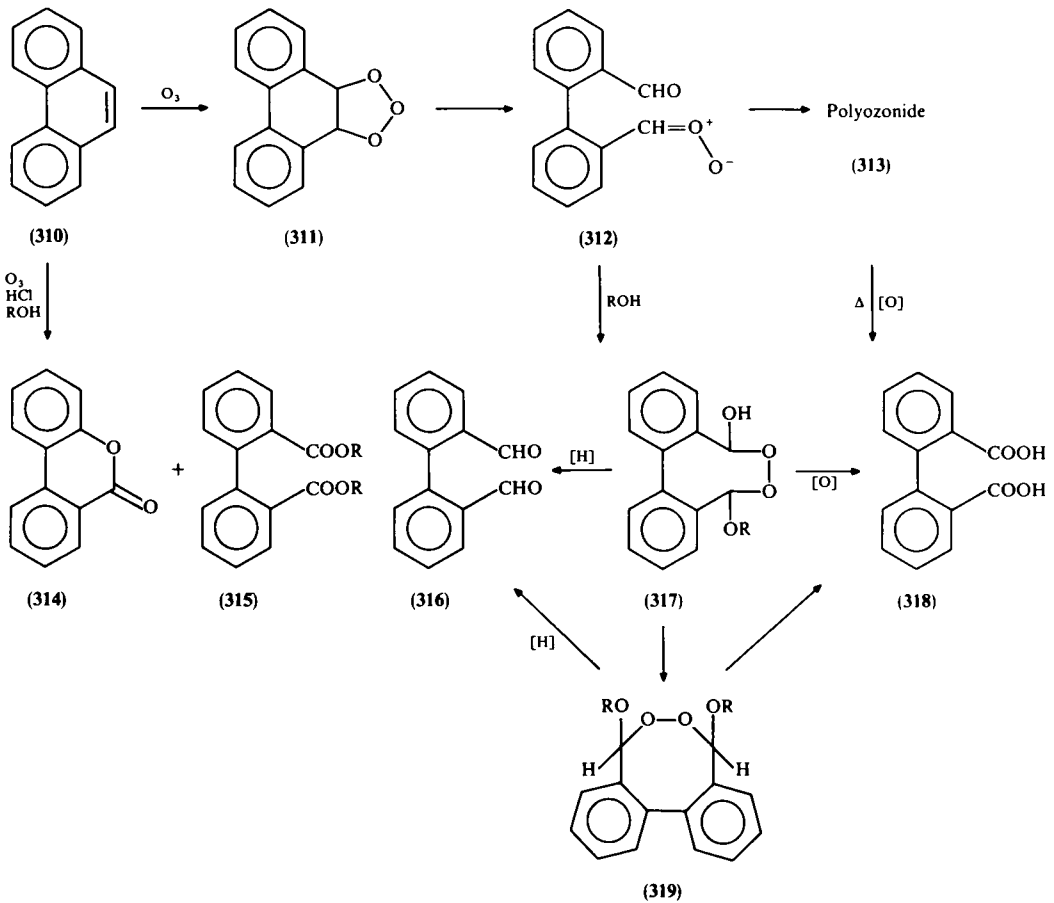
(127)

Garisson and coworkers[218] showed that the ozonolysis of naphthalene in buffered solutions resulted in cleavage of only one bond yielding *cis*- and *trans*-*o*-formylcinnamaldehyde. At a higher pH (pH = 9), only the *trans* isomer (**304**) could be observed, together with traces of 1,4-naphthoquinone (**306**) formed probably via **305**, which is the 1,4-addition product of ozone to naphthalene (Scheme 32).



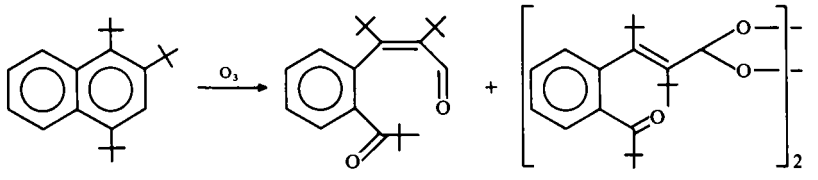
SCHEME 32

cis-*o*-Formylcinnamaldehyde (**303**) was also reported[12] as the main product of MW-generated ozonolysis of naphthalene on florisil surface. Products derived from cleavage of either one or two aromatic C—C bonds in naphthalenes were observed in aqueous ozonolysis[219].


O3
Polyozonide
(313)
(310)
(311)
(312)
O3
HCl
ROH
ROH
Δ [O]
+
COOR
COOR
CHO
CHO
[H]
OH
OR
[O]
COOH
COOH
(314)
(315)
(316)
(317)
(318)
[H]
RO
OR
H
H
(319)

SCHEME 33

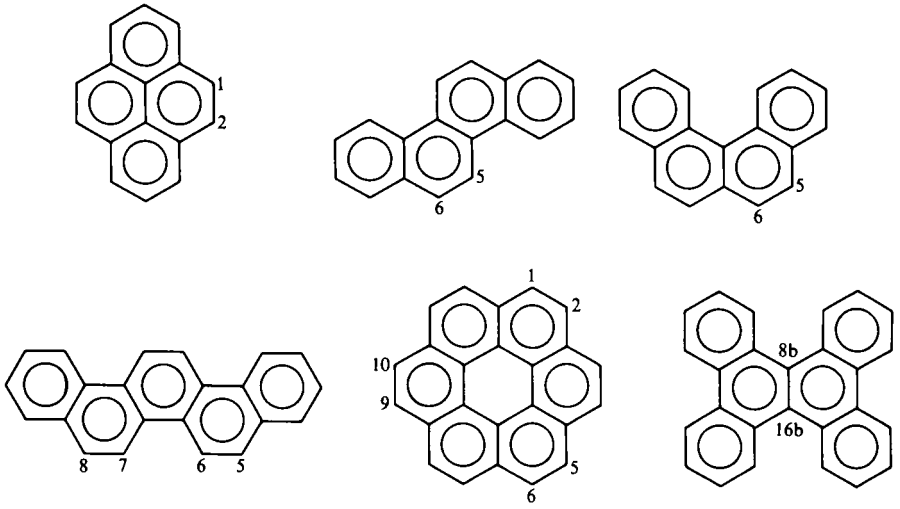
According to most reports prior to 1984, the ozonolysis of naphthalene and its derivatives in nonparticipating solvents resulted in peroxidic polymers derived from cleavage of two bonds in one ring. However, in 1984 Ito and colloborators reported that highly hindered naphthalenes absorb only one mole of ozone, resulting in a selective cleavage of the 3,4-bond[220]. Thus, 1,2,4-tri-*t*-butyl-naphthalene (**307**) gave in aprotic solvents a cinnamaldehyde derivative (**308**) as the main product. (equation 128).



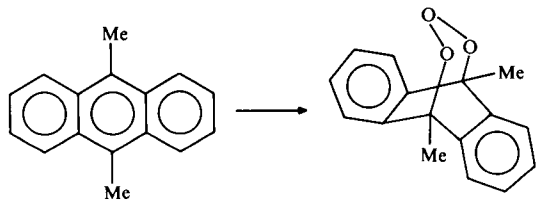
(307) (308) (309)

(128)

Ozonolysis of phenanthrene occurs always at the 9,10-bond and is faster than that of naphthalene. In nonparticipating solvents, polymeric ozonide formation was indicated which, upon oxidation with H_2O_2 or O_3 gave diphenic acid (**318**)[221]. In methanol and other alcohols phenanthrene gave with ozone the hemiperacetals **317** and **319** (Scheme 33), which could be converted to diphenic acid or the dialdehyde (**316**)[221,222]. It was recently reported[223] that upon ozonolysis of phenanthrene in alcoholic HCl the 'abnormal' lactone (**314**) was isolated in good yield together with some diphenic acid ester (**315**). In all polycyclic aromatic compounds the ozone attack occurred at the bonds of lowest bond-localization energy[224]. The sites of attack by ozone of several polycyclic hydrocarbons are given in Scheme 34. A special case is the anthracene system in which a transannular attack of ozone occurs. Ozonide (**320**) was actually isolated[225] and characterized[226].

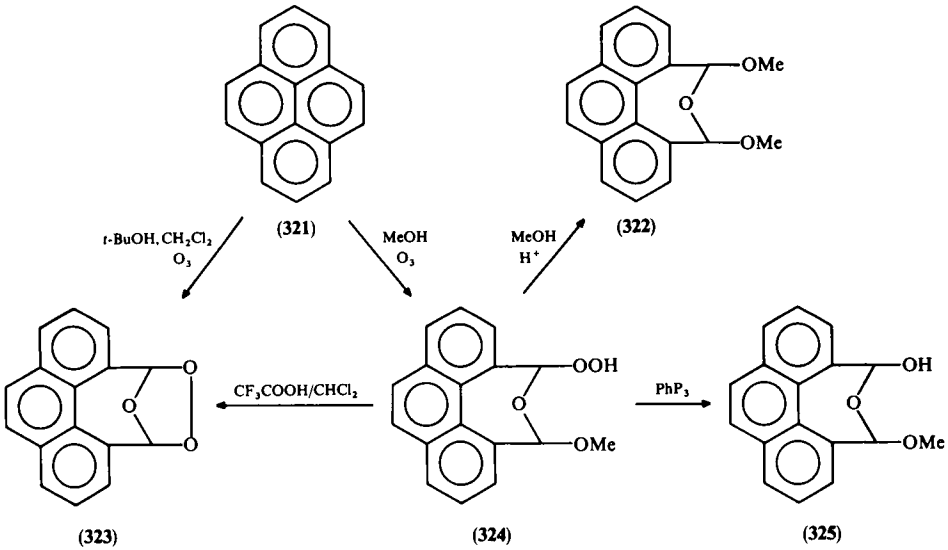


SCHEME 34



(320)

A recent study[169] on the ozonolysis of pyrene (**321**) in CH_2Cl_2/*t*-butanol or in methanol showed the formation of the expected ozonide (**323**) and the cyclic hydroperoxide (**324**), respectively. The latter could be converted to **323** by acid (Scheme 35). Reduction with PPh_3 and acid-catalyzed methanolysis gave **325** and **322**, respectively.



SCHEME 35

Whenever a polycyclic system contains a phenanthrene as well as an anthracene-type ring, there is the possibility of ozone attack at either site or both. This matter was discussed extensively in Bailey's book[2b].

V. OZONOLYSIS OF HETEROCYCLES

A. Ozonolysis of Five-membered Ring Heterocycles

Five-membered ring aromatic heterocycles are more reactive toward ozone than benzene and other carbocyclic aromatic compounds. The order of reactivity compared to six-membered aromatic heterocycles is: five-membered ring heterocycles > aromatic carbocycles > six-membered ring heterocycles.

The relative reaction rates with ozone in CH_2Cl_2 at $-78\,^{\circ}C$ within the group of five-membered ring heterocycles were evaluated by Kashima and his coworkers[227]. The

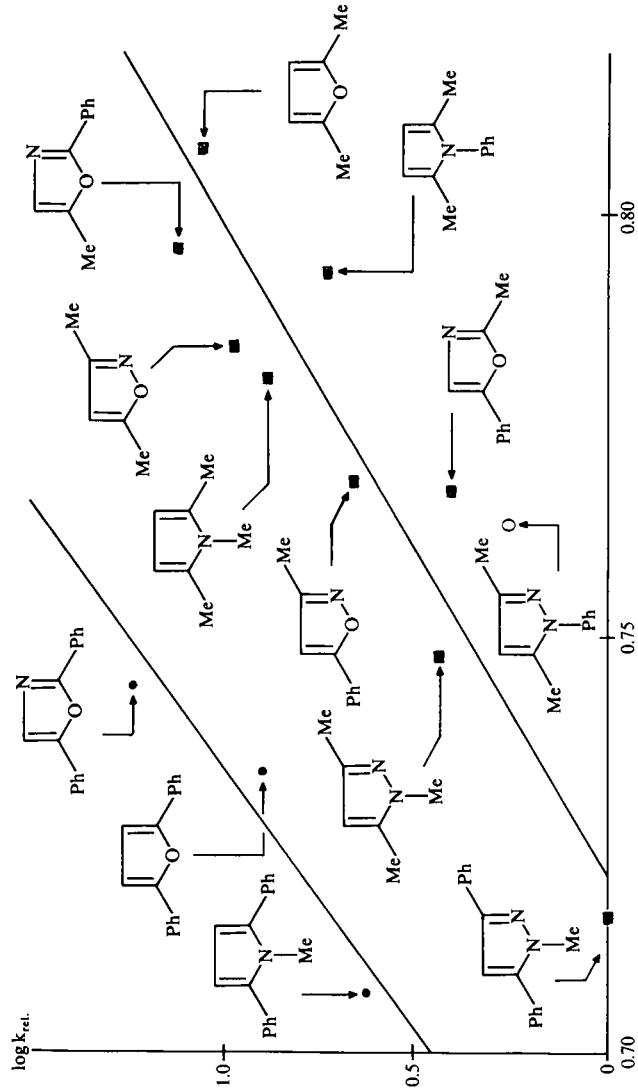
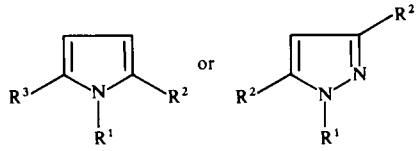


FIGURE 8. Relative reaction rates of ozonolysis of five-membered heterocycles and their correlation with the highest bond-order value. Reproduced with permission from Reference 277

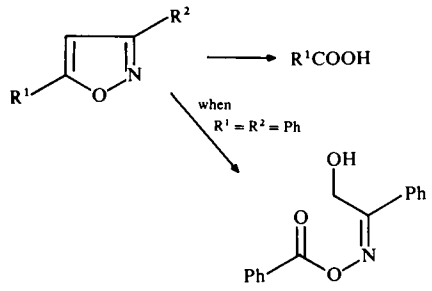
relative rates of reaction with ozone were correlated to the highest bond-order value in the corresponding ring, calculated by the HMO method. A plot of the highest bond order in a particular ring vs the logarithm of the relative rate of ozonolysis gave two straight lines (Figure 8). One line consisted of the substituted 2,5-diphenyl heterocycles, and the other consisted of the remaining heterocycles.

The results indicate that the reactivity of these heterocycles with ozone correlates with the highest value of the bond order, and that the reactivity should be predictable from simple molecular orbital calculations[227].

The products described above were isolated after treatment of the ozonolysis mixture with sodium borohydride in ethanol. Ozonolysis of nitrogen heterocycles afforded amides (equation 129), whereas furan (equations 130 and 131), isoxazole and oxazole derivatives gave acids. In the case of 3,5-diphenylisoxazole a partial ozonolysis product **326** was also identified.

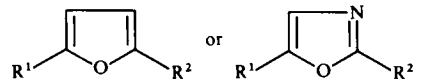


(129)



(130)

(326)

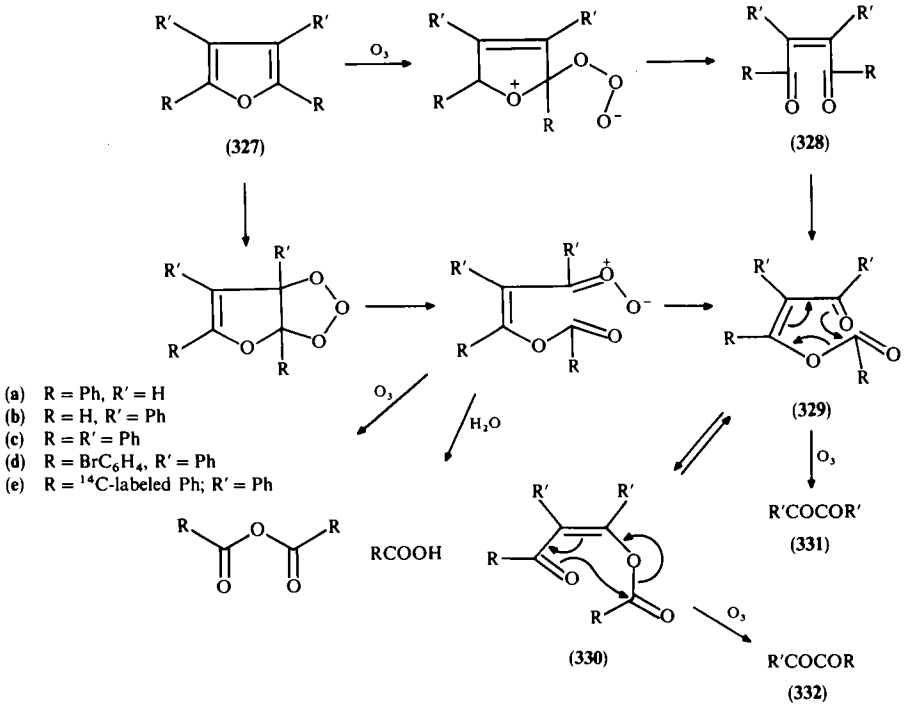


(131)

A comprehensive discussion about some early studies on the ozonation of five-membered ring heterocycles can be found in Reference 2. Some pertinent information and recent developments are included in the following Sections V.A.1–5.

1. Furans

Ozonolysis of furan itself led to the isolation of glyoxal and formic acid. Alkylfurans gave the corresponding biacyls and aliphatic acids. The course and mechanism of the ozonolysis of furan derivatives were studied by Bailey and his coworkers[228]. They studied the ozonolysis of arylfurans, e.g. 2,5-, 2,3- and 3,4-diphenylfurans, in various solvents and of tetraphenylfuran, and arrived at the route of formation of the major products of ozonolysis. Their findings are summarized in Scheme 36. One mole of ozone cleaves either bond 1,2 or bond 2,3; both bonds are cleaved by two moles of ozone.



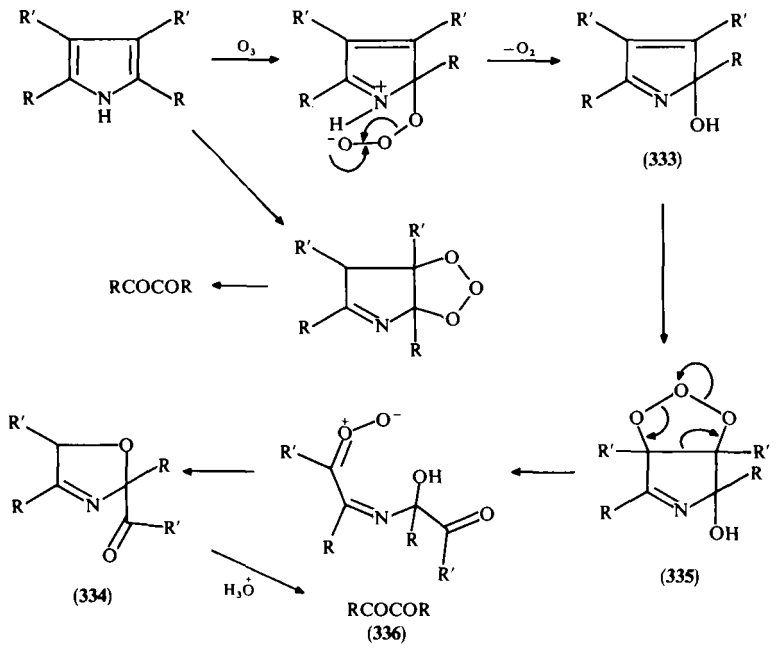
SCHEME 36

A 1,3-dipolar cycloaddition is the initial step in the cleavage of the 2,3-bond, whereas an electrophilic attack probably precedes the cleavage of the carbon oxygen (1,2-) bond. It was assumed that the enol benzoate **329** can also be formed by a Baeyer–Villiger-type oxidative rearrangement from **328** and is in equilibrium with **330**. The evidence for the latter equilibrium was established by the isolation of equal amounts of **331** and **332** on ozonolysis of **327b** ($R \neq R'$).

2. *Pyrroles*

Ozonolysis of pyrrole gave small amounts of glyoxal and formic acid, together with unidentified resinous materials. Alkylated pyrroles behave similarly, yielding 1,2-dicarbonyl compounds (biacyls) and aliphatic acids in low yields.

Studies by Lutz and Taylor[270] which were quoted in Bailey's book[2] have unravelled the complexities of the ozonation of pyrroles. They have succeeded in isolating and identifying the major product of the ozonolysis of tetraphenylpyrrole, as the cyclic hydroperoxide **334**. The mechanism which was proposed for its formation is shown in Scheme 37. It involves an electrophilic attack at position 2, followed by loss of O_2 that leads to intermediate **333**. The latter reacts with O_3 to yield **335**. It was also shown that **334** can decompose to a 1,2-dicarbonyl compound (**336**). The proposed scheme seems very reasonable, however it does not explain the formation of carboxylic acids which were often identified.



SCHEME 37

3. Thiophenes

Thiophene itself gave, on exhaustive ozonation, carbon dioxide, sulfur dioxide and unidentified products. The ozonation of thiophenes was found to be very similar to that of furans[2].

4. Pyrazoles

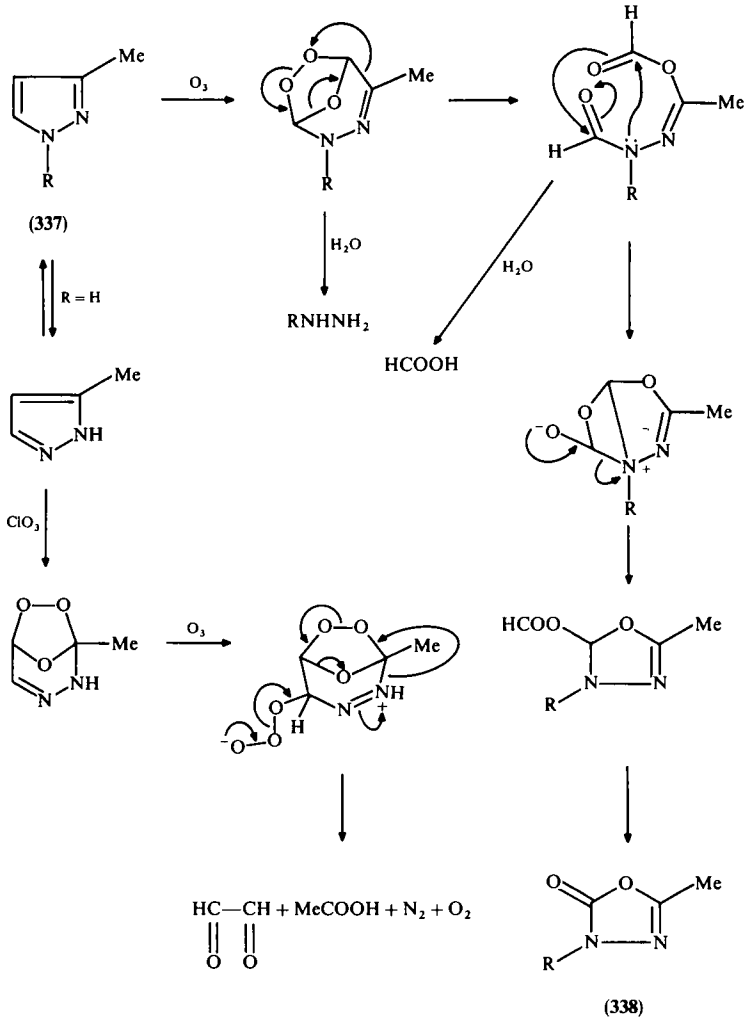
Pyrazole gave on ozonolysis glyoxal and hydrazine as the main identified products[229]. C-Alkylpyrazoles gave also carboxylic acids. The major product of N-substituted pyrazoles (**337**) was the oxadiazolone derivative (**338**), obtained by the reaction with 2 moles of ozone as shown in Scheme 38.

5. Indoles

Crystalline ozonides were reported to result from the ozonolysis of many substituted indoles in various solvents. In addition to the expected products, the ozonolysis of indole derivatives very often involves rearrangement as shown for 2-phenyl-3-methylindole (Scheme 39)[230]. The hydroperoxide **340** could be isolated and identified.

6. Oxazoles

The facile and quantitative formation of formic benzoic mixed anhydride upon ozonation of 5-phenylisoxazole in CH_2Cl_2 was utilized to devise a system for deuteroformylation of natural products, and other nucleophiles (equation 132)[231].



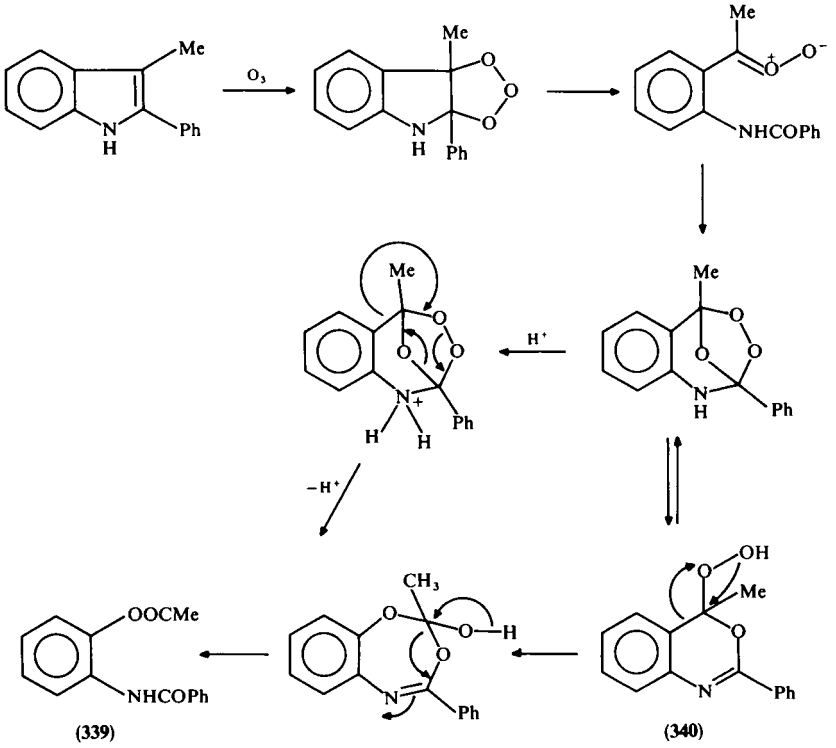
SCHEME 38

2-Deutero-5-phenylisoxazole proved to be a deuteroformylation agent superior to 5-deutero-2-phenylisoxazole, because the latter gives also the amide **341** (equation 133).

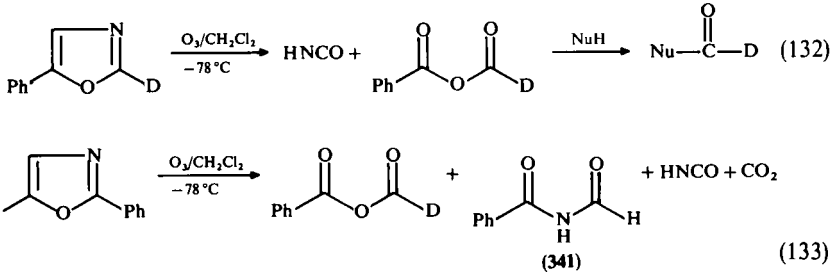
B. Ozonolysis of Six-membered Ring Heterocycles

1. Pyridine and its derivatives

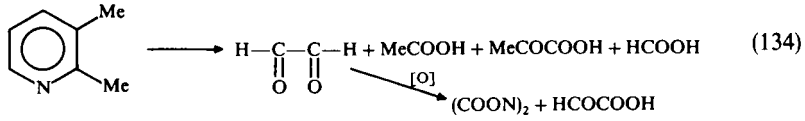
Pyridine is much more stable to ozonolysis than five-membered heterocycles or benzene. For many years it was regarded as unaffected by ozone attack, so that olefinic bonds as well as aromatic rings were ozonized in systems containing pyridine rings. Later, reports were published about destructive ozonolysis of the pyridine ring. It appears,



SCHEME 39

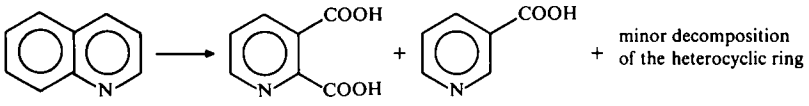


however, that because of the difficulties associated with ozonolysis of pyridine compounds, especially in regard to the sluggishness of the reaction, very little has been said about the course of reaction. The products of exhaustive ozonolysis of pyridine were glyoxal, glyoxalic acid, formic acid, oxalic acid and ammonia[232]. Methylpyridines gave, in addition, also acetic and pyruvic acids (equation 134).



2. Quinoline

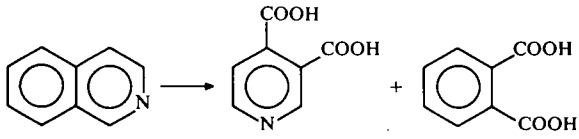
Quinoline gives upon ozonolysis derivatives of pyridine, by rupture of the carbocyclic ring. The major ozone attack occurs at the 5,6- and 7,8-bonds[233] and the main isolated products after oxidative work-up were quinolinic and nicotinic acid (equation 135). A minor competing cleavage appeared to occur at the pyridine ring.



(135)

A practical method for the preparation of substituted 2,3-pyridinedicarboxylic acids and acylpyridines was developed recently[234], based on the above facts and involves ozonation in the presence of mineral acids followed by an oxidative work-up.

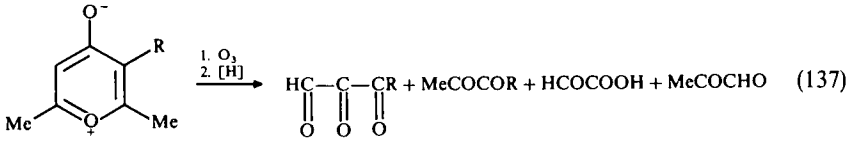
Isoquinoline was reported to yield products of cleavage of either the heterocyclic or the carbocyclic ring resulting in cinchomerinic (**342**) and phthalic acid (**343**)[233]; see equation 136.



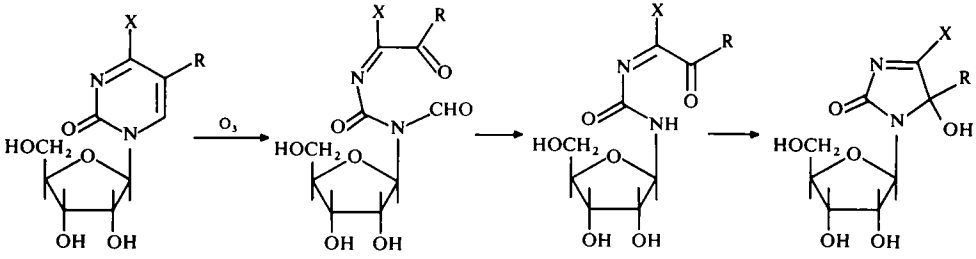
(136)

3. Pyrones

4-Pyrones react with ozone faster than benzene or toluene but slower than olefins[235]. The ozonolysis of trialkylpyrones was performed in chloroform at $-20\,^{\circ}C$, followed by reductive work-up and yielding the products shown in equation 137.



(137)



Cytidine (X = NH_2, R = H)
Uridine (X = OH, R = H)
Thymidine (X = OH, R = Me)

(138)

4. Pyrimidines

Recently, pyrimidine bases[236] and pyrimidine nucleosides[237] were reported to undergo ring contraction on reaction with ozone. The influence of substituents in positions 5 and 6 in uracil on the rate of ozonolysis was also studied. The course of the reaction is shown in equation 138.

VI. OZONOLYSIS OF CARBON–HETEROATOM DOUBLE BONDS

A. Ozonolysis of Carbon–Nitrogen Double Bonds

Carbon–nitrogen double bonds undergo cleavage upon reaction with ozone. Among the groups of compounds that were studied are Schiff bases[238,239], nitrones[238–240], hydrazones[239,241] and oximes[239,242,243]. The products of ozonolysis are summarized in equations 139–146. These compounds are generally as sensitive to ozonolysis as olefins. Various mechanisms have been suggested for these reactions. It is accepted that an initial nucleophilic ozone attack to yield intermediate **344** occurs followed by cyclization to trioxazolidine (**345**), and by cycloreversion (equation 147).

$$R_2C{=}NR' \longrightarrow R_2CO + O_2NR' \tag{139}$$

$$RCH{=}NR' \longrightarrow RCHO + O_2NR' \tag{140}$$

$$RCH{=}\overset{+}{N}(R^1){-}O^- \longrightarrow RCOOH + O_2NR' + RCHO + R'NO \tag{141}$$

$$R_2C{=}\overset{+}{N}(R'){-}O^- \longrightarrow R_2CO + O_2NR' \tag{142}$$

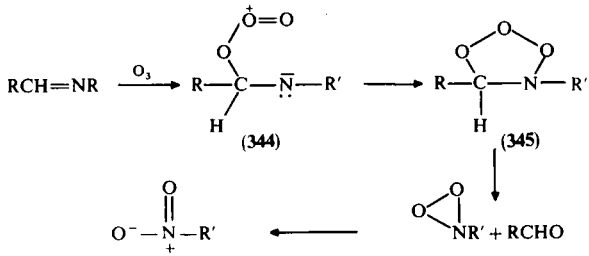
$$R_2C{=}NNHR' \longrightarrow R_2CO + R'OH + N_2 \tag{143}$$

$$R_2C{=}NNR'_2 \longrightarrow R_2CO + O{=}NR'_2 + O{=}NNR_2 \tag{144}$$

$$RCH{=}NOH \longrightarrow RCHO + RCOOH + HNO_3 \tag{145}$$

$$R_2C{=}NOR' \longrightarrow R_2CO + R'ON{=}O + R\overset{O}{\overset{\|}{C}}{-}NR(OR') \tag{146}$$

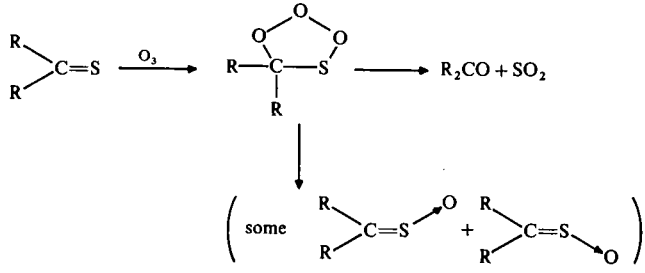
An efficient method for the synthesis of acyclic sugar aldehydes, based on the ozonolysis of *O*-methyloxime aldoses, was recently reported[243]. This method eliminates problems associated with decomposition of these aldehydes by β-elimination and formation of side products.



(147)

B. Ozonolysis of Carbon–Sulfur Double Bonds

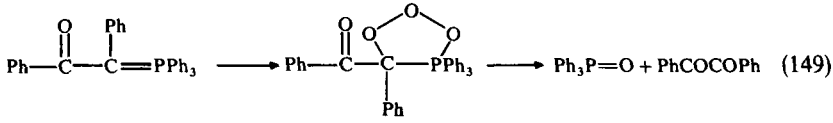
The general reaction of carbon–sulfur bonds is shown in equation 148. The route which was suggested[244] for the formation of ketones and SO_2 was also confirmed by calculations[245].



(148)

C. Ozonolysis of Phosphorous Ylides

Phosphorous ylides were shown[239,246] to undergo ozonolysis to phosphorous oxides and ketones: an example is given in equation 149.



(149)

TABLE 7. New synthetic methods involving ozonolysis

Products	Method	Reference
1,4-Dicarbonyl compounds	Claisen/ozonolysis, alternative to alkylation of enolates	247
Trialkylsilylated α-hydroperoxy aldehydes and ketones	Ozonolysis of protected allylic hydroperoxides	248
γ-Keto aldehydes	Kinetic alkylation–ozonolysis	249
ω,ω-Dialkoxy esters	Acid-catalyzed ozonolysis of unsaturated acids	250
β-Keto esters	Ozonolysis of olefins followed by *in situ* reduction in the presence of ethyl diazoacetate	251
Morpholino amino acids	Ozonolysis and reductive *N*-alkylation	252
Asymmetric synthesis of 2-substituted piperidines	Ozonolysis of pentene and reductive aminocyclization	253
Mixed anhydrides	Ozonolysis of oxazoles	254
α,β-Unsaturated esters	Reaction of ozonides with phosphorous ylides	255
α,β-Unsaturated ketones	Ozonolysis of homoallyl alcohols and elimination of water	256

VII. OZONOLYSIS IN SYNTHESIS

The use of ozonolysis in organic synthesis is now growing and new procedures of ozonolysis are being developed to suit modern synthetic work. Ozonolysis is used both for the preparation of new synthons and in manipulation of complex molecules. Ozonolysis in synthesis probably deserves a separate chapter and its detailed discussion is beyond the scope of the present one. However, we feel that it is important to mention at least some of the recent advances in this area and quote some references to guide the reader, in addition to those already quoted in the previous sections. Several new synthetic methods that involve ozonolysis are summarized in Table 7.

Some recent syntheses of natural products where ozonolysis is a key step should be mentioned, e.g. synthesis of prostaglandines[257], prostanoid synthons[149], Brefeldin[150], drimanes[258] and hydroxychromones[259]. The synthesis of numerous sex pheromones of many species of insects are included in over 50 publications of Odinokov, Tolstikov and their coworkers (see e.g. References 155–160).

VIII. OZONOLYSIS IN ORGANIC ANALYSIS

Ozonolysis was and is one of the most important chemical methods for identifying multiple bonds in organic molecules. Very often the structures of natural products and other unknowns were established by ozonolytic cleavage and identification of the resulting fragments. We shall only mention some very recent developments in the analytical field. For details, the reader should consult the references cited in Table 8.

TABLE 8. Recent analytic procedures where ozonolysis is involved

Analyzed products	Method	References
ω-3-Polyunsaturated fatty acids	Quantitative determination by ozonolysis	260
Butadiene–styrene copolymers	Structural characterization by FABMS[a] of partial ozonolysis products	261
Oleic acid	Ozonolysis in the presence of BX_3 methanol	262
Olefins	Derivatization of carbonyl compounds resulting from ozonolysis with 1,1-dimethylhydrazine	263
Mixture of octadienoates	Ozonolysis, chromatography and computer solution of linear equations	264
Octadecanoic acid isomers	Micro ozonolysis after selective trapping using MUSIC[b]	265
Styrene block copolymers	Combined ozonolysis–GPC	266
Cross-linked peptides	Cleavage by ozonolysis, leading to the separation of peptide chains	267
PVC polymers	Determination of the degree of conversion by residual double bonds	268
Alkynes and alkynoic esters	Analysis by ozonolysis followed by gas chromatography	269

[a]Fast Atom Bombardment Mass Spectrometry.
[b]Multiple Switching Intelligent Controller.

IX. REFERENCES

1. E. Keinan and H. T. Varkony, in *The Chemistry of Peroxides* (Ed. S. Patai), Wiley, Chichester, 1983, pp. 649–683.
2. (a) P. S. Bailey, *Ozonation in Organic Chemistry*, Vol. I, Academic Press, New York, 1972.
   (b) P. S. Bailey, *Ozonation in Organic Chemistry*, Vol. II, Academic Press, New York, 1982.
3. (a) R. H. Hughes, *J. Chem. Phys.*, **24**, 131 (1956).
   (b) P. G. Burton, *J. Chem. Phys.*, **71**, 961 (1979).
   (c) P. J. Hay, T. H. Dunning, Jr. and W. A. Goddard, III, *J. Chem. Phys.*, **62**, 3912 (1975).
4. J. P. Wibaut and F. L. J. Sixma, *Recl. Trav. Chim. Pays-Bas*, **71**, 761 (1952); G. P. Shulman, *Can. J. Chem.*, **43**, 3069 (1965).
5. G. A. Olah, N. Yoneda and D. G. Parker, *J. Am. Chem. Soc.*, **98**, 2251 (1976).
6. R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565, 633 (1963).
7. M. J. S. Dewar, S. Ollivella and H. S. Rzepa, *Chem. Phys. Lett.*, **47**, 80 (1977).
8. D. G. Williamson and R. I. Cvetanovic, *J. Am. Chem. Soc.*, **90**, 4248 (1968).
9. L. Long, Jr., *Chem. Rev.*, **27**, 437 (1940).
10. P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).
11. C. E. Throp, *Bibliography of Ozone Technology*, Vols. 1 and 2, Armour Res. Found., Chicago, Ill., 1955; J. S. Blew, in *Oxidation* (Ed. R. L. Augustine), Vol. 1, Chap. 6, Academic Press, New York, 1961.
12. E. Zadok, S. Rubinraut and Y. Mazur, *Tetrahedron Lett.*, **25**, 4175 (1984).
13. (a) G. A. Olah, N. Yoneda and D. G. Parker, *J. Am. Chem. Soc.*, **98**, 5261 (1976); N. Yoneda and G. A. Olah, *J. Am. Chem. Soc.*, **99**, 3113 (1977).
    (b) G. A. Olah, N. Yoneda and R. Ohnishi, *J. Am. Chem. Soc.*, **98**, 7341 (1976).
14. F. A. Stich and D. Bhattacharyya, *Environ. Prog.*, **6**(4), 224 (1987); *Chem. Abstr.*, **108**, 10697v.
15. C. F. Schönbein, *J. Prakt. Chem.*, [1], **105**, 232 (1868).
16. J. P. Desvergne, J. Bouas-Laurent, E. V. Blackburn and R. Lapoyade, *Tetrahedron Lett.*, 947 (1974); J. P. Desvergne and J. M. Thomas, *J. Chem. Soc., Perkin Trans. 2*, 584 (1975).
17. Z. Cohen, E. Keinan, Y. Mazur and T. H. Varkony, *J. Org. Chem.*, **40**, 2141 (1975).
18. K. Griesbaum, W. Volpp and R. Greinert, *J. Am. Chem. Soc.*, **107**, 5309 (1985).
19. (a) K. Griesbaum and W. Volpp, *Angew. Chem.*, **98**, 108 (1986); *Chem. Ber.*, **121**, 1795 (1988).
    (b) K. Griesbaum, W. Volpp, R. Greinert, H. J. Greunig, J. Schmid and H. Henke, *J. Org. Chem.*, **54**, 383 (1989).
    (c) K. Griesbaum, W. S. Kim, N. Nakamura, M. Mori, M. Nojima and S. Kusabayashi, *J. Org. Chem.*, **55**, 6153 (1990).
    (d) K. Griesbaum and R. Greinert, *Chem. Ber.*, **123**, 391 (1990).
    (e) K. Griesbaum, H. J. Greunig, W. Volpp and I. C. Jung, *Chem. Ber.*, **124**, 947 (1991).
20. Y. Takita, M. Iwamoto and J. H. Lunsford, *J. Phys. Chem.*, **84**, 1710 (1980).
21. L. Papalambros and J. Nikokavouras, *J. Photochem.*, **39**, 73, 85, 97 (1987).
22. W. Dreher and H. Klamberg, *Fresenius Z. Anal. Chem.*, **331**, 290 (1988).
23. R. L. Kuczkowski, in *1,3-Dipolar Cycloaddition Chemistry* (Ed. A. Padwa), Vol. 2, Wiley–Interscience, New York, 1984, pp. 197–276.
24. (a) C. D. Harries, *Untersuchungen Uber das Ozon und Seine Virkung auf Organische Verbindungen*, Springer-Verlag, Berlin, 1916.
    (b) H. Staudinger, *Ber. Dtsch. Chem. Ges.*, **58**, 1088 (1925).
25. A. Riech, *Alkyl Peroxides and Ozonides*, Steinkopf, Darmstadt, 1931.
26. E. Briner, R. Patry and E. DeLuserna, *Helv. Chem. Acta*, **7**, 62 (1924).
27. R. Criegee, in *Peroxide Reaction Mechanisms* (Ed. J. O. Edwards), Wiley–Interscience, New York, 1962, p. 29; R. Criegee, *Adv. Chem. Ser.*, **21**, 133 (1959); R. Criegee, *Chimia*, **22**, 392 (1968).
28. N. L. Bauld, J. A. Thompson, C. E. Hudson and P. S. Bailey, *J. Am. Chem. Soc.*, **90**, 1822 (1968).
29. R. P. Lattimer, R. L. Kuczkowski and C. W. Gillies, *J. Am. Chem. Soc.*, **96**, 348 (1974).
30. J. Carles and S. Fliszar, *Adv. Chem. Ser.*, **112**, 35 (1972); W. A. Pryor, D. G. Prier and D. F. Church, *J. Am. Chem. Soc.*, **105**, 2883 (1983).
31. W. A. Pryor, N. Ohto and D. F. Church, *J. Am. Chem. Soc.*, **104**, 5813 (1982); B. Nelander and L. Nord, *J. Am. Chem. Soc.*, **101**, 3769 (1979).
32. R. Criegee and G. Schroder, *Chem. Ber.*, **93**, 689 (1960); F. L. Greenwood and S. Cohen, *J. Org. Chem.*, **28**, 1159 (1963); F. L. Greenwood, *J. Org. Chem.*, **30**, 3108 (1965).
33. B. Mile, G. W. Morris and W. G. Alcock, *J. Chem. Soc., Perkin Trans., 2*, 1644 (1979).

34. P. S. Bailey, J. A. Thompson and B. A. Shoulders, *J. Am. Chem. Soc.*, **88**, 4098 (1966); P. S. Bailey, T. P. Carter, Jr., C. M. Fischer and J. A. Thompson, *Can. J. Chem.*, **51**, 1278 (1973).
35. L. J. Durham and F. L. Greenwood, *J. Org. Chem.*, **33**, 1629 (1968).
36. D. Cremer, *J. Chem. Phys.*, **70**, 1898, 1911 (1979).
37. P. Ruoff, J. Almof and S. Saebo, *Chem. Phys. Lett.*, **72**, 489 (1980).
38. (a) J. Z. Gillies, C. W. Gillies, R. D. Suenram and F. J. Lovas, *J. Am. Chem. Soc.*, **110**, 7991 (1988). (b) J. Zozom, C. W. Gillies, R. D. Suenram and F. J. Lovas, *Chem. Phys. Lett.*, **140**, 64 (1987).
39. L. M. McKee and C. M. Rohlfing, *J. Am. Chem. Soc.*, **111**, 2497 (1989).
40. M. J. S. Dewar, J. C. Hwang and D. R. Kuhn, *J. Am. Chem. Soc.*, **113**, 735 (1991).
41. (a) W. R. Wadt and W. A. Goddard III, *J. Am. Chem. Soc.*, **97**, 3004 (1975). (b) L. B. Harding and W. A. Goddard III, *J. Am. Chem. Soc.*, **100**, 7180 (1978).
42. S. D. Razumovskii and G. E. Zaikov, *J. Org. Chem. USSR (Engl. Transl)*, **8**, 468 (1972).
43. H. Henry, M. Zodor and S. Fliszar, *Can. J. Chem.*, **51**, 3398 (1973); V. Caprio, M. G. D'Amore and A. Insola, *Oxid. Commun.*, **10**, 105 (1987).
44. H. S. Choi and R. L. Kuczkowski, *J. Org. Chem.*, **50**, 901 (1985).
45. E. Tempesti, M. Fornaroli, L. Giuffre, E. Montonery and G. Airoldi, *J. Chem. Soc., Perkin Trans. 1*, 1319 (1983).
46. K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier and J. K. George, *J. Am. Chem. Soc.*, **95**, 7287 (1973); K. N. Houk, J. Sims, C. R. Watts and L. J. Luskus, *J. Am. Chem. Soc.*, **95**, 7301 (1973).
47. D. Cremer, *J. Am. Chem. Soc.*, **101**, 7199 (1979).
48. L. A. Hull, *J. Org. Chem.*, **43**, 2780 (1978).
49. (a) Bailey and T. M. Ferrell, *J. Am. Chem. Soc.*, **100**, 899 (1978) (b) P. S. Bailey, T. M. Ferrell, A. Rustiyan, S. Seyhan and L. E. Unruh, *J. Am. Chem. Soc.*, **100**, 894 (1978).
50. R. D. Suenram and E. J. Lovas, *J. Am. Chem. Soc.*, **100**, 5117 (1978).
51. W. H. Bunnelle, *Chem. Rev.*, **91**, 335 (1991).
52. W. Sander, *Angew. Chem., Int. Ed. Engl.*, **29**, 344 (1990).
53. (a) M. Miura, M. Nojima and S. Kusabayashi, *J. Chem. Soc., Perkin Trans. 1*, 2909 (1980). (b) V. Sawaki, H. Kato and Y. Ogata, *J. Am. Chem. Soc.*, **103**, 3832 (1981).
54. S. Kafafi, R. I. Martinez and J. T. Herron, *Mol. Struct. Energ.*, **6**, 283 (1988); J. Gauss and D. Cremer, *Chem. Phys. Lett.*, **133**, 420 (1987); D. Cremer, T. Schmidt, J. Gauss and T. P. Radhakrishnan, *Angew. Chem., Int. Ed. Engl.*, **27**, 427 (1988).
55. D. Cremer, T. Schmidt, W. Sander and P. Bischop, *J. Org. Chem.*, **54**, 2515 (1989).
56. R. W. Murray and R. Hagen, *J. Org. Chem.*, **36**, 1098 (1971); D. P. Higley and R. W. Murray, *J. Am. Chem. Soc.*, **98**, 4526 (1976); J. S. Su and R. W. Murray, *J. Org. Chem.*, **45**, 678 (1980); P. Mile and G. W. Morris, *J. Chem. Soc., Chem. Commun.*, 263 (1978).
57. W. Adam, R. Curci and J. O. Edwards, *Acc. Chem. Res.*, **22**, 205 (1989).
58. W. Sander, *J. Org. Chem.*, **54**, 333 (1989); **53**, 2091 (1988).
59. (a) B. J. Wojciechowski, W. H. Pearson and R. L. Kuczkowski, *J. Org. Chem.*, **54**, 115 (1989). (b) M. Mori, M. Nojima, S. Kusabayashi and K. J. McCullough, *J. Chem. Soc., Chem. Commun.*, 1550 (1988).
60. S. Fliszàr and M. Granger, *J. Am. Chem. Soc.*, **91**, 3330 (1969); **92**, 3361 (1970); S. Fliszàr and J. Renard, *Can. J. Chem.*, **45**, 533 (1967); **48**, 3002 (1970).
61. K. Griesbaum and G. Zwick, *Chem. Ber.*, **119**, 229 (1986); K. Griesbaum and A. R. Bandopadhyay, *Can. J. Chem.*, **65**, 487 (1987).
62. H. Keul, H. S. Choi and R. L. Kuczkowski, *J. Org. Chem.*, **50**, 3365 (1985).
63. W. H. Bunnelle, *J. Am. Chem. Soc.*, **111**, 7613 (1989); W. H. Bunnelle, L. A. Meyer and E. O. Schlemper, *J. Am. Chem. Soc.*, **111**, 7612 (1989).
64. Y. Yamamoto, E. Niki and Y. Kamiya, *J. Org. Chem.*, **46**, 250 (1981).
65. N. Nakamura, T. Fujisaka, M. Nojima, S. Kusabayashi and K. J. McCullough, *J. Am. Chem. Soc.*, **111**, 1799 (1989).
66. J. Cremer, *J. Chem. Phys.*, **70**, 1911 (1979).
67. D. Cremer, *J. Am. Chem. Soc.*, **103**, 3627 (1981).
68. G. Schroder, *Chem. Ber.*, **95**, 733 (1962).
69. (a) R. W. Murray and G. J. Williams, *J. Org. Chem.*, **34**, 1891 (1969). (b) J. Carles and S. Fliszar, *Can. J. Chem.*, **48**, 1309 (1970).
70. R. W. Murray, R. D. Youssefyeh and P. R. Story, *J. Am. Chem. Soc.*, **88**, 3655 (1966); R. Criegee and H. Korber, *Chem. Ber.*, **104**, 1807 (1971).

71. (a) D. Cremer, *J. Am. Chem. Soc.*, **103**, 3619 (1981).
(b) D. Cremer, *J. Am. Chem. Soc.*, **103**, 3633 (1981).
72. D. S. Privett and E. C. Nickell, *J. Am. Oil Chem. Soc.*, **41**, 72 (1964).
73. (a) G. D. Fong and R. L. Kuczkowski, *J. Am. Chem. Soc.*, **102**, 4763 (1980).
(b) M. Painter, H. S. Choi, K. W. Hillig and R. L. Kuczkowski, *J. Chem. Soc., Perkin Trans. 2*, 1025 (1986).
74. H. Kuel and R. L. Kuczkowski, *J. Am. Chem. Soc.*, **106**, 3383 (1984).
75. E. Sanhueza, I. C. Hisatsune and J. Heicklen, *Chem. Rev.*, **76**, 801 (1976); F. Su, J. G. Calvert and J. H. Show, *J. Phys. Chem.*, **84**, 239 (1980).
76. H. E. O'Neal and C. Blumstein, *Int. J. Chem. Kinet*, **5**, 397 (1973).
77. R. W. Murray and M. M. Morgan, *J. Org. Chem.*, **56**, 684 (1991).
78. (a) B. L. Feringa and R. J. Butselaar, *Tetrahedron Lett.*, **22**, 1447 (1981); B. L. Feringa, *Tetrahedron Lett.*, **22**, 1443 (1981).
(b) A. P. Schaap, S. Siddiqui, G. Prasad, A. F. M. M. Rahman and J. P. Oliver, *J. Am. Chem. Soc.*, **106**, 6087 (1984).
(c) W. Adam, H. J. Eggelte, and A. Rodriguez, *Synthesis*, **382** (1979).
79. S. Fliszar and J. Carles, *Can. J. Chem.*, **47**, 3921 (1969).
80. D. G. M. Diaper and W. M. J. Strachan, *Can. J. Chem.*, **45**, 33 (1967).
81. F. L. Grinwood, *J. Org. Chem.*, **20**, 803 (1955).
82. E. Bernatek, H. Hagen and T. Ledaal, *Acta Chem. Scand.*, **21**, 1555 (1967).
83. R. Criegee and H. Korber, *Adv. Chem. Ser.*, **112**, 22 (1972).
84. V. N. Yur'ev, S. D. Razumovskii and V. K. Tsyskovskii, *Zh. Org. Khim.*, **4**, 1720 (1968); *J. Org. Chem. USSR (Engl. Transl.)*, **4**, 1656 (1968).
85. M. I. Fremery and E. K. Fields, *J. Org. Chem.*, **28**, 2537 (1963).
86. P. R. Story, W. H. Morrison, III, T. K. Hall, J. C. Farine and C. E. Bishop, *Tetrahedron Lett.*, 3291 (1968); P. R. Story, T. K. Hall, W. H. Morrison, III and J. C. Farine, *Tetrahedron Lett.*, 5397 (1968).
87. R. Criegee and R. Huber, *Chem. Ber.*, **103**, 1855, 1862 (1970).
88. S. Hatakeyama and H. Akimoto, *Bull. Chem. Soc. Jpn.*, **56**, 655 (1983).
89. R. Criegee, H. Pilz and H. Flygare, *Ber. Dtsch. Chem. Ges.*, **72**, 1799 (1939); M. V. Pospelov, A. T. Menyailo, T. A. Bortyan, Y. A. Sustynyuk and V. S. Petrosyan, *Zh. Org. Khim.*, **9**, 311 (1973), *J. Org. Chem. (Engl. Transl.)*, **9**, 312 (1973).
90. G. O. Schenk, H. D. Becker, K. H. Schulte-Elte and C. H. Krauch, *Chem. Ber.*, **96**, 509 (1963); D. B. Sharp and T. M. Patrick, Jr., *J. Org. Chem.*, **26**, 1389 (1961).
91. N. A. Milas, R. L. Peeler, Jr., and O. L. Mageli, *J. Am. Chem. Soc.*, **76**, 2322 (1954).
92. A. Rieche and C. Bischoff, *Chem. Ber.*, **94**, 2722 (1961).
93. P. S. Bailey, S. B. Mainthia and C. J. Abshire, *J. Am. Chem. Soc.*, **82**, 6136 (1960); R. M. Carman and D. E. Cowley, *Tetrahedron Lett.*, 2723 (1968).
94. R. Criegee, A. Banciu and H. Kuel, *Chem. Ber.*, **108**, 1642 (1975).
95. R. M. Ellam and J. M. Padbury, *J. Chem. Soc., Chem. Commun.*, 1086 (1972).
96. S. L. Schreiber, R. E. Claus and J. Reagan, *Tetrahedron Lett.*, **23**, 3867 (1982).
97. L. A. Sublusky, G. C. Harris, A. Maggiolo and A. A. Tumolo. *Adv. Chem. Ser.*, **21**, 149 (1959).
98. R. Criegee, A. Kerckow and H. Zinke, *Chem. Ber.*, **88**, 1878 (1955).
99. M. Pierrot, M. El Idrissi and M. Santelli, *Tetrahedron Lett.*, **30**, 461 (1989).
100. E. S. Zelikman, L. V. Berezova, E. P. Kutueva and Y. N. Yur'ev, *Zh. Org. Khim.*, **12**, 770 (1976); *J. Org. Chem. USSR (Engl. Transl.)*, **12**, 769 (1976).
101. R. Criegee and G. Wenner, *Justus Liebigs Ann. Chem.*, **564**, 9 (1949).
102. E. Bernatek, P. Gronning and T. Ledaal, *Acta Chem. Scand.*, **18**, 1966 (1964).
103. M. V. Pospelov, A. T. Menyailo, O. B. Kaliko, T. A. Bortyan, E. S. Belyaeva and Y. Z. Karasev, *Zh. Org. Khim.*, **14**, 247 (1978); *J. Org. Chem. USSR (Engl. Transl.)*, **14**, 228 (1978).
104. M. I. Fremery and E. K. Fields, *J. Org. Chem.*, **29**, 2240 (1964).
105. M. Schulz, D. Becker and A. Rieche, *Angew. Chem.*, **77**, 548 (1965); M. Schulz, A. Rieche and D. Becker, *Chem. Ber.*, **99**, 3233 (1966).
106. G. G. Filina, T. A. Bortyan, A. T. Menyailo and M. V. Pospelov, *Zh. Org. Khim.*, **16**, 782 (1980); *J. Org. Chem. USSR (Engl. Transl.)*, **16**, 687 (1980).
107. M. Kawaguchi, O. Hayashi, M. Kanamoto, M. Hamada and Y. Yamamoto, *Agric. Biol. Chem.*, **51**, 435 (1987); M. Kawaguchi, J. Oashi, Y. Kawakami Y. Yamamoto and J. Oda, *synthesis*, 701 (1985).

108. E. K. Fields, *Adv. Chem. Ser.*, **51**, 99 (1965).
109. R. Criegee and G. Lohaus, *Justus Liebits Ann. Chem.*, **583**, 6 (1953).
110. P. Groth, *Acta Chem. Scand.*, **18**, 1301, 1801 (1964); **19**, 1497 (1965).
111. J. I. G. Cadogan, D. H. Hey and W. A. Sanderson, *J. Chem. Soc.*, 4897 (1960).
112. P. R. Story, B. Lee, C. E. Bishop, D. D. Denson and P. Busch, *J. Org. Chem.*, **35**, 3059 (1970); B. Lee, P. R. Story and J. R. Sanderson, *J. Org. Chem.*, **41**, 2314 (1976).
113. R. Criegee, *Rec. Chem. Prog.*, **18**, 111 (1957); *Justus Liebigs Ann. Chem.*, **583**, 1 (1953).
114. S. D. Razumovskii, L. V. Berezova, N. D. Gil'chenok, O. M. Oranskaya, Y. N. Yur'ev and V. K. Tsyskovskii, *Zh. Org. Khim.*, **2**, 1942 (1966); *J. Org. Chem. USSR (Engl. Trans.)*, **2**, 1910 (1966); S. D. Razumovskii, G. A. Niazashvilli, I. A. Tutorskii and Y. N. Yur'ev, *Vysokomol. Soedin. Ser.* **A13**, 190 (1971); *Polym. Sci. USSR (Engl. Transl.)*, **13**, 217 (1971).
115. F. L. Greenwood and H. Rubinstein, *J. Org. Chem.*, **32**, 3369 (1967).
116. P. S. Bailey and A. G. Lane, *J. Am. Chem. Soc.*, **89**, 4473 (1967).
117. P. S. Bailey, J. W. Ward, T. P. Carter, Jr., E. Nieh, C. M. Fisher and A. Y. Khashab, *J. Am. Chem. Soc.*, **96**, 6136 (1974).
118. R. W. Murray and A. Suzui, *J. Am. Chem. Soc.*, **95**, 3343 (1973).
119. A. R. Hochstetler, *J. Org. Chem.*, **40**, 1536 (1975).
120. D. Cremer and C. W. Bock, *J. Am. Chem. Soc.*, **108**, 3375 (1986).
121. T. A. Hinrichs, V. Ramachandran and R. W. Murray, *J. Am. Chem. Soc.*, **101**, 1283 (1979).
122. C. W. Gillies, *J. Am. Chem. Soc.*, **99**, 7239 (1977).
123. R. W. Murray, S. N. Rajadhyaksha and R. Jeyaraman, *Polycyclic Aromat. Compd.*, **1**, 213 (1990).
124. D. J. Everest, P. K. Grant, G. C. Slim and I. K. L. Yeo, *Aust. J. Chem.*, **41**, 1025 (1988).
125. J. E. Leffler, *Chem. Rev.*, **45**, 385 (1949).
126. W. G. Young, A. C. McKinnis, I. D. Webb and J. D. Roberts, *J. Am. Chem. Soc.*, **68**, 293 (1946).
127. P. Vlad and M. Souček, *Collect. Czech. Chem. Commun.*, **27**, 1726 (1962).
128. D. H. R. Barton and E. Seoane, *J. Chem. Soc.*, 4150 (1956).
129. W. H. Bunnelle, A. Meyer and E. O. Schlemper, *J. Am. Chem. Soc.*, **111**, 7612 (1989).
130. P. Kolsaker and P. S. Bailey, *Acta Chem. Scand.*, **21**, 537 (1967).
131. H. Niki, P. D. Maker, C. M. Savage, L. P. Breitenbach and M. D. Hurley, *J. Phys. Chem.*, **91**, 941 (1987).
132. R. Criegee, S. S. Bath and B. von Bornhaupt, *Chem. Ber.*, **93**, 2891 (1960).
133. R. W. Murray, P. R. Story and L. D. Loam, *J. Am. Chem. Soc.*, **87**, 3025 (1965); R. W. Murray, S. K. Agarwal, *J. Org. Chem.*, **50**, 4698 (1985).
134. (a) P. S. Bailey and S. B. Mainthia, *J. Org. Chem.*, **23**, 1089 (1958).
(b) K. Griesbaum and G. Kiesel, *Chem. Ber.*, **122**, 145 (1989).
135. R. H. Perry, Jr., *J. Org. Chem.*, **24**, 829 (1959).
136. T. Vrbaski and R. J. Cvetanovic, *Can. J. Chem.*, **38**, 1063 (1960).
137. R. Habib, C. Y. Chiang and P. S. Bailey, *J. Org. Chem.*, **49**, 2780 (1984).
138. A. F. Thomas, C. Perret and G. Bernardinelli, *Chimia*, **39**, 228 (1985).
139. C. W. Jefford, J. Boukouvalas, D. Jaggi, S. Kohmoto and G. Bernardinelli, *Helv. Chim. Acta*, **69**, 941 (1986).
140. V. N. Odinokov, O. S. Kukovinets, L. P. Bostman, L. M. Khliolov, G. A. Tolstikov, A. Y. Kosnikov, S. V. Lindeman and Y. T. Struchkov, *Zh. Org. Khim.*, **23**, 995 (1987).
141. S. Canonica, M. Ferrari, G. Jommi and M. Sisti, *Synthesis*, 697 (1988).
142. K. Jaworski and L. L. Smith, *J. Org. Chem.*, **53**, 545 (1988).
143. K. Griesbaum and G. Zwick, *Chem. Ber.*, **119**, 229 (1986).
144. M. Mittelbach and N. Poklukar, *Chem. Phys. Lipids*, **55**, 67 (1990).
145. T. Veysoglu, L. A. Mitscher and J. K. Swayze, *Synthesis*, 807 (1980).
146. P. S. Bailey, *Ind. Eng. Chem.*, **50**, 993 (1958).
147. S. W. Pelletier, K. N. Iyer and J. W. J. Chang, *J. Org. Chem.*, **35**, 3535 (1970).
148. M. Mori, M. Nojima and S. Kusabayashi, *J. Am. Chem. Soc.*, **109**, 4407 (1987).
149. T. Hudlicky, H. Luna, G. Barbieri and L. D. Kwart, *J. Am. Chem. Soc.*, **110**, 4735 (1988).
150. S. L. Schreiber and H. V. Meyers, *J. Am. Chem. Soc.*, **110**, 5198 (1988).
151. Z. Wang and G. Zvilichovsky, *Tetrahedron Lett.*, **31**, 5579 (1990).
152. (a) K. Griesbaum, I. C. Jung and H. Mertens, *J. Org. Chem.*, **55**, 6024 (1990).
(b) K. Griesbaum, H. Mertens and I. C. Jung, *Can. J. Chem.*, **68**, 1369 (1990).
153. M. Mittelbach, N. Poklukar and H. Junek, *Liebig Ann. Chem.*, 185 (1990).
154. C. L. Kirkemo and J. D. White, *J. Org. Chem.*, **50**, 1316 (1985).

155. V. N. Odinokov, V. R. Akhmetova, Kh. D. Khasanov, A. A. Abudvakhabov, V. V. Bazylchik, P. I. Fedorov and G. A. Tolstikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1156 (1989).
156. V. N. Odinokov, R. I. Galeeva, R. S. Bakeeva, R. S. Grisova and G. A. Tolstikov, *Zh. Org. Khim.*, **15**, 1403 (1979).
157. V. N. Odinokov, V. R. Akhmetova, L. P. Botman, G. A. Tolstikov, B. A. Cheskis, V. V. Veselovskii and A. M. Moiseenkov, *Zh. Org. Khim.*, **21**, 990 (1985); *J. Org. Chem. USSR (Engl. Transl.)*, **21**, 899 (1985).
158. V. N. Odinokov, G. Yu. Ishmuratov, R. I. Galeeva, V. V. Sokolskaya, Kh. F. Sagitdinov and G. A. Tolstikov, *Zh. Org. Khim.*, **26**, 57 (1990).
159. V. N. Odinokov, R. S. Mukhametzyanova, R. I. Galeeva, G. Yu. Ishmuratov and G. A. Tolstikov, *Zh. Org. Khim.*, **26**, 1619 (1990).
160. V. N. Odinokov, O. S. Kukovinets, N. I. Sakharova and G. A. Tolstikov, *Zh. Org. Khim.*, **26**, 1180 (1990).
161. N. Nakamura, T. Fujisaka, M. Nojima, S. Kusabayashi and K. J. McCullough, *J. Am. Chem. Soc.*, **111**, 1799 (1989).
162. K. J. McCullough, N. Nakamura, T. Fujisaka, M. Nojima and S. Kusabayashi, *J. Am. Chem. Soc.*, **113**, 1786 (1991).
163. M. Miura, M. Nojima, S. Kusabayashi and K. J. McCullough, *J. Am. Chem. Soc.*, **106**, 2932 (1984).
164. T. Sugimoto, N. Nakamura, M. Nojima and S. Kusabayashi, *J. Org. Chem.*, **56**, 1672 (1991).
165. M. Miura, T. Fujisaka, M. Nojima, S. Kusabayashi and K. J. McCullough, *J. Org. Chem.*, **50**, 1504 (1985).
166. K. J. McCullough, M. Nojima, M. Miura, T. Fujisaka and S. Kusabayashi, *J. Chem. Soc., Chem. Commun.*, 35 (1984).
167. P. S. Bailey, *Chem. Ber.*, **87**, 993 (1954).
168. J. K. Stille and R. T. Foster, *J. Org. Chem.*, **28**, 2703 (1963); R. H. Callighan, M. F. Tarker, Jr. and H. H. Wilt, *J. Org. Chem.*, **26**, 1379 (1961).
169. T. Sugimoto, M. Nojima and S. Kusabayashi, *J. Org. Chem.*, **55**, 3816 (1990).
170. H. Seltzer, S. Gab and F. Korte, *Angew. Chem., Int. Ed. Engl.*, **19**, 474 (1980).
171. W. A. Pryor, D. Giamalva and D. F. Church, *J. Am. Chem. Soc.*, **105**, 6858 (1983).
172. F. Gozzo and G. Camaggi, *Chim. Ind. (Milan)*, **50**, 197 (1968); C. W. Gillies, *J. Am. Chem. Soc.*, **97**, 1276 (1975).
173. S. Vaccani, H. Kuhnee, A. Bauder and H. H. Gunthard, *Chem. Phys. Lett.*, **50**, 187 (1977).
174. K. Griesbaum and J. Bruggemann, *Chem. Ber.*, **105**, 3638 (1972).
175. K. Griesbaum and P. Hofmann, *J. Am. Chem. Soc.*, **98**, 2877 (1976).
176. S. Gaeb and W. V. Turner, *J. Org. Chem.*, **49**, 2711 (1984).
177. K. Griesbaum and R. Greinert, *Chem. Ber.*, **123**, 391 (1990).
178. K. Griesbaum, A. R. Bandyopadhyay and M. Meister, *Can. J. Chem.*, **64**, 1553 (1986).
179. A. M. Caminade, M. Le Blanc, F. Khatib and M. Koenig, *Tetrahedron Lett.*, **26**, 2889 (1985).
180. G. Nagendrappa and K. Griesbaum, *J. Agric. Food Chem.*, **26**, 581 (1978).
181. R. D. Clark and C. H. Heathcock, *Tetrahedron Lett.*, 2027 (1974); *J. Org. Chem.*, **41**, 1396 (1976).
182. H. Kuel and R. L. Kuczkowski, *J. Am. Chem. Soc.*, **106**, 5370 (1984).
183. B. J. Wojciechowski, C. Y. Chiang and R. L. Kuczkowski, *J. Org. Chem.*, **55**, 1120 (1990).
184. K. A. Kopecky, J. Molina and R. Rico, *Can. J. Chem.*, **66**, 2234 (1988).
185. N. Nakamura, M. Nojima and S. Kusabayashi, *J. Am. Chem. Soc.*, **109**, 4969 (1987).
186. M. Mori, M. Nojima, S. Kusabayashi and K. J. McCullough, *J. Chem. Soc., Chem. Commun.*, 1550 (1988).
187. T. Sugiyama, M. Nojima, S. Kusabayashi and K. J. McCullough, *J. Am. Chem. Soc.*, **111**, 6884 (1989).
188. P. Kolsaker and B. Teige, *Acta Chem. Scand.*, **24**, 2101 (1970); P. Kolsaker and S. Borresen, *Acta Chem. Scand.*, **33**, 133 (1979).
189. J. K. Crandall, W. W. Conover, J. B. Komin and W. H. Machleder, *J. Org. Chem.*, **39**, 1723 (1974); J. K. Crandall and W. W. Conover, *J. Chem. Soc., Chem. Commun.*, 340 (1973).
190. H. D. Hartzler, *J. Am. Chem. Soc.*, **83**, 4990 (1961).
191. J. K. Crandall and T. Schuster, *J. Org. Chem.*, **55**, 1273 (1990).
192. C. J. M. van den Heuvel, A. Hofland, J. C. van Velzen, H. Steinberg and Th. J. de Boer, *Recl. Trav. Chim. Pays-Bas*, **103**, 233 (1984).
193. J. C. van Velzen, W. C. J. van Tunen and Th. J. de Boer, *Recl. Trav. Chim. Pays-Bas*, **105**, 225 (1986).

194. R. Criegee and M. Lederer, *Liebig Ann. Chem.*, **583**, 29 (1953); C. D. Hurd and R. E. Christ, *J. Org. Chem.*, **1**, 141 (1936); H. Paillard and C. Wieland, *Helv. Chem. Acta*, **21**, 1356 (1938); E. Dallwigk, H. Paillard and E. Briner, *Helv. Chem. Acta*, **35**, 1377 (1952).
195. G. Brus and G. Peyresblanques, *C.R. Hebd. Seances Acad. Sci.*, **190**, 685 (1930); S. D. Razumovskii and G. E. Zaikov, *Zh. Org. Khim.*, **8**, 468 (1972); *J. Org. Chem. USSR (Engl. Transl.)*, **8**, 473 (1972).
196. F. Bohlmann and H. G. Viehe, *Chem. Ber.*, **88**, 1017 (1955); F. Bohlmann and H. Sinn, *Chem. Ber.*, **88**, 1869 (1955); F. Bohlmann, *Chimia*, **16**, 353 (1962); J. Ficini and J. P. Genet, *Bull. Soc. Chim. Fr.*, 1811 (1975).
197. D. J. Miller, T. E. Nemo and L. Hull, *J. Org. Chem.*, **40**, 2675 (1975).
198. R. E. Keay and G. A. Hamilton, *J. Am. Chem. Soc.*, **97**, 6876 (1975); **98**, 6578 (1976).
199. S. Jackson and L. A. Hull, *J. Org. Chem.*, **41**, 3340 (1976).
200. W. B. De More, *Int. J. Chem. Kinet.*, **3**, 161 (1971).
201. E. Bernatek, T. Ledaal and S. Asen, *Acta Chem. Scand.*, **18**, 1317 (1964).
202. W. W. Wisaksono and J. F. Arens, *Recl. Trav. Chim. Pay-Bas*, **80**, 846 (1961).
203. J. G. Cannon and L. L. Darko, *J. Org. Chem.*, **29**, 3419 (1964).
204. T. W. Nakagawa, L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, **82**, 269 (1960).
205. F. L. J. Sixma, H. Boer and J. P. Wibaut, *Recl. Trav. Chim. Pay-Bas*, **70**, 1005 (1951).
206. C. T. Pate, R. Atkinson and J. N. Pitts, Jr., *J. Environ. Sci. Health, Part A*, **11**, 1 (1976).
207. R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker and K. Schenker, *J. Am. Chem. Soc.*, **76**, 4749 (1954); *Tetrahedron*, **19**, 247 (1963).
208. (a) K. Isobe, K. Mohri, K. Tokoro, C. Fukushima, F. Higuchi, J. Junichi and Y. Tsuda, *Chem. Pharm. Bull.*, **36**, 1275 (1988).
(b) P. G. Copeland, R. E. Dean and D. McNeil, *J. Chem. Soc.*, 3864 (1961).
209. H. R. Eisenhauer, *J. Water Pollut. Control Fed.*, **40**, 1887 (1968); **43**, 200 (1971); *Water Res.*, **5**, 467 (1971).
210. S. D. Razumovskii, V. S. Ovechkin and M. L. Konstantinova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **28**, 285 (1979); *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, **28**, 261 (1979).
211. Y. Yamamoto, E. Niki, H. Shiokawa and Y. Kamiya, *J. Org. Chem.*, **44**, 2137 (1979).
212. P. S. Bailey, in *Ozone for Water and Wastewater Treatment* (Eds. R. G. Rice and M. E. Browning), Int. Ozone Assoc., Cleveland, Ohio, 1975, pp. 101–109.
213. S. D. Razumovskii and G. E. Zaikov, *Izv. Akad. Nauk SSSR, Ser Khim.*, 2657 (1971); *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, 2524 (1971).
214. M. J. S. Dewar, *J. Am. Chem. Soc.*, **74**, 3357 (1952).
215. Bailey and F. J. Garcia-Sharp, *J. Org. Chem.*, **22**, 1008 (1957).
216. P. S. Bailey, S. S. Bath, F. Dobinson, F. J. Garcia-Sharp and C. D. Johnson, *J. Org. Chem.*, **29**, 697 (1964).
217. C. D. Johnson and P. S. Bailey, *J. Org. Chem.*, **29**, 703 (1964).
218. R. A. Larson, W. J. Garrison and K. A. Marley, *Tetrahedron Lett.*, **27**, 3987 (1986).
219. M. D. Gaul, G. A. Gregor and H. J. Svec, *Environ. Sci. Technol.*, **21**, 777 (1987).
220. Y. Ito, A. Matsuura and T. Matsuura, *J. Org. Chem.*, **49**, 4300 (1984).
221. P. S. Bailey, *J. Am. Chem. Soc.*, **78**, 3811 (1956).
222. P. S. Bailey and R. E. Erickson, *Org. Synth. Coll. Vol.*, **5**, 3297 (1973); M. Sturrock, B. L. Cline and K. Robinson, *J. Org. Chem.*, **28**, 2340 (1963).
223. J. Neumaster and K. Griesbaum, *Chem. Ber.*, **117**, 1640 (1984).
224. R. D. Brown, *J. Chem. Soc., Chem. Commun.*, 3249 (1950).
225. P. de Bruyn, *Bull. Soc. Chim. Belg.*, **69**, 328 (1960).
226. R. E. Erickson, P. S. Bailey and J. C. Davis, Jr., *Tetrahedron*, **18**, 389 (1962); J. Rigaudy, N. K. Cuong, J. P. Albouy and A. Chetrit, *Tetrahedron Lett.*, 1089 (1976).
227. C. Kashima, S. Hibi, T. Maruyama, K. Harada and Y. Omote, *J. Heterocycl. Chem.*, **24**, 637 (1987).
228. H. M. White, H. O. Colomb, Jr. and P. S. Bailey, *J. Org. Chem.*, **30**, 481 (1965).
229. J. P. Wibaut and J. W. P. Boon, *Helv. Chem. Acta*, **44**, 1171 (1961).
230. B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **74**, 3861 (1952).
231. C. Kashima and H. Arao, *Heterocycles*, **31**, 1513 (1990).
232. E. C. Kooyman and J. P. Wibaut, *Recl. Trav. Chim. Pays-Bas*, **66**, 705 (1947); J. P. Wibaut and E. C. Kooyman *Recl. Trav. Chim. Pays-Bas*, **65**, 141 (1946).
233. H. Boer, F. L. J. Sixma and J. P. Wibaut, *Recl. Trav. Chim. Pays-Bas*, **70**, 509 (1951).
234. C. O'Murchu, *Synthesis*, 880 (1989).

235. J. P. Wibaut, *J. Chim. Phys. Phys.-Chim. Biol.*, **53**, 143 (1956); *Chimia*, **11**, 321 (1957); *Adv. Chem. Ser.*, **21**, 153 (1959).
236. M. Matsui, K. Kamiya, K. Shibata, H. Muramatsu and H. Nakazumi, *J. Org. Chem.*, **55**, 1396 (1990); M. Matsui, H. Nakazumi, K. Kamiya, C. Yatome and K. Shibata, *Chem. Lett.*, 723 (1989).
237. M. Matsui, T. Inoue, K. Shibata and H. Muramatsu, *Bull. Chem. Soc. Jpn.*, **63**, 296 (1990).
238. A. H. Riebel, R. E. Erickson, C. J. Abshire and P. S. Bailey, *J. Am. Chem. Soc.*, **82**, 1801 (1960).
239. R. E. Erickson, P. J. Andrulis, Jr., J. C. Collins, M. L. Lungle and G. D. Mercer, *J. Org. Chem.*, **34**, 2961 (1969).
240. R. E. Erickson and T. M. Myszkiewicz, *J. Org. Chem.*, **30**, 4326 (1965).
241. R. E. Erickson, A. H. Riebel, A. M. Reader and P. S. Bailey, *Liebig Ann. Chem.*, **653**, 129 (1962).
242. Y. Ito, H. Yokoya, Y. Umehara and T. Matsuura, *Bull. Chem. Soc. Jpn.*, **53**, 2407 (1980).
243. D. J. Weitz and M. D. Bednarski, *J. Org. Chem.*, **54**, 4957 (1989).
244. B. Zwanenburg and W. A. J. Janssen, *Synthesis*, 617 (1973).
245. L. Carlsen, *Tetrahedron Lett.*, 4103 (1977).
246. F. Ramirez, R. B. Mitra and N. B. Desai, *J. Am. Chem. Soc.*, **82**, 5763 (1960).
247. L. Carman, L. D. Kwart and T. Hudlicky, *Synth. Commun.*, **16**, 169 (1986).
248. W. Adam, L. Catalani, C. R. Saha-Moeller and B. Will, *Synthesis*, 121 (1989).
249. N. W. A. Geraghty, N. M. Morris, *Synthesis*, 603 (1989).
250. N. Poklukar and M. Mitelbach, *Monatsh. Chem.*, **121**, 203 (1990); M. Mitelbach and N. Poklukar, *Synthesis*, 331 (1990).
251. C. R. Holmquist and E. J. Roskamp, *Tetrahedron Lett.*, **31**, 4991 (1990).
252. M. Kanamoto, M. Hamada, M. Kawaguchi, Y. Yamamoto and J. Oda, *Chem. Express*, **2**, 17 (1987); *Chem. Abstr.*, **107**, 176428n.
253. M. Kawaguchi, O. Hayashi, N. Sakai, M. Hamada, Y. Yamamoto and J. Oda, *Agric. Biol. Chem.*, **50**, 3107 (1986).
254. C. Kashima, S. Hibi, K. Harada and Y. Omote, *J. Chem. Soc., Perkin Trans. 1*, 529 (1988).
255. Y. S. Hon, L. Lu and S. Y. Li, *J. Chem. Soc., Chem. Commun.*, 1627 (1990).
256. W. H. Bunnelle, M. A. Rafferty and S. L. Hodges, *J. Org. Chem.*, **52**, 1603 (1987).
257. R. C. Larock and K. Narayanan, *Tetrahedron*, **44**, 6995 (1988).
258. A. F. Barrero, J. F. Sanchez and C. J. Altarejos, *Tetrahedron Lett.*, **30**, 5515 (1989).
259. O. H. Hishmat and S. M. S. Atta, *Egypt. J. Chem.*, **30**, 507 (1989); *Chem: Abstr.*, **114**, 42309k.
260. J. Ott and D. Meusel, *Nahrung*, **34**, 93 (1990); *Chem. Abstr.*, **114**, 243828c.
261. A. K. Banerjee and M. Jain, *J. Indian Chem. Soc.*, **67**, 82 (1990); *Chem. Abstr.*, **113**, 39720m.
262. G. Montaudo, E. Scamporrino and D. Vitalini, *Macromolecules*, **24**, 376 (1991).
263. A. B. Attygalle, A. Zlatkis and B. S. Middlelditch, *J. Chromatogr.*, **472**, 284 (1989).
264. H. J. Dutton, S. B. Johnson, F. J. Pusch, M. S. Jie, K. Lie, F. D. Gunstone and R. T. Holman, *Lipids*, **23**, 481 (1988); H. J. Dutton, S. B. Johnson, W. H. Heimermann, F. J. Pusch, R. T. Holman and F. D. Gunstone, *Dev. Food Sci.*, **11**, 61 (1985); *Chem. Abstr.*, **106**, 210272y.
265. N. Van Landuyt, B. Denoulet, F. David and P. Sandra, *Int. Anal.*, **1**, 28, 32 (1987).
266. Y. Tanaka, H. Sato and J. Adachi, *Rubber Chem. Technol.*, **60**, 25 (1987); **59**, 16 (1986).
267. M. Davril, M. Guay, K. K. Han and F. Larny, *Int. J. Pept. Res.*, **29**, 68 (1987).
268. T. I. Poznyak, Z. A. Karapetyan and D. M. Lisitsyn, *Vysokomol. Soedin, Ser. A*, **29**, 201 (1987); *Chem. Abstr.*, **106**, 102735t.
269. L. S. Silbert and T. A. Foglia, *Anal. Chem.*, **57**, 1404 (1985).
270. C. R. Taylor, Jr., Ph. D. dissertation, University of Virginia, Charlottesville, Virginia, 2970.

CHAPTER 14

Rearrangements of alcohols, phenols, diols and peroxides

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I. REARRANGEMENTS OF ALCOHOLS

The term rearrangement is most commonly used to describe the migration of a group from one atom to another within a molecule.

The most important group of molecular rearrangements involves a migration (1,2-shift) from one atom to an adjacent atom that has only six electrons in its valence shell and is therefore electron-deficient. Mechanistically similar electron-deficient rearrangements in which the group *Z* migrates farther than just to the adjacent atom (i.e. 1,3-shifts, 1,4-shifts, etc.) are exceedingly rare.

Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

The migrating group in 1,2-shifts may be hydrogen, carbon nitrogen, oxygen, sulphur or halogen, but by far the most important and common migrations are those of hydrogen and carbon.

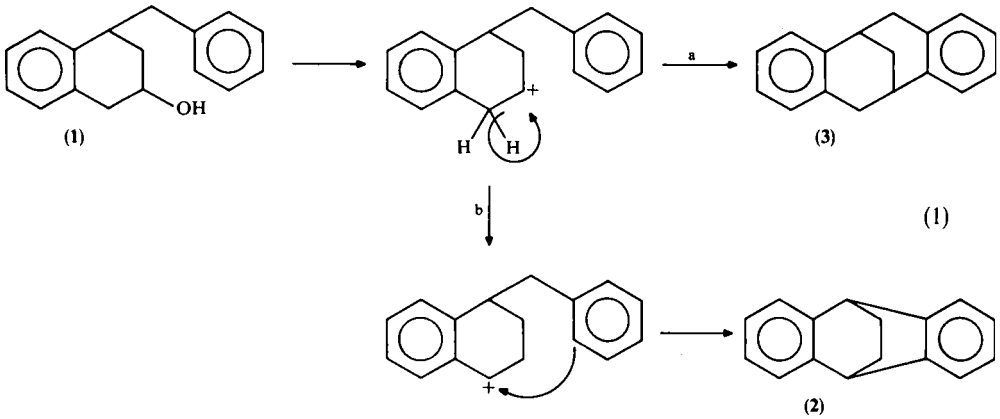
Rearrangements of alcohols under acidic conditions were originally known as the Wagner–Meerwein rearrangement, but the term has subsequently been broadened to include many other leaving groups. A wide variety of substrates and electrophilic reagents (to generate initial carbenium ions) are involved, all rearranging via carbenium ion routes.

Because of the large number of literature data on the alcohol rearrangements, we cannot hope to give a full review of all publications that have appeared. We shall therefore restrict ourselves to a brief survey of the still continuing research that has led to the currently accepted interpretation of the alcohol rearrangement; using the earlier reviews[1–10] as a starting point, we shall mainly discuss the results achieved in the past 10 years.

A. Rearrangements during Cyclodehydration and Cyclialkylation

Extensive studies of cyclodehydration and cyclialkylation reactions have been reported, but the formation of bridged polycyclic compounds in these processes has not received much attention[11,12].

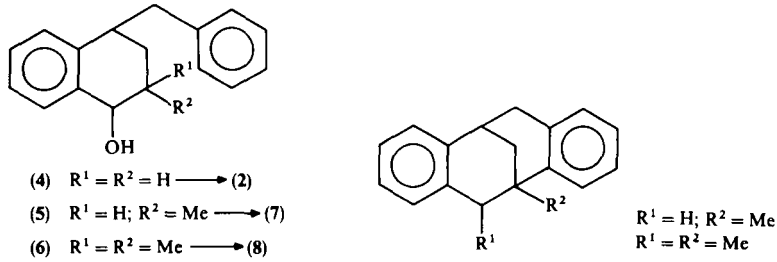
On treatment with sulphuric acid, 4-benzyl-2-tetralol (**1**) gave a 70:30 mixture of 2,3:6,7-dibenzobicyclo[3.2.2]nona-2,6-diene (**2**) and 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**3**)[13] (equation 1). The formation of these products confirms the earlier hypothesis[11] that these cyclidehydration reactions proceed via the formation of stable carbocation intermediates. The initially formed secondary carbocation can alkylate the aromatic ring directly to give the [3.3.1] system **3**, or it can rearrange through a 1,2-hydride shift to a more stable secondary *benzylic* carbocation that undergoes cyclization to yield the [3.2.2] system **2**. Rearrangement of the carbocation is considered to occur for thermodynamic reasons, an initially generated carbocation rearranging to a thermodynamically more stable carbocation[14].



Interestingly, the 1,2-hydride shift (path b) appears to be faster than direct cyclialkylation, as indicated by the product composition. It is also possible that the partitioning of the intermediate cation between two pathways depends on the relative transition-state energies for the pathways to **2** and **3**.

It has been shown[11] that on cyclodehydration 4-benzyl-1-tetralol (**4**) gives mainly the [3.2.2] bicyclic system **2**, whereas substituted benzyltetralols **5** and **6** give the [3.3.1]

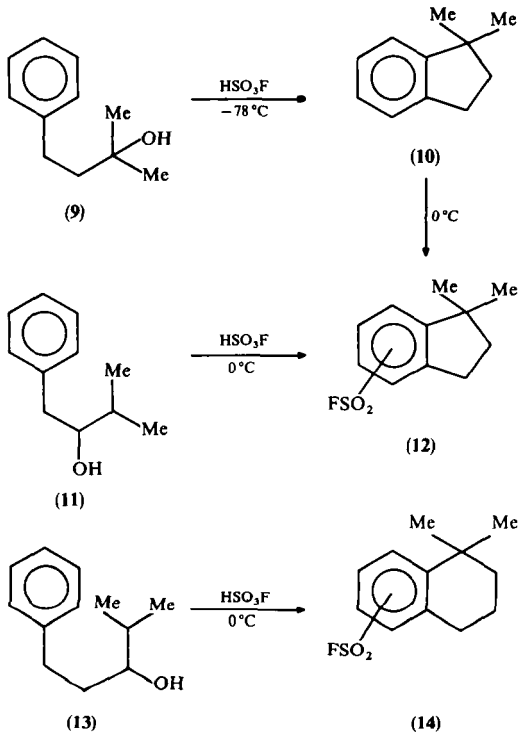
bicyclic systems **7** and **8**, suggesting that the stability of the intermediate carbocation and steric factors are important in determining the nature of the product formed (equation 2).



(2)

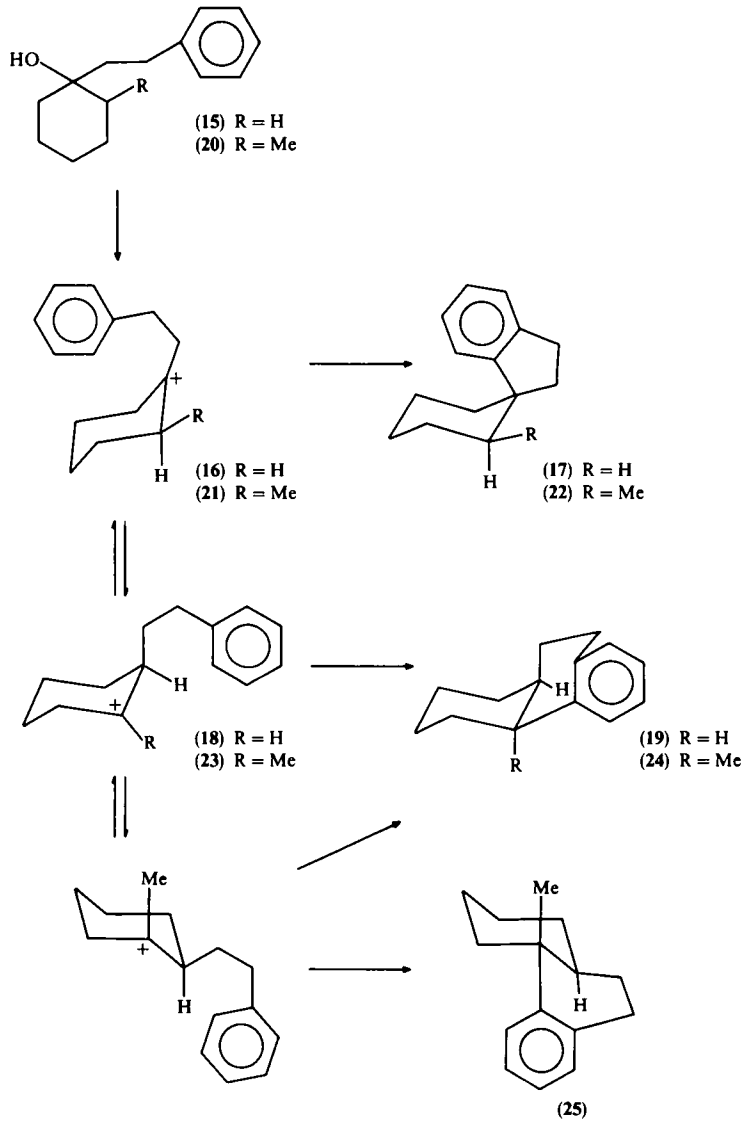
The reaction of 2-methyl-4-phenylbutan-2-ol (**9**) with fluorosulphuric acid at −78 °C gave 1,1-dimethylindane (**10**). This is a well-studied cyclialkylation, which can be effected with a variety of different acids[15,16]. The reaction contrasts, however, with that of the isomeric benzyl carbinol **11**, which reacts only at higher temperatures, to give a mixture of fluorosulphonated regioisomers **12**[17].

Higher temperatures are required in the case of **11**, since secondary alcohols are resistant to ionization, and accordingly fluorosulphonation of the indane ring occurs at 0 °C. Similarly, the 2-phenylethyl analogue **13** failed to react at −78 °C, but gave a mixture of three fluorosulphonated tetralins **14** at 0 °C. The formation of **14** results from ionization, a hydride shift, cyclization and fluorosulphonation (equation 3).



(3)

1-(Phenylethyl)cyclohexanol (**15**) reacted with HSO_3F at $-78\,^{\circ}C$ to give a 1:3 mixture of spiro(cyclohexane-1,1′-indane) (**17**) and *cis*-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (**19**). The formation of **17** results from intramolecular cyclization of the initially formed tertiary cation **16**. Successfully competing with this process is a 1,2-hydride shift to give a secondary cation **18** and cyclization to give **19**. Although the equilibrium between the tertiary cation **16** and the secondary cation **18** will be strongly in favour of **16**, trapping of the less stable cation **18** is competitive and results in the preferential formation of *cis*-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (**19**). The stereoselective formation of the

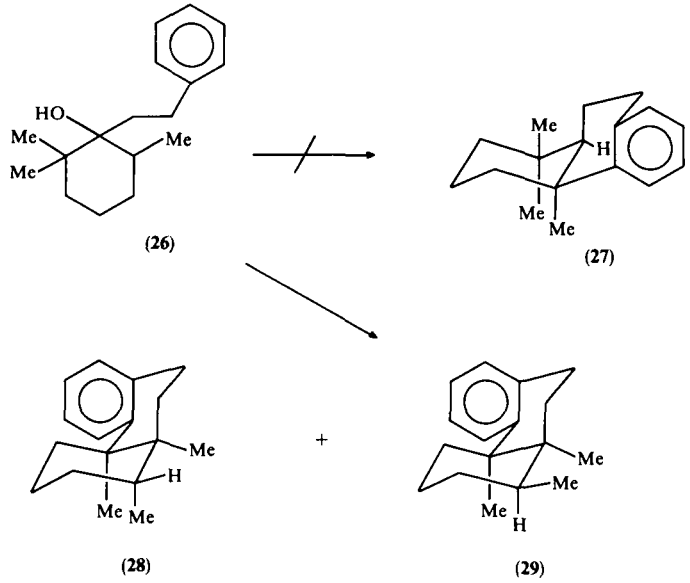


SCHEME 1

cis isomer **19** in preference to the more thermodynamically stable *trans* stereoisomer reflects a kinetic preference for formation of the *cis* isomer. It is also noteworthy that the proportion of spirane **17** formed in the reaction with HSO_3F is greater than that obtained with weak acids[18], and that this phenylethyl carbinol reacts in a different manner to 1-benzylcyclohexanol, which dimerizes in HSO_3F[19].

The reaction of 2-methyl-1-(2-phenylethyl)cyclohexanol (**20**) gave a 3:1 mixture of *cis*- and *trans*-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (**24, 25**). The presence of adjacent methyl in the initially formed tertiary carbocation **21** promotes hydride transfer to the carbocation **23**, and the formation of spirane **22** is no longer competitive with octahydrophenanthrene formation. As with the reaction of 1-(2-phenylethyl)cyclohexanol (**15**), the *cis* isomer **24** is the kinetically favoured product; however, an appreciable amount (25%) of the *trans* isomer **25** is also produced, which reflects the greater lifetime of the tertiary cation **23** relative to that of **18**, and this allows the conformational change required for formation of the *trans* stereoisomer[20] (Scheme 1).

The reaction of 2,2,6-trimethyl-1-(2-phenylethyl)cyclohexanol (**26**) with fluorosulphuric acid was examined as a potential route to the podocarpatrienes[21,22]. In the event, however, the reaction afforded 1β,4aβ,10aβ-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (**28**) (85%) along with the 1α,4aβ,10aβ-trimethyl isomer **29** (15%). The formation of **28** and **29** results from methyl migration occurring in preference to hydride migration prior to cyclization. The exclusive formation of *cis*-fused products parallels the results for the reactions of (phenylethyl)cyclohexanols **15** and **20** (Scheme 2).

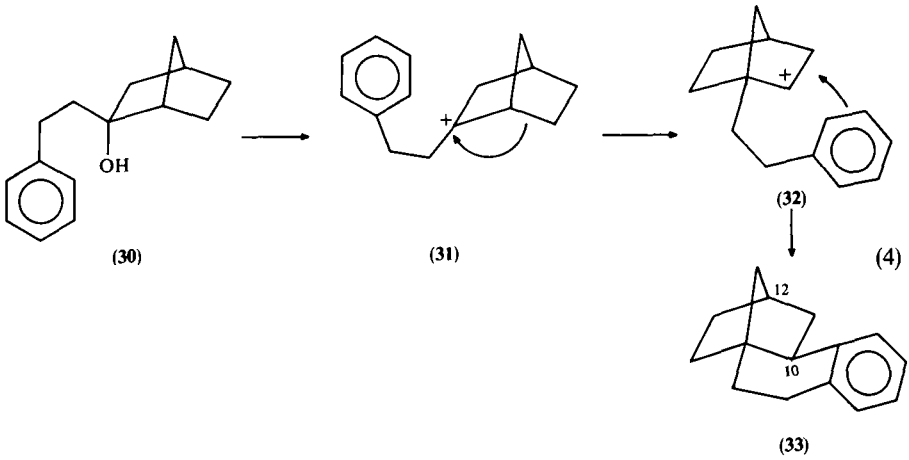


SCHEME 2

Rearrangements of closely related compounds have recently been discussed in detail[19,22–24].

2-*exo*-(2-Phenylethyl)norbornan-2-*endo*-ol (**30**) reacted with fluorosulphuric acid to give a single product in high yield, which was identified as tetracyclo-(10.2.1.$0^{1,10}$.$0^{4,9}$)-pentadeca-4,6,8-triene (**33**) (equation 4). Thus, whereas 2-*exo*-benzylnorbornan-2-*endo*-ol

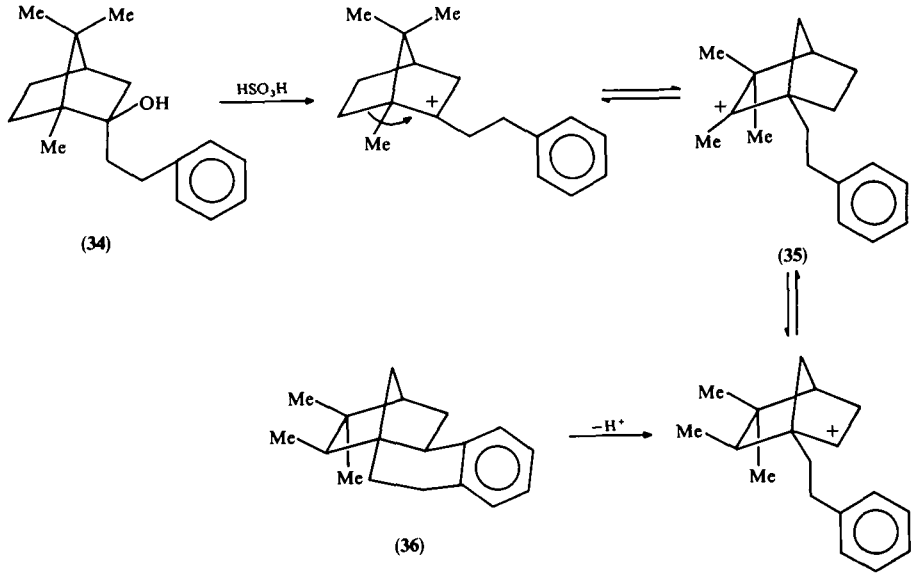
underwent ring expansion in HSO_3F[25], the 2-phenylethyl analogue **30** undergoes ionization and Wagner–Meerwein rearrangement to **32**, and cyclization from the more accessible and favoured *exo* face to give **33**.



(30) (31) (4)

(33)

The reaction of 2-(2-phenylethyl)isoborneol (**34**) with fluorosulphuric acid gave 13,13,14-trimethyltetracyclo(10.2.1.0^{1,10}.0^{4,9})pentadeca-4,6,8-triene (**36**) in good yield. The mechanism for formation of **36** is shown in Scheme 3 and differs from that for the unsubstituted analogue **33** in requiring a 2,6-hydride shift prior to cyclization. The resistance of **35** to cyclization is considered to be steric in origin and is consistent with the known preference[26] for tertiary norbornyl cations to react with nucleophiles as their Wagner–Meerwein rearranged secondary cations.

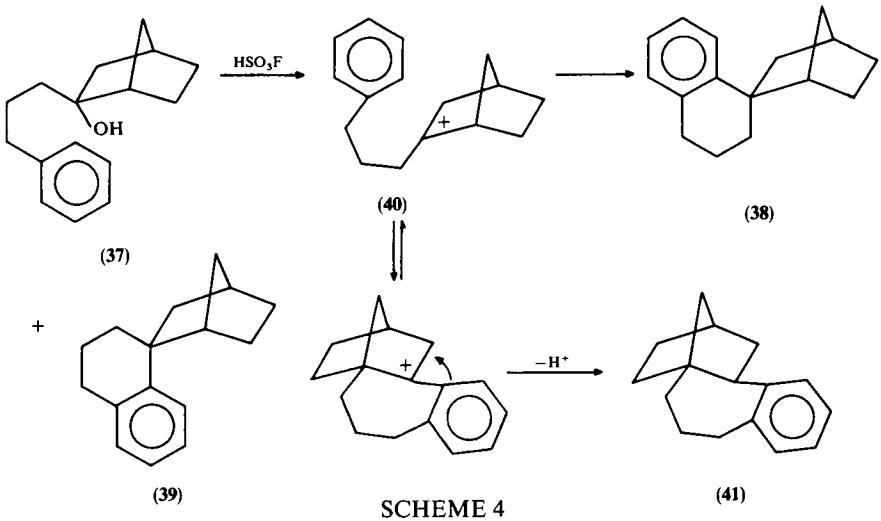


(34) (36)

SCHEME 3

The reaction of *exo*-(3-phenylpropyl)norbornan-2-*endo*-ol (**37**) with fluorosulphuric acid at −78 °C gave a mixture of three hydrocarbons in the ratio 2:1:1. These products were tentatively identified from the NMR spectra of the mixture as the two spiro hydrocarbons **38** and **39**, and the tetracyclic product **41**.

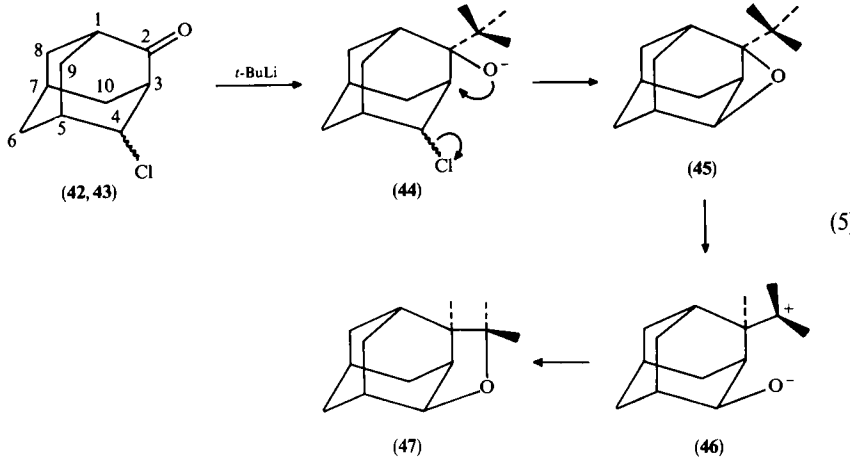
The spiro products **38** and **39** would result from direct cyclization of the initially formed cation **40** from the *exo* and *endo* faces, respectively, while **41** would result from cyclization of the Wagner–Meerwein rearranged cation (Scheme 4).



SCHEME 4

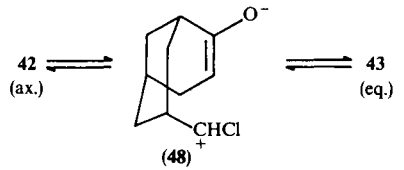
The synthesis of a number of 4-substituted-2-*t*-butyladamantan-2-ols from the corresponding ketones was recently described. Besides these addition reactions, some unexpected rearrangements were observed[27].

With *t*-butyllithium, 4-chloroadamantanones (**42, 43**) afforded the corresponding 2-*t*-butyl-4-chloroadamantanol (**44**) and the ether **47**, which contains a tetrahydrofuran moiety condensed to the adamantane framework (equation 5). According to this



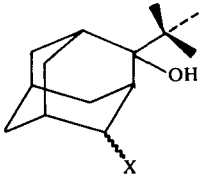
(5)

mechanism, the reaction is initiated by the formation of the anion, which may be transformed to the oxetane **45** with loss of chloride. It is reasonable to assume that ether formation is facilitated by the fact that the bulky *t*-butyl group presses the oxygen inward, i.e. towards $C_{(4)}$. **45** is presumably rather labile and undergoes rearrangement with migration to give the zwitterion **46**, which is transformed to **47**. The $C_{(2)}$ stereochemistry of this product after the rearrangement **45** → **46** nicely confirms this interpretation. For the reaction sequence, the chlorine atom in the equatorially substituted adamantanone **43** is in the proper stereochemical position, whereas that in the axial **42** is not. However, it is plausible that, by analogy with earlier observations[28], **42** can easily isomerize to **43** under basic conditions via fragmentation intermediate **48** (equation 6).



(48) (6)

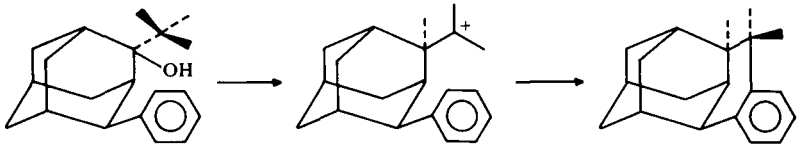
During the reaction of 4-substituted-2-*t*-butyladamantan-2-ols with triethylsilane and trifluoroacetic acid or hydroiodic acid, interesting rearrangement products were observed in many cases[29,32]. Some *t*-butyl carbinols displayed a *t*-butyl rearrangement and formed condensed tetracyclic compounds. The carbinols **49**, **50**, **51** and **52**, all having one or two oxygen atoms at $C_{(4)}$, produced the tetrahydrofuran derivative **47** as the sole product (Figure 1).



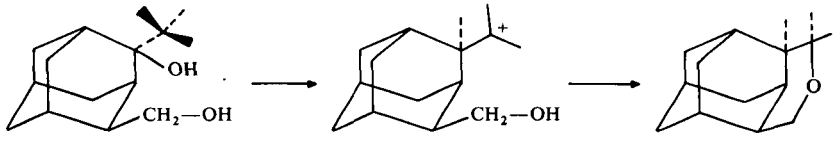
X	OH	OCH_3	=O	$C(CH_3)_3$	$(CH_3)_2$	C_6H_5	CH_2—OH
ax.	**49**	**51**	**52**	**53**	**54**	**55**	**56**
eq.	**50**						

FIGURE 1

Compounds **55** and **56** formed exclusively tetracyclic compounds **58** and **60**, with six-membered rings condensed to the adamantane framework. Isopropyl cations **57** and **59** can again be expected as intermediates (equations 7 and 8).

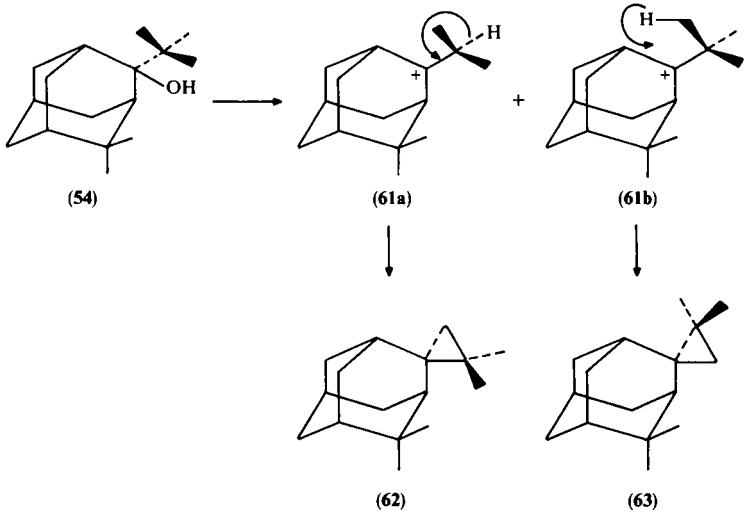


(55) (57) (58) (7)



(56) (59) (60) (8)

Obviously, the 4,4-dimethyl compound **54** is unable to form tetracyclic adamantanes such as those discussed earlier, and the cation is forced to stabilize itself by forming the isomeric spirodimethylcyclopropanoadamantanes **62** and **63** via the isopropyl cations **61a** and **61b**, respectively, in a ratio of 2:3. The stereochemistry of the respective product, **62** or **63**, depends on which methyl group a proton is abstracted from. The two spiro isomers **62** and **63** could not be separated, but they were identified unequivocally by means of NMR (equation 9).



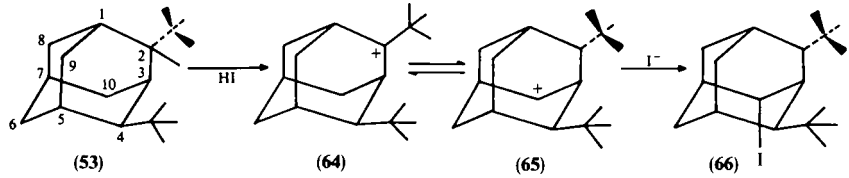
(9)

This type of reaction was reported by Saba and Fry with the $C_{(4)}$ unsaturated alcohol as starting material[30,31].

Badejo and coworkers found that acid treatment of 2-cumyl-2-adamantanol leads to both methyl- and aryl-shifted alkene as well as spiropropane products under various reaction conditions[33,34].

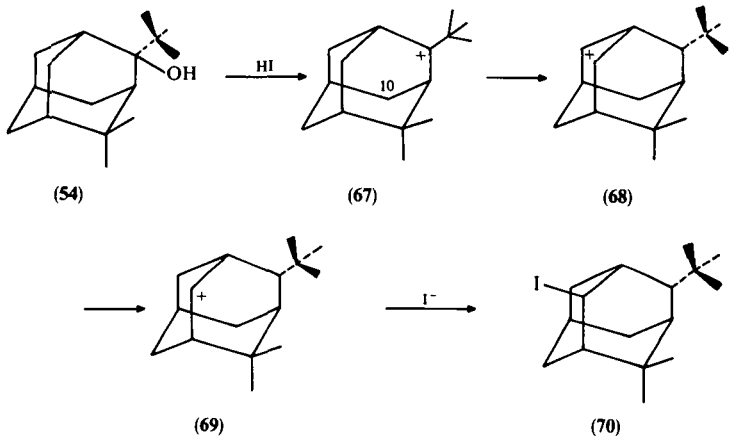
The hydroiodic acid reaction of the di-*t*-butyl carbinol **53** produced the 2,4-di-*t*-butyl-10-iodoadamantane (**66**) in a regio- and stereoselective way[29].

This can be explained by the formation of cation **64**, which may isomerize to ion/**65** in a series of three consecutive 1,3-hydride shifts ($C_{(9)} \rightarrow C_{(2)}$, $C_{(8)} \rightarrow C_{(9)}$ and $C_{(10)} \rightarrow C_{(8)}$). Attack of iodine on **65** occurs exclusively from below due to the steric hindrance of the *t*-butyl group at $C_{(2)}$ (equation 10).



(10)

The dimethyl derivative **54** afforded the iodide **70**. In this example, **69** may be formed from **68** by a 1,3-hydride shift and the iodide could approach from the least hindered side of the molecule to form **70** (equation 11).

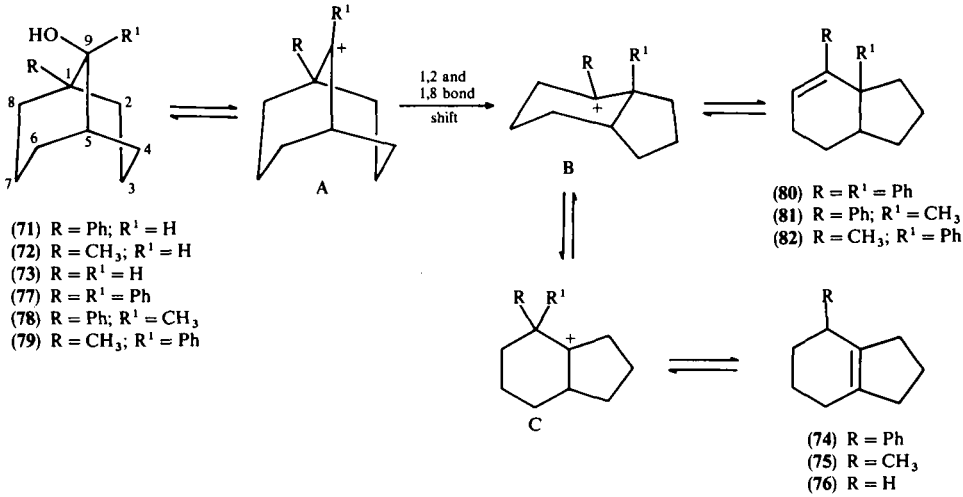


(54) (67) (68)

(69) (70)

(11)

Balata and coworkers found that the dehydration of 1-substituted secondary and from tertiary bicyclo(3.3.1)nonan-9-ols occurs with skeletal rearrangement and affords substituted hexahydroindenes in high yields[35]. The dehydrations were carried out in refluxing benzene with *p*-toluenesulphonic acid as catalyst. The process is sharply affected by the nature of the substituent at $C_{(1)}$ in the substrate. Dehydration of secondary alcohols **71**, **72** and **73** bearing an electron-releasing group is easy, and 4-substituted-2,3,4,5,6,7-hexahydroindenes **74**, **75** and **76** are produced in high yields. Tertiary alcohols behave in a similar way. Thus, 1,9-substituted substrates **77**, **78** and **79** afford *cis*-3a,4-disubstituted-2,3,3a,6,7,7a-hexahydroindenes (**80**,**81**,**82**) as the only products (equation 12).



(**71**) R = Ph; R¹ = H
(**72**) R = CH_3; R¹ = H
(**73**) R = R¹ = H
(**77**) R = R¹ = Ph
(**78**) R = Ph; R¹ = CH_3
(**79**) R = CH_3; R¹ = Ph

(**80**) R = R¹ = Ph
(**81**) R = Ph; R¹ = CH_3
(**82**) R = CH_3; R¹ = Ph

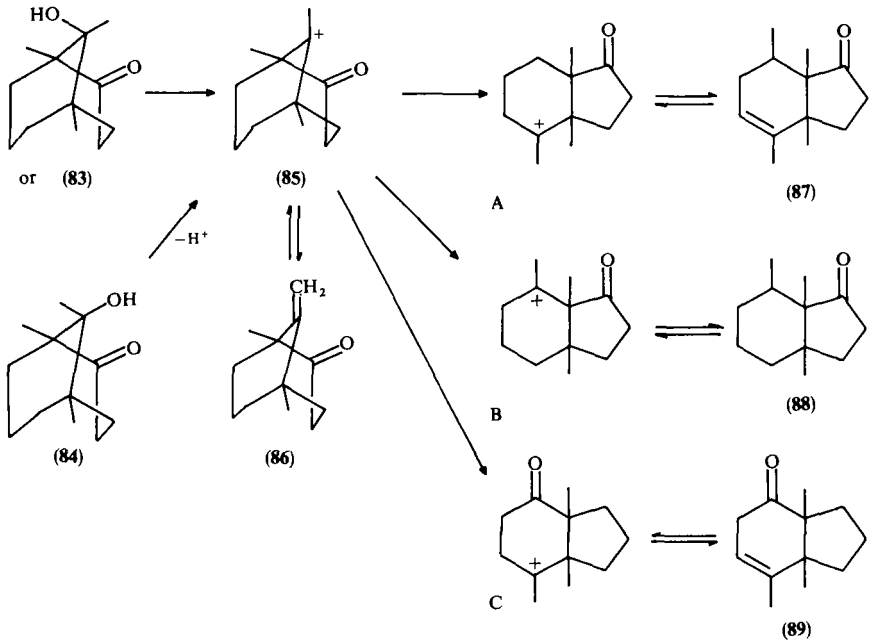
(**74**) R = Ph
(**75**) R = CH_3
(**76**) R = H

(12)

The processes leading to the products can be rationalized in terms of the relative stabilities of both the intermediate carbenium ions and the produced alkenes. The

unstable ion[36] 'A' is first formed and subsequently rearranged to 'B', which can alternatively be formed through the shift to $C_{(9)}$ of the $C_{(1)}$, $C_{(2)}$ (and $C_{(1)}$, $C_{(8)}$) or $C_{(4)}$, $C_{(5)}$ (and $C_{(5)}$, $C_{(6)}$) bonds, respectively. However, if R and/or R^1 are hydrogens, subsequent competitive rearrangements of ion 'B' take place, leading to the tertiary ion 'C', from which hexahydroindenes of types **74**, **75** and **76** are produced.

The dehydrations of the *t*-bicyclo(3.3.1)nonan-9-ol-2-ones (**83** and **84**) have been studied[37]. In both cases, 1-hydrindenones **87** and **88** were obtained almost quantitatively (1:1 ratio), together with a very small amount of 4-hydrindanone (**98**), through skeletal rearrangement of the kinetically favoured 9-methylenebicyclononane (**86**). This strongly supports the hypothesis of a stepwise rearrangement driven by the relative stabilities of the involved carbenium ions 'A', 'B' and 'C', respectively (Scheme 5).



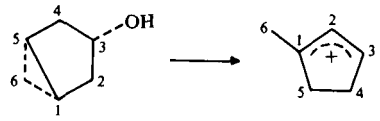
SCHEME 5

B. Rearrangements Involving Ring Opening and Ring Closure

1. Three-membered rings

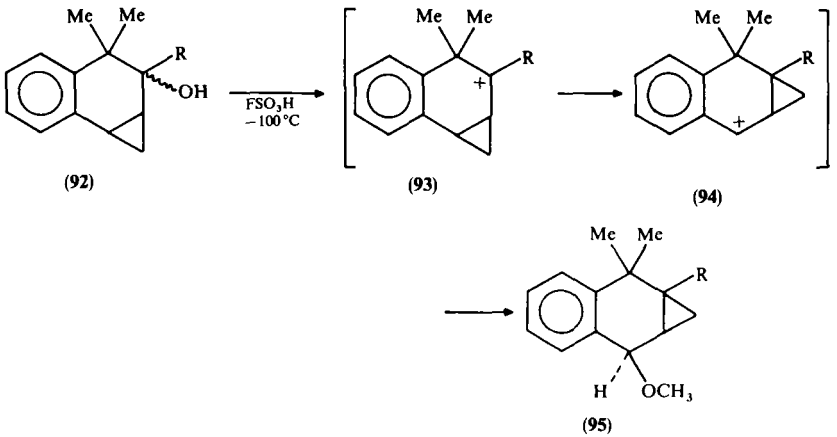
The cyclopropane ring undergoes ring expansion relatively easily: for small rings, ring expansion is a possibility for relief of the ring strain.

Data obtained from a study of the mechanism of acid-catalysed opening of the cyclopropane ring in bicyclo(3.1.0)hexan-3-ols (**90**) are consistent with the view that the reaction is initiated at the cyclopropane ring, rather than the hydroxy group, although the latter is subsequently lost during formation of the 1-methylcyclopentenium ion (**91**)[38,39] (equation 13).



(90) (91) (13)

Kelly and coworkers[40] found that ionization of 2-substituted-1,1-dimethyl-3,4-methano-1,2,3,4-tetrahydronaphthalen-2-ols (**92**) does not appear to yield the corresponding 2-cations **93**, but rather the benzylic cations **94**, as a result of a cyclopropylcarbinyl rearrangement, these ions being stabilized by ion association with a methylate anion to yield **95** (equation 14).



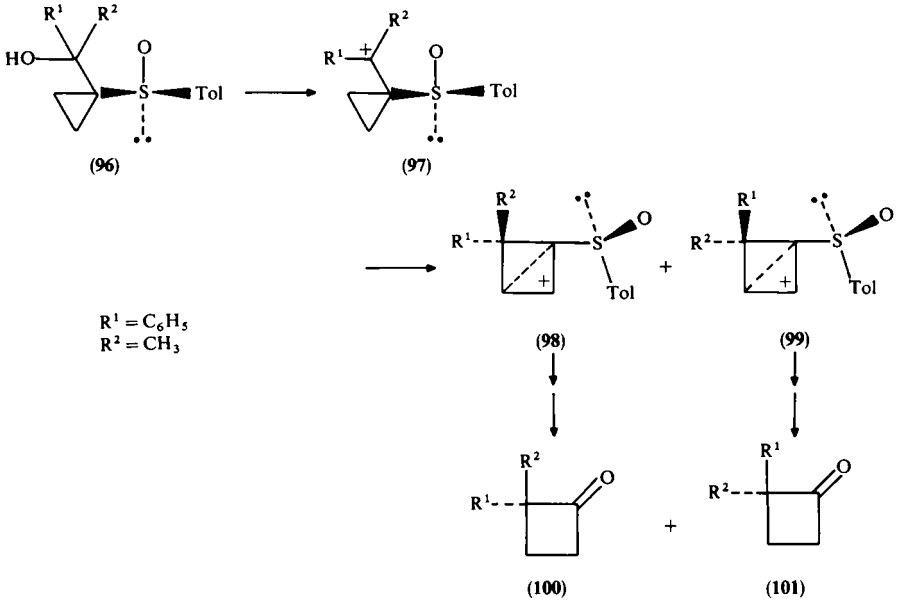
(92) (93) (94) (95) (14)

A potentially valuable method has been described for the enantioselective creation of quaternary carbons by thermal 1,2-asymmetric rearrangements in cyclopropane systems possessing a chiral sulphinyl group on the ring. The mechanistic pathway for this asymmetric induction is represented in Scheme 6. Clearly, the degree of asymmetric induction depends on the thermodynamic stability of **98** and **99**, i.e. on the difference in steric interference between R^1 or R^2 and the lone pair on the oxygen atom of the chiral sulphoxide. This 1,2-rearrangement led to the asymmetric synthesis of α,α-disubstituted-cyclobutanones **100** and **101**, respectively[41].

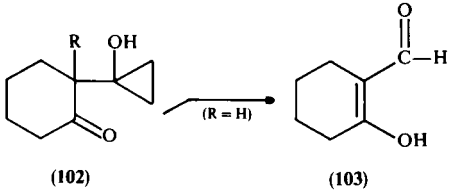
2-(2,3-Dialky-2-cyclopropenyl)-2-propanols have been found to undergo a highly selective ring expansion in protic or strongly ionizing media, leading exclusively to cyclobutanes[42]. A homoaromatic cyclobutenyl cation has been identified as an intermediate in this reaction.

There are numerous situations where the lower homologue of a desired structure is more readily available or is needed for some purpose, such as the control of stereochemistry. In these cases the synthetic chemist must resort to chain extension or ring expansion methodology to add the requisite carbon atom. A potentially valuable method involves the use of 1-(ketoalkyl)cyclopropanols to obtain cyclopentanones[43].

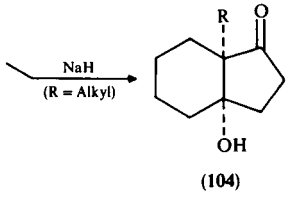
The reaction product obtained upon treatment of **102** with NaH is a β-enolate (**103**)[44]. If an alkyl group is present in place of the acidic proton α to the carbonyl group, then the conversion of a pendant cyclopropanol to the corresponding fused hydroxycyclopentanone (**104**) occurs (equation 15). This novel cyclopropanol synthesis and cyclopentane annulation reaction leads to a new synthesis of oestrone[45].

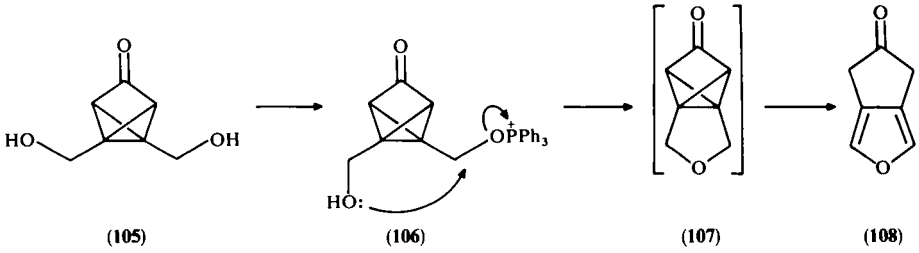


SCHEME 6



(15)

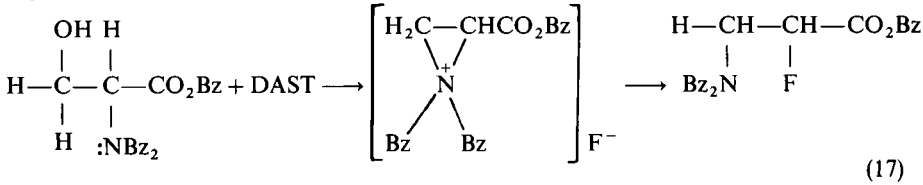




(16)

An interesting rearrangement has been found during halogenation of a diprimary diol system. Treatment of 1,5-bis(hydroxymethyl)tricyclo(2.1.0.0^{2,5})pentan-3-one (**105**) with triphenylphosphine and CCl_4 resulted in a deep-seated rearrangement to the keto furan, 3-oxybicyclo(3.3.0)octa-1,4-dien-7-one (**108**). The mechanism is thought to involve an internal displacement reaction; see **106**. The molecule now becomes a distorted bicyclo-(3.1.1)propellane (**107**) and, to escape from this dilemma, a bicyclobutane–butadiene rearrangement can occur[46] (equation 16). There are a number of reactions in the literature where three-membered intermediates can be proposed to explain the rearrangement[47,48].

A facile stereospecific synthesis of α-fluoro-β-amino acids from β-hydroxy-α-amino acids has been rationalized by postulating the intermediacy of an aziridinium ion[49] (equation 17).

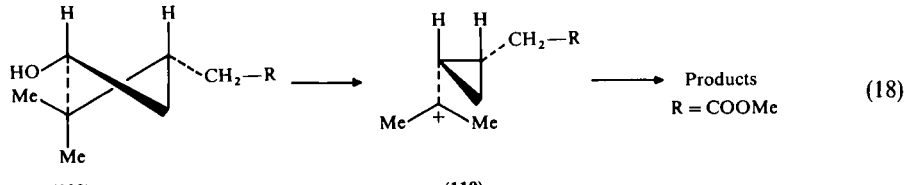


(17)

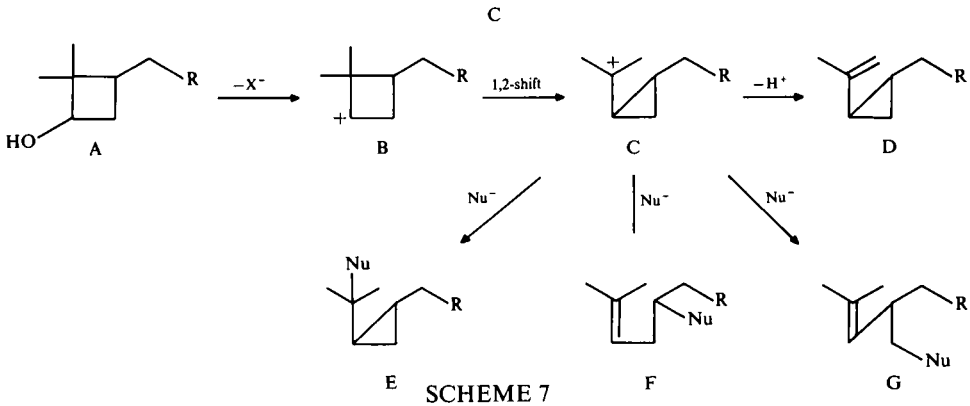
DAST = (diethylamino)sulphur trifluoride

2. *Four-membered rings*

The cyclobutane ring likewise takes part relatively readily in ring contraction and ring expansion reactions. The tendency of 3-substituted-2,2-dimethylcyclobutanol systems to undergo ring contraction preferentially is thought[50] to be due to a concerted ionization-rearrangement step (**109** → **110**), in which 1,2-bond cleavage and backside attack at $C_{(3)}$ is facilitated by the geometry of the favoured 1,3-diequatorial conformation of **109**, as shown in equation 18. The rearrangement can be rationalized according to Scheme 7.

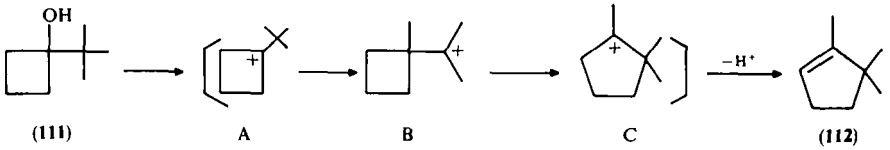


(18)



SCHEME 7

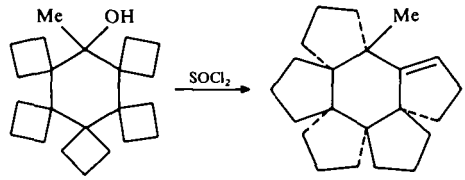
Anhydrous iron(III) chloride adsorbed on silica gel has been successfully used to induce the ring-enlargement of tertiary cyclobutanol **111**[51]. This specific rearrangement probably involves the Lewis acid-induced formation of the 1-*t*-butylcyclobutyl cation 'A' and methyl transfer, giving the cyclobutylcarbinyl cation 'B', followed by $C_{(4)} \rightarrow C_{(5)}$ ring enlargement to the corresponding cyclopentyl cation 'C' and deprotonation to give **112** (equation 19). The reaction has been extended to five-, six- and seven-membered tertiary cycloalkanols[52].



(111) A B C (112)

(19)

An interesting fivefold cyclobutyl–cyclopentyl rearrangement has been initiated[53] in 21-methylpentaspiroheneicosanol (**113**). Thus, treatment of pentaspirane **113** with thionyl chloride in pyridine yielded the hexacyclic product **114** (equation 20). It is anticipated that the perfect antiperiplanar array of all the bonds to be broken and formed accounts for this unusual cascade rearrangement.



(113) (114)

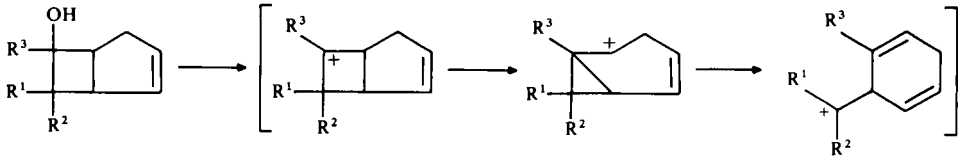
(20)

In a similar manner, the 16-methylpentaspirohexadecanols yielded hexacyclohexadecanols[54]. The overall rearrangements may thus be described in terms of sixfold 1,2-shifts with inversion at both migration origins and termini. The acid-catalysed rearrangements of 19-methylpentaspirononadecanol have been shown to afford either propellane or a hexacyclic compound, depending on the reaction conditions[55]. The rearrangements proceed diastereospecifically and are rationalized as five- and ninefold 1,2-shifts, respectively.

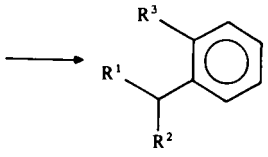
Lee-Ruff and coworkers[56] found that the formation of diarylmethanes from bicyclohept-2-en-6-ols (**115**) may involve a competitive *endo* bond cleavage of the cyclobutyl cation (**116**), leading to a norcarenyl ion (**117**). In the presence of positive charge-stabilizing groups R^1 and R^3 (e.g. aryl), *exo* cyclopropane bond scission may be expected, resulting in the formation of a 2,5-cyclohexadienylmethyl cation (**118**). Subsequent 1,2-hydride shift and proton loss lead to formation of the observed diarylmethanes (**119**) (equation 21).

The acid-catalysed rearrangement of cyclobutachromenol (**120**), followed by oxidation, furnished the tricyclic ketone **123**, which is thought to arise from the migration of an external bond in **120**, leading to a trichothecane-like cationic intermediate (**121**), followed by aryl migration[57] (equation 22).

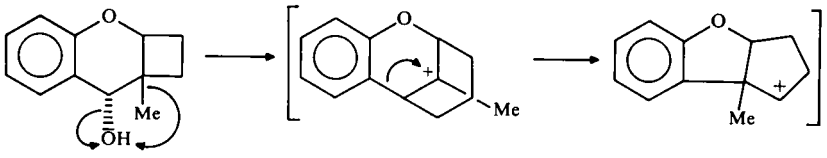
The formation of tetrahydronaphtho(2,3-*b*)thiophenes (**125**) during the acid-catalysed dehydration of α-thienylcyclobutanols (**124**) has been rationalized[58] in terms of the pathway outlined in equation 23.



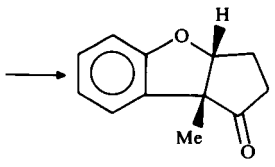
(115) (116) (117) (118)



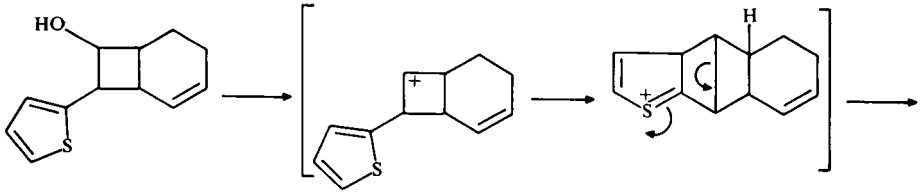
(119) (21)



(120) (121) (122)



(123) (22)



(124)

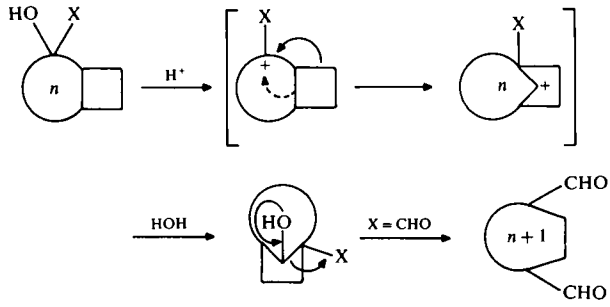
(125) (23)

The irradiation of *endo*-4-cyanotricyclo(6.4.0.0^{2,5})dodeca-1(12),6,8,10-tetraen-5-ol in the presence of HgO–I_2 has been shown to yield 4-cyanotricyclo(6.4.0.0^{2,4})dodeca-1(12),6,8,10-tetraen-5-one[59]. This appears to be the first reported example of the reorganization of a 6/4 fused-ring system to a 7/3 fused-ring system, and it is believed to proceed from an eight-membered carbon-centred radical which itself is generated by β-scission of an alkoxy radical.

A cyclobutyl–cyclopropylcarbinyl-type rearrangement of 1-oxaspirohexane derivatives has provided a new entry to functionalized norcaranes[60]. Norpinyl–norbornyl rearrangements have been induced by solvolysis of a number of bicyclo(3.1.1)heptane derivatives[61–63].

Synthesis of 7-hydroxynorbornanes from 3-hydroxy-1,6-heptadienes has been achieved by the copper(I) trifluoromethanesulphonate-catalysed ($2\pi + 2\pi$)-photobicyclization and solvolytic rearrangement of the intermediate cyclobutylcarbinyl alcohols[64].

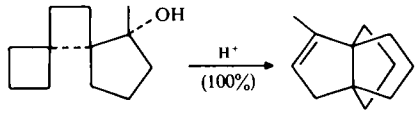
A new ring expansion of 1-(1-methylsulphinyl-1-(methylthio)alkyl)cyclobutanol derivatives to 3-methyl-2-(methylthio)cyclopentanones has been studied[65], and a simple and efficient route was recently developed towards usefully functionalized six- and seven-membered ring systems via α-hydroxycyclobutane rearrangement, followed by retroaldol cleavage[66] (equation 24).



(24)

3. *Five-membered rings*

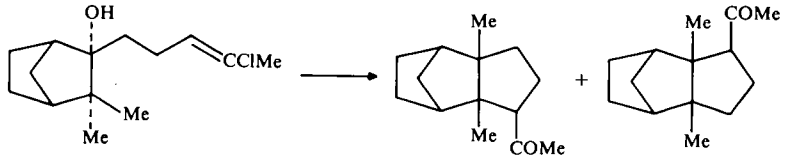
Fitjer and coworkers recently found that the dispiro(3.0.4.2)undecane (**126**) undergoes cascade rearrangements under acidic conditions, yielding (3.3.3)propellane (**127**)[67] (equation 25).



(25)

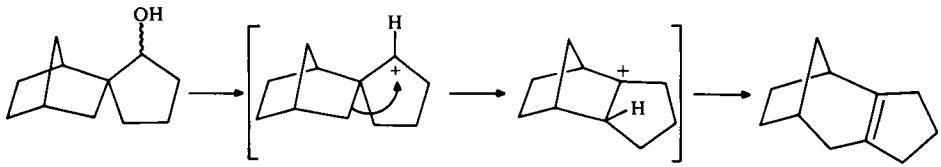
(126) (127)

It has been shown that the rearrangement of chloro-olefin **128** to both ketone isomers **129** and **130** occurs through well-precedented carbocationic pathways (equation 26). A plausible explanation for the predominant stereochemical course of the anellation reaction **128** → **129** can be formulated in terms of an *exo*-3,2-methyl shift, Wagner–Meerwein rearrangements and 2,6-hydride shifts. The minor pathway, **128** → **130**, could be rationalized through postulation of an *endo*-3,2-methyl shift. These various mechanistic descriptions of the conversion **128** → **129** and **130** were tested with the aid of ^{13}C and $^{13}C,^{2}H_2$-labelled substrates[68].



(128) (129) (130) (26)

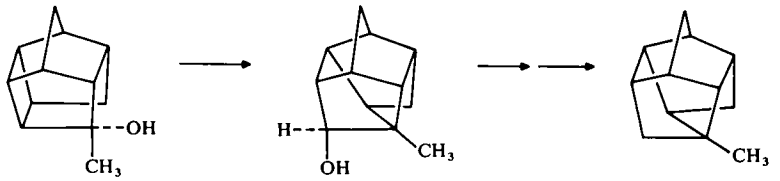
Tricyclo(6.2.1.$0^{2,6}$)undec-2(6)-ene (**132**) has been obtained by an acid-catalysed dehydrative rearrangement of *exo*-norbornane-2-spiro-1′-cyclopentan-2′-ol (**131**)[69] (equation 27).



(131) (132)

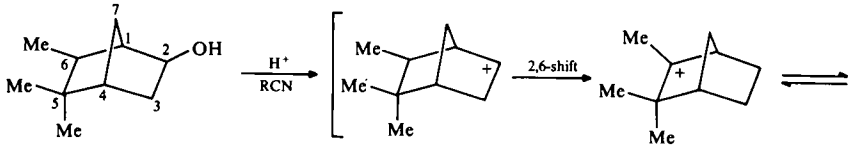
(27)

D_3-Trishomocuban-4-ol (**134**) has been prepared[70] via a carbocation rearrangement of *endo*-pentacyclo(5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$) undecan-8-ol (**133**), while the acid-catalysed rearrangement of the pentacyclic 8-methyl derivative provides a key step to the synthesis of 1-methyl-D_3-trishomocubane (**135**) (equation 28).



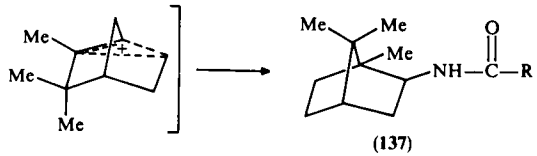
(133) (134) (135) (28)

A remarkable transformation of methylene-bridged fused-ring norbornene alcohols into a product containing the novel tetracyclo(5.3.1.$0^{2,6}$.$0^{5,9}$)undecene system has been



(136)

R = CH_2Cl
C_2H_5
$CH_2CH_2OCH_3$
$CH_2CH(CH_3)_2$
$CH_2C_6H_5$



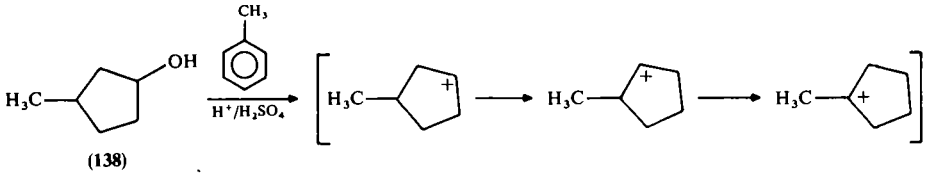
(137)

(29)

reported[71]. A rapid degenerate rearrangement involving an intramolecular 1,4-hydride transfer from alkoxide to carbonyl has been observed[72] across *exo*-9-hydroxypentacyclo-(6.2.1.1^{3,6}.0^{2,7}.0^{4,10})dodecan-5-one, and 4-hydroxytricyclo(5.2.2.0^{1,5})undecane-9-carboxylic ester has been shown to rearrange into tricyclo(6.2.1.0^{1,5})undecane lactones during treatment with mineral acid[73].

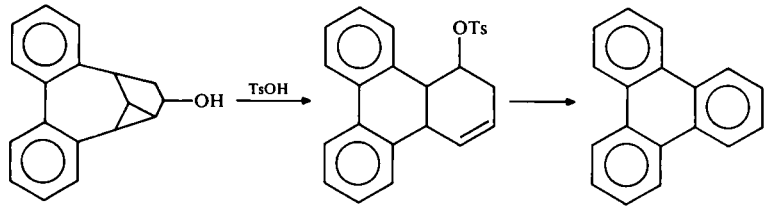
The Ritter reaction of isocamphenol (**136**) and nitriles has yielded amides **137** via a Wagner–Meerwein rearrangement[74] (equation 29).

3-Methylcyclopentanol (**138**) reacts with toluene under acidic conditions to yield 4-(1-methylcyclopentyl)toluene (**139**) via a 1,3-shift[75] (equation 30).



(138) (139) (30)

The reaction of dibenzo(*c*,*e*)tricyclo(5.3.0.0^{2,0})deca-3,5-dien-9-ol (**140**) with *p*-toluenesulphonic acid in benzene proceeds regioselectively and stereoselectively, affording the homoallylic tosylate **141**, which is further converted to triphenylene (**142**)[76] (equation 31).

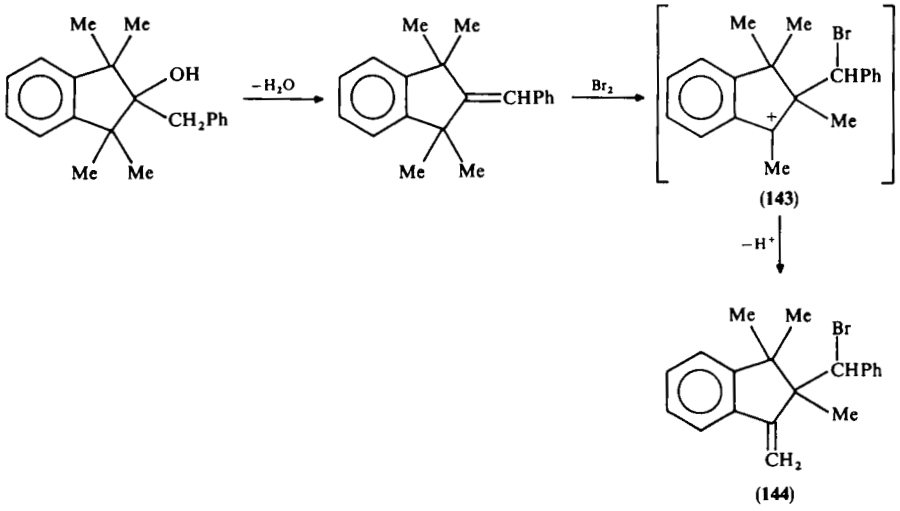


(140) (141) (142) (31)

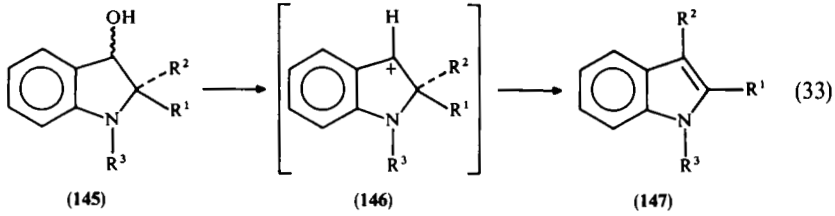
Molecular rearrangements via carbocation species (**143**) have been found to occur during the attempted synthesis of α-bromo-β,β-disubstituted-alkylstyrenes (**144**)[77] (equation 32).

The reaction intermediate in the acid-catalysed rearrangement of indolines (**145**) to the 2,3-disubstituted indoles (**147**) appears to be the carbocation **146**, which then undergoes attack on the $C_{(2)}$ substituent having the highest migratory aptitude. The migratory power follows the sequence benzyl > phenyl > alkyl. The resulting 2,3-disubstituted indoles (**147**) were obtained in quantitative yields[78] (equation 33).

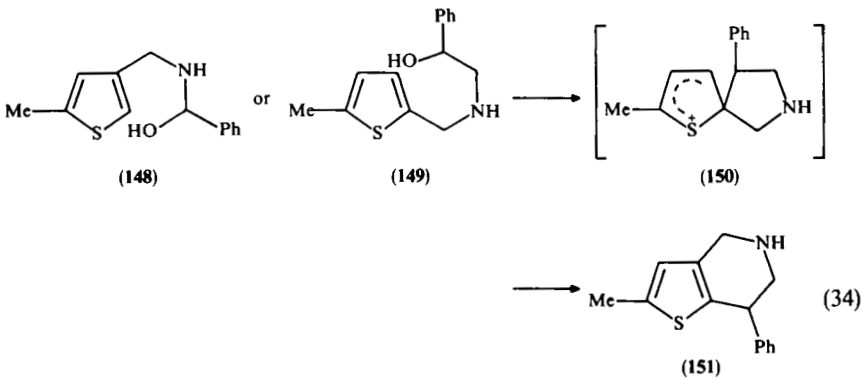
It has been reported that either *N*-(1-hydroxy-1-phenyl)-3-aminomethyl-5-methylthiophene (**148**) or *N*-(2-hydroxy-2-phenyl)-2-aminomethyl-5-methylthiophene (**149**) reacts with trifluoroacetic acid to give the 7-phenyl-4,5,6,7-tetrahydro-5-methylthieno-(3,2-*c*)-pyridine (**151**). The rearrangement of **149** is considered to proceed via **150** and the migration of CHNH in competition with benzyl[79] (equation 34).



(32)



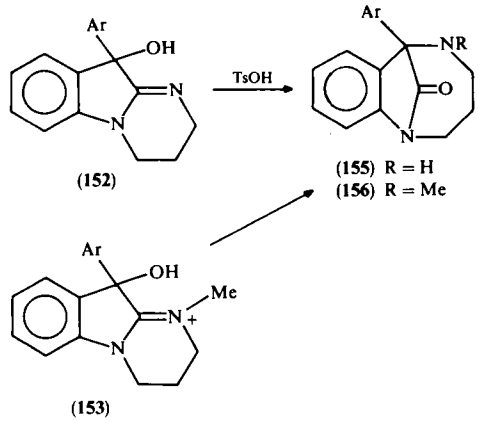
(33)



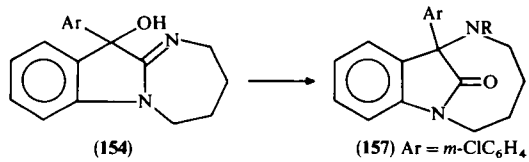
(34)

Recently, Cliffe and coworkers described an acid-catalysed ring enlargement reaction[80]. Rearrangement of the pyrimidino-(1,2-*a*)indole (**152**) and pyrimido(1,2-*a*)indolinium iodide (**153**) produces the 1,2,3,4,5,6-hexahydro-1,5-benzodiazocines **155** and **156**. The diazepino(1,2-*a*)indole (**154**) yields the 2,3,4,5,6,7-hexahydro-1,6-benzodiazonine (**154**). The rearrangement mechanism may involve formation of an indole 2,3-oxide, which is

converted via a 2*H*-indolinium cation to an aziridinium cation. The subsequent loss of a proton from the cationic species creates the lactam (equations 35 and 36).



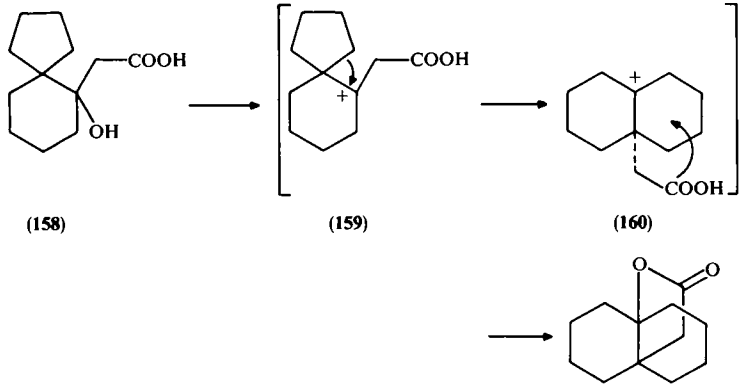
(35)



(36)

4. Six-membered and larger rings

Fujita and coworkers described a convenient praparative method for (*m.n*.3)propella-γ-lactones[81,82]. On treatment of the 3-hydroxy acid (**158**) with sulphuric acid in boiling benzene, reaction takes place readily: spiro ring migration affords the lactone **161**. As equation 37 shows, in the acid-catalysed reaction of **158** a carbenium ion (**159**) is formed, which subsequently gives intermediate **160** by migration of the spiro bond.

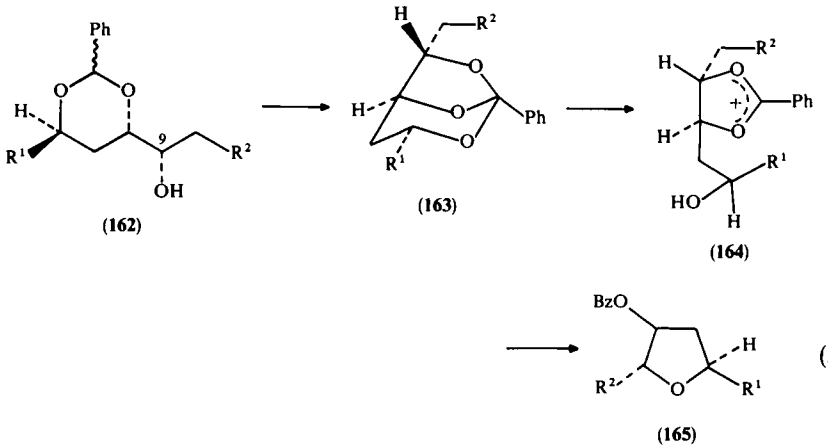


(158) (159) (160)

(37)

(161)

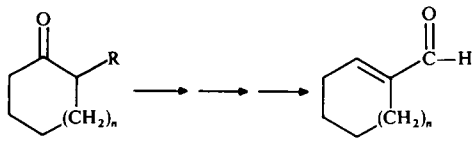
The stereocontrolled transformation of 1,3-dioxolane precursors bearing a neighbouring hydroxy group (**162**) has recently been reported[83]. A process has been proposed which involves initial carbocation capture by the neighbouring hydroxy group at $C_{(9)}$ of **162**, leading to an orthoester (**163**), opening of which affords the dioxolenium cation **164**. This cation then suffers internal nucleophilic attack at $C_{(9)}$ to provide the observed tetrahydrofuran (**165**). Although each of the oxygens of the orthoester **163** is a suitable leaving group, the observed result demonstrates that ring closure is feasible only in cases where two or three bridging methylenes separate a nucleophilic hydroxyl from its cationic partner, thus achieving an intramolecular backside collinear displacement (equation 38).



(38)

Ring contraction was observed during the lithium bromide-induced skeletal rearrangement of *cis*- and *trans*-4,4-dimethyl-2,3-epoxycyclohexanols to cyclopentene-2-carboxaldehyde[84]. Fujikura and coworkers[85] found that acid-catalysed ring contractions with extrusion of a methyl group in *endo*-2,8-trimethylene-*cis*-bicyclo(3.3.0)-octyl cations led to methylperhydrotriquinacenes. The fact that only minor amounts of these products were formed supported the earlier theoretical conclusion that methyl extrusion is in general a quite unfavourable process, owing to the formation of primary carbinyl cations at the expense of more stable secondary bridge or tertiary bridgehead ones.

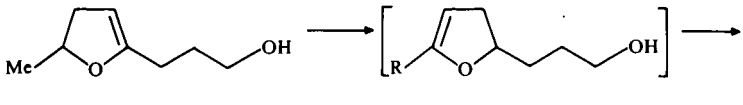
α,β-Unsaturated aldehydes have been conveniently prepared from ketones through their β-diethoxymethyl derivatives by sodium borohydride reduction, followed by acid-catalysed rearrangement of the resulting diacetal carbinols[86] (equation 39).



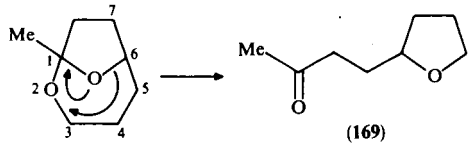
$n = O, 1$ R = H
= $CH(OEt)_2$

(39)

A number of different $C_{(4)}$, $C_{(5)}$, $C_{(6)}$, $C_{(7)}$ and $C_{(8)}$ methyl-substituted compounds of the new acetal, 2,9-dioxabicyclo(4.2.1)nonane system (**168**) have been synthesized from 4-(5-methyl-2-furyl)alkanols (**166**) and rearranged to ketones (**169**)[87] (equation 40).

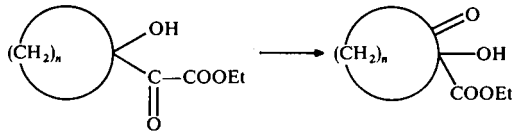


(166) (167)



(168) (169) (40)

Dibutyltin oxide has been used to catalyse the rearrangement of 2-hydroxy-2-oxocarboxylic acid esters (**170**, **171**) into the corresponding 2-hydroxy-3-oxo esters (**172**, **173**)[88]. The rearrangement described here provides a useful method for ring expansion. Thus, the cyclic ketol esters **170** and **171** were converted, essentially quantitatively, into the α-hydroxy-β-keto isomers **172** and **173**, respectively (equation 41).



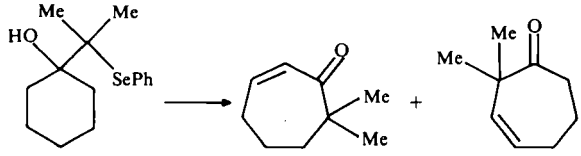
(170) $n = 4$ (172) $n = 4$ (41)
(171) $n = 5$ (173) $n = 5$

Treatment of protoadamantan-5-*endo*-ol with thionyl chloride or posphorus pentachloride led to ring enlargement, yielding a chloride compound[89], and Wagner–Meerwein rearrangement of adamantyl-1-neopentyl alcohol was observed under acidic conditions[90].

Labar and coworkers published a new method for the ring enlargement of cyclic ketones, which takes advantage of the high nucleophilicity of α-selenoalkyllithium towards carbonyl compounds, and of a novel transposition reaction of the resulting β-hydroxyselenides[91,92] (equation 42).

(42)

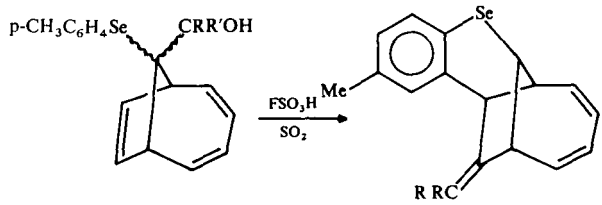
Further, α-phenylseleno alcohols (**174**) have been efficiently transformed to ring-expanded enones (**175**, **176**) upon reaction with thallium ethoxide in chloroform.



(174) (175) (176) (43)

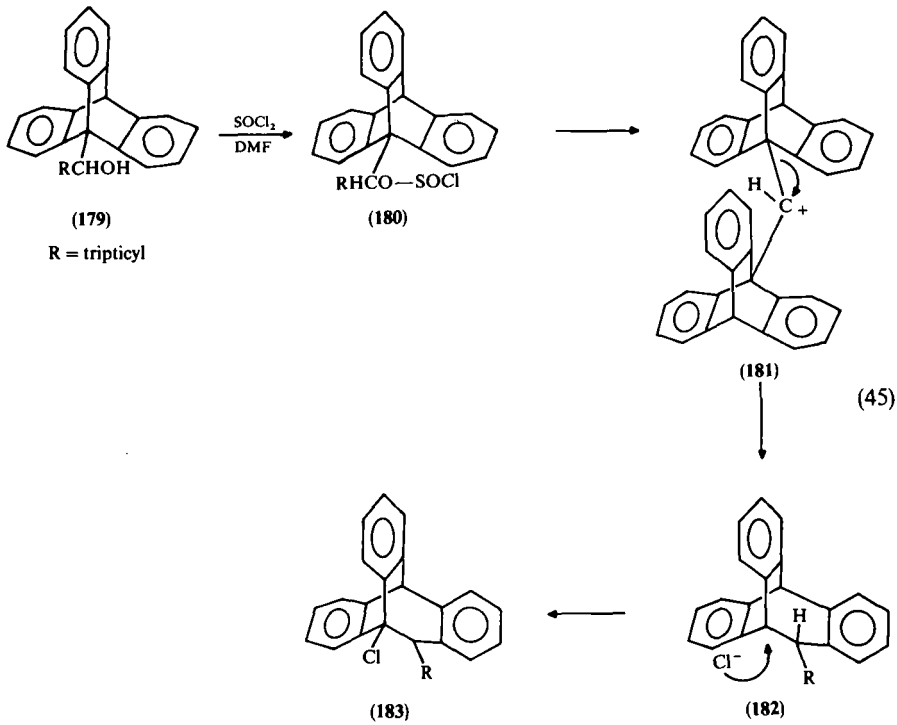
The reaction has been studied for the purpose of evaluating the relative migratory abilities of the α-vinyl and α'-alkyl groups in a variety of structural contexts[93,94] (equation 43).

Finally, the superacid-induced skeletal rearrangement of β-hydroxyselenide derivatives of bicyclo(4.2.1)nonatriene (**177**) has yielded selenides (**178**)[95]. In sulphur dioxide, **177** produces a rearranged selenide upon the addition of fluorosulphonic acid. Reductive elimination and subsequent attack of the selenyl electrophile on the ethano bridge cause migration of the butadiene moiety (equation 44).



(177) (178) (44)

Crumrine and coworkers found an interesting ring enlargement rearrangement during the halogenation of ditriptycylcarbinol[96]. It can be assumed that the thionyl chloride–DMF reagent reacts with ditriptycylcarbinol (**179**) to produce a triptycylmethylchlorosulphinate (**180**). The chlorosulphinate formed from the bulky **179**, after thermal cleavage of the chlorosulphinate carbon–oxygen bond, would give SO_2, chloride ion and a poorly solvated and very unstable carbocation (**181**) (equation 45).

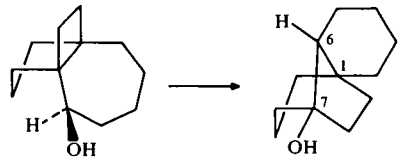


(179) R = tripticyl (180) (181) (182) (183) (45)

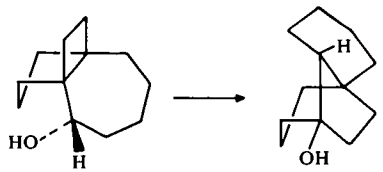
A facile rearrangement could occur very quickly from the tight ion pair. Alternatively, the chloride ion produced in the hydrophobic environment between the triptycenes would quickly move out to the solvent sheath, returning only after rearrangement. After rearrangement, the less congested and more stable rearranged cation (**182**) can be trapped by chloride ion to produce the homotriptycene derivative (**183**).

The cationic rearrangements of propellanes have been shown to be under strict stereoelectronic control, wherein the central or peripheral σ-bond of the cyclobutane ring best aligned with the leaving group is the one that undergoes initial migration[97].

The acid-catalysed rearrangement of *exo*-(5.3.2)propellanol (**184**) gave a tricyclo-(5.3.2.$0^{1,6}$)dodecane derivative (**185**), while the *endo* alcohol (**186**) gave a tricyclo(5.3.2.$0^{1,6}$)-dodecane derivative (**187**), both by 1,2-alkyl shifts of the central propellane ring[98,99] (equations 46 and 47).

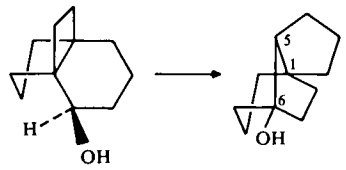


(184) (185) (46)

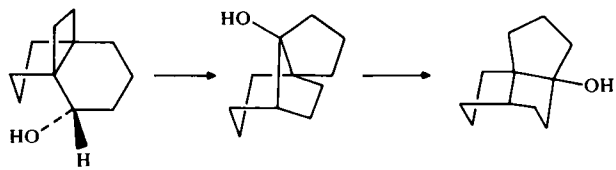


(186) (187) (47)

Similarly, *exo*-(4.3.2)propellanol (**188**) underwent rearrangement in acid to yield tricyclo(4.3.2.$0^{1,5}$)undecane derivatives (**189**) via a 1,2-alkyl shift of the central propellane bond. On the other hand, the *endo* alcohol (**190**) yielded tricyclo(4.3.2.$0^{1,5}$)undecan-5-ol (**188**) as the initial reaction product via a 1,2-alkyl shift of the external cyclobutane bond. However, **191** underwent a second alkyl shift to give the *cis,cis*-tricyclo(6.3.0.$0^{1,5}$)undecane derivatives (**192**) as major products (equations 48 and 49).

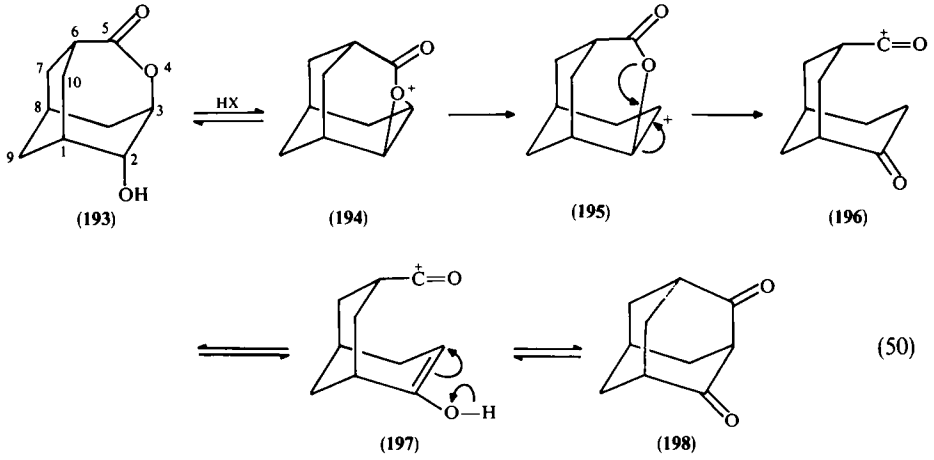


(188) (189) (48)



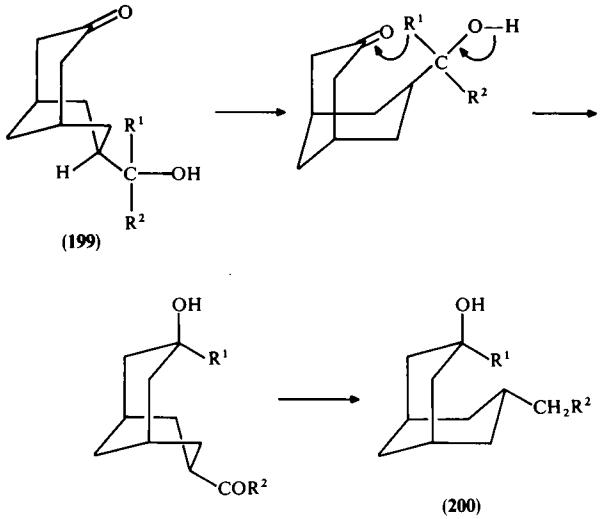
(190) (191) (192) (49)

Duddeck and coworkers observed an interesting epoxonium–ketone rearrangement[100]. In acidic media, **193** gave the epoxonium ion (**194**), which is able to undergo an epoxonium–ketone rearrangement to **196** via an intermediate carbenium ion (**195**), because of the electron-withdrawing ability of the carbonyl group. The tautomerization of **196** to **197** and subsequent loss of a proton finally leads to the diketone **198** (equation 50).



(50)

The Huang–Minlon reduction of 7α-hydroxymethylbicyclo(3.3.0)nonan-3-one (**199**; $R^1 = R^2 = H$) has been found to yield 7β-methylbicyclo(3.3.1)nonan-3β-ol (**200**; $R^1 = R^2 = H$), formed as a result of a transannular 1,6-hydride shift enforced by relief of the steric constraint in the system[101] (equation 51).

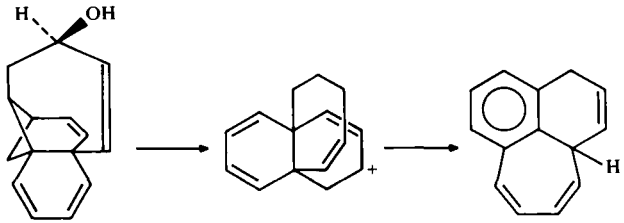


(51)

A new polycyclic saturated $(CH_2)_{2n}$ hydrocarbon, 2,9-dimethylheptacyclo-(6.4.0.$0^{2,4}$.$0^{3,7}$.$0^{5,12}$.$0^{6,10}$.$0^{8,11}$)dodecane has been synthesized from a pentacyclic cage

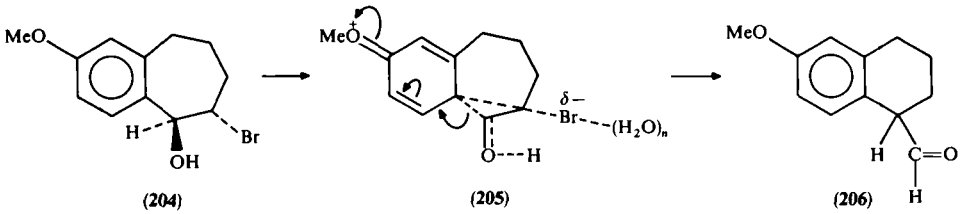
compound derived from 2,6-dimethylphenol by acid-catalysed rearrangement[102], while the significance has been discussed[103] of a Wagner–Meerwein methyl shift which operates in a recently reported synthesis of 1,6-dimethyldodecahedrane.

In a similar manner, the tetracyclo(4.4.4.$0^{1,6}$.$0^{5,8}$)tetradeca-2,9,11,13-tetraen-4-ol (**201**) has been transformed via a deep-seated carbocation rearrangement into 4a,7-dihydropleiadiene (**203**). Indirect evidence has been obtained for intervention of the (4.4.4)propella-2,4,7,9,11-pentaenyl cation (**202**) in the conversion. The overall structural change has been most economically rationalized in terms of a three-fold Wagner–Meerwein cascade from **202** that involves proton loss with concurrent aromatization[104,105] (equation 52).



(201) (202) (203) (52)

An efficient ring contraction of stereoisomeric 1,2-benzo-4-bromo-3-hydroxycyclohept-1-enes and their derivatives (**204**) to **206** has been reported, and a probable transition state (**205**) has been suggested for the process[106] (equation 53).



(204) (205) (206) (53)

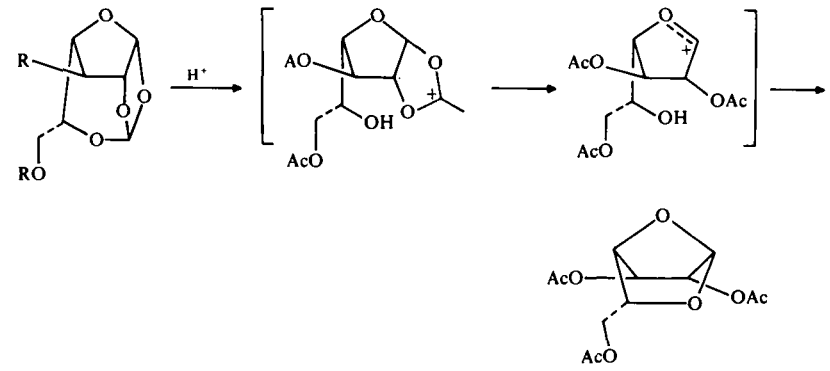
C. Rearrangements in Natural Product Systems

These studies are classified in this way because they involve rearrangements of natural product systems that may well proceed via carbocations.

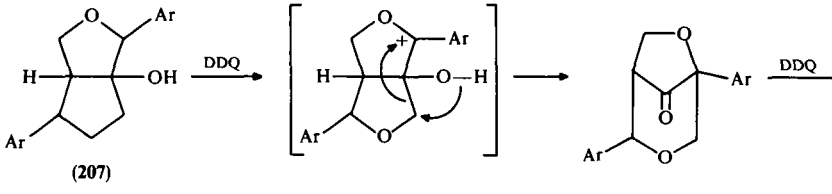
Internal carbohydrate orthoesters, and particularly *cis*-1,2-orthoacylates, have been observed to rearrange to anhydro sugars in polar aprotic solvents. Such an observation is especially interesting because in some cases it is not possible to formulate an intermediate glycosyl cation[107] (equation 54).

Stereochemically interesting transformations have been observed in the field of terpenoids. The route shown in equation 55 was invoked to account for the DDQ-induced rearrangements of paulownin (**207**; Ar = 3,4-methylenedioxyphenyl) and gmelinol (**207**; Ar = 3,4-dimethoxy-phenyl) into derivatives of 4-pyrone **208**[108].

The synthesis of (±)-cryptofauronol and related valerane sesquiterpenes has been approached by acid-catalysed rearrangement of bicyclo(5.3.0)decane precursors[109]. Rearrangement of alcohol **209** to decalone (**211**) proceeds via a 1,2-carbon-to-carbon bond shift, the resulting carbocation being stabilized by the ether oxygen; cf. structure **210** (equation 56).

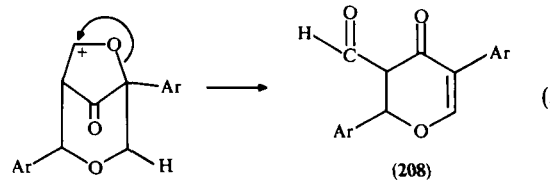


(54)

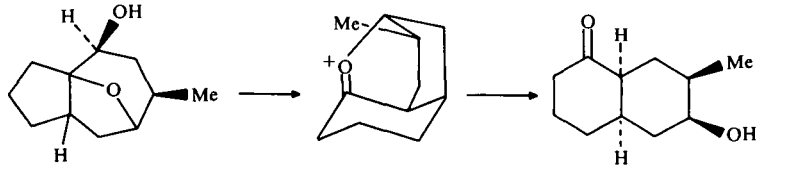


(207)

(55)



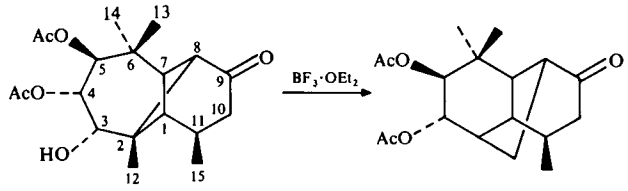
(208)



(209) (210) (211)

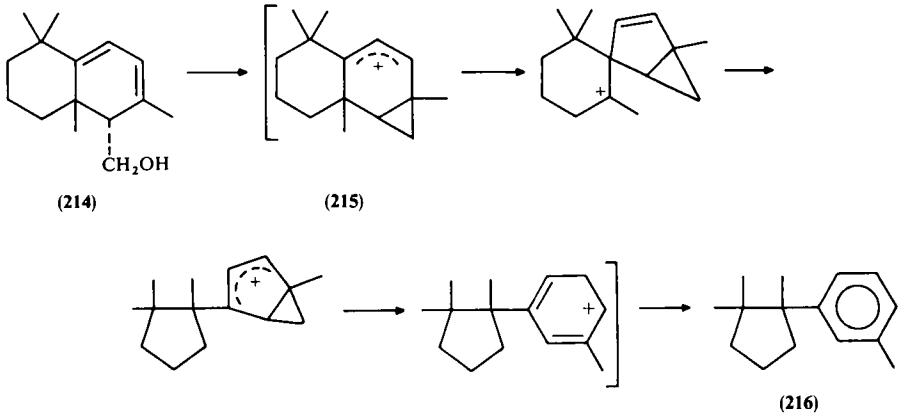
(56)

Tricyclic strained substances, such as longipinene derivatives, offer the possibility to generate new structures, because bond migration can be promoted to release the four-membered ring strain. Thus, when **212** was treated in acid media, it rearranged to afford **213**, whose formation involves the displacement of the previously protonated hydroxy group at $C_{(3)}$ of **212** by the antiperiplanar $C_{(1)}$—$C_{(2)}$ bond, followed by the formation of a double bond between $C_{(2)}$ and $C_{(12)}$[110] (equation 57). A similar mechanism was earlier proposed by Mehta and coworkers for the formation of tricycloundecane derivative from a *cis*-bicyclo(5.4.0)undecane derivative containing a himachalane-type carbon skeleton[111].



(212) (213) (57)

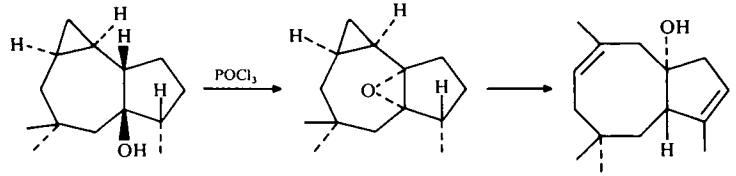
Herbertene (**216**) has been synthesized by acid-catalysed rearrangement of the drimane-type alcohol (**214**). The likely pathway, illustrated in Scheme 8, is considered to involve the formation of **215**, followed by two successive 1,2-migrations[112].



(214) (215) (216)

SCHEME 8

Africanol (**217**), an irregular isoprenoid alcohol, has been converted to dactylol (**218**) through a formal 1,2-shift of a methyl group, involving a cyclopropane-sliding reaction and subsequent cyclopropane ring opening[113] (equation 58).

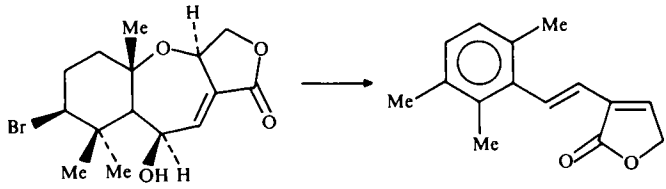


(217) (218) (58)

Vaidya and Nayak found that treatment of 9-methylenlongibornane with $BF_3 \cdot OEt_2$ in refluxing benzene yielded 9-methylisolongifolene via a 1,5-hydride shift in a cationic intermediate[114], while longibornane alcohols, when exposed to $HClO_4$ in dioxane, were rearranged to isolongifolene through a series of oxonium ions[115]. A new type of tricyclic compound, viz. 12-hydroxy-10-methylenetricyclo(7.2.0^{1,6})dodecan-11-one, has been

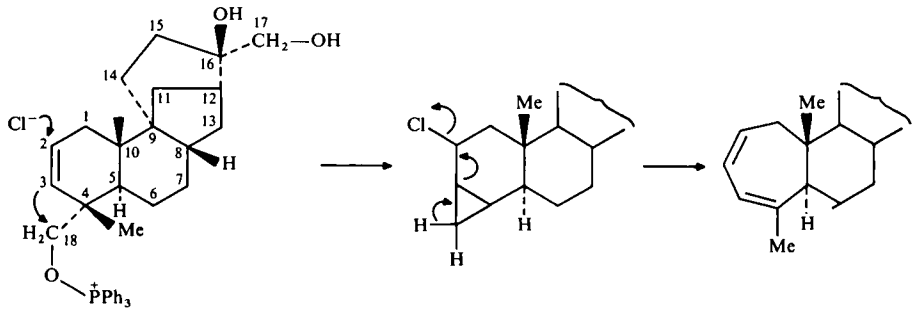
synthesized by solvolytic rearrangement of *exo*-3-methylenetricyclo(6.4.0.0^{1,4})dodecan-5-ol[116].

Capon and coworkers discovered an interesting thermal rearrangement in the case of 6β-hydroxyaplystatin (**219**). The formation of **220** when **219** was heated was rationalized[117] by assuming the heat-induced loss of bromide, methyl migration and loss of a proton. The HBr thus generated is considered to catalyse dehydration of the 6β-OH group and opening of the cyclic ether. Isomerization of the double bond followed by dehydration would lead to **220** (equation 59).



(219) (220) (59)

The participation of the Δ^2 double bond in the displacement of $C_{(18)}$ substituents on the diterpenoid aphidicolin has led to ring expansion with the probable intervention of a cyclopropyl intermediate (see Scheme 9)[118].



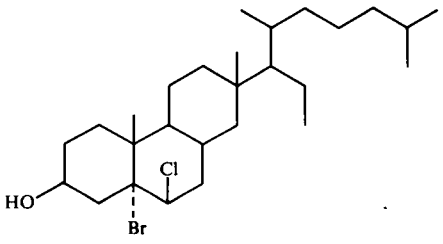
SCHEME 9

Wagner–Meerwein rearrangements have been reported in taraxerol[119] and related triterpenes such as 18-isooleanolic acid lactone[120]. Dehydration of taraxerol with PCl_5 is found to give an A-nor-3,4-dichloro product. The reactions are rationalized on the basis of conformational and ring strain in the molecule.

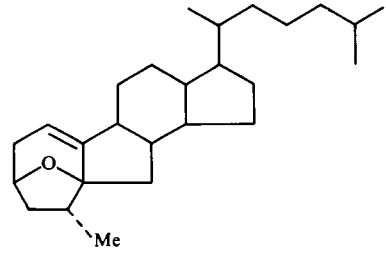
Other backbone rearrangements that have been reported include Wagner–Meerwein rearrangements in taraxasterol and pseudo-taraxasterol[123], and in D:A-friedooleananes[121] and lupanes[122].

5-Bromo-6β-chloro-5α-cholestan-3β-ol (**221**) has been converted into epoxyhomo-norcholestane (**222**) by silver perchlorate-catalysed Westphalen rearrangement[124] (Scheme 10).

The photoisomerization of 5-hydroxy-6-cholestanones (**223**) to lactones (**224**) is considered to involve ketene intermediates formed by migration of the 7α-hydrogen; the stereospecificity of the migration is independent of hydrogen bonding or has been attributed to slowing of the rotation about the $C_{(9)}$—$C_{(10)}$ bond in the alkyl acyl diradicals that are the ketene precursors[125] (equation 60).

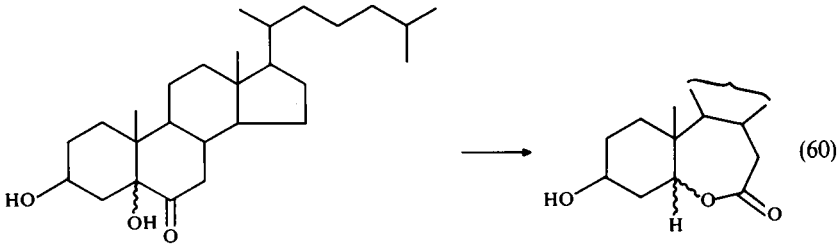


(221)



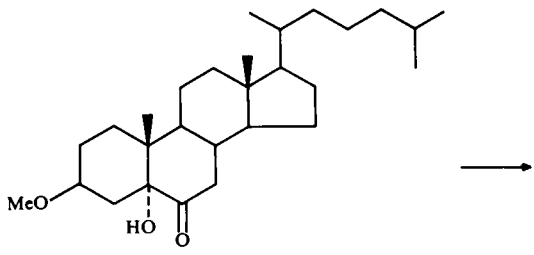
(222)

SCHEME 10

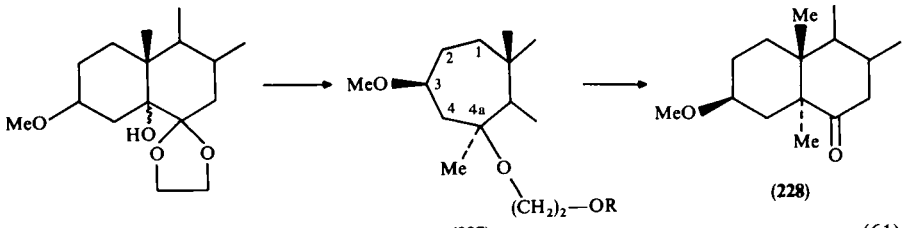


(223) (224) (60)

Spirocyclic ketones appear to be the main products of hypobromous acid treatment of 5α-hydroxy- and 5α-alkoxy-10β-vinylcholestanes[126], while the photo- and thermally-induced rearrangements of 3-hydroxy-Δ^5-steroid hypoiodites in the presence of mercury(II) oxide–iodide have been accounted for by assuming the intermediacy of an intermediate allyl radical resulting from β-scission of a 3β-oxyl radical[127].



(225)



(226) (227) (228) (61)

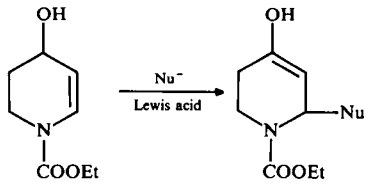
A novel sequence involving the thermal rearrangement of a steroidal α-hydroxyacetal (**226**) has been reported, in which the hydroxy group of 5-hydroxy-3β-methoxy-5α-cholestan-6-one (**225**) is replaced by a methyl group in three steps[128] (equation 61).

D. Rearrangements of Allylic Alcohols

A common type of functional group migration or rearrangement is that of an adjacent double bond. Allylic cations contain two electron-deficient centres to which nucleophiles can attach. Therefore, allylic rearrangements may very often be expected in the reactions of allylic alcohol systems catalysed systems catalysed by acids or metal salts.

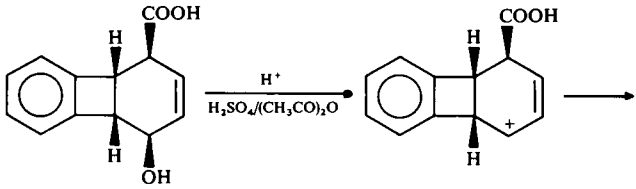
A mechanistic investigation of the acid-catalysed rearrangements of 1- and 2-methyl-1-phenylallyl alcohols was undertaken by Shandala and coworkers[129]. Doolan and coworkers reported that the anionotropic rearrangement of 1-phenylprop-2-en-1-ol to 3-phenylprop-2-en-1-ol is catalysed by tin(IV) and tin(II) chlorides[130]. Tungsten catalysts have been used[131] to achieve the selective allylic rearrangement of alcohols such as linalool, while rearrangements involving tungsten-stabilized carbocation intermediates have been reported[132].

The Lewis acid-induced reactions of *N*-carbethoxy-4-hydroxy-1,2,3,4-tetrahydropyridine with various carbon nucleophiles, reactions which bear a close resemblance to the well-known Ferrier rearrangement of glycals, were studied by Kozikowski and Park[133] as a route to 2-substituted-Δ^3-piperidines (equation 62).

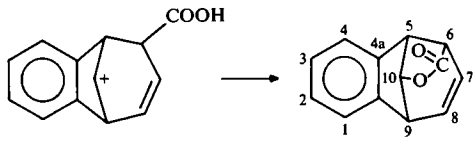


(62)

A recently reported synthesis of uvidin-C involved as key step the rearrangement of a hindered allylic alcohol during a vanadium-catalysed epoxidation[134]. The tetrakis-(triphenylphosphine)palladium(0)-catalysed rearrangement of a vinylic epoxide intermediate was utilized[135] as key reaction in a recent synthesis of (*R*)-4-hydroxy-2-benzyloxymethylcyclopent-2-en-1-one from D-glucose. A possible mechanism for the



(229) (230)

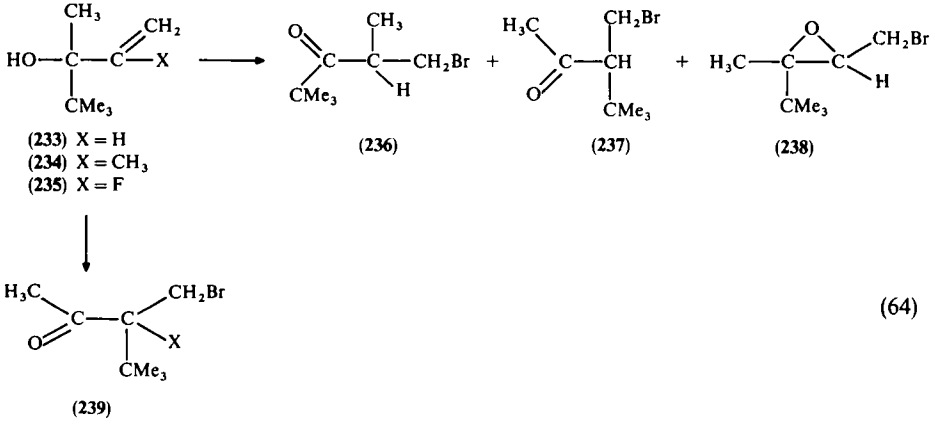


(63)

(231) (232)

acid-catalysed rearrangement of 8-hydroxy-4a,5,8,8a-tetrahydrobiphenylene-5-carboxylic acid (**229**) to the lactone of 6,9-dihydro-10-hydroxy-5,9-methano-5*H*-benzocycloheptene-6-carboxylic acid (**232**) has been discussed by Barton and coworkers[136] (equation 63).

The effects of fluorine and methyl substituents on the rate and outcome of the rearrangement that occurs with tertiary allyl alcohols on bromination have been examined[137]. The allylic alcohol **233**, bearing a methyl group and a *t*-butyl group at the hydroxylated position, was found to undergo a rearrangement when reacted with bromine (or *N*-bromosuccinimide) in an aqueous medium, and to afford a product mixture containing two regioisomeric ketones (**236, 237**) and oxirane (**238**). Introduction of an additional methyl group (**234**) or a fluorine atom (**235**) at the non-terminal olefinic centre led to a more selective discrimination between potential migratory groups (equation 64).



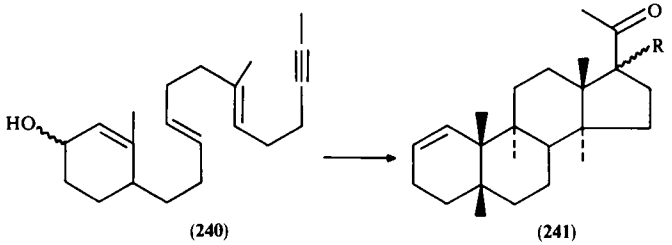
(233) X = H
(234) X = CH_3
(235) X = F

(236) (237) (238)

(239)

(64)

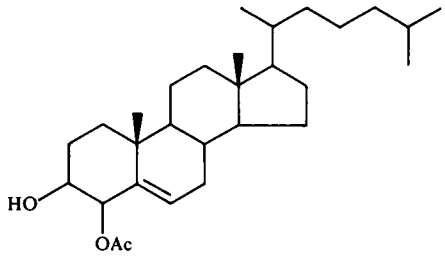
The use of a nitroalkene to trap the presumed intermediate vinyl cation formed in the acid-catalysed cyclization of allylic alcohol such as **240** also resulted in production of the nitrogen-free ketone **141**, which must have arisen by a backbone rearrangement[138] (equation 65).



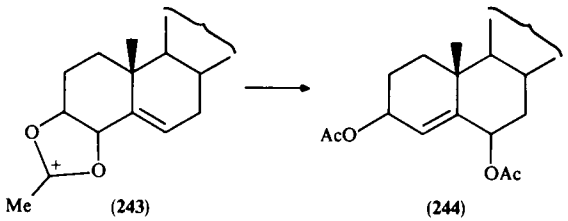
(240) (241)

(65)

An intramolecular mechanism involving a quinonoid zwitterionic intermediate has been suggested[139] to account for the acid-catalysed rearrangement of steroidal 14α-hydroxyketones with 17-alkoxy-16-en-15-ones in the presence of aqueous or alcoholic hydrochloric acid. ^2H-, ^{13}C- and ^{14}C-labelling studies have provided evidence[140,141] of the intervention of the 3β-hydroxy group, possibly via a 3β,4β-acetoxonium ion **243**, in the rearrangement and acetylation of 3β-hydroxy-4β-acetoxy-Δ^5-steroids **242** by glacial acetic acid to form 3β,6β-diacetoxy-Δ^4-steroids (**244**) (equation 66).



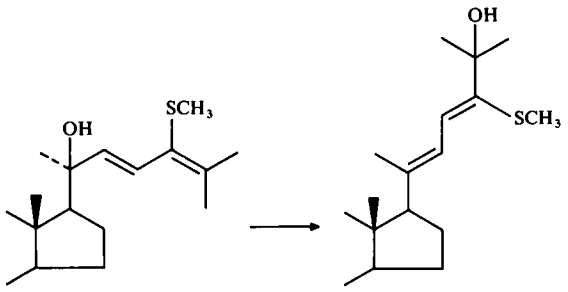
(242)



(243) (244)

(66)

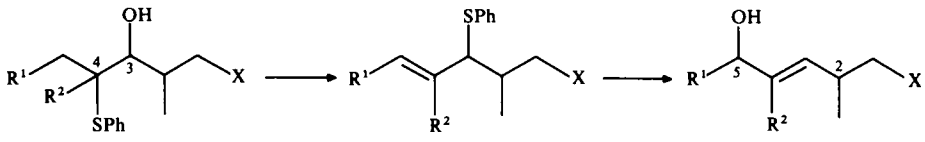
An intriguing dienol rearrangement is promoted by nickel chloride and has been used to transform a 20-hydroxysteroid (**245**) to its 25-hydroxy analogue (**246**)[142] (equation 67).



(245) (246)

(67)

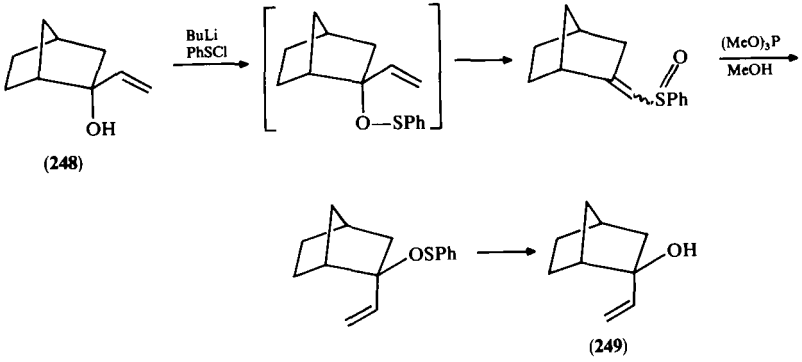
Syn- and *anti*-(*E*)-2,4-dimethylhex-3-ene-1,5-diols **247**, compounds with 1,4-related chiral centres, have been synthesized by means of a phenylthio migration protocol[143]. The rearrangement of dienols $R_2C(OH)CH{=}CHC(X){=}CR_2$ possessing a non-terminal arylthio or alkylthio substituent, to give the vicinally substituted dienols $R_2C{=}CHCH{=}C(X)CR_2(OH)$, has been effected with nickel chloride in aqueous *t*-butyl alcohol[144] (equation 68).



(247)

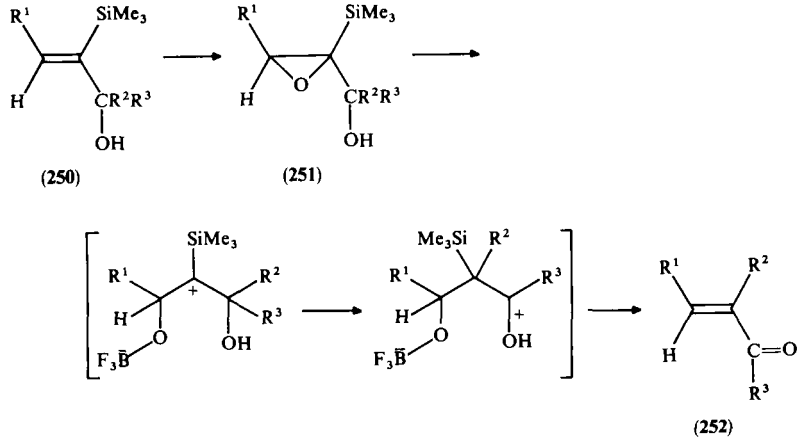
(68)

A procedure employing a (2,3) sulphoxide rearrangement has been used[145] as a general method of inverting the stereochemistry of bicyclic vinyl *endo*-alcohols (**248**) to afford the corresponding *exo* isomers (**249**); see equation 69.



(248) (249) (69)

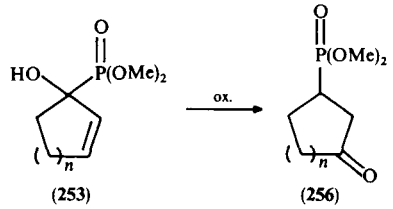
Novel cyclopentenone derivatives have been produced by the $BF_3 \cdot OEt_2$-catalysed methanolysis of 1,1-bis(methylthio)-2,4-dimethyl-5-aryl(or styryl)-2,4-pentadien-3-ols[146]. Allylic alcohols (**250**) available from silylated acetylenes have been shown[147] to yield epoxydes (**251**) which rearrange to enones (**252**) by migration of a substituent and then a Peterson reaction (equation 70). The rhodium-catalysed isomerization of β-trimethylsilylallyl alcohols has been successfully applied to the regiospecific synthesis of trimethylsilyl enol ethers[148] and to the selective synthesis of α-trimethylsilyl ketones[149] and β-trimethylsilyl ketones[150].



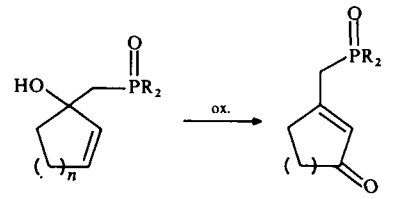
(252) (70)

The rearrangement of phosphorus-containing tertiary allylic alcohols has been observed[151], and the reactions of (1-hydroxy-2-cycloalkenyl)phosphonates (**253**) and homologous derivatives (**245, 255**) with chromium(VI) reagents proceed via oxidative rearrangement and result in formation of the 1,3-carbonyl transposed, β-substituted-α,β-unsaturated ketones (**256, 257, 258**)[152] (equations 71 and 72).

The ruthenium(III) chloride/sodium hydroxyde-catalysed isomerization of allylic alcohols to saturated ketones has been shown to occur by an intramolecular 1,3-H



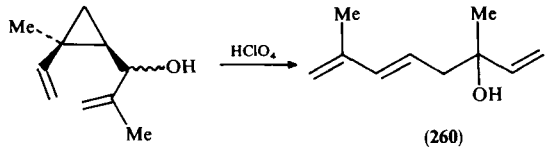
(253) (256) (71)



(254) (R = OEt)
(255) (R = Ph)
(257)
(258)
(72)

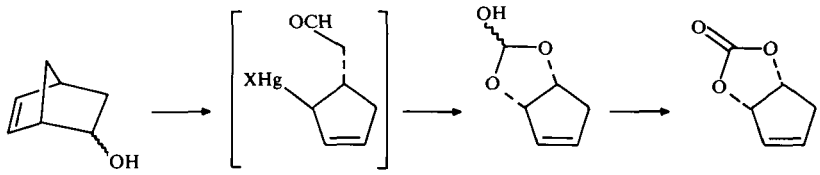
shift[153], and a remarkably mild conversion of allylic alcohols into carbonyl compounds has been achieved by use of rhodium(I) in a two-phase system[154]. γ-Hydroxy-α,β-unsaturated ketones have been isomerized to γ-diones in high yields by using HBr in ether[155].

The cyclopropenycarbinyl–allenyl rearrangement has been used[156,157] as a method of synthesizing vinylallenic alcohols and divinyl ketones. Short syntheses of the monoterpenols (±)-hotrienol (**260**) and (±)-santolina alcohol have recently been described, via the cyclopropyl–homoallyl rearrangement of adduct **259**, which is itself produced by tandem addition of vinylmagnesium bromide and an appropriate carbonyl compound to the cyclopropenes[158] (equation 73).



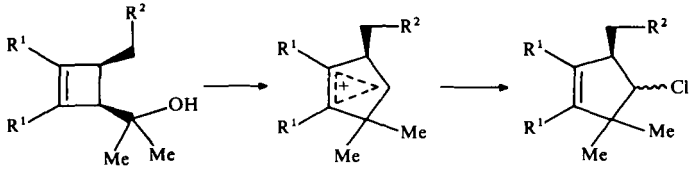
(259) (260) (73)

The heterolytic fragmentation of homoallylic alcohols incorporated in a bicyclo(2.2.1)heptane system occurs on reaction with mercury(II) acetate[159]. This fragmentation appears to be well suited for the synthesis of substituted cyclopentanes which can serve as synthons for certain cyclopentane-containing natural products (equation 74).



X = OAc, $OCOCF_3$ (74)

The ring expansion by one carbon atom reported by Miller and Ullah is notable for the control it achieves over stereo- and regiochemistry[160]. When the alcohols **261** are converted into the corresponding chlorides and the chlorides are treated with zinc chloride, the formation of 4-chlorocyclopentanes (**263**) is observed. The stereochemistry of these ring-expansion reactions is also of interest, since the products (**263**) are normally formed as one diastereomer only, with *trans* geometry. The origin of these selectivities may be related to the stability of cyclopent-3-enyl carbocations[161]. Thus, the regiochemistry would seem to depend upon a continuous stabilization, by the cyclopentane double bond, of charge development in the ring as 1,2-vinyl migration leads to carbocation **262** (equation 75).



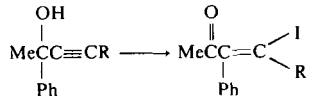
(75)

(261) (262) (263)

Allylic rearrangements have similarly been demonstrated in propargyl systems. The products are in this case α,β-unsaturated aldehydes or ketones.

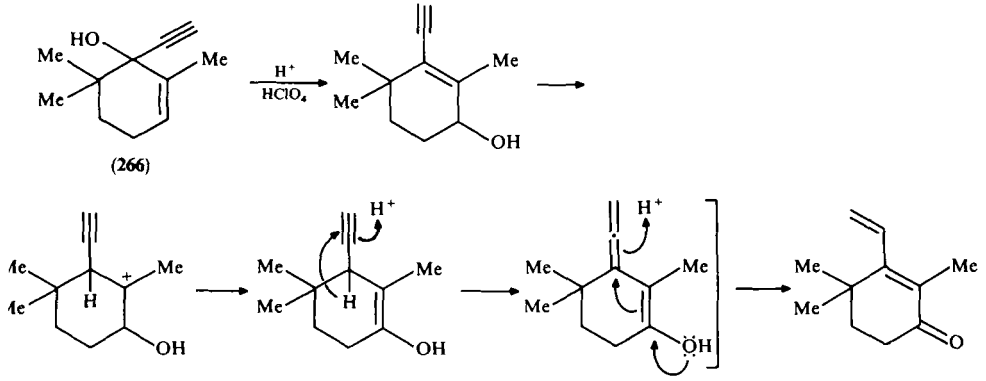
A cyclic transition state involving the vanadium atom has been proposed for the rearrangement of *t*-ethynylcarbinols to α,β-unsaturated aldehydes in the presence of (poly)vanadium organosiloxanes[162].

Iodine and several of its oxides have been shown to react with alkynyl alcohols (**264**) in methanol to afford β-iodo-α,β-unsaturated ketones (**265**). The rearrangement is considered to be stereospecific, with phenyl migration *anti* to a possible iodonium-like bridge[163] (equation 76).



(76)

(264) (265)



(266)

(267)

(77)

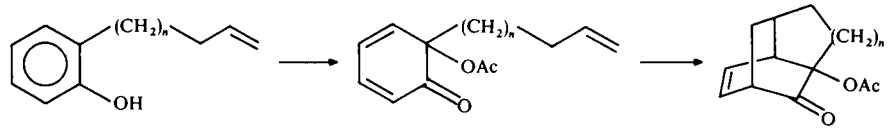
An unexpected rearrangement of an acetylenic tertiary alcohol (**266**) has fortuitously provided a convenient route to potential di- and triterpene precursors[164]. Thus, treatment of enynols (**266**) with 35% perchloric acid in THF produced the corresponding dienones (**267**), presumably through a series of prototropic shifts (equation 77).

A recently described approach to α-alkenyl ketones and carbinols from alkynes and haloketones involves a novel rearrangement and offers several advantages over the existing methodology[165], while the mercury(II)-induced cyclization of acetylenic alcohols has provided a new route to enol ethers[166].

II. REARRANGEMENTS OF PHENOLS

One of the characteristic chemical properties of phenols is their facile oxidative conversion, which is often accompanied by a rearrangement and which leads to compounds of different structural types.

Yates and coworkers[167,168] found that a tandem Wessely oxidation–Diels–Alder reaction sequence can be used for the synthesis of isotwistanes and homoisotwistanes of types **272** and **273** from 4-(2-hydroxyphenyl)-1-butanes (**268**) and from 5-(2-hydroxyphenyl)-1-pentanes (**269**) via 2,4-cyclohexadienones of types **270** and **271** (equation 78).

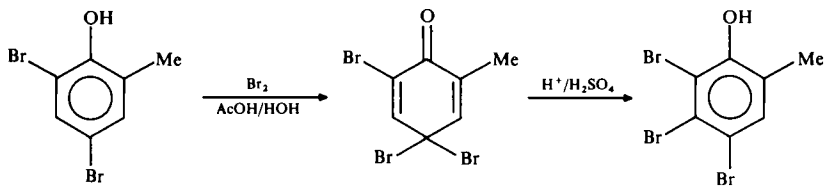


(**268**) $n = 1$ (**269**) $n = 2$ (**270**) (**271**) (**272**) (**273**)

(78)

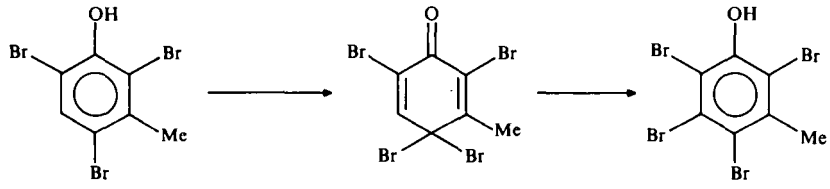
The nature of the dienones **277**, **278** and **279** derived from further bromination of the di- and tribromophenols **274**, **275** and **276** obtained from *o*-, *m*- and *p*-cresol was reinvestigated by Brittain and coworkers[169] in an attempt to rationalize the course and regiospecificity of their rearrangement to ring-substituted polybromophenols. The bromodienones **277**, **278** and **279** were prepared from the corresponding bromophenols by reaction with bromine in aqueous acetic acid. The dienones are formed quite rapidly at room temperature and can easily be isolated in nearly quantitative yields. When stirred in suspension with concentrated sulphuric acid at room temperature, each of the bromodienones **277**, **278** and **279** gives the ring-substituted bromophenols **280**, **281** and **282** nearly quantitavely through a 1,2-shift of bromine (equations 79, 80 and 81).

Abdou and Sakla found that, depending on the reaction conditions, bromination of 3,3-bis(*p*-methoxyphenyl)propionic acid gives both rearrangement and brominated products[170].

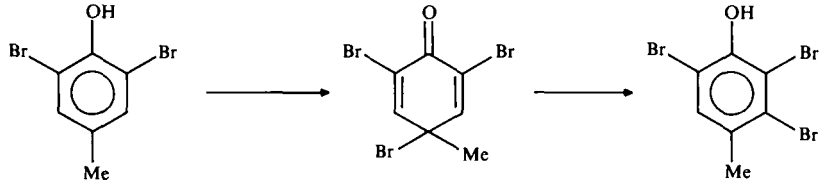


(**274**) (**277**) (**280**)

(79)

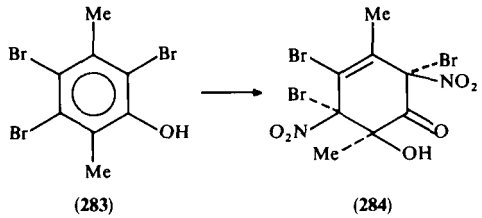


(275) (278) (281) (80)

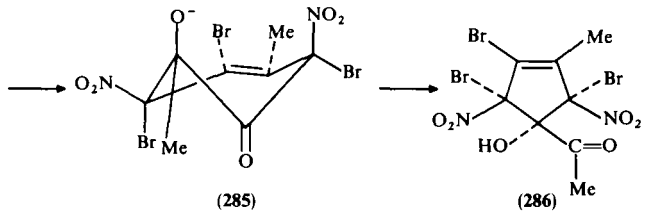


(276) (279) (282) (81)

Bates and coworkers[171] established that dinitration of 2,4,5-tribromo-3,6-dimethylphenol (**283**) gives either the tribromo compound (**284**) or its acyloin rearrangement product **286**, depending on the reaction conditions. Formation of the cyclopentenol stereoisomer in the acyloin rearrangement of hydroxy ketone **284** requires that the rearrangement should occur in the half-chair conformation **285** (equation 82).

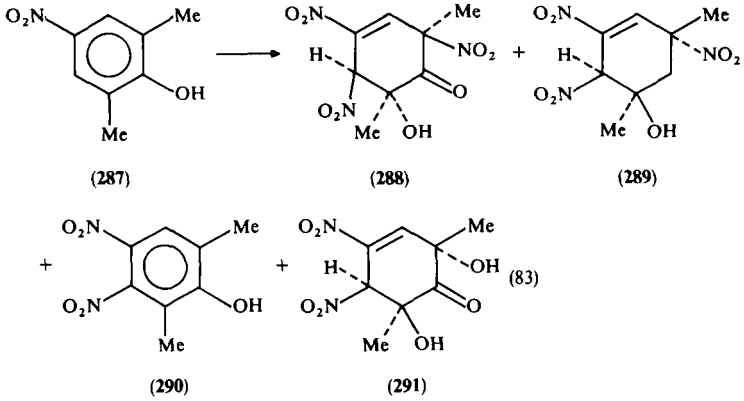


(283) (284)



(285) (286) (82)

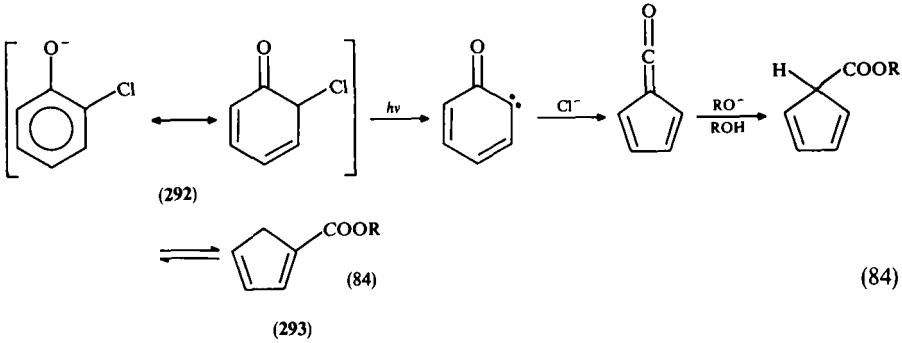
Hartshorn and coworkers reported that the nitration of poly-substituted phenols with nitrogen dioxide gives isomeric poly-substituted nitrocyclohex-3-enones[172–177]. The nitration of 2,6-dimethyl-4-nitrophenol (**287**) with fuming nitric acid or nitrogen dioxide gives the $C_{(2)}$ epimeric hydroxy trinitro ketones (**288**, **289**), the dinitro phenol (**290**) and the dihydroxy dinitro ketone (**291**)[178] (equation 83).



(83)

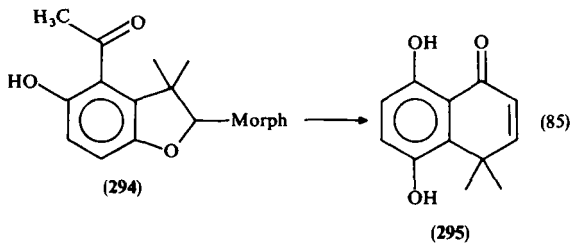
Fischer and Mathivanan[179] found that the reactions of *o*- and *p*-cresol, the xylenols and 2-naphthol with nitrogen dioxide give nitrocyclohexadienones and nitrophenols. Secondary nitrodienones, the keto tautomers of the nitrophenols, have been observed in several cases and are intermediates in the formation of the nitrophenols.

Specific contraction of the phenolate from 2-chlorophenol (**292**) into a five-membered cycle (**293**) was observed by Guyon and coworkers[180] to occur in dilute aqueous solution in response to irradiation. The reaction is considered to proceed by way of a cyclopentadienic acid formed through a Wolff rearrangement, followed by hydrolysis, as shown in equation 84.



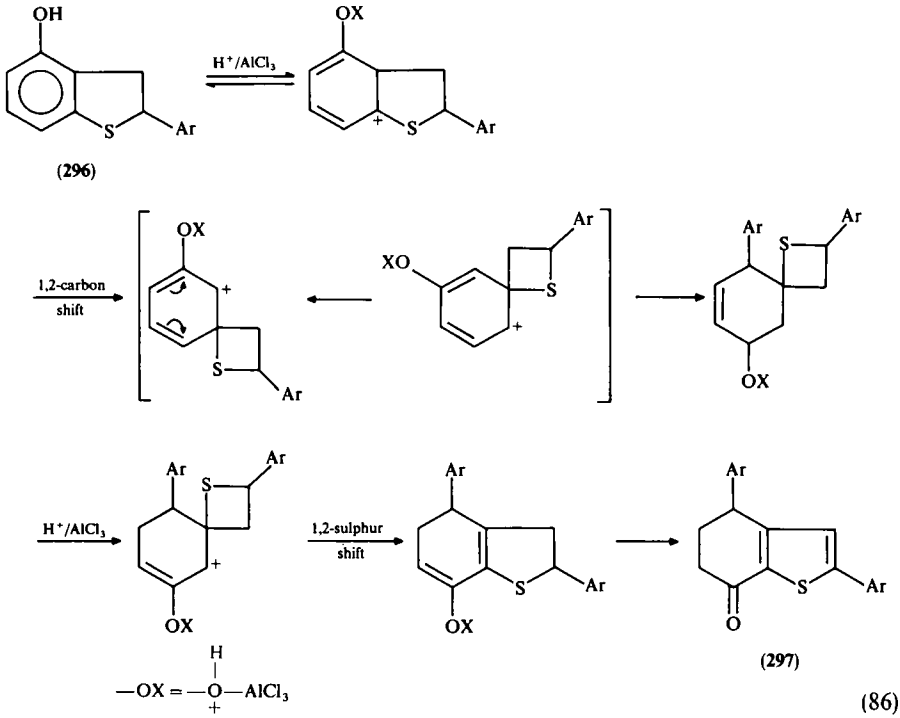
(84)

A kinetic study of the acid-catalysed rearrangement of 4-acetyl-3,3-dimethyl-5-hydroxy-2-morpholino-2,3-dihydrobenzo(*b*)furan (**294**) to 5,8-dihydroxy-4,4-dimethyl-1(4*H*)-naphthalenone (**295**) has been carried out by Castro and coworkers[181] (equation 85).



(85)

A series of carbocations and spiro-thietane intermediates have been invoked to account for the $AlCl_3$-induced rearrangement of acetoxy- and hydroxybenzo(*b*)thiophenes (**296**) into 4,5-dihydro-2,4-diphenylbenzo(*b*)thiophen-7(6*H*)-one (**297**)[182] (equation 86).



(86)

III. REARRANGEMENTS OF DIOLS

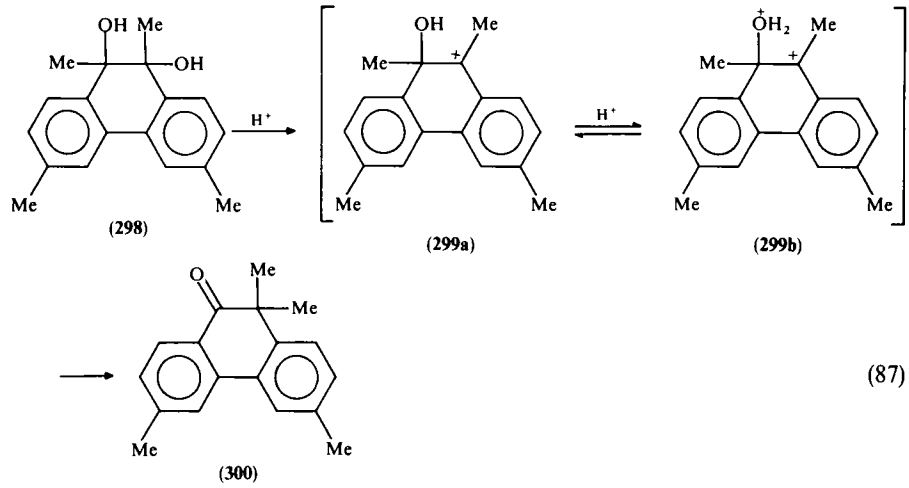
A. 1,2-Diols

Attempts to dehydrate substituted *vic*-diols (pinacols) usually lead to rearrangements with the formation of ketones. This type of reaction is called the pinacol rearrangement and is favoured because of the resonance stabilization of the rearranged ion by the attached oxygen.

The pinacol rearrangement is believed to involve two important steps: (1) loss of water from the protonated glycol to form a carbenium ion; and (2) rearrangement of the carbenium ion by a 1,2-shift to yield the protonated ketone. In some cases at least, the two steps may occur simultaneously, attachment of the migrating group helping to expel the molecule of water.

The occurrence of the carbenium cation intermediate was proved by Chikinev and coworkers[183]. An NMR study of the conversion of 3,6,9,10-tetramethyl-9,10-phenathrene-9,10-diol (**298**) into its corresponding ketone (**300**) in superacid medium (HSO_3F–SO_2ClF (1:4) at −78 °C) has demonstrated the formation of carbocation intermediates (**299a**, **299b**) (equation 87).

Many authors have confirmed the above observation under very different experimental conditions and with diols of various structures[184–187].



(87)

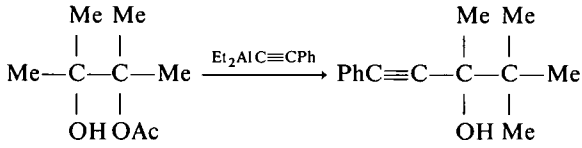
The reactivities of certain migrating groups in the pinacol rearrangement have been studied by means of the *ab initio* molecular orbital method by Nakamura and Osamura[188,189]. Transition-state structures were obtained for 1,2-shifts of hydrogen, methyl, vinyl and cyclopropyl substituents in ethanediol, concerted with dehydration. A kinetic study was undertaken by Herlihy to provide information about the pinacol rearrangement of secondary alkanediols[190,191].

The rearrangement of pinacol with water elimination can primarily be achieved in the presence of mineral acids. Additionally, the first demonstration of a gas-phase pinacol rearrangement has been reported[192] and it has been shown that acid-catalysed rearrangements such as the pinacol–pinacolone rearrangement, which are known to occur in solution, can be simulated in low-energy protonated molecular ions produced by chemical ionization in the gas phase[193].

Pinacol rearrangements have been observed[194] in the mass spectrometry of spontaneous and collision-induced fragmentations of protonated aldehydes and ketones, and collision-induced dissociation and mass-analysed ion-kinetic-energy spectrometry has been used[195,196] to identify the pinacol rearrangements of *cis*- and *trans*-1,2-dimethylcyclopentane-1,2-diols in the gas phase.

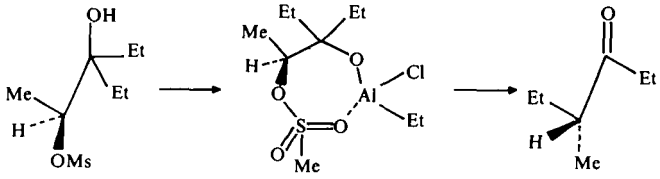
The pinacol rearrangement was recently observed in the case of methyl-substituted 1,2-diols on zeolites[197,198] and montmorillonites[199,200]. Baklan and coworkers reported that rearrangements involving six-electron transition states, such as the pinacol rearrangement, are catalysed by liquid bromine too[201]. Bartók and Molnár[202] found that 3-ethylpentane-2,3-diol is transformed on copper catalysts to 4-methylhexan-3-one via 1,2-ethyl migration, this being the first experimental observation of a 1,2-shift isomerization on copper.

Organoaluminium compounds (R_3Al) cause the rearrangement of *vic*-diol monoacetates, when R is taken up as a nucleophile on the resulting carbonyl carbon[203] (equation 88).



(88)

Organoaluminium reagents have been used to promote the migration of an alkyl group to an optically active migration terminus in the synthesis of optically pure α-alkyl ketones such as the ant alarm pheromone (**302**)[204]. This process probably proceeds *via* **301** (equation 89).

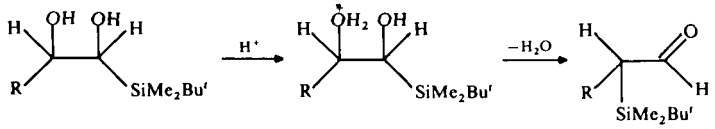


(89)

(**301**) (**302**)

A similar methodology has been used for the highly enantio and diastereo-controlled syntheses of the chiral pheromones eldanolide and protomycinolide-IV[205,206].

Evidence has been presented[207] to show that α,β-dihydroxy silanes (**303**) can undergo a 1,2-silyl group migration (silapinacol rearrangement) under certain conditions, to afford silyl aldehydes and ketones (**304**), which can be isolated in high yields in the case of *t*-butyldimethysilyl compounds (equation 90).

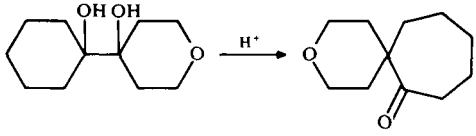


(90)

(**303**) (**304**)

A study of isomeric 1-methylcyclohexane-1,2-diols revealed that the isomers undergo transformation in the same way, but the rearrangement rates are markedly dependent on the stereochemical features of the diol: the *trans* diol rearranges more rapidly than the *cis* isomer[208].

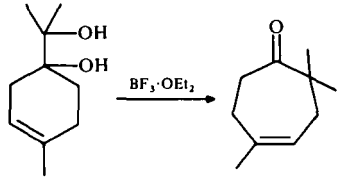
Mundy and coworkers established that, as a result of the heteroatom dipole effect, **306** was obtained as the unexpected product in the pinacol rearrangement of **305**[209] (equation 91).



(91)

(**305**) (**306**)

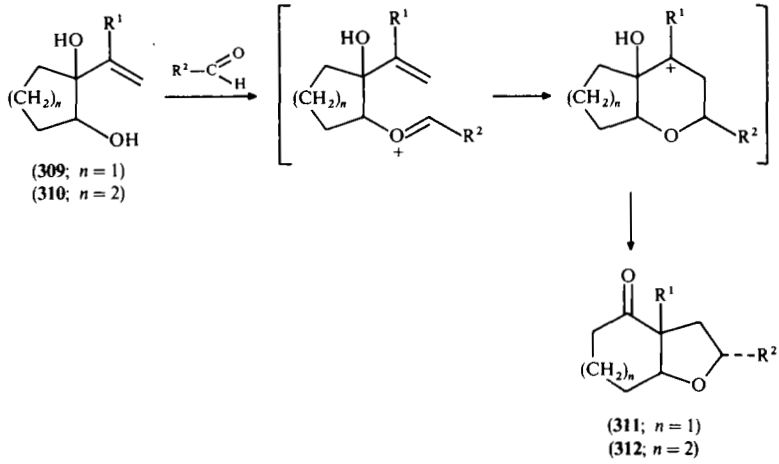
An interesting Lewis acid-catalysed pinacol rearrangement has been used in a short synthesis of karahanaenone (**308**) from the key intermediate **307**[210] (equation 92).



(92)

(**307**) (**308**)

A Prins-cyclization pinacol rearrangement was recently discovered by Herrinton and coworkers[211]. A variety of substituted *sic*-fused octahydrobenzofurans (**311**) and cycloheptatetrahydrofurans (**312**) were prepared in stereo-controlled fashion by the acid-promoted rearrangement of acetals derived from 1-alkenyl-2-hydroxycyclohexalols (**309**) and 1-alkenyl-2-hydroxycycloheptanols (**310**). These transformations are considered to occur by a Prins-cyclization pinacol rearrangement sequence as outlined in equation 93.



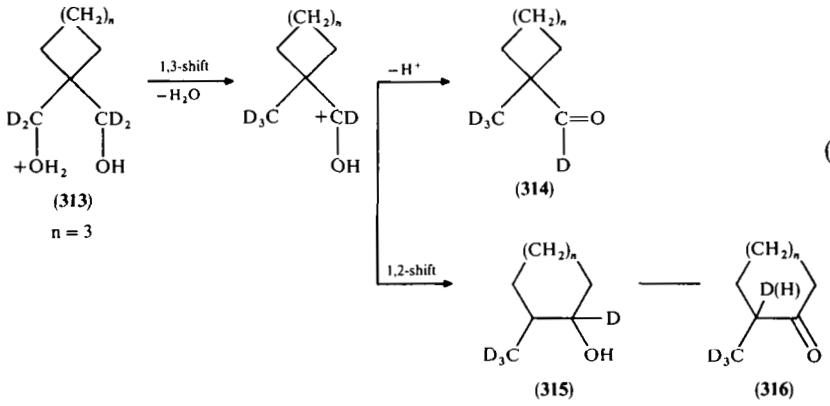
(**309**; $n = 1$)
(**310**; $n = 2$)

(**311**; $n = 1$)
(**312**; $n = 2$)

(93)

B. 1,3-Diols

A recent study described[212] the sulphuric acid-catalysed rearrangement of 1,1-bis-(hydroxymethyl)cycloalkanes (**313**) to isomeric carbonyl compounds, formed mainly with ring enlargement. A correlation was observed between the relative stabilities of carbenium ions and cycloalkane rings, datermining the product distributions. The transformation of 1,1-bis(dideuteromethyl)cyclohexane (**313**; $n = 3$) under kinetic control furnished evidence of a 1,3-hydride shift, yielding the labelled products **314**, **315** and **316** (equation 94).



(**313**)
n = 3

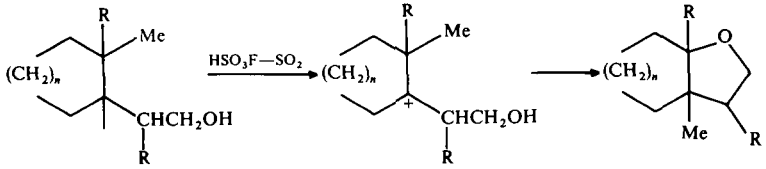
(**314**)

(**315**)

(**316**)

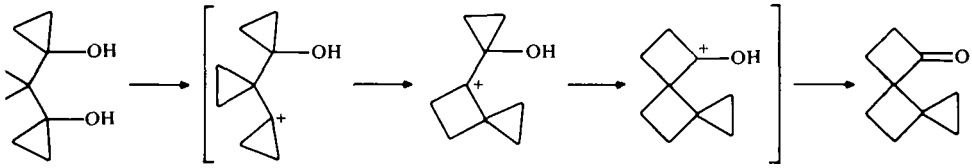
(94)

The formation of ethers (**319**) in superacids by interaction of a primary hydroxy group with a carbocation centre (**318**) has been investigated in a studies of the cyclization of suitable substrates (**317**), the cyclization being accompanied by a 1,2-methyl shift[213,214] (equation 95).



(317) n = 1, 2 (318) (319) (95)

An interesting cascade-pinacol rearrangement was observed in the case of 1,1-bis-(1-hydroxycyclopropyl)cyclopropane (**320**), which undergoes conversion in the presence of triphenylphosphine-bromine to dispiro(2.0.3.2)nonanone-5 (**321**)[215] (equation 96).

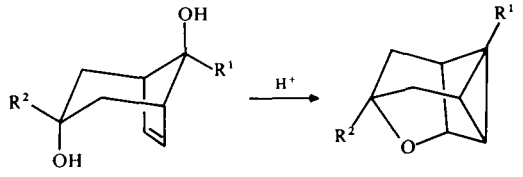


(320) (321) (96)

C. 1,4-Diols

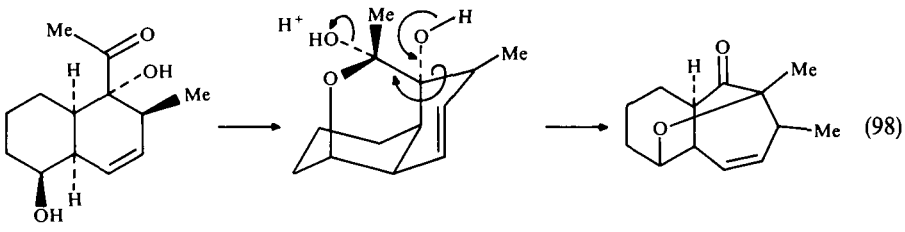
The dehydration of 1,4-diols on the action of acids is frequently accompanied by the formation of cyclic ethers.

The acid-catalysed rearrangement of *anti*-tricyclo(4.2.1.1^{2,5})deca-3,7-diene-9,10-diol **322** to **323** has been shown to proceed through concomitant electrophilic and nucleophilic attack on an alkene by an incipient carbocation and the remaining alcohol function[216] (equation 97).



(322) (323) (97)

Cyclic ether formation by dehydration of *cis*-fused 5-acetyl-1,5-dihydroxyoctahydronaphthalene (**324**) has been demonstrated to occur with 1,2-shift of the hemiacetal **325** to give 12-oxatricyclo(5.4.1^{1,7}.0^{3,8})dodecane (**326**)[217] (equation 98).



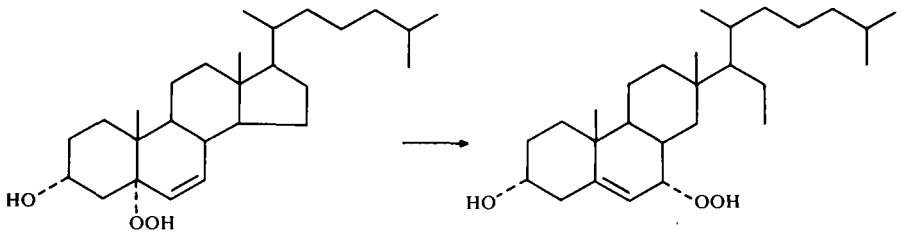
(324) (325) (326) (98)

IV. REARRANGEMENTS OF PEROXIDES

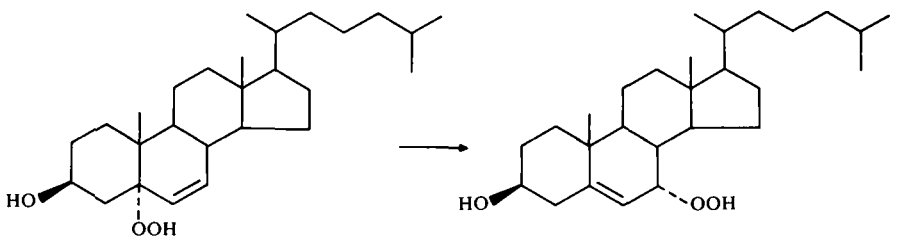
A. Rearrangements of Hydroperoxides

Hydroperoxides are the principal reaction products of the autoxidation of organic compounds with abstractable hydrogen atoms.

Davies and coworkers found that the overall rate of rearrangement of the hydroperoxides is strongly dependent on the molecular structure[218]. Rearrangements that occur within a six-membered ring, such as those of **327** and **329**, generally occur readily. It might be expected that in the hydroperoxide **327** derived from epicholesterol, in which the groups at positions 3 and 5 are both axial, the rearrangement might occur more rapidly than in the parent system (**329**) because of the destabilizing steric interactions (equation 99).



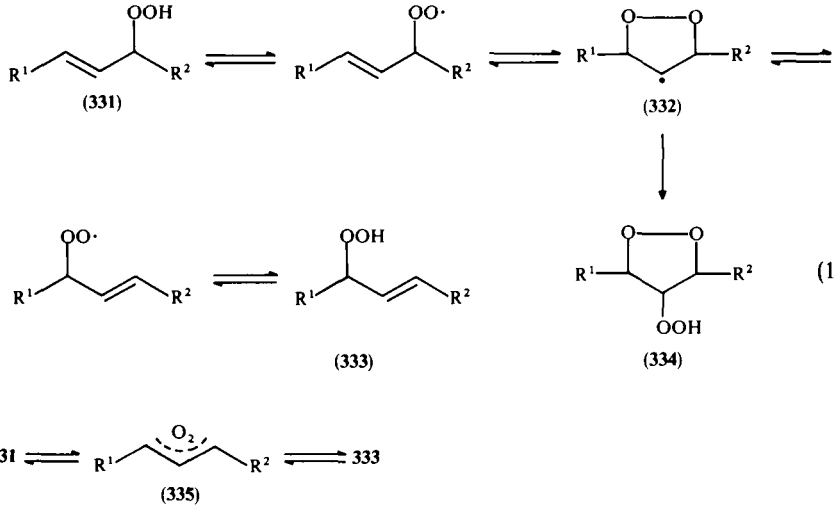
(327) (328) (99)



(329) (330)

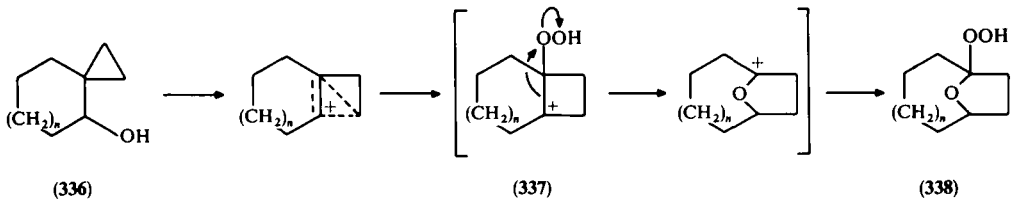
Porter and Zuraw reported that the intermediate (**332**) previously proposed for the allylic rearrangement of hydroperoxides has been trapped with oxygen[219]. The report mentions that the interconversion **331** → **332** → **333** does not occur at an appreciable

rate. It seems reasonable to suggest that **331** and **333** may interconvert by β-scission of the peroxyl radicals, to give a hypothetical intermediate involving an association of free allylic radicals and molecular oxygen (**335**), as is the case for pentadienyl radicals[220-222] (equation 100).



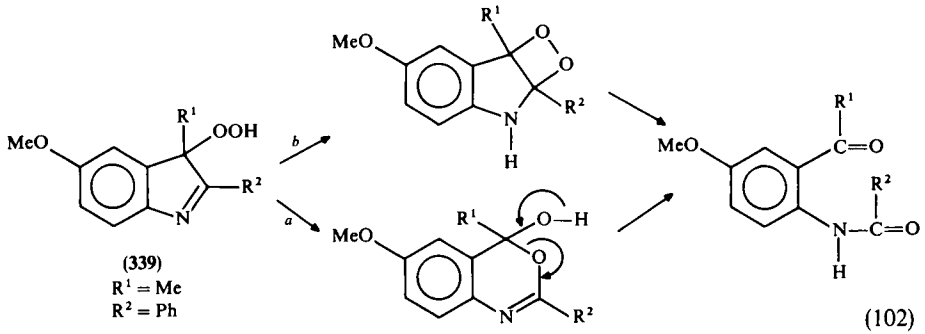
(100)

A novel hydrogen peroxide-mediated ring expansion that is suitable for the synthesis of medium- to large-ring oxybicyclic compounds was recently discovered[223,224]. The rearrangement involves the solvolysis of spiro cyclopropyl carbinols (**336**) in THF–H_2O_2. The reaction proceeds through solvolytically generated cyclobutyl hydroperoxides (**337**) that undergo facile Criegee-type rearrangements, affording oxa-bridged, hydroperoxy hemi-acetals of the corresponding 4-hydroxy ketones (**338**) (equation 101).



(101)

A kinetic study has been performed in an attempt to differentiate between Criegee rearrangement (path *a*) and dioxetane rearrangement (path *b*) mechanisms for the decomposition of 3-(hydroperoxy)indolines (**339**)[225,226]. Under the conditions of this study, the rate constant for dioxetane formation was twice that for the Criegee rearrangement. Even though dioxetane formation involves an intramolecular nucleophilic attack by an α-base, the strain brought about by formation of a four-membered ring and the forcing of an unfavourable eclipsed conformation upon the non-bonding electrons of the peroxide oxygen atoms act against this process (equation 102).

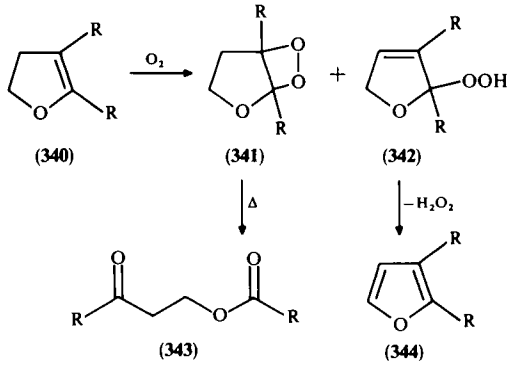


(102)

B. Rearrangements of 1,2-Dioxetanes

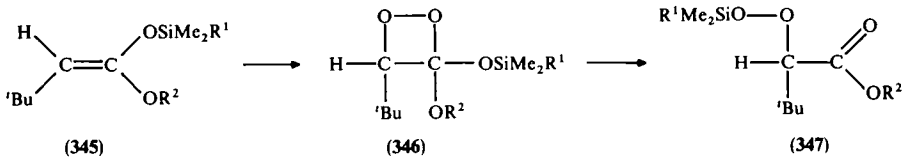
Four-membered ring peroxides are cyclobutane derivatives in which two adjacent methylene units have been replaced by oxygen atoms. The direct addition of $^1O_2$ to an activated double bond results in 1,2-dioxetane.

Singlet oxygen reacts with 4,5-disubstituted-2,3-dihydrofurans (**340**) in non-polar and polar aprotic solvents to yield dioxetanes (**341**) and allylic hydroperoxides (**342**). The dioxetanes decompose slowly with weak chemiluminescence at room temperature, giving the corresponding dicarbonyl compounds (**343**). The endocyclic allylic hydroperoxides arising from the dihydrofurans eliminate H_2O_2 to yield the corresponding furans (**344**)[227] (equation 103).



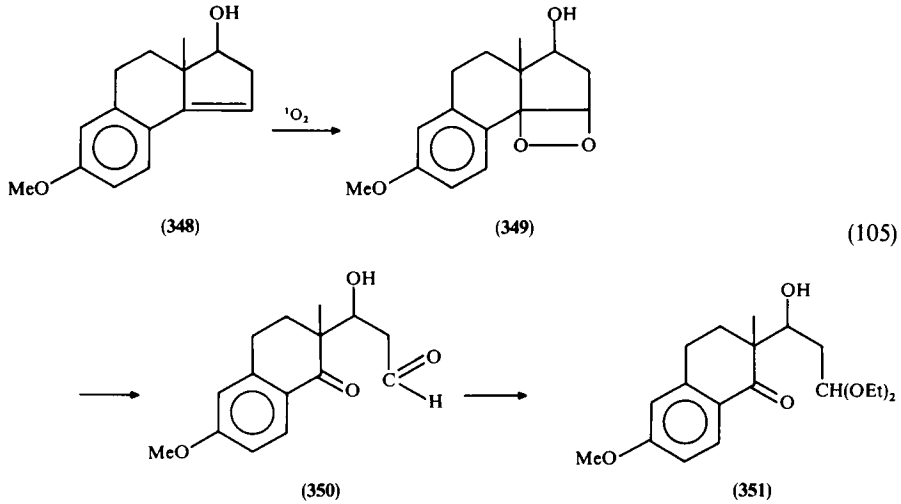
(103)

Adam and Wang found that photooxygenation of silyl ketene acetals (**345**) afforded dioxetanes (**346**), which subsequently underwent secondary reactions to give α-silylperoxy esters (**347**) as rearrangement products[228] (equation 104).



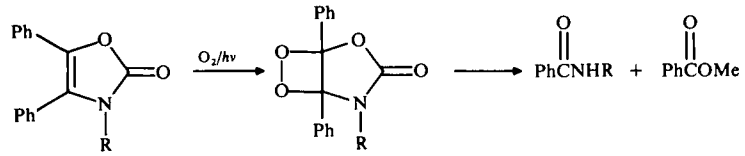
(104)

The formation of the keto acetals (**351**) in the cycloaddition of singlet oxygen to the activated strained double bond of **348** in ethanol has been accounted for in terms of cleavage of dioxetane **349** into **350** and subsequent acetalation with ethanol[229] (equation 105).



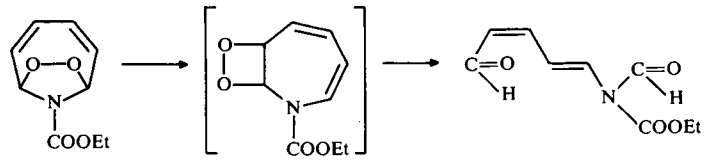
(348) (349) (350) (351) (105)

The heterocycle **352** affords *N*-alkylbenzamide (**354**) and methyl benzoates (**355**) via the postulated dioxetane (**353**) during photolysis in methanol[230] (equation 106).



(352) (353) (354) (355) (106)

Formation of the *N*-formylcarbamate (**358**) in the thermal rearrangement of the (6 + 2) cycloadduct from 1*H*-azepines and singlet oxygen, viz. **356**, has been explained[231] by ring cleavage of an initially formed dioxetane derivative (**357**) (equation 107).



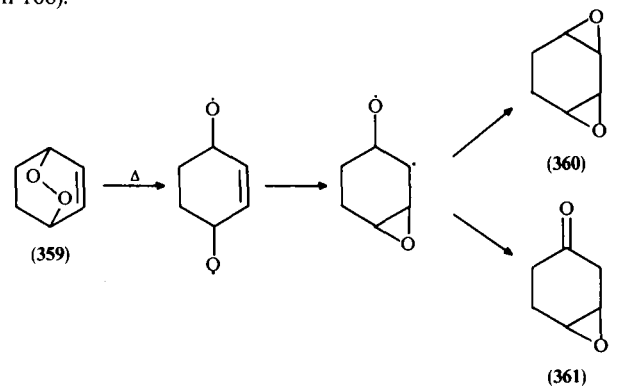
(356) (357) (358) (107)

C. Rearrangements of Endoperoxides

Singlet oxygen reacts with various types of conjugated dienes and aromatic substrates by the Diels–Alder mode of addition. This stereoselective oxygenation of the terminal

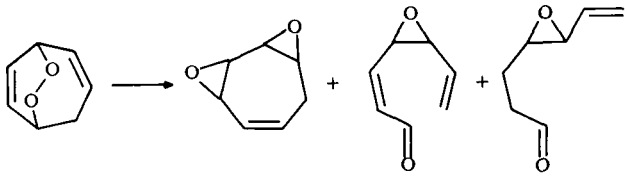
carbons of a 1,3-diene system has found widespread application in the synthesis of endoperoxides.

One of the common reactions of unsaturated bicyclic endoperoxides is the thermal cleavage of the weak oxygen–oxygen bond, followed by addition of the oxygen radicals to the adjacent double bond to give diepoxides (**360**) with *syn* configuration. However, in strained molecules and other cases, thermolysis is always accompanied by side-reactions. One of these is the formation of epoxy ketones[232,233]. Carless and coworkers[234] have obtained direct evidence that β,γ-epoxy ketones (**361**) are often formed as major products of the thermolysis or photolysis of unsaturated bicyclic endoperoxides (**359**) (equation 108).



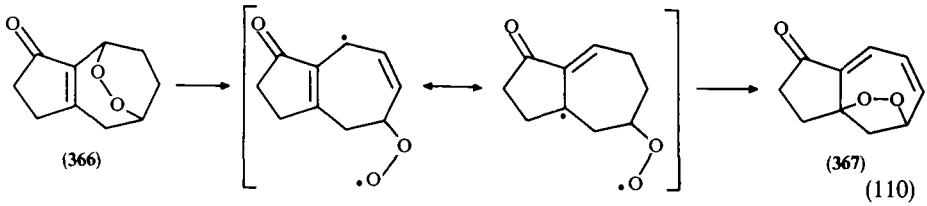
(359) (360) (361) (108)

Foote and coworkers[235] have reported that unsaturated bicyclic endoperoxides can be conveniently converted into the corresponding diepoxides by using cobalt(II) tetraphenylpophyrin (CoTPP). More recently, Balci and coworkers[236–238] successfully applied this reaction to unsaturated bicyclic endoperoxides with strained and perturbed diene moieties. They found that the CoTPP-catalysed reaction of the cycloheptatriene 1,4-diepoxide (**362**) led to diepoxide (**363**), and in addition a mixture of two isomeric open-chain aldehydes (**364**, **365**) (equation 109).



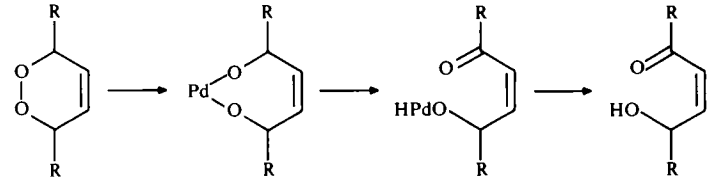
(362) (363) (364) (365) (109)

The CoTPP-catalysed thermolyses of endoperoxides derived from 2,3-dihydro-1(2*H*)-azulene (**366**) have been studied, and a new endoperoxide–endoperoxide rearrangement, **368** → **367**, has been discovered[239] (equation 110).



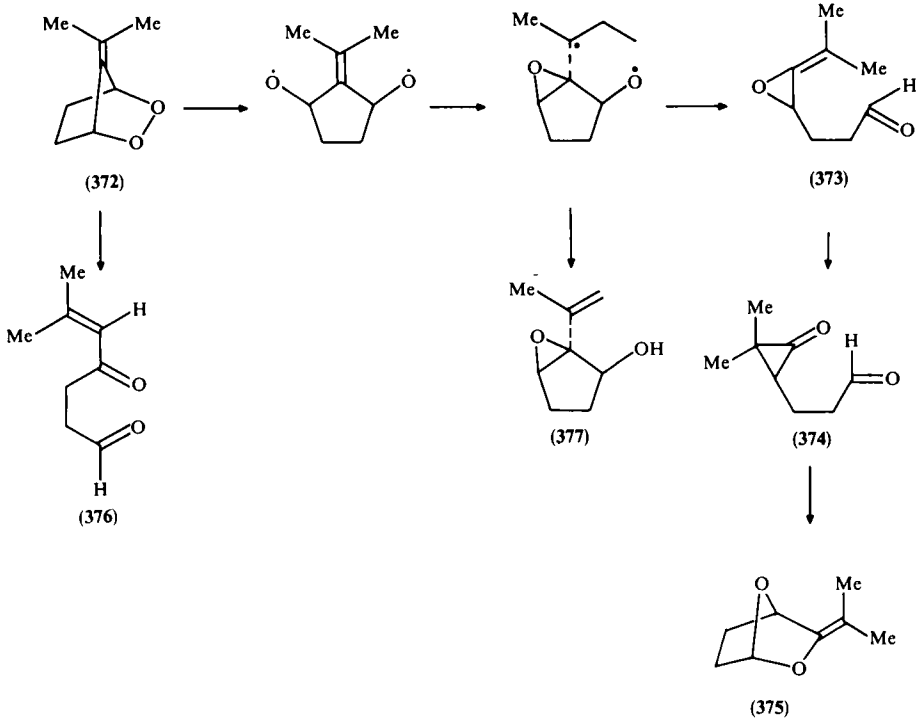
(366) (367) (110)

One interesting Pd(O)-catalysed conversion, that of epiperoxide to hydroxyenone, **368** → **371**, was interpreted in terms of a Pd(O)/Pd(II) exchange mechanism by Suzuki and coworkers[240]. Oxidative addition of the —O—O— bond of **368** to the zero-valent Pd atom produced the cyclic structure **369**, and subsequent elimination of a PdH element, giving **370**, followed by reductive elimination of Pd(O) species, led ultimately to the hydroxyenone (**371**) (equation 111).



(368) (369) (370) (371) (111)

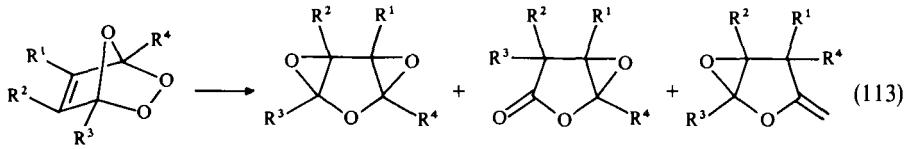
Thermolysis of the endoperoxide derived from 6,6-dimethylfulvene, viz. **372**, has been observed to yield a mixture of **375**, **376** and **377**. An attractive rationalization of the formation of these compounds is shown in equation 112. In particular, the formation of **375** presumes an intramolecular 1,3-dipolar cycloaddition of an allene oxide or a cyclopropanone, as in **373** and **374**, to the aldehyde functionality[241].



(372) (373) (376) (377) (374) (375)

(112)

The formation, thermal stability and modest thermal rearrangement of the 2,5-peroxides of 2,5-substituted and unsubstituted furans (**378**) were reported by Graziano and coworkers[242,243]. In polar solvents, the main product of thermal rearrangement is the *cis* diepoxide (**379**), accompanied by the epoxyfuranones (**380, 381**). These rearrangements are thought to proceed via a concerted process, although no distinction can be made between them and rearrangements via diradicals. In basic solvents, the rearrangements are explained by assuming ion pairs as intermediates (equation 113).



(**378**) (**379**) (**380**) (**381**) (113)

V. REFERENCES

1. A. W. Murray, in *Organic Reaction Mechanisms* (Eds. A. C. Knipe and W. E. Watts), Wiley, Chichester, 1980, pp. 548–584; 1981, pp. 500–533; 1982, pp. 422–456; 1983, pp. 459–491; 1984, pp. 476–511; 1985, pp. 496–524; 1986, pp. 479–509; 1987, pp. 513–556; 1988, pp. 609–646.
2. Y. Pocker, in *Molecular Rearrangements* (Ed. P. de Mayo), Interscience, New York, 1963, pp. 1–25.
3. P. B. D. de la Mare, in *Molecular Rearrangements* (Ed. P. de Mayo), Interscience, New York, 1963, pp. 27–110.
4. J. A. Berson, in *Molecular Rearrangements* (Ed. P. de Mayo), Interscience, New York, 1963, pp. 111–232.
5. R. Breslow, in *Molecular Rearrangements* (Ed. P. de Mayo), Interscience, New York, 1963, pp. 233–294.
6. H. Kropf and M. Maher-Detweiler, in *Methoden der Organischen Chemie* (Houben-Weyl), Bd. VI/lb, Georg Thieme Verlag, Stuttgart, 1984, pp. 555–573.
7. E. N. Marvell and W. Whalley, in *The Chemistry of the Hydroxyl Group* (Ed. S. Patai), Interscience, London, 1971, pp. 719–754.
8. M. Bartók and Á. Molnár, in Supplement E: *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues* (Ed. S. Patai), Wiley, Chichester, 1980, pp. 721–760.
9. J. A. Howard, in *The Chemistry of Peroxides* (Ed. S. Patai), Wiley, Chichester, 1983, pp. 235–258.
10. W. Adam, in *The Chemistry of Peroxides* (Ed. S. Patai), Wiley, Chichester, 1983, pp. 829–920.
11. C.-E. Low and R. M. Roberts, *J. Org. Chem.*, **38**, 1909 (1973).
12. R. M. Roberts, *J. Org. Chem.*, **38**, 1388 (1973).
13. R. S. Prasad and R. M. Roberts, *J. Org. Chem.*, **56**, 2998 (1991).
14. C. J. Barrow, S. T. Bright, J. M. Coxon and P. J. Steel, *J. Org. Chem.*, **54**, 2542 (1989).
15. A. G. Sakhabutdinov, A. G. Usmanova, P. A. Frolov, D. F. Kushnarev and D. F. Schmidt, *Zh. Org. Khim.*, **24**, 1610 (1988).
16. R. M. Roberts and A. A. Khalaf, *Friedl-Crafts Alkylation Chemistry*, Marcel Dekker, New York, 1984.
17. S. T. Bright, J. M. Coxon and P. J. Steel, *J. Org. Chem.*, **55**, 1338 (1990).
18. R. C. Bansal, C. E. Browne, E. J. Eisenbraun and J. S. Thomson, *J. Org. Chem.*, **53**, 452 (1988).
19. C. J. Barrow, S. T. Bright, J. M. Coxon and P. J. Steel, *J. Org. Chem.*, **54**, 2542 (1989).
20. D. Nasipuri and I. De Dalal, *J. Chem. Soc., Perkin Trans. 1*, 19 (1976).
21. B. K. Banik, S. Ghosh and U. R. Ghatak, *Tetrahedron*, **44**, 6947 (1988).
22. B. R. Davis, S. J. Johnson and P. D. Woodgate, *Aust. J. Chem.*, **40**, 1283 (1987).
23. B. R. Davis, M. G. Hinds and S. J. Johnson, *Aust. J. Chem.*, **38**, 1815 (1985).
24. B. W. Axon, B. R. Davis and P. D. Woodgate, *J. Chem. Soc., Perkin Trans. 1*, 2956 (1981).
25. C. J. Barrow, S. T. Bright, J. M. Coxon and P. J. Steel, *J. Org. Chem.*, **52**, 5300 (1987).
26. D. C. Kleinfelter and P. v. R. Schleyer, *J. Org. Chem.*, **26**, 3740 (1961).

27. H. Duddeck and D. Rosenbaum, *J. Org. Chem.*, **56**, 1700 (1991).
28. H.Duddeck, H.-T. Feuerhelm and G. Snatzke, *Tetrahedron Lett.*, 829 (1979).
29. H. Duddeck and D. Rosenbaum, *J. Org. Chem.*, **56**, 1707 (1991).
30. J. L. Fry and J. A. Saba, *Tetrahedron Lett.*, **23**, 1743 (1982).
31. J. A. Saba and J. L. Fry, *J. Am. Chem. Soc.*, **105**, 533 (1983).
32. H. Duddeck, M. A. McKervey and D. Rosenbaum, *Tetrahedron Lett.*, **31**, 4061 (1990).
33. I. T. Badejo, H. Choi, C. M. Hockensmith, R. Karaman, A. A. Pinkerton and J. L. Fry, *J. Org. Chem.*, **56**, 4688 (1991).
34. I. T. Badejo, H. Choi and J. L. Fry, *Tetrahedron Lett.*, **29**, 4787 (1988).
35. F. Balata, A. R. D. Jacono and A. Gamisacorta, *J. Org. Chem.*, **48**, 566 (1983).
36. R. P. Kirchen and T. S. Sorensen, *J. Am. Chem. Soc.*, **100**, 1487 (1978).
37. P. Alessandri, F. De Angelis and A. Gambacorta, *Tetrahedron*, **41**, 2831 (1985).
38. J. C. Rees and D. Wittaker, *J. Chem. Soc., Perkin Trans. 2*, 948 (1981).
39. J. C. Rees and D. Whittaker, *J. Chem. Soc., Perkin Trans. 2*, 953 (1981).
40. D. P. Kelly, D. R. Leslie and B. D. Smith, *J. Am. Chem. Soc.*, **106**, 687 (1987).
41. K. Hiroi, H. Nakamura and T. Anzai, *J. Am. Chem. Soc.*, **109**, 1249 (1987).
42. M. Vincens, C. Dumont and M. Vidal, *Bull. Soc. Chem. Fr.*, 59 (1984).
43. J. T. Carey and P. Helquist, *Tetrahedron Lett.*, **29**, 1243 (1988).
44. J. T. Carey, C. Knors and P. Helquist, *J. Am. Chem. Soc.*, **108**, 8313 (1986).
45. N. S. Narasimhan and P. A. Patil, *Tetrahedron Lett.*, **27**, 5133 (1986).
46. P. Dowd, R. Schappert and P. Garner, *Tetrahedron Lett.*, **23**, 3 (1982).
47. M. Lajunen and H. Lyytikäinen, *Acta Chem. Scand.*, **35A**, 131 (1991).
48. H. Nisshiyama, K. Itagaki, N. Osaka and K. Itoh, *Tetrahedron Lett.*, **23**, 4103 (1982).
49. L. Somekh and A. Shanzer, *J. Am. Chem. Soc.*, **104**, 5836 (1982).
50. M. Karpf and C. Djerassi, *J. Am. Chem. Soc.*, **103**, 302 (1981).
51. A. Fadel and Salaün, *Tetrahedron*, **41**, 413 (1985).
52. A. Fadel and J. Salaün, *Ttrahedron*, **41**, 1267 (1985).
53. L. Fitjer, M. Giersig, W. Clegg, N. Schormann and G. M. Scheldrick, *Tetrahedron Lett.*, **24**, 5351 (1983).
54. L. Fitjer, D. Wehle, M. Noltemeyer, E. Egert and G. M. Scheldrick, *Chem. Ber.*, **117**, 203 (1984).
55. L. Fitjer, W. Kühn, U. Klages, E. Egert, W. Clegg, N. Schormann and G. M. Scheldrick, *Chem. Ber.*, **117**, 3075 (1984).
56. E. Lee-Ruff, A. C. Hopkins, H. Kazarians-Moghaddam, B. Gupta and M. Katz, *Can. J. Chem.*, **60**, 154 (1982).
57. D. Sengupta and R. V. Venkateswaran, *J. Chem. Soc., Chem. Commun.*, 1638 (1986).
58. E. Leef-Ruff and F. J. Ablenas, *Can. J. Chem.*, **65**, 1663 (1987).
59. K. Avasthi and P. G. Salomon, *J. Org. Chem.*, **51**, 2556 (1986).
60. Y. Tobe, J.-i. Sato, T. Sorori, K. Kakiuchi and Y. Odaira, *Tetrahedron Lett.*, **27**, 2905 (1986).
61. W. Kirmse, R. Siegfried and H.-J. Wroblowsky, *Chem. Ber.*, **116**, 1880 (1983).
62. K. Banert, W. Kirmse and H.-J. Wroblowsky, *Chem. Ber.*, **116**, 2474 (1983).
63. W. Kirmse and H. J. Wroblowsky, *Chem. Ber.*, **116**, 2485 (1983).
64. K. Avasthi and R. G. Salomon, *J. Org. Chem.*, **51**, 2556 (1986).
65. K. Ogura, M. Yamashita, M. Suzuki and G. Tsuchihashi, *Chem. Lett.*, 93 (1982).
66. B. C. Ranu, D. C. Sarkar and M. K. Basu, *Tetrahedron*, **45**, 3107 (1989).
67. L. Fitjer, M. Majewski and A. Kanschick, *Tetrahedron Lett.*, **29**, 1263 (1988).
68. J. E. Baldwin and T. C. Barden, *J. Am. Chem. Soc.*, **105**, 6656 (1983).
69. N. Takaishi, Y. Inamoto and K. Aigami, *J. Org. Chem.*, **45**, 2254 (1980).
70. T. G. Dekker, D. W. Oliver and A. Venter, *Tetrahedron Lett.*, **21**, 3101 (1980).
71. K. A. Mead, K. Mackenzie and P. Woodward, *J. Chem. Soc., Perkin Trans. 2*, 571 (1982).
72. R. Cernic, G.-A. Mills and I. Watt, *J. Chem. Soc., Perkin Trans. 2*, 361 (1982).
73. D. Spitzner, W. Weber and W. Kraus, *Tetrahedron Lett.*, **23**, 2179 (1982).
74. N. G. Kozlov, L. A. Popova and G. V. Nesterov, *Zh. Obshch. Khim.*, **56**, 1562 (1986).
75. V. V. Voronenkob, I. V. Dzuba, S. I. Krukov and U. U. Dsankin, *Zh. Org. Khim.*, **26**, 2580 (1990).
76. M. Banciu, Phan-Le-Thuy, M. Elian, C. Draghici and E. Cioranescu, *Rev. Roum. Chim.*, **26**, 115 (1981).
77. R. Knorr, E. Lattke and E. Räpple, *Justus Liebigs Ann. Chem.*, 1207 (1980).

78. C. Bert, L. Greci and M. Poloni, *J. Chem. Soc., Perkin Trans. 1*, 1610 (1981).
79. C. Mackay and R. D. Waigh, *J. Chem. Soc., Chem. Commun.*, 793 (1982).
80. I. A. Cliffe, K. Heatherington and A. C. White, *J. Chem. Soc., Perkin Trans. 1*, 1975 (1991).
81. T. Fujita, S. Watanabe, K. Suga, Y. Higuchi and T. Sotoguchi, *J. Org. Chem.*, **49**, 1975 (1984).
82. T. Fujita, S. Watanabe, T. Sotoguchi, K. Ogawa and K. Sugahara, *Aust. J. Chem.*, **39**, 799 (1986).
83. D. R. Williams, Y. Harigaya, J. L. Moore and A. D'sa, *J. Am. Chem. Soc.*, **106**, 2641 (1984).
84. R. Bergman and G. Magnusson, *J. Org. Chem.*, **51**, 212 (1986).
85. Y. Fujikura, N. Takaishi and Y. Inamoto, *Tetrahedron*, **37**, 4465 (1981).
86. R. Dasgupta and R. Ghatak, *Tetrahedron Lett.*, **26**, 1581 (1985).
87. W. Francke and W. Reith, *Tetrahedron Lett.*, **22**, 2029 (1981).
88. D. H. G. Crout and D. L. Rathbone, *J. Chem. Soc., Chem. Commun.*, 290 (1987).
89. F. J. Jäggi and C. Ganter, *Helv. Chim. Acta*, **63**, 2087 (1980).
90. A. V. Fedorenko and N. L. Dovgan, *Vestn. Kiev, Politekh. Inst., (ser): Khim. Mashinostr. Tekhnol.*, **20**, 11 (1983).
91. D. Labar, J. L. Laboureur and A. Krief, *Tetrahedron Lett.*, **23**, 983 (1982).
92. D. Labar and A. Krief, *J. Chem. Soc., Chem. Commun.*, 564 (1982).
93. L. A. Paquette, J. R. Peterson and R. J. Ross, *J. Org. Chem.*, **50**, 5200 (1985).
94. A. Krief and J. L. Laboureur, *J. Chem. Soc., Chem. Commun.*, 702 (1986).
95. H. M. J. Gillisen, P. Schipper and H. M. Buck, *Recl. Trav. Chim. Pays-Bas*, **99**, 346 (1980).
96. D. S. Crumrine, M. L. Curtin and H. Iwamura, *J. Org. Chem.*, **55**, 1076 (1990).
97. Y. Tobe, M. Ohtani, K. Kakiuchi and Y. Odaira, *J. Org. Chem.*, **48**, 5114 (1983).
98. K. Kakiuchi, T. Tsuguru, M. Takeda, I. Wakaki, Y. Tobe and Y. Odaira, *J. Org. Chem.*, **50**, 488 (1985).
99. P. E. Eaton, P. G. Jobe and K. Nyi, *J. Am. Chem. Soc.*, **102**, 6636 (1980).
100. H. Duddeck, V. Wiskamp and D. Rosenbaum, *J. Org. Chem.*, **46**, 5332 (1981).
101. T. Momose, I. Itooka, T. Nishi, M. Uchimoto, K. Ohnishi and O. Muaroka, *Tetrahedron*, **43**, 3713 (1987).
102. K.-i. Hirao, Y. Ohuchi and O. Yonemitsu, *J. Chem. Soc., Chem. Commun.*, 99 (1982).
103. L. A. Paquette and D. W. Balogh, *J. Am. Chem. Soc.*, **104**, 774 (1982).
104. H. Jendralla, K. Jelich, G. DeLucca and L. A. Paquette, *J. Am. Chem. Soc.*, **108**, 3731 (1986).
105. L. A. Paquette, L. Waykole, H. Jendralla and C. E. Cottrell, *J. Am. Chem. Soc.*, **108**, 3739 (1986).
106. S. Bhattacharya, N. A. Mandal, S. R. R. Chaudhuri and A. Chatterjee, *Tetrahedron Lett.*, **25**, 3007 (1984).
107. P. Köll, H.-G. John and J. Kopf, *Justus Liebigs Ann. Chem.*, 639 (1982).
108. R. S. Ward, A. Pelter, I. R. Jack, P. Satyanarayana, S. V. G. Rao and P. Subrahmanyam, *Tetrahedron Lett.*, **22**, 4111 (1981).
109. P. G. Sammets, L. J. Street and R. J. Whitby, *J. Chem. Soc., Perkin Trans. 1*, 281 (1986).
110. L. V. Román, J. D. Hernández, R. E. del Rio and M. A. Bucio, *J. Org. Chem.*, **56**, 1938 (1991).
111. G. Mehta, S. K. Kapoor, B. P. Singh, M. S. Nair, T. S. Cameron and W. Tacreiter, *J. Org. Chem.*, **50**, 3234 (1985).
112. G. Fráter, *J. Chem. Soc., Chem. Commun.*, 521 (1982).
113. K. Hayasaka, T. Ohtsuka, H. Shirahama and T. Natsumoto, *Tetrahedron Lett.*, **26**, 873 (1985).
114. S. P. Vaidya and U. R. Nayak, *Indian J. Chem.*, **25B**, 40 (1986).
115. R. T. Reddy and U. R. Nayak, *Indian J. Chem.*, **25B**, 793 (1986).
116. M. Ue, K. Kobiro, K. Kakiuchi, Y. Tobe and Y. Odaira, *Chem. Lett.*, 1903 (1987).
117. R. Capon, E. L. Ghisalberti, P. Jefferies, B. W. Skelton and A. H. White, *Tetrahedron*, **37**, 1613 (1981).
118. J. R. Hanson, P. B. Hitchcock and B. L. Yeoh, *J. Chem. Soc., Perkin Trans. 1*, 639 (1986).
119. A. S. R. Anjaneyulu and A. V. R. Prasad, *Indian J. Chem.*, **20B**, 443 (1981).
120. A. S. R. Anjaneyulu and A. V. R. Prasad, *Indian J. Chem.*, **20B**, 988 (1981).
121. A. S. R. Ajnaneyulu and M. N. Rao, *Indian J. Chem.*, **19B**, 634 (1980).
122. A. S. R. Anjaneyulu, M. N. Rao, A. Sree and V. S. Murty, *Indian J. Chem.*, **19B**, 735 (1980).
123. A. S. R. Anjaneyulu, V. Anjaneyulu, K. H. Prasad, G. S. Rao and P. Suryanarayana, *Indian J. Chem.*, **22B**, 1179 (1983).
124. A. Kasal, *Collect. Czech. Chem. Commun.*, **49**, 892 (1984).
125. S. Stiver and P. Yates, *Tetrahedron Lett.*, **25**, 3289 (1984).
126. P. Kočovský and F. Turecek, *Tetrahedron Lett.*, **22**, 2699 (1981).

127. H. Surinome, A. Furusaki, K. Kato, N. Maeda and F. Yonebayashi, *J. Chem. Soc., Perkin Trans. 1*, 236 (1981).
128. A. W. Bridge, G. A. Morrison and N. F. Wooster, *J. Chem. Soc., Chem. Commun.*, 132 (1986).
129. M. Y. Shandala, R. G. Salih and A. M. Jamel, *Iraqi J. Sci.*, **23**, 68 (1982).
130. P. C. Doolan, P. H. Gore, R. Hollingworth, D. N. Waters, J. Al-Ka'bi and J. A. Farooqi, *J. Chem. Soc., Perkin Trans. 2*, 501 (1986).
131. T. Hosogai, Y. Fujita, Y. Ninagawa and T. Nishida, *Chem. Lett.*, 357 (1982).
132. A. Uchieda and K. Hata, *J. Mol. Catal.*, **15**, 11 (1982).
133. A. P. Kozikowski and P. Park, *J. Org. Chem.*, **49**, 1674 (1984).
134. F. E. Ziegler and B. H. Jaynes, *Tetrahedron Lett.*, **26**, 5875 (1985).
135. S. Achab, J.-P. Cosson and B. C. Das, *J. Chem. Soc., Chem. Commun.*, 1040 (1984).
136. J. W. Barton, J. A. K. Howard, M. K. Sheferd and A. M. Stringer, *J. Chem. Soc., Perkin Trans. 1*, 2443 (1987).
137. I. Nagakura, D. N.-H. Savary and M. Schlosser, *Helv. Chim. Acta*, **63**, 1257 (1980).
138. M. R. Gravestock, D. R. Morton, S. G. Boots and W. S. Johnson, *J. Am. Chem. Soc.*, **102**, 800 (1980).
139. A. B. Turner, *J. Chem. Soc., Chem. Commun.*, 771 (1984).
140. J. R. Hanson and P. B. Reese, *Tetrahedron Lett.*, **24**, 303 (1983).
141. J. R. Hanson and P. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, 331 (1985).
142. K. S. Kyler and D. S. Watt, *J. Am. Chem. Soc.*, **105**, 619 (1983).
143. V. K. Aggarwal and S. Warren, *Tetrahedron Lett.*, **28**, 1925 (1987).
144. K. S. Kyler, A. Bashir-Hashemi and D. S. Watt, *J. Org. Chem.*, **49**, 1084 (1984).
145. W. L. Brown and A. G. Fallis, *Can. J. Chem.*, **65**, 1828 (1987).
146. C. V. Asokan, H. Ila and H. Junjappa, *Tetrahedron Lett.*, **26**, 1087 (1985).
147. F. Sato, Y. Tanaka and H. Kanbara, *J. Chem. Soc., Chem. Commun.*, 1024 (1983).
148. I. Matsuda, S. Sato and Y. Izumi, *Tetrahedron Lett.*, **24**, 2787 (1983).
149. S. Sato, I. Matsuda and Y. Izumi, *Tetrahedron Lett.*, **24**, 3855 (1983).
150. S. Sato, H. Okada, I. Matsuda and Y. Izumi, *Tetrahedron Lett.*, **25**, 769 (1984).
151. P. S. Brown, A. B. McElroy and S. Warren, *Tetrahedron Lett.*, **26**, 249 (1985).
152. E. Öhler and E. Zbiral, *Synthesis*, 357 (1991).
153. W. Smadja, J. M. Valery, G. Ville and J. M. Bernassan, *J. Mol. Catal.*, **30**, 389 (1985).
154. H. Alper and K. Hachem, *J. Org. Chem.*, **45**, 2269 (1980).
155. J. B. P. Wijnberg, G. Jongedijk and A. Grot, *J. Org. Chem.*, **50**, 2650 (1985).
156. B. Ceskis, A. M. Moiseenkov, T. Y. Rudashevskaya, O. A. Nesmeyanova and A. V. Semenovskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1084 (1982).
157. A. M. Moiseenkov and B. A. Czeskis, *Collect. Czech. Chem. Commun.*, **51**, 1316 (1986).
158. A. M. Moiseenkov, B. A. Czeskis and A. V. Semenovsky, *J. Chem. Soc., Chem. Commun.*, 109 (1982).
159. J. S. Yadav, D. G. Patil, R. R. Krishna, H. P. S. Chawla and S. Dev, *Tetrahedron*, **38**, 1003 (1982).
160. J. A. Miller and G. M. Ullah, *J. Chem. Soc., Chem. Commun.*, 874 (1982).
161. J. B. Lambert, P. D. Finzel and C. A. Belec, *J. Am. Chem. Soc.*, **102**, 3281 (1980).
162. M. B. Erman, I. S. Aulchenko and L. A. Kheifets, *Zh. Org. Khim.*, **16**, 23 (1980).
163. J. J. Janas, E. T. Asirvatham and E. McNelis, *Tetrahedron Lett.*, **26**, 1967 (1985).
164. T. Leapheart and P. Magnus, *J. Chem. Soc., Chem. Commun.*, 1391 (1982).
165. P. A. Wendel, D. A. Holt and S. M. Sieburt, *J. Am. Chem. Soc.*, **105**, 3348 (1983).
166. M. Riediker and J. Schwartz, *J. Am. Chem. Soc.*, **104**, 5842 (1982).
167. P. Yates and T. S. Macas, *Can. J. Chem.*, **66**, 1 (1988).
168. N. K. Bhamare, T. Granger, C. R. John and P. Yates, *Tetrahedron Lett.*, **32**, 4439 (1991).
169. J. M. Brittain, P. B. D. de la Mare and P. A. Newman, *J. Chem. Soc., Perkin Trans. 2*, 32 (1981).
170. S. E. Abdou and A. B. Sakla, *Curr. Sci.*, **49**, 728 (1980).
171. P. A. Bates, E. J. Ditzel, M. P. Hartshorn, H. T. Ing, K. E. Richards and W. T. Robinson, *Tetrahedron Lett.*, **22**, 2325 (1981).
172. M. P. Hartshorn, R. J. Martyn, W. T. Robinson, K. H. Sutton, J. Vaughan and J. M. White, *Aust. J. Chem.*, **36**, 1589 (1983).
173. M. P. Hartshorn, K. H. Sutton and J. Vaughan, *Aust. J. Chem.*, **36**, 2339 (1983).
174. M. P. Hartshorn, B. R. Penfold, K. H. Sutton and J. Vaughan, *Aust. J. Chem.*, **37**, 809 (1984).

175. M. P. Hartshorn, W. T. Robinson, J. Vaughan, J. M. White and A. R. Whyte, *Aust. J. Chem.*, **37**, 1489 (1984).
176. M. P. Hartshorn, W. T. Robinson, K. H. Sutton and J. Vaughan, *Aust. J. Chem.*, **38**, 161 (1985).
177. M. P. Hartshorn, R. J. Martyn, W. T. Robinson, K. H. Sutton, J. Vaughan and J. M. White, *Aust. J. Chem.*, **38**, 1613 (1985).
178. M. P. Hartshorn, J. M. Readman, W. T. Robinson, J. Vaughan and A. R. Whyte, *Aust. J. Chem.*, **38**, 1693 (1985).
179. A. Fischer and N. Mathivanan, *Tetrahedron Lett.*, **29**, 1869 (1988).
180. C. Guyon, P. Boule and J. Lamaire, *Tetrahedron Lett.*, **23**, 1581 (1982).
181. C. G. Castro, J. G. Santos, J. C. Vacárcel and J. A. Valderrama, *J. Org. Chem.*, **48**, 3026 (1983).
182. P. D. Clark, L. K. A. Rahman and R. M. Scrowston, *J. Chem. Soc., Perkin Trans. 1*, 815 (1982).
183. A. V. Chikinev, V. A. Bushmelev, M. M. Shakirov and V. G. Shubin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2804 (1984).
184. V. A. Bushmelev, M. M. Shakirov, B. G. Derendyaev and V. A. Koptyung, *Zh. Org. Khim.*, **15**, 1934 (1979).
185. V. A. Bushmelev, A. V. Chikinev and M. M. Shakirov, *Zh. Org. Khim.*, **18**, 1691 (1982).
186. G. I. Borodkin, E. B. Panova, M. M. Shakirov and V. G. Shubin, *Zh. Org. Khim.*, **19**, 114 (1983).
187. V. A. Bushmelev, M. M. Shakirov, D. M. Brouwer and V. A. Koptyug, *Zh. Org. Khim.*, **15**, 1579 (1979).
188. K. Nakamura and Y. Osamura, *Nippon Kagakukaishi*, 1392 (1989).
189. K. Nakamura and Y. Osamura, *Tetrahedron Lett.*, **31**, 251 (1990).
190. K. P. Herlihy, *Aust. J. Chem.*, **34**, 107 (1981).
191. K. P. Herlihy, *J. Chem. Res. (S)*, 57 (1980); *(M)* 848 (1980).
192. M. Attina, F. Cacace, G. Ciranni and P. Giacomello, *Radiochem. Acta*, **26**, 103 (1979).
193. A. Maquetiau, R. Flammang, M. Flammang-Barbieux, H. Mispreuve, I. Howe and J. H. Beynon, *Tetrahedron*, **36**, 1993 (1980).
194. H. E. Audier, R. Flammang, A. Maquetian and A. Millet, *Nouveau J. Chim.*, **4**, 531 (1980).
195. A. Maquestiau, R. Flammang, M. Flammang-Barbieux, H. Mispreuve, I. Howe and J. H. Beynon, *Adv. Mass Spectrom.*, **8A**, 698 (1980).
196. G. de Petris, P. Giacomello, T. Pricotti, A. Pizzabiocca, G. Renzi and M. Speranza, *J. Am. Chem. Soc.*, **108**, 7491 (1986).
197. Á. Molnár, I. Bucsi and M. Bartók, *Heterogeneous Catalysis and Fine Chemicals* (Eds. M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, C. Montassier and G. Perot), Elsevier, Amsterdam, 1988, pp. 203–210. (Studies in Surface Science and Catalysis, Vol. **41**.)
198. Á. Molnár, I. Bucsi and M. Bartók, *Acta Phys. Chem., Szeged*, **31**, 571 (1985).
199. E. Gutierrez and E. Ruiz-Hitzky, *Mol. Cryst. Liq. Cryst. Inc. Nonlin. Opt.*, **161**, 453 (1988).
200. E. Gutierrez, A. Loupy, G. Bram and E. Ruiz-Hitzky, *Tetrahedron Lett.*, **30**, 945 (1989).
201. V. F. Baklin, L. S. Antipenkova, L. I. Zakharchenko, T. E. Fesenko and V. P. Kukhar, *Dopov. Akad. Nauk Ukr. R.S.R., Ser. B: Geol., Geofiz., Khim. Biol. Nauki*, 31 (1982).
202. M. Bartók and Á. Molnár, *J. Chem. Soc., Chem. Commun.*, 1178 (1980).
203. S. Kanemoto, Y. Morizawa, K. Oshima and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **55**, 3941 (1982).
204. G.-i. Tsuchihashi, K. Tomooka and K. Suzuki, *Tetrahedron Lett.*, **25**, 4253 (1984).
205. K. Suzuki, K. Tomooka, T. Matsumoto, E. Katayama and G.-i. Tsuchihashi, *Tetrahedron Lett.*, **26**, 3711 (1985).
205. K. Suzuki, K. Tomooka, T. Matsumoto, E. Katayama and G.-i. Tsuchihashi, *Tetrahedron Lett.*, **26**, 3711 (1985).
206. K. Suzuki, T. Ohkuma and G.-i. Tsuchihashi, *Tetrahedron Lett.*, **26**, 861 (1985).
207. R. F. Cunico, *Tetrahedron Lett.*, **27**, 4269 (1986).
208. P. Cecchi, R. Cippolini, A. Pizzabiocca, G. Benzi and M. Speranza, *Tetrahedron Lett.*, **44**, 4847 (1988).
209. B. P. Mundy, Y. Kim and R. J. Warnet, *Heterocycles*, **20**, 1727 (1983).
210. V. Bhushan and S. Chandrasekarn, *Chem. Lett.*, 1537 (1982).
211. P. H. Herrinton, M. H. Hopkins, P. Mishra, M. J. Brown and L. E. Overman, *J. Org. Chem.*, **52**, 3711 (1987).
212. Á. Molnár, I. Bucsi and M. Bartók, *Tetrahedron* (in press).
213. G. Carr, C. Dean and D. Whittaker, *J. Chem. Soc., Perkin Trans. 2*, 351 (1988).
214. G. Carr and D. Whittaker, *J. Chem. Soc., Perkin Trans. 2*, 359 (1989).

215. N. S. Zefirov, S. I. Kozhyshkov and T. S. Kuznetsova, *Zh. Org. Khim.*, **24**, 477 (1988).
216. C. W. Doecke and P. J. Garratt, *Tetrahedron Lett.*, **22**, 1051 (1981).
217. R. C. F. Jones and J. H. Tunnicliffe, *Tetrahedron Lett.*, **26**, 5845 (1985).
218. Hai-Shan Dang, A. G. Davies, I. G. E. Davison and C. H. Schiesser, *J. Org. Chem.*, **55**, 1432 (1990).
219. N. Porter and P. Zuran, *J. Chem. Soc., Chem. Commun.*, 1472 (1985).
220. N. A. Porter and D. J. Wujek, *J. Am. Chem. Soc.*, **106**, 2626 (1984).
221. E. Basketta, F. D. Gunstone and J. C. Walton, *J. Chem. Soc., Perkin Trans. 2*, 603 (1983).
222. H. W. S. Chan, G. Levett and J. A. Matthew, *Chem. Phys. Lipids*, **24**, 245 (1979).
223. R. C. Ronald and T. S. Lillie, *J. Am. Chem. Soc.*, **105**, 5709 (1983).
224. T. S. Lillie and R. C. Ronald, *J. Org. Chem.*, **50**, 5084 (1985).
225. S. Muto and T. C. Bruice, *J. Am. Chem. Soc.*, **102**, 7379 (1980).
226. F. McCapra and P. V. Long, *Tetrahedron Lett.*, **22**, 3009 (1981).
227. K. Gollnick and K. Knutzen-Mies, *J. Org. Chem.*, **56**, 4017 (1991).
228. W. Adam and X. Wang, *J. Org. Chem.*, **56**, 4737 (1991).
229. A. W. Nowicki and A. B. Turner, *J. Chem. Res.*, (*S*), 110 (1981).
230. F. S. Guziec, Jr. and E. T. Tewes, *J. Heterocycl. Chem.*, **17**, 1807 (1980).
231. T. Kumagai, A. Tokida, K. Idoura, O. Seshimoto and T. Mukai, *Tetrahedron Lett.*, **23**, 873 (1982).
232. W. Adam and M. Balci, *J. Am. Chem. Soc.*, **102**, 1961 (1980).
233. M. Balci, *Chem. Rev.*, **81**, 91 (1981).
234. H. A. J. Carless, R. Atkins and G. K. Fakarurhobo, *Tetrahedron Lett.*, **26**, 803 (1985).
235. J. D. Boyd, C. S. Foote and D. K. Imagawa, *J. Am. Chem. Soc.*, **102**, 3641 (1980).
236. M. Balci and Y. Sütbeyaz, *Tetrahedron Lett.*, **24**, 311 (1983).
237. M. Balci and Y. Sütbeyaz, *Tetrahedron Lett.*, **24**, 4135 (1983).
238. Y. Sützbeyaz, H. Seçen and M. Balci, *J. Org. Chem.*, **53**, 2312 (1988).
239. N. Akbulut, A. Menzek and M. Balci, *Tetrahedron Lett.*, **28**, 1689 (1987).
240. M. Suzuki, Y. Oda and R. Noyori, *Tetrahedron Lett.*, **22**, 4413 (1981).
241. I. Edden and M. A. Amputch, *Tetrahedron Lett.*, **28**, 3779 (1987).
242. K. L. Graziano, M. R. Iesce and R. Scarpati, *J. Chem. Soc., Chem. Commun.*, 720 (1981).
243. M. L. Graziano, M. R. Iesce, A. Cinotti and R. Scarpatti, *J. Chem. Soc., Perkin Trans. 1*, 1823 (1987).

CHAPTER 15

Rearrangements of open-chain and cyclic ethers

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Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

I. INTRODUCTION

This series of monographs included a report on the rearrangement of ethers in 1967[1]. The research work in this field has led to enormous progress in the past 25 years. Consequently, procedures have been initiated in the laboratory and industrial practice of synthetic organic chemistry which are today indispensable[2].

In this short review, there is no possibility for a detailed analysis of every isomerization and rearrangement reaction of all the different types of ethers. In fact, this is unnecessary in some cases, because reviews have continually been published about certain reactions, verifying the significance of these transformations. Thus, we shall consider in detail only those fields which have not been included in recent surveys, and chemical procedures on which detailed analyses were published recently will be mentioned only briefly. From the aspect of chemical reactivity, there are vast differences between certain types of open-chain ethers, and also between cyclic ethers with different ring sizes. Of course, the reactivity depends not only on the structure, but also upon the reagent used and also the experimental conditions. These general statements hold for the isomerizations and rearrangements of both open-chain and cyclic ethers.

We wish to stress that this chapter deals merely with the reactions of ehters which do not contain other functional groups. In spite of their vast importance, the transformations of ethers containing other functional groups lie outside the scope of this work.

Groups containing carbon and hydrogen atoms are linked to the oxygen atom of ethers. Numerous types of compounds are formed by alkyl, vinyl, allyl, propargyl, phenyl and benzyl groups and their different homologues. Among these, we shall treat those which undergo characteristic chemical procedures and whose chemical reactions are of greatest significance. We consider that the importance of the Claisen and Wittig rearrangements is indisputable. This review therefore surveys the most important results of studies relating to these two types of reaction. The most recent results on the rearrangements of certain vinyl, allyl, phenyl and benzyl ethers are also discussed. In the family of cyclic ethers, oxiranes (epoxides) occupy a distinguished position, and their transformations are therefore treated separately from the other cyclic ethers.

II. OPEN-CHAIN ETHERS

A. Claisen Rearrangement

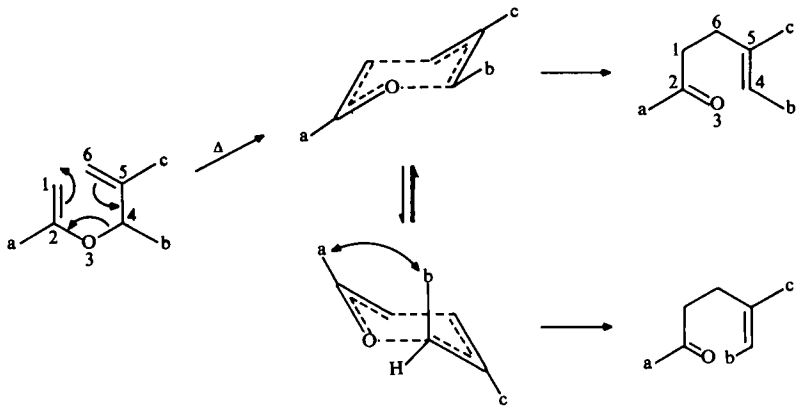
Since the recognition of the reaction (1912), the Claisen rearrangement has acquired great significance, chiefly in synthetic organic chemistry. The development is well demonstrated by the large number of surveys[3-20] that have appeared since the earlier review in this series[1]. Besides a detailed treatment, some of these surveys analyse the results published in a given period[7,13,17,20]. Others mainly report the wide-ranging employment of the reaction[6,7,10,14,15,17-19].

The Claisen rearrangement now involves more than the thermal rearrangement of vinyl allyl, vinyl propargyl and allyl phenyl ethers. It also includes the rearrangements of their derivatives containing other functional groups too, in part in response to thermal effects, in part in the presence of various catalysts. New variations of the Claisen rearrangement relating to compounds containing different hetero atoms are usually referred to by different names in the literature. Here we deal only with the rearrangement of allyl vinyl and allyl phenyl ethers, without other functional groups, and do not consider such important new results as carbanion-accelerated Claisen rearrangements[21-24], competitive rearrangements[17,20], consecutive rearrangements[17], etc.

1. Claisen rearrangement of allyl vinyl ethers

Very detailed surveys have been published on the literature relating to this topic[7,13,14,17,20]. From among the innumerable new results, we shall present a few to illustrate the current state and efficacy of the research.

The Claisen rearrangement is a suprafacial, concerted, non-synchronous pericyclic process (3,3 sigmatropic rearrangement) through a cyclic six-membered transition state. In the course of the reaction, a new C=C bond and a new C—C bond are formed (equation 1).



(1)

The Claisen rearrangement of allyl vinyl ethers provides an excellent stereoselective route to γ,δ-unsaturated carbonyl compounds, and comprises an important step in the synthesis of a number of natural products[11,15,17,18,20].

The rearrangement occurs at 150–200 °C for unsubstituted or alkyl-substituted substrates. Most frequently, the reaction is carried out in a sealed tube and, in particular, in different solvents[7]. The accelerating effect of polar solvents is proved. The successful employment of solvents containing water[25–28] is of great practical importance. This permits milder experimental conditions and the achievement of rearrangements which were previously unsuccessful.

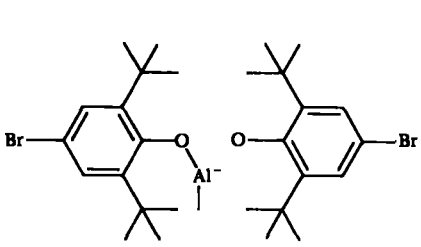
The unfavourable effect of high temperature led to the early investigation of the influence of different Lewis acid catalysts. Organoaluminum compounds (e.g. types **1–4**) have been employed in stereo- and enantioselective rearrangements in the recent past[29–32].

A characteristic comparison of thermal and catalytic rearrangements is as follows (equation 2)[29,30].

Claisen rearrangements are highly exothermic, concerted, but non-synchronous pericyclic reactions with a characteristic negative entropy and negative volume of activation. Allyl vinyl ether exhibits secondary kinetic deuterium effects[12,17,20].

The influence of donor and acceptor substituents on the rates of Claisen rearrangements has been widely investigated[20,33,34]. Molecular orbital calculations predict accelerating effects of donor substituents at C1 and both donor and acceptor substituents at positions 2 and 4 of the Claisen system. Acceptor substituents at positions 1 and 6 and donor groups at positions 5 and 6 are predicted to decelerate the reaction[20] (equation 1).

The reactions are highly stereoselective, particularly when a = H, leading predominantly to the (*E*) configuration of the newly formed C=C bond, and the controlled stereochemical disposition of the substituents on the single bond. A chair conformation



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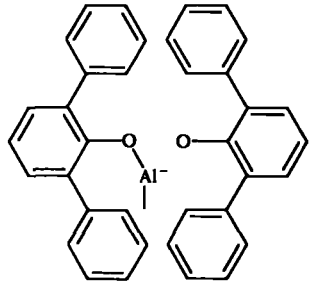

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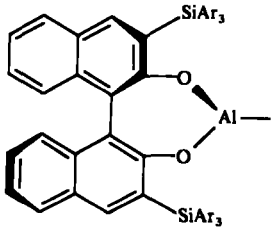

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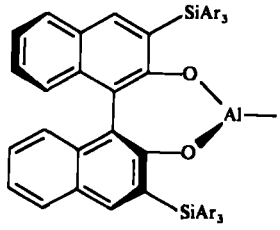

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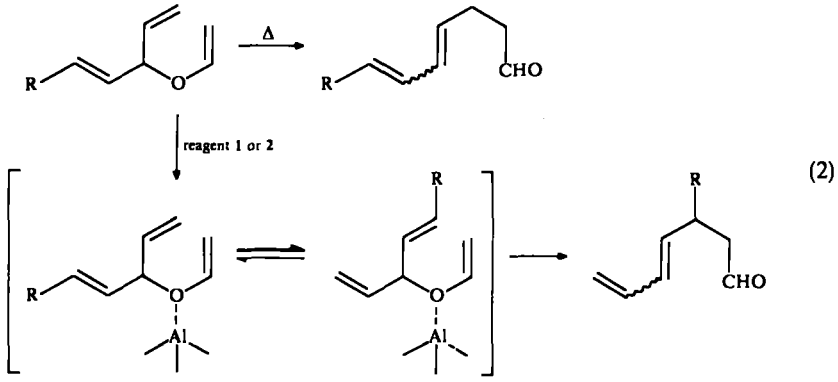
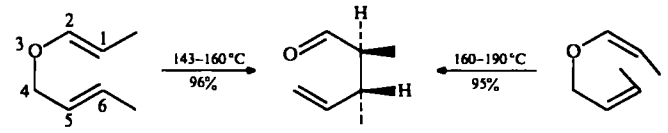


(2)

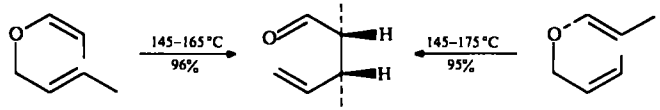
is preferred for the cyclic transition state[17,20,29,30,33,35] with the substituent **b** in the equatorial configuration, and the high stereoselectivity favouring the (*E*)-alkene is a consequence of non-bonded interaction between **a** and **b** in the alternative transition state which would give the (*Z*)-alkene (equation 1).

Naturally, the geometry of the vinyl ether bond and the conformation of the transition state are crucial parameters in this process. The configuration of the allylic chiral centre at C4 specifically relates to the configuration of the newly formed chiral centres at C1

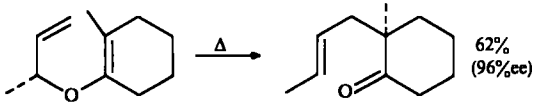
and C6. The definitive role of stereochemical factors (steric structure of allyl vinyl ethers, steric bulk of the substituents, chirality of C4, geometry of the transition state, steric demand and chirality of the catalyst, etc.) is well demonstrated by examples selected from among the latest research work (equations 3–10).



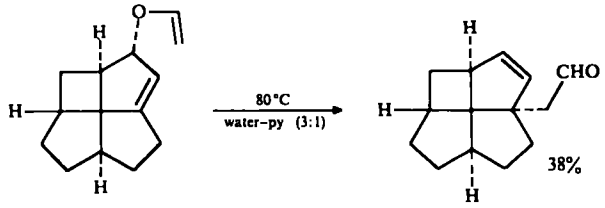
(3)[15]



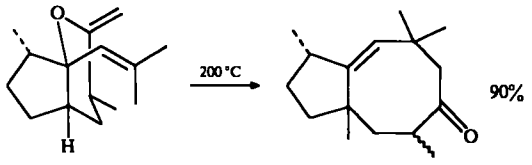
(4)[15]



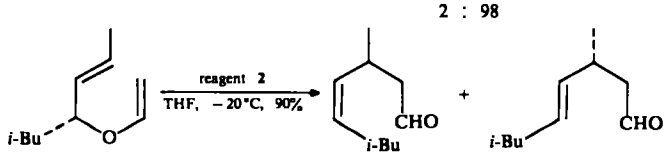
(5)[36]



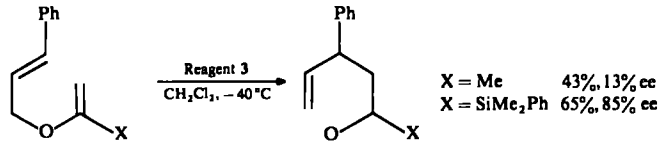
(6)[28]



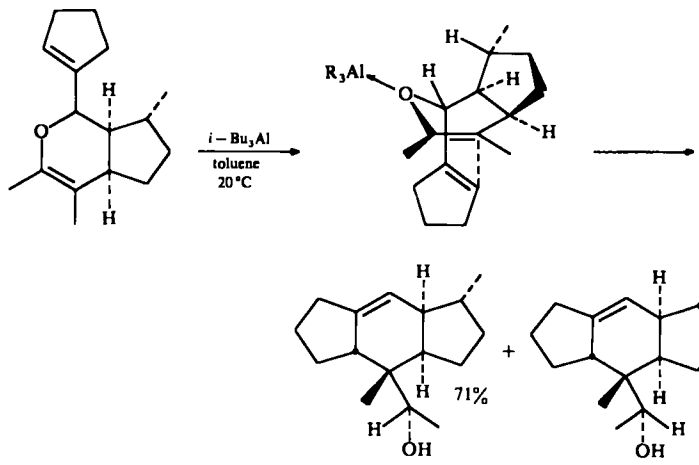
(7)[37,38,40]



(8)[39]



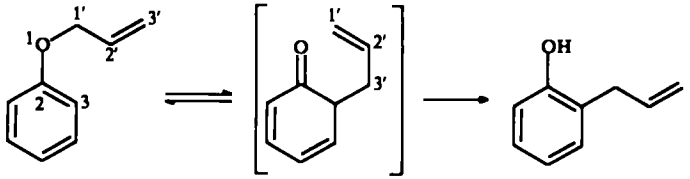
(9)[31]



(10)[32]

2. *Aromatic Claisen rearrangement*

Following the discovery of the Claisen rearrangement, research chiefly tended towards the thermal rearrangement of allyl aryl ethers. The results are well illustrated by the review published in this series in 1967[1] dealing with the Claisen, and especially the aromatic Claisen rearrangement whereas the aliphatic variant is hardly mentioned. The results have been well treated in monographs[3,4,7,8,13]. The aliphatic Claisen rearrangement has subsequently attracted interest, one recent survey[20] barely dealing with the aromatic rearrangement. The above reviews, together with those of Dalrymple, Kruger and White[1], provide a complete picture of both the theoretical (mechanism, intermediate cyclic nature, transition state) and the practical relations of the aromatic Claisen rearrangement. Therefore, the present work gives merely a very brief account of the earlier results, supplemented with some of the more recent findings. The best known aromatic sigmatropic shift is the thermal Claisen rearrangement of aryl allyl ethers, illustrated in equation 11.



(11)

The initial 3,3 step gives an *ortho*-dienone, which usually enolizes repidly to the stable product (*ortho*-Claisen rearrangement). Depending on the substituents both on the ring

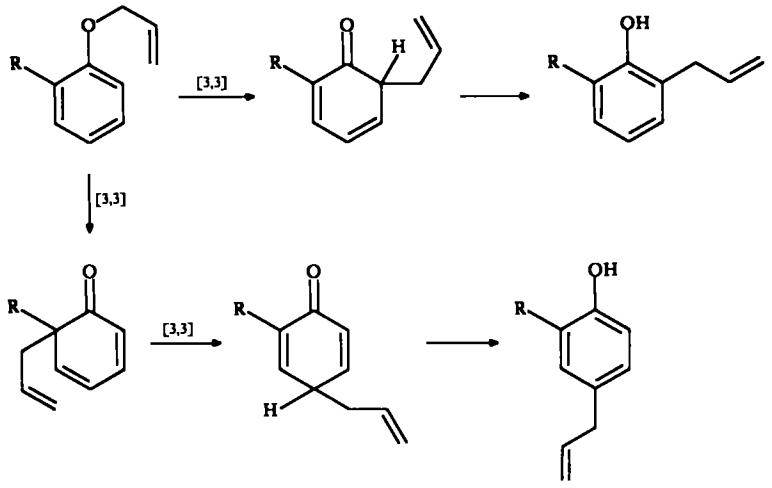
and on the allyl group in the aryl allyl ether, different variations of the rearrangement have come to light: *para* and 'abnormal' Claisen rearrangements, out-of-ring migration, coumarin formation, retro-Claisen rearrangement, and *ortho–ortho* rearrangement[1,3,7].

There is an extensive literature on the Claisen rearrangements of allyl ethers, propargyl aryl ethers[3,7,8] and pentadienyl aryl ethers[3,4,7].

These rearrangements have been accomplished simply by heating the ethers in the temperature range 150–200 °C or by using a solvent of appropriate boiling point[7] (dimethylaniline, diethylaniline, DMF, etc.).

The employment of different catalysts, chiefly of Lewis acid type[13,41,42] but also others[43–49], has recently proved popular. In the presence of these, the rearrangement takes place under milder experimental conditions and at considerably higher rate or with higher selectivity in certain cases.

The two main products of the thermal rearrangement are the *o*- and *p*-allylphenol (equation 12).

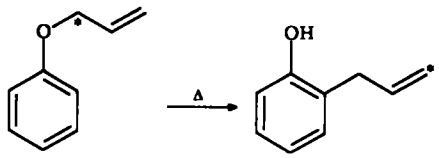


(12)

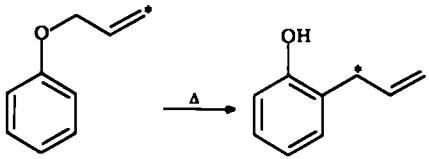
If the rearrangement is to an *ortho*-position already bearing a substituent, a second 3,3 step followed by enolization leads to the *p*-allylphenol (*para*-Claisen rearrangement). The *ortho*-Claisen rearrangement predominates in unexceptional cases, but the *para* process can compete even when both *ortho*-positions are free[13].

Indirect, kinetic methods suggest a preference for chair topology, but they provide no information about the specific degree of chair-boat selectivity. The kinetic isotop effect was measured[50] for the rearrangement at 220 °C of allyl phenyl ether labelled in various positions (equations 13–16). A loose transition structure was found for the rearrangement of allyl phenyl ether into *o*-allylphenol. In the reactions of this transition structure, the C_α—O bond undergoes 50–60% rupture, while the C_γ—C_{ortho} bond is only 10–20% formed. The results therefore underline this concerted non-synchronous rearrangement more explicitly than previously[50].

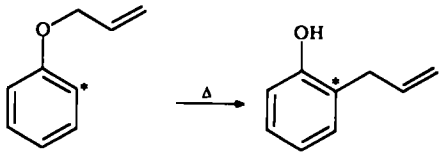
Extensive investigations have been made in connection with the mechanism of rearrangements catalysed by Lewis acids[41b,51]. The review by Lutz deals with the results in detail[13]. The intramolecular and intermolecular characters of the reaction mechanism depend chiefly upon the substituents on the ring and on the allyl group, respectively (equations 17–19)[41,42].



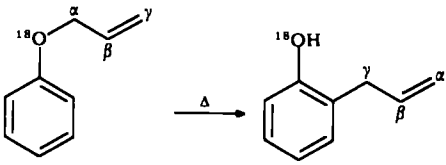
(13)



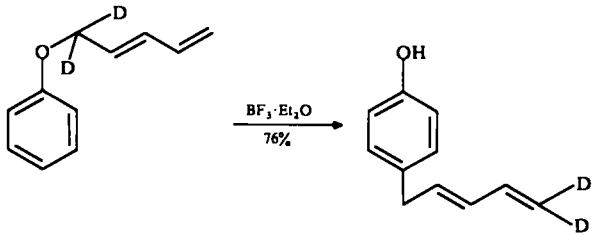
(14)



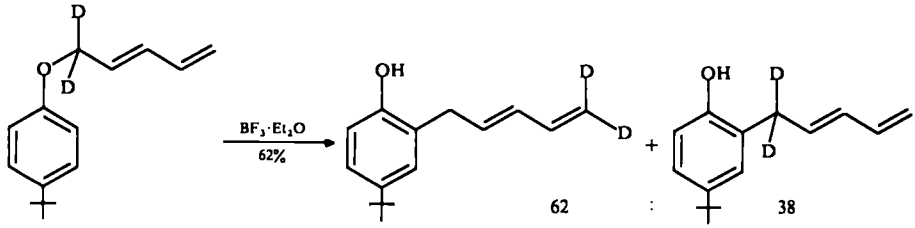
(15)



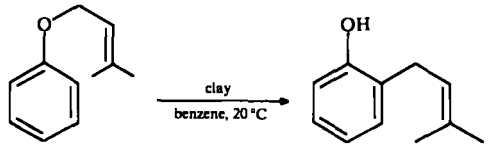
(16)



(17)

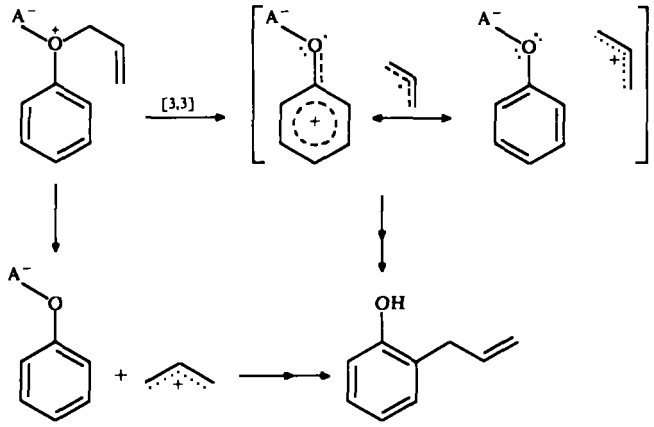


(18)



(19)

Substrates without *ortho*-substituents gave high yields of the *ortho*-rearrangement product. Substrates with one *ortho*-substituent gave substantial amounts of the *para*-rearrangement product. The Lewis acid-catalysed rearrangements were considerably less clean than their thermal counterparts when substrates were used in which both *ortho*-positions were substituted. An example of 1,3-allyl transfer is shown in equation 19. The 1,3 allyl transfer is most selective when there are two terminal substituents, presumably because of steric hindrance[42]. The essence of the reaction mechanisms is an intermolecular allyl transfer or 3,3 shift through a charge-delocalized transition state (equation 20).



(20)

The thermal aromatic Claisen rearrangement is considered to take place preferentially with chair geometry, and the use of analogous experimental probes leads to the same conclusion for the Lewis acid-catalysed reactions[13,51]. Chirality transfer in the same suprafacial sense as the thermal reaction was observed in the BCl_3-catalysed rearrangement of the optically active substrate[51].

The synthetic utilization of the aromatic Claisen rearrangement is now widespread. This is clear from both the reviews[8,13] and the numerous new publications which report the preparation of complex organic compounds through rearrangements of aromatic allyl ethers containing different functional groups[52–60].

B. Wittig Rearrangement

The base-catalysed rearrangement of different ethers is referred to as the Wittig rearrangement. This reaction results in the formation of isomeric carbinols[61,62].

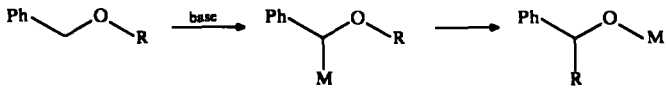
Depending on the structure of the ether and the reaction conditions, the rearrangement may be of 1,2, 2,3, 1,4 or 3,4 type[63]. Previously, the 1,2 rearrangement was the main subject of research. Thus, e.g., Reference 1 dealt almost only with the above topic. As a

result of the comprehensive research in the past 20 years, the 2,3 sigmatropic rearrangement of ethers, their analogues and heteroanalogues containing different functional groups has become a significant method of stereoselective synthesis.

The progress in research on the Wittig rearrangement and the continuous broadening of its use in organic syntheses is well illustrated by the reviews published since 1967 in this field[8,14,63–69]. Considering these numerous reviews, and the fact that some of them appeared in the past two years[67–70], we shall give only a short summary of this topic, with references to the relevant reviews. At the same time, several characteristic examples demonstrate the importance of the Wittig rearrangement and the chemical behaviour of ethers containing different hydrocarbon groups under basic conditions. In the course of the Wittig rearrangement, the question is the transformation of allyl, propargyl and benzyl ethers under basic conditions. In such compounds, a stabilized carbanion may be formed in the first step, on the action of the base. The 1,2 and 2,3 rearrangements are treated in accordance with their importance.

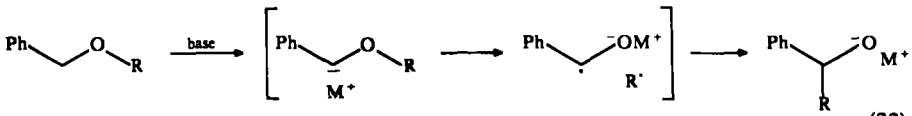
1. 1,2 Rearrangement

Benzyl alkyl ethers can be transformed into carbinols with high selectivity in basic medium (equation 21)[61,64]. The mechanism of the carbanion rearrangement was earlier the subject of intensive investigations[64].



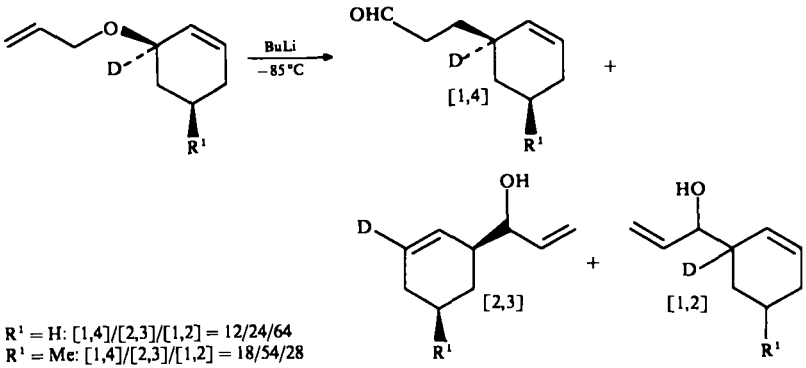
(21)

Of the several mechanisms proposed for this reaction, a sequence involving homolysis of the anion intermediate, followed by recombination of the radical and radical anion fragments, best accommodates the experimental findings[63] (equation 22).



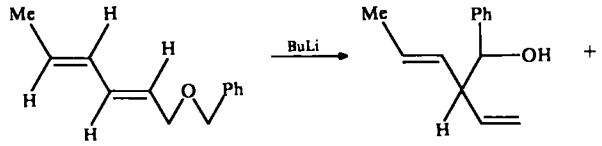
(22)

As can be seen in the examples below, depending on the structures of the compounds and the reaction conditions (mainly the temperature), the 1,4 and particularly the 2,3 shift compete with the 1,2 shift (equations 23–26).



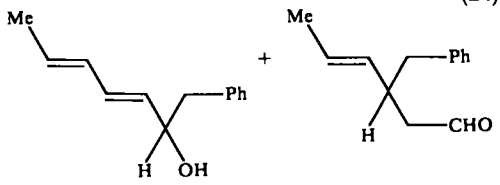
(23)[71]

R^1 = H: [1,4]/[2,3]/[1,2] = 12/24/64
R^1 = Me: [1,4]/[2,3]/[1,2] = 18/54/28



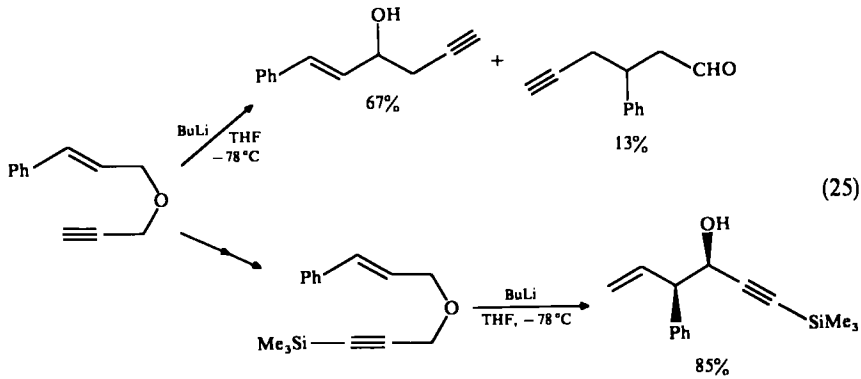
[2,3]

(24)[72]

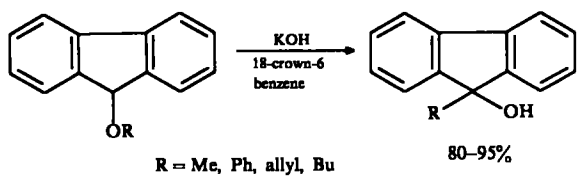


[1,2] [1,4]

in THF: [1,2]/[2,3]/[1,4] = 66/16/18
in THF–HMPA: [1,2]/[2,3]/[1,4] = 72/0/28



(25)[73]



R = Me, Ph, allyl, Bu

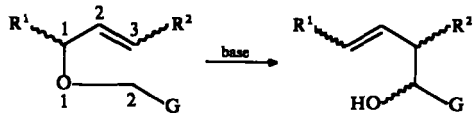
80–95%

(26)[74]

Since lower temperature favours the 2,3 sigmatropic rearrangement, temperature elevation promotes the 1,2 shift. The anionoid Wittig rearrangement of benzyl and allyl ethers has been also investigated in the gas phase[75–78]

2. 2,3 Sigmatropic rearrangement

The 2,3 Wittig rearrangement is a reaction of allyl ethers (diallyl, allyl propargyl and allyl benzyl ethers), involving the formation of homoallyl alcohols, on the action of bases (equation 27).

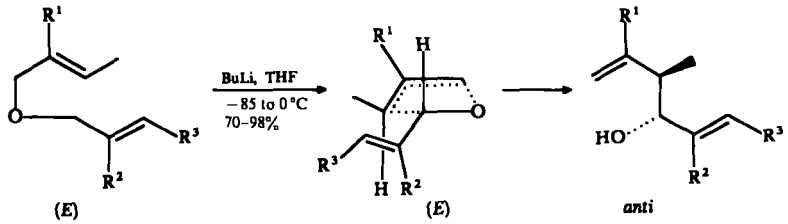


(27)

The 2,3 sigmatropic reaction of allyl ethers can be defined as a thermal isomerization that usually proceeds through a highly ordered five-membered cyclic transition state to create new C=C and C—C bonds. This rearrangement is a concerted, thermally allowed sigmatropic process following the Hoffmann–Woodward rule[63,66,68].

The 2,3 Wittig rearrangement proceeds under mild conditions (standard conditions: BuLi, THF, −85 °C) at as low a temperature as possible to avoid the 1,2 product.

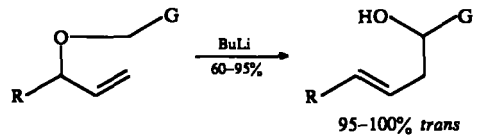
The transition state of the 2,3 Wittig rearrangement has an envelope conformation[66,79–85] (equation 28).



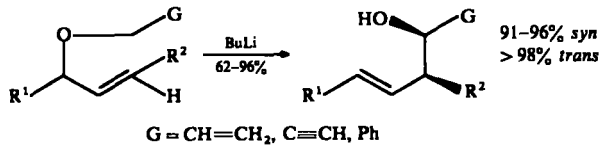
(28)

The consequence of this conformation is the strong stereoselectivity of this reaction. The most recent surveys pay great attention to the stereocontrolled transformations of 2,3 rearrangements. The rearrangement reactions are described in two ways. Marshall[63] groups them according to the allyl ether type (allyl propargyl, allyl benzyl, dipropargyl and diallyl ethers), whereas Brückner[67,68] does so according to the type of stereocontrol (double-bond configuration, selectivity, diastereoselectivity, enantioselectivity through chirality transfer and asymmetric induction). Several characteristic 2,3 rearrangement reactions chosen from different fields are presented below:

General outline (equations 29 and 30):

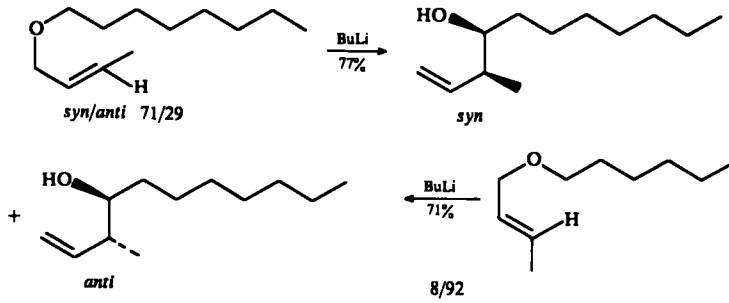


(29)[86]



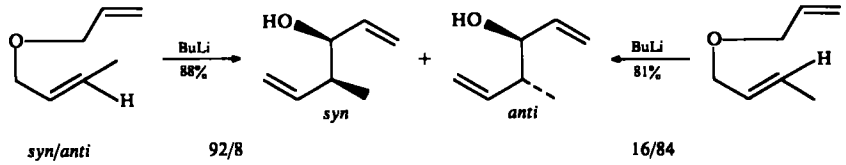
(30)[80,87,88]

Rearrangement of allyl alkyl ethers[89] (equation 31):



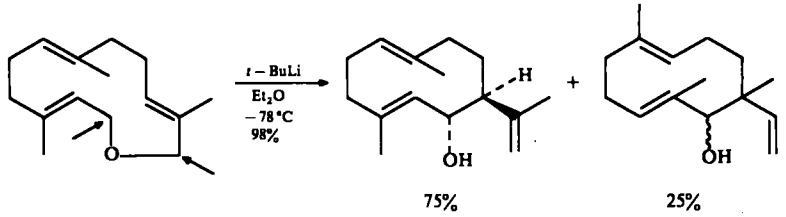
(31)

Rearrangement of diallyl ethers[79,83,86,90–92] (equation 32):



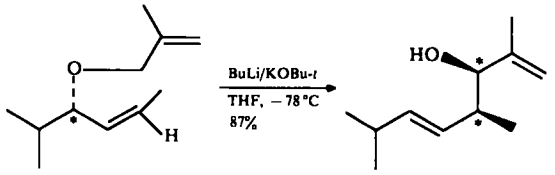
(32)[86]

Transannular 2,3 Wittig rearrangement[79] (equation 33):

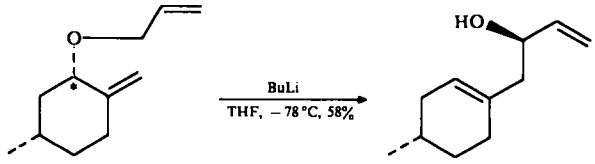


(33)

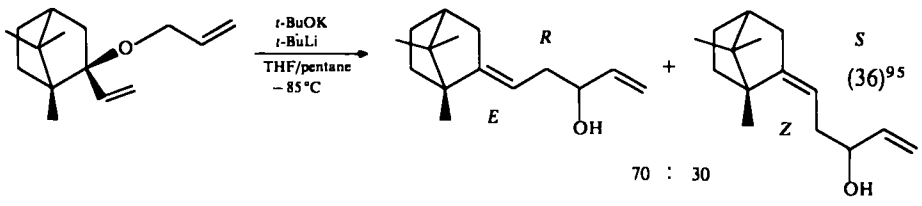
Chirality transfer in rearrangement[80,88,93–95] (equations 34–37):



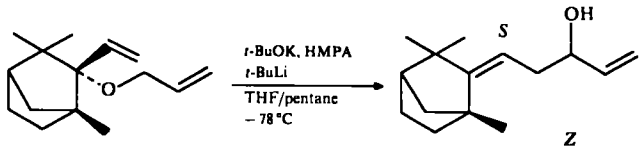
(34)[88]



(35)[93]

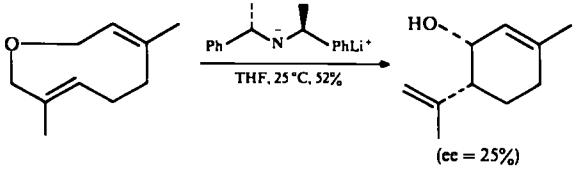


(36)[95]



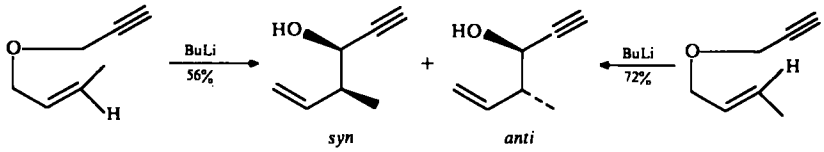
(37)[95]

In the presence of chiral amides[92] (equation 38):



(38)

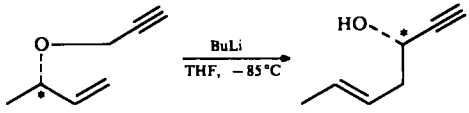
Rearrangement of allyl propargyl ethers[87,96–99] (equation 39):



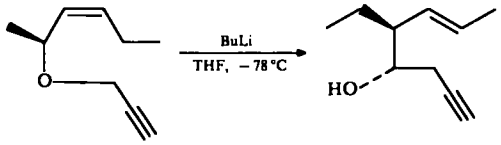
(39)[87]

syn/anti 90/10 1/99

Chirality transfer in rearrangement (equations 40 and 41):

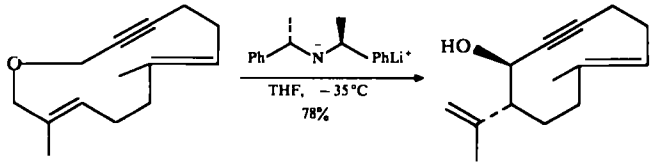


(40)[100]



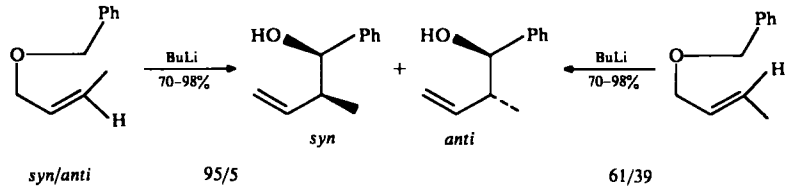
(41)[101]

Rearrangement in the presence of chiral amides[102,103] (equation 42):



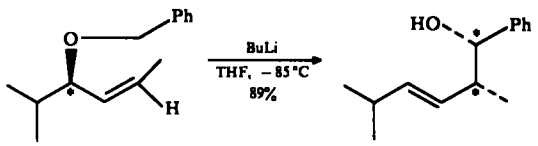
(42)

Rearrangement of allyl benzyl ethers[83] (equation 43):



(43)

Chirality transfer in rearrangement[80,104] (equation 44):



(44)[80]

The above examples not only demonstrate the stereochemical regularities of the 2,3 sigmatropic Wittig rearrangement of ethers, but also draw attention to the wide-ranging use of the reaction and hence its importance in synthetic organic chemistry.

III. CYCLIC ETHERS

A. Rearrangement of Oxiranes

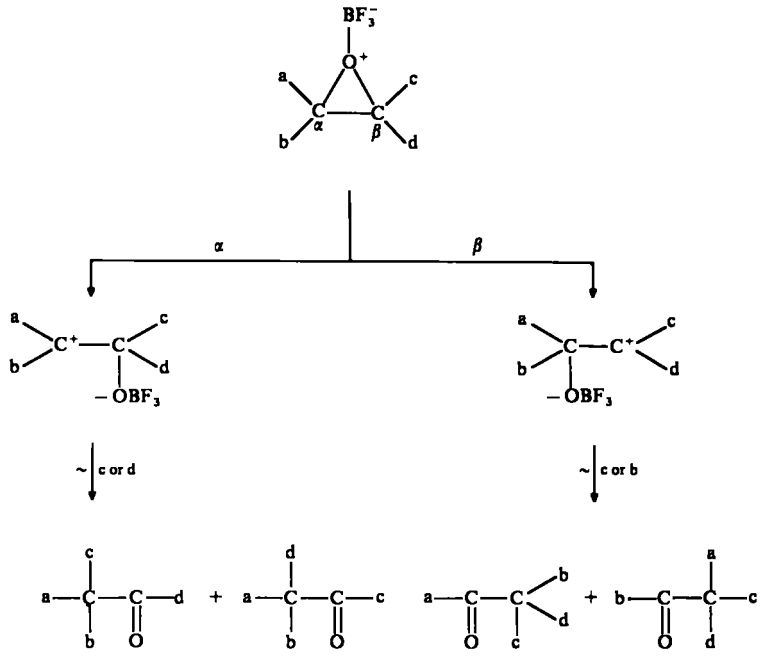
Since our earlier review[105] in this series of monographs, interest in the rearrangement reactions of oxiranes (or epoxides) has continued to grow. This is attested to not only by the numerous original papers, but also by the subsequent reviews on this topic.

It can be stated on the whole that the two main directions of the rearrangement of epoxides (the formation of α,β-unsaturated alcohols or carbonyl compounds) depend chiefly upon the structures of the starting compounds and the reagent/catalyst used. The utilization of the rearrangement of epoxides for synthetic purposes has now become almost indispensable.

1. Homogeneous reactions with acid catalysts

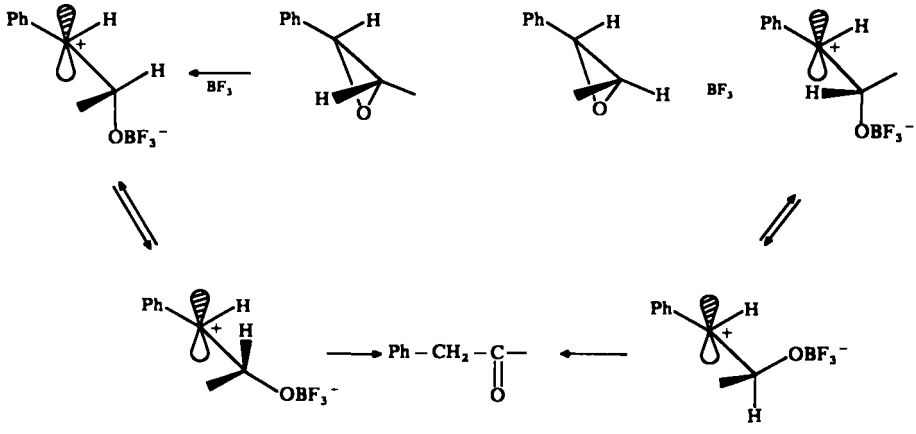
a. Formation of carbonyl compounds. Since the above review[105], short surveys have been made of the results in this field[106–110]. Most of these[106–109] deal with the results up to 1980; a review on the rearrangement of epoxy alcohols[110a] was published in 1990.

Protic and Lewis acids cause epoxides to rearrange to carbonyl compounds (ketones and aldehydes)[110b]. The first step involves binding of the catalyst, followed by splitting of the C_α—O or C_β—O bond (equation 45).



(45)

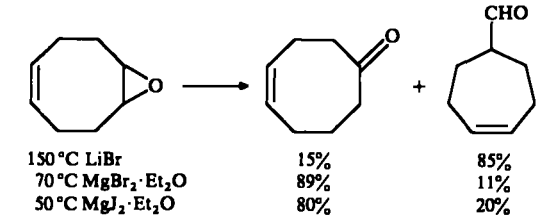
A classical carbenium ion next develops, with the migration of one of the groups. In certain cases, these two steps proceed synchronously (equation 46)[111].



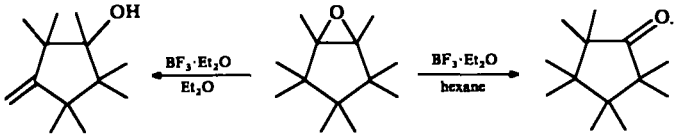
(46)

Most commonly the rearrangement has been effected with the use of $BF_3 \cdot Et_2O$[111–119], but it has also been carried out with polymer-bound $BF_3 \cdot Et_2O$[120], toluene-*p*-sulphonic acid[121–123], sulphuric acid[124–126], sulphonated polystyrene cation exchange resin[126], HNO_3[125], $HClO_4$[125,127], trifluoroacetic acid[128], electrogenerated acids[129,130], lithium salts[131–136], superacids[137] and different Lewis acids[136,138–140].

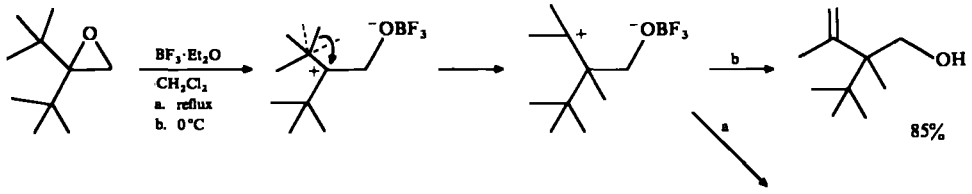
Not only the catalyst[111,135] influences the nature of the products formed in the rearrangement (equation 47)[135], but also the reaction conditions (equation 48[112] and equation 49)[115].



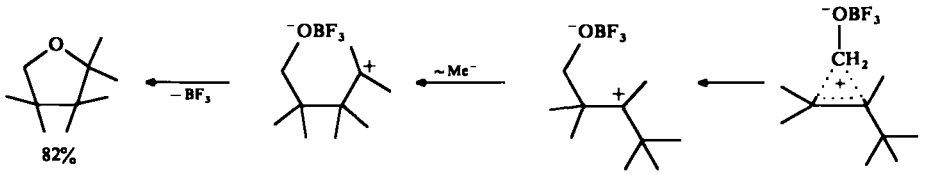
(47)



(48)



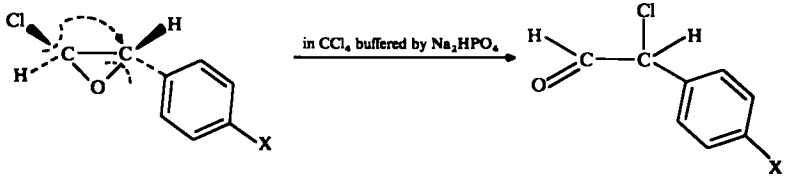
(49)



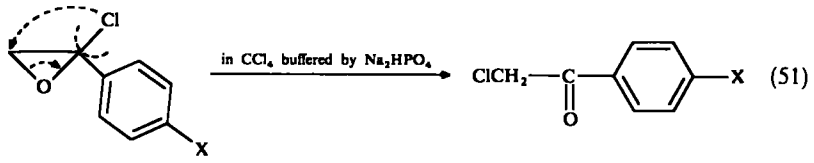
Though the main products of the acid-catalysed rearrangement of epoxides are the carbonyl compounds, other compounds may also be formed, depending upon the nature of the epoxide (number of substituents, functional groups, steric structure). Some examples will be given later.

As concerns the formation of carbonyl compounds, Smith[108] summarizes the experimental results as follows. Two general considerations determine the identity of the carbonyl product: the direction of ring opening of the epoxide, and the identity of

the migrating substituent. From the many examples of epoxide rearrangement reactions which have been reported, it appears as if electron-releasing functional groups promote ring opening, and the relative migratory aptitude of the substituents on the epoxide has been determined to be aryl > acyl > H > Et > Me. Numerous literature data can be found on the migration of other groups[141–143]. Equations 50 and 51 serve as characteristic examples of rearrangements involving heteroatom migration[142].

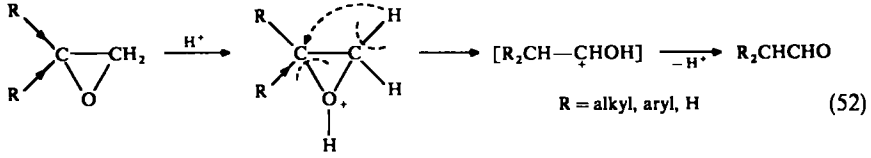


(50)



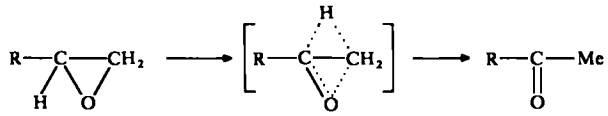
(51)

Mono- and 1,1-disubstituted epoxides generally give aldehydes on rearrangement with acids[108] (equation 52). In the presence of acids, the opening of the oxirane ring proceeds through formation of the more stable carbocation.



(52)

The BF_3-catalysed rearrangement of styrene oxide to phenylacetaldehyde has been optimized[144]. Some examples differ from the general picture mentioned above. Attempts have been made[139] to develop general methods for selectively rearranging an epoxide to the isomeric ketone.

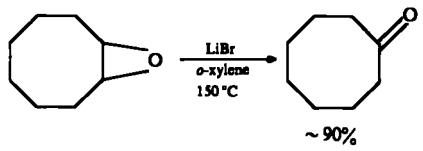


(53)

Terminal epoxides have been selectively converted into Me ketones with mildly acidic catalysts (SmIO, SmI_2, t-$BuOSmI_2$, MnI_2). The catalyst attacks on the carbon atom which is less sterically hindered (equation 53). The reaction mechanism is essentially more complicated than shown here.

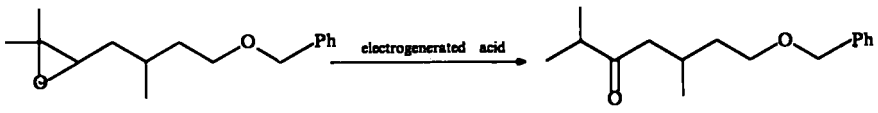
The BF_3-catalysed rearrangement of 2,2-di-t-butyloxirane, involving competitive reactions of transient carbenium ions, could be selectively directed towards either 2,2,3,3,4,4-hexamethyltetrahydrofuran or 2-t-butyl-2,3-dimethyl-3-buten-1-ol[115] (equation 49).

High selectivity was likewise experienced in the rearrangements of other disubstituted epoxides (equations 47 and 54)[111,135].

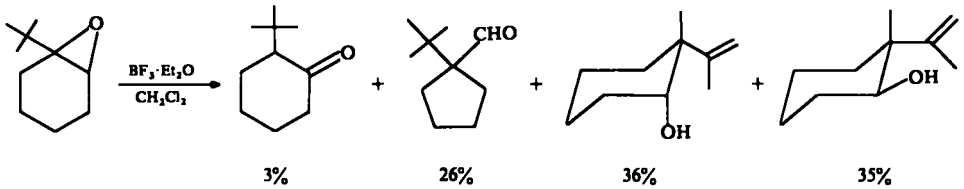


(54)[135]

For trisubstituted epoxides, a variety of factors determine the identity of the product. These include the nature of the substituents on the epoxide, the stereochemistry and the acid catalyst used (equations 55 and 56)[117,129].

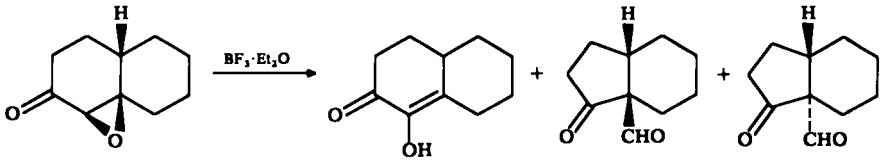


(55)

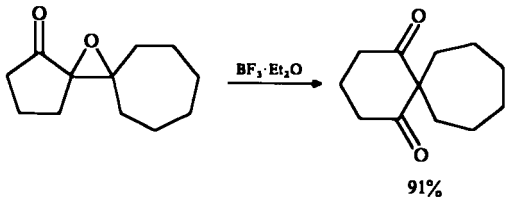


(56)

The facile Lewis acid-catalysed acyl migration of several α,β-epoxy ketones has afforded a practical route to hydrindanone derivatives (equation 57)[145] or cyclic spiro 1,3-diketones with complete stereospecificity (equation 58)[118].

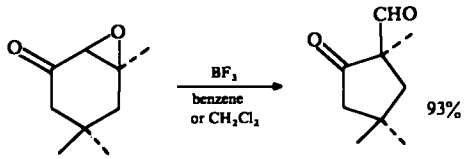


(57)

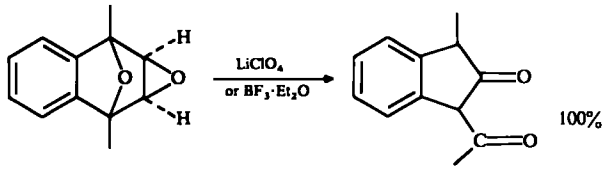


(58)

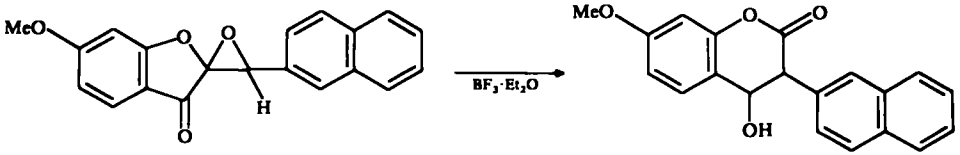
In the case of cyclic epoxides and epoxides containing different functional groups, rearrangements involving ring contraction or enlargement also take place[136,146–155,115,118]. Some examples are illustrated by equations 59–61.



(59)[146,147]



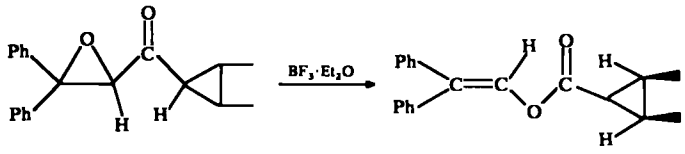
(60)[136]



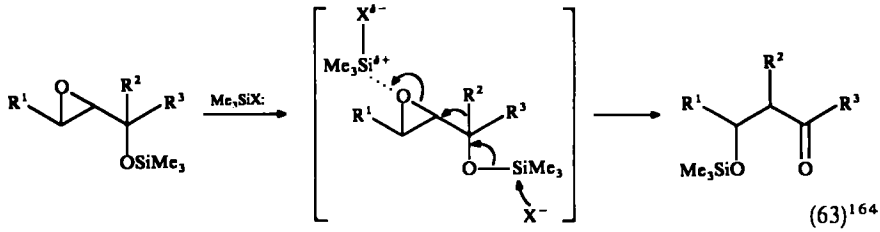
(61)[151]

The application of the procedure in synthetic organic chemistry has been significantly widened (see, e.g., equations 62–65) by other investigations and studies of acid-catalysed rearrangements of epoxides containing different functional groups[114,119,125,138,156–166].

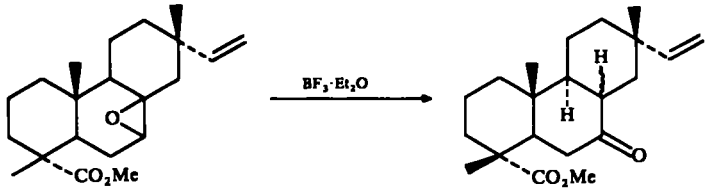
In this respect, the value of the epoxy alcohol–aldol rearrangement may be emphasized, which takes place with high stereospecificity and yield (equation 66)[152,164,167–169].



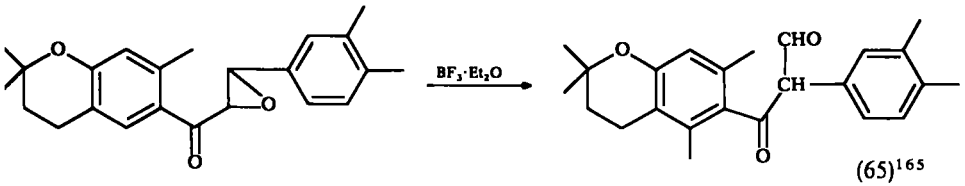
(62)[114]



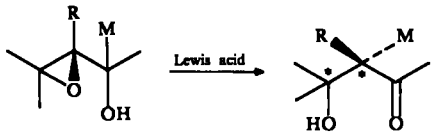
(63)[164]



(64)[119]

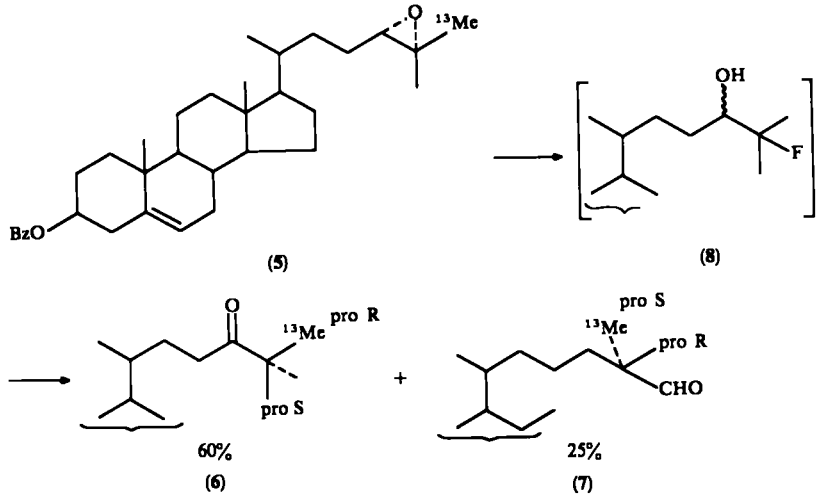


(65)[165]



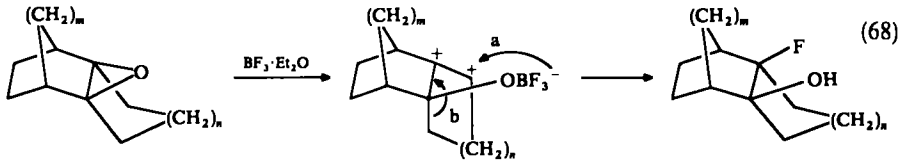
(66)

b. Mechanistic investigations. New results have emerged in connection with the mechanism of the rearrangement[111,112,170–172]. The experimental observations reflected in equation 67 were interpreted by the authors as follows.



(67)

In the BF_3-catalysed rearrangement of **5** to **6** and **7**, C24-H migration leading to the 24-oxo compound **6** occurs with retention of the configuration at the migration terminus (C25), whereas C23-alkyl group migration leading to the aldehyde **7** proceeds with inversion of the configuration at C25[172]. This work emphasizes the general importance of a fluorohydrin intermediate **8** in the migration of hydride in the BF_3-catalysed rearrangement of oxiranes. This reaction route has been verified by the isolation of fluorohydrins (equation 68)[173].



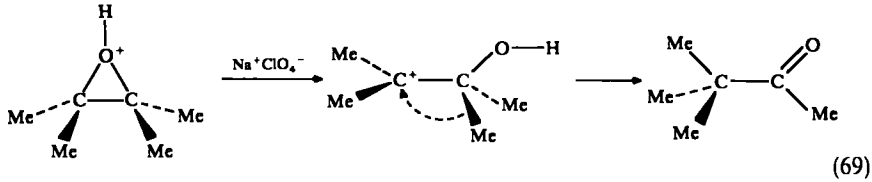
(68)

From a mechanistic point of view, the rearrangement of oxiranes can be interpreted in terms of either a concerted mechanism or the participation of an open carbenium ion[111]. For oxirane rearrangements catalysed by $BF_3 \cdot Et_2O$, a mechanistic pathway involving an open carbenium ion is generally accepted[105–109]. Product selectivities are then determined by the migratory aptitudes of the different groups, the ease of formation of the transition state and the rate of rotation about the C—C bond of the carbenium ion intermediate.

Studies of 2-substituted oxiranes labelled with deuterium on C3 either *cis* or *trans* to the substituent revealed a slight diastereotopic selection of the *trans* H or D in rearrangements[133]. This means that the rate of hydride/deuteride migration is comparable with the rate of rotation. The selective formation of ketone in equation 46 reflects a fast rotation relative to migration. It allows the generation of a conformation which ensures the necessary alignment of the migrating hydrogen and the empty p orbital.

Investigations of the reactions of epoxides in a quasi-neutral medium, when the spontaneous ring-opening process occurs, contribute essential data on the mechanism of rearrangement of epoxides to carbonyl compounds.

In dilute aqueous media below pH 4, tetramethyloxirane undergoes hydrolysis to yield pinacol. With increasing amounts of $NaClO_4$ at constant acid concentration there is a dramatic change in the product: pinacolone is formed[174]. The rearrangement, arising from a novel salt effect in aqueous media, reveals a mechanistic pathway switch for this acid-catalysed epoxide ring opening. The initiating step is the formation of the intermediate protonated epoxide (equation 69).

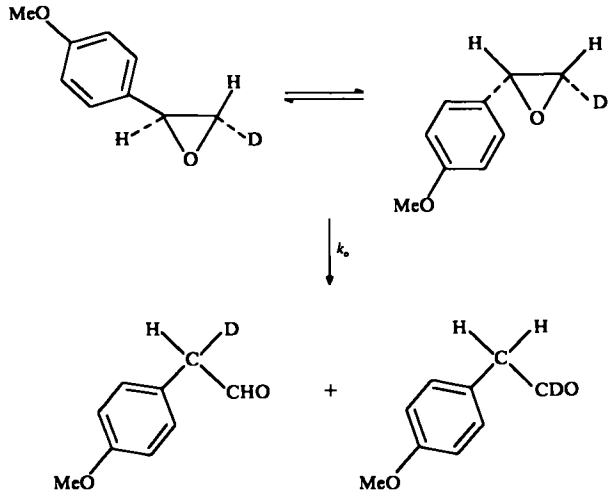


(69)

Ab initio and semi-empirical MO calculations on the gas-phase hydrolysis of protonated oxirane have predicted[175] that the inductively destabilized 2-hydroxy-carbenium ion is a transition state for rearrangement to the conjugate acid of the carbonyl compound.

A ^1H NMR study of the 'spontaneous' reaction of *p*-methoxy-*trans*-β-deuterostyrene

oxide and its *cis*-β-deutero isomer has provided evidence that the *trans*-β-D and *cis*-β-D display equal migrating aptitudes in the aldehyde-forming reaction (equation 70)[176–178].



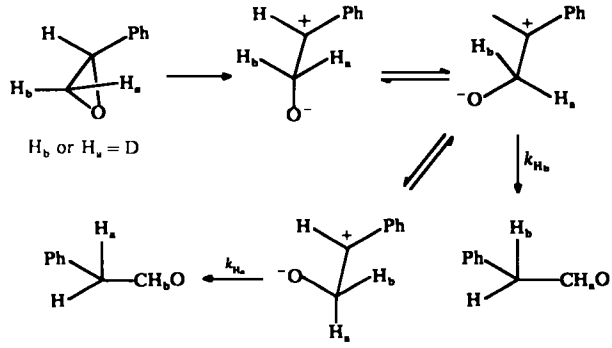
(70)

The spontaneous ring opening of epoxides in aqueous solution has been characterized mechanistically[179]. The complete pH–rate profile has been mapped. The aldehyde formed by rearrangement in both the acidic and spontaneous limbs reveals that the ionic strength exerts a profound effect.

c. Stereochemistry. Numerous new observations can be found on the stereochemistry of the rearrangement. It can be stated that in general, besides the structure of the epoxide, the stereochemistry of the rearrangement is mainly influenced by the nature of the reagent used and the reaction conditions[111].

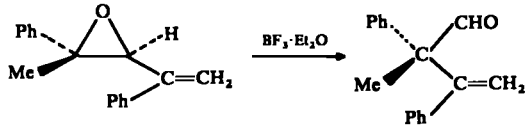
The BF_3-catalysed rearrangement of (+)-isophorone oxide proceeds with partial or extensive racemization of the solvent used (equation 59)[146,147].

Rearrangement of styrene oxide with $LiClO_4$ and BF_3 to give phenylethanal exhibits diastereotopic selection, with migration of the H *trans* to the phenyl group being favoured 1.4 and 1.14 times, respectively[133]. The rate of rotation about the C1—C2 bond of the intermediate is comparable to, but greater than, the rate of H migration (equation 71).



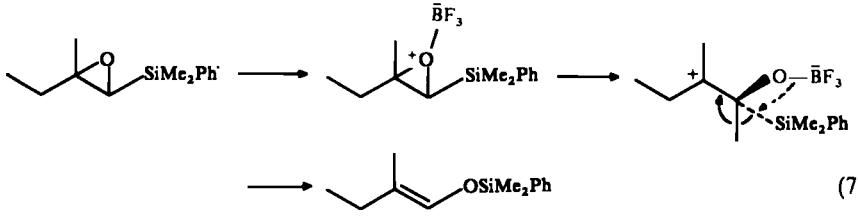
(71)

The first example of the stereochemistry of vinyl migration with an optically active substrate has been reported (equation 72)[113].



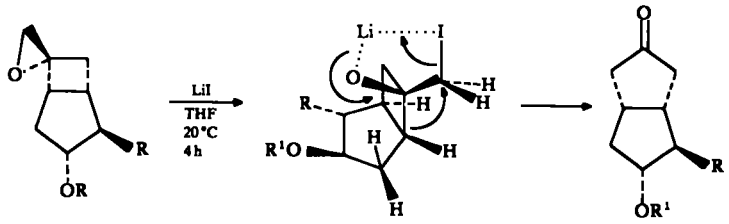
(72)

2,2-Disubstituted vinylsilane epoxides have been shown to rearrange stereospecifically in the presence of $BF_3 \cdot Et_2O$ to give silyl enol ethers of 2,2-disubstituted aldehydes[180] (equation 73).

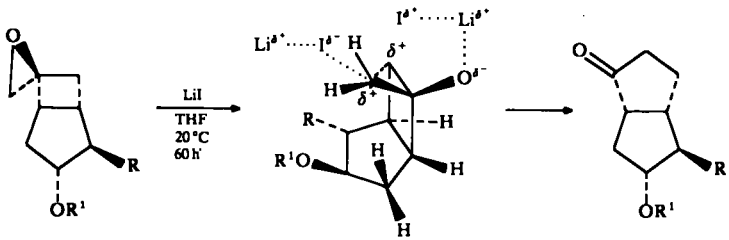


(73)

Treatment of the α-epoxide (equation 74) and the β-epoxide (equation 75) with LiI leads to a regioselective epoxide–carbonyl rearrangement[155].



(74)



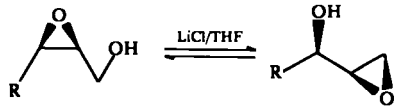
(75)

It has been suggested that the mechanistic mode of these epoxide–carbonyl rearrangements is largely dictated by the considerable steric interactions and torsional strain inherent in the bicyclo[3,2,0]heptane system. Thus, the α-epoxide, being readily susceptible to nucleophilic attack, is thought to form a five-membered anti-periplanar transition state, which then undergoes a synchronous rearrangement to the ketone. Owing to the steric crowding at the α-face however, this pathway is not available for

the β-epoxide, which is thought to form the ketone via the corner-protonated cyclopropane transition state.

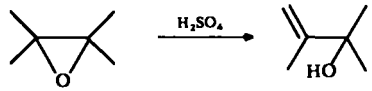
d. Other rearrangements. Reference was made earlier to the fact that, depending upon the structures of the compounds, the reaction conditions and the catalyst, carbonyl compounds are not the only products during the acid-catalysed rearrangement of epoxides. The diversity of the reactions is illustrated by several examples below.

A new example of the Payne rearrangement[181,182] can be seen in equation 76[134].

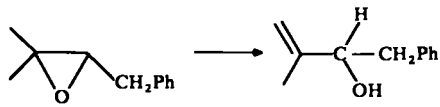


(76)

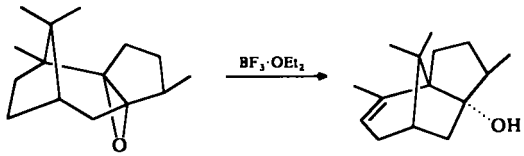
The acid-catalysed rearrangement of epoxides to unsaturated alcohols is outlined in equations 77–80.



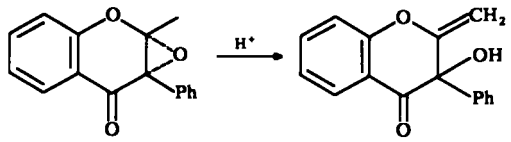
(77)[124]



(78)[130]



(79)[183]



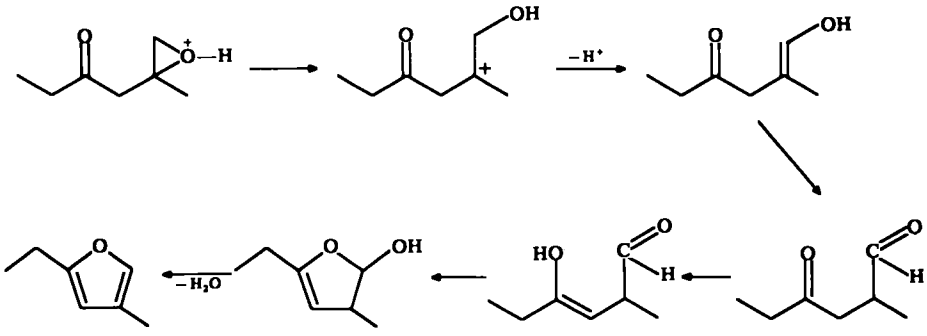
(80)[184]

Very interesting rearrangements of epoxides to compounds with a furan skeleton have also been observed. Epoxy ketones and epoxy alcohols can be transformed into furans and dihydrofurans, respectively (equations 81–84)[116,123,128,185].

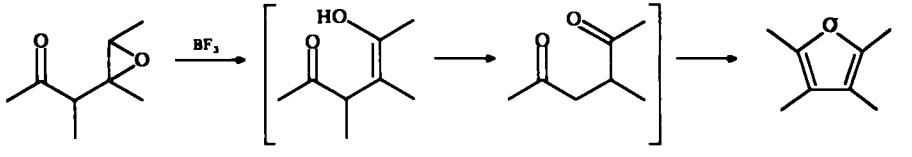
The formation of tetrahydrofuran derivatives is depicted in equations 85–87[186–189].

Four-membered cyclic ethers (oxetanes) can also be formed in the rearrangement of certain epoxides in the presence of $BF_3 \cdot Et_2O$ (equations 88 and 89)[156,190].

The Friedel–Crafts cyclialkylation of some epoxides[113,191,192] results in the formation of alcohols isomeric with the starting epoxides (equations 90 and 91)[140]. Isomerization to the corresponding ketones and aldehydes is a side-reaction. Depending upon the



(81)[185]



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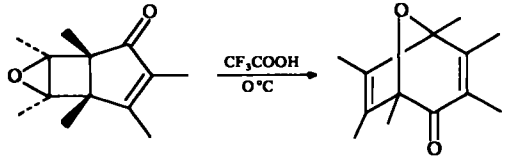
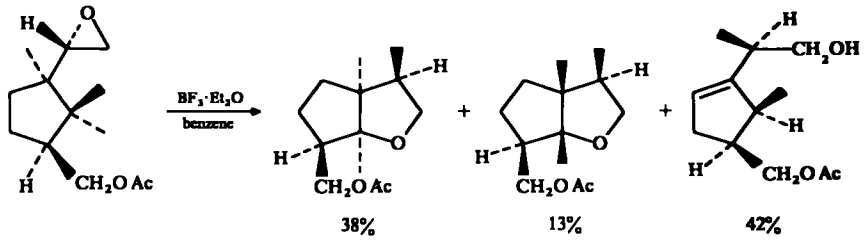


(83)[128]

(84)[116]



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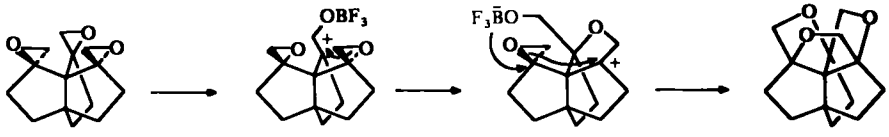
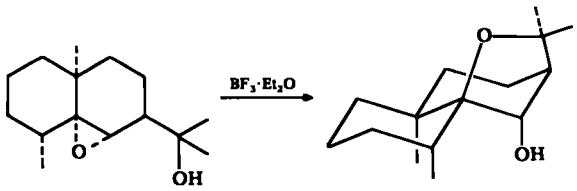


(86)[187]



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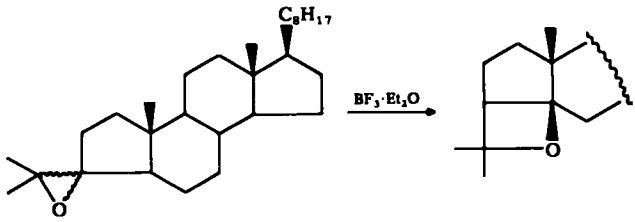

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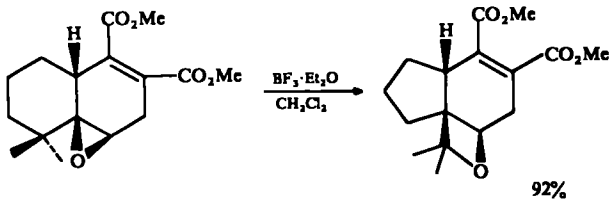
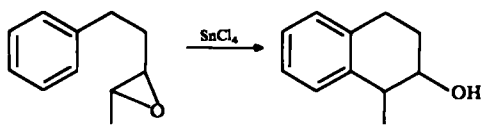
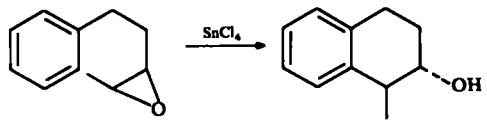


92%

(89)[156]



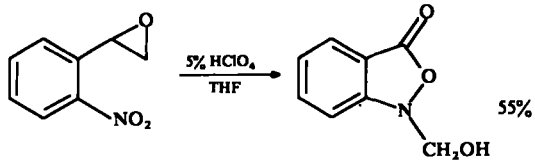
(90)



(91)

nature of the starting compound and the reaction conditions, the cyclization can exceed even 90%.

An unusual rearrangement product is formed from *ortho*-nitrostyrene oxide (equation 92)[127]. Several mechanisms have been postulated to account for this process.



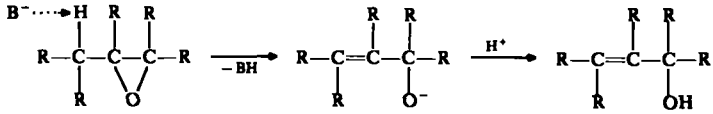
(92)

2. Base-catalysed isomerization of oxiranes

Since our earlier review in this series[105], interest has also grown in the rearrangements of epoxides in the presence of bases. This is clearly proved by the numbers of original publications and reviews of this topic during the past ten years[106–110,193,194]. The most detailed survey was published by Crandall and Apparu[194], who covered the literature up to 1982. Their work is significant not only in that the literature data are reviewed with adequate exhaustiveness, but also in the method of treatment of the experimental results, which are arranged in groups and tables that are easy to survey and analyse; the dependence of the reaction directions on the structures of the epoxides and on the experimental conditions is given, and some characteristic experimental descriptions are reported.

We now present more recent experimental results on the rearrangements of epoxides in solution in response to different bases. The chief regularities of the base-catalysed rearrangements of epoxides had been discovered ten years ago. The new investigations confirm these regularities and extend them to compounds not previously studied.

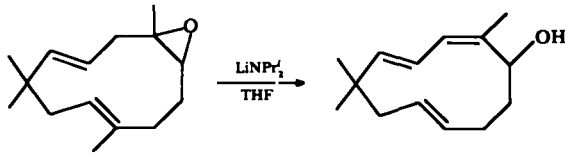
a. Formation of allyl alcohols. One of the important synthetic applications of epoxides is their rearrangement to allyl alcohols. Aliphatic epoxides and cycloalkene oxides in which the epoxide is not fused to a medium ring isomerize to allyl alcohols in the presence of bases. The rearrangement process is shown in equation 93.



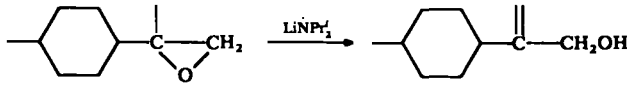
(93)

The conversion to an allyl alcohol occurs via abstraction of an acidic hydrogen from a carbon adjacent to the epoxide ring (β-carbon).

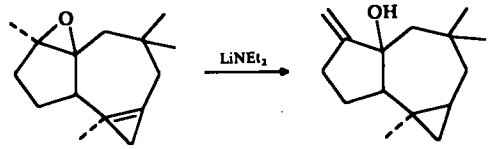
Lithium dialkylamides (mainly $LiNEt_2$) have been used as basic catalysts for the rearrangement of epoxides to allyl alcohols. Characteristic examples are given in equations 94–96[195–197].



(94)[195]

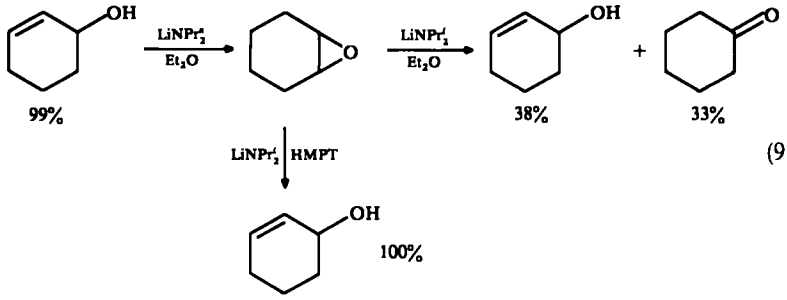


(95)[196]

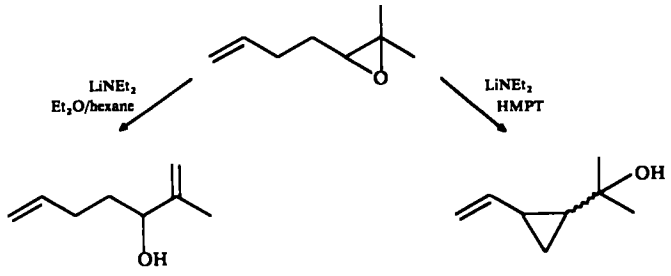


(96)[197]

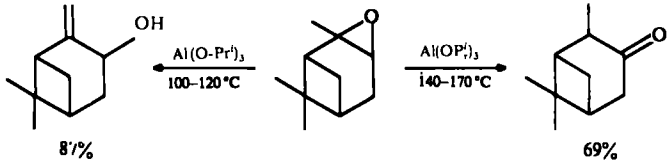
Apart from the structure of the epoxide, the bases used (e.g. the size of R in $LiNR_2$; other bases) and the reaction conditions (temperature and mainly the solvent used as reaction medium) strongly influence the selectivity of the rearrangement. This is demonstrated by equations 97–101[194,198–201].



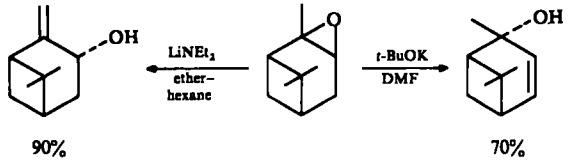
(97)[194]



(98)[198]



(99)[199]



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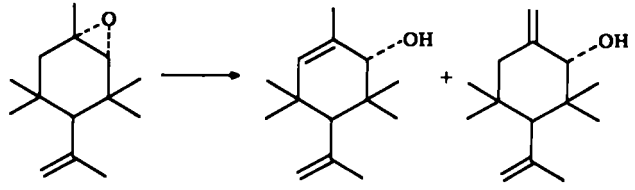
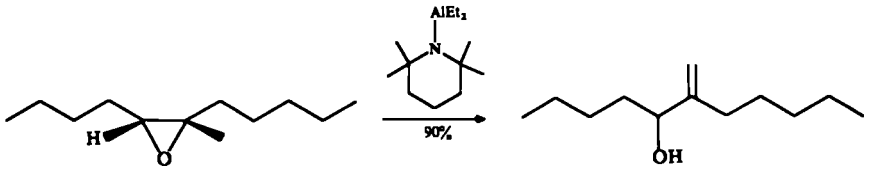
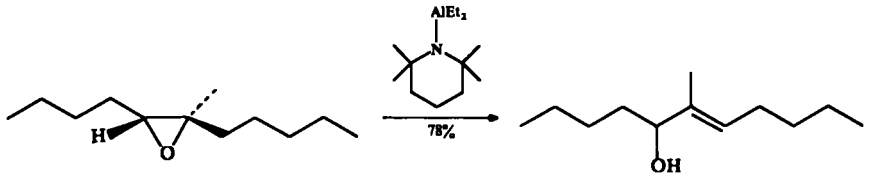


(101)[201]

Since the base employed for rearrangement has substantial steric requirements, the reaction is highly regioselective, involving proton abstraction from the least substituted carbon (equations 102 and 103)[202].

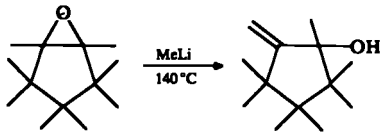


(102)



(103)

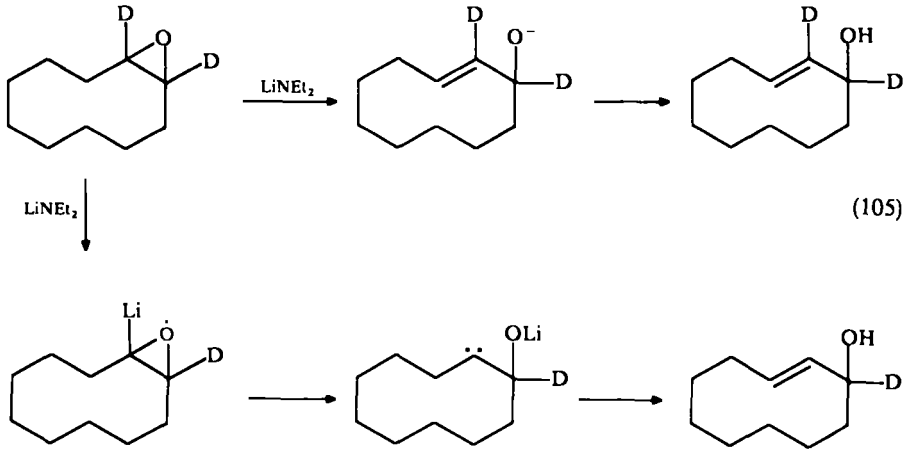
A variety of other methods (bases) have been reported to effect the rearrangement of epoxides to allyl alcohols. These include $Al(OPr^i)_3$[199,203,204], neutral alumina[205], $Ti(OPr^i)_4$[206,207], *t*-BuOK[200,208], n-BuLi[209], $AlEt_2NR_2$[202,210,211], $Cl_2Ti[N(i\text{-}Pr)(C_6H_{11})]_2$[212], $C_6H_{11}NPr^i \cdot MgBr$[213]. Examples are given in equations 99 and 101–104.



(104)[112]

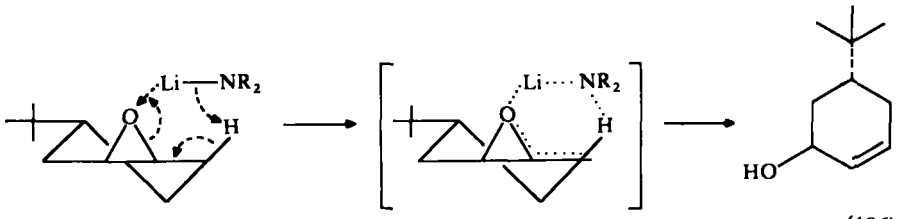
Chiral lithium dialkylamides have been used to convert epoxides to optically active allyl alcohols[214]. The mechanism of formation of allyl alcohols is better interpreted in terms of β- rather than α-elimination (equation 105)[194].

The mechanism of isomerization is decisively determined by the structure of the epoxide and the type of the base employed. Thus, whereas an α-elimination route cannot be excluded as a minor mechanistic contribution, this pathway has yet to be conclusively demonstrated. Consequently, a β-elimination mechanism is assumed for much of the discussion concerning allyl alcohol formation.

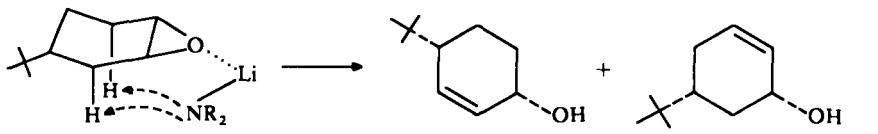


(105)

On the basis of the experimental data, the mechanism of the β-elimination may be explained in accordance with equations 106 and 107. The rearrangement involves a cyclic transition state.



(106)

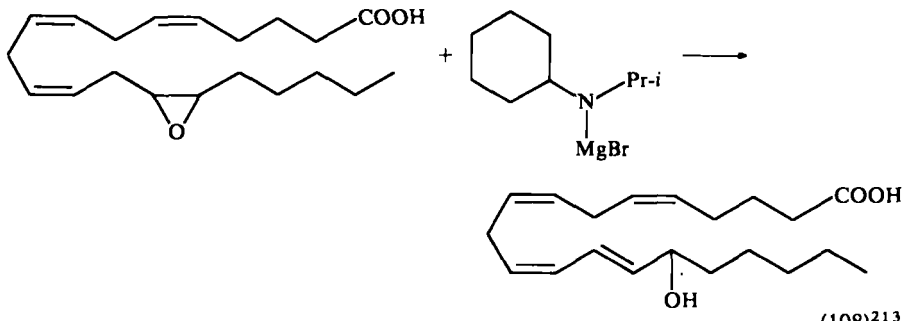


(107)

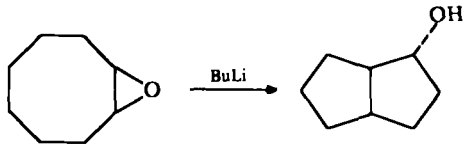
The results obtained with deuterated epoxides have led to postulation of a cyclic *syn*-elimination mechanism for the rearrangement (equations 106 and 107)[108,194].

Proton abstraction occurs at the least substituted carbon and, when the resulting olefin bond can exhibit *cis/trans* isomerism, the *trans* double bond is formed stereoselectively (equations 103 and 108)[213].

b. Other rearrangements. If the β-elimination involving formation of α,β-unsaturated alcohols is hindered, then, in accordance with the mechanism of α-elimination, different cyclic alcohols may be formed with the participation of transannular hydrogen[198,209,215] (equations 98 and 109). Crandall and Apparu give full details of the mechanism and stereochemistry of these reactions[194].



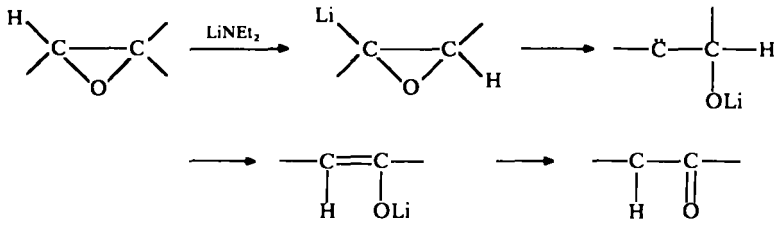
(108)[213]



(109)[209]

In a number of base-catalysed rearrangements of epoxides, ketones are generated as primary products. This type of reaction is useful only for epoxides in which neither β-elimination nor transannular insertion processes are effective. (It should be noted that ketones can also arise from further isomerization of allyl alcohols under the given reaction conditions. Consequently, it is not always clear whether the observed ketone products are formed directly from the epoxides or are secondary products.)

The formation of ketones can also be interpreted in terms of α-elimination (equation 110)[194].



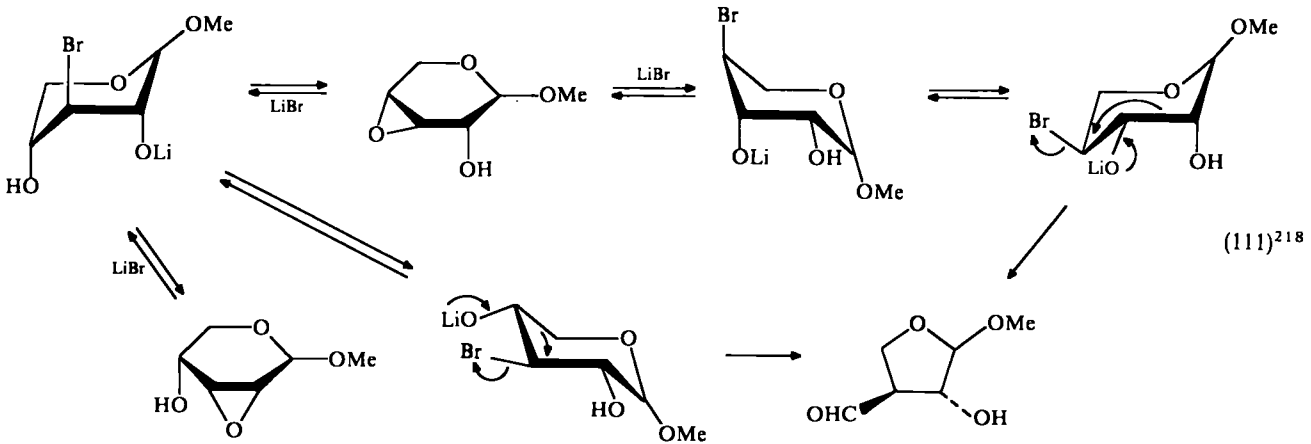
(110)

It was found[216] that 1,2-epoxycyclohexanes rearrange to five-membered ring aldehydes and ketones on treatment with LiBr/HMPA in refluxing benzene. A mechanism was postulated involving intermediate bromohydrin salts, indicating that the reaction medium was strongly basic (equation 111)[217,218].

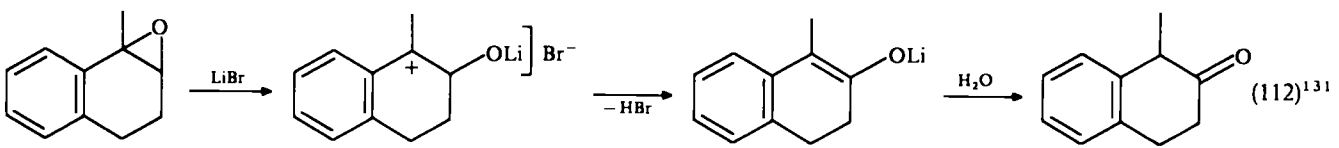
Similar regioselective epoxide–carbonyl rearrangements can be seen in equations 112–115.

Rearrangements to carbonyl groups have also been described on other catalysts, under mildly basic conditions[221–223]. The reactions are highly stereoselective (equations 116–118).

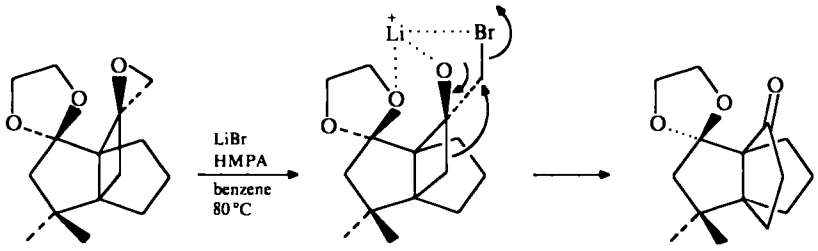
A methodology has recently been presented for the selective base-catalysed isomerization into ketones of certain epoxides containing a β-proton (equation 119)[224].



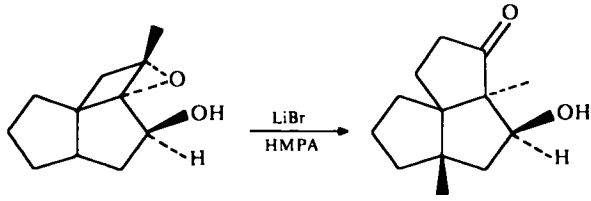
(111)[218]



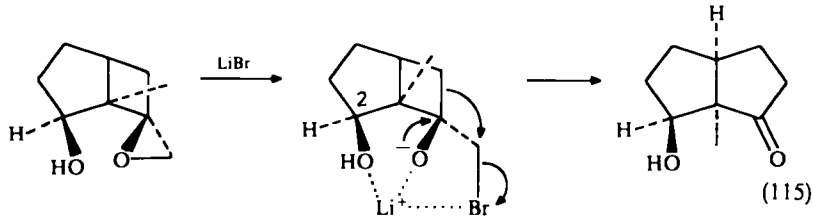
(112)[131]



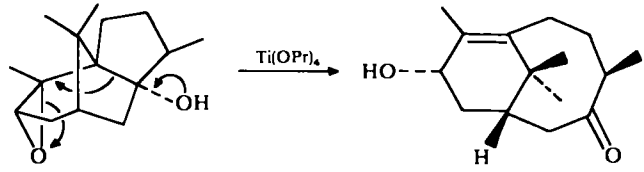
(113)[132]



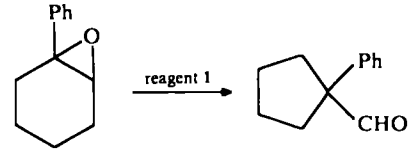
81% (114)[219]



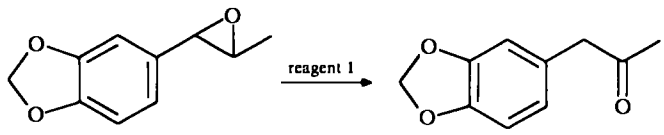
(115)[220]



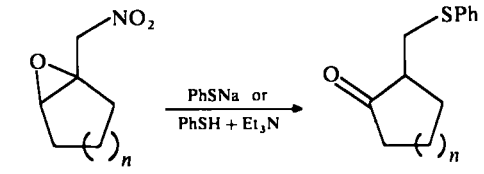
(116)[222]



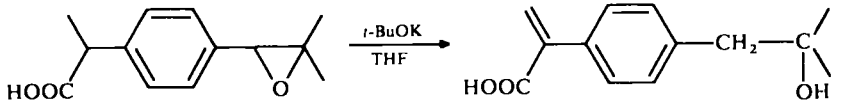
96% (117)[223]



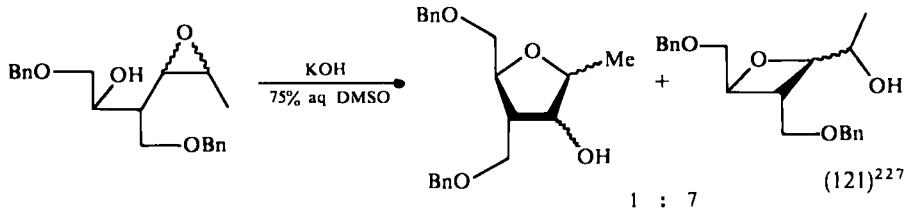
90% (118)[223]



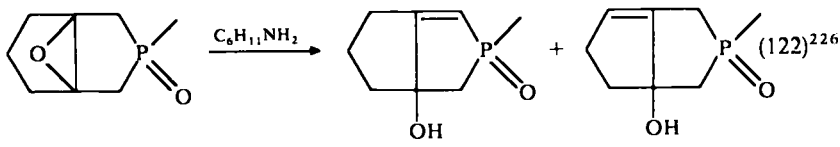
(119)[224]



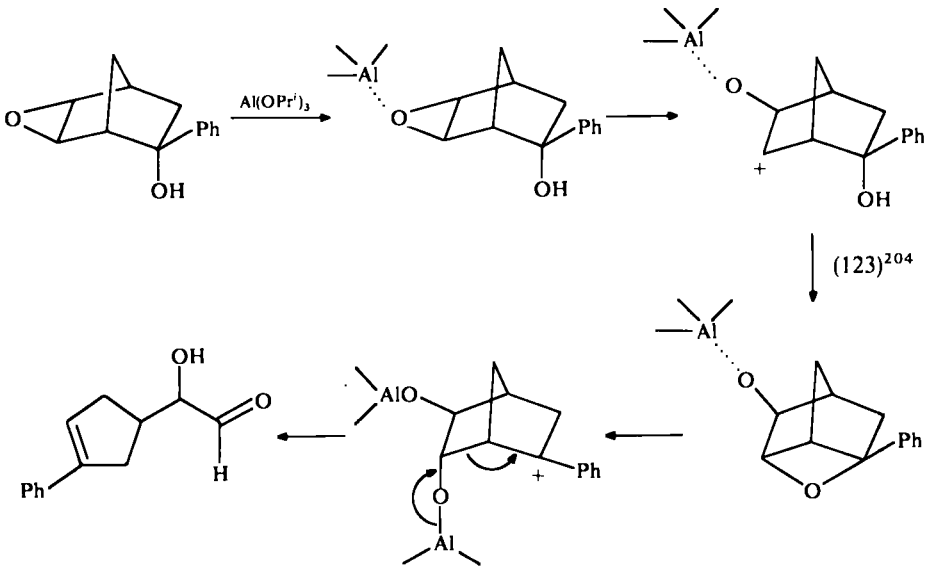
(120)[208]



(121)[227]



(122)[226]

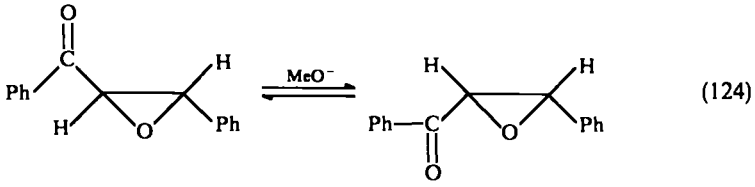


(123)[204]

Some of the special transformations of epoxides containing functional groups[204,221,224–233] are shown in equations 108 and 119–123.

Finally, equations 124–126 demonstrate some new examples of rearrangements of epoxides in the course of which epoxide rings with other structures or steric structures are formed. Equation 124 depicts the base-catalysed *trans–cis* rearrangement of chalcone epoxides[234]. The rearrangement of epoxide alcohols, recognized by Payne[181], which also takes place in basic medium (equation 125), has been applied to further compounds[235].

Alkylative epoxide rearrangement[236] has been elaborated (equation 126). This new route is shorter than the approach utilizing the Payne rearrangement and produces epoxides with the opposite absolute configuration.



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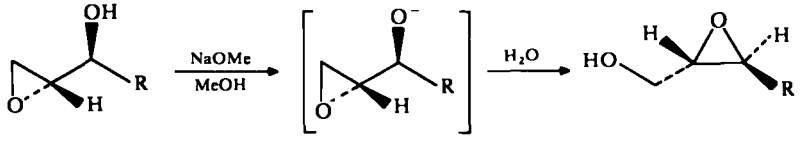
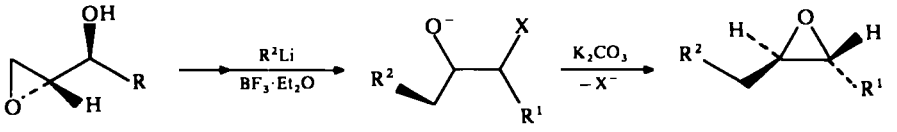


(125)



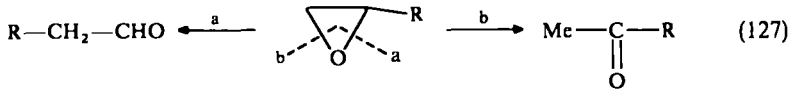
(126)

3. Heterogeneous rearrangement on solid acid or base catalysts

The relevant literature was reviewed by Arata and Tanabe in 1983[106]. This research field has subsequently continued to expand from both theoretical and practical aspects. On the basis of the publications, the results will be summarized in three subsections, arranged according to compound types. In the majority of cases, the literature relates to investigations where the catalytic activity of metal oxides was utilized.

a. Alkene oxides. It has long been known that the terminal alkene oxides are transformed into aldehydes or ketones, depending upon the character of the catalyst (equation 127)[106].

Strong acid sites favour aldehyde formation[106,237], whereas weak acid sites and basic

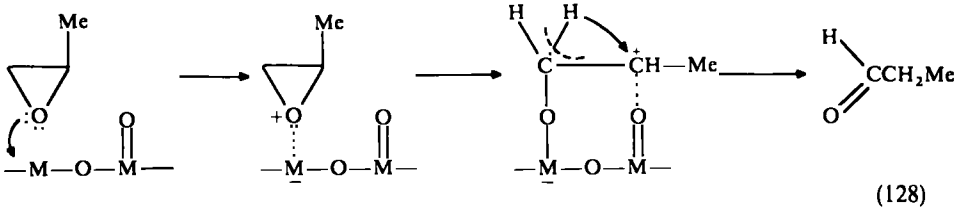


(127)

sites favour ketone[106] formation. IR studies have established that alkene oxides react with silanol groups on the surface of silica. Carbonyl compounds have been detected in some experiments[238]. On Cab—O—Sil (BDH silica) below 650 °C, isomerization does not occur, but Si—O—CH_2—CH_2—OH is formed[239].

As the exact functions of the catalytic effects of the two kinds of sites were not available, CaO, ZrO_2, BeO, Al_2O_3, Nb_2O_5 and WO_3 were chosen for investigations of the correlation between the acid–base properties of the oxides and the regioselectivity of the ring opening of propylene oxide and 2-butyloxirane-[3,3-$^2H_2$][240]. As regards selectivity, the formation of propanal is favoured by increasing acidity, while the formation of acetone shows an opposite trend, giving the highest selectivity on CaO. Supposing the mutual action of Lewis acid and base site pairs, i.e. electron pair acceptor and electron pair donor sites, the formation of the two products can be interpreted as shown in equations 128 and 129.

The positions of the deuterium atoms in the product carbonyl compounds serve as clear evidence of the mechanisms suggested (equation 130[240]).



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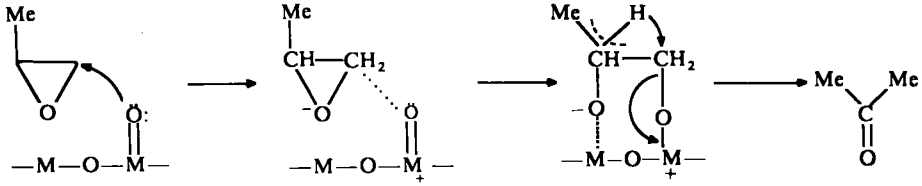

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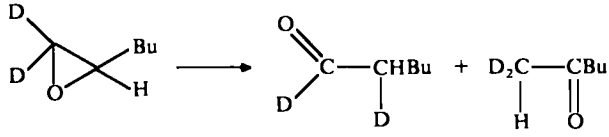


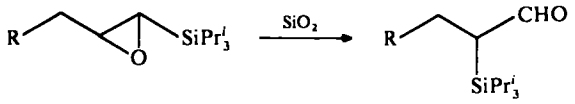
(130)

In the two processes depicted above, the selectivity-determining factors governing the formation of the isomeric carbonyl compounds are different. On acidic oxides, the selectivity is determined by the difference in stability of the possible carbenium ions, resulting in enhanced yields of propanal. In contrast, on basic oxides, the transformation is mainly controlled by steric factors, permitting a higher selectivity for the formation of acetone.

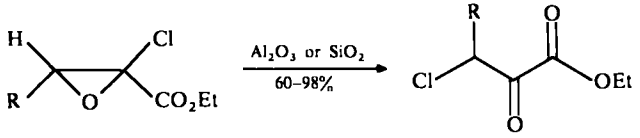
In conclusion, a strong correlation has been found between the regioselectivity of the ring opening of 2-methyloxirane and the surface acidity and basicity of six oxide catalysts. This correlation may occur when weak and medium strong Lewis acid–Lewis base site

pairs are the active centre ensembles for the reaction. Within this scope and limitation, 2-methyloxirane can be used as a test molecule to characterize the surface acid–base properties of oxide catalysts and to assess the relative strength and significance of the acidic or basic sites within the site pairs.

Two examples are shown in equations 131 and 132 to illustrate the reactions of alkene oxides containing functional groups on the action of alumina and silica, respectively[241–243].



(131)[242]



(132)[243]

R = Et, Pr, *i*-Pr, Bu, *i*-Bu, n-C_5H_{11}

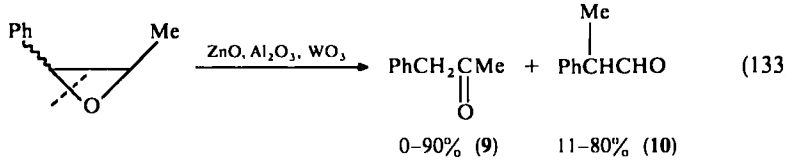
b. Phenyl epoxides. Several new observations have been published on the rearrangement of epoxystyrene into phenylacetaldehyde[238,244–247], and on the rearrangements of other phenyl epoxides[111,248,249].

The transformation of epoxystyrene has been studied on alumina[247], alumina impregnated with different metal salts[246,250], different silica-aluminas[244,245] and Nb_2O_5[245]. With the exception of the latter, phenylacetaldehyde can be prepared with high selectivity and high conversion. The 'three-step mechanism' was suggested as the reaction route of the rearrangement[244]. The activity of zeolites in the rearrangement of phenyl epoxides into aldehydes was proved with new experimental data[245,248].

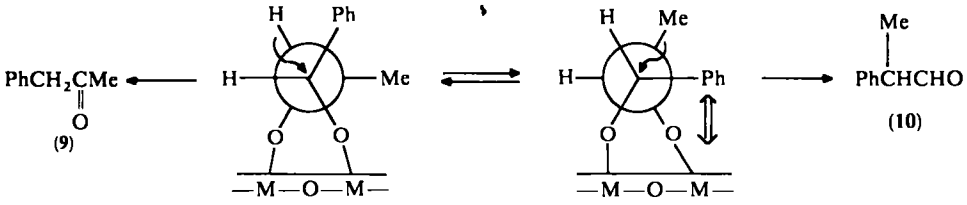
The rearrangement of light and deuterium-labelled *cis*- and *trans*-2-methyl-3- phenyloxiranes[111] was studied on ZnO, Al_2O_3 and WO_3. Both in the gas phase (473–673 K) and in the liquid phase (298–413 K), 1-phenyl-2-propanone (**9**) and 2-phenylpropanal (**10**) were formed with high selectivities (0–90% and 11–80%, respectively); see equation 133.

Ring opening was found to occur by selective fission of the benzyl C—O bond. Mechanistic studies revealed the formation of an open carbenium ion or a double-bonded surface intermediate. The acidic (electrophilic) and basic characters of the oxides determine the product distributions by affecting the relative importance of the competing mechanisms (equation 134).

The activities of the catalysts and the selectivity of formation of **9** increase with increasing acidic (electrophilic) character of the oxides. The differences in selectivity



(133)



(134)

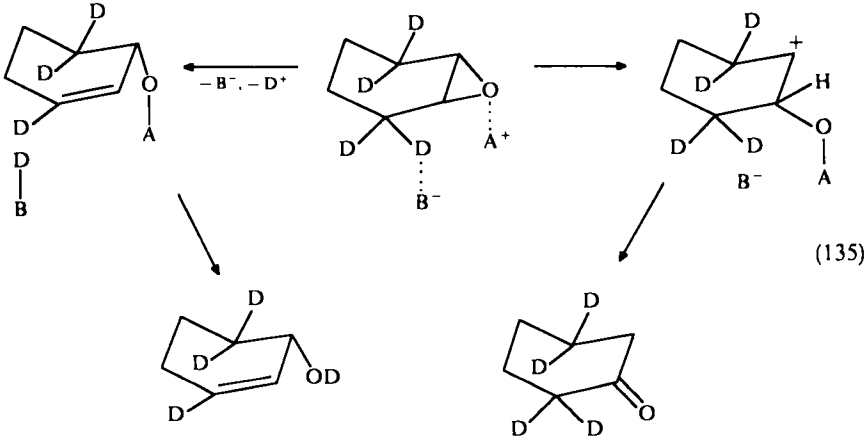
under different reaction conditions were explained in terms of different reaction mechanisms. Selective ring opening catalysed by WO_3 occurs through an open carbenium ion. This allows free rotation around the C—C bond, permitting the highly selective formation of **9** from both isomers. Rearrangement on Al_2O_3 and ZnO takes place via a double-bonded surface intermediate with the participation of both acidic and basic sites. The limited conformational motion in this species results in the formation of both **9** and **10**.

c. Cyclic alkene oxides. Arata and Tanabe[106] discuss in detail the results published up to 1980. These investigations are also significant in practice: some products of the rearrangements of cyclic alkene oxides are valuable as raw materials for perfumes, cosmetics and pharmaceuticals.

For this procedure, predominantly alumina, supported alumina and silica gel catalysts are used. The rearrangement mainly results in the formation of the corresponding carbonyl compounds. The selectivity of the reaction, which depends considerably on the structure of the epoxide, can be influenced by modification of the catalyst. In this respect, the general regularities described in the previous two subsections hold here too. The high activities are caused by high surface acidities[251].

Cyclopentene oxides are transformed into the corresponding cyclopentanones in the vapour phase over Cu–Zn and SiO_2–Al_2O_3[252] or fluorinated alumina[253] as catalyst.

There are new experimental observations on the rearrangements of mono-, bi- and tricyclic epoxides with cyclohexane skeletons[106]. The isomerization of cyclohexene oxide catalysed by solid acids and bases was investigated by Arata and Tanabe[254]. A complex



(135)

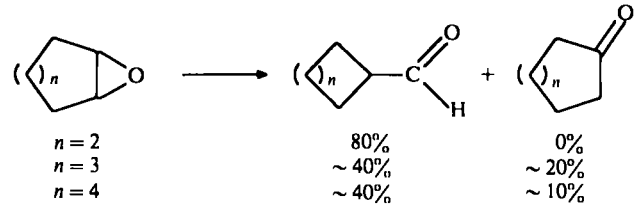
mixture of products, including cyclohexanone and 2-cyclohexen-1-ol, was formed on the catalysts examined. In order to obtain information on the reaction path, the rearrangement of deuterated cyclohexene oxide was studied[106,254]. The rearrangement process is shown in equation 135.

From these observations it was concluded that ketone is formed on the acid sites. The epoxide adsorbs on both an acid and a basic site. The extents of the two types of adsorption determine the selectivity.

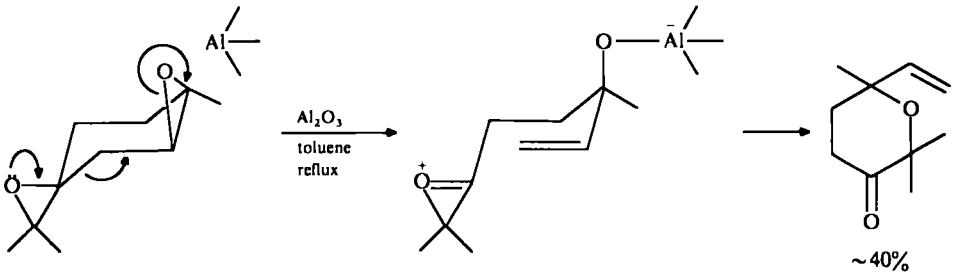
The selectivity of the rearrangement was studied on LiBr/alumina catalyst (gas phase or toluene reflux) as a function of the ring size[250] (equation 136).

A novel rearrangement of 1,2:4,8-diepoxy-*p*-menthane has been found (equation 137)[255].

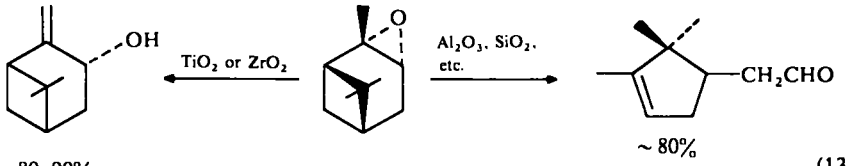
The role of acidic and basic active sites on the selectivity of rearrangement is shown by the isomerization of α-pinene oxide over solid acids and bases (equation 138)[256,257].



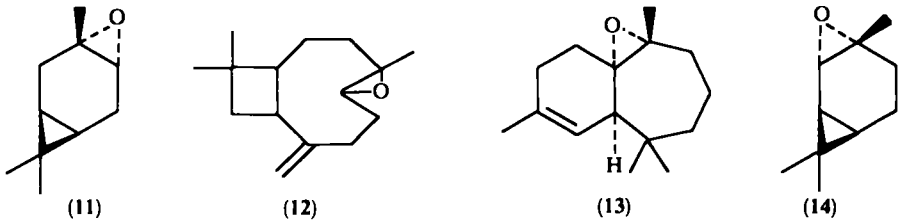
(136)



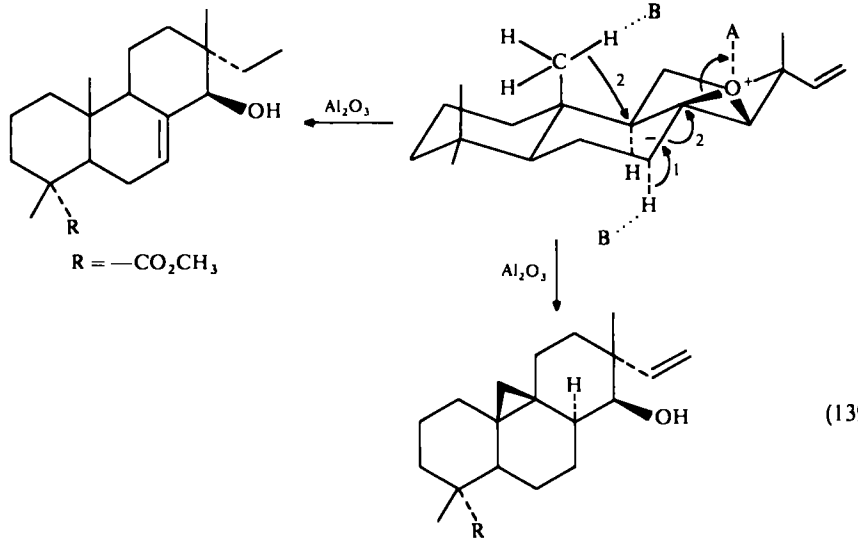
(137)



(138)



The rearrangements of other bicyclic cycloalkene oxides have also been studied on solid catalysts similar to the above[106,258]. The reactions of diterpene epoxides **11–14** on active neutral alumina have revealed the existence of new rearrangements of the diterpene skeleton[205,259]. From among the numerous identified products of these rearrangements, we present characteristic examples in which a new diterpene skeleton is formed (equations 139–141).



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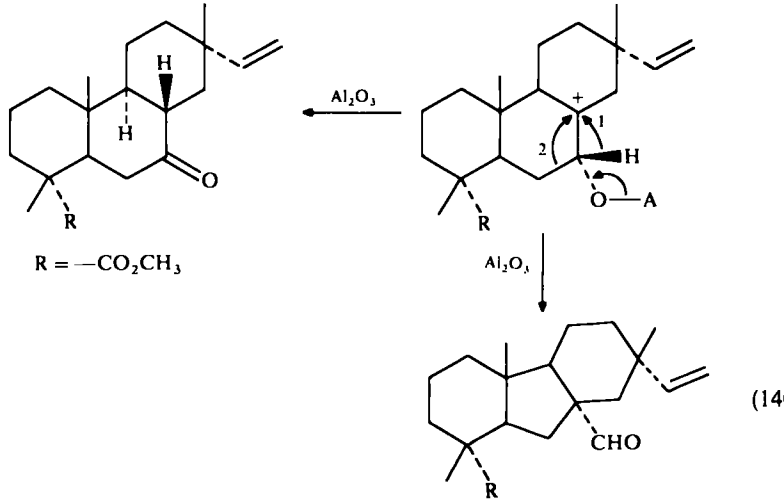

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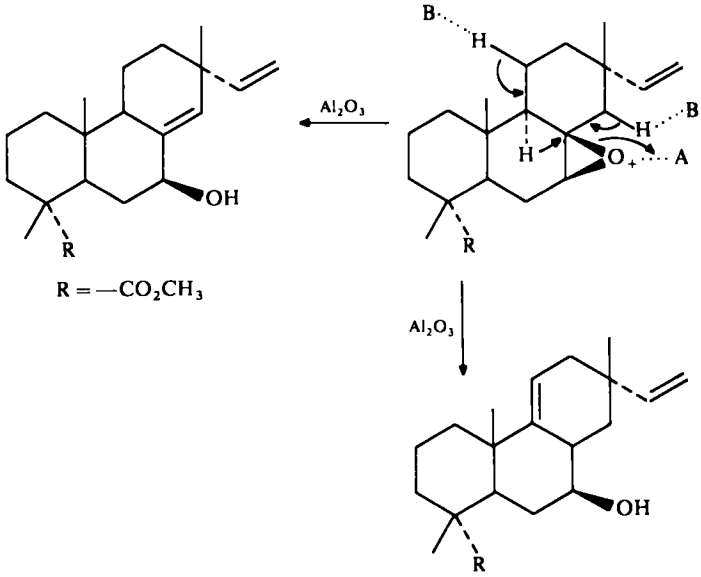


(141)

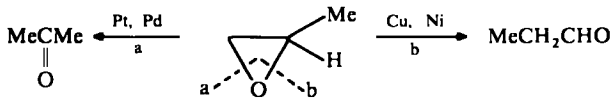
4. Heterogeneous rearrangement induced by metals and metal complexes

a. Rearrangement of oxiranes by metals. Mainly, the metals in group 8 of the periodic table catalyse the rearrangement of oxiranes into carbonyl compounds. The earlier results in this field have been briefly reviewed[109,260].

More recently, results have been reported on the rearrangements on different metals of ethylene oxide[261–265], 2-alkyl-[266–271], 2,3-dialkyl-[268,269,272,273] and 2,2,3,3-tetraalkyloxiranes[274,275] (chiefly the Me analogues). These studies involved the dependence of the regioselectivity on the nature of the metal, the stereochemistry of the rearrangement and new aspects of the reaction mechanism.

Even at the beginning of the investigations, during the hydrogenolysis of epoxides into alcohols it appeared that hydrogen addition and isomerization are parallel reactions; the presence of hydrogen or one of its isotopes is needed for isomerization[260].

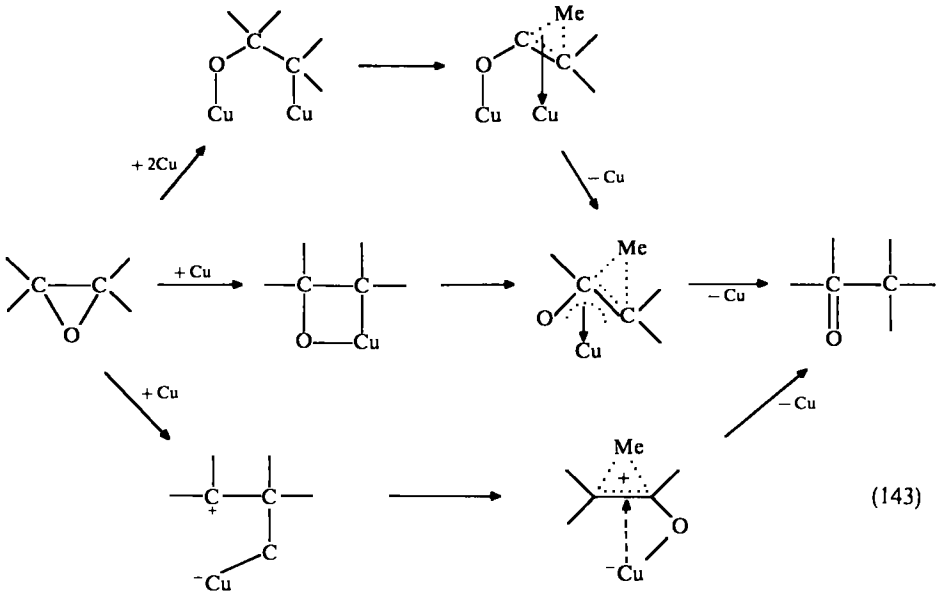
For oxiranes with asymmetrical structures, isomerization takes place in both directions (equation 142)[266,267,273,276,277].



(142)

Investigations into the rearrangement of tetramethyloxirane on various types of metals provided the first experimental proof that 1,2-bond shift isomerization on noble metals also takes place in the case of compounds containing C—O bonds (and not only for hydrocarbons)[274].

On copper intercalated graphite, tetramethyloxirane undergoes rearrangement to *t*-butyl methyl ketone via 1,2-Me migration and to 2,3-dimethylbut-3-en-2-ol via a 1,3-hydrogen shift (equations 143 and 144)[275].



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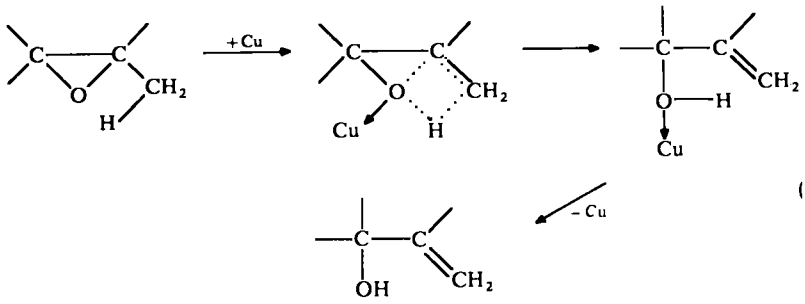
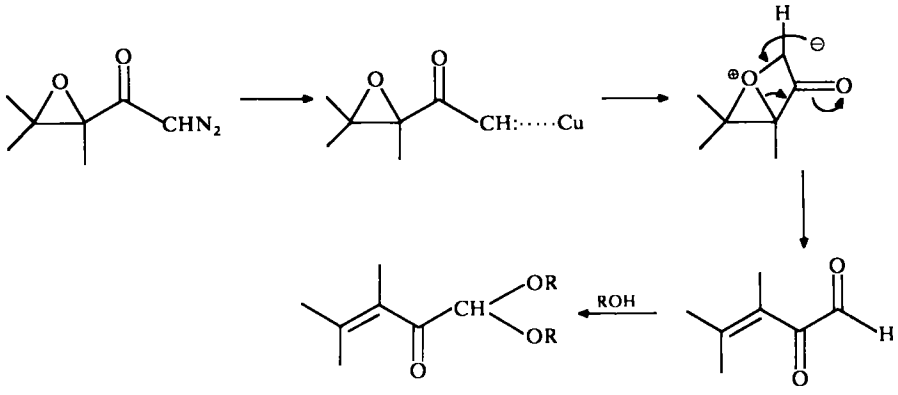


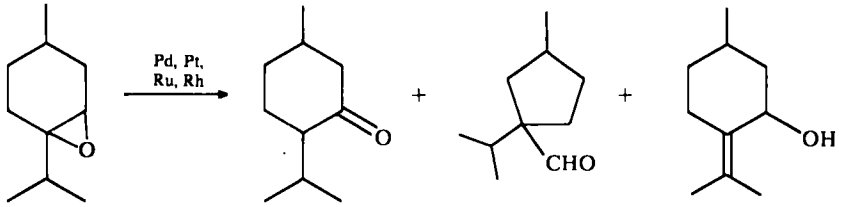
(144)



(145)

An interesting reaction has been observed during the transformation of epoxydiazomethyl ketones in the presence of copper (equation 145)[278].

The preparation of thymol from *p*-menthane-3,4-epoxide on different metal catalysts is followed by rearrangement reactions (equation 146)[279].



15–35% 10–20% 10–20%

(146)

Studies of the stereochemistry of hydrogenolysis and deuterolysis of cyclohexene epoxides on different metals revealed rearrangement into ketones[280,281].

During studies of the isomerization of epoxides on metal catalysts, it was found that different metals have different regioselectivities (equation 142). On Cu and Ni catalysts, primarily the C—O bond adjacent to the substituent is split, leading to the formation of a primary alcohol or aldehyde[266,267], while on Pt and Pd catalysts mainly the more distant C—O bond undergoes cleavage[269,273], yielding a secondary alcohol or ketone.

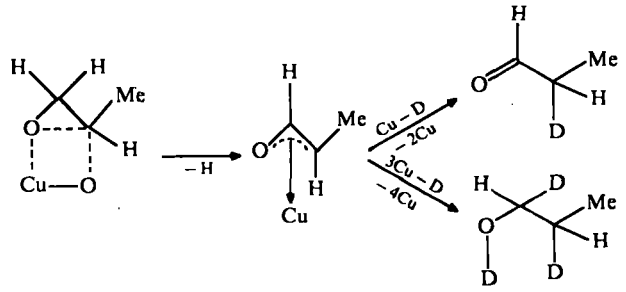
An explanation of why the regioselectivity on Cu and Ni is different from that on Pt or Pd demands a knowledge of the mechanism of the reaction. On Pt and Pd catalysts, a C—O bond in the oxiranes undergoes cleavage through the participation of chemisorbed hydrogen: the regioselectivity is governed by stereochemical factors. On Ni and Cu, ionic insertion takes place and the opposite regioselectivity is observed. Through deoxidation, oxirane is able to oxidize the Cu and Ni surfaces, resulting in ionic surface sites (Lewis acid–base sites). In the cases of Pt and Pd, the oxide formed in this way is rapidly reduced in the presence of hydrogen.

The results show that the observed difference in regioselectivity can be explained by the different affinities of the metals for oxygen, i.e. the regioselectivity is determined by the nature of the metal.

The regioselectivity of the transformation of methyloxirane on Pt is independent of the catalyst structure[271]. The selectivity of acetone formation exhibits a curve with a slight minimum character as a function of the degree of dispersion, since this selectivity is determined by the hydrogen availability on the surface. New kinetic and stereochemical investigations have led to a better knowledge of the mechanism of rearrangement.

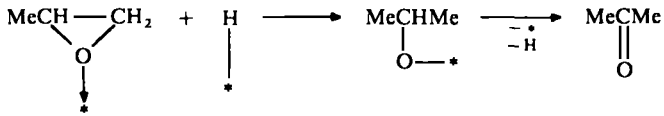
The isomerization of ethylene oxide to acetaldehyde has been examined over a single-crystal Ag(111) surface. The rate-determining step was observed to change: at lower temperatures, the rate of isomerization of the reactant was rate-limiting; at higher temperatures, the rate of adsorption became rate-controlling[261]. The adsorption of ethylene oxide has been studied in detail on Ni(111)[262,265], Cu(110)[263] and Ag(110)[264] surfaces.

Experimental proofs has been obtained that the mechanisms of the isomerizations to aldehydes and ketones differ. Aldehydes are formed on the action of the electrophilic sites of the metal catalysts[282,283]. For example, on a copper–copper oxide interface, the isomerization in the presence of deuterium in all probability takes place as outlined in equation 147[267] (the active sites consisted of a Lewis acid site–basic site pair).



(147)

The reaction kinetic data allow the rearrangement to ketones[260,269] to be interpreted in terms of both associative and dissociative mechanisms, depending upon the experimental conditions (mainly the hydrogen coverage of the catalyst and the temperature of the reaction). The associative mechanism is shown in equation 148 and the dissociative one in equation 149. The presence of H or D is necessary for the isomerization.



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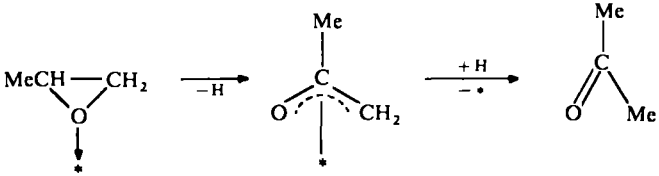


(149)

* = active site of the catalyst.

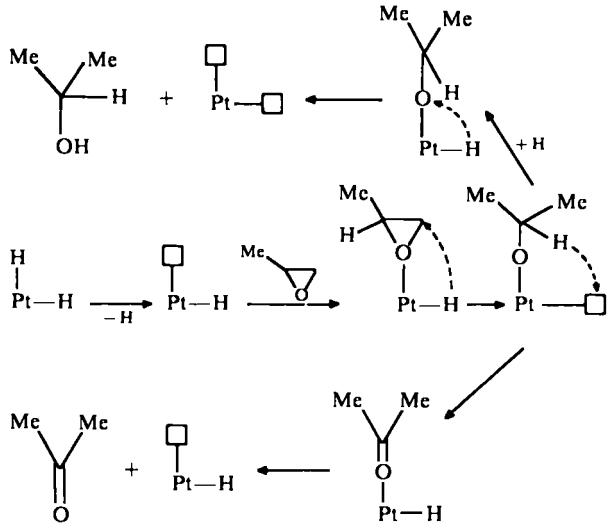
cis-2,3-Dimethyloxirane is transformed at a much higher rate than the *trans* isomer on Pt and Pd catalysts[269,276]. On Ni[272,276] no difference could be detected between the transformation rates. Ionic insertion is believed to take place on a Ni catalyst, whereas on Pt and Pd the C—O bond in the oxiranes undergoes cleavage through the participation of chemisorbed hydrogen[277,284]. Besides the difference in the mechanism, there is also a difference in the stereochemistry of adsorption of the oxirane. The fact that *cis*-2,3-epoxybutane is transformed at a higher rate than the *trans* isomer means that the structures of the critical transition states differ for pairs of isomers[272]. If the rate-limiting step occurs after the metallacycle is destroyed, the distinction between the stereoisomers is lost. This happens in the ionic-type insertion on a Ni catalyst.

For Pt and Pd catalysts, the rate-limiting step is the chemisorption, which results in the insertion of the Pt or Pd atom into the C—O bond. The original stereochemistry of the ring is retained in the rate-determining step. The steric interaction between the Me groups is larger for the *cis* oxiranes than for the *trans* isomers. Since the *cis* isomer is transformed at a higher rate, the steric interaction between the molecule and the

catalyst predominates in the transition state. This is in good agreement with the assumed flat-lying adsorption[268,273].

The transformation of methyloxirane on various Pt catalysts is a structure-sensitive reaction[270,271]. The total turnover frequency (i.e., number of reactions per surface site per second) of the reaction exhibits a maximum curve as a function of dispersion. The structure sensitivity is caused by the change in the number of active sites.

The isomerization of methyloxirane take place via a mechanism in which hydrogen is involved in the rate-determining step. This reaction occurs on the step sites ^{2}M (i.e. on surface atoms with two coordinative unsaturations) (equation 150)[270,271].

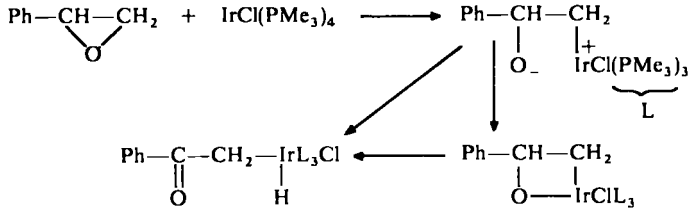


(150)

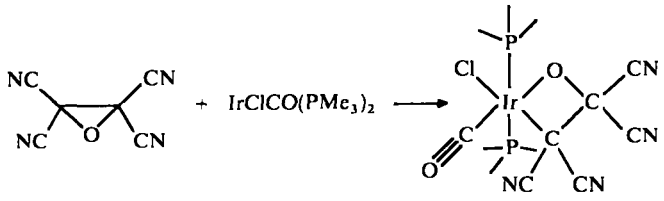
b. Rearrangement of oxiranes with metal complexes. It is increasingly reported that epoxides isomerize into carbonyl compounds and unsaturated alcohols. In certain cases, geometrical isomerization has also been observed.

In order to interpret the rearrangement of epoxides to ketones, it was presumed that the isomerization takes place through oxametallacyclobutane intermediates. This supposition was proved experimentally by the isolation of stable complexes which can be regarded as intermediates of the rearrangement in the reactions of Ir complexes and epoxides (equations 151 and 152)[285,286].

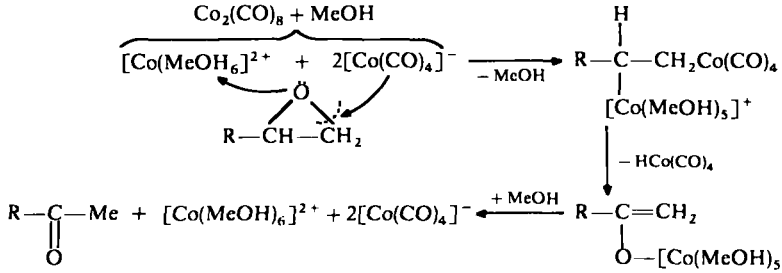
Terminal epoxides have been selectively converted into methyl ketones with $Co_2(CO)_8$ (equation 153)[139]. The rearrangement of internal epoxides into ketones is much slower, allowing the specific transformation of terminal epoxides. The scope of the reaction and tentative mechanisms have been discussed (equation 153)[139].



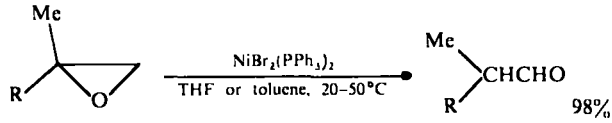
(151)



(152)



(153)



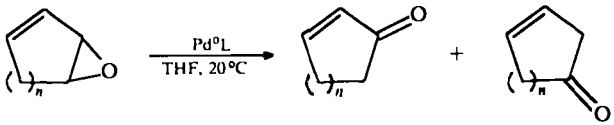
(154)

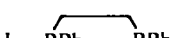
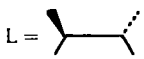
R = H, Me, Ph

$NiBr_2(PPh_3)_2$ catalysed the ring-opening isomerization of epoxides to yield exclusively the corresponding aldehydes (equation 154)[287].

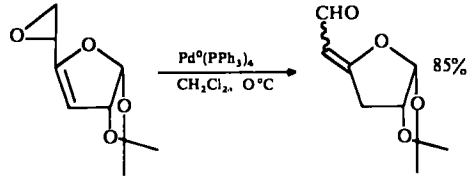
The regioselectivity for the C—O bond cleavage of epoxides is determined by the nature of the ligand coordinated to the metal center.

The catalytic hydrogenation of styrene oxide with cationic Rh complexes was investigated to develop its selective conversion into the corresponding alcohol and aldehyde[288]. The catalytic activity and selectivity depended strongly on the ligand.

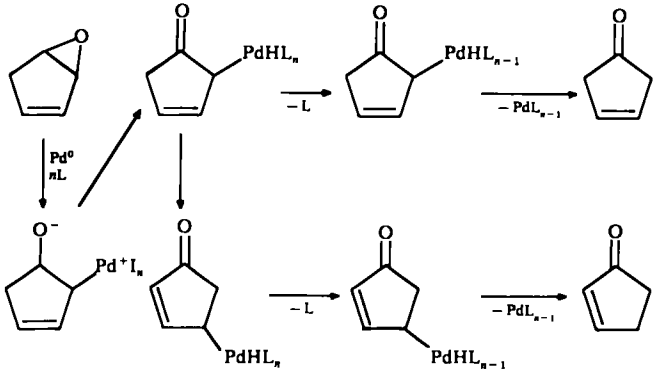


n =	1/2	1/2
L = PPh_3	0/0	100/100
L = 	32/10	68/90
L = 	100/87	0/13

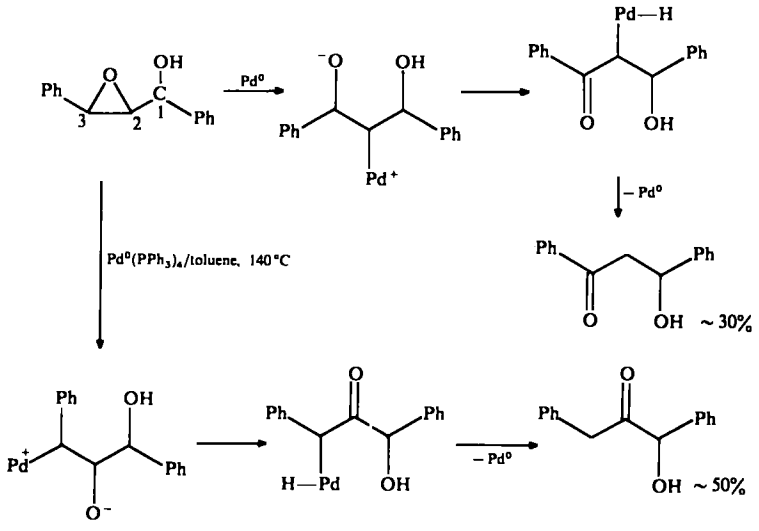
(155)


CHO
$Pd^0(PPh_3)_4$
CH_2Cl_2, 0 °C
85%

(156)


$PdHL_n$
$PdHL_{n-1}$
$-L$
$-PdL_{n-1}$
Pd^0
nL
Pd^+I_n
$PdHL_n$
$PdHL_{n-1}$

(157)


Ph
OH
Ph
Pd^0
Pd—H
$-Pd^0$
$Pd^0(PPh_3)_4$/toluene, 140 °C
~30%
H—Pd
~50%

(158)

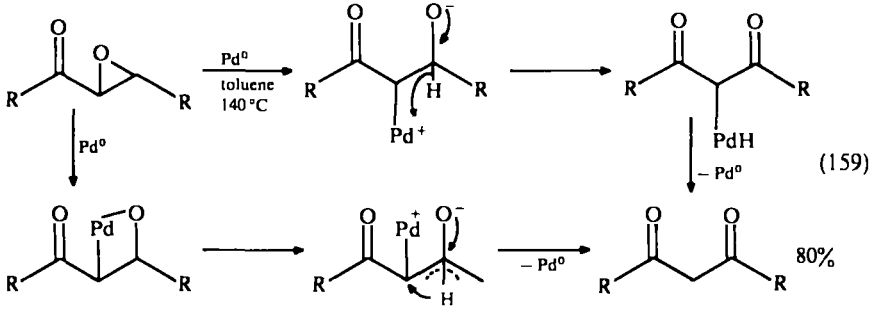
It was reported that $Pd(PPh_3)_4$[289–291] and $RhH(PPh_3)_4$[292] are selective catalysts for the formation of α,β-unsaturated carbonyl compounds from 1,3-diene monoepoxides; however, it was found that $RhH(PPh_3)_4$ is ineffective for cyclopentadiene monoepoxide. The selectivity for the Pd-catalysed rearrangement depends strongly on the type of ligand used and is kinetic in origin (equations 155 and 156). The mechanism of the procedure can be interpreted according to equation 157[291].

The isomerization with $Pd(PPh_3)_4$ of 2,3-epoxy alcohols containing an aryl group at C1 and/or C3 leads to the formation of α- and β-hydroxy ketones (equation 158)[293].

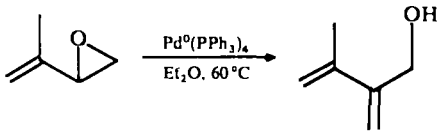
In the presence of Pd-phosphine complexes, α,β-epoxy ketones rearrange into β-diketones (equation 159)[294–296].

1,3-Diene epoxides rearrange into unsaturated alcohols in the presence of Pd-phosphine complexes (equations 160–162)[289,297].

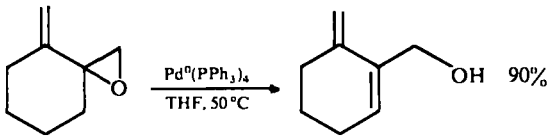
Achiral oxiranes are isomerized to optically active allyl alcohols by catalytic amounts of cob(I)alamine (B_{12}) in protic polar solvents (equation 163)[298].



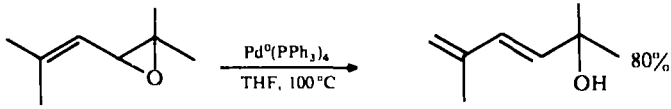
(159)



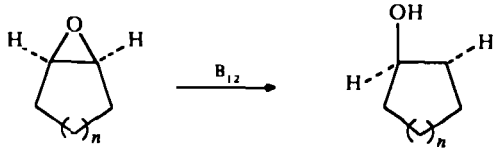
(160)



(161)



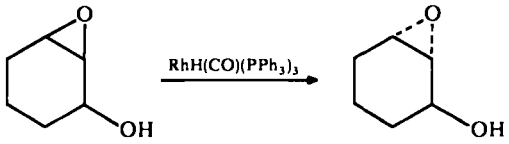
(162)



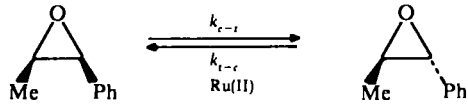
(163) (163)

Cyclic epoxy alcohols undergo geometric isomerization on the action on RhH(CO)-$(PPh_3)_3$ (equation 164)[299].

Groves and coworkers[300] have discovered that a variety of ruthenium(II) porphyrin complexes catalyse the *cis–trans* isomerization of epoxides (equation 165).



(164)



(165)

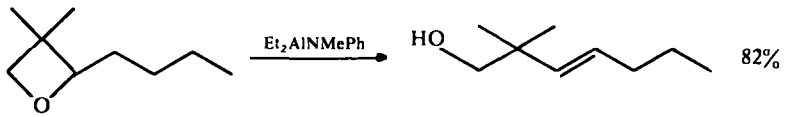
B. Rearrangement of Four-, Five- and Six-membered Cyclic Ethers

The literature dealing with the rearrangement of four- (oxetanes), five- (oxolanes) and six-membered (oxanes) cyclic ethers is far less extensive than that on the epoxides. This is clearly mainly due to the greater reactivity of the three-membered strained ring system. Consequently, the rearrangements and isomerizations of oxetanes, oxolanes and oxanes are of much lower practical significance than those of epoxides in synthetic organic chemistry.

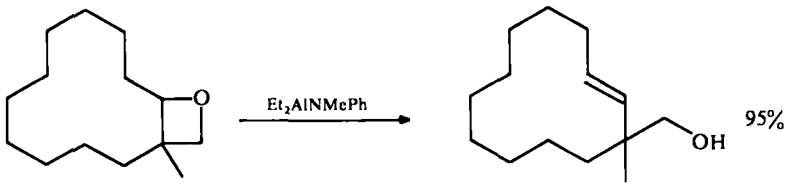
Rearrangement of the less strained cyclic ethers requires stronger reaction conditions. On the other hand, the presence of certain functional groups on the ring may facilitate rearrangement. New examples of the rearrangement of four-, five- and six-membered cyclic ethers will be presented in that order, and the latest results on their metal-catalysed isomerizations will be reviewed.

1. Rearrangement of oxetanes

A novel oxetane ring-opening rearrangement with an organoaluminum reagent occurred regio- and stereoselectively in about 90% isolated yield (equations 166 and 167)[301]. The unusual specificity of this rearrangement was explained by a cyclic

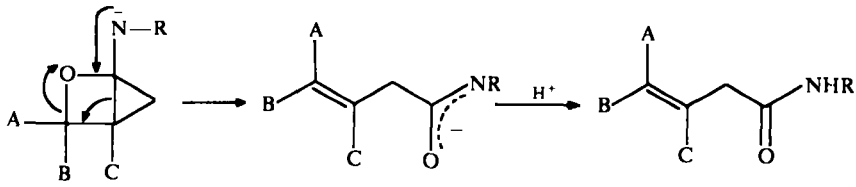


(166)

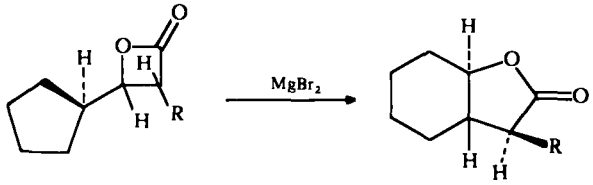


(167)

syn-elimination mechanism in which the ring opening has substantial stereochemical requirements. Equations 168[302] and 169[303] give two examples of the rearrangement of oxetanes containing functional groups.



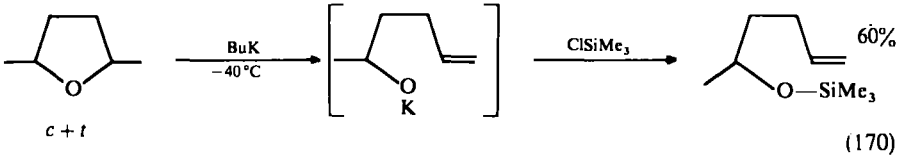
(168)



(169)

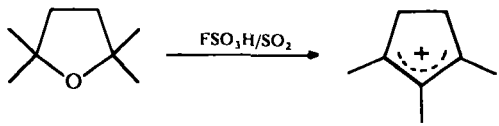
2. Rearrangement of oxolanes

The rearrangement and isomerization of unsubstituted oxolanes require very strong reagents; *cis*- and *trans*-2,5-Dimethyloxolane are isomerized by BuK formed *in situ* (equation 170)[304].



(170)

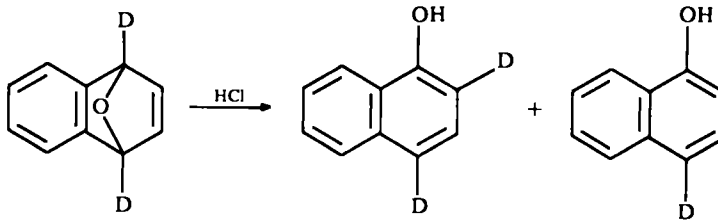
The reactions of oxolanes in superacidic media have been studied. They decompose only at 0 °C or above, yielding unsaturated carbocations. The reaction of tetramethyloxolane probably involves cleavage of the ether to a hydroxy carbocation, dehydration and recyclization (equation 171)[137].



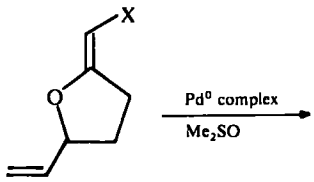
(171)

Experimental data have been reported on the rearrangement and isomerization of unsaturated oxolanes. A deuteride shift takes place (equation 172)[305,306]. The acid-catalysed aromatization results in partial retention of D at the 2-position of 1-naphthol.

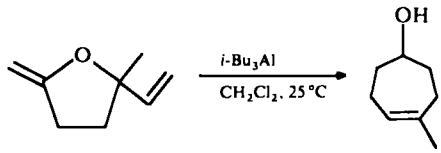
Five-membered ring enol ethers with vinyl substitents (allyl vinyl ethers) are transformed to seven-membered rings or cyclopentanones via a 3,3 sigmatropic rearrangement by different reagents and form vinylcyclopropane derivatives with organoaluminum reagents (equations 173–177)[307–311].



(172)

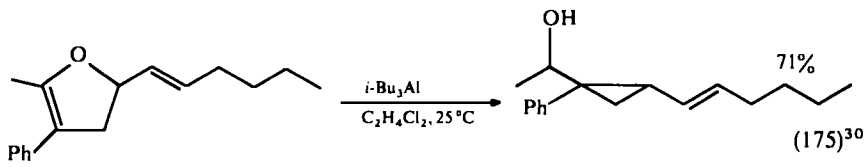


(173)[307]

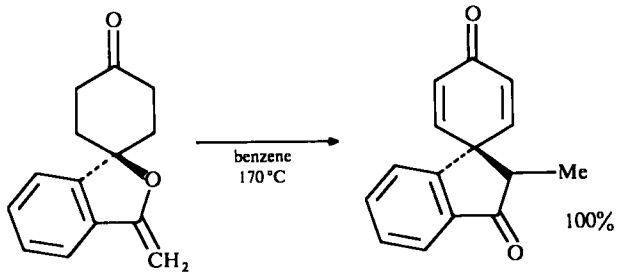


82%

(174)[308]

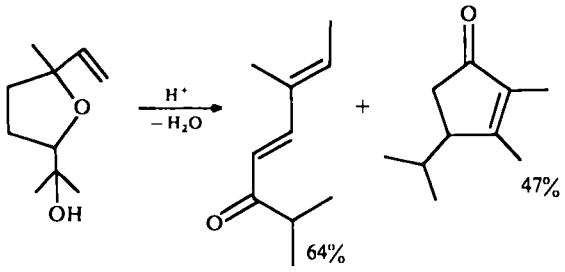


(175)[308]



(176)[309]

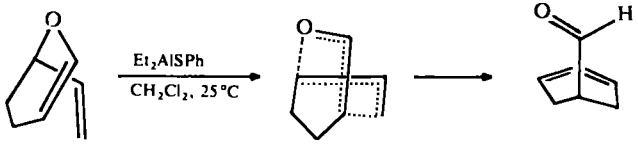
The selectivity of the Pd^0-catalysed rearrangement of vinyl alkylidene oxolanes depends on the solvent and the ligands on the Pd[307,312]. The stereospecificity of this reaction is extraordinary.



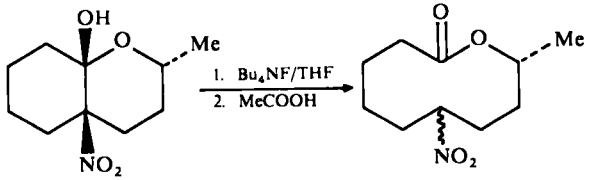
(177)[311]

3. *Rearrangement of oxanes*

Experimental observations have been reported on the rearrangement of compounds containing different functional groups. A rearrangement of Claisen type is outlined in equation 178[313]. Similar examples were presented earlier[32,37,38,40]. Equation 179[314] shows a ring enlargement.

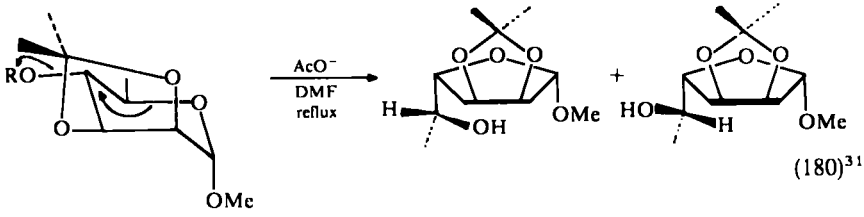


(178)

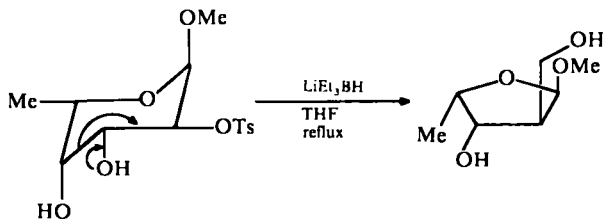


(179)

Compounds with pyranoside structure can be transformed into furanosides through a rearrangement involving ring contraction, under different experimental conditions (equations 180 and 181)[315–318].



(180)[315]

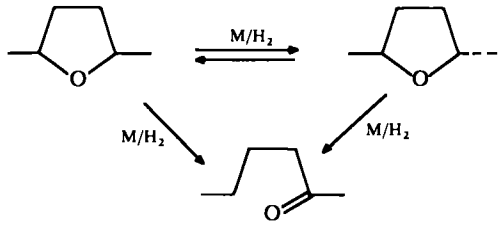


(181)[317]

4. Isomerization of cyclic ethers on metal catalysts

Alkyl- and aryl-substituted cyclic ethers isomerize into carbonyl compounds in the presence of Pt, Pd or Ni and hydrogen. Since our earlier survey of this field[319], numerous new observations have been reported on the four-[268,272,277,284], five-[268,272,273,277,284,320–324] and six-membered[272,277] cyclic ethers.

In the case of stereoisomers, not only isomerization to a ketone but also geometrical isomerization took place (equation 182)[272,321].



(182)

The hydroisomerization character of the isomerization is confirmed by recent experimental results[284,321]. New experimental data have contributed to the recognition of the stereochemistry[272,320,321] and mechanism[268,273,277,321–324] of the isomerization.

The most important conclusions are as follows:

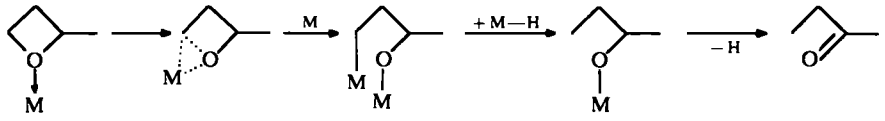
(a) In the majority of cases, the mechanism of the process depends on the ring size and the nature of the metal.

(b) The mechanisms of formation of ketones and aldehydes are not the same. In the formation of aldehydes, the electrophilic centres (M/support phase boundary sites, metal ions) play the decisive role, whereas in the formation of ketones, the metal ions do so.

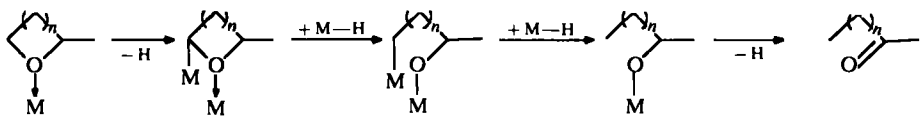
(c) The first step of cyclic ether adsorption is the formation of an oxygen–metal bond.

(d) The structure of the adsorbed species chiefly depends on the ring size and the geometry of the reactant.

The details concerning these conclusions can be found in the works cited above. Ketones are the main products of isomerization of cyclic ethers. The reaction route of their formation is shown in equation 183 for oxetanes, and in equation 184 for oxolanes and oxanes.



(183)



$n = 2, 3$

(184)

IV. REFERENCES

1. D. L. Dalrymple, T. L. Kruger and W. N. White, in *The Chemistry of the Ether Linkage* (Ed. S. Patai), Wiley, London, 1967, pp. 617–667.
2. B. M. Trost and I. Fleming (Eds.), *Comprehensive Organic Synthesis*, Pergamon Press, Oxford, 1991.
3. A. Jefferson and F. Scheinmann, *Quart. Rev.*, **22**, 391 (1968).
4. H. J. Hansen and H. Schmid, *Chem. Brit.*, **5**, 111 (1969).
5. H. J. Hansen, in *Mechanism of Molecular Migrations* (Ed. B. S. Thyagarajan), Vol. 3, Interscience, New York, 1971, p. 177.
6. D. J. Faulkner, *Synthesis*, 175 (1971).
7. S. J. Rhoads and N. R. Raulins, *Org. React. (N.Y.)*, **22**, 1 (1975).
8. A. W. Murray, in *Organic Reaction Mechanisms* (Eds. A. C. Knipe and W. E. Watts), Wiley, Chichester, 1975–1988.
9. F. E. Ziegler, *Acc. Chem. Res.*, **10**, 227 (1977).
10. G. B. Bennett, *Synthesis*, 589 (1977).
11. P. A. Bartlett, *Tetrahedron*, **36**, 3 (1980).
12. J. Gajewski, in *Hydrocarbon Thermal Isomerizations*, Academic Press, New York, 1981.
13. R. P. Lutz, *Chem. Rev.*, **84**, 205 (1984).
14. R. K. Hill, in *Asymmetric Synthesis* (Ed. J. D. Morrison), Vol. 3, Academic Press, New York, 1984, p. 503.
15. W. Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd ed., Cambridge University Press, Cambridge, 1986.
16. C. J. Moody, *Adv. Heterocycl. Chem.*, **42**, 203 (1987).
17. F. E. Ziegler, *Chem. Rev.*, **88**, 1423 (1988).
18. S. Blechert, *Synthesis*, 71 (1989).
19. J. Kallmerten and M. D. Wittman, *Stud. Nat. Prod. Chem.*, **3**, 233 (1989).
20. P. Wipf, in *Comprehensive Organic Synthesis* (Eds. B. M. Trost and I. Fleming), Vol. 5, p. 827, Pergamon Press, Oxford, 1991.
21. S. E. Denmark and M. A. Harmata, *J. Am. Chem. Soc.*, **104**, 4972 (1982).
22. S. E. Denmark, M. A. Harmata and K. S. White, *J. Am. Chem. Soc.*, **111**, 8878 (1989).
23. S. E. Denmark and J. E. Marlin, *J. Org. Chem.*, **56**, 1003 (1991).
24. S. E. Denmark, H. Stadler, R. L. Dorow and J.-H. Kim, *J. Org. Chem.*, **56**, 5063 (1991).
25. J. J. Gajewski, J. Jurayj, D. R. Kimbrough, M. E. Gande, B. Ganem and B. K. Carpenter, *J. Am. Chem. Soc.*, **109**, 1170 (1987).
26. R. M. Coates, B. D. Rogers, S. J. Hobbs, D. R. Peck and D. P. Curran, *J. Am. Chem. Soc.*, **109**, 1160 (1987).
27. E. Brandes, P. A. Grieco and J. J. Gajewski, *J. Org. Chem.*, **54**, 515 (1989).
28. P. A. Grieco, E. B. Brandes, S. McCann and J. D. Clark, *J. Org. Chem.*, **54**, 5849 (1989).
29. K. Maruoka, H. Banno, K. Nonoshita and H. Yamamoto, *Tetrahedron Lett.*, **30**, 1265 (1989).
30. K. Nanoshita, H. Banno, K. Maruoka and H. Yamamoto, *J. Am. Chem. Soc.*, **112**, 316 (1990).
31. K. Maruoka, H. Banno and H. Yamamoto, *J. Am. Chem. Soc.*, **112**, 7791 (1990).
32. L. A. Paquette, D. Friedrich and R. D. Rogers, *J. Org. Chem.*, **56**, 3841 (1991).
33. M. J. S. Dewar and C. Jie, *J. Am. Chem. Soc.*, **111**, 511 (1989).
34. J. J. Gajewski, K. R. Gee and J. Jurayj, *J. Org. Chem.*, **55**, 1813 (1990).
35. R. L. Vance, N. G. Rondan, K. N. Houk, F. Jensen, W. T. Borden, A. Komornicki and E. Wimmer, *J. Am. Chem. Soc.*, **110**, 2314 (1988).
36. T. J. Grattan and J. S. Whitehurst, *J. Chem. Soc., Perkin Trans. 1*, 11 (1990).
37. W. A. Kinney, M. J. Coghlan and L. A. Paquette, *J. Am. Chem. Soc.*, **107**, 7352 (1985).
38. L. A. Paquette and H. J. Kang, *J. Am. Chem. Soc.*, **113**, 2610 (1991).
39. K. Maruoka, K. Nonoshita, H. Banno and H. Yamamoto, *J. Am. Chem. Soc.*, **110**, 7922 (1988).
40. C. M. G. Philippo, N. H. Vo and L. A. Paquette, *J. Am. Chem. Soc.*, **113**, 2762 (1991).
41. (a) Y. Naruta, N. Nagai and K. Maruyama, *J. Chem. Soc., Perkin Trans. 1*, 1143 (1988).
    (b) L. S. Hart and C. R. Waddington, *J. Chem. Soc., Perkin Trans. 2*, 1607 (1985).
42. W. G. Dauben, J. M. Cogen and V. Behar, *Tetrahedron Lett.*, **31**, 3241 (1990).
43. L. M. Harwood, *J. Chem. Soc., Chem. Commun.*, 1120 (1982); 530 (1983).
44. G. Balavoine, G. Bram and F. Guibe, *Nouv. J. Chim.*, **2**, 207 (1978).
45. R. D. H. Murray, M. Sutcliffe and M. Hasegawa, *Tetrahedron*, **31**, 2966 (1975).

46. S. Ozawa, Y. Sasaki and Y. Ogino, *Bull. Chem. Soc. Jpn.*, **60**, 4279 (1987).
47. M. S. Syamala and V. Ramamurthy, *Tetrahedron*, **44**, 7223 (1988).
48. T. Hayashi, Y. Okada and T. Inaba, *Bull. Chem. Soc. Jpn.*, **62**, 3835 (1989).
49. H. Ishii, T. Ishikawa, S. Takeda, S. Ueki, M. Suzuki and T. Harayama, *Chem. Pharm. Bull.*, **38**, 1775 (1990).
50. L. Kupczyk-Subotkowska, W. H. Saunders and H. J. Shine, *J. Am. Chem. Soc.*, **110**, 7153 (1988).
51. T. Borgulya, R. Madeja, P. Gahrni, H.-J. Hansen, H. Schmid and R. Barner, *Helv. Chim. Acta*, **56**, 14 (1973).
52. R. C. Cambie, T. A. Howe, M. G. Pausler, P. S. Rutledge and P. D. Woodgate, *Aust. J. Chem.*, **40**, 1063 (1987).
53. A. S. R. Anjaneyulu and U. V. Mallavadhani, *J. Chem. Soc., Perkin Trans. 1*, 623 (1988).
54. R. S. Subramanian and K. K. Balasubramanian, *Tetrahedron Lett.*, **29**, 6797 (1988).
55. G. A. Kraus, S. Liras, T. O. Man and M. T. Molina, *J. Org. Chem.*, **54**, 3137 (1989).
56. S. E. Drewes, N. D. Emslie, N. Karodia and G. Loizou, *Synth. Commun.*, **20**, 1437 (1990).
57. F. M. Hauser and P. Hewawasam, *J. Org. Chem.*, **53**, 4515 (1988).
58. S. N. Kilényi, J. M. Mahaux and E. Van Durme, *J. Org. Chem.*, **56**, 2591 (1991).
59. G. Bruce, *Chemtracts: Org. Chem.*, 302 (1990).
60. O. Reinaud, P. Capdevielle and M. Maumy, *Synthesis*, 293 (1988).
61. G. Wittig and L. Löhmann, *Justus Liebigs Ann. Chem.*, **550**, 260 (1942).
62. G. Wittig, H. Döser and I. Lorenz, *Justus Liebigs Ann. Chem.*, **562**, 192 (1949).
63. J. A. Marshall, in *Comprehensive Organic Synthesis* (Eds. B. M. Trost and I. Fleming), Vol. 3, Pergamon Press, Oxford, 1991, p. 975.
64. U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.*, **9**, 763 (1970).
65. R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **18**, 563 (1979).
66. T. Nakai and K. Mikami, *Chem. Rev.*, **86**, 885 (1986).
67. R. Brückner, *Kontakte (Darmstadt)*, (2), (3) (1991).
68. R. Brückner, in *Comprehensive Organic Synthesis* (Eds. B. M. Trost and I. Fleming), Vol. 6, Pergamon Press, Oxford, 1991, p. 873.
69. F. E. Ziegler, in *Comprehensive Organic Synthesis* (Eds. B. M. Trost and I. Fleming), Vol. 5, Pergamon Press, Oxford, 1991, p. 875.
70. R. B. Bates, T. J. Siahaan and K. Suvannachut, *J. Org. Chem.*, **55**, 1328 (1990).
71. N. Sayo, Y. Kimura and T. Nakai, *Tetrahedron Lett.*, **23**, 795 (1982).
72. Z. Li, T. Wang, E. Yao and Z. Gao, *Chin. J. Chem.*, 265 (1990); Z. Li, T. Wang and Ch. Kao, *Youji Huaxue*, **10**, 427 (1990); *Chem. Abstr.*, **114**, 80978k (1991).
73. K. Hayakawa, A. Hayashida and K. Kanematsu, *J. Chem. Soc., Chem. Commun.*, 1108 (1988).
74. A. A. Solov'ianov, A. A. Akmhed, I. P. Beletskaia and O. A. Reutov, *Zh. Org. Khim.*, **23**, 1365 (1987).
75. P. C. H. Eichinger, J. H. Bowie and T. Blumenthal, *J. Org. Chem.*, **51**, 5078 (1986).
76. P. C. H. Eichinger and J. H. Bowie, *J. Chem. Soc., Perkin Trans. 2*, 1499 (1987).
77. P. C. H. Eichinger and J. H. Bowie, *J. Chem. Soc., Perkin Trans. 2*, 497 (1988).
78. P. C. H. Eichniger and J. H. Bowie, *J. Chem. Soc., Perkin Trans. 2*, 1763 (1990).
79. T. Takahashi, H. Nemoto, Y. Kanada, J. Tsuji, Y. Fukazawa, T. Okajima and Y. Fujise, *Tetrahedron*, **43**, 5499 (1987).
80. D. J.-S. Tsai and M. M. Midland, *J. Org. Chem.*, **49**, 1842 (1984).
81. L. A. Paquette, J. P. Gilday and C. S. Ra, *J. Am. Chem. Soc.*, **109**, 6858 (1987).
82. M. Marsch, K. Harms, W. Massa and G. Boche, *Angew. Chem., Int. Ed. Engl.*, **26**, 696 (1987).
83. K. Mikami, Y. Kimura, N. Kishi and T. Nakai, *J. Org. Chem.*, **48**, 279 (1983).
84. Y.-D. Wu, K. N. Houk and J. A. Marshall, *J. Org. Chem.*, **55**, 1421 (1990).
85. E. Nakai and T. Nakai, *Tetrahedron Lett.*, **29**, 4587 (1988).
86. T. Nakai, K. Mikami, S. Taya and Y. Fujita, *J. Am. Chem. Soc.*, **103**, 6492 (1981).
87. K. Mikami, K. Azuma and T. Nakai, *Tetrahedron*, **40**, 2303 (1984).
88. D. J.-S. Tsai and M. M. Midland, *J. Am. Chem. Soc.*, **107**, 3915 (1985).
89. C. A. Broka and T. Shen, *J. Am. Chem. Soc.*, **111**, 2981 (1989).
90. K. Mikami and T. Nakai, *Chem. Lett.*, 1349 (1982).
91. T. Takahashi, H. Nemoto, Y. Kanda, J. Tsuji and Y. Fujise, *J. Org. Chem.*, **51**, 4315 (1986).
92. J. A. Marshall and J. Lebreton, *J. Org. Chem.*, **53**, 4108 (1988).
93. J. C. Barrish, P. M. Wovkulich, P. C. Tang, A. D. Batcho and M. R. Uskokovic, *Tetrahedron Lett.*, **31**, 2235 (1990).

94. J. A. Marshall and T. M. Jenson, *J. Org. Chem.*, **49**, 1707 (1984).
95. D. S. Keegan, M. M. Midland, R. T. Werley and J. I. McLoughlin, *J. Org. Chem.*, **56**, 1185 (1991).
96. J. A. Marshall, J. Lebreton, B. S. Dehoff and T. M. Jenson, *Tetrahedron Lett.*, **28**, 723 (1987).
97. J. A. Marshall, J. Lebreton, B. S. Dehoff and T. M. Jenson, *J. Org. Chem.*, **52**, 3883 (1987).
98. J. A. Marshall, T. M. Jenson and B. S. Dehoff, *J. Org. Chem.*, **51**, 4316 (1986).
99. J. A. Marshall, T. M. Jenson and B. S. Dehoff, *J. Org. Chem.*, **52**, 3860 (1987).
100. N. Sayo, F. Shirai and T. Nakai, *Chem. Lett.*, 255 (1984).
101. S. Y. Wei, K. Tomooka and T. Nakai, *J. Org. Chem.*, **56**, 5973 (1991).
102. J. A. Marshall and J. Lebreton, *J. Am. Chem. Soc.*, **110**, 2925 (1988).
103. J. A. Marshall and J. Lebreton, *Tetrahedron Lett.*, **28**, 3323 (1987).
104. N. Sayo, E. Kitahara and T. Nakai, *Chem. Lett.*, 259 (1984).
105. M. Bartók and K. L. Láng, in *The Chemistry of Functional Groups*, Supplement E (Ed. S. Patai), Wiley, Chichester, 1980, pp. 609–681.
106. K. Arata and K. Tanabe, *Catal. Rev. Sci. Eng.*, **25**, 365 (1983).
107. A. S. Rao, S. K. Paknikar and J. G. Kirtane, *Tetrahedron*, **39**, 2323 (1983).
108. J. G. Smith, *Synthesis*, 629 (1984).
109. M. Bartók and K. L. Láng, in *The Chemistry of Heterocyclic Compounds* (Ed. A. Hassner), Vol. 42, Wiley, New York, 1985, pp. 61–76.
110. (a) G. Magnusson, *Org. Prep. Proced. Int.*, **22**, 547 (1990).
(b) B. Rickborn in *Comprehensive Organic Synthesis* (Eds. B. M. Trost and I. Fleming) Vol. 3, p. 733, Pergamon Press, Oxford, 1991.
111. Á. Molnár, I. Bucsi and M. Bartók, in *Studies in Surface Science and Catalysis (Heterogeneous Catalysis and Fine Chemicals II)* (Eds. M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, G. Pérot, R. Maurel and C. Montassier), **59**, 549 (1991). (Elsevier, Amsterdam).
112. H. Mayr, R. Koschinsky, E. Will and E. Bäuml, *J. Org. Chem.*, **52**, 1342 (1987).
113. S. K. Taylor, D. S. Bisehoff, C. L. Blankespoor, P. A. Deck, S. M. Harvey, P. L. Johnson, A. E. Marolewski, S. V. Mork, D. H. Motry and R. Van Eenenaam, *J. Org. Chem.*, **55**, 4202 (1990).
114. F. L. M. Smets, L. Thigs and B. Zwanenburg, *Tetrahedron*, **36**, 3269 (1980).
115. N. De Kimpe, L. De Buyck, R. Verhé and N. Schamp, *Tetrahedron*, **40**, 3291 (1984).
116. P. Uebelhart and C. H. Eugster, *Helv. Chim. Acta*, **71**, 1983 (1988).
117. T. Corona, P. Crotti, M. Ferretti and F. Macchia, *J. Chem. Soc., Perkin Trans. 1*, 1607 (1985).
118. R. D. Bach and R. C. Klix, *J. Org. Chem.*, **50**, 5438 (1985).
119. M. Taran and B. Delmond, *Tetrahedron*, **42**, 4787 (1986).
120. J. F. Kinstle and G. L. Quinlan, *Polym. Prepr., Am. Chem. Soc., Div. Polym. Chem.*, **22**, 166 (1981).
121. R. A. Cormier and M. D. Francis, *Synth. Commun.*, **11**, 365 (1981).
122. E. Mincione and P. Bovicelli, *J. Chem. Res. (S)*, 370 (1988); *Chem. Abstr.*, **110**, 231352x (1989).
123. R. A. Cormier, C. A. Grosshans and S. L. Skibbe, *Synth. Commun.*, **18**, 677 (1988).
124. A. VanZon and R. Huis, *Recl. Trav. Chim. Pays-Bas*, **100**, 425 (1981).
125. A. M. Zvonok, N. M. Kuz'menok and L. S. Stanishevskii, *Zh. Org. Khim.*, **23**, 1972 (1987).
126. M. H. Elmallah, F. A. Zaher and M. M. Elhefnaw, *Res. Ind.*, **34**, 286 (1989).
127. W. Wierenga, A. W. Harrison, B. R. Evans and C. G. Chidester, *J. Org. Chem.*, **49**, 438 (1984).
128. H. Hart, S.-M. Chen and S. Lee, *J. Org. Chem.*, **45**, 2096 (1980).
129. K. Uneyama, A. Isimura, K. Fujii and S. Torii, *Tetrahedron Lett.*, **24**, 2857 (1983).
130. K. Uneyama, N. Nisiyama and S. Torii, *Tetrahedron Lett.*, **25**, 4137 (1984).
131. H. Banks and H. Ziffer, *J. Org. Chem.*, **47**, 3743 (1982).
132. Y. Tobe, S. Yamashita, T. Yamashita, K. Kakiuchi and Y. Odaira, *J. Chem. Soc., Chem. Commun.*, 1259 (1984).
133. J. M. Coxon and D. Q. McDonald, *Tetrahedron Lett.*, **29**, 2575 (1988).
134. P. C. B. Page, C. M. Rajner and I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 356 (1988).
135. L. I. Zakharkin, V. V. Guseva and D. A. Kamernitskii, *Zh. Org. Khim.*, **25**, 111 (1989).
136. L. G. French, E. E. Fenion and T. P. Charlton, *Tetrahedron Lett.*, **32**, 851 (1991).
137. M. A. Baig, D. V. Banthorpe, G. Carr and D. Whittaker, *J. Chem. Soc., Perkin Trans. 2*, 1981 (1989).
138. A. Defoin, J. Baranne-Lafont and J. Rigaudy, *Bull. Soc. Chim. Fr. II*, 145 (1984).
139. J. Prandi, J. L. Namy, G. Menoret and H. B. Kagan, *J. Organomet. Chem.*, **285**, 449 (1985).
140. S. K. Taylor, C. L. Blankespoor, S. M. Harvey and L. J. Richardson, *J. Org. Chem.*, **53**, 3309 (1988).

141. R. N. McDonald, in *Mechanisms of Molecular Migrations* (Ed. B. S. Thyagarajan), Vol. 3, Wiley, New York, 1971, pp. 67–107.
142. R. N. McDonald and R. C. Cousins, *J. Org. Chem.*, **45**, 2976 (1980).
143. W. K. Kim, C. K. Sohn and I. Lee, *Bull. Korean Chem. Soc.*, **7**, 279 (1986); *Chem. Abstr.*, **106**, 195663 (1987).
144. J. D. Kim and J. S. Cha, *Taehan Hwahakhoe Chi*, **27**, 73 (1983); *Chem. Abstr.*, **98**, 178862 (1983).
145. R. C. Klix and R. D. Bach, *J. Org. Chem.*, **52**, 580 (1987).
146. R. D. Bach and R. C. Klix, *Tetrahedron Lett.*, **26**, 985 (1985).
147. F. Kunisch, K. Hobert and P. Welzel, *Tetrahedron Lett.*, **26**, 6039 (1985).
148. J. A. Marshall and J. A. Kerschen, *Synth. Commun.*, **10**, 409 (1980).
149. R. A. Holton, R. R. Juo, H. B. Kim, A. D. Williams, S. Harusawa, R. E. Lowenthal and S. Yogai, *J. Am. Chem. Soc.*, **110**, 6558 (1988).
150. J. K. Ganguly, U. K. Som, K. E. Haque, K. P. Dhara and C. P. Dutta, *Indian J. Chem., Sect. B*, **21**, 1065 (1982).
151. B. A. Brady, M. M. Healy and W. I. O Sullivan, *J. Chem. Soc., Perkin Trans. 1*, 1151 (1983).
152. K. Maruoka, T. Ooi and H. Yamamoto, *J. Am. Chem. Soc.*, **111**, 6431 (1989).
153. S. P. Tanis, Y.-H. Chuang and D. B. Head, *Tetrahedron Lett.*, **26**, 6147 (1985).
154. F. J. Parodi and N. H. Fisher, *J. Chem. Soc., Chem. Commun.*, 1405 (1986).
155. T. W. Hart and M.-T. Comte, *Tetrahedron Lett.*, **26**, 2713 (1985).
156. S. P. Tanis, Y. M. Abdallah and P. G. Williard, *Tetrahedron Lett.*, **26**, 3651 (1985).
157. E. Cabrera, A. Garcia-Granados and M. A. Quecuty, *J. Nat. Prod.*, **51**, 475 (1988).
158. G. N. Komratov, R. A. Barzykin, G. V. Korovina, S. G. Entelis, *Vysokomol. Soedin., Ser. A*, **23**, 2733 (1981).
159. B. Papillaud, F. Tiffon, M. Taran, B. Arreguy-San Miguel and B. Delmond, *Tetrahedron*, **41**, 1845 (1985).
160. M. Taran and B. Delmond, *Tetrahedron*, **41**, 1859 (1985).
161. M. Taran and B. Delmond, *Tetrahedron*, **42**, 4795 (1986).
162. J. M. Shafiullah, *Indian J. Chem., Sect. B*, **28**, 973 (1989).
163. H. K. Chenault and S. J. Danishefsky, *J. Org. Chem.*, **54**, 4249 (1989).
164. K. Suzuki, M. Miyazawa and G. Tsuchihashi, *Tetrahedron Lett.*, **28**, 3515 (1987).
165. R. V. Suresh, I. C. S. Rukmani and P. R. Iyer, *Indian J. Chem., Sect. B*, **24**, 254 (1985).
166. L. Pettersson, T. Frejd and G. Magnusson, *Tetrahedron Lett.*, **28**, 2753 (1987).
167. K. Maruoka, M. Hasegawa, H. Yamamoto, K. Suzuki, M. Shimasaki and G. Tsuchihashi, *J. Am. Chem. Soc.*, **108**, 3827 (1986).
168. K. Suzuki, M. Shimazaki and G. Tsuchihashi, *Tetrahedron Lett.*, **27**, 6233 (1986).
169. M. Shimazaki, H. Hara, K. Suzuki and G. Tsuchihashi, *Tetrahedron Lett.*, **28**, 5891 (1987).
170. Y. Sato and Y. Sonoda, *Chem. Pharm. Bull.*, **29**, 356 (1981).
171. I. G. Pitt, R. A. Russell, R. B. Waring and R. N. Warrenger, *J. Chem. Soc., Chem. Commun.*, 1489 (1987).
172. Y. Fujimoto, Y. Kanzawa, Y. Ikuina, K. Kakinuma and N. Ibekawa, *J. Chem. Soc., Chem. Commun.*, 1107 (1989).
173. N. Takaishi, H. Takahashi and Y. Inamoto, *Tetrahedron Lett.*, **26**, 2361 (1985).
174. Y. Pocker and B. P. Ronald, *J. Am. Chem. Soc.*, **102**, 5311 (1980).
175. G. P. Ford and C. T. Smith, *J. Am. Chem. Soc.*, **109**, 1325 (1987).
176. V. C. Ukachukwu, J. J. Blumenstein and D. L. Whalen, *J. Am. Chem. Soc.*, **108**, 5039 (1986).
177. J. M. Coxon and M. P. Hartshorn, *Tetrahedron Lett.*, **28**, 1333 (1987).
178. V. C. Ukachukwu and D. L. Whalen, *Tetrahedron Lett.*, **29**, 293 (1988).
179. Y. Pocker, B. P. Ronald and K. W. Anderson, *J. Am. Chem. Soc.*, **110**, 6492 (1988).
180. I. Fleming and T. W. Newton, *J. Chem. Soc., Perkin Trans. 1*, 119 (1984).
181. G. B. Payne, *J. Org. Chem.*, **27**, 3819 (1962).
182. C. H. Behrens, Y. K. Soo, K. B. Sharpless and F. J. Walker, *J. Org. Chem.*, **50**, 5687 (1985).
183. H. Itokawa, H. Nakanishi and S. Mihashi, *Chem. Pharm. Bull.*, **31**, 1991 (1983).
184. J. A. Donnelly and D. E. Maloney, *Tetrahedron*, **35**, 2875 (1979).
185. R. A. Cormier and M. D. Francis, *Synth. Commun.*, **11**, 365 (1981).
186. I. Kitagawa, H. Shibuya, H. Fujioka, Y. Yamamoto, A. Kajiwara, K. Kitamura, A. Miyao, T. Hakoshima and K. Tomita, *Tetrahedron Lett.*, 1963 (1980).
187. H. E. Simmons and J. E. Maggio, *Tetrahedron Lett.*, **22**, 287 (1981).
188. L. A. Paquette and M. Vazeux, *Tetrahedron Lett.*, **22**, 291 (1981).

189. R. Ramage and I. A. Southwell, *J. Chem. Soc., Perkin Trans. 1*, 1323 (1984).
190. I. Morelli, S. Catalano, V. Scartoni, M. Ferretti and A. Marsili, *J. Chem. Soc., Perkin Trans. 1*, 1665 (1979).
191. S. K. Taylor, G. H. Hockermann, G. L. Karrick, S. B. Lyle and S. B. Schramm, *J. Org. Chem.*, **48**, 2449 (1983).
192. S. K. Taylor, M. E. Davisson, B. R. Hissom, Jr., S. L. Brown, H. A. Pristach, S. B. Schramm and S. M. Harvey, *J. Org. Chem.*, **52**, 425 (1987).
193. A. W. Murray, in *Organic Reaction Mechanisms*, (Eds. A. C. Knipe and W. E. Watts), Wiley, Chichester, 1981–1988.
194. J. K. Crandall and M. Apparu, *Org. React. (N.Y.)*, **29**, 345 (1983).
195. H. Shirahama, B. R. Chhabra and T. Matsumoto, *Chem. Lett.*, 717 (1981).
196. T. J. Brocksom and J. T. B. Ferreira, *Synth. Commun.*, **11**, 105 (1981).
197. H. Shirahama, K. Hayano, Y. Kanemoto, S. Misumi, T. Ohtsuka, N. Hashiba, A. Furusaki, S. Murata, R. Noyori and T. Matsumoto, *Tetrahedron Lett.*, **21**, 4835 (1980).
198. M. Apparu and M. Barrelle, *Tetrahedron*, **34**, 1691 (1978).
199. F. Scheidl, *Synthesis*, 728 (1982).
200. S. G. Traynor, B. J. Kane, J. B. Coleman and C. G. Cardenas, *J. Org. Chem.*, **45**, 900 (1980).
201. R. J. Giguere and H. M. R. Hoffmann, *Tetrahedron Lett.*, **22**, 5039 (1981).
202. H. Yamamoto and H. Nozaki, *Angew. Chem.*, **90**, 180 (1978); *Angew. Chem., Int. Ed. Engl.*, **17**, 169 (1978).
203. S. Terao, M. Shiraishi and K. Kato, *Synthesis*, 467 (1979).
204. T. G. Waddell and P. A. Ross, *J. Org. Chem.*, **52**, 4802 (1987).
205. M. Taran and B. Delmond, *Tetrahedron Lett.*, **23**, 5535 (1982).
206. D. J. Morgans, Jr., K. B. Sharpless and S. G. Traynor, *J. Am. Chem. Soc.*, **103**, 462 (1981).
207. C. L. Edwards and S. E. Wilson, U. S. Patent, No. 4,496,776; *Chem. Abstr.*, **103**, 71553p (1985).
208. R. R. Kurtz and D. J. Houser, *J. Org. Chem.*, **46**, 202 (1981).
209. R. K. Boeckman, Jr., *Tetrahedron Lett.*, 4281 (1977).
210. A. Yasuda, H. Yamamoto and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **52**, 1705 (1979).
211. L. E. Overman and L. A. Flippin, *Tetrahedron Lett.*, **22**, 195 (1981).
212. B. M. Fraga, J. R. Hanson, M. G. Hernandez and F. G. Tellado, *Tetrahedron Lett.*, **30**, 6899 (1989).
213. E. J. Corey, A. Marfat, J. R. Falck and J. O. Albright, *J. Am. Chem. Soc.*, **102**, 1433 (1980).
214. J. K. Whitesell and S. W. Felman, *J. Org. Chem.*, **45**, 755 (1980).
215. Z. Kotkowska-Machnik and J. Zakrzewski, *Tetrahedron Lett.*, **21**, 2091 (1980).
216. B. Rickborn and R. M. Gerkin, *J. Am. Chem. Soc.*, **93**, 1693 (1971).
217. R. Bergman and G. Magnusson, *J. Org. Chem.*, **51**, 212 (1986).
218. A. Sundin, T. Frejd and G. Magnusson, *J. Org. Chem.*, **51**, 3927 (1986).
219. Y. Tobe, T. Yamashita, K. Kakiuchi and Y. Odaira, *J. Chem. Soc., Chem. Commun.*, 898 (1985).
220. Y. Tobe, T. Kishida, T. Yamashita, K. Kakiuchi and Y. Odaira, *Chem. Lett.*, 1437 (1985).
221. T. Kiersznicki and M. Bogacka, Polish Patent, 120,015; *Chem. Abstr.*, **99**, 175227 (1983).
222. R. A. Holton, *J. Am. Chem. Soc.*, **106**, 5731 (1984).
223. K. Maruoka, S. Nagahara, T. Ooi and H. Yamamoto, *Tetrahedron Lett.*, **30**, 5607 (1989).
224. R. Tamura, Y. Kusama and D. Oda, *J. Org. Chem.*, **55**, 595 (1990).
225. J. A. Marshall and W. J. DuBay, *J. Org. Chem.*, **56**, 1685 (1991).
226. L. D. Quin and H. F. Lawson, *Phosphorus Sulfur*, **15**, 195 (1983); *Chem. Abstr.*, **99**, 122538w (1983).
227. M. Nagai, K. Kato, T. Takita, S. Nishiyama, S. Yamamura and Y. Terada, *Tetrahedron Lett.*, **31**, 119, 4777 (1990).
228. P. A. Wender and S. L. Eck, *Tetrahedron Lett.*, **23**, 1871 (1982).
229. M. Miyano, *J. Org. Chem.*, **46**, 1846 (1981).
230. D. R. Williams and J. G. Phillips, *J. Org. Chem.*, **46**, 5452 (1981).
231. D. J. Morgans, K. B. Sharpless and S. G. Traynor, *J. Am. Chem. Soc.*, **103**, 462 (1981).
232. G. R. Clark, *Tetrahedron Lett.*, **25**, 2839 (1984).
233. R. Tamura, M. Kato, K. Saegusa, D. Oda, T. Egawa and T. Yamamoto, *J. Org. Chem.*, **52**, 1640 (1987).
234. F. G. Weber and H. Liepert, *Z. Chem.*, **20**, 22 (1980).
235. J. Mulzer, L. Autenrieth-Ansorge, M. Kinstein, T. Matsuoka and W. Münch, *J. Org. Chem.*, **52**, 3784 (1987).

236. T. W. Bell and J. A. Clacclo, *Tetrahedron Lett.*, **29**, 865 (1988).
237. M. Hrusovsky, J. Hrcka, Z. Cvengrosova and K. Fancovic, Czech. Patent, 224,913; *Chem. Abstr.*, **103**, 22171 (1985).
238. B. Casal and E. Ruiz-Hitzky, *An. Quim.*, **80**, 315 (1984).
239. N. Sotani, *J. Catal.*, **50**, 373 (1977).
240. Á. Molnár, I. Bucsi, M. Bartók, G. Resofszki and G. Gáti, *J. Catal.*, **129**, 303 (1991).
241. Y. Osaka and T. Higashizuka, *Japan Kokai*, 78 25,512; *Chem. Abstr.*, **89**, 59660f (1978).
242. J. M. Muchowski, R. Naef and M. L. Maddox, *Tetrahedron Lett.*, **26**, 5375 (1985).
243. S. Tsuboi, H. Furutani and A. Takeda, *Synthesis*, 292 (1987).
244. E. Ruiz-Hitzky and B. Casal, *J. Catal.*, **92**, 291 (1985).
245. T. Hanaoka, K. Takeuchi, T. Matsuzaki and Y. Sugi, *Catal. Lett.*, **5**, 13 (1990).
246. Daicel Chemical Industries, *Japan Kokai*, 59 141, 534; *Chem. Abstr.*, **102**, 24284 (1985).
247. A. B. Holmes, W. Jones and G. C. Slim., Brit. Patent, 2,205,835; *Chem. Abstr.*, **111**, 75277 (1989).
248. T. Tsukuma and I. Nagayama, *Japan Kokai*, 78 31,637 (1978); *Chem. Abstr.*, **89**, 42801e (1978).
249. R. M. Munavu and J. A. Ogur, *Kenya J. Sci. Technol., Ser. A*, **4**, 37 (1983); *Chem. Abstr.*, **103**, 104803 (1985).
250. H. Suga and H. Miyake, *Synthesis*, **5**, 394 (1988).
251. K. Arata and M. Hino, *Bull. Chem. Soc. Jpn.*, **53**, 535 (1980).
252. T. Iwahashi, F. Matsubara and Y. Yoshihiro, *Yukagaku*, **29**, 920 (1980); *Chem. Abstr.*, **94**, 156374 (1981).
253. T. N. Shakhtakhtinskii, Sh. T. Bagirov, F. M. Mamedov and Z. M. Nagiev, U.S.S.R. Patent, 721,399; *Chem. Abstr.*, **93**, 132139 (1980).
254. K. Arata and K. Tanabe, *Bull. Chem. Soc. Jpn.*, **53**, 299 (1980).
255. T.-L. Ho and C. J. Stark, *Justus Liebigs. Ann. Chem.*, 1446 (1983).
256. K. Arata and K. Tanabe, *Chem. Lett.*, **8**, 1017 (1979).
257. T. Kurata and T. Koshiyama, *Yukagaku*, **32**, 130 (1988); *Chem. Abstr.*, **110**, 95552h (1989).
258. E. N. Manukov and G. N. Bazhina, *Zh. Org. Khim.*, **24**, 121 (1988).
259. M. Taran and B. Delmond, *Can. J. Chem.*, **66**, 1558 (1988).
260. M. Bartók, in *Hydrogen Effects in Catalysis* (Eds. Z. Paál and P. G. Menon), Marcel Dekker, New York and Basel, 1988, pp. 521–542.
261. R. B. Grant and R. M. Lambert, *J. Catal.*, **93**, 92 (1985).
262. C. Benndorf and B. Nieber, *J. Electron Spectrosc. Relat. Phenom.*, **44**, 109 (1986).
263. C. Benndorf, B. Krüger and B. Nieber, *Appl. Catal.*, **25**, 165 (1986).
264. B. Krüger and C. Benndorf, *Surf. Sci.*, **178**, 704 (1986).
265. B. Nieber and C. Benndorf, *Surf. Sci.*, **235**, 129 (1990).
266. F. Notheisz, M. Bartók and Á. G. Zsigmond, *React. Kinet. Catal. Lett.*, **29**, 339 (1985).
267. F. Notheisz, Á. Molnár, Á. G. Zsigmond and M. Bartók, *J. Catal.*, **98**, 131 (1986).
268. M. Bartók, F. Notheisz, Á. G. Zsigmond and G. V. Smith, *J. Catal.*, **100**, 39 (1986).
269. F. Notheisz, Á. G. Zsigmond, M. Bartók and G. V. Smith, *J. Chem. Soc., Faraday Trans. 1*, **83**, 2359 (1987).
270. D. Ostgard, F. Notheisz, Á. G. Zsigmond, G. V. Smith and M. Bartók, *J. Catal.*, **129**, 519 (1991).
271. F. Notheisz, Á. G. Zsigmond, M. Bartók, D. Ostgard and G. V. Smith, in *Studies in Surface Science and Catalysis (Heterogeneous Catalysis and Fine Chemicals II)* (Eds. M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, G. Pérot, R. Maurel and C. Montassier), **59**, 153 (1991). (Elsevier, Amsterdam).
272. M. Bartók, F. Notheisz and Á. G. Zsigmond, *J. Mol. Catal.*, **44**, 337 (1988).
273. M. Bartók, F. Notheisz, Á. G. Zsigmond and G. V. Smith, *J. Catal.*, **102**, 471 (1986).
274. M. Bartók and F. Notheisz, *J. Chem. Soc., Chem. Commun.*, 744 (1979).
275. Á. Molnár, Á. Mastalir and M. Bartók, *J. Chem. Soc., Chem. Commun.*, 124 (1989).
276. M. Bartók, F. Notheisz and Á. G. Zsigmond, *J. Catal.*, **63**, 364 (1980).
277. F. Notheisz and M. Bartók, *J. Catal.*, **71**, 331 (1981).
278. L. Thijs and B. Zwanenburg, *Tetrahedron*, **36**, 2145 (1980).
279. T. Kurata, *Yukagaku*, **37**, 49 (1979); *Chem. Abstr.*, **93**, 239662z (1980).
280. G. C. Accrombessi, P. Geneste and J.-L. Olivé, *J. Org. Chem.*, **45**, 4139 (1980).
281. J. Ishiyama, H. Yashima, H. Matsuo, Y. Senda, S. Imaizumi, K. Hanaya and T. Muramatsu, *Chem. Lett.*, 989 (1989).
282. M. Bartók, F. Notheisz and J. T. Kiss, *J. Catal.*, **68**, 249 (1981).
283. M. Kraus and H. Davidova, *J. Catal.*, **68**, 252 (1981).

284. M. Bartók and F. Notheisz, *J. Catal.*, **68**, 209 (1981).
285. D. Milstein and J. C. Calabrese, *J. Am. Chem. Soc.*, **104**, 3773 (1982).
286. R. B. Osborne and J. A. Ibers, *J. Organomet. Chem.*, **232**, 273 (1982).
287. A. Miyashita, T. Shimada, A. Sugawara and H. Nohira, *Chem. Lett.*, **8**, 1323 (1986).
288. H. Fujitsu, S. Shirahama, E. Matsumura, K. Takeshita and I. Mochida, *J. Org. Chem.*, **46**, 2287 (1981).
289. M. Suzuki, Y. Oda and R. Noyori, *J. Am. Chem. Soc.*, **101**, 1623 (1979).
290. S. Achab, J.-P. Cosson and B. C. Das, *J. Chem. Soc., Chem. Commun.*, 1040 (1984).
291. G. Visentin, O. Piccolo and G. Consiglio, *J. Mol. Catal.*, **61**, 1 (1990).
292. S. Sato, I. Matsuda and Y. Izumi, *J. Organomet. Chem.*, **359**, 255 (1989).
293. Y. D. Vankar, N. C. Chaudhuri and S. P. Singh, *Synth. Commun.*, **16**, 1621 (1986).
294. M. Suzuki, A. Watanabe and R. Noyori, *J. Am. Chem. Soc.*, **102**, 2095 (1980).
295. M. Suzuki, A. Watanabe and R. Noyori, *Recl. Trav. Chim. Pays-Bas*, **107**, 230 (1989).
296. T. Lukac, M. Soukup and E. Widmer, Eur. Pat. Appl. EP., 133,711 (1983); *Chem. Abstr.*, **103**, 104604 (1985).
297. T. Tsuda, M. Tokai, T. Ishida and T. Saegusa, *J. Org. Chem.*, **51**, 5216 (1986).
298. H. Su, L. Walder, Z. D. Zhang and R. Scheffold, *Helv. Chim. Acta*, **71**, 1073 (1988).
299. J. E. Lyons, U. S. Patent, 4,123,445 (1978); *Chem. Abstr.*, **90**, 168426a (1979).
300. J. T. Groves, K. H. Ahn and R. Quinn, *J. Am. Chem. Soc.*, **110**, 4217 (1988).
301. Y. Kitagawa, A. Itoh, S. Hashimoto, H. Yamamoto and H. Nozaki, *J. Am. Chem. Soc.*, **99**, 3864 (1977).
302. P. Sulmon, N. De Kimpe, N. Schamp, J.-P. Declercq and B. Tinant, *J. Org. Chem.*, **53**, 4457 (1988).
303. T. H. Black and W. J. DuBay, *Tetrahedron Lett.*, **29**, 1747 (1988).
304. R. Lehmann and M. Schlosser, *Tetrahedron Lett.*, **25**, 745 (1984).
305. M. D. Cooke, T. A. Dramsfield and J. M. Vernon, *J. Chem. Soc., Perkin Trans. 2*, 1377 (1984).
306. D. G. Batt, D. G. Jones and S. La Greca, *J. Org. Chem.*, **56**, 6704 (1991).
307. B. M. Trost and T. A. Runge, *J. Am. Chem. Soc.*, **103**, 2485 (1981).
308. I. Mori, K. Takai, K. Oshima and H. Nozaki, *Tetrahedron*, **40**, 4013 (1984).
309. G. W. Morrow, S. Wang and J. S. Swenton, *Tetrahedron Lett.*, **29**, 3441 (1988).
310. J. S. Swenton, D. Bradin and B. D. Gates, *J. Org. Chem.*, **56**, 6156 (1991).
311. T.-L. Ho and S. H. Liu, *Justus Liebigs Ann. Chem.*, 761 (1983).
312. B. M. Trost, T. A. Runge and L. N. Jungheim, *J. Am. Chem. Soc.*, **102**, 2840 (1980).
313. K. Takai, I. Mori, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, **22**, 3985 (1981).
314. H. Stach and M. Hesse, *Tetrahedron*, **44**, 1573 (1988).
315. J. Kihlberg, T. Frejd, K. Jansson and G. Magnusson, *Carbohydr. Res.*, **176**, 287 (1988).
316. V. Pozsgay and A. Neszméli, *Tetrahedron Lett.*, **21**, 211 (1980).
317. H. H. Baer, D. J. Astles, H.-C. Chin and L. Siemsen, *Can. J. Chem.*, **63**, 432 (1985).
318. R. W. Binkley, *J. Org. Chem.*, **50**, 5646 (1985).
319. M. Bartók, in *The Chemistry of Functional Groups*, Supplement E (Ed. S. Patai), Wiley, Chichester, 1980, pp. 683–720.
320. M. Bartók and F. Notheisz, *J. Chem. Soc., Chem. Commun.*, 746 (1980).
321. J. C. Duchet and D. Cornet, *J. Catal.*, **44**, 57 (1976).
322. Z. G. Yuskovets, N. V. Nekrasov, M. M. Kostyukov, M. V. Shimanskaya and S. L. Kiperman, *Kinet. Catal.*, **25**, 1162 (1984).
323. U. Gennari, R. Kramer and H. L. Gruber, *Appl. Catal.*, **11**, 341 (1984).
324. U. Gennari, R. Kramer and H. L. Gruber, *Appl. Catal.*, **44**, 239 (1988).

CHAPTER 16

The electrochemistry of hydroxyl groups and ethers

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I. INTRODUCTION

Since the electrochemistry of hydroxyl and ether groups has been reviewed in *Supplement E* of this series[1], this chapter will deal with those studies which have been published since 1979.

II. ANODIC OXIDATION

A. Hydroxyl Groups

The anodic oxidation of alcohols by removal of electrons from the unshared electron pairs on the oxygen atom of the OH group is hardly achievable due to the rather high oxidation potentials of alcohols (2.5–2.7 V vs Ag/Ag^+). On the other hand, however, alcohols are often oxidized by the anodic method as has been described in *Supplement E*[1]. This apparent contradiction may be explained by the difference of the reaction mechanism. Some of the mechanisms which are proposed for the oxidation of alcohols are shown in equations 1–3.

$$RCH_2OH \xrightarrow{-e} RCH_2\overset{+}{O}{}^{\cdot}H \xrightarrow{-H^+} RCH_2O^{\cdot} \xrightarrow{Y^{\cdot}} RCHO \qquad (1)$$

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$$RCH_2OH \xrightarrow[Y^{\cdot}]{-H^{\cdot}} R\dot{C}HOH \xrightarrow[-H^{+}]{-e} RCHO \quad (2)$$

$$RCH_2O^{-} \xrightarrow{-e} RCH_2O^{\cdot} \xrightarrow{Y^{\cdot}} RCHO \quad (3)$$

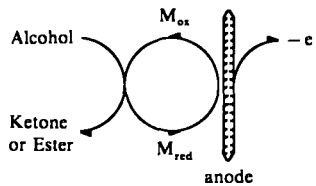
$Y^{\cdot}$ = a radical species generated in solution or on the anode surface by anodic oxidation

The first mechanism (equation 1) is the oxidation initiated by the removal of electrons from the unshared electron pairs and hardly ever takes place, as mentioned above. In the second mechanism (equation 2), the initiation of the oxidation is not the direct oxidation of alcohols but the formation of certain radical species by the anodic oxidation of solvent or supporting electrolyte. The radical will abstract a hydrogen atom from the C—H bond adjoining the OH group and the resultant radical species is rather easily oxidized electrochemically to a cation which forms the carbonyl compound through the ejection of a proton from the OH group. In the third mechanism (equation 3), the actual species which is anodically oxidized is not alcohol itself but the corresponding alkoxide anion. When the supporting electrolyte is a basic compound or the oxidation is carried out without a diaphragm, the formation of an alkoxide anion is acceptable. It is well known that the vicinity of the cathode is always basic in electrolysis. Hence in oxidations carried out without a diaphragm, some of the alcohol molecules which are adsorbed on the cathode or located close to it may be transformed to alkoxide anions. The latter are rather easily oxidized to alkoxy radicals and a hydrogen is abstracted from the C—H group adjoining the O$^{\cdot}$ group of the radical by some radical species including the alkoxy radical itself to yield the carbonyl compound.

On the other hand, completely different patterns of oxidation have been proposed for the oxidation of methanol and some other simple alcohols in connection with fuel cells. Although the reaction patterns proposed are varied, the point which strikingly contrasts with the mechanisms in equations 1–3 shown above is that, in the initial stage of oxidation, the Pt anode abstracts hydrogen atoms from the Me and OH groups of methanol, which is adsorbed on the Pt anode. Since the oxidation of an alcohol in a fuel cell seems to be a rather exceptional reaction in organic chemistry, its details are not dealt with in this chapter.

As is shown above, the mechanism of oxidation of alcohol is complex. Hence, in order to achieve effectively the anodic oxidation of alcohol, the design of new reaction systems is necessary and has been one of the main interests in studies on the anodic oxidation of alcohols in the past decade.

One of the most effective methods of electrochemical oxidation of alcohols is that using a mediator (M in equation 4).



(4)

The clean oxidation of a variety of alcohols using KI as the mediator has been described[2]. Secondary alcohols are oxidized to ketones and primary alcohols are transformed to the corresponding esters. The mechanisms in equations 5 and 6 have been proposed for these oxidations.

$$I^- \xrightarrow{-2e} I^+$$

$$RCH_2OH \xrightarrow{I^+} RCH_2\overset{+}{O}H \xrightarrow[I]{} \xrightarrow{-H^+} RCH_2OI \xrightarrow{-HI} RCHO \xrightarrow{I^+} \overset{+}{R}CHOI \tag{5}$$

$$\xrightarrow[-H^+]{RCH_2OH} \underset{RCH_2O}{\underset{|}{R-CH-OI}} \xrightarrow{-HI} \underset{OCH_2R}{\underset{|}{R-C=O}}$$

$$R^1R^2CHOH \xrightarrow[-H^+]{I^+} R^1R^2CHOI \xrightarrow{-HI} R^1R^2C=O \tag{6}$$

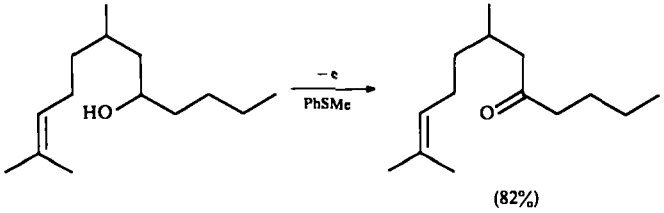
The oxidation using KI as the mediator has been extended to the preparation of benzyl benzoate from benzyl alcohol[3]. On the other hand, when the oxidation is carried out in the presence of bromide ion, benzyl alcohol is oxidized to benzaldehyde in a reasonable yield. This method has successfully been applied to the preparation of benzaldehydes bearing electron-withdrawing substituents such as 2,3,4,5,6-pentafluoro (yield 65%) and *p*-NO_2 (67%) groups. It has also been suggested in this oxidation that low concentration of Br^- is desirable in order to get satisfactory results[4].

Subsequently, much effort has been devoted to the investigation of new effective mediators. In addition to halide ions, organic sulfides such as thioanisole have been found to be effective as organic mediators[5]. The proposed mechanism of oxidation of an alcohol mediated with thioanisole is shown in equation 7.

$$PhSMe \xrightarrow{-e} Ph-\overset{+}{S}-Me \xrightarrow[R^1R^2CHOH]{-e,\,-H^+} \underset{Me}{\underset{|}{Ph-\overset{+}{S}-OCHR^1R^2}}$$

$$\xrightarrow{-H^+} \underset{CH_2^-}{\underset{|}{Ph-S-O-CR^1R^2}} \underset{H}{\underset{|}{}} \longrightarrow PhSMe + R^1R^2C=O \quad (77\text{–}99\%) \tag{7}$$

Since the anode potential is sufficient to remove electrons from the sulfur atom, the first step is the formation of a sulfide cation radical, which then reacts with the alcohol to form a sulfonium ion intermediate. Subsequent proton abstraction from the Me group of the intermediate followed by intramolecular proton migration yields the carbonyl compound and thioanisole. The regenerated thioanisole again plays the role of the mediator. The recovery of thioanisole is about 80%. Secondary alcohols are generally effectively oxidized by this method, whereas primary alcohols do not always give satisfactory results. One of the remarkable points of this oxidation is that carbon–carbon unsaturated bonds remain unchanged, as is typically shown by the oxidation of an unsaturated alcohol (equation 8).



(82%) (8)

Somewhat later, nitrate ion was proposed as a mediator for the oxidation of alcohols, although its mechanism of oxidation is completely different from that with halide ion as the mediator. Since nitrate ion is oxidized at about 1.6V vs Ag/Ag^+, the initiation of the reaction is oxidation of the nitrate ion to a nitrate radical. The latter abstracts a hydrogen from the C—H group adjoining the OH group of the alcohol. The resultant radical is further oxidized by nitrate radicals or by electron transfer to the anode, to give the carbonyl compound as is shown in equation 9.

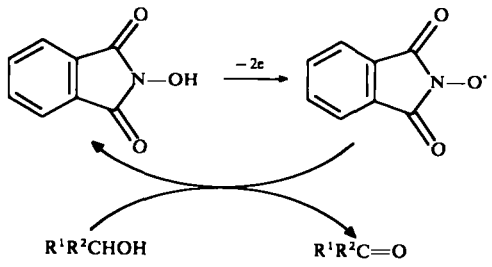
$$NO_3^- \xrightarrow{-e} NO_3^{\cdot}$$

$$R^1R^2CHOH \xrightarrow[-H^{\cdot}]{NO_3^{\cdot}} R^1R^2\dot{C}OH \xrightarrow[-e/-H^+]{NO_3^{\cdot}\ \text{or}} R^1R^2C{=}O \qquad (9)$$

(57–83%)

The yield of 2-butanone from 2-butanol is 83% when the oxidation is carried out in a mixed solvent of MeCN (90%) with H_2O (10%)[6].

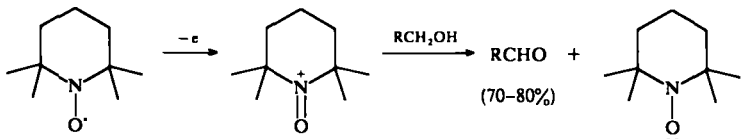
Later, *N*-hydroxyphthalimide (NHPI) was found to be an effective mediator for the oxidation of secondary alcohols although primary alcohols, except for ethanol, gave rather poor results (equation 10)[7].



(10)

Since NHPI is oxidized to phthalimide *N*-oxyl at about 0.85 V vs SCE in MeCN containing pyridine, the radical species oxidizes secondary alcohols to ketones according to the similar mechanism to that with nitrate radical (equation 9). The yield of ketone is in the range of 60–96% and the recovery of NHPI is 10–90%.

2,2,6,6-Tetramethylpiperidinenitroxyl (TEMPO) has also been found to be an effective mediator to oxidize alcohols to aldehydes and ketones. In this oxidation, however, the active oxidizing agent is not TEMPO itself but an oxoammonium salt formed easily by electrochemical oxidation of TEMPO at about 0.4V vs Ag/Ag^+. As is shown in equation 11, alcohols are oxidized to carbonyl compounds by the oxoammonium salt and the salt is reduced to a hydroxylamine.



TEMPO (11)

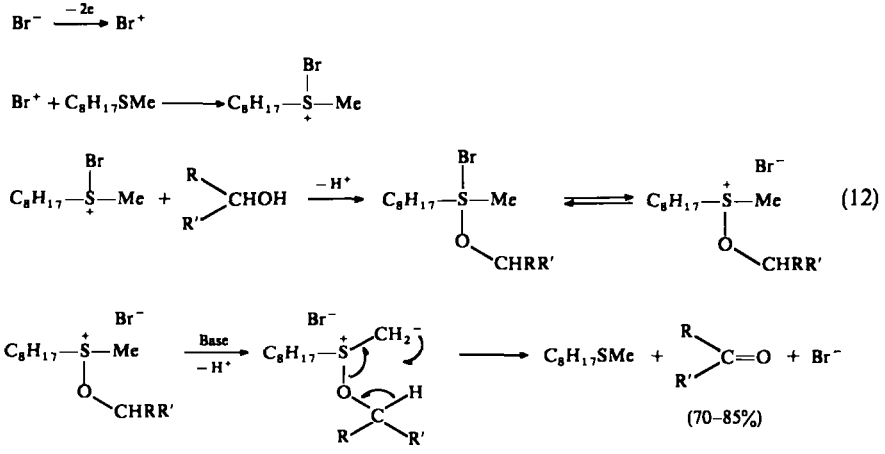
Since the reaction of the hydroxylamine with the oxoammonium salt generates TEMPO, it is not necessary to oxidize electrochemically the hydroxylamine itself (about 0.8 V vs Ag/Ag^+) but the catalytic cycle can be set up at potentials just sufficient for oxidation TEMPO. Primary alcohols are oxidized rapidly to aldehydes even at −60 °C

(yield, 80–90%), whereas secondary alcohols react more slowly than primary ones and a longer reaction does not significantly increase the degree of conversion. The conversion of 5-dodecanol is 30% after 23 hours. The turnovers of TEMPO are about ten[8].

The chemical modification of the surface of graphite with TEMPO has been studied in order to prepare anodes which are coated by TEMPO and effective for the oxidation of alcohols[9–11]. So far, the best turnover of the anode is more than 1560 in the oxidation of nerol to neral.

As has been already stated above, the role of the mediator is to make it possible to oxidize an alcohol at lower anode potential than that required for its direct oxidation. One of the typical organic mediators, thioanisole, is, for instance, oxidized at about 1.60 V vs SCE, which is far lower than the oxidation potentials of alcohols. A new concept of the mediator, namely a double mediatory system, was proposed in 1980 to dramatically decrease the anode potential[12].

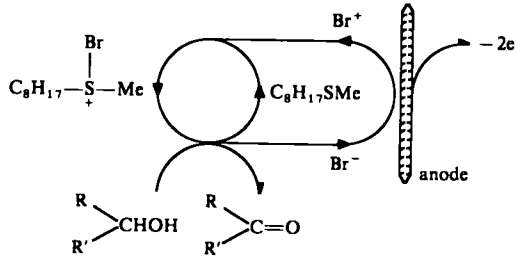
Thus, the oxidation of 2-octanol carried out in the presence of n-octyl methyl sulfide and tetraethylammonium bromide yields 2-octanone in 85% yield, while the similar oxidation using tetraethylammonium *p*-toluenesulfonate instead of the corresponding bromide gives the product in only 25% yield. This result suggests that the presence of bromide ion is requisite in this oxidation, although bromide ion itself is not always effective to oxidize alcohols when it is used alone as the mediator. The oxidation of n-octyl methyl sulfide cannot be the initiation reaction since its oxidation potential (1.93 V vs SCE) is much higher than that of bromide ion (1.1 V vs SCE). Hence, the initiation of the reaction must be the oxidation of the bromide ion. In the next step, a sulfonium bromide is formed from n-octyl methyl sulfide and the sulfonium ion reacts with the alcohol in a similar mechanism[13] to that proposed for the chemical oxidation of alcohols by means of dimethyl sulfide and halogens (equation 12).



(12)

The concept of this oxidation can be represented schematically by equation 13, which is named a double mediatory system. The anode potential required for oxidation of alcohols is undoubtedly lowered significantly with the employment of this double mediatory system.

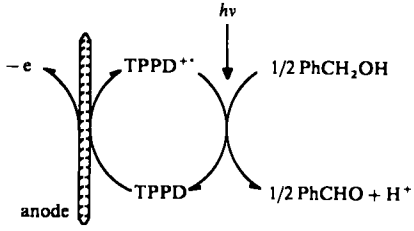
In the double mediatory system mentioned above, the active species generated by oxidation of bromide ion reacts with the sulfide to form the oxidizing reagent. Similar oxidation systems have been studied using a crosslinked polymer of 4-vinylpyridine as the acceptor of the active species generated by oxidation of the bromide ion, although



(13)

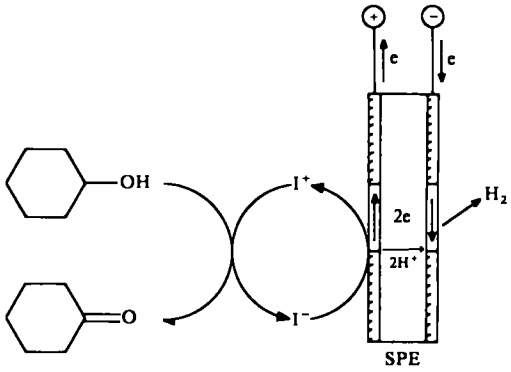
the mechanism had not clearly been proposed. Secondary alcohols are preferentially oxidized by this method when both secondary and primary hydroxyl groups are present in a molecule. Primary alcohols generally yield mixtures of carboxylic acids and esters[14].

In the oxidation system using *N,N,N',N'*-tetraphenyl-*p*-phenylenediamine (TPPD) as the mediator, the cation radical itself formed by the anodic oxidation of TPPD is not effective but irradiation of the cation radical (λ_{max} 342, 405, 815 nm) in the presence of benzyl alcohol with a 500-watt high-pressure mercury lamp at $\lambda > 360$ nm results in the oxidation of benzyl alcohol to benzaldehyde. Although the mechanism has not clearly been shown, electron transfer from the alcohol to the photochemically excited cation radical of TPPD has been suggested as the initiation of oxidation (equation 14)[15].



(14)

The oxidation with iodide ion as the mediator has been applied to the reaction system using Pt-SPE (SPE = solid polymer electrolyte) composite electrodes which are prepared by deposition of platinum on both sides of Nafion® 415, a perfluorinated cation exchange membrane. The current efficiency of oxidation of cyclohexanol with 0.08 MI_2, for instance, is about 30% (equation 15)[16].



(15)

Anodic oxidation of mixtures of Br^- and Cl^- in CH_2Cl_2 has been reported to yield mixed halogen species which are representable by polybromochloride ions, $Br_mCl_n^-$. The ability of the polybromochloride ions to act as the reagents for the oxidation of alcohols has been shown to be controlled by the amount of electricity which is passed to generate the polybromochloride ion. The polybromochloride ion formed by passing 2.0 F per mol (Br^-) of electricity shows higher yield and lower selectivity in oxidation of alcohols than the corresponding ion obtained by passing 1.0 F per mol (Br^-) of electricity[17]. In this method, the oxidation of alcohols with the polybromochloride ion is carried out without passing electricity. Hence, the oxidizing reagent is not regenerated.

The electrochemical recovery of the oxidizing reagent has been studied by employing a double-layer reaction system comprising aqueous and organic layers. In the organic layer (CCl_4), the usual oxidizing reagent, RuO_4, oxidizes alcohols and is reduced to RuO_2. The recovery of RuO_4 is achieved in the aqueous layer by oxidation of RuO_2 with an active chlorine generated by anodic oxidation of chloride ion in the aqueous layer[18].

In contrast with alcohols, glycols are generally easily oxidized by the direct anodic oxidation as has been mentioned in *Supplement E*[1]. Therefore, it is not always necessary to use the mediatory system in the electrochemical oxidation of glycols, though it is also effective[19].

The use of $[(bpy)(trpy)RuO]^{2+}$ complex (bpy = 2,2′-bipyridine; trpy = 2,2′: 6′,2″-terpyridine) as the mediatory oxidizing agent has been studied in the oxidation of 1,2-, 1,3- and 1,4-glycols. The complex oxidizes substrate and is reduced to the $[(bpy)(trpy)Ru(OH_2)]^{2+}$ aqua complex. The former complex is regenerated by anodic oxidation of the latter on a platinum electrode at 0.8 V vs SCE. Thus, the former complex can be used as the mediator and recovered at the end of the reaction[20].

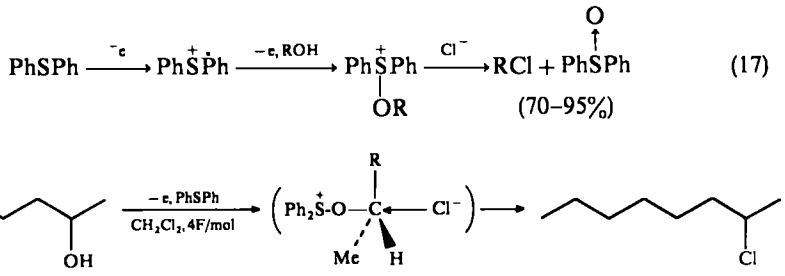
All the oxidation reactions mentioned above take place in homogeneous solution, when the mediatory oxidizing agent formed at the anode is soluble in the solution. The oxidizing agent is, however, not always required to be soluble and an oxidizing agent which is fixed on the anode may also be effective for the oxidation of alcohols. A layer of a nickel(III)oxide hydroxide, which is electrochemically generated from nickel(II)oxide deposited on a nickel anode, is a typical example which is effective in the oxidation of alcohols[21].

Oxidation takes place by heterogeneous chemical reaction between the oxide hydroxide and alcohols. The oxide hydroxide is similar to the well-known oxidant nickel peroxide and the first step of the oxidation is radical hydrogen abstraction from the α-methylene group of alcohols. The oxide hydroxide layer is continuously regenerated on the anode. Primary alcohols, α,ω-diols and secondary alcohols are easily transformed with high yields to carboxylic acids, dicarboxylic acids and ketones, respectively (equation 16).

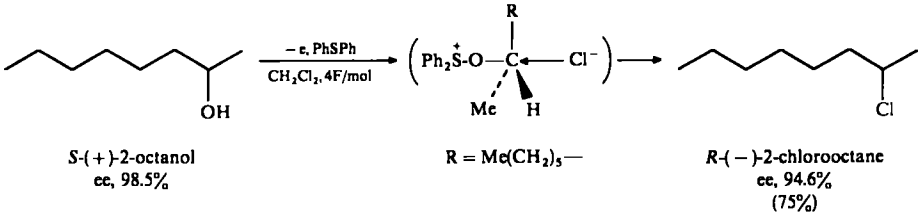
$$\begin{aligned}
&Ni(OH)_2 + OH^- \rightleftharpoons NiOOH + H_2O + e^- \\
&NiOOH + RCH_2OH_{ads} \xrightarrow{\text{slow}} Ni(OH)_2 + R\dot{C}HOH \\
&R\dot{C}HOH \longrightarrow \longrightarrow RCO_2^- \\
&RCH_2OH + 5OH^- \longrightarrow RCO_2^- + 4H_2O + 4e^- \\
&\qquad\qquad (34\text{–}86\%)
\end{aligned} \tag{16}$$

The oxidation of alcohols with mediators generally yields carbonyl compounds, as has already been shown above. On the other hand, when the electrochemical reaction of primary and secondary alcohols is carried out in CH_2Cl_2 containing Ph_2S, the alcohols are transformed to the corresponding chlorides in good yields[22].

Although the role of Ph_2S in this reaction is similar to that of PhSMe in the mediatory oxidation of alcohols, the last step of the reaction is different, as shown in equation 17. Here, the intermediate sulfonium ion is substituted by Cl^- which is generated by cathodic reduction of CH_2Cl_2 and the sulfide is not regenerated because of its oxidation to sulfoxide. The nucleophilic substitution with Cl^- anion has been confirmed to be an S_N2 reaction by the transformation of *S*-(+)-2-octanol to *R*-(−)-2-chlorooctane (equation 18).



(17)



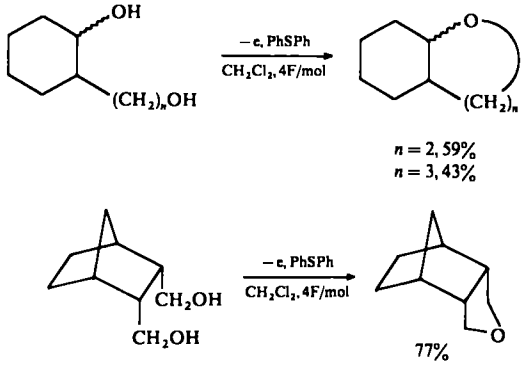
S-(+)-2-octanol
ee, 98.5%

R = Me(CH₂)₅—

R-(−)-2-chlorooctane
ee, 94.6%
(75%)

(18)

Similar electrochemical reactions of 1,4- and 1,5-diols yield not the chlorides but the corresponding cyclic ethers (equation 19).

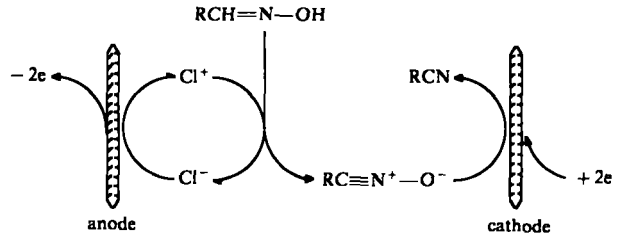


(19)

The hydroxyl group of aldoxime is also transformed by the electrochemical method with a mediator and the product is the corresponding nitrile[23].

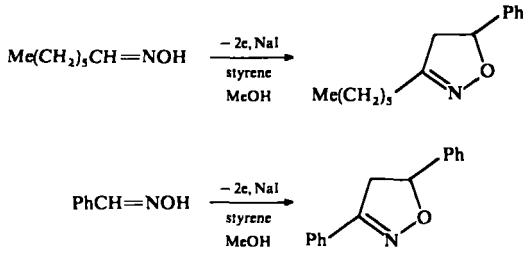
It is interesting that this transformation does not take place without passing electricity, though it is formally a simple dehydration process which is unrelated to oxidation and reduction. As the reaction mechanism is shown schematically in equation 20, the mediator Cl^- is oxidized first at the anode and the oxidized mediator oxidizes the aldoxime to a nitrile oxide, which is subsequently reduced to nitrile at the cathode under the same reaction conditions.

The intermediary formation of the nitrile oxide has been confirmed by its isolation and by the fact that cathodic reduction of the isolated nitrile oxide yields nitrile. Nitrile oxides are, however, generally for unstable to be isolated. Hence, the formation of



(20)

unstable nitrile oxides has been confirmed by formation of isoxazolines when the reaction is carried out in the presence of styrene (equation 21). Isoxazolines are the 1,3-dipolar adducts of the nitrile oxides with styrene.

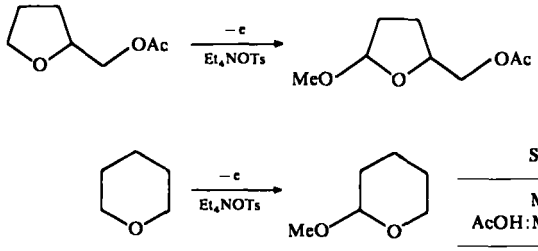


(21)

B. Ethers

In contrast to glycol ethers, the direct anodic oxidation of aliphatic ethers generally gives poor results, as has already been mentioned in *Supplement E*[1]. However, the use of a tetrafluoroborate salt instead of sodium methoxide as the supporting electrolyte has been found to increase the yield of oxidation of ethers in methanol[24].

Recently, it has also been found that the oxidation in a mixed solvent of acetic acid and methanol (1:10) generally gives better results than that in methanol alone (equation 22)[25].



Solvent	Yield (%)
MeOH	18
AcOH:MeOH = 1:10	73

Solvent	Yield (%)
MeOH	59
AcOH:MeOH = 1:10	71

(22)

Although it has not always clearly been determined, the first step of the direct oxidation of aliphatic ethers is removal of an electron from the lone pair electrons of the oxygen atom. A different mechanism has been proposed for the oxidation of some cycloaliphatic ethers with Pt anode in aqueous 1 M H_2SO_4[26]. In this oxidation, the surface of platinum anode is covered with oxides $(PtO)_s$ (s denotes a surface bound or adsorbed state) in the first step and the ether is adsorbed at the oxide surface. The oxide surface is also further oxidized to a higher oxidation state $(PtOOH)_s$ at the very positive working

potential. In the next step, the adsorbed ether is oxidized chemically to an α-hydroxylated ether by PtOOH and $(PtO)_s$ is regenerated. The mechanism according to which the surface of the anode is oxidized to a peroxide and the adsorbed organic molecule is oxidized by the peroxide has already been mentioned when discussing the oxidation of alcohols with a Ni anode.

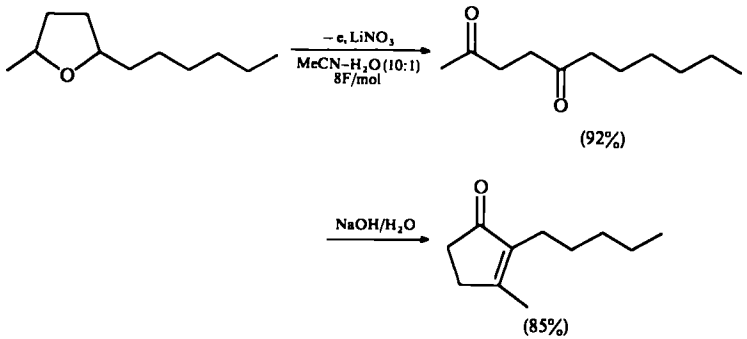
Although the direct anodic oxidation of aliphatic ethers is in some cases possible, the use of a mediator will give better results.

Recently, it has been found that anodic oxidation of ethers in a mixed solvent ($MeCN:H_2O = 10:1$) containing ammonium or lithium nitrate yields the corresponding carbonyl compounds or carboxylic acids with reasonable yields[27]. In this oxidation, only 0.1 equivalent of the nitrate salt is enough to promote the oxidation, and a nitrate radical is generated by oxidation of nitrate ion in the first step. The mechanism is similar to the oxidation of alcohols (equation 23).

$$NO_3^- \xrightarrow{-e} NO_3^{\cdot}$$

$$(RCH_2)_2O \xrightarrow[MeCN:H_2O = 10:1]{NO_3^{\cdot}} 2RCO_2H \quad (68\text{–}85\%) \tag{23}$$

This mediatory oxidation of ethers is conveniently applicable to a variety of organic syntheses as exemplified by the synthesis of dihydrojasmone (equation 24).



(24)

It has already been mentioned[1] that the C—O bond of *p*-methoxybenzyl alkyl ethers is cleaved at the benzylic position by the anodic oxidation carried out in the presence of tris(*p*-bromophenyl)amine as the mediator. On the other hand, it has recently been found that some aliphatic ethers are methoxylated at the α-position by the use of tris(2,4-dibromophenyl)amine as mediator, though the chemical yields are not high[28].

In this oxidation, the key step is formation of a complex between ether and a cation radical of the mediator followed by a bonded electron transfer between ether and the mediator (equation 25). The presence of a base is essential to the electron transfer and otherwise oxidation does not take place.

In the presence of a Ru(IV) complex, $[(bpy)(trpy)RuO]^{2+}$ (bpy = 2,2′-bipyridine, trpy = 2,2′:6′,2″-terpyridine), some allylic ethers are electrochemically oxidized to the corresponding alcohols, ketones or carboxylic acids depending on whether the allylic position is tertiary, secondary or primary. The Ru(IV) complex oxidizes the substrate and it is reduced to the aqua complex $[(bpy)(trpy)Ru(OH_2)]^{2+}$. The former complex is regenerated with platinum anode at 0.8V vs SCE in a buffer solution (pH 8.1) and hence a catalytic amount of the complex is enough to promote the oxidation (equation 26)[29].

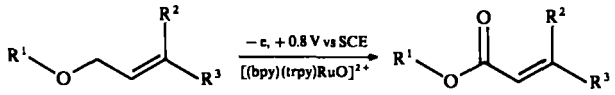
$$Ar_3N \overset{-e}{\rightleftharpoons} Ar_3N^{+\cdot}$$

$$Ar_3N^{+\cdot} + R{-}O{-}CH_2R' \rightleftharpoons [Ar_3N^{+\cdot}\cdots R{-}O{-}CH_2R']$$

$$[Ar_3N^{+\cdot}\cdots R{-}O{-}CH_2R'] + B \longrightarrow Ar_3N + R{-}O{-}\dot{C}HR' + HB^+ \qquad (25)$$

$$R{-}O{-}\dot{C}HR' + Ar_3N^{+\cdot} \rightleftharpoons R{-}O{-}\overset{+}{C}HR' + Ar_3N$$

$$R{-}O{-}\overset{+}{C}HR' + MeOH \longrightarrow R{-}O{-}\underset{\displaystyle OMe}{\underset{|}{C}}HR' + H^+$$



(40–53%) (26)

III. CATHODIC REDUCTION

It was mentioned in *Supplement E*[1] that alcohols and ethers which are not activated by some other functional group are usually not reducible by the electrochemical method. Although some benzylic, allylic and propargylic alcohols may be reduced on a mercury cathode at very negative potentials, they are believed to be not reducible on a platinum cathode. It has been found, however, that some allylic alcohols are reduced on a platinum cathode to the corresponding olefins and saturated hydrocarbons under acidic conditions. The reduction may involve solvolytic formation of an allylic cation intermediate followed by cathodic reduction of the cation to a radical. The radical is reduced further by hydrogen, which is generated by reduction of proton on the platinum cathode[30].

Hydroxyl groups located at the α-position of a carbonyl group are also reduced in a similar way.

The reductive cleavage of the C—O bond of methanesulfonates of aliphatic alcohols and of phosphates of phenols has been mentioned in *Supplement E*[1] without citation of the references. The former[31] and latter[32] are given in this chapter.

IV. REFERENCES

1. T. Shono, in *Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues* (Ed. S. Patai), Chap. 8, Wiley, Chichester, 1980.
2. T. Shono, Y. Matsumura, J. Hayashi and M. Mizoguchi, *Tetrahedron Lett.*, 165 (1979).
3. G. Dixit, R. Rastogi and K. Zutshi, *Electrochim. Acta*, **27**, 561 (1982).
4. T. Takiguchi and T. Nonaka, *Bull. Chem. Soc. Jpn.*, **60**, 3137 (1987).
5. T. Shono, Y. Matsumura, M. Mizoguchi and J. Hayashi, *Tetrahedron Lett.*, 3861 (1979).
6. J. E. Leonald, P. C. Scholl, T. P. Steckel, S. E. Lentsch and M. R. Van De Mark, *Tetrahedron Lett.*, **21**, 4695 (1980).
7. M. Masui, T. Ueshima and S. Ozaki, *J. Chem. Soc.*, Chem. Commun., 479 (1983).
8. M. F. Semmelhack, C. S. Chou and D. A. Cortes, *J. Am. Chem. Soc.*, **105**, 4492 (1983).
9. A. Deronzier, D. Limosin and J-C. Moutet, *Electrochim. Acta*, **32**, 1643 (1987).
10. T. Osa, U. Akiba, I. Segawa and J. M. Bobbitt, *Chem. Lett.*, 1423 (1988).
11. T. Osa, Y. Kashiwagi, K. Mukai, A. Ohsawa and J. M. Bobbitt, *Chem. Lett.*, 75 (1990).
12. T. Shono, Y. Matsumura, J. Hayashi and M. Mizoguchi, *Tetrahedron Lett.*, **21**, 1867 (1980).
13. E. J. Corey and C. V. Kim, *J. Am. Chem. Soc.*, **94**, 7586 (1972).
14. J. Yoshida, R. Nakai and N. Kawabata, *J. Org. Chem.*, **45**, 5269 (1980).
15. J-C. Moutet and G. Reverdy, *J. Chem. Soc., Chem. Commun.*, 654 (1982).

16. Z. Ogumi, S. Ohashi and Z. Takehara, *Electrochim. Acta*, **30**, 121 (1985).
17. A. Konno, K. Fukui, T. Fuchigami and T. Nonaka, *Tetrahedron*, **47**, 887 (1991).
18. S. Torii, T. Inokuchi, S. Matsumoto, T. Saeki and T. Oki, *Bull. Chem. Soc. Jpn.*, **63**, 852 (1990).
19. A. Yoshiyama, T. Nonaka, M. M. Baizer and T-C. Chou, *Bull. Chem. Soc. Jpn.*, **58**, 201 (1985).
20. M. Navarro, W. F. De Giovani and J. R. Romero, *Tetrahedron*, **47**, 851 (1991).
21. J. Kaulen and H. J. Schäfer, *Tetrahedron*, **38**, 3299 (1982).
22. T. Shono, Y. Matsumura, J. Hayashi and M. Usui, *Denki Kagaku*, **51**, 131 (1983).
23. T. Shono, Y. Matsumura, K. Tsubata, T. Kamada and K. Kishi, *J. Org. Chem.*, **54**, 2249 (1989).
24. J. Cramer, German Patent DE 3000243 A1, Hoechst AG (1981); *Chem. Abstr.*, **95**, 104904 (1981).
25. T. Shono, Y. Matsumura, O. Onomura and Y. Yamada, *Synthesis*, 1099 (1987).
26. B. Wermeckers and F. Beck, *Chem. Ber.*, **120**, 1679 (1987); B. Wermeckers, F. Beck and H. Schulz, *Electrochim. Acta*, **32**, 577 (1987).
27. T. Shono, S. Kashimura, unpublished results.
28. K-D. Ginzel and E. Steckhan, *Tetrahedron*, **43**, 5797 (1987).
29. J. L. Campos, W. F. De Giovani and J. R. Romero, *Synthesis*, 597 (1990).
30. G. Horányi, *Electrochim. Acta*, **31**, 1095 (1986) and references cited therein.
31. T. Shono, Y. Matsumura, K. Tsubata and Y. Sugihara, *J. Org. Chem.*, **47**, 3090 (1982).
32. T. Shono, Y. Matsumura, K. Tsubata and Y. Sugihara, *J. Org. Chem.*, **44**, 4508 (1979).

CHAPTER 17

Formations and reactions of peroxides in biological systems

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ABBREVIATIONS*

AAPH	2,2'-azobis(2-amidinopropane)-dihydrochloride	PA	phosphatidic acid
		PC	phosphatidylcholine
CL	cardiolipin	PE	phosphatidylethanolamine
HDL	high density lipoprotein	PG	phosphatidylglycerol
HPETE	hydroperoxy eicosapentaenoic acid	PI	phosphatidylinositol
LDL	low density lipoprotein	PS	phosphatidylserine
LH	lipid-H	SM	sphingomyelin
LPC	lysolecithin	SOD	superoxide dismutase

*See also the general list after the list of Contents of this volume.

Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

I. INTRODUCTION

There is now much evidence which suggests that the formation and reactions of peroxides in biological systems are involved in a variety of pathological events, cancer and aging (for a recent review see Reference 1). At the same time, various kinds of peroxides are known to have specific biological activities and play an important role *in vivo*. Therefore, the formation and reactions of peroxides, especially lipid peroxides, were extensively studied recently by investigations in various disciplines. The defense systems against active oxygen-induced and free radical-mediated peroxidations *in vivo* have also received much attention. In this chapter, the formation and reactions of peroxides and their inhibition in biological systems are briefly reviewed.

II. NONENZYMATIC, FREE RADICAL-MEDIATED CHAIN OXIDATION OF LIPIDS

The biological membranes are composed mainly of lipids, proteins and carbohydrates. The lipids observed in the membranes are phospholipids, glycolipids and cholesterol. Various phospholipids are found in the membranes, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidic acid (PA), phosphatidylglycerol (PG), cardiolipin (CL), lysolecithin (LPC), phosphatidylinositol (PI) and sphingomyelin (SM). The phospholipids contain much unsaturated fatty acid residues which enhance fluidity and permeability of the membranes. The polyunsaturated fatty acids which have two or more double bonds are oxidized easily and preferentially, since the doubly allylic hydrogens of the methylene group between two double bonds are quite reactive toward free radicals. Table 1 shows the polyunsaturated fatty acids observed *in vivo*.

The free radical-mediated oxidations of lipids proceed by a chain mechanism, which is composed of three steps as shown in Figure 1. In the chain initiation step, the lipid carbon-centered radical L· is formed by a doubly-allylic hydrogen atom abstraction from the lipid LH. The lipid radicals react rapidly with oxygen to give lipid peroxyl radicals (Table 2), which attack another lipid molecule and abstract active hydrogen intermolecularly to give lipid hydroperoxide and, at the same time, another lipid radical. In some cases, the lipid peroxyl radical adds to the double bond intramolecularly to give a carbon-centered radical (see subsequent text). These radicals react with oxygen to give peroxyl radicals. Thus, reactions 1 and 2 take place repeatedly to continue the chain propagation. In the chain termination step, the radicals disappear by their mutual

TABLE 1. Polyunsaturated fatty acids observed *in vivo*

Fatty acid	Carbon number	Number of double bonds
Linoleic acid (octadeca-9,12-*cis*-dienoic acid)	18	2
Linolenic acid (octadeca-9,12,15-*cis*-trienoic acid)	18	3
Arachidonic acid (Eicosa-5,8,11,14-*cis*-tetraenoic acid)	20	4
Eicosapentaenoic acid (Eicosa-5,8,11,14,17-*cis*-pentaenoic acid)	20	5
Docosahexaenoic acid (Docosa-4,7,10,13,16,19-*cis*-hexaenoic acid)	22	6

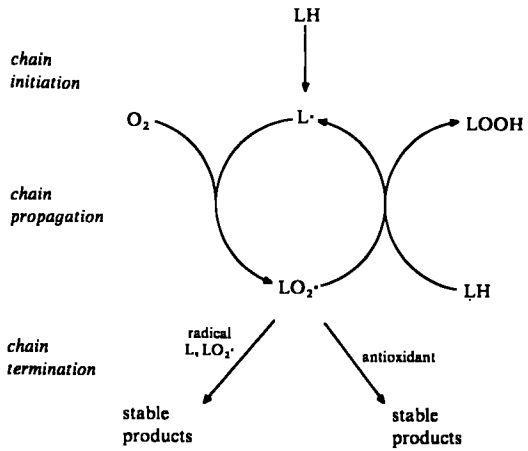


FIGURE 1. Oxidation of lipids by a free radical chain mechanism: LH, lipid; L·, carbon-centered lipid radical; LO_2·, lipid peroxyl radical; LOOH, lipid hydroperoxide

TABLE 2. Rate constants for reactions of carbon-centered radicals with oxygen molecules[2]

Radical	k ($M^{-1}s^{-1}$)
Methyl	$(4.7 \pm 0.7) \times 10^9$
Ethyl	$(2.9 \pm 0.8) \times 10^9$
Hydroxymethyl	$(4.2 \pm 0.5) \times 10^9$
Hydroxyethyl	4.6×10^9
Linoleate	3×10^8
Linolenate	3×10^8
Arachidonate	2×10^8

bimolecular interactions (reaction 3) and/or by stabilization with a radical-scavenging antioxidant.

$$L\cdot + O_2 \longrightarrow LO_2\cdot \quad (1)$$

$$LO_2\cdot + LH \longrightarrow LOOH + L\cdot \quad (2)$$

$$2\,LO_2\cdot \longrightarrow \text{nonradical products} \quad (3)$$

A. Rate of Oxidation of Lipids

One of the characteristics of the free radical-mediated peroxidation of lipids is that it proceeds by a chain mechanism. It has been proved experimentally that the oxidations of lipids proceed with a long kinetic chain length in homogeneous solution, micelles and liposomal membranes in aqueous dispersions[3]. However, it is not known whether the lipid peroxidation *in vivo* proceeds by a chain mechanism, and if it does, how long the chain continues, primarily because of the difficulty in measuring the rate of chain

initiation. Nevertheless, it has been shown experimentally that the *in vitro* oxidations of erythrocytes[4,5] and low density lipoproteins[6] (LDL) proceed by a free radical-chain mechanism, the kinetic chain length being considerably longer than 1.

Erythrocytes are susceptible to oxidation. Their membranes are rich in polyunsaturated fatty acids and continuously exposed to high concentration of oxygen carried by hemoglobin which may catalyze the oxidation. It was found that when human erythrocyte ghost membranes (without hemoglobin) were oxidized at 37 °C in phosphate buffer (pH 7.4) with a water-soluble radical initiator, 2,2′-azobis(2-amidinopropane)dihydrochloride (AAPH), the oxidation proceeded with a kinetic chain length ranging from 7 to 100[4]. The intact erythrocytes were also found to be oxidized by AAPH with a long kinetic chain length much larger than 1. The oxidation of erythrocyte membranes eventually causes hemolysis[7].

LDL is a microemulsion composed of lipids and apoprotein B. Phosphatidylcholine and free cholesterol constitute an outer monolayer, while cholesterol ester and triglyceride are located within a core. The process of oxidation brings about a modification of LDL, which is now accepted as one of the important primary events of atherogenesis[8]. It has been found that the oxidation of LDL induced by AAPH proceeds by a free radical chain mechanism to yield PC-hydroperoxides and cholesterol ester hydroperoxides as major products[6].

The kinetics of the oxidation of lipids have been studied extensively by Barclay and his colleagues in *in vitro* model systems[9–13]. They found that the kinetic orders in substrate concentration and rate of chain initiation were unity and one-half, respectively, both in micelles and in liposomal membranes, suggesting that the classical rate law of autoxidation for the oxidation in homogeneous solution applies also to the oxidations in micelles and in bilayer membranes. The rate constants obtained in different reaction media are summarized in Table 3[13]. It shows that the rate constants for both chain propagation and chain termination in the model membranes are reduced compared to those in homogeneous solution, but that the oxidizability expressed by $k_p/(2k_t)^{1/2}$ is larger in the membranes than in homogeneous solution. Barclay and coworkers[12] interpreted these results in terms of hydrogen bonding by polar peroxyl radicals that diffuse toward the aqueous phase.

Table 4 shows the rate constants for reactions of several free radicals with fatty acids and their oxidizabilities. Hydroxyl, *tert*-butoxyl and trichloromethylperoxyl radicals are quite reactive and less selective. On the other hand, the lipid peroxyl radicals, which act as chain carrier, are much less reactive but more selective and attack only weak C—H

TABLE 3. Absolute rate constants for chain propagation k_p and chain termination k_t and oxidizabilities $k_p/(2k_t)^{1/2}$ for linoeate autoxidation as measured by the rotating sector method

Temperature (°C)	Medium	k_p ($M^{-1}s^{-1}$)	$2k_t$ ($M^{-1}s^{-1}$)	$k_p/(2k_t)^{1/2}$ $(M \cdot s)^{-1/2}$	Reference
30	Chlorobenzene	62	8.8×10^6	0.021	14
30	Acetonitrile	94.9–96.5	$(4.42–4.33) \times 10^6$	0.046	10
30	*t*-Butyl alcohol	75.6–78.5	$(15.1–15.5) \times 10^6$	0.020	10
30	SDS[a] micelles	36.2	0.352×10^6	0.061	10
37	SDS[a] micelles	39.1	0.417×10^6	0.061	15
30	DLPC[b]	21–30	$(0.085–0.108) \times 10^6$	0.082	13
37	DLPC[b]	36.1–41.6	$(0.127–0.132) \times 10^6$	0.11	15

[a]Sodium dodecyl sulfate.
[b]Dilinoleoylphosphatidylcholine liposomes.

TABLE 4. Absolute rate constants for the reactions of free radicals with fatty acids and oxidizabilities[a]

Fatty acid	Absolute rate constants ($M^{-1}s^{-1}$)				Oxidizability[e]
	HO·	HO_2·[b]	$(CH_3)_3CO$·[c]	Cl_3COO·[d]	$k_p/(2k_t)^{1/2}$ $(M \cdot s)^{-1/2}$
Stearic			2.3×10^6		
Oleic (18:1)		0	3.8×10^6	1.7×10^6	
Linoleic (18:2)	$10^9 \sim 10^{10}$	1.2×10^3	8.8×10^6	3.9×10^6	2.03×10^{-2}
Linolenic (18:3)	8×10^9	1.7×10^3	13.0×10^6	7×10^6	4.07×10^{-2}
Arachidonic (20:4)	10×10^9	3.1×10^3	20.5×10^6	7.3×10^6	5.75×10^{-2}
Docosahexaenoic (22:6)					10.2×10^{-2}

[a]Compiled from Reference 16.
[b]Reference 17.
[c]Reference 18.
[d]Reference 19.
[e]Reference 20.

bonds. Table 4 shows that the reactivities and oxidizabilities are determined primarily by the number of bis-allylic hydrogens.

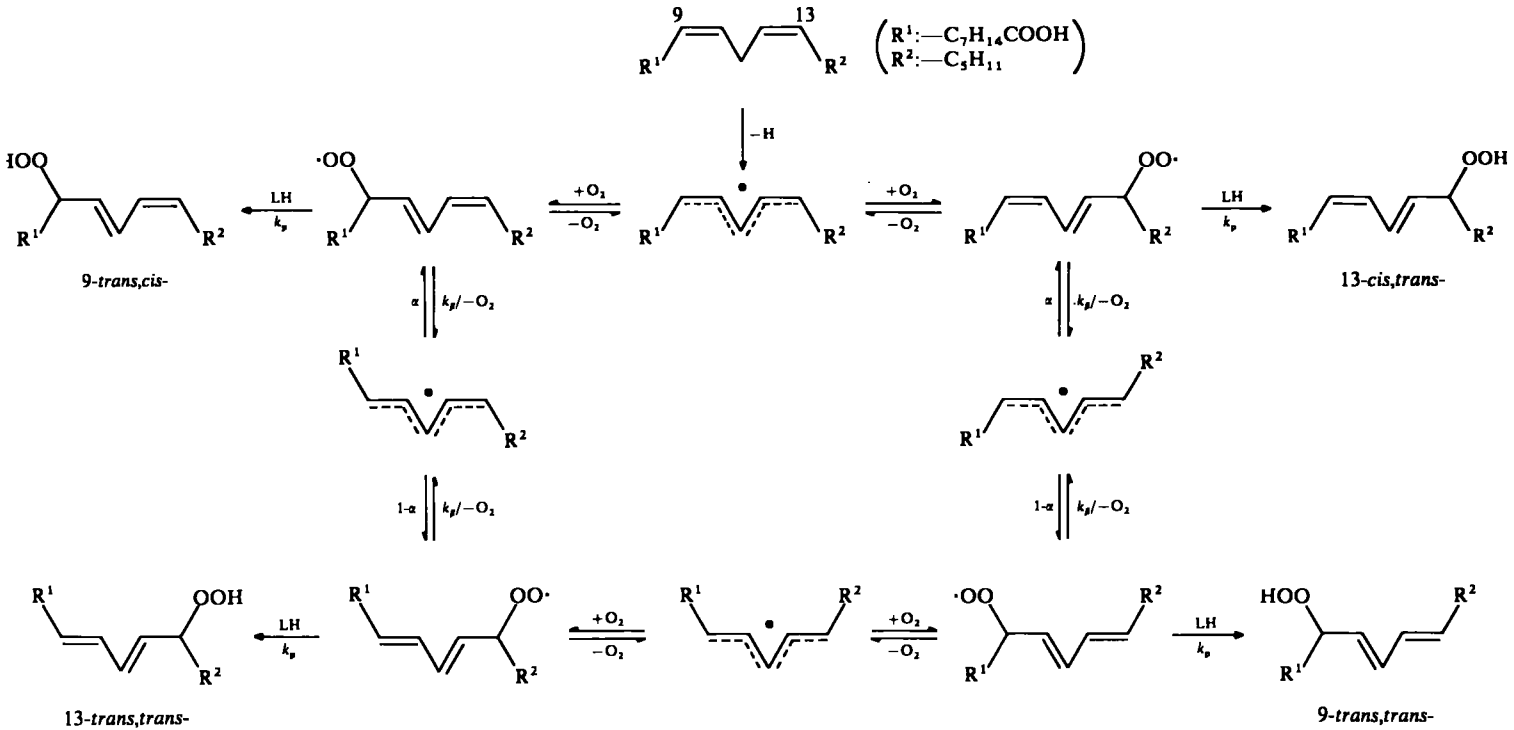
B. Products and Mechanism of Lipid Peroxidation

As mentioned above, polyunsaturated fatty acids and their esters are oxidized preferentially since the doubly allylic hydrogens of the methylene group between the double bonds are much more reactive toward peroxyl radicals than those of monoolefins and of saturated fatty acids and their derivatives. Table5 shows the compositions of fatty acids in red blood cell membranes and lipoproteins[21]. The most important fatty acids

TABLE 5. Fatty acid composition (in %) in human red blood cell membrane and low (LDL) and high (HDL) density lipoproteins[21]

Fatty acids[a]	Red blood cell (%)	LDL (%)	HDL (%)
14:0	0.6	1.2	0.8
16:0	35.5	24.5	30.1
16:1	0.2	—	—
18:0	16.9	3.2	7.2
18:1	13.9	14.0	11.8
18:2	10.6	46.1	35.3
18:3	—	0.5	0.3
20:3	0.8	0.5	0.8
20:4	11.9	5.0	6.5
20:5	—	1.5	2.0
22:0	0.5	—	—
22:4	1.5	0.2	0.2
22:5	—	0.2	0.3
22:6	5.9	1.9	2.6
unknown	3.3	—	—

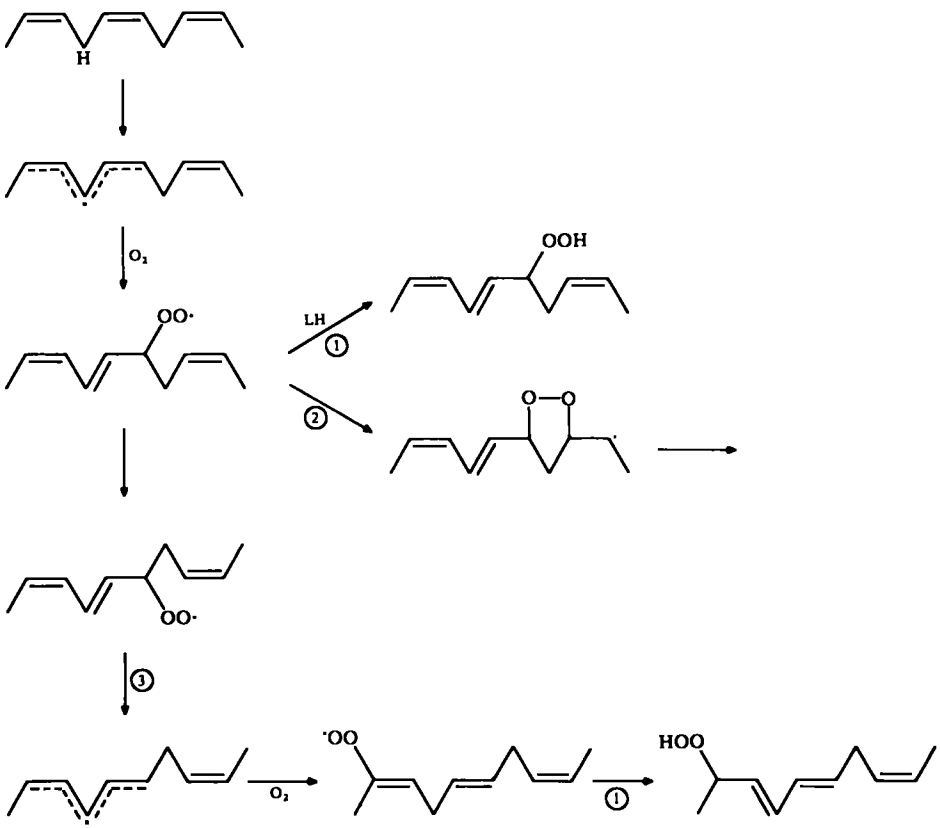
[a]Number of C atoms: number of double bonds.



SCHEME 1. Oxidation mechanism for unsaturated lipids having two double bonds

in vivo are linoleic acid and arachidonic acid, and their esters. In some cases, depending on the diet, such polyunsaturated fatty acids as linolenic acid, eicosapentaenoic acid, docosahexaenoic acid and their esters are also considered to be important substrates. The products and mechanism of the oxidations of free fatty acids and their esters in membranes and aggregates are substantially the same as those in the homogeneous solution. The fatty acids having two double bonds are oxidized to give conjugated diene hydroperoxides quantitatively as the primary product, while those having three or more double bonds are oxidized to give cyclic peroxides and epoxides as well as conjugated diene hydroperoxides[22-24].

The oxidations of lipids having two double bonds proceed by a mechanism shown in Scheme 1. The abstraction of a doubly allylic hydrogen gives a pentadienyl radical, which reacts with oxygen rapidly to yield a *trans,cis*-peroxyl radical. The latter may abstract a hydrogen atom from another lipid molecule to give a *trans,cis*-conjugated diene hydroperoxide or it may be converted to a *trans,trans*-peroxyl radical by a sequence of sigma-bond rotation, release of oxygen molecule and addition of oxygen. This peroxyl radical yields a *trans,trans*-hydroperoxide by a hydrogen atom abstraction. The ratio of



SCHEME 2. Oxidation of lipids having three or more double bonds: (1) hydrogen atom abstraction; (2) intramolecular addition; (3) release of oxygen molecule

TABLE 6. Isomeric distributions of fatty acid hydroperoxides[23]

Fatty acids	9-OOH	10-OOH	12-OOH	13-OOH	15-OOH	16-OOH
(1) Autoxidation						
Linoleate	50			50		
Linolenate	30		12	12		46
(2) Photosensitized oxidation						
Oleate	50	50				
Linoleate	31	18	18	33		
Linolenate	21	13	13	14	13	25

trans,cis-hydroperoxide to *trans,trans*-hydroperoxide is determined by the rate of hydrogen atom abstraction, that is, the reactivities and concentrations of hydrogen donors. Thus, the oxidations of linoleic acid and its esters gives four kinds of conjugated diene hydroperoxides quantitatively[22-25].

The oxidations of triene, tetraene and higher unsaturated fatty acids proceed by a more complex pathway than that of diene fatty acids (Scheme 2). In the oxidation of linolenate, the hydrogen atoms are abstracted from the two activated, doubly allylic methylene groups on carbon-11 and carbon-14 to form two kinds of pentadienyl radicals. Arachidonic acid has three methylene groups flanked by two double bonds and gives six kinds of peroxyl radicals. Hydrogen atom abstraction by these peroxyl radicals gives the corresponding *trans,cis*-conjugated diene hydroperoxides. The *trans,cis*-peroxyl radicals may be converted to *trans,trans*-peroxyl radicals as described above to give eventually *trans,trans*-conjugated diene hydroperoxides. The 8-, 9-, 11- and 12-peroxyl radicals may also add to the double bond at adjacent centers to form five- and six-membered ring products[26]. The resulting radical formed after cyclization can either cyclize again to form bicycloendoperoxides which are structurally related to the prostaglandins, or undergo cleavage to produce malonaldehyde[27] or react with oxygen followed by hydrogen atom abstraction to yield precursors to prostaglandins and analogues. On the other hand, the 5- and 15-peroxyl radicals do not have a competitive cyclization pathway and do not give cyclic peroxides. Thus, the external hydroperoxides are formed in amounts significantly higher than the internal hydroperoxides[28,29]. For example, the amounts of 9- and 16-hydroperoxides are much larger than those of 12- and 13-hydroperoxides in the oxidation of linolenate (Table 6)[23], since the internal 12- and 13-peroxyl radicals can undergo intramolecular 1,3-cyclization while the external 9- and 16-peroxyl radicals cannot[30,31]. As expected, such cyclization was completely inhibited by the addition of 5% α-tocopherol as a hydrogen donor, when an even distribution of the 9-, 12-, 13- and 16-hydroperoxides were formed[32].

Thus, the product distribution is determined by the relative importance of three competing reactions of peroxyl radicals, that is, hydrogen atom abstraction, intramolecular addition to double bonds, and release of oxygen. The rate constant for loss of oxygen[33] (β-scission) from the peroxyl radical is $150\,s^{-1}$, while that for intramolecular cyclization[34] is $800\,s^{-1}$. Thus, the β-scission of peroxyl radical leading to *trans,trans*-hydroperoxides does not compete effectively with the intramolecular cyclization.

C. Secondary Reactions of Lipid Hydroperoxides

As described above, hydroperoxides are the primary oxidation products from polyunsaturated lipids. They are not stable and can undergo various secondary reactions

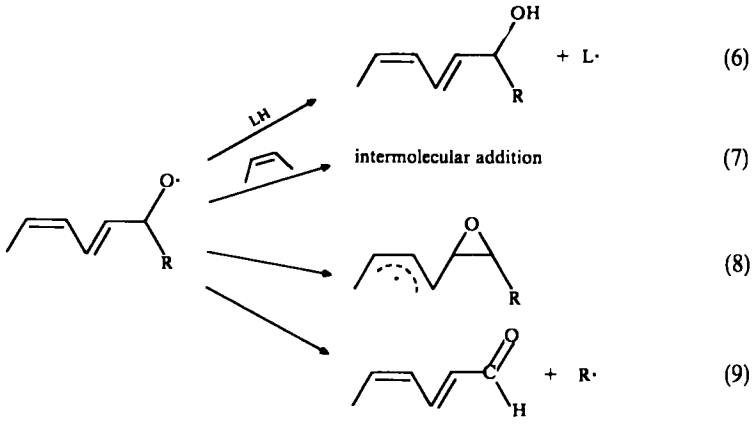
to give a wide range of carbonyl compounds such as aldehydes and ketones, alcohols, epoxides, carboxylic acids and hydrocarbons[23]. Some reactions proceed enzymatically and others nonenzymatically, by nonradical and radical mechanisms. Lipid hydroperoxides can be the target of free radicals to give bifunctional products such as dihydroperoxides and epoxyhydroperoxides. Bifunctional secondary products can interact with proteins; for example, malondialdehyde derived from cyclic peroxides reacts with amino groups of proteins, enzymes and DNA and the resulting crosslinking products can affect vital cell functions.

One of the most important reactions of hydroperoxides is the cleavage of peroxidic oxygen–oxygen bonds by heat, light and transition metal ions. In vivo, the decomposition of lipid hydroperoxides by ferrous or cuprous ions is the most important, although substantially all such metal ions are sequestered by proteins.

$$LOOH + Fe^{2+} \longrightarrow LO\cdot + {}^{-}OH + Fe^{3+} \quad (4)$$

$$LOOH + Cu^{+} \longrightarrow LO\cdot + {}^{-}OH + Cu^{2+} \quad (5)$$

The alkoxyl radical may undergo several competing reactions. It may attack another lipid molecule and abstract hydrogen atom (reaction 6) and/or add to a double bond (reaction 7). It may also add to the double bond intramolecularly to give epoxide (reaction 8). Another important reaction is the β-scission to give an aldehyde and an alkyl radical (reaction 9). The decomposition of a 5-membered cyclic peroxide may give malondialdehyde (reaction 10)[27]. It has been shown that various aldehydes are formed and they are particularly important since they often crosslink with amino groups of proteins, enzymes and DNA[35].



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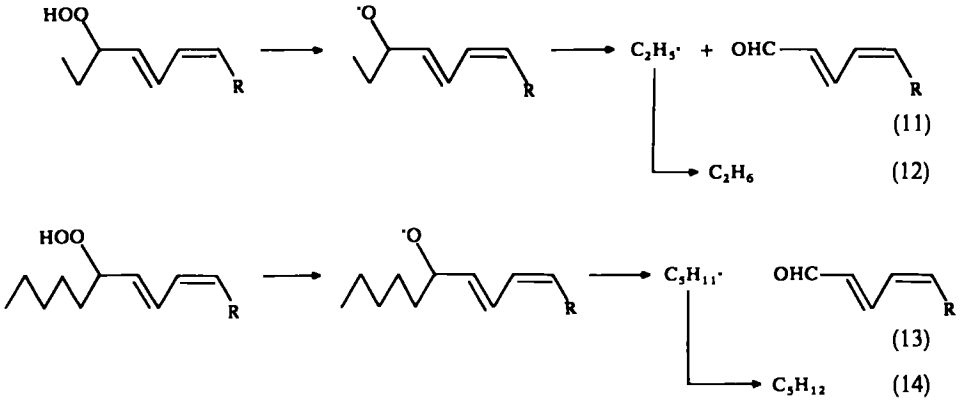
The products and mechanisms of the reactions of methyl linoleate hydroperoxides have been studied in detail using pure 9- and 13-hydroperoxides prepared by lipoxygenases. Various products have been identified in the decomposition of the *cis,trans*-13-hydroperoxide of methyl linoleate. Hamberg[36] identified *threo*-11-hydroxy-

12,13-epoxy-9-octadecenoic acid as a major product together with 13-keto and hydroxy dienes, *erythro*- and *threo*-11-hydroxy-12,13-epoxy-9-monoene isomers and 9-hydroxy-12,13-epoxy-10-monoene. Gardner and coworkers[37] identified isomeric mixtures of keto dienes, hydroxy dienes, hydroxy epoxy and keto epoxy monoene compounds in the decomposition of linoleic hydroperoxides catalyzed by Fe(III)-cysteine.

A large number of low molecular weight volatile products are formed during the oxidation of lipids. Above all, alkanes observed in the exhaled gas are accepted as a good measure for the lipid peroxidation taking place *in vivo*[38]. For example, ethane and pentane are formed from the β-scission of the alkoxyl radical derived from (ω-3) and (ω-6) fatty acid moieties.



D. Oxidation of Cholesterol

Lipid peroxidation is usually studied with unsaturated fatty acid derivatives, but it is also observed for cholesterol and related unsaturated sterols, which serve as important constituents in biological membranes. It is known that the oxidized cholesterol derivatives have biological activities including cytotoxic effects, stimulatory or inhibitory effects on specific enzymes and cell membrane effects. Cholesterol may be oxidized both enzymically by specific enzymes and nonenzymically to give cholesterol hydroperoxides, epoxides and cholestanediols as major products[39].

Table 7 summarizes the oxidation products from cholesterol[39]. The initial stable cholesterol autoxidation products are the epimeric cholesterol 7-hydroperoxides[40]. On

TABLE 7. Oxidation products from cholesterol

Oxidant	Initial products	Secondary products
$^3O_2$ (autoxidation)	Cholesterol 7-hydroperoxides, **1**	Cholest-5-ene-3β,7-diols, **2** 3β-hydroxycholest-5en-7-one, **3** Cholesterol 5,6-epoxides, **4** Cholesta-3,5-dien-7-one, **5** 5α-cholestane-3β,5,6β-triol, **6**
$^1O_2$	3β-hydroxy-5α-cholest-6-ene-5-hydroperoxide, **7**	5α-cholest-6-ene-3β,5-diol, **8** Cholesta-4,6-dien-3-one, **9** 7-oxygenated sterols, **10**
Soybean lipoxygenase	**1,2,3,4,6**	
Horseradish peroxidase	**1,2,3**	

the other hand, singlet oxygen oxidizes cholesterol to give 5-hydroperoxides[39,41]. Thus, it is conceptually possible to distinguish among the several oxidants by analyzing the oxidized cholesterol derivatives formed.

The oxidation of fatty acid esters of cholesterol has also received much attention in connection with atherogenesis induced by oxidative modification of LDL. Free cholesterol is located in the outer surface layer of LDL, whereas cholesterol esters reside in the core of LDL. The cholesterol esters having polyunsaturated fatty acid residues are oxidized readily to give similar products from polyunsaturated fatty acid moieties.

E. Oxidations in Biology

There is an increasing amount of experimental evidence which implies the potential role of lipid peroxidation in the pathogenesis of atherosclerosis[8,42]. Human low-density lipoprotein is not only rich in cholesterol, but also in polyunsaturated fatty acids as shown in Table 5. Various lines of biochemical, clinical and epidemiological studies suggest that oxidatively modified LDL is atherogenic. That is, the oxidatively modified LDL is taken up via a scavenger receptor of monocyte-derived macrophages which is not under the control of the cholesterol-dependent regulation and results in the accumulation of cholesterol and eventually foam cells.

LDL is a spherical particle with a dimeter of 22 nm and a molecular weight of about 2.5 million Da. It consists of a central core of 1500 molecules of cholesterol ester and about 200 molecules of triglycerides, and an outer shell of a monolayer composed of about 800 molecules of phospholipids and 500 molecules of free, unesterified cholesterol. Embedded in the outer monolayer is a large protein termed apolipoprotein B whose molecular weight is half a million Da. The human LDL isolated from plasma is composed of 8–9% free cholesterol, 43–45% cholesterol ester, 6–9% triglycerides, 18–19% phospholipids and 20–23% protein[43]. The total number of fatty acids in an LDL particle is 2500, approximately half of which are polyunsaturated fatty acids (Table 5). Linoleic acid is the major fatty acid with smaller amounts of arachidonic acid. More highly unsaturated fatty acids are also observed. The fatty acid distribution is primarily determined by diet. Interestingly, these fatty acids are unequally distributed among the different lipid classes[44]. Linoleic acid is found mainly in the cholesterol ester, whereas arachidonic acid is predominantly associated with the phospholipid.

The oxidations of LDL *in vitro* have been studied most extensively by Esterbauer and his colleagues[42,44,45]. Polyunsaturated fatty acids in LDL are preferentially oxidized by the same mechanism as in the homogeneous solution described before. Hydroperoxides are formed as the primary products, but aldehydes such as malondialdehyde, hexanal, 4-hydroxynonenal and propanal are also formed[44]. Figure 2 shows the example of the oxidation of human LDL induced by either copper or water-soluble azo initiator AAPH[46]. Cholesterol ester and phosphatidylcholine are oxidized to give corresponding hydroperoxides as the major, primary products. The oxidation of LDL is also induced by various cells such as endothelial cells and also by lipoxygenases.

Red blood cell membranes are composed of phospholipids, cholesterol and proteins. The polyunsaturated phospholipids are the primary target of free radicals and they are oxidized by the free radical chain mechanism to give hydroperoxides and secondary products. Proteins are also oxidized to give both crosslinked and degraded products. These oxidations eventually cause hemolysis[47,48].

III. PHOTOOXIDATION

The unsaturated lipids are also oxidized photochemically by singlet oxygen. Usually, light is first absorbed by a sensitizer such as chlorophyll and the energy is transferred from the photosensitizer to a ground state oxygen molecule to give a singlet oxygen.

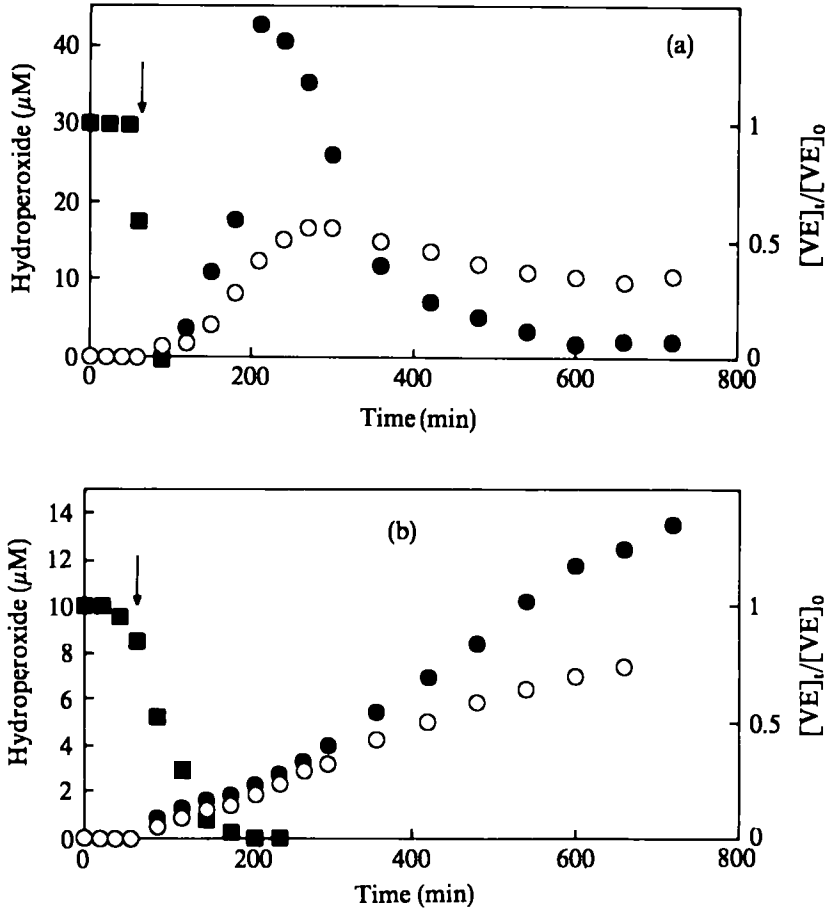


FIGURE 2. Oxidation of human low density lipoprotein (1 mg/ml) at 37 °C in air induced by either (a) 5 μM copper(II) or (b) 3 mM water-soluble azo compound, AAPH[46]. Copper or AAPH was added to the aqueous suspensions in each case 50 min (indicated by arrow), ■ refers to α-tocopherol, ○ to phosphatidylcholine hydroperoxides, and ● to cholesteryl ester hydroperoxide

Singlet oxygen reacts with double bonds rapidily, the rate constant being 10^5–10^6 $M^{-1}s^{-1}$, and oxidizes unsaturated lipids to give hydroperoxides by 'ene-reaction'.

$$\text{Sensitizer} \xrightarrow{\text{light}} \text{Sensitizer*(excited)} \tag{15}$$

$$\text{Sensitizer*} + {}^3O_2 \longrightarrow \text{Sensitizer} + {}^1O_2 \tag{16}$$

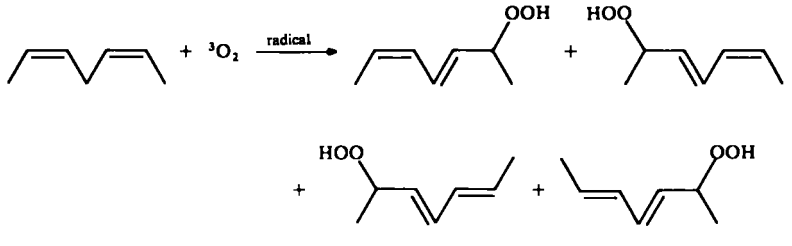
$$^1O_2 + \text{(alkene)} \longrightarrow \text{(allylic hydroperoxide, OOH)} \tag{17}$$

TABLE 8. Product distributions of fatty acid oxidations of singlet oxygen

	Hydroperoxide products (%)											
Fatty acid	5-	6-	8-	9-	10-	11-	12-	13-	14-	15-	16-	Reference
Oleic acid				50	50							50
Linoleic acid				31	18[a]		18[a]	33				50
Linolenic acid				21	13[a]		13	14		13[a]	25	50
Arachidonic acid	14	5[a]	13	13		14	13		7[a]	20		51

[a]Specific for singlet oxygen oxidation, not formed in the autoxidation.

Although only polyunsaturated lipids are oxidized by autoxidation, monoolefins as well as polyolefins are also oxidized by singlet oxygen. Furthermore, the autoxidation of polyunsaturated fatty acids gives conjugated diene hydroperoxides exclusively, whereas the oxidation by singlet oxygen gives nonconjugated hydroperoxides in addition to conjugated diene hydroperoxides. Some examples of the product distributions of the singlet oxygen oxidations of oleic acid, linoleic acid, linolenic acid and arachidonic acid are shown in Table 8.



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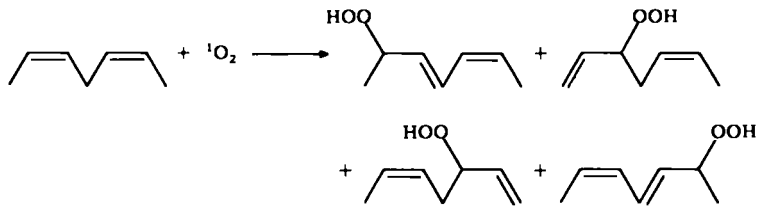

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Another important point is that singlet oxygen is not a free radical and the oxidation by singlet oxygen proceeds not by a free radical chain mechanism but stoichiometrically, involving in the process only one singlet oxygen molecule and one lipid molecule. It is not clear at present how much singlet oxygen is formed and how important the oxidation by singlet oxygen is *in vivo*[49].

IV. ENZYMATIC OXIDATION

The enzymatic oxidation plays an important role *in vivo* in the production of various oxygenated compounds (which have specific and essential biological activities) and also in the metabolism of various endogenous compounds and exogenous drugs. It is induced by enzymes called oxygenases which catalyze the insertion of an oxygen molecule directly

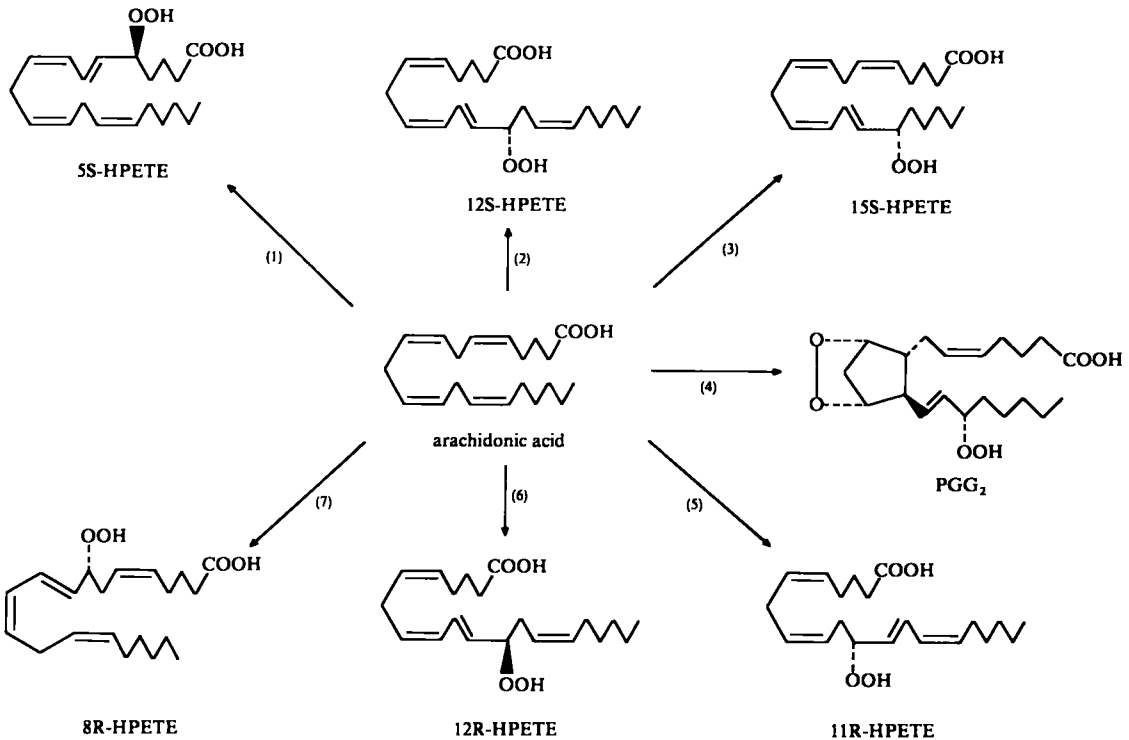

FIGURE 3. Oxidation of arachidonic acid by lipoxygenases: (1) 5-lipoxygenase (neutrophils); (2) 12-lipoxygenase (platelets); (3) 15-lipoxygenase (neutrophils, soybean); (4) cyclooxygenase; (5) (lung tissue, mast cells); (6) (sea urchin); (7) (coral)

into the substrates[52]. This was discovered in 1955 independently by the groups of Mason[53] and of Hayaishi[54]. Two types of oxygenases are known: monooxygenases which catalyze the incorporation of one oxygen atom into the substrate, and dioxygenases which introduce dioxygen into the substrate,

$$S + O_2 + AH_2 \longrightarrow SO + H_2O + A \quad (20)$$

$$S + O_2 \longrightarrow SO_2 \quad (21)$$

where S is substrate and AH_2 is a hydrogen donor. The monooxygenase which catalyzes the hydroxylation of a substrate is called hydroxylase.

Dioxygenases play an important role in the peroxidation of lipids, especially lipoxygenase and cyclooxygenase (sometimes called prostaglandin H synthetase) are well known for prostaglandin (PG) biosynthesis in arachidonate oxygenation pathways. Unsaturated fatty acids such as arachidonic acid produced from phospholipids induced by phospholipases are converted enzymatically to various hydroperoxy acids such as 5-, 12- and 15-hydroperoxyarachidonic acids[55]. 5-Hydroperoxyarachidonic acid is further converted to leukotriene C or D[56]. The HPETE compounds are precursors of a range of chemicals with potent biological activity known as leukotrienes. Leukotrienes differ structurally from prostanoids in that the leukotrienes have no cyclopentane ring, but have a conjugated triene structure. Arachidonic acid is also oxidized by cyclooxygenase to produce prostaglandin endoperoxides such as PGG_2 and PGH_2. The endoperoxides are unstable and undergo enzymatic conversion to various biologically active compounds such as thromboxane A_2, PGE_2, PGD_2, $PGF_{2\alpha}$ and PGI_2. These oxygenated products exhibit various physiological functions such as chemotaxis and vasodilation and cause some deteriorative reactions in various degenerative disorders[57]. For example, PGH_2 and thromboxane aggregate platelets, whereas PGI_2 inhibits platelet aggregation. These materials have been implicated in the inflammatory process in heart attack, strokes and smooth muscle contraction[58].

The prostaglandins, leukotrienes, thromboxanes and various families of hydroxy fatty acids are collectively referred to as eicosanoids, because they are synthesized from polyunsaturated fatty acids with twenty carbon atoms. The most important fatty acid of this type in humans is arachidonic acid, 5,8,11,14-eicosatetraenoic acid. Others include 8,11,14-eicosatrienoic acid and 5,8,11,14,17-eicosapentaenoic acid.

One of the characteristics of the enzymatic oxidations is that they proceed stereoselectively and regioselectively. Lipoxygenases have different substrate specificity and produce different ratios of products. They have also different pH optima. As shown in Figure 3 and Table 9, various mammalian lipoxygenases attack arachidonic acid regio-

TABLE 9. Stereospecific oxidation by lipoxygenases

Enzyme	Substrate	Products	H abstraction	Insertion of dioxygen
5-Lipoxygenase	Arachidonic acid	5-HPETE	7-pro-(S)	5S
	5-HPETE	$5,6\text{-LTA}_4$	10-pro-(R)	—
12-Lipoxygenase	Arachidonic acid	12-HPETE	10-pro-(R)	12S
	15-HPETE	$14,15\text{-LTA}_4$	10-pro-(R)	—
15-Lipoxygenase	Arachidonic acid	15-HPETE	13-pro-(S)	15S
Cyclooxygenase	Arachidonic acid	PG_2	13-pro-(S)	9α,11α,15S

selectively to give the corresponding hydroperoxides. Soybean lipoxygenase-1 has a pH optimum of 9 and attacks linoleic acid to give exclusively (9*Z*, 11*E*)-13-hydroperoxy-9,11-octadecadienoic acid, while soybean lipoxygenase-2 has the optimum at pH 6.8, prefers arachidonic acid as a substrate and converts linoleic acid into approximately equal amounts of 13- and 9-hydroperoxides. The bicycloendoperoxides from linolenate have mainly *cis* substituents[59], in contrast to the *trans* stereochemistry of the prostaglandins derived enzymatically from arachidonic acid[58]. The physiological importance of this difference in stereochemistry between the nonenzymatic and enzymatically produced bicyclic peroxides remains to be established.

It is often assumed that free radicals are involved in these enzymatic oxidations for example by lipoxygenases. However, that the above enzymatic oxidations are quite stereospecific, in contrast to the random oxidation induced by free radicals, suggests that the radicals formed during the enzymatic oxidation are, if at all, not really 'free' and the oxidation proceeds by a concerted mechanism.

V. INHIBITION OF OXIDATION

Aerobic organisms utilize molecular oxygen to sustain life. As described above, the essential biofactors having specific physiological activities are prepared *in vivo* by controlled oxidations. The active oxygen species are also essential in the self-defense mechanisms, for example, phagocytosis. Oxygen and its reactive intermediates, however, may also react with cellular components and essential molecules to cause damage in the membranes and tissues. We are protected from such oxidative damage by an array of defense systems. Our life becomes possible only through protection by strategically prepared and placed antioxidants and by continual repair and replacement[60].

Figure 4 illustrates the defense systems against oxidative damage by antioxidants with different functions. They can be divided into four categories according to their functions. The first line of defense is that of preventive antioxidants which inhibit or suppress the formation of active oxygen and free radicals. Active oxygen and free radicals are formed *in vivo* by various reactions under different circumstances and they may also be taken into the body exogenously. Among others, the redox decompositions of hydroperoxides and/or hydrogen peroxide by transition metal ions, especially iron and copper, are important. In the cases the enzymes reduce the peroxides without generating free radicals or active oxygen. The enzymes include catalase, glutathione peroxidase, glutathione-S-transferase, peroxidase and phospholipid hydroperoxide glutathione peroxidase (Table 10)[61].

Iron and copper are sequestered by specific proteins so that these metal ions may not decompose hydroperoxides and hydrogen peroxide. Ferritin, transferrin and lactoferrin sequester iron, while ceruloplasmin sequesters copper. Iron and copper at a lower valence state, that is, Fe(II) and Cu(I), decompose peroxides much faster than their corresponding ions at a higher valence state, Fe(III) and Cu(II), respectively. Accordingly, those which oxidize metal ions can act as an antioxidant. Ceruloplasmin has a ferroxidase activity of oxidizing iron(II) to iron(III), and by doing this it can act as an antioxidant. On the other hand, superoxide, an anion radical formed by one-electron reduction of molecular oxygen, reduces chelated iron(III) and copper(II) to yield active Fe(II) and Cu(I), respectively. Superoxide dismutase, SOD[62], rapidly traps superoxide and catalyzes its disproportionation to oxygen and hydrogen peroxide. Although the mechanism by which superoxide causes damage has not been unequivocally proved, it is generally accepted that SOD functions as one of the important antioxidants *in vivo* and its therapeutic application has in fact been tested. The production of natural, modified and artificial SOD has received much attention recently.

Carotenoids such as β-carotene and xanthophylls also act as preventive antioxidants

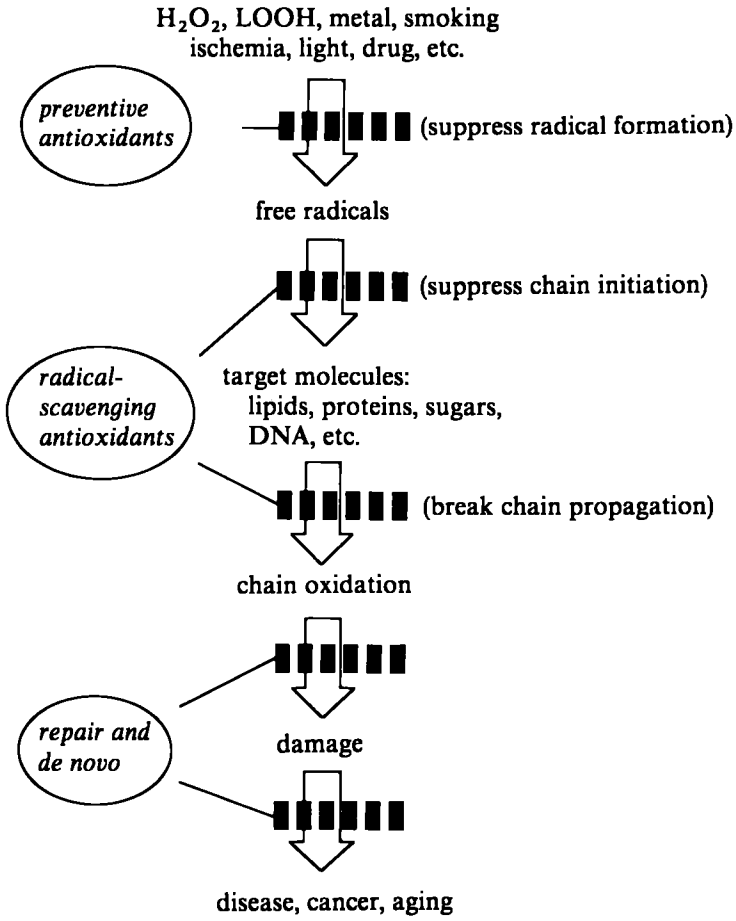

FIGURE 4. Defense systems in aerobic organism against oxidative damage induced by active oxygens and free radicals

TABLE 10. Antioxidant enzymes which reduce hydroperoxides and hydrogen peroxide

Enzyme	Function
Glutathione peroxidase	Reduction of hydroperoxides and hydrogen peroxide $LOOH + 2\,GSH \longrightarrow LOH + H_2O + GSSG$ $H_2O_2 + 2\,GSH \longrightarrow 2\,H_2O + GSSG$
Glutathione-S-transferase	Reduction of hydroperoxide
Phospholipid hydroperoxide glutathione peroxidase	Reduction of phospholipid hydroperoxide $PLOOH + 2\,GSH \longrightarrow PLOH + H_2O + GSSG$
Peroxidase	Reduction of hydroperoxides and catalase $LOOH + AH_2 \longrightarrow LOH + H_2O + A$ $H_2O_2 + AH_2 \longrightarrow 2\,H_2O + A$
Catalase	Reduction of hydrogen peroxide $2\,H_2O_2 \longrightarrow 2\,H_2O + O_2$

primarily by quenching singlet oxygen[63]. Its function as a radical scavenging antioxidant has been also reported[64].

The second line of defense is that of the radical scavenging antioxidants, which inhibit or suppress the chain initiation by scavenging radicals before they attack the target molecules and/or break the chain propagation by trapping chain-carrying peroxyl radicals. Vitamin C[65,66] and vitamin E[67,68] are well-known radical scavenging antioxidants. Water-soluble radical-scavenging antioxidants such vitamin C, uric acid, bilirubin and albumin usually scavenge hydrophilic radicals before they attack the membranes. On the other hand, the lipophilic radical-scavenging antioxidants such as vitamin E, ubiquinol and carotenoids incorporated into the membranes scavenge both hydrophilic radicals attacking from the water phase and lipophilic radicals within the lipophilic compartment. The antioxidant activities are determined by physical factors such as the mobility at the microenvironment as well as the chemical reactivity toward radicals.

The third line of defense is the repair and *de novo* functions. There are several types of enzymes which repair the damaged lipids, proteins and DNA. Many enzymes possessing phospholipase activity have been characterized, but phospholipase A_2 has received most attention in relation to the defense against oxygen toxicity[69]. It is now generally accepted that the oxidation of membrane phospholipids stimulates their hydrolysis by phospholipase A_2, that is, the oxidized fatty acyl moiety at the 2-position of phosphatides is released to give oxidized free fatty acid and lysophospholipid. The former, such as hydroperoxy fatty acid, is reduced to stable alcohol by the enzymes shown in Table 10, while the latter is converted to original phospholipids by acylation catalyzed by a lysophospholipid acyl-CoA transferase[70]. Although the hydrolysis by phospholipase A_2 is not strictly specific to the peroxidized lipids but considerable release of intact fatty acids takes place, this action provides an effective means for sparing membrane structure and efficient phospholipid turnover.

The last line of defense is the 'adaptation' mechanism; that is, the formation of antioxidant enzymes such as SOD is induced by an oxidative stress and transferred to the specific site. This is quite a vital function which only the living organism has and which is difficult to provide artificially to materials such as oil, plastic and rubber.

These antioxidants function independently and cooperatively, sometimes even synergistically to protect membranes and tissues from oxidative injury.

VI. REFERENCES

1. H. Sies (Ed.), *Oxidative Stress, Oxidants and Antioxidants*, Academic Press, London, 1991.
2. A. B. Ross and P. Neta, *Natl. Stand. Ref. Data Ser., Natl. Bur. Stand.*, 1982.
3. E. Niki, Y. Yamamoto, E. Komuro and K. Sato, *Am. J. Clin. Nutr.*, **53**, 201S (1991).
4. Y. Yamamoto, E. Niki, J. Eguchi, Y. Kamiya and H. Shimasaki, *Biochim. Biophys. Acta*, **819**, 29 (1985).
5. M. Miki, H. Tamai, M. Mino, Y. Yamamoto and E. Niki, *Arch. Biochem. Biophys.*, **258**, 373 (1987).
6. K. Sato, E. Niki and H. Shimasaki, *Arch. Biochem. Biophys.*, **279**, 402 (1990).
7. E. Niki, E. Komuro, M. Takahashi, S. Urano, E. Ito and K. Terao, *J. Biol. Chem.*, **263**, 19809 (1988).
8. D. Steinberg, S. Parrthasarathy, T. E. Carew, J. C. Khoo and J. L. Witztum, *New Engl. J. Med.*, **320**, 915 (1989).
9. L. R. C. Barclay, D. Kong and J. Van Kessel, *Can. J. Chem.*, **64**, 2103 (1986).
10. L. R. C. Barclay, K. A. Baskin, S. J. Locke and T. D. Schaefer, *Can. J. Chem.*, **65**, 2529 (1987).
11. L. R. C. Barclay, K. A. Baskin, S. J. Locke and T. D. Schaefer, *Can. J. Chem.*, **65**, 2541 (1987).
12. L. R. C. Barclay, K. A. Baskin, S. J. Locke and M. R. Vingvist, *Can. J. Chem.*, **67**, 1366 (1989).

13. L. R. C. Barclay, K. A. Baskin, K. A. Dakin, S. J. Locke and M. R. Vingvist, *Can. J. Chem.*, **68**, 2258 (1990).
14. J. A. Howard, *Adv. Free Radical Chem.*, **4**, 49 (1972).
15. N. A. Porter and D. G. Wujek, *J. Am. Chem. Soc.*, **106**, 2626 (1984).
16. L. G. Forni, in *Membrane Lipid Oxidation*, Vol. I (Ed. C. Vigo-Pelfrey), CRC Press, Boca Raton, 1990, pp. 15–32.
17. B. H. J. Bielski, R. L. Arudi and M. W. Sutherland, *J. Biol. Chem.*, **258**, 4579 (1983).
18. R. D. Small, J. C. Sciani and L. K. Patterson, *Photochem. Photobiol.*, **29**, 49 (1979).
19. L. G. Forni, J. E. Packer, T. F. Slater and R. L. Willson, *Chem.-Biol. Interact.*, **45**, 171 (1983).
20. J. P. Cosgrove, D. F. Church and W. A. Pryor, *Lipids*, **22**, 299 (1987).
21. M. Mino, M. Miki, M. Miyake and T. Ogihara, *Ann. N.Y. Acad. Sci.*, **570**, 297 (1989).
22. N. A. Porter, *Acc. Chem. Res.*, **19**, 262 (1986).
23. E. N. Frankel, *J. Sci. Food Agric.*, **54**, 495 (1991).
24. H. W. Gardner, *Free Rad. Biol. Med.*, **7**, 65 (1989).
25. Y. Yamamoto, E. Niki and Y. Kamiya, *Lipids*, **17**, 879 (1982).
26. N. A. Porter, M. O. Funk, D. W. Gilmore, R. Isaac and J. R. Nixon, *J. Am. Chem. Soc.*, **98**, 6000 (1976).
27. W. A. Pryor, J. P. Stanley and E. Blair, *Lipids*, **11**, 370 (1976).
28. E. N. Frankel, C. D. Evans, O. G. McConnell, E. Selek and H. J. Dutton, *J. Org. Chem.*, **26**, 4663 (1961).
29. H. W. S. Chem and G. Levett, *Lipids*, **12**, 837 (1977).
30. D. J. Coxon, K. R. Price and H. W. S. Chem, *Chem. Phys. Lipids*, **28**, 365 (1981).
31. W. E. Neff, E. N. Frankel and D. Weisleder, *Lipids*, **16**, 439 (1981).
32. K. E. Peers, D. J. Coxon and H. W. S. Chem, *J. Sci. Food Agric.*, **32**, 898 (1981).
33. N. A. Porter, B. A. Weber, H. Weenen and J. A. Khan, *J. Am. Chem. Soc.*, **102**, 5597 (1980).
34. N. A. Porter, L. S. Lehman, B. A. Weber and K. J. Smith, *J. Am. Chem. Soc.*, **103**, 6447 (1981).
35. H. Esterbauer, R. J. Schaur and H. Zollner, *Free Rad. Biol. Med.*, **11**, 81 (1991).
36. M. Hamberg, *Lipids*, **10**, 87 (1975).
37. H. W. Gardner, R. Kleiman and D. Weisleder, *Lipids*, **9**, 696 (1974).
38. C. A. Riley, G. Cohen and M. Lieberman, *Science*, **183**, 208 (1974).
39. L. L. Smith, J. I. Teng, Y. Y. Lin, P. K. Sertz and M. F. McGehee, in *Lipid Peroxide in Biology and Medicine* (Ed. K. Yagi), Academic Press, New York, 1982, pp. 81–105.
40. J. I. Teng, M. J. Kulig, L. L. Smith, G. Kan and J. E. van Lier, *J. Org. Chem.*, **38**, 119 (1973).
41. C. S. Foote, F. C. Shook and R. A. Abakerli, *J. Am. Chem. Soc.*, **102**, 2503 (1980).
42. H. Esterbauer, M. Dieber-Rotheneder, G. Waeg and G. Striegl, *Chem. Res. Toxicol.*, **3**, 77 (1990).
43. J. L. Goldstein and M. S. Brown, *Annu. Rev. Biochem.*, **46**, 897 (1987).
44. H. Esterbauer, M. Rotheneder, G. Striegl, G. Waeg, A. Shy, W. Sattler and G. Jurgens, *Fat Sci. Technol.*, **91**, 316 (1989).
45. H. Esterbauer, G. Striegl, H. Puhl, S. Oberreither, M. Rotheneder, M. El-Saadani and G. Jurgens, *Ann. N.Y. Acad. Sci.*, **570**, 254 (1989).
46. N. Gotoh, K. Shimizu, E. Komuro, J. Tsuchiya, N. Noguchi and E. Niki, *Biochim. Biophys. Acta*, in press.
47. D. Chiu, B. Lubin and S. B. Shohet, in *Free Radicals in Biology* (Ed. W. A. Pryor), Vol. 5, Academic Press, Orlando, 1982, pp. 115–160.
48. M. Mino, M. Miki, H. Tamai, H. Yasuda and H. Maeda, in *Lipid Peroxidation in Biological Systems* (Ed. A. Sevanian), Am. Oil Chem. Soc., Champaign, 1988, pp. 51–70.
49. J. R. Kanofsky, *Chem.-Biol. Interact.*, **70**, 1 (1989).
50. E. N. Frankel, W. E. Neff and T. R. Besssler, *Lipids*, **14**, 961 (1979).
51. J. Terao and S. Matsushita, *Agric. Biol. Chem.*, **45**, 587 (1981).
52. O. Hayaishi, *Oxygenases*, Academic Press, New York, 1962.
53. H. S. Mason, W. L. Fowlks and L. Person, *J. Am. Chem. Soc.*, 77, 2914 (1955).
54. O. Hayaishi, M. Katagiri and S. Rothberg, *J. Am. Chem. Soc.*, 77, 5450 (1955).
55. M. Hamberg and B. Samuelson, *J. Biol. Chem.*, **242**, 5336 (1967).
56. L. Orning, S. Hammarstrom and B. Samuelson, *Proc. Natl. Acad. Sci. U.S.A.*, 77, 2014 (1980).
57. A. L. Tappel, *Fed. Proc.*, **32**, 1870 (1973).
58. N. A. Porter, in *Free Radicals in Biology* (Ed. W. A. Pryor), Vol. IV, Academic Press, New York, 1980, pp. 261–294.

59. D. E. O'Connor, E. D. Mihelich and M. C. Coleman, *J. Am. Chem. Soc.*, **103**, 223 (1981).
60. C. K. Chow, (Ed.), *Cellular Antioxidant Defense Mechanisms*, Vols. I, II, III, CRC Press, Boca Raton, 1988.
61. M. Maiorino, C. Gregolin and F. Ursini, in *Methods in Enzymology*, Vol. 186 (Eds. L. Packer and A. N. Glazer), Academic Press, San Diego, 1990, pp. 448–457.
62. J. M. McCord and I. Fridovich, *J. Biol. Chem.*, **244**, 6049 (1969).
63. N. I. Krinsky, *Free Rad. Biol. Med.*, **7**, 617 (1989).
64. G. W. Burton and K. U. Ingold, *Science*, **224**, 569 (1984).
65. A. Bendich, L. J. Machlin, O. Scandurre, G. W. Burton and D. D. M. Wayner, *Adv. Free Rad. Biol. Med.*, **2**, 419 (1986).
66. E. Niki, *World Rev. Nutr. Diet.*, **64**, 1 (1991).
67. G. W. Burton and M. G. Traber, *Annu. Rev. Nutr.*, **10**, 357 (1990).
68. E. Niki, *Chem. Phys. Lipids*, **44**, 227 (1987).
69. A. Sevanian, in *Cellular Antioxidant Defense Mechanisms* (Ed. C. K. Chow), Vol. II, CRC Press, Boca Raton, 1988, pp. 77–95.
70. A. Arduini, G. Macinelli, G. L. Radatti, G. Dottori and R. R. Ramsay, in *Biological Free Radical Oxidations and Antioxidants* (Eds. F. Ursini and E. Cadenas), CLEUP, Padova, 1992, pp. 159–171.

CHAPTER **18**

Diols and polyols

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Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

ABBREVIATIONS

See also the list of abbreviations following the Contents list of this volume.

aibn	azobisisobutyronitrile
9-bbn	9-borabicyclo[3.3.1]nonane
binap	2,2'-bis(diphenylphosphino)-1,1'-dinaphthyl
Bn	benzyl
bom	benzyloxymethyl
cod	cycloocta-1,5-diene
m-cpba	*m*-chloroperbenzoic acid
CWP	tris(cetylpyridinium) 12-tungstenophosphate
dast	(diethylamido)sulphur trifluoride
dccd	dicyclohexylcarbodiimide
dead	diethyl azodicarboxylate
deips	diethylisopropylsilyl
Dibal	diisobutylaluminium hydride
diop	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane
dmap	4-dimethylaminopyridine
de	diastereomeric excess
HMPT	hexamethylphosphorotriamide
L	ligand
L-Selectride	lithium tri-*sec*-butylborohydride
LS-Selectride	lithium trisiamylborohydride
mem	methoxyethoxymethyl
Mes	methanesulphonyl
mom	methoxymethyl
nmm	*N*-methylmorpholine
nmo	*N*-methylmorpholine *N*-oxide
nmp	*N*-methylpyrrolidin-2-on
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
tbdms	*t*-butyldimethylsilyl
tbdps	*t*-butyldiphenylsilyl
teba	tetrabutylammonium chloride
Tf	trifluoromethanesulphonyl
Thex	thexyl (—CMe_2CHMe_2)
thp	tetrahydropyranyl
tms	trimethylsilyl
Vitride	sodium bis(2-methoxyethoxy)aluminium hydride

I. INTRODUCTION

An extremely large number of publications deal with the chemistry of di- and polyhydric compounds, and a vast quantity of published data is available on natural products with hydroxy functions. The limited space available led me to decide to survey compounds in which the only functional groups are hydroxy groups. As a result, carbohydrates are virtually not discussed at all. *gem*-Diols are likewise excluded.

In view of the large amount of material available, this review cannot be an encyclopaedic coverage of the topic. It is selective rather than comprehensive. It treats both typical and special reaction types, with emphasis on recent results.

The discussion starts with a short description of the physical properties of diols and polyols, followed by several sections dealing with their synthesis. Synthetic methods are divided according to the structure of the compounds to be synthesized, with emphasis on the synthesis of diols. Since the characteristic preparation of polyols involves the progressive accumulation of hydroxy groups, only a short overview of their synthesis is given. Section V presents the few data available on the synthesis of di- and polyhydric phenols.

Section VI relates to the chemical properties. Subsections are organized in order of increasing complexity of the transformations. Here attention is focused on the features that result from the presence of two or more hydroxy groups in a molecule. However, the presence of more than two hydroxy functions rarely induces chemical properties which require the participation of all these hydroxy groups. Accordingly, reactions of diols are discussed in most detail. Since increasing distance between hydroxy groups results in a decreasing interaction, the emphasis is on the transformations of 1,2-diols. These subsections include the reactions of di- and polyhydric phenols.

Although the material in this chapter has not been covered in the preceding volumes in this series, the present review deals only with literature data published since 1980. The literature coverage extends up to the middle of 1991, but relevant publications in leading organic chemistry journals accessible after this date have also been included.

II. PHYSICAL PROPERTIES

A. Acidity

Since an earlier review paper in this series[1], very few papers have dealt with the acidity of polyols. Of four hexitols, galactitol and D-glucitol are monoprotic, while D-mannitol and *meso*-inositol are diprotic in strongly alkaline solution[2]. Bearing only secondary

TABLE 1. Acidity values of benzenediols and benzenetriols[a]

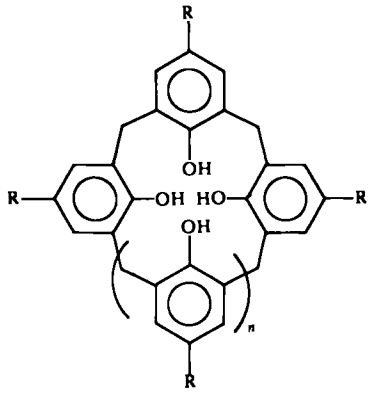
Compound	pK_1	pK_2	Reference
Catechol	9.34	13.14	4
Resorcinol	9.28	11.02	
Hydroquinone	9.89	11.55	
Pyrogallol[b]	8.96	11.12	5
Hydroxyhydroquinone	9.02	11.38	
Phloroglucinol	8.42	8.76	

[a]Potentiometric measurements with a hydrogen electrode. Experimental conditions: 25 °C, 1 M $NaClO_4$ solution; pH = 0.6–6.4 for benzenediols, 2–7 for benzenetriols.

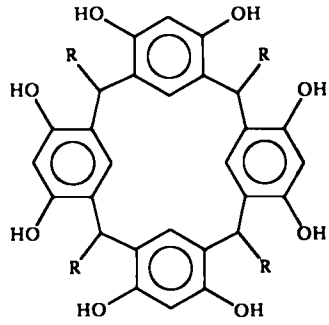
[b]The loss of the third proton cannot be quantitatively evaluated.

hydroxy groups, *meso*-inositol is the weakest acid of the four compounds. The unusually high acidity of 1,3,5-trideoxy-1,3,5-tris(trimethylamino)-*cis*-inositol ($pK_1 = 8.14$, $pK_2 = 13.0$) is attributed to electrostatic interaction between the charged substituents of the cyclohexane ring[3].

Data on the protolytic equilibria of benzenediols and benzenetriols (Table 1) indicate that the triols are stronger acids than the diols. The trends of decreasing acidities in the first dissociation, resorcinol > catechol > hydroquinone, and phloroglucinol > pyrogallol = hydroxyhydroquinone, are explained by inductive and mesomeric effects. The lack of hydrogen bonding makes the symmetric phloroglucinol the strongest acid of the six compounds. The first dissociation constant indicates that the calixarenes (1) exhibit superacidic properties[6,7].



(1)



(2)

B. Hydrogen Bonding

Intramolecular hydrogen bonding is a very important feature of cyclic diols and lower diol homologues, determining the conformation of the molecules in solution. The results of early spectroscopic studies have been reviewed[1,8,9].

More recent thermochemical studies[10,11] and X-ray data[12] indicate that in α,ω-alkanediols two hydrogen bonds are formed per molecule. This means that, with the exception of ethylene glycol, intramolecular hydrogen bonds can be excluded. In contrast, intramolecular hydrogen bonding is characteristic of 1,2-alkanediols[13]. In the crystalline state, bi- and tricyclic diols form either a hexagonal tubular or a layered structure through intermolecular hydrogen bonds[14–16].

In solution (CS_2, CCl_4), open-chain and cyclic 1,2- and 1,3-diols exist predominantly in a hydrogen-bonded conformation[17–21]. Data on the effects of solvents with different polarities on the conformation show that acyclic vicinal diols prefer an intramolecularly hydrogen-bonded *gauche* arrangement of the C—O bonds in solvents of low polarity and protic solvents[22]. The formation of cyclic trimers of some simple 1,3-diols as a result of self-association has been observed[23]. IR spectroscopic studies have proved that intramolecularly hydrogen-bonded 1,4-butanediol molecules form chains via intermolecular hydrogen bonds[24]. A similar self-organization of long-chain 1,2-diols and tetrols[25], 4-alkylcyclohexyl-substituted 1,3-propanediols[26] and 1,4-butanediols[27] results in the formation of liquid crystal phases.

Microwave spectroscopy has confirmed that ethylene glycol[28], 1,2-propanediol[29] and 1,3-butanediol[30] exist in a cyclic hydrogen-bonded conformation in the gas phase. In

the latter two molecules, the primary hydroxy group donates hydrogen to the hydrogen bond. Theoretical calculations indicate that in the isomeric butanediols, the strongest intramolecular hydrogen bond exists in 1,4-butanediol[31].

Hydrogen bonding can also determine the conformation of polyol molecules. In the calixarenes (**1**), the cone conformation is stabilized by intramolecular hydrogen bonds[32]. The strengths of these bonds are affected by the structure of the molecules[33,34]. Of the [*m*.3.3] propellanediols, the molecules with a short and rigid polymethylene chain ($m = 3, 4$) are flat, while the *anti,anti*-diols with longer chains ($m = 10, 12, 20$) fold in solvents of low polarity to adopt a puckered conformation[35]. This difference allows an unambiguous configurational assignment by means of mass spectrometry[36].

The effect of hydrogen bonding on the polarity of molecules permits the chromatographic separation of isomers[35,37]. Results are also available concerning a relationship between the degree of sweetness and hydrogen-bonding network in carbohydrates and pseudosugars[38,39].

The molecular recognition of open-chain and cyclic diols[40], carbohydrates[41] and dicarboxylic acids[42] by the resorcinol–dodecanal cyclotetramer (**2**) is likewise based on hydrogen bonding. Satisfying the stereochemical and geometric requirements, *cis*-1,4-cyclohexanediol exhibits an exceptionally large binding constant, attributed to effective two-point hydrogen bonding[40]. The binding sites in the host cyclotetramer molecule are two pairs of phenolic hydroxy groups.

Hydrogen bonding may also be involved in chiral recognition. Chiral recognition chromatography allows the resolution of chiral diols on a chiral stationary phase[43,44]. Optically active diols are used as host compounds for determination of the optical purity of various chiral organic molecules[45–47] and for resolution[47–51]. Racemic polyols too can be resolved by a similar technique, applying chiral organic compounds[52–54].

C. Complexation

Because of its biological and practical importance, the complexation of diols and polyols by metal cations is of interest. The very extensive research activity relating to the complexing properties of calixarenes (**1**, **2**) has been reviewed[55]. Similar properties of other polyols are treated in a review[56] and in other publications[57–62].

III. SYNTHESIS OF DIOLS

A. Synthesis of 1,2-Diols

1. *Bis-hydroxylation of alkenes*

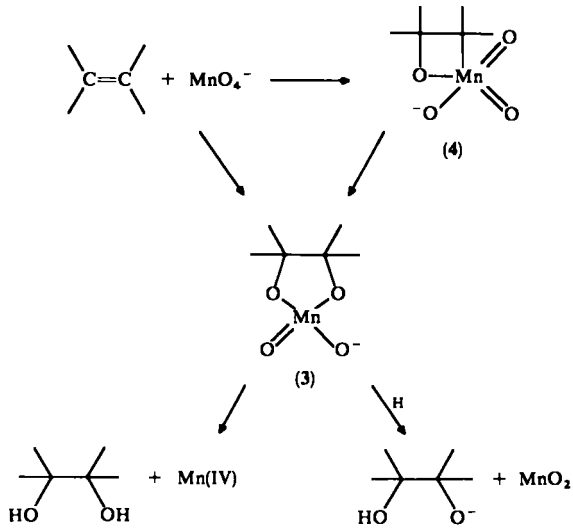
$KMnO_4$ and OsO_4 are well-known reagents for *syn*-dihydroxylation of the carbon–carbon double bond.

$KMnO_4$ is mainly used under mild, alkaline conditions to prevent further oxidation of the 1,2-diols formed. The rather low yields can be improved by extensive stirring in dilute solution (equation 1)[63], phase transfer catalysis[64], or by using hexadecyltrimethylammonium permanganate (equation 1)[65].

(1)

$KMnO_4$, MeOH–H_2O, NaOH, 12 °C, 3.3 h 83–87%
$C_{16}H_{33}N^+Me_3MnO_4^-$, *t*-BuOH–$H_2O$, 20 °C, 1 h 86%

Despite the large number of experimental observations, there is still disagreement as concerns the structure of the detectable intermediate formed during the oxidation of alkenes. It has been believed for a century that the intermediate is the cyclic manganate(V) diester ion **3**, produced in a [3 + 2]-cycloaddition[66] (Scheme 1). Certain observations are in accordance with the formation of oxametallacyclobutane **4**[67,68]. This results from a [2 + 2]-cycloaddition and rearranges to **3**. Recent kinetic, iodometric and spectroscopic observations are in favour of the cyclic diester **3**, which is gradually reduced to Mn(IV)[69,70]. The novel concept of the formation of soluble, colloidal MnO_2 via the rapid decomposition of **3** by abstraction of a hydrogen atom from the solvent[67,68,71] and its role in oxidation seems to be ruled out[69,70].



SCHEME 1

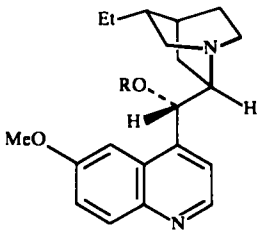
TABLE 2. Stoichiometric asymmetric dihydroxylation of *trans*-stilbene with OsO_4

Reaction conditions	Chiral amine	Yield (%)	Enantiomeric excess (%)	Configuration	Reference
Toluene, RT, 12 h	**5a**	85	82.0	*R,R*	76
	6a	90	83.2	*S,S*	
Toluene, 0 °C, 10 h	**5b**	*a*	99	*a*	77
THF, −110 °C, 6 h	**7a**	97	85	*S,S*	78, 79
	7b	96	71	*R,R*	78
Toluene, −100 °C, 6 h	**7c**	62	77	*R,R*	80
CH_2Cl_2, RT, 24 h	**8**	69	34	*R,R*	81
Toluene, −78 °C, 12 h	**9a**	65	54	*S,S*	82
CH_2Cl_2 −78 °C, 12 h	**9a**	54	52	*R,R*	
Toluene, −78 °C, overnight	**9b**	96	100	*S,S*	83
CH_2Cl_2, −90 °C, 2 h	**10**	95	92	*S,S*	84

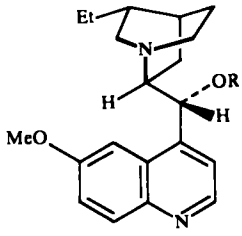
[a]No data.

OsO_4 is widely recognized to be the most reliable reagent for accomplishing the bis-hydroxylation of alkenes[72–74]. The traditional, stoichiometric oxidation is now carried out in the presence of tertiary amines or diamines which brings about a dramatic rate increase[72]. A catalytic amount of OsO_4 has been successfully used with suitable co-oxidants. These are usually *t*-BuOOH or amine *N*-oxides, which continuously regenerate OsO_4. Hexacyanoferrate(III) ion has recently been found to be very effective[75]. Since overoxidation often takes place in the catalytic process, stoichiometric oxidation generally gives better yields.

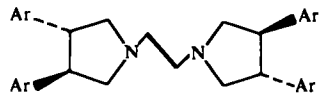
Sharpless has developed an asymmetric osmylation method by using cinchona alkaloid derivatives (**5**, **6**) as chiral ligands in stoichiometric oxidation[76]. The results and examples of further variations involving mainly diamines (**7**–**10**) are given in Table 2. The use of appropriate ligands ensures large improvements in enantioselectivity[85] (equation 2).



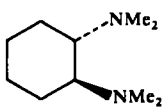
(**5a**) R = Ac
(**5b**) R = *p*-ClC_6H_4
(**5c**) R = Ph
(**5d**) R = 9-phenanthryl
(**5e**) R = 4-methyl-2-quinolyl



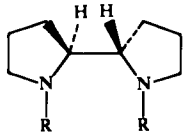
(**6a**) R = Ac
(**6b**) R = *p*-ClC_6H_4



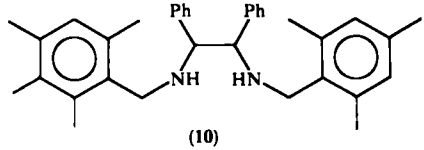
(**7a**) Ar = Ph
(**7b**) mirror image of **7a**
(**7c**) Ar = 3,5-xylyl



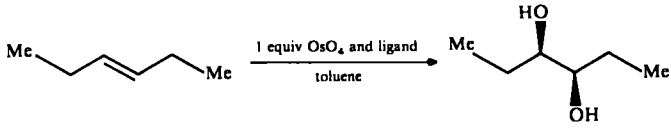
(**8**)



(**9a**) R = Pr
(**9b**) R = neopentyl



(**10**)



(2)

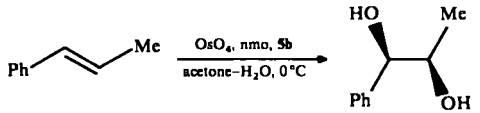
	%ee
0 °C, **5c**,	85
0 °C, **5b**,	71
−78 °C, **5c**,	95

Catalytic osmylation can also be carried out in the presence of chiral amine ligands (Table 3). The first examples of this ligand-accelerated catalysis were given by Sharpless[86]. Substantial increase in enantioselectivity can be achieved by slow addition of the alkene[90] (equation 3). Hexacyanoferrate(III) ion as co-oxidant gives the best results[87] (equation 3).

TABLE 3. Catalytic asymmetric dihydroxylation of *trans*-stilbene with OsO_4

Reaction conditions	Co-oxidant	Chiral amine	Yield (%)	Enantiomeric excess (%)	Configuration	Reference
Acetone, H_2O, 7 h	nmo	**5b**	*a*	88	*R,R*	86
Acetone, H_2O, 17 h	nmo	**6b**	*a*	78	*S,S*	
Acetone, H_2O, 0 °C, slow addition, 10 h	nmo	**5b**	*a*	80	*a*	77
t-BuOH, H_2O, RT, K_2CO_3, 8–24 h	$K_3[Fe(CN)_6]$	**5b**	*a*	99	*a*	87
		5d[b]	*a*	99	*R,R*	88
		5e[b]	*a*	98	*R,R*	
Acetone, H_2O, 10 °C, 2–3 days	nmo	**5b**[c]	81–87	85–93	*a*	89

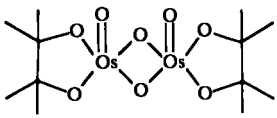
[a]No data.
[b]$K_2OsO_2(OH)_4$ was used.
[c]Polymer-bound.



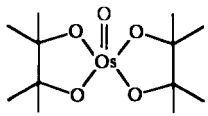
(3)

	%ee
normal addition	65
slow addition	86
normal addition, co-oxidant = $K_3[Fe(CN)_6]$	91

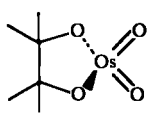
Oxidation with OsO_4 is a much studied process. The reaction takes place via osmium(VI) intermediates, which are the dimeric monoester (**11**)[72,91] or the monomeric diester (**12**)[72], generally written as a simple tetrahedral species (**13**). Reductive or oxidative hydrolysis gives the product 1,2-diol. Amines affect the rate by transforming tetrahedral OsO_4 to hexacoordinated octahedral osmium(VIII) as a result of complexation[90,92–94]. Similarly as in permanganate oxidation, [2 + 2]-cycloaddition leading to oxametallacyclobutane (**14**) has been suggested[76,79,80,95]. However, most of the experimental evidence supports direct [3 + 2]-cycloaddition[84,93,94], and only species such as **15**, **16** and **17** have been identified[79,83,90,93,96].



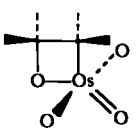
(11)



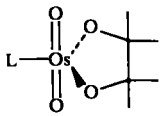
(12)



(13)



(14)



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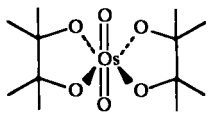

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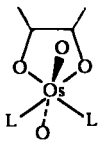
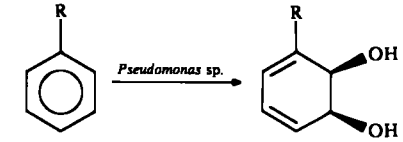


(17)

A mechanistic study[97] and new observations on the oxidation process with $K_3[Fe(CN)_6]$ as the stoichiometric reoxidant[98] have recently been published.

Among other oxidizing agents, H_2O_2 with a catalytic amount of Re_2O_7[99], and tungsten peroxo complexes[100], provide 1,2-diols with very good selectivities. High yields with complete *anti* stereoselectivity were achieved with *m*-cpba in aqueous solution[101]. (The stereochemical descriptors *syn* and *anti* are used as defined by Masamune[102], and where appropriate *eythro/threo* as defined in the Beilstein Handbook[103].)

The microbial oxidation of arenes to yield *cis*-dihydrobenzenediols (**18**) is of current interest in many laboratories[104–108] (equation 4). The method is also used to hydroxylate other cyclic unsaturated compounds[109,110]. The product dihydrodiols, which are well suited for further functionalization, can serve as synthetic precursors in the synthesis of cyclitols (see Section IV.D). (Compounds produced by a mutant strain of *Pseudomonas putida* are available on the market in multigram quantities.)

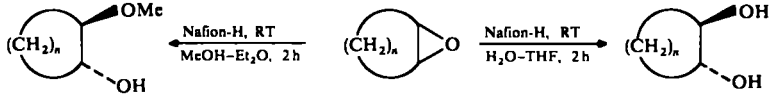


(4)

R = H, Me, Et, CH_2OAc, CF_3, F, Cl, $CH{=}CH_2$, C≡CH (**18**)

2. Transformations of oxiranes

a. Hydrolysis and alcoholysis. 1,2-Diols can be synthesized by acid or basic hydrolysis of epoxides[111]. The ring opening is stereospecific with inversion on one of the ring carbons: *cis*- and *trans*-oxiranes are transformed to *threo*- and *erythro*-diols[112], respectively, while *cis*-cycloalkene oxides yield the corresponding *trans*-diols as the main product[113–115]. Good yields have been achieved in the Nafion-H-catalysed process[113] (equation 5).

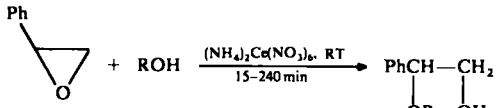


77% 74% $n = 1$ $n = 2$ 80% 73%

(5)

Ring opening in the presence of alcohols or carboxylic acids leads to diol monoethers and monoacylated diols, respectively. Since Posner's finding of alumina-promoted ring opening[116], more selective catalysts have been described. Nafion-H[113] (equation 5), dichlorodicyano-*p*-quinone[117], Ce(IV)ammonium nitrate[118] (equation 6) and organotin phosphate condensates[119] (equation 7)[120] have been used under mild reaction conditions.

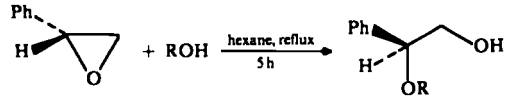
Enzymatic hydrolysis[121–124] or alcoholysis[125] of oxiranes leads to chiral 1,2-diols or their derivatives.



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

80–90%

(6)



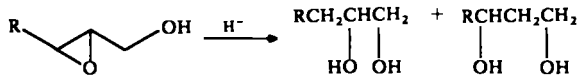
(7)

(*R*)-epoxide

(*S*)-diol ether

R	%Yield	%ee
Me	84	98
Bn	79	98

b. Hydride reductions. Depending on the site of attack, complex metal hydrides can reduce disubstituted 2,3-epoxy alcohols (**19**) to 1,2- (**20**) or 1,3-diols (**21**)[126] (equation 8). $LiBH_4$ is more selective than Dibal in the formation of 1,2-diols (Table 4), while Red-Al is the reagent of choice in the selective synthesis of 1,3-diols (see Section III.B.2). The reaction conditions and protection of the hydroxy group strongly affect the degree of selectivity. Sharpless asymmetric epoxidation[130,131] makes chiral epoxy alcohols readily available, and subsequent hydride reduction can produce polyhydroxylated natural products with the desired chiral centres (see Section IV.A.2.b).



(8)

(**19**) (**20**) (**21**)

c. Ring opening with other nucleophiles. Organolithium, organocopper, organomagnesium and organoaluminium reagents are used to transform hydroxy epoxides to diols. Monosubstituted compounds, which always open at the primary ring carbon atom on attack, are suitable starting materials in the synthesis of 1,2-diols[132–134], but disubstituted compounds can also yield 1,2-diols under certain conditions[135].

TABLE 4. Regioselectivity in ring opening of 2,3-epoxy alcohols (**19**) (ratio of 1,2- to 1,3-diol) (equation 8)

	Reducing agents				
R in **19**	$LiBH_4$		Dibal		Reference
C_7H_{15}	Ti(OPr-*i*)$_4$, THF, 50 °C	5.9:1	THF	5:1	127
	Ti(OPr-*i*)$_4$, benzene, 10 °C	145:1			
Ph	Ti(OPr-*i*)$_4$, THF, 10 °C	54:1	THF	20:1	
Pr	Hexane, RT	6.7:1			128
	Ti(OPr-*i*)$_4$, benzene, RT	49:1			
Pr[a]	Hexane, RT	24:1			
$BnO(CH_2)_2$			Benzene, RT	13:1	129

[a]Methyl ether.

In an attractive new method MgI_2 is employed in the ring opening of epoxy alcohols[136]. The intermediate iododiols formed are reduced *in situ* with Bu_3SnH to yield 1,2-diols with high (95–99%) selectivity.

A chiral diepoxide has been transformed to symmetric chiral 1,2-diol with organomagnesium and organocopper reagents[137].

3. *Syntheses from carbonyl compounds*

a. Pinacol coupling. Aldehydes and ketones can be coupled under reductive conditions to give 1,2-diols[138–143]. The low-valent titanium species originally developed for the reductive coupling of carbonyl compounds to give alkenes[139] is the most widely used catalyst.

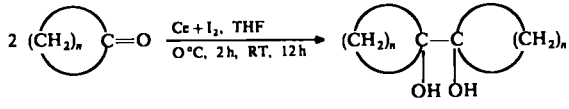
Besides reduction of $TiCl_4$ with $LiAlH_4$, the method developed by McMurry[138,139], low-valent titanium species are also prepared from $TiCl_4 + Zn$[144,145], $TiCl_3$ and the Zn + Cu couple[146], $TiCl_4 + Mg$[147,148], $TiCl_3 + Li$[149] and $TiCl_4$ + K-graphite (C_8K)[150]. Lanthanides[151–156], different cyclopentadienyltitanium[157,158] and vanadium[159,160] reagents, $UCl_4 + Na(Hg)$[161], and electrochemical reduction[162–165] have also been successfully applied. Most of these reagents are used in the self-coupling of aromatic carbonyl compounds. Characteristic examples are given in Table 5.

TABLE 5. Pinacol self-coupling of aromatic carbonyl compounds

Reaction conditions (catalyst, solvent)	Temperature, time, yield of diol			Reference
	benzaldehyde	acetophenone	benzophenone	
$TiCl_3$, MeOH, H_2O, 30% NaOH	RT, a few min 88%	RT, a few min 87%	RT, a few min 53%	166
$TiCl_3$, Li, DME, sonification		RT, 45 min 75%		149
$TiCl_3$, MeOH, H_2O, 30% NaOH or NH_4OH		20 °C, 5–10 min 83%	20 °C, 5–10 min 50%	167
$Cp_2Ti(CO)_2$, THF, 2:1[a]	Reflux, 3 h 50%	Reflux, 30 h 57%		157
$Cp_2TiCl_2Et_2O$, *i*-BuMgCl			RT, 3 h 67%	168
Yb, THF–HMPA 1:2[a]		RT, 5 h 73%	RT, 5 min 97%	153, 154
Sm, THF–HMPA 1:1[a]			RT, 30 min 62%	154
SmI_2, THF	RT, 0.5 min 95%	RT, 0.5 min 95%		169
Zn, $ZnCl_2$, H_2O–THF = 1:1	RT, 3 h 11%		RT, 1 h 84%	170
Zn, $ZnCl_2$	RT, 3 h 46%		RT, 6 h 86%	170
Al, liq. NH_3, NaCl, sonification		25 °C, 4 h 90%		171
DMF, $CrCl_3 \cdot 6H_2O$, cathodic reduction	85%		70%	163
2-Propanol, irradiation, 300 nm			48 h no data	172

[a]Molar ratio of reagent to carbonyl compound.

Certain catalysts and reaction conditions can also be utilized for the coupling of non-aromatic carbonyl compounds[145,147,148,150,164] (equation 9)[151] and the cross-coupling of different carbonyl compounds[148,155,159] (equation 10)[154]. Examples are also known for the intramolecular coupling of dicarbonyl compounds[144,156,160] (equation 11)[146]. For the 5, 6 and 8-membered rings, *cis* stereochemistry predominates, but *trans*-diols are formed from higher homologues[146,156].



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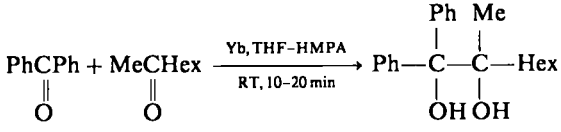

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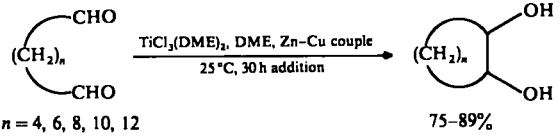
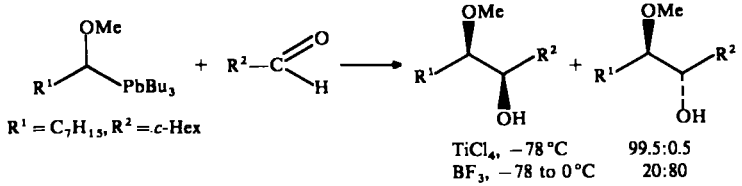


(11)

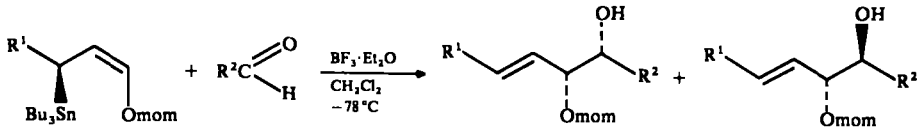
b. Reaction of carbonyl compounds with alkoxy organometallics. α-Alkoxy organolithium[173], organomagnesium[173], organotin[174] and organolead[175] compounds reacting with carbonyl compounds yield 1,2-diol monoethers. A high *syn* selectivity has been observed in the transformation of an organomagnesium reagent containing an alkoxy substituent with a high steric demand[173]. The diastereoselectivity can be altered through chelation vs. non-chelation control (see Section III.A.3.c) by changing the Lewis acid catalyst[175] (equation 12).



(12)

A high *syn* selectivity is also characteristic of a similar utilization of (γ-alkoxy)allyl boron[176–179], tin[180,181] and lithium[182] compounds in the synthesis of 3-alkene-1,2-diol monoethers[181] (equation 13). In contrast, a chiral (γ-silyl)allyl boron reagent exhibits excellent *anti* selectivity[183].

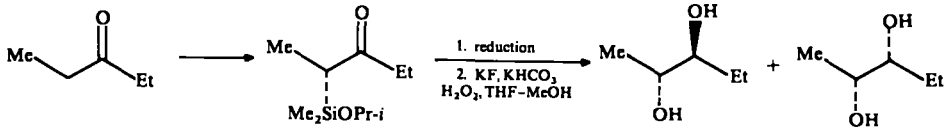
Regio-, diastereo- and enantioselective syntheses of 1,2-diols have been carried out via α-silyl ketones (**22**)[184,185]. The method starts with the asymmetric synthesis of **22** accomplished by silylation of the corresponding chiral hydrazones. Since (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) or the corresponding (*R*)-compound (RAMP) are



(13)

R^1	R^2	*syn*:*anti*
Me	*c*-Hex	95: 5
Me	Ph	95: 5
Bu	*c*-Hex	98: 2
Bu	Hex	85:15

used to prepare the hydrazones, the process is called the SAMP/RAMP hydrazone method[186]. Reduction of **22** with L-Selectride followed by desilylation leads to 1,2-diols with high diastereoselectivity (equation 14).

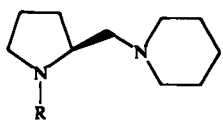


(14)

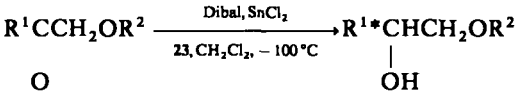
L-Selectride, toluene, −78 °C 94: 6
L-Selectride + $SnCl_4$, Et_2O, −78 °C 2:98

c. Reduction of α-hydroxy carbonyl compounds. The stereocontrolled addition of hydride ion from metal hydrides to acyclic hydroxy (alkoxy, silyloxy) ketones has been widely used for the synthesis of optically active diols and polyols[187–189].

Enantioselectivities that depend strongly on the nature of the protecting groups have been achieved by using metal hydride modified with chiral ligands (**23**)[190] (equation 15).



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

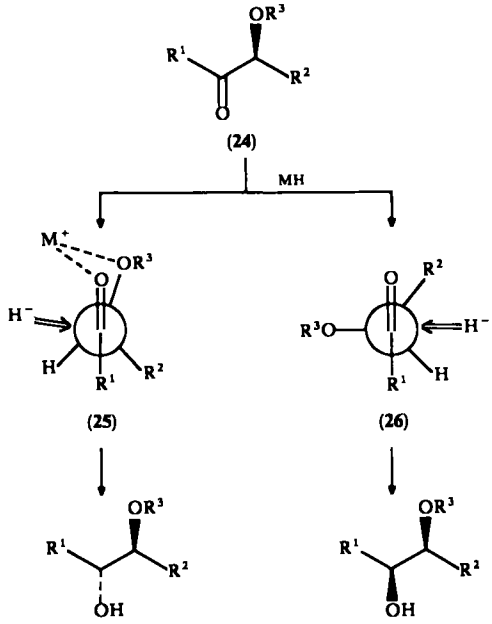


(15)

R^1 = Me, Ph 35–88% yield
R^2 = thp, mom, mem, Ac, Bz, tbdms, Ph_3C 32–93% ee

Diastereofacial selections, i.e. the formation of *syn*- or *anti*-1,2-diols in the hydride reduction of the chiral α-hydroxy ketones **24** (Scheme 2), are interpreted by Cram's cyclic model[191] and the Felkin–Anh open-chain model[192,193]. In the former, the five-membered cyclic transition state **25** is formed through chelation of the metal ion with both oxygen

atoms. This ensures hydride ion delivery from the less hindered side and therefore formation of the product with the *anti* arrangement of the hydroxy groups (chelation control). The Felkin–Anh model neglects chelation and emphasizes non-bonding interactions. The large hydroxy (alkoxy) group is assumed to be arranged perpendicularly to the carbonyl group (**26**), permitting the favoured hydride attack indicated (non-chelation control). This model predicts the formation of *syn*-diols.



SCHEME 2

The high coordinating ability of Zn(II) accounts for the very high *anti* selectivity of reductions with $Zn(BH_4)_2$ (Table 6). The lack of such ability of monovalent ions in other

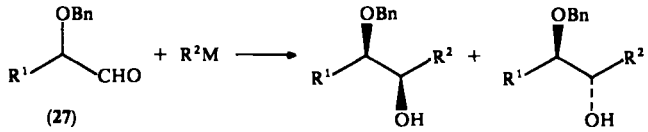
TABLE 6. Selectivity in hydride reductions of α-hydroxy ketones (Scheme 2)

Reducing agent	Substituents in **24**			*anti/syn* ratio	Reference
	R^1	R^2	R^3		
$Zn(BH_4)_2$	*i*-Pr	Ph	bom	19:1	173
	i-Pr	Et	bom	24:1	
	Pr	Pr	H	99:1	194
	Ph	Me	H	49:1	
	Bu	Me	mom	5:1	195
	Et	4-Pentenyl	Bn	24:1	196
Vitride	Me	4-Pentenyl	tbdps	1:49	194
L-Selectride	Bu	Me	mom	1:8	195
	Et	Pe	Bn	1:9	196
$PhMe_2SiH$	Ph	Me	Bn	1:24	197

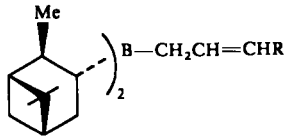
reducing agents and sterically demanding protecting groups result in a high *syn* selectivity through the open-chain transition state (Table 6).

The baker's yeast-mediated reduction of hydroxy ketones to yield optically active 1,2-diols has found wide-ranging application[198–202].

d. Reaction of α-hydroxy carbonyl compounds with organometallics. Numerous review articles deal with the transformation of alkoxy (silyloxy) aldehydes with carbon nucleophiles of organometallic reagents[188,203–205]. Such reactions raise similar stereochemical problems to those involved in hydride reductions (see Section III.A.3.c). Here, the addition of alkyl or allyl reagents to α-oxygenated aldehydes under chelation control (usually in the presence of a Lewis acid) leads to *syn*-1,2-diols (equation 16, Table 7). The diastereofacial selectivity can also be controlled by means of enantiomeric organometallic reagents[211] [**28a** and **28b**, prepared from (+)- or (−)-α-pinene, respectively] (Table 7, last two entries).



(27) (16)



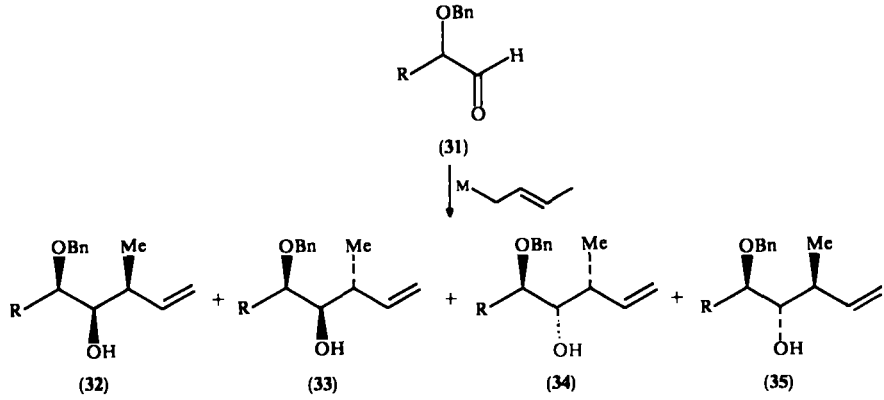
(**28a**) R = H
(**28b**) mirror image of **28a**
(**29a**) R = Me, *Z*-isomer
(**29b**) mirror image of **29a**
(**30a**) R = Me, *E*-isomer
(**30b**) mirror image of **30a**

The reaction of chiral α-alkoxy (silyloxy) aldehydes with crotylmetal reagents is an important transformation. This provides compounds with two new asymmetric centres (Scheme 3) and further possibilities of functionalization on the double bond also exist.

The Lewis acid-mediated addition of crotylstannane or silane reagents to the chiral α-alkoxy aldehydes **31** (Scheme 3) takes place with excellent diastereofacial selectivity (4,5-*syn* arrangement, **32** + **33** vs. **34** + **35**) as a result of chelation control[212,213] (Table 8, entries 1 and 2). The C—C bond construction selectivity (3,4-*syn* vs. *anti* arrangement,

TABLE 7. Selectivity in transformations of α-benzyloxy aldehydes with organometallic reagents (equation 16)

Organometallic reagent + Lewis acid	Substituent in aldehyde **27**	*syn/anti* ratio	Reference
$Et_4Pb + TiCl_4$	Me	49:1	206
$CH_2{=}CHCH_2SnPh_3 + SnCl_4$	$PhCH_2CH_2$	24:1	207
	c-Hex	99:1	
$CH_2{=}CHCH_2SnBu_3 + TiCl_4$	*c*-Hex	250:1	208
$CH_2{=}CHCH_2SiMe_3 + SnCl_4$	Me	35:1	209
$Ph(CH_2)_3MgBr$	$C_{10}H_{21}$	16:1	210
28a	Me	16:1	211
28b	Me	1:16	



SCHEME 3

32 + **34** vs. **33** + **35**) is also high. The anomalous *anti* diastereoselectivity observed with *β*-methylcrotyl reagents has been explained in terms of a synclinal transition state[213] (Table 8, entries 3–7). Double asymmetric synthesis with chiral crotyldiisopinocampheylborane reagents[211,214] (**29** and **30**) permits predictable transmission of the olefin geometry via cyclic transition states[214]. The *Z*-crotyl compounds **29a** and **29b** result in products with a *syn* arrangement around the newly formed bond (**32** + **34**, Table 8, entries 8 and 9), while the 3,4-*anti* compounds (**33** + **35**) are formed by using the *E*-isomers **30a** and **30b** (Table 8, entries 10 and 11).

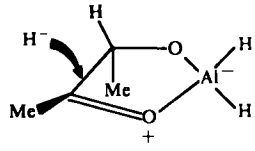
The stereoselective transformation of α-hydroxy ketones has been less successful. Besides Still's observation[215], only Sakurai's recent finding is known[216,217]. The method affords extremely high regio- and diastereospecific addition of 2-alkenyltrifluoro- or trialkoxysilanes, proceeding via a chelated bicyclic transition state.

e. Reduction of dicarbonyl compounds. Metal hydrides preferentially reduce symmetric 1,2-dioxo compounds into *meso*-1,2-diols[218,219]. The chemistry of the process involves stepwise reduction, generating first the complex **36** (depicted here for $LiAlH_4$). It is

TABLE 8. Selectivity in transformations of α-benzyloxy aldehydes with crotylmetal reagents (Scheme 3)

Entry	Reagent	Substituent in aldehyde **31**	Product composition				Reference
			32	**33**	**34**	**35**	
1	MeCH=CHCH$_2$SnBu$_3$ + TiCl$_4$	*c*-Hex	63	37			212
2	MeCH=CHCH$_2$SnBu$_3$ + MgBr$_2$	*c*-Hex	92	8			
3	(*E*)-MeCH=C(Me)CH$_2$SnBu$_3$ + MgBr$_2$	Me	24	76			213
4	(*E*)-MeCH=C(Me)CH$_2$SiBu$_3$ + MgBr$_2$	Me	11	89			
5	(*E*)-MeCH=C(Me)CH$_2$SiBu$_3$ + SnCl$_4$	Me	3	97			
6	(*Z*)-MeCH=C(Me)CH$_2$SiBu$_3$ + SnCl$_4$	Me	6	94			
7	(*Z*)-MeCH=C(Me)CH$_2$SiBu$_3$ + BF$_3$·OEt$_2$	Me	8	1	88	3	
8	**29a**	Me	73		27		214
9	**29b**	Me	1		99		
10	**30a**	Me		95		5	
11	**30b**	Me		3		97	

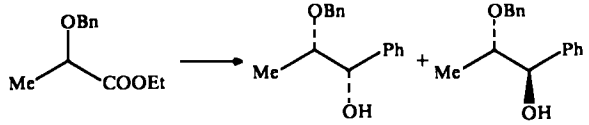
attacked in the second reduction step by hydride anion from the less hindered side[218]. Homogeneous asymmetric hydrogenation of biacetyl with $RuBr_2$[(*S*)-binap] affords (*S*,*S*)-2,3-butanediol with high enantiomeric purity[220]. (−)-(1*R*,2*S*)-1-Phenylpropanediol-1,2 has been prepared by baker's yeast reduction of the corresponding diketone[221].



(36)

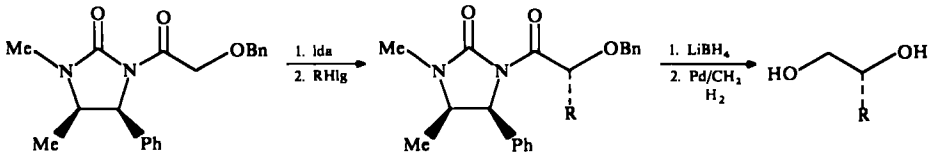
4. Transformation of α-substituted carboxylic acids and derivatives

Either *syn*- or *anti*-1,2-diols can be synthesized by sequential reduction and Grignard addition to α-alkoxy esters[222] (equation 17). Enantioselective synthesis of primary–secondary 1,2-diols has been carried out by Grignard addition to (−)-8-phenylmenthyl esters[223] or via alkylation of the chiral glycolate imides **37**, followed by reduction (equation 18)[224].



PhMgBr is added to ester + $LiBH_4$ (THF, 0 °C) 91.5: 8.5
Dibal + ester, then PhMgBr is added (hexane-ether, −78 °C) 12.5:87.5

(17)



(37)

(18)

5. Synthesis of ethylene glycol

In the catalytic transformation of synthesis gas, different oxygenates are very desirable products. The direct synthesis of ethylene glycol through homogeneous catalytic hydrogenation of carbon monoxide is being actively pursued[225]. Co[226,227], Rh[226–230], Ru[231,232] and Re[233] complexes have been found to exhibit high activity and selectivity. Tertiary phosphines[228–230,234], basic solvents[226,235] and acidic compounds[230] facilitate the Rh-catalysed process. Halide or acetate salts combined with basic solvents enhance the activity of rhenium carbonyl[233] and ruthenium carbonyl[231]. Ni[233] and Rh[231,232], respectively, are effective co-catalysts. Steric and electronic effects of substituted phosphines have been observed to play important roles in activity and selectivity[234]. It has been found that formaldehyde is a key intermediate in the process giving ethylene glycol through either glycol aldehyde[231] or glycolic acid[233].

Simple acid derivatives (methyl formate or dimethyl oxalate) can also serve as useful starting materials in the synthesis of ethylene glycol[236–238]. $Ru(CO)_2(AcO)_2(PBu_3)_2$ brings about a 95% conversion of dimethyl oxalate to ethylene glycol under optimized conditions (200 atm hydrogen, 180 °C, 144 h, pretreatment of the catalytic system with ethylene glycol)[236].

A viable alternative to the hydrolysis of ethylene oxide, the most important industrial process for the production of ethylene glycol, is the base-catalysed methanolysis of ethylene carbonate, also generating dimethyl carbonate[239].

B. Synthesis of 1,3-Diols

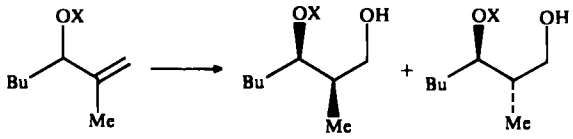
1. Transformation of allylic alcohols

a. Hydroboration–oxidation. Hydroboration–oxidation of alkenes leading to the formation of an alcoholic hydroxy group can be utilized to produce diols and polyols through the choice of appropriate starting materials. The basic principle of hydroboration is that boron attacks the sterically less hindered site (anti-Markovnikov addition), but both steric and electronic factors may affect the position of the newly formed OH groups (see Section III.C.2). It is customary to carry out *in situ* oxidation of the organoborane intermediate.

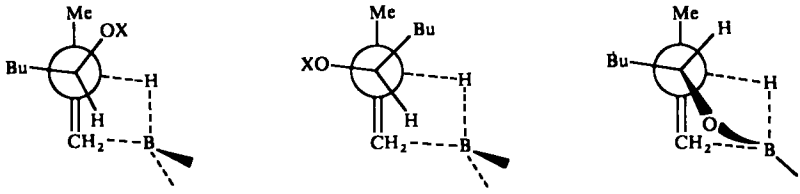
The stereoselective hydroboration of alkenes directed by pre-existing stereogenic centres has frequently been employed in the synthesis of natural products. The transformation of allylic alcohols and derivatives (equation 19) leads to *anti*-1,3-diols with high stereoselection (Table 9). Although labelling studies[244,245] give contradictory results, a satisfactory explanation of the stereochemistry can be given by assuming irreversible complexation of the alkene to the reagent. Theoretical studies[246,247] have indicated that *anti*-diols are produced via complex **39**, where the largest and the smallest groups adopt the *anti* and the congested inside position, respectively (Houk steric model[247]). The *anti* alkyl group plays an important role in stabilizing the transition state.

TABLE 9. Stereodirection (*syn/anti* ratio) in hydroboration of **38** (equation 19)

Reaction conditions	X						Reference
	H	Ph_3C	CF_3CO	tms	tbdms	vinyl	
Uncatalysed reaction							
9-bbn, THF,	1:11	1:5.5	1:14	1:10.5	1:9		240
−78 °C to RT, or 25 °C	1:11.5				1:8		241
	1:11	1:5.5	1:14		1:9		242
Intramolecular reaction							
Thexylborane, THF, −85 °C to RT, 18 h						200:1	243
Catalysed reactions							
Catecholborane, THF, $RhCl(PPh_3)_3$, 25 °C	3:1				24:1		241
Catecholborane, THF, $[Rh(cod)Cl]_2$, PPh_3, 48 h	2.2:1	18:1	7.5:1		24:1		242



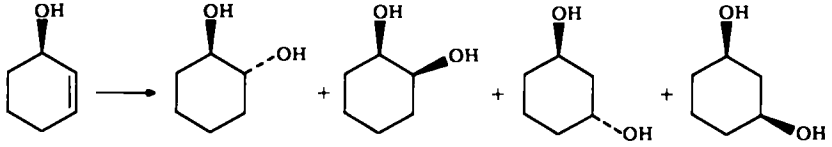
(38) (19)



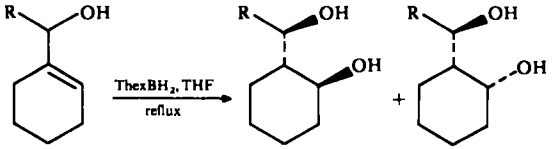
(39) (40) (41)

In marked contrast, the opposite, i.e. *syn* selectivity, is observed in both intramolecular and catalysed hydroborations (Table 9). Electronic and steric interactions suggest the formation of complex **40**, in which the electron-donating group occupies the *anti* position[242]. The best diastereoselection is to be expected if the protected alcohol is also the largest group. Recent results[248] are in agreement with Burgess' original postulate[242], which states that stereoelectronic effects governing the coordination of alkene to rhodium account for diastereofacial selectivity. In the intramolecular hydroboration of unsaturated alcohol and dienol derivatives, the stereoselection is explained by assuming the formation of **41**[243,249].

The catalysed and uncatalysed processes also exhibit opposite regioselectivities[241] (equation 20). Pure steric effects seem to control the hydroboration of exocyclic allylic alcohols **42** (equation 21)[250]. The Houk steric model[247] has also been successfully applied to homoallylic 1-cyclohexylcyclohexene alcohols[251].



uncatalysed 83:2: 5:10
catalysed 18:1:72: 9 (20)

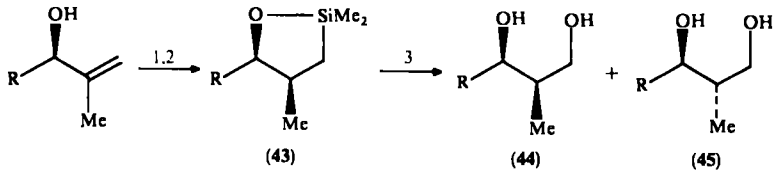


(42) R = Me 87:13
R = *i*-Pr 100: 0 (21)

A detailed treatment of the topic can be found in a recent review[252].

b. Hydrosilylation–oxidation. The method has been developed for the stereoselective synthesis of 1,3-diol skeletons, starting with allyl and homoallyl alcohols[253–255].

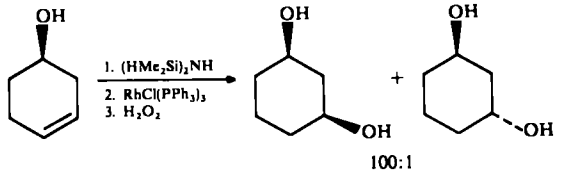
Intramolecular hydrosilylation is attained with a hydrosilyl group anchored to a hydroxy group in the presence of transition metal catalysts (platinum or rhodium). The cyclic siloxane **43** gives diols after oxidation (equation 22). Similarly as in intramolecular hydroboration, *syn* selectivity has been observed[253]. Cyclic homoallylic alcohols give *cis*-1,3-diols (equation 23), while the stereocontrol in the hydrosilylation of the corresponding acyclic alcohols strongly depends on the structures of the compounds.



(22)

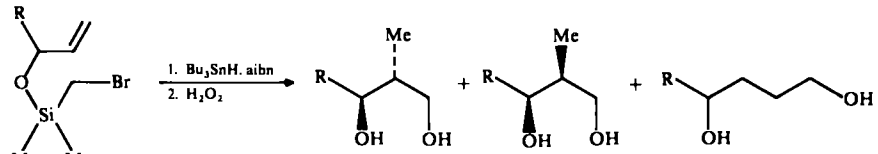
1 $(HMe_2Si)_2NH$, RT, 1 h
2 H_2PtCl_6 or $RhCl(PPh_3)_3$, RT to 60 °C
3 30% H_2O_2–$NaHCO_3$, MeOH–THF, 60 °C

R	%Yield	44/45
Bu	73	2.4:1
i-Pr	66	24:1
t-Bu	52	100:1
Ph	55	6.7:1



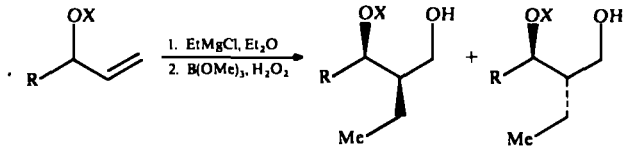
(23)

In a process similar to hydrosilylation–oxidation, free radical-mediated cyclization can be applied to form the intermediate siloxane from (bromomethyl)dimethylsilyl allylic ethers[256] (equation 24). Depending on the substituent, 1,3- or 1,4-diols can be the main products.



(24)

c. Carbomagnesation–oxidation. The zirconium-catalysed reaction of an unprotected or protected allylic alcohol according to equation 25 ensures the stereoselective formation of a carbon–carbon bond, yielding the *syn*- or *anti*- diol, respectively[257].



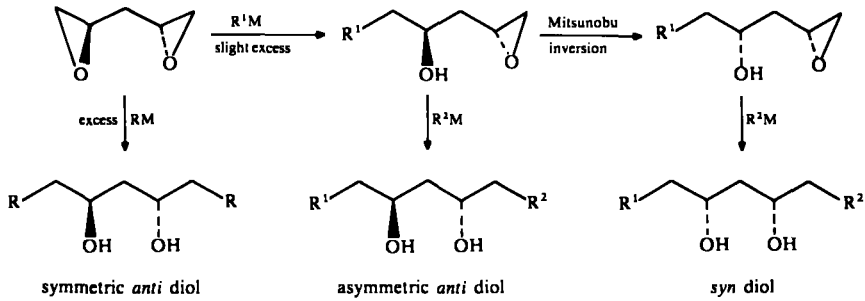
(25)

R	X	Catalyst	%Yield	*syn*:*anti*
C_9H_{19}	H	Cp_2ZrCl_2	70	95: 5
c-Hex	Me	Cp_2ZrBu_2	92	4:96

2. *Transformations of oxiranes*

Oxiranes react with hydrosilanes and CO in the presence of $Co_2(CO)_8$ to yield 1,3-diol bis silyl ethers[258] (see also Section III.B.4).

Optically pure *syn*- or *anti*-1,3-diols can be synthesized by reacting isomeric 1,2:4,5-diepoxypentanes with organometallic reagents[259] (Scheme 4).



SCHEME 4

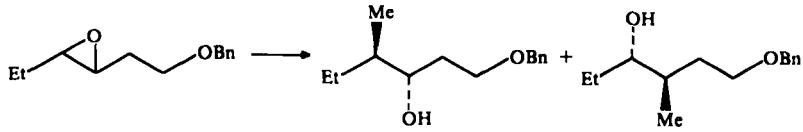
In the hydride reduction of disubstituted 2,3-epoxy alcohols (equation 8), Red-Al is the reagent of choice in the selective synthesis of 1,3-diols[126] (Table 10).

TABLE 10. Regioselectivity in ring opening of 2,3-epoxyalcohols (ratios of 1,2- to 1,3-diol) (equation 8)

	Reducing agents				
R in **19**	$LiAlH_4$		Red-Al		Reference
$BnO(CH_2)_2$			Benzene, RT	1:19	129
			THF, −20 °C	1:150	
C_7H_{15}	THF, 0 °C	1:1	THF, 0 °C	1:1	260
$BnO(CH_2)_2$	THF, 0 °C	1:4	THF, 0 °C	1:40	
C_7H_{15}	THF, −15 °C	1:4	THF, 0 °C	1:150	261
			CH_2Cl_2, 0 °C	1:1	
C_7H_{15}[a]			THF, reflux	1.5:1	
BnO			THF, 0 °C	1:40	

[a]Benzyl ether.

1,3-Diols are also the main products in the ring opening of 3,4-epoxy alcohol derivatives, but highly selective ring opening is characteristic of organoaluminium reagents[262,263] (equation 26)[264].

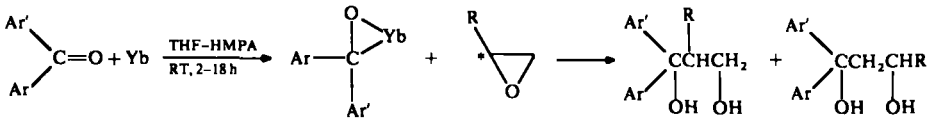


(26)

3. Reactions of carbonyl compounds

a. Transformation of carbonyl compounds with oxiranes. Carbonyl compounds and oxiranes react to afford 1,3-diols. Either the oxirane[265,266] or the carbonyl compound[154,155,267] is activated under the reaction conditions.

Yb metal umpoled diaryl ketones may react with chiral oxiranes to yield chiral 1,3-diols (equation 27)[267]. A highly selective synthesis of 2-vinyl-1,3-diols has been achieved by reacting 2-methyl-2-vinyloxirane with aldehydes in the presence of $SnCl_2$ and Bu_4NBr or LiI[268].



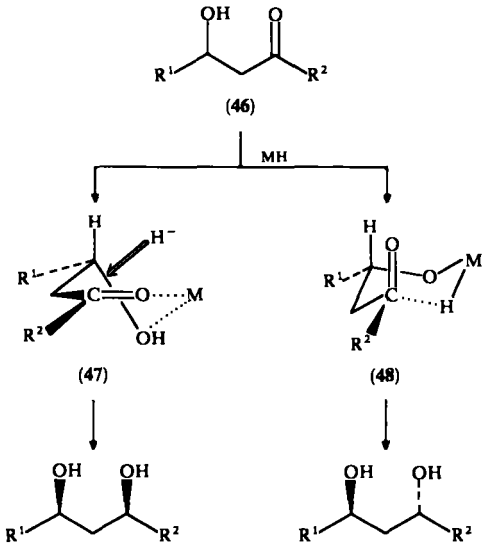
(27)

TABLE 11. Selectivity in hydride reductions of β-hydroxy ketones (Scheme 5)

Reducing agent	Substituents in **46**		*syn/anti* ratio	Reference
	R^1	R^2		
Dibal	Ph	Me	19:1	269
$Bu_3SnH + ZnCl_2$	*i*-Pr	Ph	7:1	
$NaBH_4 + Et_2BOMe$	Ph	Ph	99:1	270
	Bu	Bu	99:1	
Catecholborane	*i*-Pr	*i*-Pr	10:1[a]	271
			6:1[b]	
Catecholborane + $RhCl(PPh_3)_3$	*i*-Pr	*i*-Pr	12:1[a]	271
			20:1[b]	
$Bu_3B + NaBH_4$	Ph	Ph	49:1	272
$Zn(BH_4)_2$	Bu	Me	2.4:1[c]	195
$Me_4N(AcO)_3BH$	*i*-Pr	*i*-Pr	1:24	273
$(i\text{-Pr})_2SiHCl + SnCl_4$	*i*-Pr	*i*-Pr	1:120	274
d	Ph	Ph	1:3	197

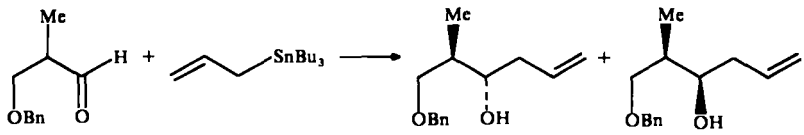
[a]At −10 °C.
[b]At −35 °C.
[c]The mom ether was used.
[d]F^--catalysed intramolecular hydrosilylation of the Me_2HSi ether.

b. Hydride reduction of β-alkoxy (silyloxy) carbonyl compounds. The *syn* isomer is the major product if chelation control prevails in the reduction of β-hydroxy ketones (Table 11). A six-membered cyclic transition state (**47**) is formed through coordination with both oxygen atoms of either the metal ion of the hydride reagent or an additive (Scheme 5). In contrast, intramolecular hydride delivery (**48**) leads to the *anti*-diol (Table 11, last three entries). The incorporation of a methyl substituent, i.e. an additional stereogenic centre at the α-position, does not cause overriding of the diastereofacial bias exerted by the β-substituent[271–273,275]. An α-ethyl group might also play a minor role[275], or can result in a reversal of the selectivity[272]. A bulky silyloxy group preventing chelation ensures a high level of 1,2-*anti* asymmetric induction[276]. In the reduction with $LiEt_3BH$ of compounds with trimethylsilylvinyl or trimethylsilylcyclopropyl groups in the α-position, the substituents establish a *syn* relationship between the vinyl (cyclopropyl) and the newly formed hydroxy groups[277,278].



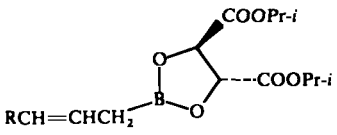
SCHEME 5

c. Reaction of β-hydroxy carbonyl compounds with organometallics. In the transformation of β-oxygenated aldehydes with alkyl or allyl reagents chelation control furnishes *anti*-1,3-diols[206,279,280], while an α-methyl group establishes an *anti* arrangement of the newly formed hydroxy group[209,281] (equation 28)[282]. Enantiomeric allylboron reagents exert opposite asymmetric induction[283,284]. A reversal of the selectivity has also been observed in an intramolecular allylsilane addition catalysed by $TiCl_4$ or $SnCl_4$[285].

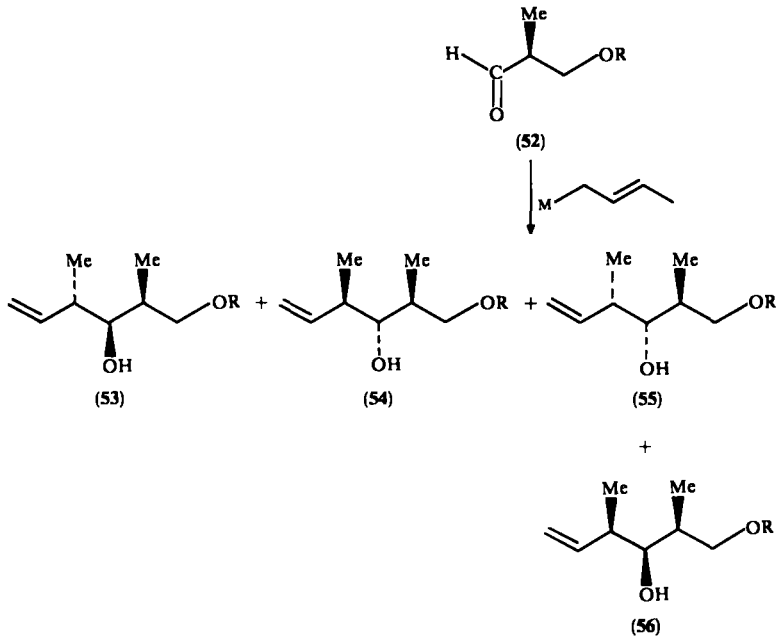


$TiCl_4$ 82:18
$SnCl_4$ 98: 2 (28)

In the reactions of α-methyl-β-alkoxy (silyloxy) aldehydes yielding 1,3-diols, opposite selectivities have been observed with pinacol-(*E*)- or (*Z*)-crotylboronates[286]. This observation indicates that the sense of the asymmetric induction also depends on the nature of the achiral reagent. The successful selective synthesis of three isomeric 1,3-diols containing a 1,3-dimethyl unit (Scheme 6) has been carried out by selecting an appropriate protecting group and tartrate ester-modified chiral crotyl reagents **49** and **50**[284] (Table 12). These reagents can ensure selective *syn* or *anti* bond construction, while the crotylstannane reagent yields *syn* products[282] (**55** + **56**) (Table 12).



(**49a**) R^v = Me, *E*-isomer
(**49b**) mirror image of **49a**
(**50a**) R = Me, Z-isomer
(**50b**) mirror image of **50a**
(**51a**) R = H
(**51b**) mirror image of **51a**



SCHEME 6

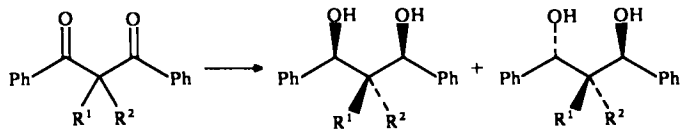
d. Reduction of dicarbonyl compounds. The reaction conditions and the nature of the complex metal hydrides employed markedly affect the selectivity in the reduction of 1,3-alkanediones (equation 29, Table 13). If cyclic systems prevail in both consecutive reduction steps, the all-*syn* (*meso*) isomer **58** is the dominant product in the reduction of 2-monosubstituted 1,3-ketones (R^2 = H)[287] (Table 13). $NaBH_4$ has been used to reduce steroid formyl ketones to isomeric 1,3-diols[288].

TABLE 12. Selectivity in transformations of α-methyl-β-alkoxy (silyloxy) aldehydes (**52**) with crotylmetal reagents (Scheme 6)

Reagent	Protecting group in aldehyde **52**	Product composition				Reference
		53	**54**	**55**	**56**	
49a	tbdms	97	3	—	—	284
49b	tbdms	10	90	—	—	
50a	tbdms	—	4	95	1	
50b	tbdms	9	3	24	64	
$MeCH{=}CHCH_2SnBu_3 + ZnBr_2$	tbdps	2	4	27	67	282
$MeCH{=}CHCH_2SnBu_3 + BF_3{\cdot}OEt_2$	tbdps	—	—	10	90	
$MeCH{=}CHCH_2SnBu_3 + BF_3{\cdot}OEt_2$	tbdms	—	—	5	95	
$MeCH{=}CHCH_2SnBu_3 + MgBr_2$	Bn	10	2	81	7	

TABLE 13. Selectivity in hydride reduction of 1,3-diketones (equation 29)

Substituents in **57**		Reaction conditions	Yield (%)	**58/59** ratio	Reference
R^1	R^2				
Me	Me	$LiAlH_4$, Et_2O, RT, 12 h	100	1:4	218
		$LiBH_4$, Et_2O, 0 °C, 1 h	89	1.2:1	219
		$LiBH_4 + TiCl_4$, Et_2O, 0 °C, 1 h	100	11.5:1	
Me	H	$LiAlH(OBu\text{-}t)_3$, THF, −30 °C, 14 h	90	1:49	287
		$LiAlH_4 + TiCl_4$, CH_2Cl_2, 25 °C, 14 h	91	19:1	
		$LiAlH(OBu\text{-}t)_3 + TiCl_4$, CH_2Cl_2, 25 °C, 14 h	95	32:1	
Bn	H	$LiAlH(OBu\text{-}t)_3$, THF, 25 °C, 14 h	93	1:24	
		$LiAlH_4 + TiCl_4$, CH_2Cl_2, 25 °C, 14 h	93	32:1	



(57) (58) (59) (29)

A high enantiomeric excess has been achieved in the reduction of 1,3-diketones with homogeneous Rh(II) complexes[220]. Acetylacetone has been transformed to (*R*,*R*)-2,4-pentanediol of high optical purity on Raney nickel modified with (*R*,*R*)-tartaric acid and NaBr[289,290].

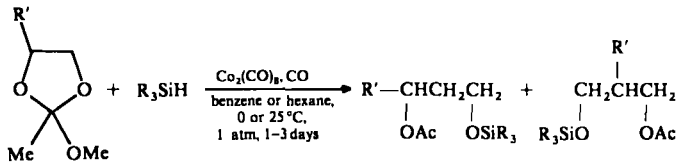
4. Transformation of β-substituted carboxylic acids and derivatives

(*R*)-1,3-Butanediol can be prepared from the biopolymer polyhydroxybutyric acid by reductive depolymerization[291,292].

A two-step process is often used to transform β-keto esters into optically active 1,3-diols. Yeast reduction is first applied to transform the keto group. The ester group is then either reduced with complex metal hydrides[293–295] or transformed with organometallic reagents[296].

Of the different metal hydrides used in the reduction of diethyl 2-phenylmalonate Dibal proved to be the best reagent, producing 2-phenyl-1,3-propanediol with 100% selectivity, while $LiAlH_4$ yielded a significant amount of metalation product[297].

The homologation of 1,2-diols can be carried out according to equation 30. During the reaction, which takes place under mild conditions, the cyclic orthoester **60** reacts with the incorporation of carbon monoxide[298].



(30)

(60)

$R_3SiH = MeEt_2SiH$ or Me_3SiH
R' = H, Me, Bu, $ClCH_2$, $MeOCH_2$, Ph

R'	41–94% yield Selectivity
Me	91:9
Bu	94:6
Ph	0:100

5. Reduction of 1,3-dicarboxylic acid derivatives

2-Substituted 1,3-propanediols are prepared by the conventional $LiAlH_4$ reduction of the easily accessible diethyl malonate derivatives[299–301]. Thiol esters (**61**) formed in the Knoevenagel condensation of *S,S'*-diethyl dithiomalonate and aldehydes are conveniently reduced to 2-RCH_2-substituted 1,3-propanediols[302].

$$RCH{=}C(COSEt)_2$$

(61)

C. Synthesis of Other Diols

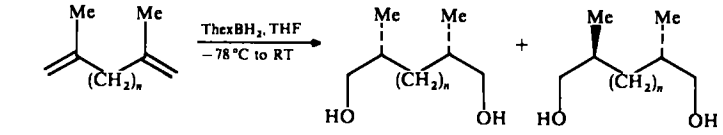
1. Direct oxidation

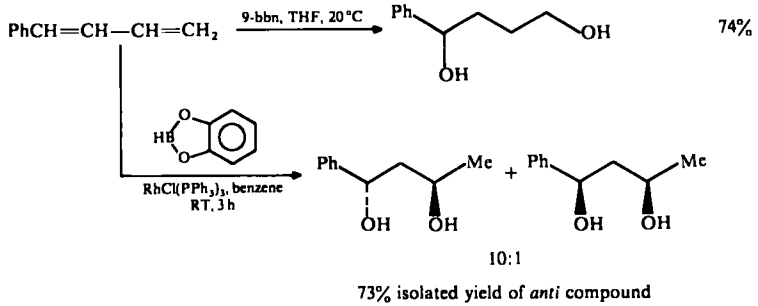
HOF in acetonitrile-chloroform, an oxidizing solution, has been used for the tertiary hydroxylation of 1-acetoxy- or 1-acetoxymethyl-4-alkyl-cyclohexanes[303]. Site-selective hydroxylation of steroids has been achieved with metalloporphyrins covalently attached to the $C_{(17)}$—OH[304]. With iodosylbenzene as the source of oxygen, hydroxylation at $C_{(9)}$ and $C_{(12)}$ was performed.

2. From dienes and unsaturated alcohols

If dienes are subjected to hydroboration, intermolecular hydroboration of the less hindered double bond first takes place. In the second step, intramolecular hydroboration leads to a boracycle which, after the subsequent oxidation, yields a diol. If the initially formed borane contains an asymmetric carbon, a new chiral centre can be created in the intramolecular hydroboration by remote asymmetric induction[305,306]. The formation of *meso*-diols as major product as a result of high asymmetric induction was observed in the transformation of the symmetric dienes **62a** and **62b**[305] (equation 31). The stereochemistry was explained in terms of seven- and eight-membered bridged cyclic

transition states, respectively. The reaction conditions, however, can strongly affect the outcome of the reaction[307] (Scheme 7).





SCHEME 7

Oxymercuration with $Hg(OAc)_2$ and subsequent reduction with $NaBH_4$[14,15], and Cp_2ZrCl_2-catalysed diene coupling[308], are likewise useful processes for the transformation of dienes to diols.

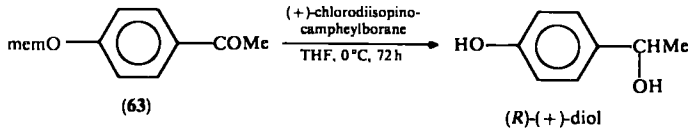
The Cp_2ZrCl_2-catalysed carbomagnesation of homoallylic alcohols and ethers displays certain unique features[309]. In contrast with the transformation of the corresponding allylic compounds, where the alcohols and the ethers exhibited opposite diastereoselectivity in the formation of 1,3-diols[257] (equation 25), the homoallylic compounds furnish 1,4-diols with the same stereochemical induction. This difference was explained by assuming strong coordination of both the alcohol and the ether oxygen to the transition metal in the transformation of the homoallylic compounds.

Two novel syntheses of 1,4-diols start with 1,2-oxaborolanes synthesized from allyl alcohol. These can be transformed into 1,2-oxaborinanes which, after oxidation, afford 1,4-diols in good to high yields[310].

Chirality transmission involving free-radical cyclization and oxidation of a 1,2-siloxane intermediate is used for the stereocontrolled synthesis of branched-chain 1,4-diols[311] (see also equation 24).

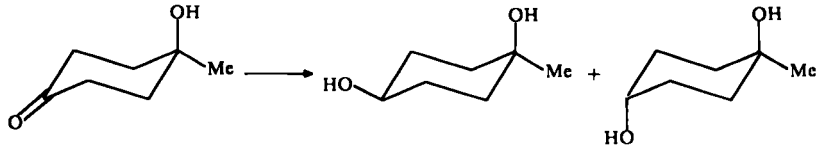
3. *From carbonyl compounds*

A one-step reduction and simultaneous deprotection of **63** is a general route to enantiomeric 1-(4-hydroxyphenyl)alkanols[312] (equation 32).



The chromium(II)-mediated addition of chiral allylic bromides to aldehydes takes place with high Felkin–Anh selectivity[313]. In a similar, Lewis acid-catalysed synthesis with methoxyallylsilane, $TiCl_4$ and $BF_3 \cdot OEt_2$ exhibited different stereocontrol[314].

The stereoselective synthesis of *cis*- and *trans*-1-methyl-1,4-cyclohexanediol has been carried out by using different hydride reagents[315] (equation 33).

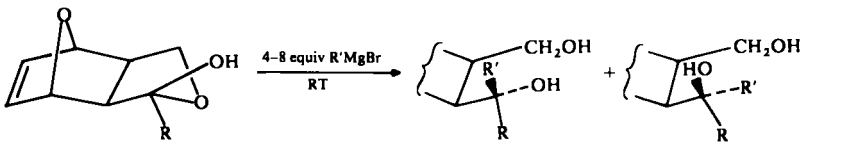


(33)

$LiAlH_4$, THF, reflux, 30 min	7.2:1
LS-Selectride, THF, −78 °C, 2 h	1:2.1

Reductive cleavage of 2,2-dialkyloxetanes yields isomeric oxyanions which in turn, if trapped by carbonyl compounds, are transformed in modest yield to 1,4- or 1,5-diols[316].

Five-membered lactols (hemiacetals), equivalents of γ-hydroxy carbonyl compounds are transformed to 1,4-diols through nucleophilic ring opening. Nucleophilic addition to γ-chiral lactols proceeds in a highly diastereoselective manner[317]. A seven-membered cyclic transition state yielding *syn*-1,4-diols has been proposed. 2-Methyl-1,4-diols with a 1,2-*anti* arrangement of the substituents can be prepared in a similar way from α-chiral lactols[318]. Of the various reagents, $MeTi(OPr\text{-}i)_3$ exhibits the highest selectivity. An unusually strong solvent effect has been observed in the addition of Grignard reagents to the **64** lactols, allowing the formation of diastereoisomeric diols by a simple change of solvent[319] (equation 34).



(64)

(34)

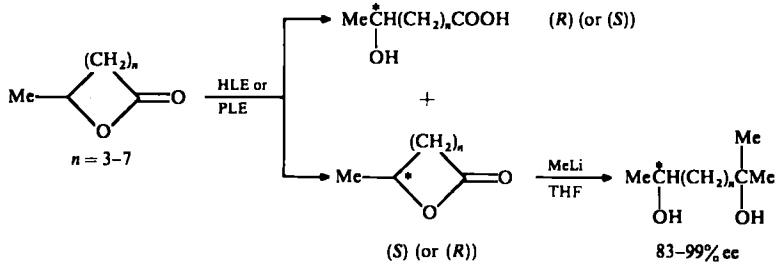
Solvent	R	R′	%Yield	Selectivity
THF	Me	Bu	58	>95:5
	Bu	Et	55	>98:2
Et_2O	Me	Bu	59	<2:98
	Bu	Et	72	<2:98

1,4- and 1,5-dicarbonyl compounds have been transformed to the corresponding isomeric diols by reduction[15,218,320–322] or by the addition of organometallic reagents[14,15]. A detailed study of the stereochemistry of the reduction of propellanediones with $NaBH_4$ in water-containing surfactants has been published[320].

4. *From substituted carboxylic acids and derivatives*

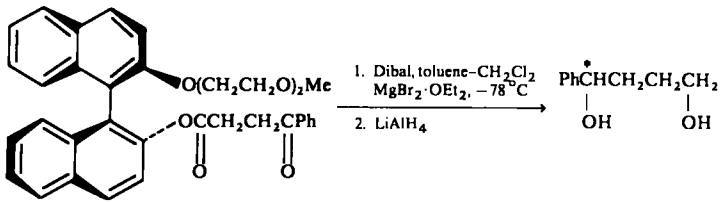
Lactones are frequently reduced with $LiAlH_4$ to diols[295,323–327]. Prior to the reduction, stereoselective reactions are used to prepare a substituted lactone ring[323,325,326], or natural products are used as starting materials[328].

The synthesis of chiral secondary–tertiary diols in high enantiomeric excess has been carried out by enzymatic resolution of medium-ring lactones (horse liver or pig liver esterase, HLE or PLE), followed by transformation of the optically active lactones[329] (Scheme 8).



SCHEME 8

Stereoselective reduction of the keto group in keto acids or esters as the starting reaction in a two-step process, followed by metal hydride reduction of the carboxylic group, is also used in the synthesis of 1,4-diols[330,331] (see also Section III.B.4). In a new approach described recently, a derivative of (*R*)-1,1′-naphthalene-2,2′-diol was used to achieve a remote 1,7-asymmetric induction in the first reduction step[331]. The chiral auxiliary was esterified with the keto acid, and compound **65** formed was reduced (equation 35). The product (*S*)-1-phenyl-1,4-butanediol with 82% ee was isolated after reduction of the hydroxy ester.



(65) (35)

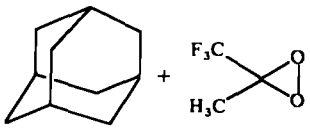
If six-membered cyclic orthoesters are applied, the homologation reaction depicted in equation 30 affords the corresponding 1,4-diol derivatives with high regioselectivities, in fair to high yields[298].

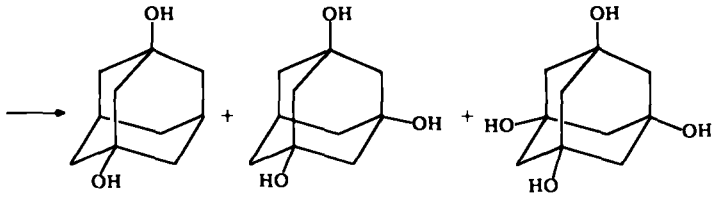
Hydrosilylation in the presence of Cp_2TiCl_2 as catalyst converts the ester group in phenol or keto esters to a primary hydroxy group in good yields[332].

IV. SYNTHESIS OF POLYOLS

Methods in which more than two hydroxy groups are generated in a single step are very rare, although polyoxo compounds can easily be transformed to the corresponding polyols by means of different reduction methods[333–335]. A unique example is the selective oxidation of adamantane[336] (equation 36).

The typical way to produce polyols is to introduce hydroxy groups into substituted alcohols progressively. All the methods discussed above for the synthesis of diols can be applied. Characteristic examples below illustrate some of the major varieties.





(36)

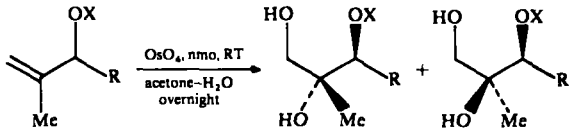
	diol:triol:tetrol
2 equiv reagent, 40 min	93 : 0 : 0
6 equiv reagent, 2 h	8 : 0 : 0
20 equiv reagent, 3 h	0 :24 :73

In many instances, the ready availability of naturally occurring compounds provides easy access to significant polyols. Because of the importance of certain antibiotics containing 1,3-polyol units with strict stereochemistry of the hydroxy groups and methyl substituents, strategies to build up such polyol chains have been developed. Special methods are used to synthesize cyclic polyols.

A. Progressive Accumulation of Hydroxy Groups

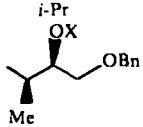
1. *Transformations of unsaturated compounds*

The double bonds in dienes[337] and in unsaturated mono- or polyhydroxy compounds are mainly transformed by osmylation. In this reaction, the oxygen-bearing chiral centre exerts a great influence on the stereochemical outcome of the reaction. Empirical formulations to predict the stereochemistry in the OsO_4 oxidation of mono- and polyhydroxylated alkenes are known[338,339]. Equation 37 illustrates the importance of



(37)

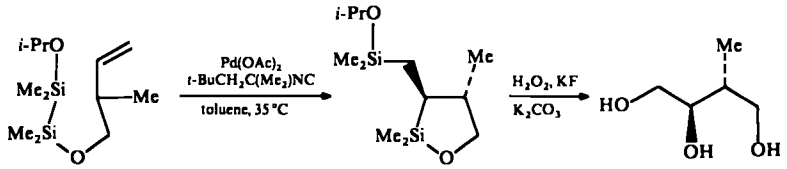
(66) (67) (68)

R	X	67/68
Et	Bn	5.1:1
i-Pr	Bn	17:1
	H	35:1
	Ac	16:1

steric factors in the oxidation of **66**[340]. Excellent regio- and stereoselectivities have been observed for oxygenated allylic silanes[341] and for iron complexes of multiply unsaturated compounds[342,343]. A meaningful model for interpretation of the above results is still lacking.

The formation of several stereogenic centres has been attained in the intramolecular hydroboration of dienol and dienediol silyl ethers[249].

A pH-dependent microbial asymmetric dihydroxylation of the remote double bond of geraniol has recently been reported[344]. A unique new intramolecular bis-silylation is illustrated in equation 38[345].

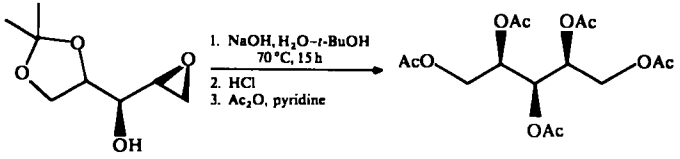


(38)

2. Syntheses starting from epoxy alcohols

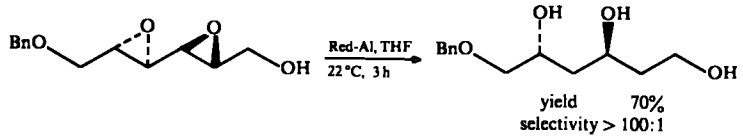
A detailed review article about this topic has recently been published[126].

a. Hydrolysis and alcoholysis. The hydrolysis of chiral hydroxy epoxides permits the stereospecific synthesis of polyol derivatives[131,346–348] (equation 39)[349]. Glycerol derivatives are often prepared from protected hydroxymethyloxirane (glycidol) in similar ways[126,350,351].



(39)

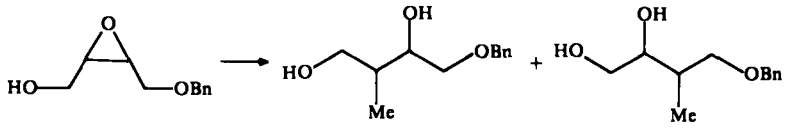
b. Hydride reductions. Since Sharpless asymmetric epoxidation[130,131] makes chiral epoxy alcohols readily available, subsequent hydride reduction can lead to polyhydroxylated natural products with the desired chiral centres[260] (equation 40).



(40)

c. Ring opening with carbon nucleophiles. Regioselectivity has been observed in the ring opening of monoprotected 2,3-epoxy-1,4-diols. Organoaluminium compounds[352–354], organocuprates[353,354] and Grignard reagents[355,356] exhibit varying selectivities in the formation of isomeric monoprotected 1,2,4-triols (equation 41)[354,355].

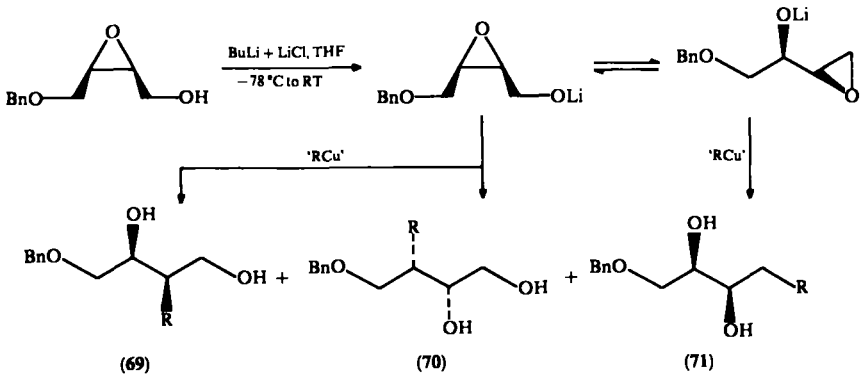
A useful preparative method for the synthesis of triols is the base-catalysed Payne rearrangement of hydroxy epoxides, combined with nucleophilic trapping of the alkoxide generated[357]. Organocopper reagents yield the rearranged compound **71** as the main



(41)

Me_3Al, pentane–CH_2Cl_2, RT 1:9
Me_2CuLi, Et_2O, −40 °C 7:3
MeMgI, THF–Et_2O, −40 °C 4.8:1

product, while the more reactive higher-order cuprate reagents give mainly products (**69** and **70**) from the unrearranged epoxide (Scheme 9).



(69) (70) (71)

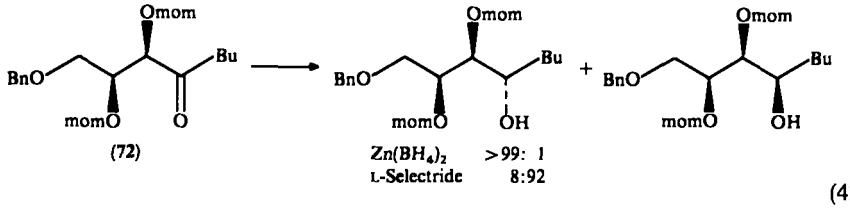
'RCu'	% Yield	Selectivity
MeCuCNLi	95	1:1:50
Me_2CuLi	95	3:2:1
BuCuCNLi	90	1:1:50
Bu_2CuLi	93	2:1:0

SCHEME 9

3. *From hydroxy (alkoxy) carbonyl compounds*

a. Hydride reductions. The stereocontrolled addition of hydride ion from metal hydrides to acyclic di(poly)hydroxy (alkoxy, silyloxy, acyloxy) ketones has been widely used for the synthesis of optically active polyols[188,189]. The selectivity in the reduction of dihydroxy ketones to triols can be controlled with different hydride reagents[358–360] or baker's yeast[361,362]. $NaBH_4$ has been successfully applied in the one-step reduction of two carbonyl groups in substituted hydroxy steroids[363,364].

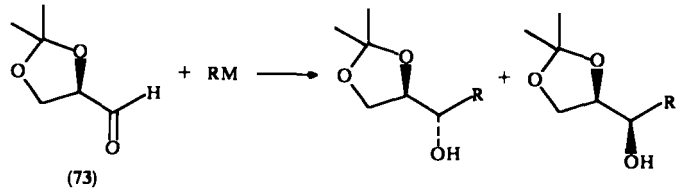
Results on the reduction of α- and β-mom-substituted ketones have revealed that the high *syn* selectivity in the reduction of the polyoxygenated ketone **72** arises via the reinforcing effect of the non-chelate Felkin–Anh and chelation transition states[195] (equation 42).



(42)

The reduction of carbohydrates will be discussed in Section IV.B.

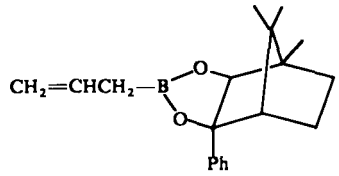
b. Reactions with nucleophiles. Because of the possibilities of the further synthetic utility of the products formed, numerous studies deal with the stereochemistry of nucleophilic addition to 2,3-*O*-isopropylideneglyceraldehyde (**73**) to produce 1,2,3-triols[188,365,366]. The presence of the rigid dioxolane system with the two oxygen atoms permits prediction of the predominant formation of the *anti* isomer[188] (equation 43). The results of the systematic study of Mulzer are in agreement with this prediction, the only exception being a titanium reagent[367], but merely low or medium selectivities were observed (Table 14, entries 1–3). In contrast, *in situ* prepared cuprates[368] (entries 4 and 5) and chiral allylboronates[283,369,370] (entries 6–10) exhibit excellent diastereoselectivity. Opposite diastereoselectivities were observed during the use of $RCu \cdot MgBr_2$ and $RTi(OPr\text{-}i)_3$, but the level of selectivity was much lower than in the transformation of the corresponding acyclic α,β-dialkoxy compounds[358].



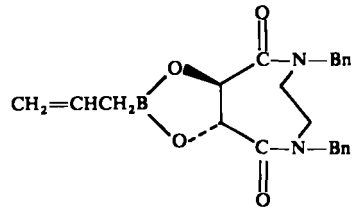
(43)

TABLE 14. Selectivity in transformations of (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**73**) with organometallic reagents (equation 43)

Entry	Organometallic reagent	Reaction conditions	*anti/syn* ratio	Reference
1	$(CH_2CH{=}CH)_2Zn$	THF, −78 °C, 2 h	10:1	367
2	$BuTi(OPr\text{-}i)_3$	Et_2O, 22 °C, 12 h	10:1	
3	$PhTi(OPr\text{-}i)_3$	THF, −78 °C, 24 h	1:10	
4	BuMgBr + CuI	THF–Me_2S, −78 °C to RT, 2 h	16:1	368
5	PhMgBr + CuI		>99:1	
6	**74**	Light petroleum, −78 °C to RT, 13 h	24:1	369
7	**51a**	Toluene, −78 °C, 2–3 h 4A molecular sieves	49:1	370
8	**51b**		1:13	
9	**75a**	Toluene, −78 °C, 43 h 4A molecular sieves	300:1	283
10	**75b**		1:49	

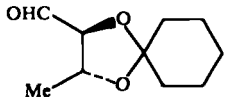


(74)

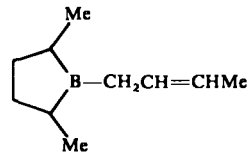


(75a) *R,R*
(75b) *S,S*

Detailed studies with crotylboronate reagents (**49** and **50**) have been published by Roush and coworkers[371–373]. The effects of the reagents and the reaction conditions on the diastereoselectivity and bond construction selectivity were similar to those for simple α- and β-alkoxy aldehydes (see Sections III.A.3.d and III.B.3.c). Besides **73**, L-4-deoxythreose cyclohexyl ketal (**76**) has also been tested[371,372,374]. An important conclusion of these studies is that it is not the stereochemical constraint imposed by the rigid dioxolane system but the favourable lone pair/dipole interaction between the tartrate ester carbonyl and the alkoxy C—O bond which is responsible for the increased selectivity in the transformation of these cyclic derivatives[374]. Borolanes (**77**)[375], *in situ*-prepared crotylchromium reagents[376–378] and other organometallics[378–380] have been used in similar studies.



(76)



(77)

Organocopper reagents ($MeCu \cdot MgBr_2$, Me_2CuLi) exhibit the highest diastereoselectivity in the addition to 2-formyl-1,3-propanediol to yield protected *tris*(hydroxymethyl)methane[381].

Ring opening with the addition of organometallic reagents to L-erythrose[382] or of Me_3Al to an epoxy ribopyranoside[383] to produce tetrols has recently been reported.

Results have also been reported on the selectivities in the reactions of γ-alkoxy allylboronates[384], γ-alkoxy (silyloxy) allylstannanes[385,386] and diisopropyl tartrate modified γ-silyl allylboronates[387,388] with mono- and polyalkoxyaldehydes. A stereocontrolled samarium ion-promoted intramolecular pinacol coupling of hydroxy(dihydroxy) δ-ketoaldehydes is similarly a new observation[389].

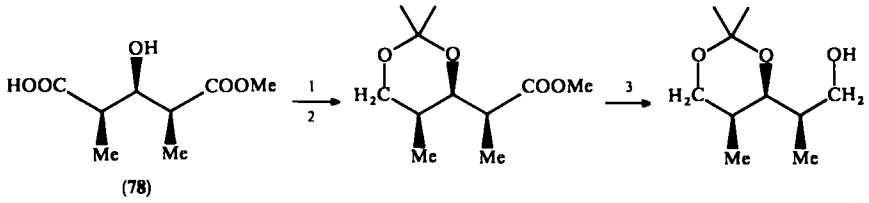
4. *Transformations of substituted carboxylic acids*

The two-step process for the transformation of β-keto esters to 1,3-diols (microbial and metal hydride reductions, see Section III.B.4) can be applied to the synthesis of triols[390,391].

Many examples are known for the transformation of tartaric acid derivatives to 1,2,3,4-tetrols. The protected (*R,R*)- or (*S,S*)-diesters are reduced with $NaBH_4$[392], $LiBH_4 + LiBEt_3H$[393] or $LiAlH_4$[195,394–396], or transformed with organometallic reagents[296,397,398].

Reduction of the hydroxy dicarboxylic acid **78** has been performed in a stepwise

manner[399,400] (equation 44). Protection after the first reduction step prevents undesired lactone formation.



(44)

1. $BH_3 \cdot Me_2S$ 2. $Me_2C(OMe)_2$ 3. $LiAlH_4$

B. Transformations of Natural Products to Polyols

(*S*)-1,2-*O*-Isopropylideneglycerol, an important chiral building block, is often prepared from polyhydroxy compounds via the oxidative cleavage of a vicinal glycol subunit in them. The glyceraldehyde formed is then reduced with complex metal hydrides. D-Mannitol[401–404], butane-1,2,3,4-tetrol prepared from tartaric acid[395,405] and carbohydrates[406,407] are used as starting materials. Labelled glycerols have also been prepared by this method[402,404,407]. L-Serine has been used to produce the corresponding (*R*)-compound[401].

After saturation of the enediol double bond in L-ascorbic acid, the same two-step procedure can be applied to yield glycerol[408,409]. If direct oxidation is used, then $LiAlH_4$ reduction of the ester of the four-carbon acid formed furnishes butane-1,2,3,4-tetrol[410,411].

The production of D-mannitol from D-glucose and that of D-sorbitol from D-fructose are two important processes[412]. Supported Cu[413,414], Ru[415] and Ni catalysts[413] and Raney-Ni[416,417] are used for the reduction of the carbonyl function. On Cu-on-silica, the preferential hydrogenation of D-fructose in the presence of D-glucose has been observed[414]. The combined action of an enzyme (D-glucose isomerase) and a metal catalyst (Cu-on-silica) in the conversion of a D-fructose–D-glucose mixture furnishes D-mannitol in 62–66% yield[418]. Other carbohydrates are also transformed to polyols[419,420].

C. Synthesis of Polyol Chains

Several different methods have been developed for the synthesis of polyketide-derived natural products[421–424]. The important synthetic routes used in the construction of polyol chains with *syn*- or *anti*-1,3-diol units are treated in detail in a recent review[425]. Newer examples are as follows:

(i) Ring opening of chiral epoxides, followed by hydroboration[426] or epoxidation of the product, and repetition of this two-step sequence[133].

(ii) Two-directional chain synthesis, with ring opening of a diepoxide, followed by 1,2-Witting rearrangement and epoxidation[422,427].

(iii) A lactone replication protocol permitting the sequential introduction of methyl and hydroxy groups[428].

(iv) Epoxide ring opening with glyceraldehyde dithianes and stereoselective reduction of the resulting carbonyl with lithium aluminium hydrides in the presence of LiI to yield all-*syn* products[429,430].

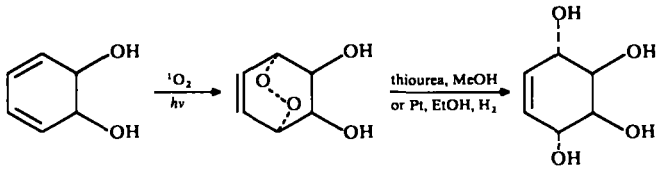
(v) Convergent syntheses in which two polyol segments are combined[431,432].

Interesting examples of the stereoselective homologation of chiral hydroxy (alkoxy) aldehydes to build up polyhydroxyaldehydes are likewise worth mentioning[433–435].

D. Synthesis of Polyhydroxycycloalkanes

Of the different polyhydroxycycloalkanes, also known as cyclitols, the cyclohexanehexols (inositols) are the most important compounds occurring in various plant sources. The major compounds of the nine possible isomers are the *myo*-, *chiro*- and *scyllo*-inositols. The significance of these compounds is that *myo*-inositol-1,4,5-triphosphate has been recognized as a second messenger in the cellular metabolism. They also serve as model compounds for sugars.

The most useful starting compounds for the synthesis of cyclohexanehexols are dihydrobenzenediols. *cis*-Dihydrobenzenediol (**18**, R = H) was used by Nakajima[436] in the first total synthesis of conduritols (5-cyclohexene-1,2,3,4-tetrols), which are key intermediates in the synthesis of inositols[107,437]. Dihydrobenzenediols are currently produced by the microbial oxidation of substituted benzene derivatives (see Section III.A.1). A number of different approaches have recently been developed for the further transformation of *cis*- and *trans*-dihydrobenzenediol[105–107,428–440]. A favoured procedure is singlet oxygen photooxygenation, followed by reduction of the endoperoxide **79** to conduritol (**80**)[439–441] (equation 45).



(79) (80) (45)

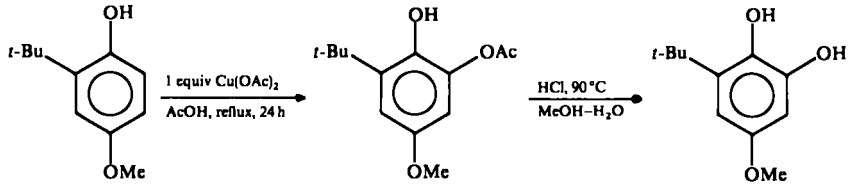
Another significant method exploits the *exo*-facial selectivity of the substitution of 7-oxabicyclo[2.2.1]heptene-5 derivatives ('naked sugars') in the synthesis of conduritols[442–444].

Pseudosugars (carbocyclic analogues of carbohydrates) are a large and similarly important group of polyhydroxycycloalkanes. Most synthetic methods start from chiral precursors (carbohydrates[445–448] or quinic acid[449–451]). Other routes are also of interest[452–455].

V. SYNTHESIS OF DI- AND POLYPHENOLS

A. Oxygenation of Aromatics

It seems that copper possesses a specific activity for the creation of hydroxy functions on aromatic rings. The direct conversion of benzene to hydroquinone in the presence of Cu(I) ion has been studied, but rather low yields were achieved[456–458]. Phenols have also been used in similar studies. The selective *ortho*-oxidation of substituted phenols by $Cu(O) + CuCl_2 + O_2$, i.e. the formation of catechols, has been described[459]. Other examples are the photochemical oxygenation of phenols with heterocyclic *N*-oxides[460] and biomimetic hydroxylation of anisol by PhIO or H_2O_2 in the presence of Fe(III)- or Mn(III)-*meso*-tetraarylporphyrins[461]. Selective acetoxylation is illustrated in equation 46[462].



56% (46)

A novel procedure employing Ti-containing ZSM-5 zeolite (titano-silicalite) as catalyst and H_2O_2 as oxidant attains a much higher conversion of phenol to a catechol + hydroquinone mixture than in other industrial processes[463–465].

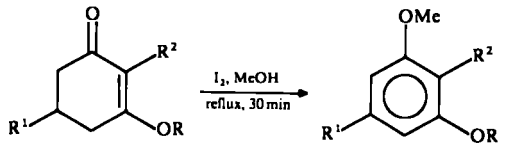
B. Coupling of Phenols to Macrocyclic Polyphenols

Calixarenes (**1**, **2**) are prepared by the base-induced reaction of *p*-substituted phenols with formaldehyde or from the acid-catalysed reaction of resorcinol with aldehydes[466–468]. A detailed treatment of this topic can be found in the excellent review articles by Gutsche[469,470].

Very recent papers disclose a remarkably simple, one-step cyclization of substituted benzyl alcohols[471], $TiCl_4$-induced condensation[472,473] and the use of pyrogallol in the acid-catalysed reaction[474]. New data on the synthesis of metacyclophanes (compounds with long chains connecting the aromatic rings) are also available[475].

C. Other Methods

Quinones or hydroxyquinones have been reduced to the corresponding di- or triphenols with SmI_2[476], $Na_2S_2O_4$[477] and Ph_3Sb[478]. 1,3-Cyclohexanedione monoenol derivatives were transformed by oxidative aromatization to resorcinol derivatives with a vanadium reagent[479], $RhCl_3 \cdot 3H_2O$[480], $Hg(OAc)_2$[481] and iodine (equation 47)[482].

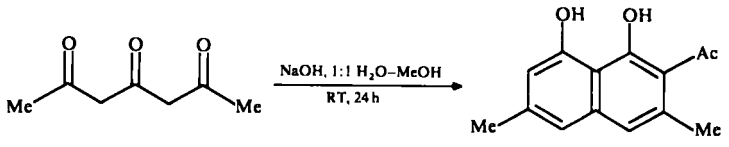


R = H, Ac
R¹ = H, Me, Pr, Ph
R² = H, Me

83–93% (47)

In a hydrothermal process under near-critical conditions, D-fructose led to the formation of 1,2,4-benzenetriol[483].

The synthesis of polyhydroxylated naphthalenes is of interest in connection with the biosynthesis and deoxygenation of certain polyketide-derived natural compounds. In the self-condensation of 2,4,6-heptanetrione, a modification of the Prelog condensation



(**81**)

74% (48)

has resulted in a significantly better yield of **81** (equation 48)[484]. Diethyl 3-oxoglutarate has been transformed to 1,3,6,8-tetrahydroxynaphthalene in a multistep synthesis[485].

VI. REACTIONS OF DIOLS AND POLYOLS

A. Transformation to Derivatives

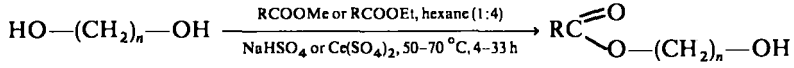
1. *Selective derivatization*

The transformations of diols (polyols) to selectively protected derivatives are important reactions. The use of appropriate reaction conditions or reagents permits selective monoderivatization, and differentiation between primary and secondary, or equatorial and axial hydroxy groups.

a. Monoprotection of symmetric diols. New variants of the Williamson synthesis can be used to carry out the etherification of diols, either through Tl(I) alkoxide[486] (for diprimary and disecondary diols) or under phase-transfer conditions[487] (only for disecondary diols). $Ph_3Bi(OAc)_2$ is employed for monophenylation[488,489]. Different diethylphenylphosphoranes, excellent reagents in the cyclodehydration of 1,2-, 1,4- and 1,5-diols (see Section VI.D.2), lead to the formation of the monoethyl ethers of 1,3-diols[490]. Pyrogallol is selectively monomethylated with Me_2SO_4 in the presence of boric acid under basic conditions[491].

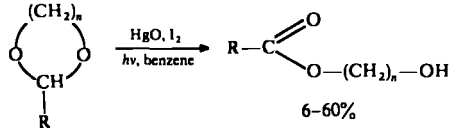
Many selective monoprotected diol derivatives are prepared via the ring cleavage reactions of cyclic diol derivatives. Ring opening of cyclic tin derivatives yields monoethers or monoacylated compounds[492–494]. Cyclic acetals are transformed to monoethers by reductive cleavage[495–497] or to monoenol ethers by isomerization[498].

Monoacylation under mild reaction conditions can be carried out with metallic sulphates supported on silica gel[499] (equation 49) or by the oxidative cleavage of aldehyde cyclic acetals[500] (equation 50). Examples of specific reactions are the monoacylation of diols with amino acids catalysed by immobilized papain[501], and with chlorophyll *a* catalysed by chlorophyllase[502]. Selective monocarbamoylation is illustrated in equation 51[503].



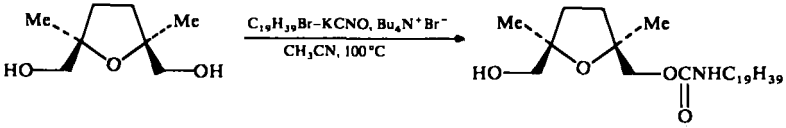
(49)

R = Me, Et, *i*-Pr
n = 2, 4–6



(50)

R = Pen, $C_{11}H_{23}$, *c*-Hex, Ph, *p*-An, Bn
n = 2–4

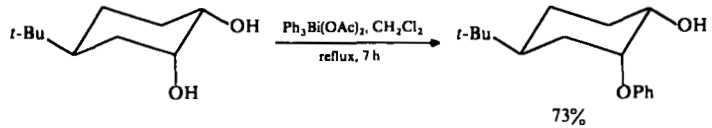


(51)

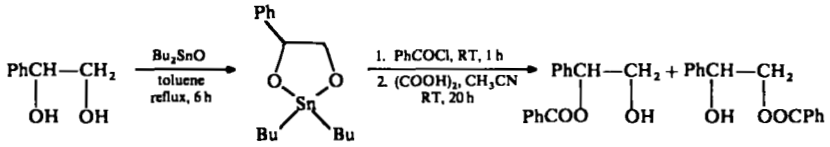
cis-diol 17 h, 77%
trans-diol 48 h, 42%

Although not a protection reaction, the selective formation of mono $MeSCH_2$ derivatives of cyclic 1,2-diols with Mo peroxide-DMSO is worth mentioning[504].

b. Regio- and chemoselective reactions. The modified Williamson procedure transforms primary–secondary diols (triols) to derivatives protected on the primary hydroxy group[486]. Protection of the primary hydroxy group in the form of a mixed acetal is carried out in a direct Co(II)-catalysed reaction with ethyl vinyl ether[505] or by the reductive cleavage of cyclic trialkyl carbonates[506]. $Ph_3Bi(OAc)_2$ exerts a strong preference for the axial hydroxy in a six-membered ring (equation 52)[507]. In organotin-mediated reactions, transformation of the cyclic intermediate **82** can ensure regioselective alkylation at the primary hydroxy group[494,508]. In monoacylation, however, reversed selectivity can be observed (equation 53)[509]. An example of the chemoselective benzoylation of the more hindered hydroxy in 1,2-diols by using the Mitsunobu reaction[510] is given in equation 54[511]. The mechanism involves formation of the 1,3,2λ^5-dioxaphospholane **83** which, after a proton-assisted, higly stereoselective ring opening, allows inversion. 1,3-Butanediol, which does not form the cyclic intermediate, reacts at the primary hydroxy group[512]. Exclusive or highly selective formation of primary carbonates can be carried out by using an *in situ* prepared reagent (**84**) with a catalytic amount of 4-dimethylaminopyridine (dmap) (equation 55)[513].

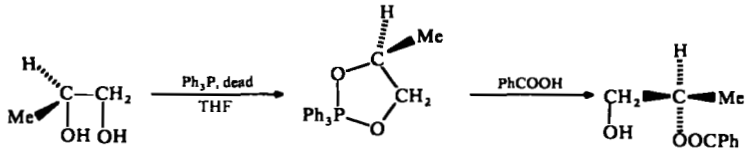


73% (52)



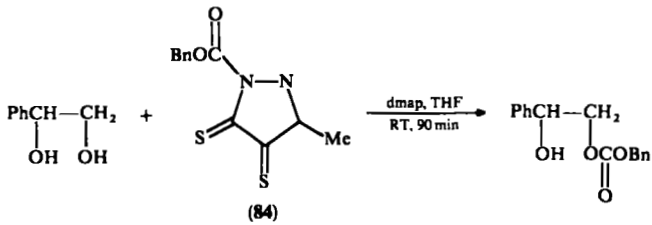
(82)

yield 90%
selectivity 86:14 (53)



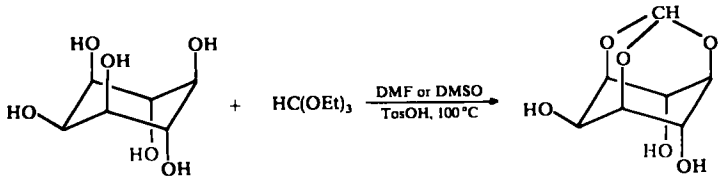
(*S*)-diol (83)

(*R*)-monobenzoate
88% selectivity (54)



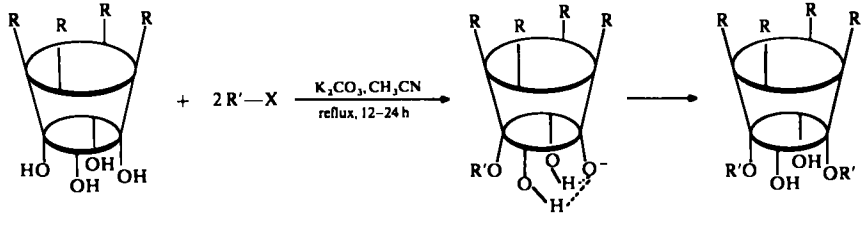
(84) (55)

The axial 1,3,5-hydroxy groups in *myo*-inositol (**85**) react with triethyl orthoformate to yield the cyclic orthoformate **86**[514,515] (equation 56). A highly efficient, regioselective formation of disiloxane bridges between the axial 3,4- and 1,6-hydroxy groups was achieved with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane[516].



(85) (86) (56)

The selective mono- or difunctionalization of the phenolic hydroxy groups in calixarenes (**1**, $n = 4$, R = H) is of recent interest. Since calixarenes exist in the cone conformation depicted in a simplified way in equation 57, these transformations are called functionalizations at the lower rim. If **1** reacts with 2 equiv of alkyl tosylates[517,518] or halides[518,519] in the presence of 1 equiv of K_2CO_3, selective 1,3-functionalization occurs (equation 57). This was explained by assuming formation of the monoalkylated anion **87**. This intermediate is stabilized by two hydrogen bonds, ensuring selective attack by the second mole of reagent at the diametrical position[518]. The selective synthesis of monoalkyl ethers was achieved by selective removal of one or three of the R′ groups with Me_3SiI from **88** or from the tetraethers, respectively[520]. $TiBr_4$ was used for 1,2-bis-demethylation to prepare proximal dimethylcalixarenes[521]. Change of the molar ratio in equation 57 (with 0.6 equiv of K_2CO_3) or the use of CsF permits direct monoalkylation[522]. One example of direct 1,2-functionalization is known[523].

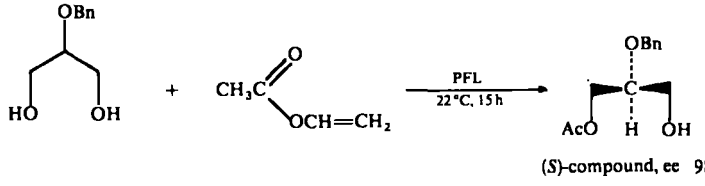


(1) (87) (88)

R′ = Me, Bn, allyl 96–99% (57)

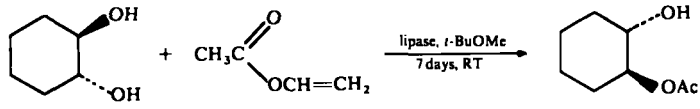
Enzymatic derivatizations (transesterifications) are frequently carried out[524–529]. Different enzymes can exhibit different regioselectivities. When reacted with trifluoroethyl butyrate, 5α-androstane-3β,17β-diol is exclusively monoacylated at the 3-hydroxy group in the lipase-catalysed process, while subtilisin exhibits a marked preference for acylation of the 17-hydroxy group[525].

c. Enantioselective derivatization. The numerous examples of asymmetric transformations of diols catalysed by enzymes have been reviewed[529–531]. In most newer examples, lipase from *Pseudomonas fluorescens* (PFL) is used in transesterification with vinyl acetate. Prochiral 2-substituted 1,3-propanediols[532–534], glycerol derivatives[535] (equation 58) and 1,4-diols[536] are transformed in phosphate buffer, in an organic solvent or in a solvent-free system. In a similar process, the monoacetylation of *racemic trans*-1,2-cycloalkanediols and the preparation of optically pure *trans*-1,2-cycloalkanediols have been achieved (equation 59)[537].



(*S*)-compound, ee 98%

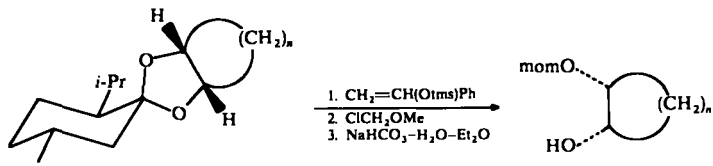
(58)



42% yield, ee 95%

(59)

Examples of non-enzymatic enantioselective derivatizations are also known[538]. *meso*-1,2-Diols are enantioselectively monophenylated in the presence of $Ph_3Bi(OAc)_2$, $Cu(OAc)_2$ and chiral pyridinyloxazolines[539]. The process permits kinetic resolution of racemic diols. Another method uses *l*-menthone to carry out the enantioselective derivatization of prochiral 1,2- 1,3- and 1,4-diols. The spiroacetal **89**, separated from the minor isomer by column chromatography, is cleaved with allyltrimethylsilane[540] or acetophenone enol trimethylsilyl ether[540–542] promoted by $TiCl_4$ (equation 60)[542]. The free hydroxy group in the intermediate formed is first protected; then, after removal of the chiral auxiliary, the monoprotected chiral product **90** is isolated. Asymmetric monoacylation can be achieved[543,544] if the cyclic tin derivatives **82** of *meso*-1,2-diols or glycerol are cleaved with chiral acid chlorides.

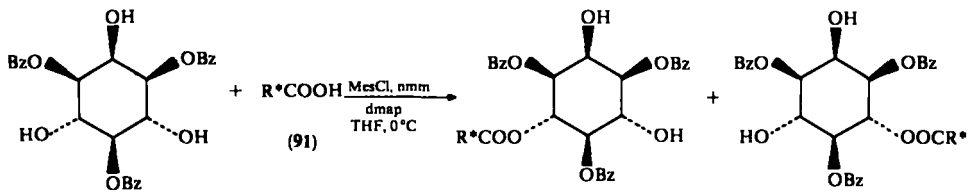


(**89**)
$n = 3,4$

(**90**)
ee > 95%

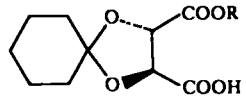
(60)

The synthesis of inositol phosphates of biological interest requires the use of different selective transformations[545,546]. A new method employs tartaric acid monoesters (**91**) for asymmetric monoesterification[547] (equation 61).



(**91a**) 98: 2 de 96%
(**91b**) 97: 3 de 94%
(**91c**) 2:98 de 96%

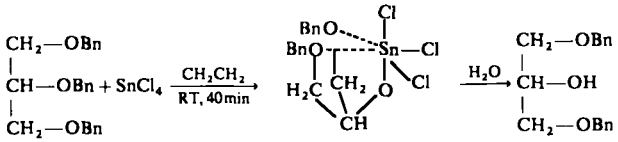
(61)

R*COOH = 

(91a) R = Me
(91b) R = Et
(91c) mirror image of **91b**

d. Selective deprotection. A protection–deprotection sequence is often used in selective transformations, which makes selective deprotections equally important reactions. Selectively protected diol (polyl) derivatives can likewise be prepared by the selective removal of a protective group.

A review paper covered the selective cleavage of ethers up to 1981[548]. Since then, the selective demethylation of phenol ethers has been carried out with BCl_3[549] and Me_3SiSNa[550]. $AlCl_3 + Bu_4I$[551] and $AlCl_3 + NaI$[552] have been found to cleave a methyl ether in the presence of cyclohexanone ketals. A regioselective de-*O*-benzylation with Lewis acids which requires three suitably situated benzyloxy groups can be seen in equation 62[553].



(62)

Acetal groups can be removed with *p*-thiocresol + NaH[554], with tonsil (a Mexican bentonitic earth)[555] or with $PdCl_2(CH_3CN)_2$[556].

In some cases, one acyl group from polyacyl derivatives of polyols is selectively removed in an enzymatic reaction[528,557,558]. A process more frequently used to prepare optically pure monoacetates is the selective monohydrolysis of diacetates[537,559–563].

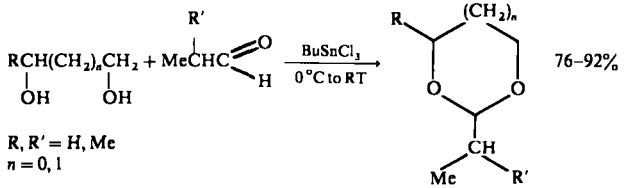
A selective distinction between silyl ethers (deips, tbdms) and alkyl ethers in diols and diphenols has been achieved with KF + a catalytic amount of HBr[564], with $MgBr_2 + BuSH$[565], and in a solvent-dependent $Pd(OH)_2$-catalysed hydrogenolysis[566]. Pyridinium *p*-toluenesulphonate removes tbdms ethers in the presence of tbdps ethers[567].

2. *Transformation to cyclic derivatives*

a. Cyclic acetals (1,3-dioxacycloalkanes). Acetalization is mainly used to protect carbonyl groups, but cyclic acetals are also useful as chiral auxiliaries in asymmetric syntheses[568].

The reaction of diols with carbonyl compounds is direct acetalization. It takes place through the hemiacetal and is mainly carried out with acid catalysis. The different synthetic methods were reviewed in 1981[569].

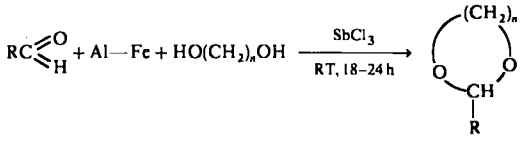
Diols may react with carbonyl compounds in the presence of an equimolar amount of $BuSnCl_3$ (equation 63)[570], or with a large excess of Me_3SiCl, which acts as both a



76–92%

(63)

dehydrating agent and an acid catalyst[571]. A recent very effective and versatile method uses aluminium-iron powder with $SbCl_3$ as a catalyst[572] (equation 64).



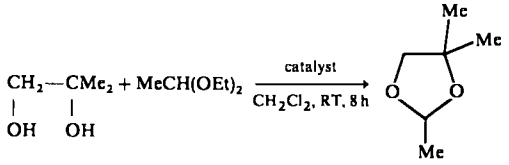
(64)

R = alkyl, alkenyl, aryl
$n = 2, 3$

50–99%

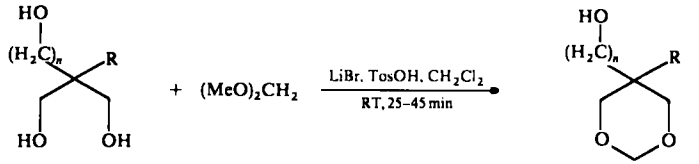
Cationic Pd(II) and Pt(II) complexes[573] and a family of Rh(III) complexes[574] are very effective in acetalization. Mechanistic considerations indicate direct metal participation in the catalytic cycle[573,574]. Hydrous zirconium oxide has also been employed in the transformation of ethylene glycol to 1,3-dioxolanes[575].

Besides direct acetalization, transacetalization is likewise an important process for the formation of acetals. In this case diols are reacted with simple acetals to form cyclic acetals. Some of the reagents mentioned above are also effective in this transformation[570,573] (equation 65). A LiBr-assisted process is more selective than the corresponding direct process in the transformation of triols[576] (equation 66). D-Mannitol (**92**), an inexpensive hexitol used in the synthesis of chiral building blocks[577], reacts to form bis-acetals (**93**)[578,579] (equation 67).



(65)

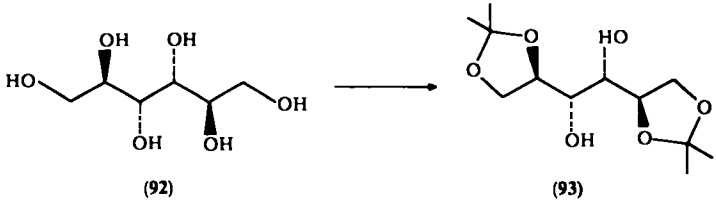
catalyst = $[Pd(OH)_2(Ph_2PCH_2CH_2PPh_2)](CF_3SO_3)_2$



(66)

R = H, Me, Et
$n = 0–2$

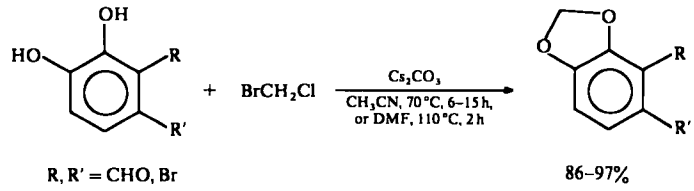
near 100% selectivity



(67)

$Me_2C(OMe)_2$, $MeOCH_2CH_2OMe$, $SnCl_2$, reflux, 1.5 h 54%
2-methoxypropene, TosOH, 0 °C, 1–2 h 92%

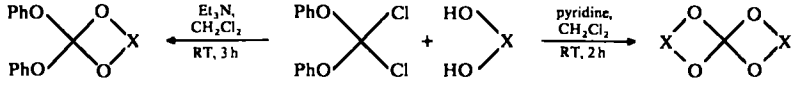
Diols react in a Pd(II)-catalysed process with terminal alkenes containing an electron-withdrawing group, to yield cyclic acetals[580,581]. A simple, high-yield method for the methylenation of 1,2-diphenols is illustrated in equation 68[582].



R, R' = CHO, Br 86–97% (68)

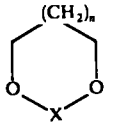
b. Cyclic carboxylic and carbonic acid derivatives. The importance of certain cyclic derivatives of vicinal diols (thiocarbonates, 2-alkoxy-, 2-acyloxy- and 2-dialkylamino-1,3-dioxolanes) stems from the fact that they are transformed to alkenes in a selective deoxygenation (see Section VI.E.2). The synthetic methods have been reviewed[583].

Polyols react with simple orthocarboxylic acid esters in an acid-catalysed process to form cyclic orthoesters. The reaction is applied in the chemistry of *myo*-inositol phosphates as a selective protection procedure (see Section VI.A.1.b). Orthocarbonic acid derivatives [$(PhO)_2CCl_2$[584], $(MeO)_4C$[585]] react similarly to yield spiro derivatives (equation 69).



85–95% $X = (CH_2)_3, CH_2CMe_2CH_2$, $(CH_2)_4, CH_2CH{=}CHCH_2$ 75–90% (69)

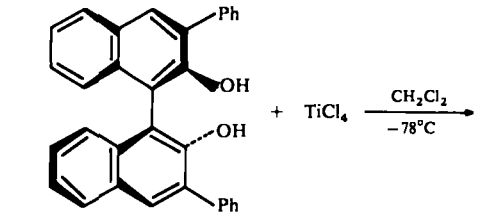
c. Cyclic derivatives of inorganic oxoacids. Diols react with appropriate reagents to yield cyclic compounds with the general formula **94**. Since many of these derivatives are used as chiral auxiliaries in asymmetric syntheses (chiral Lewis acids[586], boronic esters[587,588], chiral reducing agents[589,590]), their preparation often starts with chiral diols, such as binaphthols (**95**, **99**), tartrate esters (**98**) and tetrols derived from tartrate esters (**96**). The reactions are frequently carried out *in situ*.



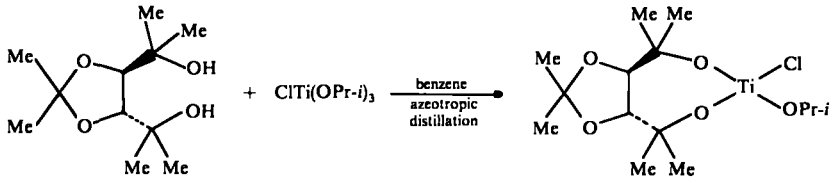
(94)

$X = TiCl_2$, Ti(OR)Cl, Ti=O, $ZrCl_2$, $ZrCp_2$, $SnCl_2$, $SiCl_2$, SiR_2, B—R, B—Br, B—H, Zn, Al—R, S=O, P(O)OH, P(O)Cl, $P(OAr)_3$
$n = 0–2$

General methods for the transformation of diols to these compounds are the reactions of diols with Lewis acids ($TiCl_4$, $ZrCl_4$, $SnCl_4$, $AlCl_3$)[591] (equation 70), Lewis acid derivatives (Et_2AlCl[591], $EtAlCl_2$[592]) or alkoxy derivatives [$Ti(OR)_4$[593,594], $ClTi(OPr\text{-}i)_3$[296], $Cl_2Ti(OPr\text{-}i)_2$[595,596], $(OPr\text{-}i)_2Ti{=}O$[597]] (equation 71). Monomeric and dimeric cyclic compounds are formed with the reagents $R^1R^2SiCl_2$[598–603] or $R^1R^2Si(OR)_2$[602,603]. Diphenols can also form anionic pentacoordinated siliconates with $RSi(OR')_3$[604,605]. Chiral aluminium hydride reagents are prepared by reacting $LiAlH_4$ with chiral diols in the presence of an alcohol[589,590].

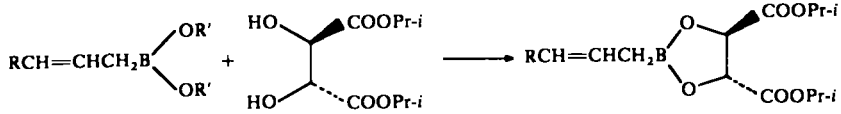


(95) (70)



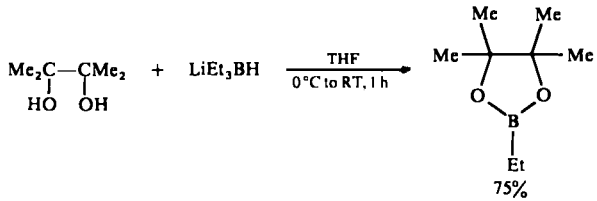
(96) (71)

The reactions of boronic acid (**97**, R′ = H) or boronic esters (**97**, R′ = alkyl) with diols are the two main processes used in the synthesis of cyclic boronic ester derivatives[370,435,606–611] (equation 72). High yields are achieved with the bromoborane reagent $RCH{=}CH{-}BBr_2{\cdot}SMe_2$[608] and lithium trialkylborohydrides[612] (equation 73). Catechol borane, an important reagent in the hydroboration of alkenes[244,245,248,304], is prepared in the reaction of catechol with BH_3[613]. Diols and polyols also form cyclic mono- and diborates, which exist in pH-dependent equilibria[614,615].



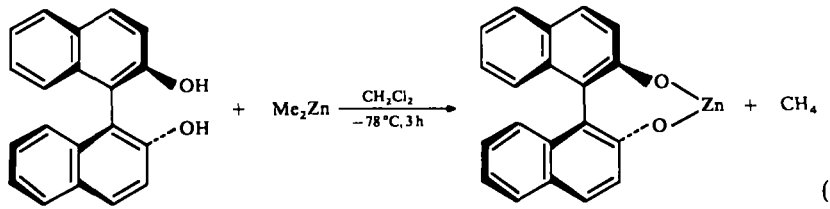
(97) (98)
R = H, Me
R′ = H, *i*-Pr

(72)



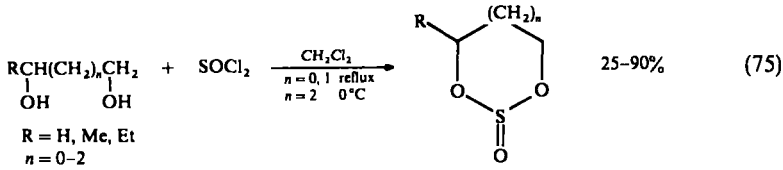
(73)

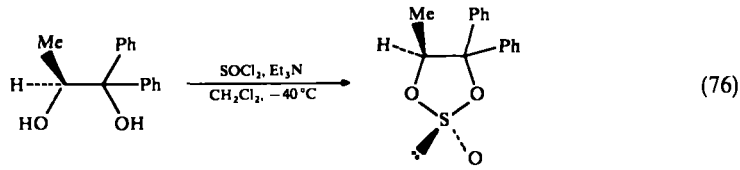
Diols may react with organometallic reagents (Me_3Al[616], Cp_2ZrMe_2[617], Me_2Zn[618]) to yield cyclic derivatives (equation 74).



(99) (74)

Cyclic sulphites are formed in the reactions of diols with $SOCl_2$, usually in the presence of a base[619-621] (equation 75)[622]. If triethylamine is added to a mixture of the chiral diol **100** and $SOCl_2$, the *trans* cyclic sulphite **101** is formed with high (9:1) selectivity[623] (equation 76). Since only cyclic diols are able to form cyclic sulphates[622], the sulphates of other diols are prepared via the oxidation of sulphites. Diols are transformed to cyclic phosphoric acid derivatives by using $POCl_3$[624-626], phosphoryl tris-triazole[627], or triaryl phosphites + *N*-chlorodiisopropylamine[628,629].

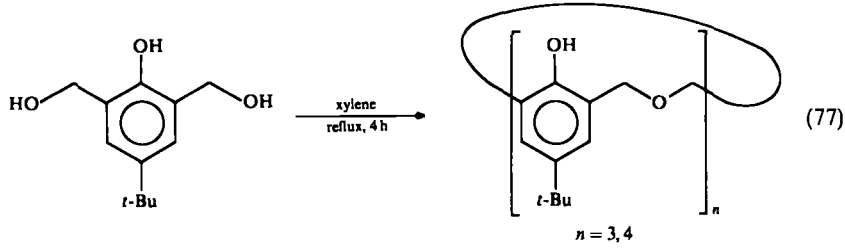




3. *Formation of oligo- and polyethers*

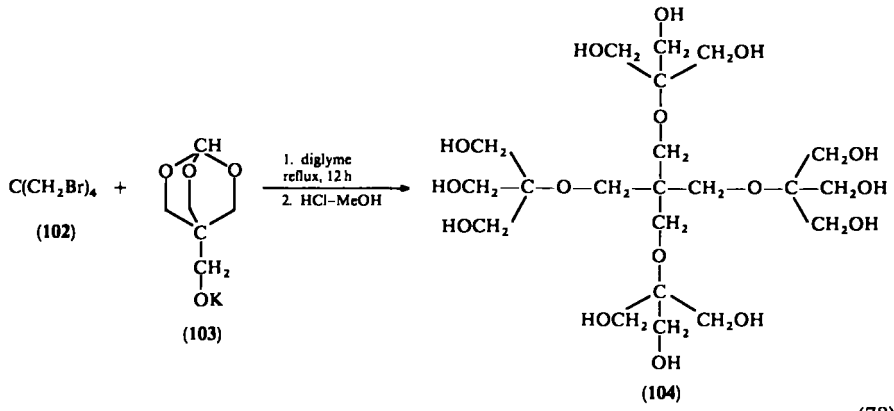
Diols can react to form linear and cyclic oligomeric and polymeric ethers. The most general method is the reaction of the dianions of dihydroxy compounds with dihalides (ditosylates)[630]. Recent modifications have the aim of achieving the unequivocal synthesis of homogeneous oligoethers by modifying the reaction conditions[631,632]. In a different approach, reductive cleavage of bis(cyclic acetals) with $BH_2Cl \cdot SMe_2$ permits the selective synthesis of chiral triether diols[633].

The importance of crown ethers as cation carriers explains the several review papers in this field[630,634,635], which also address their synthesis. Subsequent papers describe compounds with special structural features[636-638] or novel synthetic methods[639] (equation 77)[640]. Linear oligo- and polyethers can also be transformed to mixed oligoether-esters and polyether-esters[641,642].



One subclass of the new family of multibranched macromolecules (dendrimers, arborols)[643,644] comprises special polyethers. They are three-dimensional, highly ordered polymeric molecules, usually with a high number of hydroxy functions on their outer

surface. Their hyperbranched, globular structure is reminiscent of many important biomolecules[644]. In their divergent syntheses, an initiator core (**102**) is reacted with a protected repeating unit (**103**)[645] (equation 78). Deprotection leads to a first generation dendrimer (**104**). After conversion of the hydroxy groups to a reactive function (tosylation), the sequence can be repeated. Variations arise by using different cores and repeating units[645-648] and by applying a convergent method[649-651].

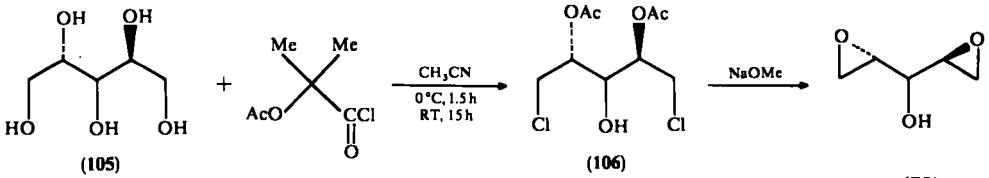


(78)

B. Selective Substitution

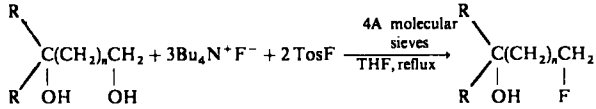
Several reagents are known to transform diols into haloalcohols. α,ω-Diols are selectively transformed to iodoalcohols with P_2I_4[652]. Certain diols that react with chlorine-containing reagents and PPh_3 undergo selective monochlorination. 3-Chloropropanol is formed if 1,3-propanediol is treated with PPh_3 + *t*-BuOCl[653]. $PPh_3 + CCl_4$ is used to prepare epoxides from 1,2-diols in the presence of K_2CO_3 (Section VI.D.2). If applied without the base, it transforms pinacol and *trans*-1,2-cyclohexanediol into the corresponding 2-chloroalcohols in 80 and 88% yields[654]. (*R*)-1,3-Butanediol has been transformed to (*R*)-2-hydroxy-4-bromobutane through the monomesylate with LiBr[655].

In the synthesis of the immunosuppressive agent FK-506, arabitol (**105**) selectively yields the dichloro diacetate **106**[656], which in turn is transformed to a diepoxide (equation 79).



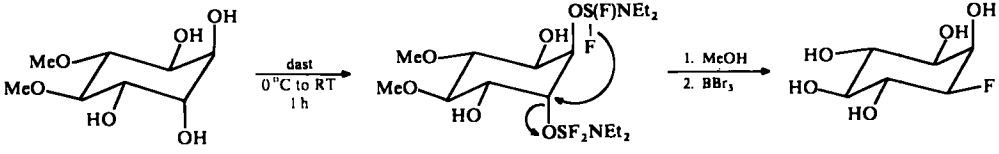
(79)

Selective monofluorination can be carried out according to equation 80[657]. (Diethylamido)sulphur trifluoride (dast) is used to synthesize selectively monofluorinated inositols[658,659] (equation 81)[660]. The selective reaction of the two axial hydroxy groups and the ready displacement of the activated hydroxy group in intermediate **107** explain the selectivity. Difluorination can also be accomplished with this reagent[660].



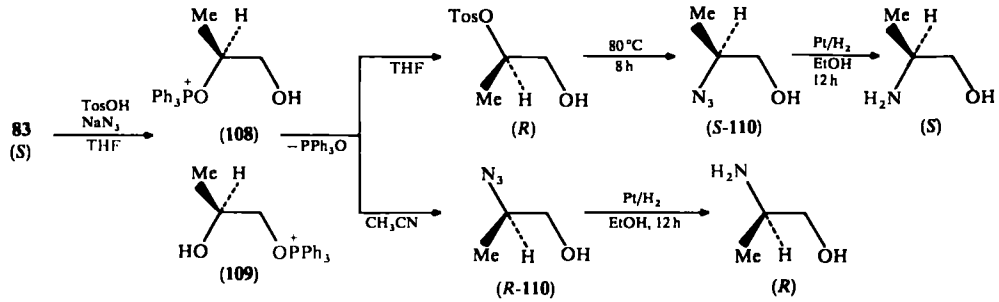
R = H, Me, Bu
n = 8, 9

(80)



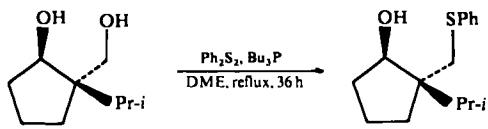
(81)

The versatile dioxaphospholane methodology of Evans has recently been used to achieve regioselective and stereospecific replacement of the secondary hydroxy group in primary–secondary 1,2-diols[661]. The multistep process starts with the synthesis of the 1,3,2λ^5-dioxaphospholane **83** from (*S*)-1,2-propanediol according to equation 54. If **83** is reacted with a mixture of TosOH and NaN_3 in THF, the isomeric oxaphosphonium ions **108** and **109** are formed, which are in equilibrium through a cyclic form (Scheme 10). Their further reaction takes place with exclusive substitution at $C_{(2)}$. In THF, the intermediate *S*-**110** is formed by the consecutive attack of $TosO^-$ and N_3^- ensuring double inversion (retention) (88%, 87% ee). In contrast, direct attack by N_3^- in acetonitrile results in inversion, with the formation of *R*-**110** (93%, 90% ee). Catalytic reduction eventually furnishes the two enantiomeric aminoalcohols.



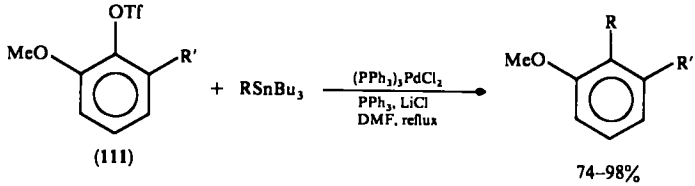
SCHEME 10

Highly selective amination of the primary hydroxy group in primary–secondary 1,3-alkanediols is carried out with diethyl *N*-Boc-phosphoramidate[662]. Hydroxythiols and thioethers can be prepared with thiourea[663] or with the Hata reagent (equation 82)[664].



(82)

2,6-Disubstituted phenol triflates (**111**) undergo an efficient Pd(0)-catalysed cross-coupling with $RSnBu_3$[665,666] (equation 83). Substitution of the R group for TfO leads to R-substituted diphenols and hydroxyphenols.



(111) 74–98% (83)

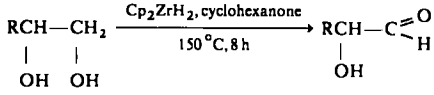
R′ = MeO, $MeOCH_2$
R = Me, Ph, allyl, vinyl

C. Selective Oxidation

The selective oxidation of one hydroxy group in di- or polyhydroxy compounds is a great challenge in organic synthesis. There are, however, selective oxidizing agents which can transform the primary hydroxy group in primary–secondary diols to yield hydroxy aldehydes, hydroxy carboxylic acids and lactones. The same diols can similarly be transformed to hydroxy ketones. Other selective reagents can produce dicarbonyl compounds.

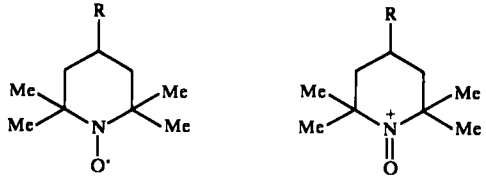
1. Oxidation to hydroxy carbonyl compounds

Zirconocene complexes in the presence of hydrogen acceptors catalyse the oxidation of primary–secondary 1,2-diols (equation 84) and 1,3-diols into hydroxy aldehydes[667]. OsO_4[668] exhibits similar selectivity. Reagents for the selective oxidation of the benzylic hydroxy group are $Fe + FeCl_2$ or $Cu + CuCl + FeCl_2$ with molecular oxygen in methanol[669], and Ag_2FeO_4[670]. Cu(I) or Cu(II) benzylic alcoholates are transformed with $Me_2N{-}O$ under anaerobic conditions[671]. Organic oxommonium salts (**113**) generated *in situ* from **112** are used to catalyse the oxidation of the primary hydroxy group with



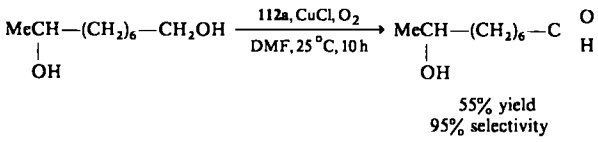
R = Me, Et, Ph 71–77% (84)

a co-oxidant [alkali metal hypochlorites[672,673], sodium bromite[674], oxygen and Cu(II) ions[675] (equation 85)] or by electrooxidation[676,677]



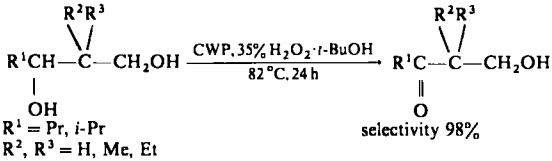
(**112a**) R = H
(**112b**) R = MeO
(**112c**) R = PhCOO

(**113**)

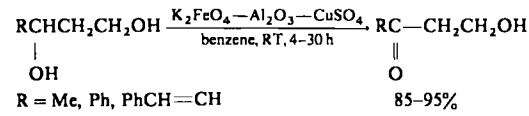


(85)

Hydrogen peroxide or *t*-butyl hydroperoxide together with peroxotungstophosphate[678], tris(cetylpyridinium) 12-tungstophosphate (CWP)[679] (equation 86) or tris(cetylpyridinium) 12-molybdatophosphate[680], $VO(acac)_2$[681], with $Mo(CO)_6$ + quaternary ammonium salts[682], or with a chromia-pillared montmorillonite catalyst[683], are used to transform primary–secondary 1,2- and 1,3-diols into hydroxy ketones. Other mild and selective reagents are Ce(IV) salts with $NaBrO_3$[684,685], NaOCl in acetic acid[686], and K_2FeO_4[687] (equation 87). A polypyridine ruthenium complex was used to catalyse the electrolytic oxidation of 1,2- and 1,3-butanediol[688]. Microbial oxidation with methanol yeast is also employed in the selective oxidation of diols and triols[689].



(86)

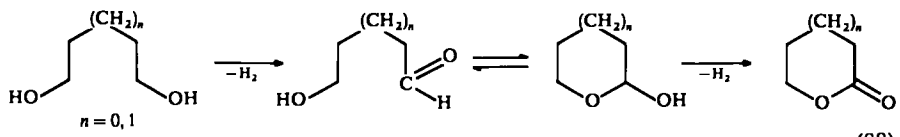


(87)

Some of the reagents mentioned above (zirconocene complexes[667], NaOCl + **112a** or **112b**[672], Cl_2 + **112b**[690]) are selective in the oxidation of diprimary and disecondary diols. OsO_4 selectively oxidizes the axial 7-hydroxy group in ethyl cholate[668].

2. *Oxidation to lactones and hydroxy carboxylic acids*

Diols bearing at least one primary hydroxy group can be transformed to lactones with high selectivity. The reaction is mainly characteristic of 1,4- and 1,5-diols. The selective dehydrogenation of the primary hydroxy is believed to occur in two steps through a hemiacetal intermediate[691–694] (equation 88). Selected examples of the transformations of 1,4-butanediol and 1,5-pentanediol are given in Table 15.



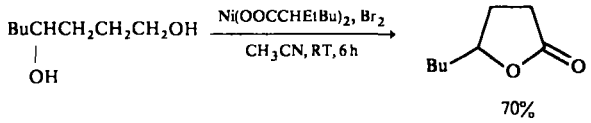
(88)

Besides the reagents indicated in Table 15, $BaMnO_4$[700], Ce(IV) salts with $NaBrO_3$[684], and electrolytic oxidation with RuO_2 in a two-phase system[701] are also very effective. Similar high conversions and selectivities can be achieved in the oxidation of primary–secondary diols[674,690–693,701,702] (equation 89)[703].

TABLE 15. Transformation of 1,4-butanediol and 1,5-pentanediol to the corresponding lactone

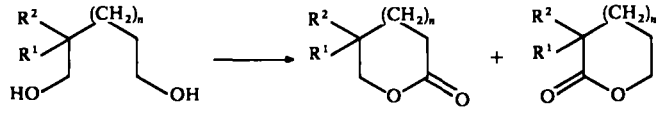
Reagent	Hydrogen acceptor	Reaction conditions	Conversion (%)	Selectivity (%)	Reference
		1,4-Butanediol			
$Pd(OAc)_2/PPh_3$	PhBr	85 °C, 12 h	74	100	695
$Ru_3(CO)_{12}$	Tolane	Diglyme, 145 °C	100	100	696
$RuH_2(PPh_3)_4$	Acetone	Toluene, 180 °C, 3 h	90	99	692
Pd/K-L zeolite		O_2,nmp, 118 °C, 24 h	99.4	91.5	697
CuO		200 °C, 15 h	95	80	698
N-Iodosuccinimide/AgOAc		5–7 h, in the absence of light	80–85[a]		694
$CWP + H_2O_2$		*t*-BuOH, reflux, 24 h	97	98	699
112a + LiOCl		CH_2Cl_2–H_2O, 10–15 °C	69[a]		672
112b + Cl_2		CH_2Cl_2, RT, 10 min	81[a]		690
112c + $NaBrO_2$		CH_2Cl_2–H_2O–$NaHCO_3$, RT, 3 h	95[a]		674
112c + NaBr[b]		CH_2Cl_2–H_2O	97[a]		677
$KMnO_4/CuSO_4$		CH_2Cl_2	58[a]		693
		1,5-Pentanediol			
$RuH_2(PPh_3)_4$	Acetone	Toluene, 180 °C, 2 h	86	95	692
Pd/K-L zeolite		O_2, nmp, 118 °C, 24 h	54.6[a]		697
CuO		230 °C, 10 h	85	41	698
N-Iodosuccinimide/AgOAc		5–7 h, in the absence of light	72–80[a]		694
$CWP + H_2O_2$		*t*-BuOH, reflux, 24 h	78	94	699
112b + LiOCl		CH_2Cl_2–H_2O, 10–15 °C	58[a]		672
112b + Cl_2		CH_2Cl_2, RT, 30 min	40[a]		690
112c + $NaBrO_2$		CH_2Cl_2–H_2O–$NaHCO_3$, RT, 3 h	94[a]		674
112c + NaBr[b]		CH_2Cl_2–H_2O	97[a]		677
$KMnO_4/CuSO_4$		CH_2Cl_2	85[a]		693

[a]Yield.
[b]Electrolysis.



(89)

Diprimary diols bearing alkyl (aryl) or bulky alkoxy[692] substituents on the $C_{(2)}$ atom undergo regioselective oxidation of the less hindered hydroxy group (equation 90, Table 16), the only exception being a palladium reagent[695]. Both the nature and the structure of the oxidizing agent may affect the selectivities.



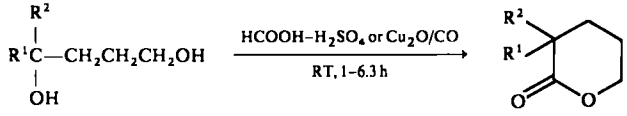
(90)

TABLE 16. Selectivity in the oxidation of **114** to lactone (equation 90)

Substituents in **114**						
n	R^1	R^2	Reagent	Yield (%)	**115:116** ratio	Reference
0	Me	H	$RuH_2(PPh_3)_4$[a]	94	93:7	704
			$RhH(PPh_3)_4$[a]	82	86:14	705
			$CWP + H_2O_2$	80	51:49	699
	Ph	H	$RuH_2(PPh_3)_4$[a]	90	97:3	704
			$RuCl_2(PPh_3)_3$[a]	98	77:23	
			$RhH(PPh_3)_4$[a]	100	85:15	705
			$CWP + H_2O_2$	82	78:22	699
	Me	Me	$Pd(OAc)_2/PPh_3$[a]	98.7	30:70	695
			$RuCl_2(PPh_3)_3$	94	95:5	706
			$RuH_2(PPh_3)_4$[a]	100	99.6:0.4	704
			$RhH(PPh_3)_4$[a]	95	98:2	705
			$Ni(OAc)_2 + Br_2$	95	58:42	707
			$Ni(OOCCHMeEt)_2 + Br_2$	82	93.3:6.7	
	Ph	Ph	$Ni(OAc)_2 + Br_2$	90	95.2:4.8	707
			$Ni(OOCCHMeEt)_2 + Br_2$	99	99:1	
1	Me	H	$RuH_2(PPh_3)_4$[a]	100	84:16	704
			$RhH(PPh_3)_4$[a]	86	73:27	705
	Ph	H	$RuH_2(PPh_3)_4$[a]	93	98:2	704
			$RhH(PPh_3)_4$[a]	57	79:21	705
	Me	Me	$Pd(OAc)_2/PPh_3$[a]	97.4	39:61	695
			$RuH_2(PPh_3)_4$[a]	100	99.5:0.5	704
			$RuCl_2(PPh_3)_3$[a]	88	95:5	
			$RhH(PPh_3)_4$[a]	95	91:9	705
			$CWP + H_2O_2$	96	83:17	699

[a]In the presence of a hydrogen acceptor.

The unique reaction illustrated in equation 91 allows formation of the homologue lactones from 1,4-diols[708].



(91)

R^1 = Me R^2 = alkyl
R^1—R^2 = $(CH_2)_4$, $(CH_2)_5$

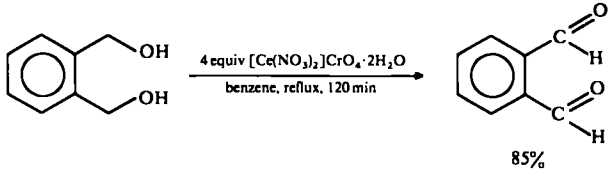
72–100%

If used in enantioselective oxidations, the chiral metal complex RhH[(−)-diop]$_2$ yields chiral lactones with very low enantioselectivity[705]. In contrast, enzymatic oxidation of cyclic dimethanols with horse liver alcohol dehydrogenase occurs with complete enantiotopic specificity[709,710]. The oxidation of the *S*-centre CH_2OH group was interpreted via a cubic-space model of the active site.

The higher diol homologues exhibiting much lower conversions and selectivities may yield polyesters under certain experimental conditions[696,698]. Glycerol[711] or 1,2-*O*-isopropylideneglycerol[712] can in turn be transformed to glyceric acid by selective electrooxidation.

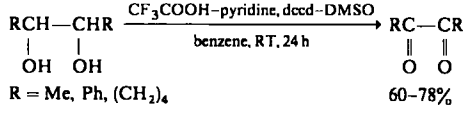
3. *Oxidation to dicarbonyl compounds*

The challenge in the oxidation of diprimary and primary–secondary diols is to avoid overoxidation to the carboxylic acid and to prevent C—C bond cleavage. Selective oxidation of benzylic hydroxy groups can be carried out with aqueous HNO_3[713] in a biphasic system, with (pyridine)$_4Ag_2Cr_2O_7$[714], by electrooxidation[676], or according to equation 92[715]. Trifluoroacetic acid in the form of its pyridinium salt[716] (equation 93) or as an activator of dimethyl sulphoxide[717,718] can produce diketones in high yields. Oxidations catalysed by oxoammonium salts (**113**) may also furnish dicarbonyl compounds[672,677]. Other methods involving the use of activated dimethyl sulphoxide (Swern and related oxidations) have been reviewed[718,719].



(92)

85%



(93)

R = Me, Ph, $(CH_2)_4$

60–78%

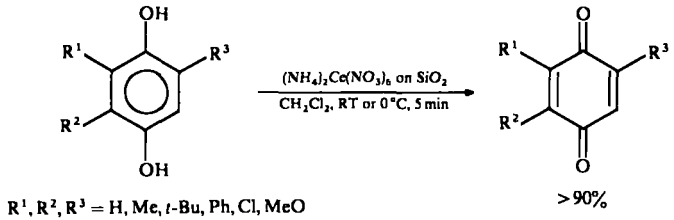
4. *Oxidation of diphenols to quinones*

There is a very wide choice of efficient oxidizing agents which allow the facile and convenient transformation of simple diphenols (catechol, hydroquinone) and their substituted derivatives to quinones (Table 17). Other reagents are NaOCl[730], Ph_2Se_2[731]

TABLE 17. Transformation of diphenols to quinones

Reagent	Reaction conditions	Yield (%)	Reference
	Catechol		
MnO_2 impregnated with HNO_3	CH_2Cl_2, RT, 15 min	68	720
$[Ce(NO_3)_2]CrO_4$	CH_2Cl_2, reflux, 12 min	100	721
CF_3COOH–pyridine + dccd–DMSO	Benzene, RT, 24 h	70	716
$(NH_4)_2Ce(NO_3)_6/SiO_2$	CH_2Cl_2, O °C, 5 min	91	722
	Hydroquinone		
$(PhSeO)_2O$	THF, RT	84	723
MnO_2	CH_2Cl_2, RT, 15 min	90	720
$[Ce(NO_3)_2]CrO_4$	CH_2Cl_2, reflux, 12 min	90	721
$Ce(OH)_3OOH$	Benzene, reflux, 5 min	90	724
$H_2O_2 + I_2$ or HI	MeOH or H_2O, RT, 4 h	93–97	725
112a + NaOCl	H_2O–CH_2Cl_2, 10–15 °C	95	672
Nicotinium dichromate	CH_2Cl_2–pyridine, RT, 15 min	90	726
$BnMe_3N^+Br_3^-$	CH_2Cl_2–H_2O, NaOAc, RT, 2 h	100	727
$(NH_4)_2Ce(NO_3)_6/SiO_2$	CH_2Cl_2, RT, 5 min	98	722
$(NH_4)_2Cr_2O_7/SiO_2$	CH_2Cl_2, RT, 5 min	96	
$PhI(OAc)_2$	CH_3CN–CH_2Cl_2, RT	94	728
$NaIO_4$ on SiO_2	H_2O–CH_2Cl_2, RT, 15 min	100	729

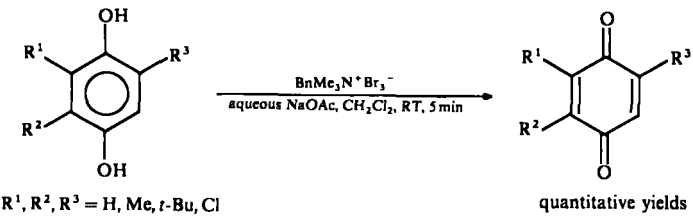
and $NaIO_4$[732], all used under phase-transfer conditions. Other hypervalent iodine oxides (PhIO, $PhIO_2$, Bu_4NIO_4)[732], dimethyldioxirane[733], and *t*-BuOOH + $RuCl_2(PPh_3)_3$[734] exhibit similar activity and selectivity. The two examples in equation 94[722] and equation 95[727] illustrate extremely mild conditions, very short reaction times and excellent yields.



R^1, R^2, R^3 = H, Me, *t*-Bu, Ph, Cl, MeO

>90%

(94)



R^1, R^2, R^3 = H, Me, *t*-Bu, Cl

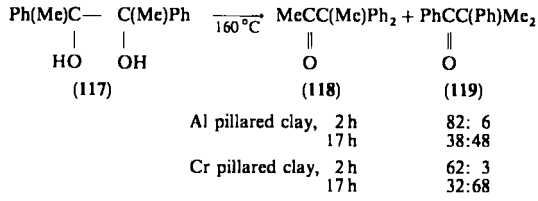
quantitative yields

(95)

D. Dehydration

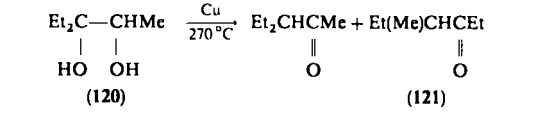
1. Formation of carbonyl compounds

a. Pinacol rearrangement of 1,2-diols. Studies of this old and well-known transformation still yield valuable and interesting results. Pillared clays and ion-exchanged montmorillonites as new catalysts have been found to exhibit excellent activities. Both Cr(III) and Al(III) montmorillonites lead to the near quantitative formation of 3,3-dimethyl-2-butanone from pinacol in dry media on thermal treatment[735–737]. A considerable rate enhancement is brought about by microwave irradiation[738]. Due to the interconversion of isomeric ketones (**118, 119**) formed from 2,3-diphenyl-2,3-butanediol (**117**), the transformation is less selective than dehydration in the liquid phase. The product distribution depends strongly on the acidity of the catalysts and the reaction conditions[735–737] (equation 96). Other acidic catalysts, such as $AlPO_4$–Al_2O_3[739], Nafion–H[740], DMSO in catalytic amounts[741] or zeolites[742–744], may also be employed. An analysis of the reactivities and product distributions of *racemic* and *meso*-2,3-butanediols and 2-methyl-2,3-butanediol on zeolites has revealed differences in the mechanism of dehydration[744]. Interesting results on the intramolecular and intermolecular dehydrations of ethylene glycol (formation of acetaldehyde vs. 1,4-dioxane) were observed on different acidic catalysts[745].



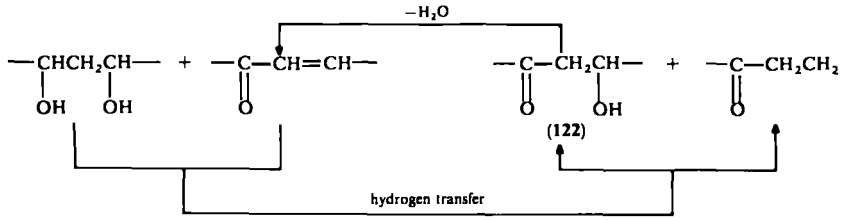
(96)

Other, non-acidic reaction conditions may also lead to the formation of carbonyl compounds. Examples are the transformation of *cis*-1,2-cyclohexanediol monomesylate to cyclohexanone in the presence of a base[746], and the reaction of tetraaryl glycols to carbonyl compounds on the action of chlorosulphonyl isocyanate[747]. The dehydration of 3-ethylpentane-2,3-diol (**120**) to **121** is the first example of a 1,2-bond shift isomerization on copper (equation 97)[748].



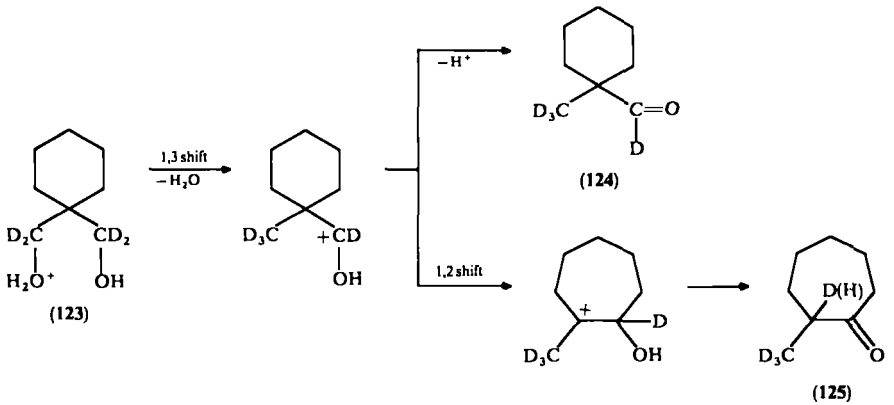
(97)

b. Transformation of other diols. The formal dehydration of 1,3-diols to yield carbonyl compounds on different copper catalysts[749,750] and on other metals (Ag, Co, Rh)[749,751] has been proved to proceed via dehydrogenation/hydrogen transfer and dehydration of the intermediate β-hydroxy carbonyl compounds (**122**) (Scheme 11). The results of the transformation of labelled compounds[752], in association with kinetic data, support this mechanism and explain the large difference in the reactivities of 1,2- and 1,3-diols on copper[753]. The dehydration of 1,3-diols in the presence of $RhCl_3/PPh_3$ under homogeneous conditions proceeds through the same steps[751].



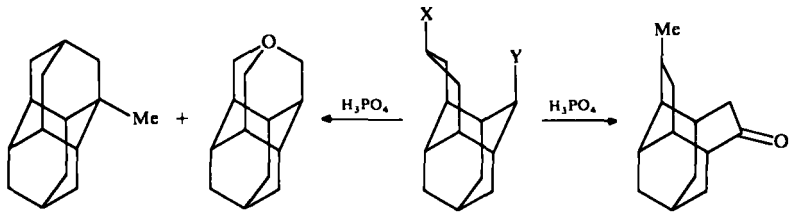
SCHEME 11

A recent study described the sulphuric acid-catalysed dehydration of 1,1-bis(hydroxymethyl)cycloalkanes to isomeric carbonyl compounds, formed mainly with ring enlargement[301]. A correlation was observed between the relative stabilities of carbenium ions and cycloalkane rings, these determining the product distributions. The transformation of 1,1-bis(dideuterohydroxymethyl)cyclohexane (**123**) under kinetic control furnished evidence of a 1,3-hydride shift yielding the labelled products **124** and **125** (Scheme 12).



SCHEME 12

Higher diol homologues rarely produce carbonyl compounds during dehydration. As an exception, **126a**, one of two isomeric homodiadamantane 1,6-diols, affords the ketone **127** as the sole product, formed via skeletal rearrangement[327] (equation 98).

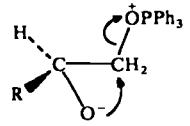


(98)

2. Formation of oxacycloalkanes

1,2- and 1,3-diols cannot usually be transformed directly to oxiranes and oxetanes, respectively, by the elimination of water[111]. 1,2-Epoxycyclohexane, however, is formed in the presence of $PPh_3 + CCl_4 + K_2CO_3$[645,754], while ethylene glycol is uniquely transformed to 1,4-dioxane[745,755–757].

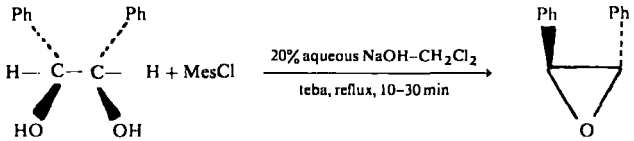
In general, cyclic intermediates formed by the action of *N,N*-dimethylformamide dimethylacetal[758,759], diethyl azodicarboxylate[759,760] or diethyl carbonate[761] are decomposed to the corresponding oxacycloalkanes. Among such reagents, different phenylphosphoranes have been studied in detail[490,762–766]. In the transformation of (*S*)-1,2-propanediol and (*S*)-2-phenylethane-1,2-diol, the predominant retention at $C_{(2)}$ results in the formation of the corresponding (*S*)-oxiranes. Steric considerations show that the intramolecular displacement of Ph_3PO at the primary carbon in **130**, one of the two possible betain intermediates, is kinetically favoured[766,767].



R = Me, Ph

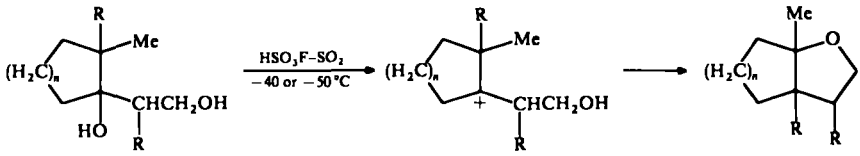
(**130**)

A new, useful modification of the more general method of 1,3-elimination of diol monosulphonates in the presence of a base[111] is a one-pot synthesis with a phase-transfer catalyst (equation 99)[768]. A variation of the well-known HBr/AcOH method[769] makes use of 2-acetoxybenzoyl bromide, thereby allowing the transformation of diols that tend to form a carbenium ion[770]. Chloroacetates (**106**) prepared from diols in a selective transformation are reacted under basic conditions to form epoxides[656] (equation 79). BuLi + TosCl is applied to prepare oxetanes from 1,3-diols[771].



(99)

The superacid-catalysed dehydration of the primary–tertiary 1,3-diols **131** leads to the tetrahydrofuran derivatives **133**[772] (equation 100). Detailed NMR studies have revealed the involvement of tertiary carbenium ions (**132**) and hydride (methyl) shifts in the transformation.



(**131**) R = H, Me
$n = 1, 2$

(**132**)

(**133**)

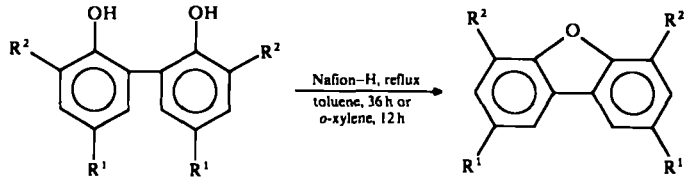
(100)

There have been a plethora of methods for the cyclodehydration of higher diol homologues. Characteristic examples are presented in Table 18. Additionally, TosOH in CH_2Cl_2[777], $HClO_4$ in methanol[778] and DMSO + Me_3SiCl[779] are used for the

cyclodehydration of primary–tertiary 1,4-diols, while $PPh_3 + t$-BuOCl[653] and $PPh_3 + CCl_4$[754,767] are applicable only for simple 1,4-diols.

A comprehensive study of the stereochemistry and the mechanism of cyclodehydration of *racemic* and *meso*-2,5-hexanediols on the action of various dehydrating agents proved the generality of the intramolecular S_N2 mechanism for acid-catalysed ring closure[776]. Certain Lewis acids, and conc. H_2SO_4 and HMPT, however, bring about different degrees of racemization. Dimethyl sulphoxide applied in a catalytic amount was found to be an excellent agent for the production of oxacycloalkanes in good yields[741]. Both the direct action of the reagent and proton catalysis have been demonstrated.

A recent paper supplies a new example of the specific activity of Nafion-H in dehydrations[780]. In contrast with older methods requiring long reaction times, elevated temperature and the use of excess acid in cyclodehydration of diphenols (**134**), Nafion-H ensures high yields under mild conditions in a short time (equation 101). Interestingly, loss of the substituents occurs in the transformation of the *t*-Bu-substituted compounds.

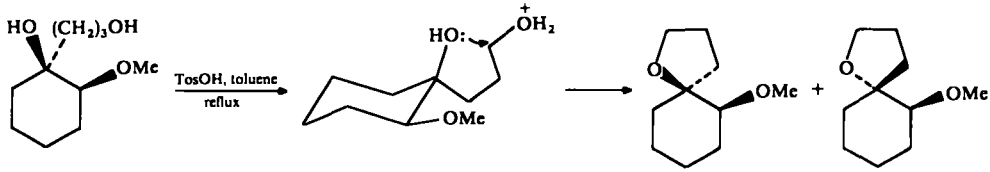


(134)

$R^1, R^2 = H, Me$

40–96% (101)

In contrast with the transformation of the 1,3-diols **131**, which takes place via the tertiary carbenium ion **132** (equation 100), the dehydration of similar 1,4-diols displays a remarkable departure from the expected chemical reactivity of the two hydroxy groups[781]. Under appropriate reaction conditions, the α-heteroatom-substituted diol **135** is transformed via selective displacement of the primary hydroxy group (**136**), resulting in almost complete retention (equation 102).



(135) (136) 96:4 (102)

Of the isomeric homodiadamantane 1,6-diols, isomer **126b** exhibits a normal water loss, behaviour strikingly different from that of **126a**[327]. **126b** gives a mixture of compounds, with two main components, **129** being the only product formed without a rearrangement (equation 98).

The oxidative cyclization of *cis*-2-butene-1,4-diols to furans is a special dehydration. It is catalysed by pyridinium chlorochromate[782], or is carried out in the presence of $Pd(OAc)_2 + Cu(OAc)_2 + O_2$[783].

Few papers deal with the dehydration of polyols. In boiling 3 M H_2SO_4 or on the action of an ion-exchange resin, D-glucitol and D-mannitol yield the corresponding 1,4-anhydro and 1,4:3,6-dianhydro compounds[784]. The transformation of 1-deuterio-D-mannitol proves that an S_N2 mechanism is operative. In the dehydration of four hexitols

TABLE 18. Cyclodehydration of higher diol homologues

Compound	Reaction conditions (catalyst, temperature)	Product	Isolated yield (%)	Reference
1,4-Butanediol	HMPT, 220 °C	Tetrahydrofuran	83	756
	$BuSnCl_3$, 150–190 °C		94	773, 774
	Nafion-H, 135 °C		91	755
	Al(III) montmorillonite, 200 °C		100	757
	Al(III) montmorillonite, 180 °C		95	775
	$AlPO_4$–Al_2O_3		94	739
	DMSO, 180 °C		100	741
	Bis(neopentyloxy)triphenyl-phosphorane, 40 °C		99	764
	Diethoxydiphenylpolystyryl-phosphorane		99	490
1,5-Pentanediol	HMPT, 220 °C	Tetrahydropyran	89	756
	$BuSnCl_3$, 150–210 °C		98	773, 774
	Nafion-H, 135 °C		86	755
	Al(III) montmorillonite, 200 °C		95	757
	$AlPO_4$–Al_2O_3		80	739
	DMSO, 195 °C		100	741
	NaHY zeolite, 300 °C		95	743
	Bis(neopentyloxy)triphenyl-phosphorane, 40 °C		95	764
	Diethoxydiphenylpolystyryl-phosphorane		85	490

1,6-Hexanediol	HMPT, 220 °C	Oxepane	10	756
	$BuSnCl_3$, 200–230 °C		40	773
	Nafion-H, 135 °C		72	755
	$AlPO_4$–Al_2O_3		60	739
1,7-Heptanediol	Nafion-H, 135 °C	Oxocane	51	755
2,5-Hexanediol	$BuSnCl_3$, 150–200 °C	*cis*- and *trans*-	98	773
(isomeric mixture)	Nafion-H, 135 °C	2,5-dimethyloxolane	91	755
	$AlPO_4$–Al_2O_3	(isomeric mixture)	84	739
	DMSO, 195 °C		95	741
	NaHY zeolite, 300 °C		94	743
racemic 2,5-Hexanediol[a]	DMSO, 190 °C	98:2	100	776
	NaHY zeolite, 300 °C	96:4	100	743
meso-2,5-Hexanediol[a]	DMSO, 190 °C	2:98	100	776

[a]Isomer purity: 98%.

(galactitol, D-glucitol, D-mannitol, L-iditol) at higher temperature (200 °C), a mixture of 10 mono- and dianhydro compounds was isolated and they were identified[785]. All monoanhydro compounds except the 2,5-anhydro derivative retained the original configurations. The favourable arrangement of bulky substituents allowed the selective formation of 1,4-anhydro-D,L-glucitol (99%) and 1,4-anhydro-L-iditol (96%).

1,4-Anhydro compounds are the main products on Raney copper catalysts modified with the deposition of different metals to poison the dehydroxylation activity[786,787], and also on a sulphur-modified Ru catalysts[788]. 1,4-Anhydroerythritol and 1,4:3,6-dianhydro-D-glucitol were prepared with the highest selectivities.

3. *Transformation to other compounds*

1,2-Eliminations leading to the formation of unsaturated alcohols and dienes are characteristic of diols with tertiary hydroxy groups; they are brought about with acidic reagents such as $BuSnCl_3$[789], zeolites[743,790], DMSO[741], montmorillonite[791] and superacids[772,792]. A mild dehydration using 1,1,1-trifluoroacetone in the presence of TosOH transforms 1,4-cyclohexanediol to 1,4-cyclohexadiene in 92% yield[793]. Such eliminations are often side-reactions in cyclodehydrations[741,765,779]. In most cases, mixtures of isomeric unsaturated alcohols and dienes are formed. 2,4-Pentanediol, however, yields dienes in high selectivity on NaX zeolite[790] (equation 103). Terpene diols can also form aromatic compounds[739,757,775].

$$\underset{\substack{|\\OH}}{MeCHCH_2}\underset{\substack{|\\OH}}{CHMe} \xrightarrow[300\,^\circ C]{NaX\ zeolite} MeCH{=}CHCH{=}CH_2 + CH_2{=}CHCH_2CH{=}CH_2 \qquad 95\%\ selectivity \qquad (103)$$

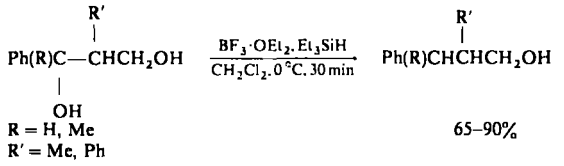
N,N-Dimethylformamide dimethylacetal can be used to transform 1,3- and 1,4-diols to unsaturated alcohols. The method is regiospecific for 1,3-diols producing α,β-unsaturated alcohols through the loss of an axial hydroxy group in cyclic diols[794]. 1,4-Diols yield a mixture of unsaturated alcohols[795].

E. Deoxygenation

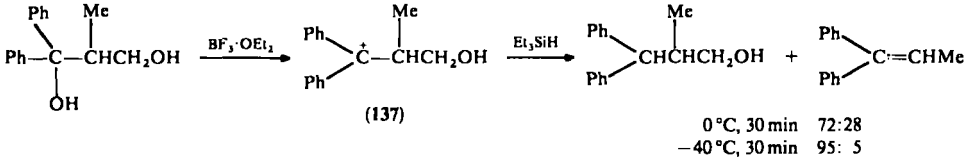
1. *Replacement of hydroxy groups with hydrogen*

Virtually all of the methods surveyed in this subsection are unique transformations. The only exception is the use of tributyltin hydride. This can be used for the monodeoxygenation of vicinal diols via the cyclic thiocarbonate in a radical process[769–798]. Regioisomers may be formed from disecondary diols. The reaction conditions may also affect the product distributions[797]. This is an especially attractive reaction for the deoxygenation of sterically hindered compounds, mainly carbohydrates[796].

The selective reduction of the secondary or tertiary benzylic hydroxy groups of 1,3-diols in the presence of a primary hydroxy group can be carried out in high yields with the $BF_3{\cdot}OEt_2 + EtSiH_3$ reagent[799] (equation 104). A possible explanation to account for the alkene by-product is the formation of the intermediate carbenium ion **137** (equation 105). It is either trapped by Et_3SiH to yield the deoxygenated product alcohol, or it may participate in a two-step elimination process to give the alkene. Phenylethylene glycol, a 1,2-diol, exhibits a much lower reactivity and gives a lower yield (64% after 20 h reaction at room temperature).



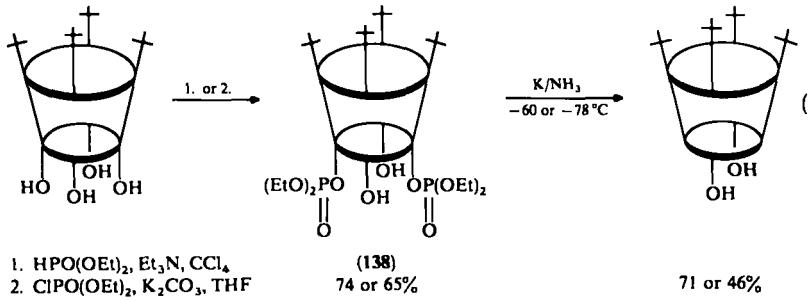
(104)



(105)

The TfO group in **111** (equation 83) is uniquely replaced by hydrogen if tetrabutyltin is used as the reagent[666].

Partially or totally hydroxy-depleted calixarenes are prepared in a two-step process. The loss of the phosphate ester groups in the selectively 1,3-bis-substituted *p*-*t*-Bu-calix[4]arene (**138**) has been achieved with potassium in liquid ammonia[800,801] (equation 106). A similar process was used to remove all hydroxy groups from *p*-*t*-Bu-calix[4]arene and *p*-*t*-Bu-calix[8]arene[802].



(106)

$HCo(CO)_4$ catalyses the high-selectivity hydrogenolysis of symmetric diaryl-1,2-diols to diarylethanes[803]. A multistep pathway was proposed, involving a 1,2-hydride shift of the initially formed carbenium ion, followed by C=O hydrogenation and C—O hydrogenolysis.

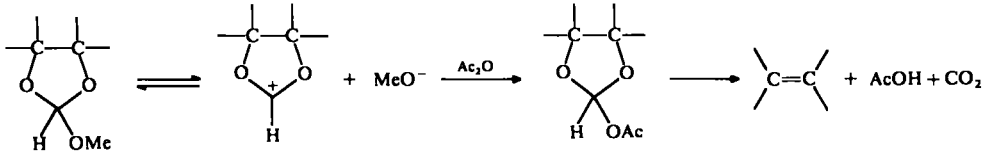
2. *Bis-deoxygenation of 1,2- and 1,3-diols*

A number of methods have been developed for the regio- and stereoselective deoxygenation of 1,2-diols to alkenes[583,796,798]. The majority of the processes require transformation of the diol to an activated group. This is frequently a cyclic derivative which is subsequently converted to the alkene by *syn* elimination. A comprehensive review[583] surveys the data up to 1984.

The decomposition of thiocarbonates of 1,2-diols to alkenes, often termed the Corey–Winter reaction, occurs on heating in $(MeO)_3P$[551] or $(EtO)_3P$[804]. A useful modi-

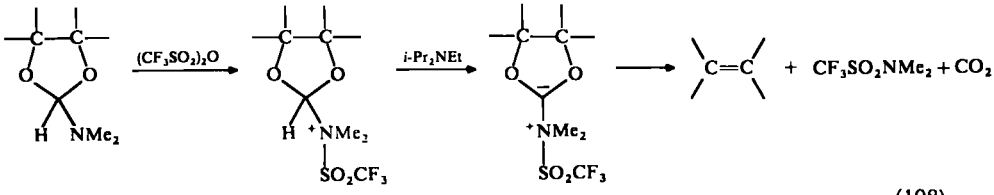
fication avoids long, high-temperature treatment by applying 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine[805]. The stereospecific formation of alkenes in high yields is achieved at low temperature (40 °C, 2–24 h, 70–94%).

The treatment of cyclic orthocarboxylic acid derivatives (2-alkoxy- and 2-acyloxy-1,3-dioxolanes) at elevated temperature in the presence of carboxylic acids (Eastwood deoxygenation) leads to alkenes in excellent yields in most cases[583,806,807]. Mechanistic studies indicate that 2-alkoxy-1,3-dioxolanes, formed in the reaction of the diol with methyl or ethyl orthoformate, are transformed through the carbenium ion **139** in acetic anhydride[583,806] (equation 107). The intermediate is captured by AcO^- to form **140**, which in turn decomposes thermally to the products.



(139) (140) (107)

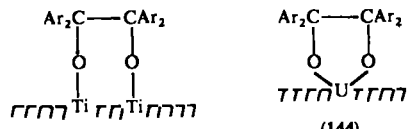
2-Dialkylamino-1,3-dioxolanes can likewise decompose to alkenes in the presence of MeI or Ac_2O[583]. It has been found that trifluoromethanesulphonic anhydride allows extremely mild reaction conditions[808]. In the intermediate (**141**), the acidity of the 2-hydrogen is greatly enhanced (equation 108). The facile removal of this proton by the hindered amine applied yields the ylide **142**, which furnishes the alkene end-product in a concerted process. The isomerization of *trans*- and *cis*-stilbene formed from *racemic* and *meso*-hydrobenzoin, respectively, was not observed under these conditions.



(141) (142) (108)

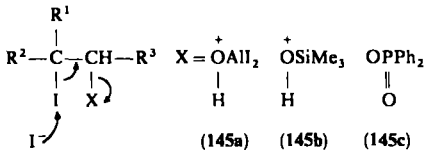
One-step procedures not requiring use of the cyclic diol derivatives are also known. The most widely used method is deoxygenation induced by low-valent titanium[138,139,142,583]. It is frequently carried out with the $TiCl_3 + K$ reagent. $TiCl_3 + LiAlH_4$[809,810] and $TiCl_3$ + potassium graphite[811] have recently been applied in the deoxygenation of complex organic molecules. The active species is believed to be Ti(0).

The titanium-induced deoxygenation is closely connected to the well-known reductive carbonyl coupling reactions pioneered mainly by McMurry[138,139]. A viable intermediate in both the coupling and the deoxygenation processes is the titanium-bound surface pinacol species **143**[139,812]. Studies with an active uranium powder prepared by the reduction of UCl_4 indicate the formation of similar surface-bound species, but with different stoichiometry (**144**)[813].



(143) (144)

Several other novel reagents have been developed for the one-step deoxygenation of 1,2-diols. These are AlI_3[814], $Me_3SiCl + NaI$[815] and $Ph_2PCl + I_2 +$ imidazole[816]. All reagents give high yields at room temperature. The former two can be used in the stereospecific deoxygenation of secondary–tertiary and allylic bis-secondary 1,2-diols. In both cases the formation of positively charged intermediates (**145a, 145b**) was suggested, via the OH/I exchange of the more reactive hydroxy group. They are subsequently transformed to the olefin through attack by I^-. A similar intermediate, the iodo diphenylphosphinate **145c**, was isolated when $Ph_2PCl + I_2$ was applied in the presence of imidazole[816].

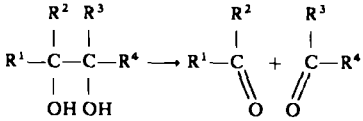


Only two examples are known of the deoxygenation of 1,3-diols furnishing a cyclopropane ring. The transformation is achieved by reacting the diols with $TiCl_3 + LiAlH_4$[817], or by electroreduction of the corresponding dimesylates[299].

F. Transformation with C—C Bond Cleavage

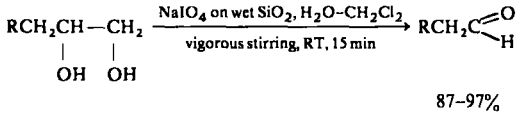
1. Oxidative cleavage of 1,2-diols

The oxidative cleavage of 1,2-diols is a key reaction in the determination of the structure of various polyhydroxylated substances. Oxidation involving cleavage of the C—C bond of the vicinal glycol subunit leads to two carbonyl compounds[818] (equation 109). If $R^2 = R^3 = H$, the intermediate aldehydes formed may be further oxidized to carboxylic acids under suitable reaction conditions.



(109)

The transformation is carried out with stoichiometric reagents, or catalytic systems may be applied. The two traditional stoichiometric oxidants are $NaIO_4$ in an aqueous solution and $Pb(OAc)_4$ in an organic solvent. Improvements of the former make use of phase-transfer catalysis[819] or a three-phase system with powdered[820] or supported[729] reagent (equation 110).



(110)

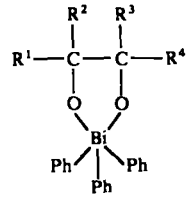
Examples of the use of other stoichiometric oxidizing agents in the cleavage of 1,2-diols are to be found in Table 19. Most of the reagents exhibit high activity in the transformation of all types of 1,2-diols. In contrast, pyridinium chlorochromate[822] is not active in the cleavage of ditertiary diols, while $[(NO_3)_3Ce]_3H_2IO_6$ can oxidize only diols bearing primary and secondary hydroxy groups[824].

TABLE 19. Oxidative cleavage of 1,2-diols with stoichiometric oxidants

Substrate	Product	Oxidant (molar ratio) Reaction conditions	Yield (%)	Reference
MeCH(OH)CH(OH)Me	MeCHO	*N*-Iodosuccinimide (0.54) THF, RT, 1 h[a]	80–86	821
cis-1,2-Cyclohexanediol	Adipaldehyde	Pyridinium chlorochromate (2) CH_2Cl_2, 25 °C, 1.5 h	79	822
	Adipic acid	$NaBO_3 \cdot 4H_2O$ (10) AcOH, 100 °C, 3 h	40	823
$Me_2C(OH)C(OH)Me_2$	Acetone	*N*-Iodosuccinimide (0.54) THF, RT, 1 h[a] or 30 min[b]	90–94	821
$PhCH(OH)CH_2OH$	PhCHO	$[(NO_3)_3Ce]_3H_2IO_6$ (2) Benzene, reflux, 1.5 h	95–100	824
		N-Iodosuccinimide (0.54) THF, RT, 3 h[a]	95–98	821
$PhCH(OH)CH_2OH$	PhCOOH	$NaBO_3 \cdot 4H_2O$ (10) AcOH, 100 °C, 3 h	60	823
PhCH(OH)CH(OH)Ph	PhCHO	Pyridinium chlorochromate (2) CH_2Cl_2, 25 °C, 1.5 h	98	822
		$Co(OAc)_3$ (2) AcOH, 50 °C, 1.5 h	93	825
		$[(NO_3)_3Ce]_3H_2IO_6$ (2) Benzene, reflux, 1.5 h	90–95	824
		Ph_3BiO (1.1–2) CH_2Cl_2, 40 °C, 1.5 h	97	826
PhCH(OH)CH(OH)Ph	PhCOOH	$NaBO_3 \cdot 4H_2O$ (10) AcOH, 100 °C, 3 h	88	823
$Ph_2C(OH)C(OH)Ph_2$	Ph_2CO	$Co(OAc)_3$ (2) AcOH, 50 °C, 70 h	100	825
		N-Iodosuccinimide (0.54) THF, RT, 15 min	90–98	821

[a]In the dark.
[b]With irradiation.

Catalytic systems which use a reoxidant to recycle a variable valence state ion are also known. Of the different catalytic systems presented in Table 20, the organobismuth reagents have been most studied[826,830,831]. In the reactions involving stoichiometric pentavalent bismuth(V) reagents, a cyclic organobismuth intermediate (**146**) was postulated, which breaks down to yield the carbonyl compounds and Ph_3Bi[826]. This

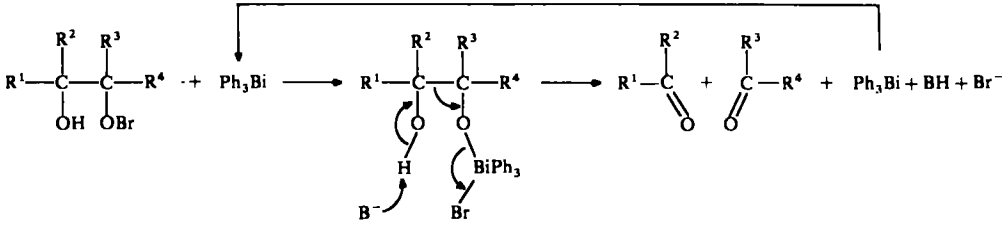


(146)

TABLE 20. Catalytic oxidative cleavage of 1,2-diols

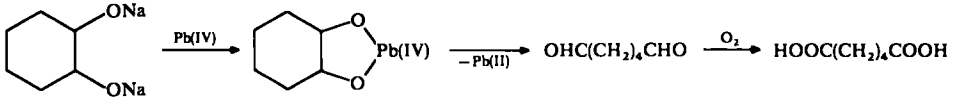
Substrate	Product	Catalyst, oxidant (molar ratio) Reaction conditions	Yield (%)	Reference
MeCH(OH)CH(OH)Me	MeCOOH	Na_2WO_4–H_3PO_4 (0.04), 40% aq. H_2O_2 (2–4) 90 °C, pH = 2, 5 h	87	827
trans-1,2-Cyclohexanediol	Adipic acid	$MoO_2(acac)_2$ (0.1), *t*-BuOOH Chlorobenzene, 60 °C, 24 h	79	828
$Me_2C(OH)C(OH)Me_2$	Acetone	$[VO(acac)_2]$ (0.15), *t*-BuOOH Benzene, 70 °C, overnight	79	829
		Ph_3Bi (0.01), NBS CH_3CN–1% H_2O, K_2CO_3, RT, 1.5 h	100	830
$PhCH(OH)CH_2OH$	PhCOOH	Na_2WO_4–H_3PO_4 (0.04), 40% aq. H_2O_2 (2–4) 90 °C, pH = 2, 5 h	87	827
PhCH(OH)CH(OH)Ph	PhCHO	Ph_3Bi (0.1), NBS CH_3CN–1% H_2O, K_2CO_3, RT, 10–25 min	76–80	831
$Ph_2C(OH)C(OH)Ph_2$	Ph_2CO	$MoO_2(acac)_2$ (0.1), *t*-BuOOH Chlorobenzene, 60 °C, 24 h	96	828
		Moperoxide (0.16), DMSO Toluene, reflux	89	504
		$[VO(acac)_2]$ (0.15), *t*-BuOOH Benzene, 70 °C, 40 h	100	829
		Ph_3Bi (0.1), NBS CH_3CN–1% H_2O, K_2CO_3, RT, 2 h	100	831

mechanism is closely related to that of periodic acid glycol cleavage. In the catalytic system (Ph_3Bi, NBS, CH_3CN, K_2CO_3 with 1% water), the insertion of Ph_3Bi into hypobromite **147**, originating from the reaction of the diol with NBS, generates the pentavalent intermediate **148**[831] (equation 111). Fragmentation of the latter provides the product carbonyl compounds.



(147) (148) (111)

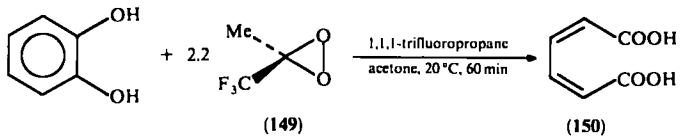
Catalytic systems utilizing molecular oxygen to reoxidize the catalyst have recently been studied in detail. Expanded lattice ruthenium pyrochlore oxide catalysts with the general formula $A_{2+x}Ru_{2-x}O_{7-y}$ (A = Pb or Bi) have proved to be active and selective in the low-temperature oxidation of 1,2-cyclohexanediols in strongly basic solution[832,833]. Combined mechanistic and surface studies indicate that the overall six-electron oxidative cleavage takes place on the action of a Pb(IV) species to yield adipaldehyde[833] (equation 112). Ruthenium serves to reoxidize the catalyst through electron transfer to oxygen. Adipaldhyde is eventually oxidized by way of free radical processes to provide adipic acid.



(112)

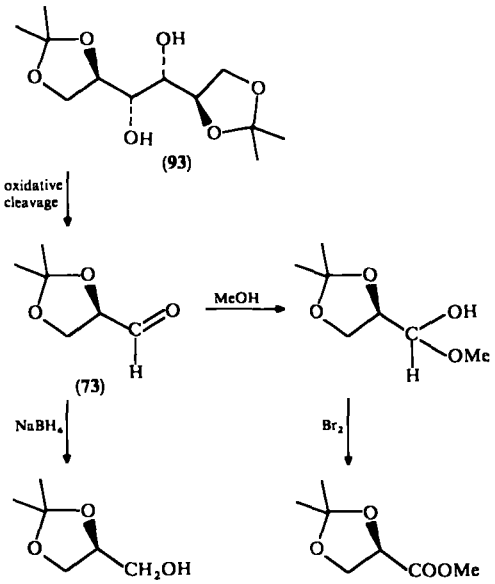
Other less general processes include the use of K_2O[834] and Ce(III)-exchanged zeolites[835]. Polycyclic secondary–tertiary diols are transformed to keto acids with the Jones reagent[836].

The oxidative cleavage of 1,2-diols is an important enzymatic process in the metabolism of certain compounds. This has stimulated the use of iron complexes in the oxidative cleavage. Tetraaryl glycols are readily cleaved with tris(1,10-phenanthroline)iron(III) complexes[172]. Iron(III) porphyrin complexes have been employed to carry out the visible light photolysis[837], photocatalytic[838] or oxidative cleavage with molecular oxygen[839,840] of aryl glycols. The latter process serves as a biomimetic oxidation to simulate cytochrome P-450. For a similar reason, to mimic the action of certain enzymes, the oxidative cleavage of catechol to (*Z*,*Z*)-muconic acid (**150**) was also studied. CuCl[841,842] or bis(2,6-dicarboxylato)iron(II)[843] with oxygen, and $Fe(OAc)_3$ with peroxyacetic acid[844] are active in the process. The very effective methyl(trifluoromethyl)dioxirane (**149**) has recently been employed in this transformation[845] (equation 113).



(149) (150) (113)

Many oxidizing agents are used in the synthesis of glyceraldehyde. In most cases, 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**93**), prepared according to equation 67, is oxidized. Besides the usual reaction conditions ($NaIO_4$[401,403,846–848], $Pb(OAc)_4$[402,403]), solid $NaIO_4$[579,729,820] is also used. Organobismuth reagents[826,830,831] and H_5IO_6[404] are likewise effective. Instead of the isolation of **73**, in many cases *in situ* reduction or oxidation provides glycerol[401,403,404,846,848] or glyceric acid[847] derivatives, respectively (Scheme 13). Electrolytic oxidation at a Ni(III) oxide hydroxide electrode in aqueous alkaline solution directly produces the potassium salt or the methyl ester of the protected glyceric acid[849].



SCHEME 13

2. Other reactions taking place with C—C bond cleavage

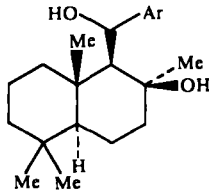
A homogeneous Ru catalyst hydrogenates fructose to mannitol and glucitol at 100 °C and 20 atm[850]. Addition of KOH results in a dramatic improvement in the selective hydrocracking to glycerol under milder reaction conditions (50 °C, 1 atm). Glycerol yields are comparable to those achieved with heterogeneous catalysts. A retro-aldol condensation leading to glyceraldehyde and hydroxyacetone, and subsequent hydrogenation of the carbonyl group, were proposed in the interpretation of the results. A fermentation process by the bacterium *Clostridium thermosaccharolyticum* transforms D-glucose to (*R*)-(−)-1,2-propanediol with >99% ee[851].

Retro-aldol condensation was assumed in the ruthenium-catalysed hydrogenolysis of sorbitol in basic medium, yielding compounds containing two and three carbon atoms[852]. Recent detailed studies on different metals (Ru, Ni, Rh, Ir, Cu) and on a whole range of polyols disclosed a more complicated picture. Transition metals result in drastic hydrogenolysis, with the formation of methane[853,854]. In contrast, no hydrogenolysis was observed on Raney copper. Here, dehydroxylation, retro-Claisen condensation and benzylic rearrangement are invoked to explain the formation of C_2—C_4 diols, triols

and tetrols[787,853,854]. Certain copper catalysts exhibit high selectivity in the formation of 1,2-propanediol and glycerol. The formation of glycerol from sorbitol was explained by the retro-Michael reaction[853,854]. A sulphur-modified Ru catalyst displayed behaviour very similar to that of Raney copper[788]. If such activities of Raney copper are poisoned, selective dehydration becomes the characteristic transformation (See Section VI.D.2).

C—C bond cleavage can occur as a side-reaction in the copper-catalysed dehydration of 1,3-diols. The intermediate β-hydroxy carbonyl compounds (**122**) (Scheme 11) may undergo a thermally induced or catalytic retro-aldol reaction, yielding two carbonyl compounds containing a smaller number of carbon atoms[753]. The reaction conditions[750] and the properties of the catalysts[749,753] affect the product distributions. The most important factor, however, is the structure of the reacting diols. Bulky substituents on $C_{(2)}$[855] and increasing substitution of the molecule[753] increase the probability of C—C bond cleavage. Similar correlations were found for the transformations of 1,3-diols on zeolites[743,790].

In the drimanic diol (**151**), a benzylic hydroxy group exhibited highly reactive nucleophilic leaving group behaviour. As a result, a remarkably facile 1,3-diol fragmentation leading to an unsaturated ketone was observed[856].

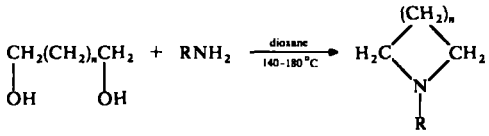


Ar = 3,5-dimethoxyphenyl

(151)

G. Transformation of Diols with Mono- and Diamines

Ruthenium complexes catalyse the transformations of different diols with aliphatic and aromatic primary amines to monoazacycles. Following early observations[857], recent detailed studies have revealed certain regularities. 1,2-Diols react with substituted anilines in the presence of $RuCl_2(PPh_3)_3$ to yield indole derivatives[858]. A similar transformation of 1,3-propanediol and 1,3-butanediol to quinolines is catalysed by $RuCl_3 \cdot nH_2O + PBu_3$[858]. 1,4-, 1,5- and 1,6-diols may react with aliphatic and aromatic amines to furnish *N*-substituted azacycloalkanes[859–861] (equation 114). A clue to the mechanism was provided by the isolation of an aminoalcohol in some cases[859]. This is formed as a result of the condensation of an intermediate hydroxy aldehyde followed by the hydrogenation of the resulting hydroxy imine. The same steps, involving an intramolecular condensation, lead to the end-product.



(114)

n	R	Catalyst	Yield
2, 3	alkyl	$RuCl_3 \cdot nH_2O + PBu_3$	59–91%
2–4	aryl	$RuCl_2(PPh_3)_3$	45–100%

Selective amination with $MeNH_2$ of ethylene glycol[862] and 1,6-hexanediol[863] can be carried out with Cu/Al_2O_3 catalysts. *N,N*-Dimethyl-2-aminoethanol was prepared from ethylene glycol with high selectivity (70% at 230 °C) in the presence of hydrogen[862]. When the latter was replaced by nitrogen, the selectivity of the side-product 1,2-bis(*N,N*-dimethylamino)ethene increased to 55%. No similar influence of hydrogen could be observed in the transformation of 1,6-hexanediol[863]. Independently of the partial pressure of hydrogen, *N,N*-dimethyl-6-amino-1-hexanol (>90% selectivity at 180 °C) or 1,6-bis(*N,N*-dimethylamino)hexane (65% selectivity at 230 °C) could be synthesized. Observations indicate two consecutive amination steps in the formation of the products.

A $ZnO–ZnCr_2O_4$ catalyst promoted by Pd was found to be active in the reaction of 1,2-propanediol with 1,2-diaminoethane in excess steam to 2-methylpyrazine[864–866]. Under optimum conditions, a slight excess of the diol minimizes the formation of undesired by-products (about 30 different compounds) and allows highly selective formation of the product (>80% selectivity at 100% conversion)[866].

VII. REFERENCES

1. C. H. Rochester, in *The Chemistry of the Hydroxyl Group* (Ed. S. Patai), Wiley, London, 1971, pp. 327–392.
2. M. Vicedomini, *Ann. Chim. (Rome)*, **71**, 213 (1981).
3. K. Hegetschweiler, I. Erni, W. Schneider and H. Schmalle, *Helv. Chim. Acta*, **73**, 97 (1990).
4. P. Silvestri, F. Talarico and M. Vicedomini, *Ann. Chim. (Rome)*, **69**, 19 (1979).
5. G. Carlini, P. Silvestri and M. Vicedomini, *Ann. Chim. (Rome)*, **69**, 533 (1979).
6. K. Araki, K. Iwamoto, S. Shinkai and T. Matsuda, *Bull. Chem. Soc. Jpn.*, **63**, 3480 (1990).
7. S. Shinkai, K. Araki, H. Koreishi, T. Tsubaki and O. Manabe, *Chem. Lett.*, 1351 (1986).
8. H. S. Aaron, in *Topics in Stereochemistry*, Vol. 11 (Eds. N. L. Allinger and E. L. Eliel), Wiley, New York, 1979, pp. 1–52.
9. W. A. P. Luck, in *The Hydrogen Bond*, Vol. 2 (Eds. P. Schuster, G. Zundel and C. Sandorfy), North-Holland, Amsterdam, 1976, pp. 542–545.
10. P. Knauth and R. Sabbah, *Can. J. Chem.*, **68**, 731 (1990).
11. P. Knauth and R. Sabbah, *Struct. Chem.*, **1**, 43 (1990).
12. M. Lindgren, T. Gustafsson, J. Westerling and A. Lund, *Chem. Phys.*, **106**, 441 (1986).
13. P. Knauth and R. Sabbah, *Thermochim. Acta*, **164**, 145 (1990).
14. I. G. Dance, R. Bishop, S. C. Hawkins, T. Lipari, M. L. Scudder and D. C. Craig, *J. Chem. Soc., Perkin Trans. 2*, 1299 (1986).
15. S. C. Hawkins, M. L. Scudder, D. C. Craig, A. D. Rae, R. B. A. Raof, R. Bishop and I. G. Dance, *J. Chem. Soc., Perkin Trans. 2*, 855 (1990).
16. A. T. Ung, R. Bishop, D. C. Craig, I. G. Dance and M. L. Scudder, *J. Chem. Soc., Chem. Commun.*, 1012 (1991).
17. G. Schilling and R. Maier, *Justus Liebigs Ann. Chem.*, 2229 (1985).
18. R. W. Hoffmann and U. Weidmann, *Chem. Ber.*, **118**, 3980 (1985).
19. F. A. J. Singelenberg and J. H. van der Maas, *J. Mol. Struct.*, **240**, 213 (1990).
20. F. A. J. Singelenberg and J. H. van der Maas, *J. Mol. Struct.*, **243**, 111 (1991).
21. K. Yamamoto, Y. Nakao, Y. Kyogoku and H. Sugeta, *J. Mol. Struct.*, **242**, 75 (1991).
22. F. B. Gallwey, J. E. Hawkes, P. Haycock and D. Lewis, *J. Chem. Soc., Perkin Trans. 2*, 1979 (1990).
23. Y. Nakao, H. Sugeta and Y. Kyogoku, *Spectrochimica Acta*, **42A**, 251 (1986).
24. H. Kleeberg, D. Klein and W. A. P. Luck, *J. Phys. Chem.*, **91**, 3200 (1987).
25. F. Hentrich, C. Tschierske and H. Zaschke, *Angew. Chem., Int. Ed. Engl.*, **30**, 440 (1991).
26. C. Tschierske, H. Altmann, H. Zaschke, G. Brezesinski and F. Kuschel, *Mol. Cryst. Liq. Cryst.*, **191**, 295 (1990).
27. G. Brezesinski, A. Madicke, C. Tschierske, H. Zaschke and F. Kuschel, *Mol. Cryst. Liq. Cryst. Lett.*, **5**, 155 (1988).
28. P.-E. Kristiansen, K.-M. Marstokk and H. Møllendal, *Acta Chem. Scand., Ser. A*, **41**, 403 (1987).

29. W. Caminati, *J. Mol. Spectr.*, **86**, 193 (1981).
30. W. Caminati and G. Corbelli, *J. Mol. Struct.*, **78**, 197 (1982).
31. A. A. Hasanein and I. Hubač, *Chem. Zvesti*, **35**, 9 (1981).
32. R. Ungaro, A. Pochini, G. D. Andreetti and P. Domiano, *J. Chem. Soc., Perkin Trans. 2*, 197 (1985).
33. S. W. Keller, G. M. Schuster and F. L. Tobiason, *Polym. Mater. Sci. Eng.*, **57**, 906 (1987); *Chem. Abstr.*, **109**, 5990b (1988).
34. V. Böhmer, H. Goldmann, W. Vogt, E. F. Paulus, F. L. Tobiason and M. J. Thielman, *J. Chem. Soc., Perkin Trans. 2*, 1769 (1990).
35. A. Natrajan, J. D. Ferrara, J. D. Hays, M. Khot, J. Colonell, W. J. Youngs and C. N. Sukenik, *J. Org. Chem.*, **55**, 2164 (1990).
36. Y. Klopstock, P. Ashkenazi, A. Mandelbaum, D. Müller, W. J. Richter and D. Ginsburg, *Tetrahedron*, **44**, 5893 (1988).
37. B. Koppenhoefer and B. Lin, *J. Chromatogr.*, **481**, 17 (1989).
38. R. J. Woods, W. A. Szarek and V. H. Smith, Jr., *J. Am. Chem. Soc.*, **112**, 4732 (1990).
39. O. R. Martin, S.-L. Korppi-Tommola and W. A. Szarek, *Can. J. Chem.*, **60**, 1857 (1982).
40. Y. Kikuchi, Y. Kato, Y. Tanaka, H. Toi and Y. Aoyama, *J. Am. Chem. Soc.*, **113**, 1349 (1991).
41. K. Kurihara, K. Ohto, Y. Tanaka, Y. Aoyama and T. Kunitake, *J. Am. Chem. Soc.*, **113**, 444 (1991).
42. Y. Tanaka, Y. Kato and Y. Aoyama, *J. Am. Chem. Soc.*, **112**, 2807 (1990).
43. Y. Dobashi and S. Hara, *J. Org. Chem.*, **52**, 2490 (1987).
44. W. H. Pirkle and T. C. Pochapsky, *Chem. Rev.*, **89**, 347 (1989).
45. Y. Dobashi, A. Dobashi, H. Ochiai and S. Hara, *J. Am. Chem. Soc.*, **112**, 6121 (1990).
46. M. Michalik and C. Döbler, *Tetrahedron*, **46**, 7739 (1990).
47. F. Toda, R. Toyotaka and H. Fukuda, *Tetrahedron Asymmetry*, **1**, 303 (1990).
48. F. Toda, K. Tanaka and T. C. W. Mak, *Chem. Lett.*, 2085 (1984).
49. F. Toda, *Top. Curr. Chem.*, **140**, 43 (1987).
50. F. Toda, K. Mori, Z. Stein and I. Goldberg, *Tetrahedron Lett.*, **30**, 1841 (1989).
51. T. Fujiwara, N. Tanaka, R. Ooshita, R. Hino, K. Mori and F. Toda, *Bull. Chem. Soc. Jpn.*, **63**, 249 (1990).
52. F. Toda and K. Tanaka, *J. Org. Chem.*, **53**, 3607 (1988).
53. P. P. Castro, T. M. Georgiadis and F. Diederich, *J. Org. Chem.*, **54**, 5835 (1989).
54. M. Kawashima and A. Hirayama, *Chem. Lett.*, 2299 (1990).
55. J. C. Bünzli and J. M. Harrowfield, in *Calixarenes* (Eds. J. Vicens and V. Böhmer), Kluwer, Dordrecht, 1990, pp. 211–231.
56. K. Burger and L. Nagy, in *Biocoordination Chemistry: Coordination Equilibria in Biologically Active Systems* (Ed. K. Burger), Ellis Horwood, New York, 1990, pp. 236–283.
57. P. B. Lond, P. S. Salmon and D. C. Champeney, *J. Am. Chem. Soc.*, **113**, 6420 (1991).
58. L. Nagy, L. Zsikla, K. Burger, A. Rockenbauer and J. T. Kiss, *J. Cryst. Spectr. Res.*, **19**, 911 (1989).
59. L. Nagy, L. Korecz, I. Kiricsi, L. Zsikla and K. Burger, *Struct. Chem.*, **2**, 231 (1991).
60. L. Nagy, H. Ohtaki, T. Yamaguchi and M. Nomura, *Inorg. Chim. Acta*, **159**, 201 (1989).
61. I. Labádi, K. Burger, G. Liptay, M. Czugler and A. Kálmán, *J. Thermal Anal.*, **31**, 1171 (1986).
62. I. Labádi, K. Burger, G. Liptay, A. Horváth, S. Papp and L. Korecz, *J. Thermal Anal.*, **32**, 1575 (1987).
63. J. E. Taylor, *Can. J. Chem.*, **62**, 2641 (1984).
64. T. Ogino, *Tetrahedron Lett.*, **21**, 177 (1980).
65. V. Bhushan, R. Rathore and S. Chandrasekaran, *Synthesis*, 431 (1984).
66. A. J. Fatiadi, *Synthesis*, 85 (1987).
67. F. Freeman, L. Y. Chang, J. C. Kappos and L. Sumarta, *J. Org. Chem.*, **52**, 1460 (1987).
68. F. Freeman and L. Y. Chang, *J. Am. Chem. Soc.*, **108**, 4504 (1986).
69. T. Ogino, K. Hasegawa and E. Hoshino, *J. Org. Chem.*, **55**, 2653 (1990).
70. T. Ogino and N. Kikuiri, *J. Am. Chem. Soc.*, **111**, 6174 (1989).
71. D. G. Lee and T. Chen, *J. Am. Chem. Soc.*, **111**, 7534 (1989).
72. M. Schröder, *Chem. Rev.*, **80**, 187 (1980).
73. H. S. Singh, in *Organic Synthesis by Oxidation with Metal Compounds* (Eds. W. J. Mijs and C. R. H. I. de Jonge), Plenum Press, New York, 1986, pp. 633–693.
74. K. Tomioka, *Synthesis*, 541 (1990).

75. M. Minato, K. Yamamoto and J. Tsuji, *J. Org. Chem.*, **55**, 766 (1990).
76. S. G. Hentges and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 4263 (1980).
77. B. B. Lohray, T. H. Kalantar B. M. Kim, C. Y. Park, T. Shibata, J. S. M. Wai and K. B. Sharpless, *Tetrahedron Lett.*, **30**, 2041 (1989).
78. K. Tomioka, M. Nakajima and K. Koga, *J. Am. Chem. Soc.*, **109**, 6213 (1987).
79. K. Tomioka, M. Nakajima, Y. Iitaka and K. Koga, *Tetrahedron Lett.*, **29**, 573 (1988).
80. K. Tomioka, M. Nakajima and K. Koga, *Tetrahedron Lett.*, **31**, 1741 (1990).
81. M. Tokles and J. K. Snyder, *Tetrahedron Lett.*, **27**, 3951 (1986).
82. M. Hirama, T. Oishi and S. Ito, *J. Chem. Soc., Chem. Commun.*, 665 (1989).
83. T. Oishi and M. Hirama, *J. Org. Chem.*, **54**, 5834 (1989).
84. E. J. Corey, P. D. Jardine, S. Virgil, P.-W. Yuen and R. D. Connell, *J. Am. Chem. Soc.*, **111**, 9243 (1989).
85. T. Shibata, D. C. Gilheany, B. K. Blackburn and K. B. Sharpless, *Tetrahedron Lett.*, **31**, 3817 (1990).
86. E. N. Jacobsen, I. Markó, W. S. Mungall, G. Schröder and K. B. Sharpless, *J. Am. Chem. Soc.*, **110**, 1968 (1988).
87. H.-L. Kwong, C. Sorato, Y. Ogino, H. Chen and K. B. Sharpless, *Tetrahedron Lett.*, **31**, 2999 (1990).
88. K. B. Sharpless, W. Amberg, M. Beller, H. Chen, J. Hartung, Y. Kawanami, D. Lübben, E. Manoury, Y. Ogino, T. Shibata and T. Ukita, *J. Org. Chem.*, **56**, 4585 (1991).
89. B. M. Kim and K. B. Sharpless, *Tetrahedron Lett.*, **31**, 3003 (1990).
90. J. S. M. Wai, I. Markó, J. S. Svendsen, M. G. Finn, E. N. Jacobsen and K. B. Sharpless, *J. Am. Chem. Soc.*, **111**, 1123 (1989).
91. C. P. Casey, *J. Chem. Soc., Chem. Commun.*, 126 (1983).
92. J. S. Svendsen, I. Markó, E. N. Jacobsen, Ch. P. Rao, S. Bott and K. B. Sharpless, *J. Org. Chem.*, **54**, 2263 (1989).
93. E. J. Corey and G. I. Lotto, *Tetrahedron Lett.*, **31**, 2665 (1990).
94. K. A. Jørgensen, *Tetrahedron Lett.*, **31**, 6417 (1990).
95. M. Schröder and E. C. Constable, *J. Chem. Soc., Chem. Commun.*, 734 (1982).
96. M. R. Sivik, J. C. Gallucci and L. A. Paquette, *J. Org. Chem.*, **55**, 391 (1990).
97. K. A. Jørgensen, *Tetrahedron: Asymmetry*, **2**, 515 (1991).
98. Y. Ogino, H. Chen, H.-L. Kwong and K. B. Sharpless, *Tetrahedron Lett.*, **32**, 3965 (1991).
99. S. Warwel, M. Rüsch gen. Klaas and M. Sojka, *J. Chem. Soc., Chem. Commun.*, 1578 (1991).
100. C. Venturello and M. Gambaro, *Synthesis*, 295 (1989).
101. F. Fringuelli, R. Germani, F. Pizzo and G. Savelli, *Synth. Commun.*, **19**, 1939 (1989).
102. S. Masamune, Sk. A. Ali, D. L. Snitman and D. S. Garvey, *Angew. Chem., Int. Ed. Engl.*, **19**, 557 (1980).
103. R. Luckenbach (Ed.), *Beilstein Handbook of Organic Chemistry*, 5th Supplementary Series, Vol. 17/1, Springer, Berlin, 1984, p. LIII.
104. S. V. Ley and F. Sternfeld, *Tetrahedron*, **45**, 3463 (1989).
105. T. Hudlicky, J. D. Price, F. Rulin and T. Tsunoda, *J. Am. Chem. Soc.*, **112**, 9439 (1990).
106. H. A. J. Carless and O. Z. Oak, *J. Chem. Soc., Chem. Commun.*, 61 (1991).
107. S. V. Ley, M. Parra, A. J. Redgrave and F. Sternfeld, *Tetrahedron*, **46**, 4995 (1990).
108. D. R. Boyd, M. R. J. Dorrity, M. V. Hand, J. F. Malone, N. D. Sharma, H. Dalton, D. J. Gray and G. N. Sheldrake, *J. Am. Chem. Soc.*, **113**, 666 (1991).
109. D. R. Boyd, M. R. J. Dorrity, J. F. Malone, R. A. S. McMordie, N. D. Sharma, H. Dalton and P. Williams, *J. Chem. Soc., Perkin Trans. 1*, 489 (1990).
110. P. J. Geary, R. J. Pryce, S. M. Roberts, G. Ryback and J. A. Winders, *J. Chem. Soc., Chem. Commun.*, 204 (1990).
111. M. Bartók, in *Small Ring Heterocycles*, Part 3 (Ed. A. Hassner), Wiley, New York, 1985, pp. 1–196.
112. G. D. Prestwich, S. McG. Graham, J.-W. Kuo and R. G. Vogt, *J. Am. Chem. Soc.*, **111**, 636 (1989).
113. G. A. Olah, A. P. Fung and D. Meidar, *Synthesis*, 280 (1981).
114. A. M. Ross, T. M. Pohl, K. Piazza, M. Thomas, B. Fox and D. L. Whalen, *J. Am. Chem. Soc.*, **104**, 1658 (1982).
115. M. Raban, E. Hortelano, J. Quin, III, N. King and J. Koch, *J. Chem. Soc., Chem. Commun.*, 1557 (1985).

116. G. H. Posner, M. Hulce and R. K. Rose, *Synth. Commun.*, **11**, 737 (1981).
117. N. Iranpoor and I. M. Baltork, *Tetrahedron Lett.*, **31**, 735 (1990).
118. N. Iranpoor and I. M. Baltork, *Synth. Commun.*, **20**, 2789 (1990).
119. J. Otera, Y. Niibo and H. Nozaki, *Tetrahedron*, **47**, 7625 (1991).
120. Y. Niibo, T. Nakata, J. Otera and H. Nozaki, *Synlett*, 97 (1991).
121. J. B. Jones, *Tetrahedron*, **42**, 3351 (1986).
122. D. Wistuba and V. Schurig, *Angew. Chem., Int. Ed. Engl.*, **25**, 1032 (1986).
123. G. Bellucci, C. Chiappe, L. Conti, F. Marioni and G. Pierini, *J. Org. Chem.*, **54**, 5978 (1989).
124. G. Bellucci, C. Chiappe, F. Marioni and M. Benetti, *J. Chem. Soc., Perkin Trans. 1*, 361 (1991).
125. R. Seemayer and M. P. Schneider, *Recl. Trav. Chim. Pays-Bas*, **110**, 171 (1991).
126. R. M. Hanson, *Chem. Rev.*, **91**, 437 (1991).
127. L.-X. Dai, B.-L. Lou, Y.-Z. Zhang and G.-Z. Guo, *Tetrahedron Lett.*, **27**, 4343 (1986).
128. K. Sugita, M. Onaka and Y. Izumi, *Tetrahedron Lett.*, **31**, 7467 (1990).
129. J. M. Finan and Y. Kishi, *Tetrahedron Lett.*, **23**, 2719 (1982).
130. T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980).
131. A. Pfenninger, *Synthesis*, 89 (1986).
132. S. Okamoto, T. Shimazaki, Y. Kitano, Y. Kobayashi and F. Sato, *J. Chem. Soc., Chem. Commun.*, 1352 (1986).
133. B. H. Lipshutz and J. C. Barton, *J. Org. Chem.*, **53**, 4495 (1988).
134. J. M. Klunder, T. Onami and K. B. Sharpless, *J. Org. Chem.*, **54**, 1295 (1989).
135. A. Pfalz and A. Mattenberger, *Angew. Chem., Int. Ed. Engl.*, **21**, 71 (1982).
136. C. Bonini, G. Righi and G. Sotgiu, *J. Org. Chem.*, **56**, 6206 (1991).
137. P. N. Devine and T. Oh, *Tetrahedron Lett.*, **32**, 883 (1991).
138. J. E. McMurry, *Acc. Chem. Res.*, **16**, 405 (1983).
139. J. E. McMurry, *Chem. Rev.*, **89**, 1513 (1989).
140. H. B. Kagan and J. L. Namy, *Tetrahedron*, **42**, 6573 (1986).
141. B. E. Kahn and R. D. Rieke, *Chem. Rev.*, **88**, 733 (1988).
142. J.-M. Pons and M. Santelli, *Tetrahedron*, **44**, 4295 (1988).
143. D. Lenoir, *Synthesis*, 883 (1989).
144. J. Nakayama, S. Yamaoka and M. Hoshino, *Tetrahedron Lett.*, **28**, 1799 (1987).
145. A. P. Marchand, V. Vidyasagar, W. H. Watson, A. Nagl and R. P. Kashyap, *J. Org. Chem.*, **56**, 282 (1991).
146. J. E. McMurry and J. G. Rico, *Tetrahedron Lett.*, **30**, 1169 (1989).
147. J.-M. Pons and M. Santelli, *J. Org. Chem.*, **54**, 877 (1989).
148. B. P. Mundy, R. Srinivasa, Y. Kim, T. Dolph and R. J. Warnet, *J. Org. Chem.*, **47**, 1657 (1982).
149. S. K. Nayak and A. Banerji, *J. Org. Chem.*, **56**, 1940 (1991).
150. A. Fürstner and H. Weidmann, *Synthesis*, 1071 (1987).
151. T. Imamoto, T. Kusumoto, Y. Hatanaka and M. Yokoyama, *Tetrahedron Lett.*, **23**, 1353 (1982).
152. J. L. Namy, J. Souppe and H. B. Kagan, *Tetrahedron Lett.*, **24**, 765 (1983).
153. Z. Hou, K. Takamine, Y. Fujiwara and H. Taniguchi, *Chem. Lett.*, 2061 (1987).
154. Z. Hou, K. Takamine, O. Aoki, H. Shiraishi, Y. Fujiwara and H. Taniguchi, *J. Org. Chem.*, **53**, 6077 (1988).
155. Z. Hou, K. Takamine, O. Aoki, H. Shiraishi, Y. Fujiwara and H. Taniguchi, *J. Chem. Soc., Chem. Commun.*, 668 (1988).
156. J. L. Chiara, W. Cabri and S. Hanessian, *Tetrahedron Lett.*, **32**, 1125 (1991).
157. T. L. Chen, T. H. Chan and A. Shaver, *J. Organomet. Chem.*, **268**, C1 (1984).
158. Y. Handa and J. Inanaga, *Tetrahedron Lett.*, **28**, 5717 (1987).
159. P. M. Takahara, J. H. Freudenberger, A. W. Konradi and S. F. Pedersen, *Tetrahedron Lett.*, **30**, 7177 (1989).
160. A. S. Raw and S. F. Pedersen, *J. Org. Chem.*, **56**, 830 (1991).
161. C. Villiers, R. Adam, M. Lance, M. Nierlich, J. Vigner and M. Ephritikhine, *J. Chem. Soc., Chem. Commun.*, 1144 (1991).
162. F. Fournier, J. Berthelot and Y.-L. Pascal, *Can. J. Chem.*, **61**, 2121 (1983).
163. D. W. Sopher and J. H. P. Utley, *J. Chem. Soc., Perkin Trans. 2*, 1361 (1984).
164. E. Kariv-Miller and T. J. Mahachi, *J. Org. Chem.*, **51**, 1041 (1986).
165. Y. Ikeda, *Chem. Lett.*, 1719 (1990).
166. A. Clerici and O. Porta, *Tetrahedron Lett.*, **23**, 3517 (1982).
167. A. Clerici and O. Porta, *J. Org. Chem.*, **50**, 76 (1985).

168. Y. Zhang and T. Liu, *Synth. Commun.*, **18**, 2173 (1988).
169. J. Souppe, L. Danon, J. L. Namy and H. B. Kagan, *J. Organomet. Chem.*, **250**, 227 (1983).
170. K. Tanaka, S. Kishigami and F. Toda, *J. Org. Chem.*, **55**, 2981 (1990).
171. R. Sato, T. Nagaoka, T. Goto and M. Saito, *Bull. Chem. Soc. Jpn.*, **63**, 290 (1990).
172. J. H. Penn, Z. Lin and D.-L. Deng, *J. Am. Chem. Soc.*, **113**, 1001 (1991).
173. G. J. McGarvey and M. Kimura, *J. Org. Chem.*, **47**, 5420 (1982).
174. J. S. Sawyer, A. Kucerovy, T. L. Macdonald and G. J. McGarvey, *J. Am. Chem. Soc.*, **110**, 842 (1988).
175. J. Yamada, H. Abe and Y. Yamamoto, *J. Am. Chem. Soc.*, **112**, 6118 (1990).
176. R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **21**, 555 (1982).
177. P. G. M. Wuts and S. S. Bigelow, *J. Org. Chem.*, **47**, 2498 (1982).
178. R. W. Hoffmann, B. Kemper, R. Metternich and T. Lehmeier, *Justus Liebigs Ann. Chem.*, 2246 (1985).
179. H. C. Brown, P. K. Jadhav and K. S. Bhat, *J. Am. Chem. Soc.*, **110**, 1535 (1988).
180. M. Koreeda and Y. Tanaka, *Tetrahedron Lett.*, **28**, 143 (1987).
181. J. A. Marshall, G. S. Welmaker and B. W. Gung, *J. Am. Chem. Soc.*, **113**, 647 (1991).
182. Y. Yamamoto, Y. Saito and K. Maruyama, *J. Organomet. Chem.*, **292**, 311 (1985).
183. A. G. M. Barrett and J. W. Malecha, *J. Org. Chem.*, **56**, 5243 (1991).
184. D. Enders and S. Nakai, *Helv. Chim. Acta*, **73**, 1833 (1990).
185. D. Enders and S. Nakai, *Chem. Ber.*, **124**, 219 (1991).
186. D. Enders, H. Kipphardt and P. Fey, *Org. Synth.*, **65**, 183 (1987).
187. T. Oishi and T. Nakata, *Acc. Chem. Res.*, **17**, 338 (1984).
188. J. Jurczak, S. Pikul and T. Bauer, *Tetrahedron*, **42**, 447 (1986).
189. M. Nógrádi, *Stereoselective Synthesis*, VCH, Weinheim, New York, 1986, pp. 131–148.
190. T. Mukaiyama, K. Tomimori and T. Oriyama, *Chem. Lett.*, 1359 (1985).
191. D. J. Cram and D. R. Wilson, *J. Am. Chem. Soc.*, **85**, 1245 (1963).
192. M. Chérest, H. Felkin and N. Prudent, *Tetrahedron Lett.*, 2199 (1968).
193. N. T. Anh and O. Eisenstein, *Nouv. J. Chim.*, **1**, 61 (1977).
194. T. Nakata, T. Tanaka and T. Oishi, *Tetrahedron Lett.*, **24**, 2653 (1983).
195. N. Yamazaki and C. Kibayashi, *J. Am. Chem. Soc.*, **111**, 1396 (1989).
196. K. Matsumoto, N. Suzuki and H. Ohta, *Tetrahedron Lett.*, **31**, 7163 (1990).
197. M. Fujita and T. Hiyama, *J. Org. Chem.*, **53**, 5405 (1988).
198. S. Servi, *Synthesis*, 1 (1990).
199. C. Fuganti, P. Grasselli, G. Poli, S. Servi and A. Zorzella, *J. Chem. Soc., Chem. Commun.*, 1619 (1988).
200. P. Ferraboschi, P. Grisenti, A. Manzocchi and E. Santaniello, *J. Chem. Soc., Perkin Trans. 1*, 2469 (1990).
201. M. Kodama, H. Minami, Y. Mima and Y. Fukuyama, *Tetrahedron Lett.*, **31**, 4025 (1990).
202. R. Csuk and B. I. Glänzer, *Chem. Rev.*, **91**, 49 (1991).
203. Y. Yamamoto, *Acc. Chem. Res.*, **20**, 243 (1987).
204. M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, **23**, 556 (1984).
205. Y. Yamamoto, T. Komatsu and K. Maruyama, *J. Organomet. Chem.*, **285**, 31 (1985).
206. Y. Yamamoto and J. Yamada, *J. Am. Chem. Soc.*, **109**, 4395 (1987).
207. M. Shimagaki, H. Takubo and T. Oishi, *Tetrahedron Lett.*, **26**, 6235 (1985).
208. G. E. Keck and E. P. Boden, *Tetrahedron Lett.*, **25**, 265 (1984).
209. C. H. Heathcock, S. Kiyooka and T. A. Blumenkopf, *J. Org. Chem.*, **49**, 4214 (1984).
210. K.-Y. Ko and E. L. Eliel, *J. Org. Chem.*, **51**, 5353 (1986).
211. H. C. Brown, K. S. Bhat and R. S. Randad, *J. Org. Chem.*, **54**, 1570 (1989).
212. G. E. Keck and E. P. Boden, *Tetrahedron Lett.*, **25**, 1879 (1984).
213. K. Mikami, K. Kawamoto, T.-P. Loh and T. Nakai, *J. Chem. Soc., Chem. Commun.*, 1161 (1990).
214. H. C. Brown, K. S. Bhat and R. S. Randad, *J. Org. Chem.*, **52**, 3701 (1987).
215. W. C. Still and J. H. McDonald, III, *Tetrahedron Lett.*, **21**, 1031 (1980).
216. K. Sato, M. Kira and H. Sakurai, *J. Am. Chem. Soc.*, **111**, 6429 (1989).
217. H. Sakurai, *Synlett*, 1 (1989).
218. G. Maier, C. Roth and R. K. Schmitt, *Chem. Ber.*, **118**, 704 (1985).
219. G. Maier, R. K. Schmitt and U. Seipp, *Chem. Ber.*, **118**, 722 (1985).
220. M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya and R. Noyori, *J. Am. Chem. Soc.*, **110**, 629 (1988).

221. E. C. S. Brenelli, P. J. S. Moran and J. A. R. Rodrigues, *Synth. Commun.*, **20**, 261 (1990).
222. S. D. Burke, D. N. Deaton, R. J. Olsen, D. M. Armistead and B. E. Blough, *Tetrahedron Lett.*, **28**, 3905 (1987).
223. J. K. Whitesell, D. Deyo and A. Bhattacharya, *J. Chem. Soc., Chem. Commun.*, 802 (1983).
224. G. Cardillo, M. Orena, M. Romero and S. Sandri, *Tetrahedron*, **45**, 1501 (1989).
225. B. D. Dombek, in *Advances in Catalysis*, Vol. 32 (Eds. D. D. Eley, H. Pines and P. B. Weisz), Academic Press, New York, 1983, pp. 325–416.
226. W. Keim, M. Berger and J. Schlupp, *J. Catal.*, **61**, 359 (1980).
227. D. R. Fahey, *J. Am. Chem. Soc.*, **103**, 136 (1981).
228. H. Tanaka, Y. Hara, E. Watanabe, K. Wada and T. Onoda, *J. Organomet. Chem.*, **312**, C71 (1986).
229. M. Tamura, M. Ishino, T. Deguchi and S. Nakamura, *J. Organomet. Chem.*, **312**, C75 (1986).
230. Y. Ohgomori, S. Mori, S. Yoshida and Y. Watanabe, *J. Mol. Catal.*, **43**, 127 (1987).
231. M. Ishino, M. Tamura, T. Deguchi and S. Nakamura, *J. Catal.*, **105**, 478 (1987).
232. J. F. Knifton, *J. Chem. Soc., Chem. Commun.*, 729 (1983).
233. M. Ishino, T. Deguchi, T. Takano and S. Nakamura, *J. Mol. Catal.*, **49**, 315 (1989).
234. Y. Ohgomori, S. Yoshida and Y. Watanabe, *J. Mol. Catal.*, **43**, 249 (1987).
235. Y. Ohgomori, S. Mori, S. Yoshida and Y. Watanabe, *J. Mol. Catal.*, **40**, 223 (1987).
236. U. Matteoli, G. Menchi, M. Bianchi and F. Piacenti, *J. Mol. Catal.*, **44**, 347 (1988).
237. J. S. Lee, J. C. Kim and Y. G. Kim, *Appl. Catal.*, **57**, 1 (1990).
238. U. Matteoli, G. Menchi, M. Bianchi and F. Piacenti, *J. Mol. Catal.*, **64**, 257 (1991).
239. J. F. Knifton and R. G. Duranleau, *J. Mol. Catal.*, **67**, 389 (1991).
240. W. C. Still and J. C. Barrish, *J. Am. Chem. Soc.*, **105**, 2487 (1983).
241. D. A. Evans, G. C. Fu and A. H. Hoveyda, *J. Am. Chem. Soc.*, **110**, 6917 (1988).
242. K. Burgess, J. Cassidy and M. J. Ohlmeyer, *J. Org. Chem.*, **56**, 1020 (1991).
243. T. Harada, Y. Matsuda, J. Uchimura and A. Oku, *J. Chem. Soc., Chem. Commun.*, 1429 (1989).
244. D. A. Evans and G. C. Fu, *J. Org. Chem.*, **55**, 2280 (1990).
245. K. Burgess, W. A. van der Donk and A. M. Kook, *J. Org. Chem.*, **56**, 2949 (1991).
246. D. A. Evans, J. Bartroli and T. Godel, *Tetrahedron Lett.*, **23**, 4577 (1982).
247. K. N. Houk, N. G. Rondan, Y.-D. Wu, J. T. Metz and M. N. Paddon-Row, *Tetrahedron*, **40**, 2257 (1984).
248. K. Burgess, W. A. van der Donk, M. B. Jarstfer and M. J. Ohlmeyer, *J. Am. Chem. Soc.*, **113**, 6139 (1991).
249. T. Harada, Y. Matsuda, I. Wada, J. Uchimura and A. Oku, *J. Chem. Soc., Chem. Commun.*, 21 (1990).
250. D. H. Birtwistle, J. M. Brown and M. W. Foxton, *Tetrahedron Lett.*, **27**, 4367 (1986).
251. T. W. Bell, J. R. Vargas and G. A. Crispino, *J. Org. Chem.*, **54**, 1978 (1989).
252. K. Burgess and M. J. Ohlmeyer, *Chem. Rev.*, **91**, 1179 (1991).
253. K. Tamao, T. Nakajima, R. Sumiya, H. Arai, N. Higuchi and Y. Ito, *J. Am. Chem. Soc.*, **108**, 6090 (1986).
254. K. Tamao, T. Tanaka, T. Nakajima, R. Sumiya, H. Arai and Y. Ito, *Tetrahedron Lett.*, **27**, 3377 (1986).
255. K. Tamao, T. Tohma, N. Inui, O. Nakayama and Y. Ito, *Tetrahedron Lett.*, **31**, 7333 (1990).
256. H. Nishiyama, T. Kitajima, M. Matsumoto and K. Itoh, *J. Org. Chem.*, **49**, 2298 (1984).
257. A. H. Hoveyda and Z. Xu, *J. Am. Chem. Soc.*, **113**, 5079 (1991).
258. T. Murai, E. Yasui, S. Kato, Y. Hatayama, S. Suzuki, Y. Yamasaki, N. Sonoda, H. Kurosawa, Y. Kawasaki and S. Murai, *J. Am. Chem. Soc.*, **111**, 7938 (1989).
259. S. D. Rychovsky, G. Griesgraber, S. Zeller and D. J. Skalitzky, *J. Org. Chem.*, **56**, 5161 (1991).
260. P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless and S. M. Viti, *J. Org. Chem.*, **47**, 1378 (1982).
261. S. M. Viti, *Tetrahedron Lett.*, **23**, 4541 (1982).
262. L. A. Flippin, K. Jalali-Araghi and P. A. Brown, *J. Org. Chem.*, **54**, 3006 (1989).
263. T. Hanamoto, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **63**, 1039 (1990).
264. L. A. Flippin, P. A. Brown and K. Jalali-Araghi, *J. Org. Chem.*, **54**, 3588 (1989).
265. T. Cohen, I.-H. Jeong, B. Mudryk, M. Bhupathy and M. M. A. Awad, *J. Org. Chem.*, **55**, 1528 (1990).
266. O. Fujimura, K. Takai and K. Utimoto, *J. Org. Chem.*, **55**, 1705 (1990).
267. K. Takaki, S. Tanaka, F. Beppu, Y. Tsubaki and Y. Fujiwara, *Chem. Lett.*, 1427 (1990).
268. Y. Masuyama, J. Nakata and Y. Kurusu, *J. Chem. Soc., Perkin Trans. 1*, 2598 (1991).

269. S. Kiyooka, H. Kuroda and Y. Shimasaki, *Tetrahedron Lett.*, **27**, 3009 (1986).
270. K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repic and M. J. Shapiro, *Tetrahedron Lett.*, **28**, 155 (1987).
271. D. A. Evans and A. H. Hoveyda, *J. Org. Chem.*, **55**, 5190 (1990).
272. K. Narasaka and F.-C. Pai, *Tetrahedron*, **40**, 2233 (1984).
273. D. A. Evans, K. T. Chapman and E. M. Carreira, *J. Am. Chem. Soc.*, **110**, 3560 (1988).
274. S. Anwar and A. P. Davis, *Tetrahedron*, **44**, 3761 (1988).
275. S. Anwar, G. Bradley and A. P. Davis, *J. Chem. Soc., Perkin Trans. 1*, 1383 (1991).
276. R. Bloch, L. Gilbert and C. Girard, *Tetrahedron Lett.*, **29**, 1021 (1988).
277. K. Suzuki, M. Miyazawa, M. Shimazaki and G. Tsuchihashi, *Tetrahedron*, **44**, 4061 (1988).
278. M. Shimazaki, H. Hara and K. Suzuki, *Tetrahedron Lett.*, **30**, 5447 (1989).
279. M. T. Reetz and A. Jung, *J. Am. Chem. Soc.*, **105**, 4833 (1983).
280. M. T. Reetz, K. Kesseler and A. Jung, *Tetrahedron Lett.*, **25**, 729 (1984).
281. S. D. Burke, A. D. Piscopio, B. E. Marron, M. A. Matulenko and G. Pan, *Tetrahedron Lett.*, **32**, 857 (1991).
282. G. E. Keck and D. E. Abbott, *Tetrahedron Lett.*, **25**, 1883 (1984).
283. W. R. Roush and L. Banfi, *J. Am. Chem. Soc.*, **110**, 3979 (1988).
284. W. R. Roush, A. D. Palkowitz and K. Ando, *J. Am. Chem. Soc.*, **112**, 6348 (1990).
285. M. T. Reetz, A. Jung and C. Bolm, *Tetrahedron*, **44**, 3889 (1988).
286. R. W. Hoffmann and U. Weidmann, *Chem. Ber.*, **118**, 3966 (1985).
287. J. Barluenga, J. G. Resa, B. Olano and S. Fustero, *J. Org. Chem.*, **52**, 1425 (1987).
288. Gy. Schneider, E. Meskó, Gy. Dombi, D. Zeigan and G. Engelhardt, *J. Chem. Res. (S)*, 12 (1987).
289. A. Tai, K. Ito and T. Harada, *Bull. Chem. Soc. Jpn.*, **54**, 223 (1981).
290. A. Tai, T. Kikukawa, T. Sugimura, Y. Inoue, T. Osawa and S. Fujii, *J. Chem. Soc., Chem. Commun.*, 795 (1991).
291. D. Seebach and M. Züger, *Helv. Chim. Acta*, **65**, 495 (1982).
292. M. Braun, U. Mahler and S. Houben, *Justus Liebigs Ann. Chem.*, 513 (1990).
293. A. S. Gopalan and H. K. Jacobs, *J. Chem. Soc., Perkin Trans. 1*, 1897 (1990).
294. G. Quinkert, U. Döller, M. Eichhorn, F. Küber, H. P. Nestler, H. Becker, J. W. Bats, G. Zimmermann and G. Dürner, *Helv. Chim. Acta*, **73**, 1999 (1990).
295. J. T. B. Ferreira and F. Simonelli, *Tetrahedron*, **46**, 6311 (1990).
296. D. Seebach, A. K. Beck, R. Imwinkelried, S. Roggo and A. Wonnacott, *Helv. Chim. Acta*, **70**, 954 (1987).
297. Y. M. Choi and R. W. Emblidge, *J. Org. Chem.*, **54**, 1198 (1989).
298. N. Chatani, Y. Kajikawa, H. Nishimura and S. Murai, *Organometallics*, **10**, 21 (1991).
299. T. Shono, Y. Matsumura, K. Tsubata and Y. Sugihara, *J. Org. Chem.*, **47**, 3090 (1982).
300. H. Sakamoto, K. Kimura, Y. Koseki, M. Matsuo and T. Shono, *J. Org. Chem.*, **51**, 4974 (1986).
301. Á. Molnár, I. Bucsi and M. Bartók, *Tetrahedron*, **48**, 4929 (1992).
302. P. A. Rose and H.-J. Liu, *Synth. Commun.*, **21**, 2089 (1991).
303. S. Rozen, M. Brand and M. Kol, *J. Am. Chem. Soc.*, **111**, 8325 (1989).
304. T. L. Stuk, P. A. Grieco and M. M. Marsh, *J. Org. Chem.*, **56**, 2957 (1991).
305. W. C. Still and K. P. Darst, *J. Am. Chem. Soc.*, **102**, 7385 (1980).
306. Y. Yokoyama, H. Kawashima and H. Masaki, *Chem. Lett.*, 453 (1989).
307. Y. Matsumoto and T. Hayashi, *Tetrahedron Lett.*, **32**, 3387 (1991).
308. K. S. Knight and R. M. Waymouth, *J. Am. Chem. Soc.*, **113**, 6268 (1991).
309. A. Hoveyda, Z. Xu, J. P. Morken and A. F. Houri, *J. Am. Chem. Soc.*, **113**, 8950 (1991).
310. D. Hongxun, Z. Weike and B. Junchai, *Tetrahedron Lett.*, **28**, 2599 (1987).
311. M. Koreeda and L. G. Hamann, *J. Am. Chem. Soc.*, **112**, 8175 (1990).
312. E. T. Everhart and J. C. Craig, *J. Chem. Soc., Perkin Trans. 1*, 1701 (1991).
313. J. Mulzer, L. Kattner, A. R. Strecker, C. Schröder, J. Buschmann, C. Lehmann and P. Luger, *J. Am. Chem. Soc.*, **113**, 4218 (1991).
314. Y. Nishigaichi, A. Takuwa and A. Jodai, *Tetrahedron Lett.*, **32**, 2383 (1991).
315. J. H. Bushweller, L. Anzalone and T. A. Spencer, *Synth. Commun.*, **19**, 745 (1989).
316. B. Mudryk and T. Cohen, *J. Org. Chem.*, **56**, 5760 (1991).
317. K. Tomooka, T. Okinaga, K. Suzuki and G. Tsuchihashi, *Tetrahedron Lett.*, **28**, 6335 (1987).
318. K. Tomooka, T. Okinaga, K. Suzuki and G. Tsuchihashi, *Tetrahedron Lett.*, **30**, 1563 (1989).
319. R. Bloch and C. Brillet, *Tetrahedron: Asymmetry*, **2**, 797 (1991).
320. A. Natrajan and C. N. Sukenik, *J. Org. Chem.*, **53**, 3559 (1988).

321. S. Bhanumati, P. Ashkenazi, S. Migdal and D. Ginsburg, *Helv. Chim. Acta*, **66**, 2703 (1983).
322. A. P. Marchand and G. M. Reddy, *Tetrahedron*, **47**, 6571 (1991).
323. N. C. Barua and R. R. Schmidt, *Synthesis*, 1067 (1986).
324. G. Fytas, N. Kolocouris and G. B. Foscolos, *Synth. Commun.*, **18**, 1773 (1988).
325. B. L. Feringa, B. de Lange and J. C. de Jong, *J. Org. Chem.*, **54**, 2471 (1989).
326. J. F. G. A. Jansen and B. L. Feringa, *Tetrahedron Lett.*, **30**, 5481 (1989).
327. J. Janků, S. D. Isaev, L. V. Cybulskii, L. Vodička and A. G. Yurchenko, *Collect. Czech. Chem. Commun.*, **55**, 2475 (1990).
328. T. Kitahara and K. Mori, *Tetrahedron*, **40**, 2935 (1984).
329. E. Fouque and G. Rousseau, *Synthesis*, 661 (1989).
330. H. Jacobs, K. Berryman, J. Jones and A. Gopalan, *Synth. Commun.*, **20**, 999 (1990).
331. Y. Tamai, S. Koike, A. Ogura and S. Miyano, *J. Chem. Soc., Chem. Commun.*, 799 (1991).
332. S. C. Berk, K. A. Kreutzer and S. L. Buchwald, *J. Am. Chem. Soc.*, **113**, 5093 (1991).
333. S. E. Denmark, *J. Org. Chem.*, **46**, 3144 (1981).
334. A. A. Bakibaev, T. I. Savchenko, V. D. Filimonov and V. M. Ketskalo, *Zh. Org. Khim.*, **24**, 775 (1988).
335. C. Almansa, E. Carceller, M. L. Garcia and F. Serratosa, *Synth. Commun.*, **18**, 1079 (1988).
336. R. Mello, L. Cassidei, M. Fiorentino, C. Fusco and R. Curci, *Tetrahedron Lett.*, **31**, 3067 (1990).
337. C. Y. Park, B. M. Kim and K. B. Sharpless, *Tetrahedron Lett.*, **32**, 1003 (1991).
338. J. S. Brimacombe, R. Hanna, A. K. M. S. Kabir, F. Bennett and I. D. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 815 (1986).
339. J. K. Cha, W. J. Christ and Y. Kishi, *Tetrahedron*, **40**, 2247 (1984).
340. D. A. Evans and S. W. Kaldor, *J. Org. Chem.*, **55**, 1698 (1990).
341. J. S. Panek and P. F. Cirillo, *J. Am. Chem. Soc.*, **112**, 4873 (1990).
342. A. Gigou, J.-P. Beaucourt, J.-P. Lellouche and R. Gree, *Tetrahedron Lett.*, **32**, 635 (1991).
343. A. J. Pearson and K. Srinivasan, *J. Chem. Soc., Chem. Commun.*, 392 (1991).
344. X. M. Zhang, A. Archelas and R. Furstoss, *J. Org. Chem.*, **56**, 3814 (1991).
345. M. Murakami, P. G. Andersson, M. Suginome and Y. Ito, *J. Am. Chem. Soc.*, **113**, 3987 (1991).
346. W. R. Roush and R. J. Brown, *J. Org. Chem.*, **47**, 1371 (1982).
347. T. Katsuki, A. W. M. Lee, P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless, D. Tuddenham and F. J. Walker, *J. Org. Chem.*, **47**, 1373 (1982).
348. G. A. Morrison and J. B. Wilkinson, *J. Chem. Soc., Perkin Trans. 1*, 2003 (1989).
349. M. Kusakabe and F. Sato, *J. Chem. Soc., Chem. Commun.*, 989 (1986).
350. P. N. Guivisdalsky and R. Bittman, *J. Org. Chem.*, **54**, 4643 (1989).
351. P. N. Guivisdalsky and R. Bittman, *J. Am. Chem. Soc.*, **111**, 3077 (1989).
352. T. Suzuki, H. Saimoto, H. Tomioka, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, **23**, 3597 (1982).
353. W. R. Roush, M. A. Adam and S. M. Peseckis, *Tetrahedron Lett.*, **24**, 1377 (1983).
354. T. K. Chakraborty and S. P. Joshi, *Tetrahedron Lett.*, **31**, 2043 (1990).
355. M. A. Tius and A. H. Fauq, *J. Org. Chem.*, **48**, 4131 (1983).
356. M. A. Tius and A. H. Fauq, *J. Am. Chem. Soc.*, **108**, 1035 (1986).
357. P. C. B. Page, C. M. Rayner and I. O. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1375 (1990).
358. K. Mead and T. L. Macdonald, *J. Org. Chem.*, **50**, 422 (1985).
359. W. A. Slusarchyk, M. G. Young, G. S. Bisacchi, D. R. Hockstein and R. Zahler, *Tetrahedron Lett.*, **30**, 6453 (1989).
360. E. Cesarotti, A. Mauri, M. Pallavicini and L. Villa, *Tetrahedron Lett.*, **32**, 4381 (1991).
361. F. Aragozzini, E. Maconi, D. Potenza and C. Scolastico, *Synthesis*, 225 (1989).
362. E. Schrötter, J. Weidner and H. Schick, *Justus Liebigs Ann. Chem.*, 397 (1991).
363. Gy. Schneider, J. Wölfling, L. Hackler, E. Meskó and Gy. Dombi, *Synthesis*, 194 (1985).
364. I. Vincze, Cs. Somlai, Gy. Schneider and Gy. Dombi, *Justus Liebigs Ann. Chem.*, 973 (1988).
365. Y. Yamamoto and K. Maruyama, *Heterocycles*, **18**, 357 (1982).
366. G. J. McGarvey, M. Kimura, T. Oh and J. M. Williams, *J. Carbohydr. Chem.*, **3**, 125 (1984).
367. J. Mulzer and A. Angermann, *Tetrahedron Lett.*, **24**, 2843 (1983).
368. F. Sato, Y. Kobayashi, O. Takahashi, T. Chiba, Y. Takeda and M. Kusakabe, *J. Chem. Soc., Chem. Commun.*, 1636 (1985).
369. R. W. Hoffmann, A. Endesfelder and H.-J. Zeiss, *Carbohydr. Res.*, **123**, 320 (1983).
370. W. R. Roush, L. K. Hoong, M. A. J. Palmer and J. C. Park, *J. Org. Chem.*, **55**, 4109 (1990).
371. W. R. Roush and R. L. Halterman, *J. Am. Chem. Soc.*, **108**, 294 (1986).

372. W. R. Roush, M. A. Adam, A. E. Walts and D. J. Harris, *J. Am. Chem. Soc.*, **108**, 3422 (1986).
373. J. W. Coe and W. R. Roush, *J. Org. Chem.*, **54**, 915 (1989).
374. W. R. Roush, L. K. Hoong, M. A. J. Palmer, J. A. Straub and A. D. Palkowitz, *J. Org. Chem.*, **55**, 4117 (1990).
375. J. Garcia, B. M. Kim and S. Masamune, *J. Org. Chem.*, **52**, 4831 (1987).
376. G. Fronza, C. Fuganti, P. Grasselli, G. Pedrocchi-Fantoni and C. Zirotti, *Chem. Lett.*, 335 (1984).
377. J. Mulzer, P. de Lasalle and A. Freissler, *Justus Liebigs Ann. Chem.*, 1152 (1986).
378. H. Nagaoka and Y. Kishi, *Tetrahedron*, **37**, 3873 (1981).
379. M. T. Reetz and K. Kesseler, *J. Org. Chem.*, **50**, 5434 (1985).
380. D. R. Williams and F. D. Klingler, *Tetrahedron Lett.*, **28**, 869 (1987).
381. G. Guanti, L. Banfi and E. Narisano, *Tetrahedron Lett.*, **31**, 6421 (1990).
382. B. Mekki, G. Singh and R. H. Wightman, *Tetrahedron Lett.*, **32**, 5143 (1991).
383. T. Inghardt, T. Frejd and G. Svensson, *Tetrahedron*, **47**, 6469 (1991).
384. P. G. M. Wuts, S. S. Bigelow, *J. Org. Chem.*, **48**, 3489 (1983).
385. G. E. Keck, D. E. Abbott and M. R. Wiley, *Tetrahedron Lett.*, **28**, 139 (1987).
386. J. A. Marshall and G. P. Luke, *J. Org. Chem.*, **56**, 483 (1991).
387. W. R. Roush, P. T. Grover and X. Lin, *Tetrahedron Lett.*, **31**, 7563 (1990).
388. W. R. Roush and P. T. Grover, *Tetrahedron Lett.*, **31**, 7567 (1990).
389. J. Uenishi, S. Masuda and S. Wakabayashi, *Tetrahedron Lett.*, **32**, 5097 (1991).
390. D. Seebach and M. Eberle, *Synthesis*, 37 (1986).
391. D. W. Brooks, R. P. Kellog and C. S. Cooper, *J. Org. Chem.*, **52**, 192 (1987).
392. S. Takano, A. Kurotaki, Y. Sekiguchi, S. Satoh, M. Hirama and K. Ogasawara, *Synthesis*, 811 (1986).
393. G. Adam and D. Seebach, *Synthesis*, 373 (1988).
394. E. Hungerbühler and D. Seebach, *Helv. Chim. Acta*, **64**, 687 (1981).
395. M. Ohno, K. Fujita, H. Nakai, S. Kobayashi, K. Inoue and S. Nojima, *Chem. Pharm. Bull.*, **33**, 572 (1985).
396. E. A. Mash, K. A. Nelson, S. Van Deusen and S. B. Hemperly, *Org. Synth.*, **68**, 92 (1990).
397. I. Hoppe, U. Schöllkopf, M. Nieger and E. Egert, *Angew. Chem., Int. Ed. Engl.*, **24**, 1067 (1985).
398. K. Nakayama and J. D. Rainier, *Tetrahedron*, **46**, 4165 (1990).
399. M. Born and C. Tamm, *Helv. Chim. Acta*, **73**, 2242 (1990).
400. M. Born and C. Tamm, *Synthesis*, 435 (1991).
401. G. Hirth and W. Walther, *Helv. Chim. Acta*, **68**, 1863 (1985).
402. C. A. Townsend and S.-S. Mao, *J. Chem. Soc., Chem. Commun.*, 86 (1987).
403. U. Peters, W. Bankova and P. Welzel, *Tetrahedron*, **43**, 3803 (1987).
404. R. Roy, M. Letellier, D. Fenske and H. C. Jarrell, *J. Chem. Soc., Chem. Commun.*, 378 (1990).
405. A. H. Al-Hakim, A. H. Haines and C. Morley, *Synthesis*, 207 (1985).
406. G. Fronza, C. Fuganti, G. Pedrocchi-Fantoni and S. Servi, *Chem. Lett.*, 2141 (1989).
407. H. Uzawa, Y. Nishida, S. Hanada, H. Ohrui and H. Meguro, *J. Chem. Soc., Chem. Commun.*, 862 (1989).
408. M. E. Jung and T. J. Shaw, *J. Am. Chem. Soc.*, **102**, 6304 (1980).
409. C. Hubschwerlen, *Synthesis*, 962 (1986).
410. K. Yamagata, Y. Yamagiwa and T. Kamikawa, *J. Chem. Soc., Perkin Trans. 1*, 3355 (1990).
411. E. Abushanab, P. Vemishetti, R. W. Leiby, H. K. Singh, A. B. Mikkilineni, D. C.-J. Wu, R. Saibaba and R. P. Panzica, *J. Org. Chem.*, **53**, 2598 (1988).
412. M. Makkee, A. P. G. Kieboom and H. van Bekkum, *Starch/Starke*, **37**, 133 (1985).
413. J. Ruddlesden, A. Stewart, D. J. Thompson and R. Whelan, *Faraday Discuss. Chem. Soc.*, **72**, 397 (1981).
414. M. Makkee, A. P. G. Kieboom and H. van Bekkum, *Carbohydr. Res.*, **138**, 225 (1985).
415. A. A. Wismeijer, A. P. G. Kieboom and H. van Bekkum, *React. Kinet. Catal. Lett.*, **29**, 311 (1985).
416. J. Court, J. P. Damon, J. Masson and P. Wierzchowski, in *Studies in Surface Science and Catalysis*, Vol. 41 (Eds. M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, C. Montassier and G. Pérot), Elsevier, Amsterdam, 1989, pp. 189–196.
417. P. J. Cerino, G. Fleche, P. Gallezot and J. P. Salome, in *Studies in Surface Science and Catalysis*, Vol. 59 (Eds. M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, G. Pérot, R. Maurel and C. Montassier), Elsevier, Amsterdam, 1991, pp. 231–236.

418. M. Makkee, A. P. G. Kieboom and H. van Bekkum, *Carbohydr. Res.*, **138**, 237 (1985).
419. S. V. Attwood and A. G. M. Barrett, *J. Chem. Soc., Perkin Trans. 1*, 1315 (1984).
420. G. H. Veeneman, L. J. G. Gomes and J. H. van Boom, *Tetrahedron*, **45**, 7433 (1989).
421. I. Paterson and M. M. Mansuri, *Tetrahedron*, **41**, 3569 (1985).
422. S. L. Schreiber, *Chem. Scr.*, **27**, 5636 (1987).
423. R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **26**, 489 (1987).
424. B. H. Lipshutz, *Synthesis*, 325 (1987).
425. T. Oishi and T. Nakata, *Synthesis*, 635 (1990).
426. J. A. Marshall and B. E. Blough, *J. Org. Chem.*, **55**, 1540 (1990).
427. S. L. Schreiber and M. T. Goulet, *J. Am. Chem. Soc.*, **109**, 4718 (1987).
428. S. Hanessian, N. G. Cooke, B. Dehoff and Y. Sakito, *J. Am. Chem. Soc.*, **112**, 5276 (1990).
429. Y. Mori and M. Suzuki, *J. Chem. Soc., Perkin Trans. 1*, 1809 (1990).
430. Y. Mori, Y. Kohchi, M. Suzuki, S. Carmeli, R. E. Moore and G. M. L. Patterson, *J. Org. Chem.*, **56**, 631 (1991).
431. S. D. Rychnovsky, *J. Org. Chem.*, **54**, 4982 (1989).
432. S. D. Rychnovsky, S. Zeller, D. J. Skalitzky and G. Griesgraber, *J. Org. Chem.*, **55**, 5550 (1990).
433. A. Dondoni, G. Fantin, M. Fogagnolo and A. Medici, *Angew. Chem., Int. Ed. Engl.*, **25**, 835 (1986).
434. A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici and P. Pedrini, *J. Org. Chem.*, **54**, 693 (1989).
435. D. S. Matteson and M. L. Peterson, *J. Org. Chem.*, **52**, 5116 (1987).
436. M. Nakajima, I. Tomida and S. Takei, *Chem. Ber.*, **92**, 163 (1959).
437. M. Balci, Y. Sütbeyaz and H. Secen, *Tetrahedron*, **46**, 3715 (1990).
438. H. A. J. Carless and K. Busia, *Tetrahedron Lett.*, **31**, 1617 (1990).
439. H. Secen, Y. Sütbeyaz and M. Balci, *Tetrahedron Lett.*, **31**, 1323 (1990).
440. H. A. J. Carless and K. Busia, *Tetrahedron Lett.*, **31**, 3449 (1990).
441. H. A. J. Carless and O. Z. Oak, *Tetrahedron Lett.*, **30**, 1719 (1989).
442. P. Vogel, D. Fattori, F. Gasparini and C. Le Drian, *Synlett*, 173 (1990).
443. M. Lautens, A. C. Smith, A. S. Abd-El-Aziz and A. H. Huboux, *Tetrahedron Lett.*, **31**, 3253 (1990).
444. C. Le Drian, J.-P. Vionnet and P. Vogel, *Helv. Chim. Acta*, **73**, 161 (1990).
445. T. V. RajanBabu, T. Fukunaga and G. S. Reddy, *J. Am. Chem. Soc.*, **111**, 1759 (1989).
446. J. J. Gaudino and C. S. Wilcox, *Carbohydr. Res.*, **206**, 233 (1990).
447. N. Chida, M. Ohtsuka, K. Nakazawa and S. Ogawa, *J. Chem. Soc., Chem. Commun.*, 436 (1989).
448. H. Hönig, P. Seufer-Wasserthal, A. E. Stütz and E. Zenz, *Tetrahedron Lett.*, **30**, 811 (1989).
449. J. R. Falck and P. Yadagiri, *J. Org. Chem.*, **54**, 5851 (1989).
450. J. E. Audia, L. Boisvert, A. D. Patten, A. Villalobos and S. J. Danishefsky, *J. Org. Chem.*, **54**, 3738 (1989).
451. T. K. M. Shing, Y.-X. Cui and Y. Tang, *J. Chem. Soc., Chem. Commun.*, 756 (1991).
452. R. J. Parry and K. Haridas, *Tetrahedron Lett.*, **31**, 7549 (1990).
453. C. Marschner, G. Penn and H. Griengl, *Tetrahedron Lett.*, **31**, 2873 (1990).
454. W. Schmid and G. M. Whitesides, *J. Am. Chem. Soc.*, **112**, 9670 (1990).
455. T. Takahashi, H. Kotsubo, A. Iyobe, T. Namiki and T. Koizumi, *J. Chem. Soc., Perkin Trans. 1*, 3065 (1990).
456. J. van Gent, A. A. Wismeijer, A. W. P. G. P. Rit and H. van Bekkum, *Tetrahedron Lett.*, **27**, 1059 (1986).
457. S. Ito, A. Kunai, H. Okada and K. Sasaki, *J. Org. Chem.*, **53**, 296 (1988).
458. S. Ito, T. Yamasaki, H. Okada, S. Okino and K. Sasaki, *J. Chem. Soc., Perkin Trans. 2*, 285 (1988).
459. P. Capdevielle and M. Maumy, *Tetrahedron Lett.*, **23**, 1577 (1982).
460. M. Sako, S. Ohara, K. Hirota and Y. Maki, *J. Chem. Soc., Perkin Trans. 1*, 3339 (1990).
461. M.-N. Carrier, C. Scheer, P. Gouvine, J.-F. Bartoli, P. Battioni and D. Mansuy, *Tetrahedron Lett.*, **31**, 6645 (1990).
462. Y. Takizawa, A. Tateishi, J. Sugiyama, H. Yoshida and N. Yoshihara, *J. Chem. Soc., Chem. Commun.*, 104 (1991).
463. B. Notari, in *Studies in Surface Science and Catalysis*, Vol. 37 (Eds. P. J. Grobet, W. J. Mortier, E. F. Vansant and G. Schulz-Ekloff), Elsevier, Amsterdam, 1987, pp. 413–425.
464. A. Tuel, S. Moussa-Khouzami, Y. Ben-Taarit and C. Naccache, *J. Mol. Catal.*, **68**, 45 (1991).
465. A. Thangaraj, R. Kumar and P. Ratnasamy, *J. Catal.*, **131**, 294 (1991).

466. C. D. Gutsche and M. Iqbal, *Org. Synth.*, **68**, 234 (1990).
467. C. D. Gutsche, B. Dhawan, M. Leonis and D. Stewart, *Org. Synth.*, **68**, 238 (1990).
468. J. A. Munch and C. D. Gutsche, *Org. Synth.*, **68**, 243 (1990).
469. C. D. Gutsche, *Calixarenes*, The Royal Society of Chemistry, Cambridge, 1989.
470. C. D. Gutsche, in *Topics in Inclusion Science*, Vol. 3 (Eds. J. Vicens and V. Böhmer), Kluwer, Dordrecht, 1990, pp. 3–37.
471. E. Dahan and S. E. Biali, *J. Org. Chem.*, **54**, 6003 (1989).
472. S. Shinkai, T. Arimura, H. Kawabata, H. Murakami, K. Araki, K. Iwamoto and T. Matsuda, *J. Chem. Soc., Chem. Commun.*, 1734 (1990).
473. J. de Mendoza, P. M. Nieto, P. Prados and C. Sánchez, *Tetrahedron*, **46**, 671 (1990).
474. G. Cometti, E. Dalcanale, A. Duvosel and A.-M. Levelut, *J. Chem. Soc., Chem. Commun.*, 163 (1990).
475. M. Tashiro, A. Tsuge, T. Sawada, T. Makishima, S. Horie, T. Arimura, S. Mataka and T. Yamoto, *J. Org. Chem.*, **55**, 2404 (1990).
476. Y. Zhang and R. Lin, *Synth. Commun.*, **17**, 329 (1987).
477. C. Saitz, J. A. Valderrama and R. Tapia, *Synth. Commun.*, **20**, 3103 (1990).
478. A. Alberola, A. M. Gonzalez and F. J. Pulido, *Rev. Roum. Chim.*, **29**, 441 (1984).
479. T. Hirao, M. Mori and Y. Ohshiro, *J. Org. Chem.*, **55**, 358 (1990).
480. I. S. Blagbrough, G. Pattenden and R. A. Raphael, *Tetrahedron Lett.*, **23**, 4843 (1982).
481. J. E. Oliver, K. R. Wilzer and R. M. Waters, *Synthesis*, 1117 (1990).
482. A. S. Kotnis, *Tetrahedron Lett.*, **32**, 3441 (1991).
483. G. C. A. Luijkx, F. van Rantwijk and H. van Bekkum, *Recl. Trav. Chim. Pays-Bas*, **110**, 343 (1991).
484. S. H. Bertz, *Synthesis*, 708 (1980).
485. F. Viviani, M. Gaudry and A. Marquet, *J. Chem. Soc., Perkin Trans. 1*, 1255 (1990).
486. H.-O. Kalinowski, G. Crass and D. Seebach, *Chem. Ber.*, **114**, 477 (1981).
487. J. de la Zerda, G. Barak and Y. Sasson, *Tetrahedron*, **45**, 1533 (1989).
488. D. H. R. Barton, J.-P. Finet and C. Pichon, *J. Chem. Soc., Chem. Commun.*, 65 (1986).
489. H. Brunner, U. Obermann and P. Wimmer, *J. Organomet. Chem.*, **316**, C1 (1986).
490. J. W. Kelly, P. L. Robinson and S. A. Evans, Jr., *J. Org. Chem.*, **50**, 5007 (1985).
491. T. Shirasaka, Y. Takuma and N. Imaki, *Synth. Commun.*, **20**, 1213 (1990).
492. A. Shanzer, *Tetrahedron Lett.*, **21**, 221 (1980).
493. M. H. Marx and R. A. Wiley, *Tetrahedron Lett.*, **26**, 1379 (1985).
494. S. David and S. Hanessian, *Tetrahedron*, **41**, 643 (1985).
495. A. Mori, J. Fujiwara, K. Maruoka and H. Yamamoto, *J. Organomet. Chem.*, **285**, 83 (1985).
496. A. Mori, K. Ishihara, I. Arai and H. Yamamoto, *Tetrahedron*, **43**, 755 (1987).
497. H. Kotsuki, Y. Ushio, N. Yoshimura and M. Ochi, *J. Org. Chem.*, **52**, 2594 (1987).
498. T. Sugimura, T. Futagawa, M. Yoshikawa and A. Tai, *Tetrahedron Lett.*, **30**, 3807 (1989).
499. T. Nishiguchi and H. Taya, *J. Am. Chem. Soc.*, **111**, 9102 (1989).
500. H. Suginome and J. B. Wang, *J. Chem. Soc., Perkin Trans. 1*, 2825 (1990).
501. D. Cantacuzène and C. Guerreiro, *Tetrahedron*, **45**, 741 (1989).
502. T. J. Michalski, J. E. Hunt, C. Bradshaw, A. M. Wagner, J. R. Norris and J. J. Katz, *J. Am. Chem. Soc.*, **110**, 5888 (1988).
503. M. Prashad, J. C. Tomesch and W. J. Houlihan, *Synthesis*, 477 (1990).
504. Y. Masuyama, M. Usukura, Y. Kurusu, *Chem. Lett.*, 1951 (1982).
505. J. Iqbal, R. R. Srivastava, K. B. Gupta and M. A. Khan, *Synth. Commun.*, **19**, 901 (1989).
506. M. Takasu, Y. Naruse and H. Yamamoto, *Tetrahedron Lett.*, **29**, 1947 (1988).
507. S. David and A. Thieffry, *J. Org. Chem.*, **48**, 441 (1983).
508. F. Bauer, K.-P. Ruess and M. Liefländer, *Justus Liebigs Ann. Chem.*, 765 (1991).
509. G. Reginato, A. Ricci, S. Roelens and S. Scapecchi, *J. Org. Chem.*, **55**, 5132 (1990).
510. O. Mitsunobu, *Synthesis*, 1 (1981).
511. A. Pautard-Cooper and S. A. Evans, Jr., *J. Org. Chem.*, **54**, 2485 (1989).
512. A. M. Pautard and S. A. Evans, Jr., *J. Org. Chem.*, **53**, 2300 (1988).
513. M. Allainmat, P. L'Haridon, L. Toupet and D. Plusquellec, *Synthesis*, 27 (1990).
514. H. W. Lee and Y. Kishi, *J. Org. Chem.*, **50**, 4402 (1985).
515. D. C. Billington, R. Baker, J. J. Kulagowski, I. M. Mawer, J. P. Vacca, S. J. deSolms and J. R. Huff, *J. Chem. Soc., Perkin Trans. 1*, 1423 (1989).
516. Y. Watanabe, M. Mitani, T. Morita and S. Ozaki, *J. Chem. Soc., Chem. Commun.*, 482 (1989).

517. P. J. Dijkstra, J. A. J. Brunink, K.-E. Bugge, D. N. Reinhoudt, S. Harkema, R. Ungaro, F. Ugozzoli and E. Ghidini, *J. Am. Chem. Soc.*, **111**, 7567 (1989).
518. J.-D. van Loon, A. Arduini, L. Coppi, W. Verboom, A. Pochini, R. Ungaro, S. Harkema and D. N. Reinhoudt, *J. Org. Chem.*, **55**, 5639 (1990).
519. E. M. Collins, M. A. McKervey and S. J. Harris, *J. Chem. Soc., Perkin Trans. 1*, 372 (1989).
520. A. Casnati, A. Arduini, E. Ghidini, A. Pochini and R. Ungaro, *Tetrahedron*, **47**, 2221 (1991).
521. A. Arduini, A. Casnati, L. Dodi, A. Pochini and R. Ungaro, *J. Chem. Soc., Chem. Commun.*, 1597 (1990).
522. L. C. Groenen, B. H. M. Ruël, A. Casnati, W. Verboom, A. Pochini, R. Ungaro and D. N. Reinhoudt, *Tetrahedron*, **47**, 8379 (1991).
523. F. Bottino, L. Giunta and S. Pappalardo, *J. Org. Chem.*, **54**, 5407 (1989).
524. A. L. Margolin, D. L. Delinck and M. R. Whalon, *J. Am. Chem. Soc.*, **112**, 2849 (1990).
525. S. Riva and A. M. Klibanov, *J. Am. Chem. Soc.*, **110**, 3291 (1988).
526. S. Riva, R. Bovara, G. Ottolina, F. Secundo and G. Carrea, *J. Org. Chem.*, **54**, 3161 (1989).
527. S. Ramaswamy, B. Morgan and A. C. Oehlschlager, *Tetrahedron Lett.*, **31**, 3405 (1990).
528. E. W. Holla, *Angew. Chem., Int. Ed. Engl.*, **28**, 220 (1989).
529. A. M. Klibanov, *Acc. Chem. Res.*, **23**, 114 (1990).
530. G. M. Whitesides and C.-H. Wong, *Angew. Chem., Int. Ed. Engl.*, **24**, 617 (1985).
531. C.-S. Chen and C. J. Sih, *Angew. Chem., Int. Ed. Engl.*, **28**, 695 (1989).
532. S. Atsuumi, M. Nakano, Y. Koike, S. Tanaka, M. Ohkubo, T. Yonezawa, H. Funabashi, J. Hashimoto and H. Morishima, *Tetrahedron Lett.*, **31**, 1601 (1990).
533. K. Tsuji, Y. Terao and K. Achiwa, *Tetrahedron Lett.*, **30**, 6189 (1989).
534. E. Santaniello, P. Ferraboschi and P. Grisenti, *Tetrahedron Lett.*, **31**, 5657 (1990).
535. O. Ghisalba, R. Lattmann and D. Gygax, *Recl. Trav. Chim. Pays-Bas*, **110**, 263 (1991).
536. C. Andreu, J. A. Marco and G. Asensio, *J. Chem. Soc., Perkin Trans. 1*, 3209 (1990).
537. R. Seemayer and M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, 49 (1991).
538. R. S. Ward, *Chem. Soc. Rev.*, **19**, 1 (1990).
539. H. Brunner, U. Obermann and P. Wimmer, *Organometallics*, **8**, 821 (1989).
540. T. Harada, Y. Ikemura, H. Nakajima, T. Ohnishi and A. Oku, *Chem. Lett.*, 1441 (1990).
541. T. Harada, T. Hayashiya, I. Wada, N. Iwa-ake and A. Oku, *J. Am. Chem. Soc.*, **109**, 527 (1987).
542. T. Harada, I. Wada and A. Oku, *J. Org. Chem.*, **54**, 2599 (1989).
543. T. Mukaiyama, I. Tomioka and M. Shimizu, *Chem. Lett.*, 49 (1984).
544. T. Mukaiyama, Y. Tanabe and M. Shimizu, *Chem. Lett.*, 401 (1984).
545. D. C. Billington, *Chem. Soc. Rev.*, **18**, 83 (1989).
546. B. V. L. Potter, *Nat. Prod. Rep.*, **7**, 1 (1990).
547. Y. Watanabe, A. Oka, Y. Shimizu and S. Ozaki, *Tetrahedron Lett.*, **31**, 2613 (1990).
548. M. V. Bhatt and S. U. Kulkarni, *Synthesis*, 249 (1983).
549. C. F. Carvalho, A. V. Russo and M. V. Sargent, *Aust. J. Chem.*, **38**, 777 (1985).
550. J. R. Hwu and S.-C. Tsay, *J. Org. Chem.*, **55**, 5987 (1990).
551. T. Akiyama, H. Shima and S. Ozaki, *Tetrahedron Lett.*, **32**, 5593 (1991).
552. T. Akiyama, N. Takechi, H. Shima and S. Ozaki, *Chem. Lett.*, 1881 (1990).
553. H. Hori, Y. Nishida, H. Ohrui and H. Meguro, *J. Org. Chem.*, **54**, 1346 (1989).
554. K. V. Rao and S. K. Chattopadhyay, *J. Org. Chem.*, **55**, 1427 (1990).
555. R. Cruz-Almanza, F. J. Pérez-Flores and M. Avila, *Synth. Commun.*, **20**, 1125 (1990).
556. B. H. Lipshutz, D. Pollart, J. Monforte and H. Kotsuki, *Tetrahedron Lett.*, **26**, 705 (1985).
557. H. M. Sweers and C.-H. Wong, *J. Am. Chem. Soc.*, **108**, 6421 (1986).
558. M. Therisod and A. M. Klibanov, *J. Am. Chem. Soc.*, **109**, 3977 (1987).
559. H. Hemmerle and H.-J. Gais, *Tetrahedron Lett.*, **28**, 3471 (1987).
560. U. Ader, D. Breitgoff, P. Klein, K. E. Laumen and M. P. Schneider, *Tetrahedron Lett.*, **30**, 1793 (1989).
561. Z.-W. Guo, S.-H. Wu, C.-S. Chen, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc.*, **112**, 4942 (1990).
562. G. Guanti, E. Narisano, T. Podgorski, S. Thea and A. Williams, *Tetrahedron*, **46**, 7081 (1990).
563. D. Basavaiah, P. R. Krishna and T. K. Bharathi, *Tetrahedron Lett.*, **31**, 4347 (1990).
564. A. K. Sinhababu, M. Kawase and R. T. Borchardt, *Synthesis*, 710 (1988).
565. S. Kim, I. S. Kee, Y. H. Park and J. H. Park, *Synlett*, 183 (1991).
566. K. Toshima, K. Yanagawa, S. Mukaiyama and K. Tatsuta, *Tetrahedron Lett.*, **31**, 6697 (1990).
567. C. Prakash, S. Saleh and I. A. Blair, *Tetrahedron Lett.*, **30**, 19 (1989).

568. A. Alexakis and P. Mangeney, *Tetrahedron:Asymmetry*, **1**, 477 (1990).
569. F. A. J. Meskens, *Synthesis*, 501 (1981).
570. D. Marton, P. Slaviero and G. Tagliavini, *Gazz. Chim. Ital.*, **119**, 359 (1989).
571. T. H. Chan, M. A. Brook and T. Chaly, *Synthesis*, 203 (1983).
572. W.-B. Wang, L.-L. Shi and Y.-Z. Huang, *Tetrahedron*, **46**, 3315 (1990).
573. F. Gorla and L. M. Venanzi, *Helv. Chim. Acta*, **73**, 690 (1990).
574. J. Ott, G. M. Ramos Tombo, B. Schmid, L. M. Venanzi, G. Wang and T. R. Ward, *Tetrahedron Lett.*, **30**, 6151 (1989).
575. M. Shibagaki, K. Takahashi, H. Kuno and H. Matsushita, *Bull. Chem. Soc. Jpn.*, **63**, 1258 (1990).
576. J.-L. Gras, R. Nouguier and M. Mchich, *Tetrahedron Lett.*, **28**, 6601 (1987).
577. T. D. Inch, *Tetrahedron*, **40**, 3161 (1984).
578. J.-L. Debost, J. Gelas and D. Horton, *J. Org. Chem.*, **48**, 1381 (1983).
579. C. R. Schmid, J. D. Bryant, M. Dowlatzedah, J. L. Phillips, D. E. Prather, R. D. Schantz, N. L. Sear and C. S. Vianco, *J. Org. Chem.*, **56**, 4056 (1991).
580. T. Hosokawa, T. Ohta, S. Kanayama and S.-I. Murahashi, *J. Org. Chem.*, **52**, 1758 (1987).
581. T. Hosokawa, Y. Ataka and S.-I. Murahashi, *Bull. Chem. Soc. Jpn.*, **63**, 166 (1990).
582. R. E. Zelle and W. J. McClellan, *Tetrahedron Lett.*, **32**, 2461 (1991).
583. E. Block, *Org. React. (N.Y.)*, **30**, 457 (1984).
584. P. Mues and H.-J. Buysch, *Synthesis*, 249 (1990).
585. T. Endo and M. Okawara, *Synthesis*, 837 (1984).
586. K. Narasaka, *Synthesis*, 1 (1991).
587. D. S. Matteson, *Acc. Chem. Res.*, **21**, 294 (1988).
588. D. S. Matteson, *Tetrahedron*, **45**, 1859 (1989).
589. R. Noyori, I. Tomino, Y. Tanimoto and M. Nishizawa, *J. Am. Chem. Soc.*, **106**, 6709 (1984).
590. K. Yamamoto, K. Ueno and K. Naemura, *J. Chem. Soc., Perkin Trans. 1*, 2607 (1991).
591. C. Chapuis and J. Jurczak, *Helv. Chim. Acta*, **70**, 436 (1987).
592. F. Rebiere, O. Riant and H. B. Kagan, *Tetrahedron:Asymmetry*, **1**, 199 (1990).
593. M. Hayashi, T. Matsuda and N. Oguni, *J. Chem. Soc., Chem. Commun.*, 1364 (1990).
594. B. Schmidt and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **30**, 99 (1991).
595. K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima and J. Sugimori, *J. Am. Chem. Soc.*, **111**, 5340 (1989).
596. K. Mikami, M. Terada and T. Nakai, *J. Am. Chem. Soc.*, **112**, 3949 (1990).
597. T. Mukaiyama, A. Inubushi, S. Suda, R. Hara and S. Kobayashi, *Chem. Lett.*, 1015 (1990).
598. R. H. Cragg and R. D. Lane, *Inorg. Chim. Acta*, **54**, L115 (1981).
599. S. D. Pastor, J. D. Spivack, R. K. Rodebaugh and D. Bini, *J. Org. Chem.*, **49**, 1297 (1984).
600. R. H. Cragg and R. D. Lane, *J. Organomet. Chem.*, **289**, 23 (1985).
601. A. W. Hanson, A. W. McCulloch and A. G. McInnes, *Can. J. Chem.*, **64**, 1450 (1986).
602. R. H. Cragg and R. D. Lane, *J. Organomet. Chem.*, **267**, 1 (1984).
603. M. Lalonde and T. H. Chan, *Synthesis*, 817 (1985).
604. A. Boudin, G. Cerveau, C. Chuit, R. J. P. Corriu and C. Reye, *Bull. Chem. Soc. Jpn.*, **61**, 101 (1988).
605. A. Hosomi, S. Kohra, K. Ogata, T. Yanagi and Y. Tominaga, *J. Org. Chem.*, **55**, 2415 (1990).
606. R. Haruta, M. Ishiguro, N. Ikeda and H. Yamamoto, *J. Am. Chem. Soc.*, **104**, 7667 (1982).
607. H. C. Brown, B. T. Cho and W. S. Park, *J. Org. Chem.*, **52**, 4020 (1987).
608. H. C. Brown, D. Basavaiah, S. U. Kulkarni, N. G. Bhat and J. V. N. Vara Prasad, *J. Org. Chem.*, **53**, 239 (1988).
609. J. Morgan and J. T. Pinhey, *J. Chem. Soc., Perkin Trans. 1*, 715 (1990).
610. T. Imai, H. Mineta and S. Nishida, *J. Org. Chem.*, **55**, 4986 (1990).
611. W. R. Roush, K. Ando, D. B. Powers, A. D. Palkowitz and R. L. Halterman, *J. Am. Chem. Soc.*, **112**, 6339 (1990).
612. L. Garlaschelli, G. Mellerio and G. Vidari, *Tetrahedron Lett.*, **30**, 597 (1989).
613. A. Arase, Y. Nunokawa, Y. Masuda and M. Hoshi, *J. Chem. Soc., Chem. Commun.*, 205 (1991).
614. M. van Duin, J. A. Peters, A. P. G. Kieboom and H. van Bekkum, *Tetrahedron*, **41**, 3411 (1985).
615. C. D'Silva and D. Green, *J. Chem. Soc., Chem. Commun.*, 227 (1991).
616. K. Maruoka, T. Itoh, T. Shirasaka and H. Yamamoto, *J. Am. Chem. Soc.*, **110**, 310 (1988).
617. D. W. Stephan, *Organometallics*, **9**, 2718 (1990).
618. S. Sakane, K. Maruoka and H. Yamamoto, *Tetrahedron*, **42**, 2203 (1986).
619. B. M. Kim and K. B. Sharpless, *Tetrahedron Lett.*, **30**, 655 (1989).

620. P. Hug, S. Kolly, H. Meier, R. Pitteloud, D. Poppinger, G. Rihs and G. Rist, *Helv. Chim. Acta*, **73**, 618 (1990).
621. Y. Tamaru, K. Nagao, T. Bando and Z. Yoshida, *J. Org. Chem.*, **55**, 1823 (1990).
622. M. S. Berridge, M. P. Franceschini, E. Rosenfeld and T. J. Tewson, *J. Org. Chem.*, **55**, 1211 (1990).
623. F. Rebiere, O. Samuel, L. Ricard and H. B. Kagan, *J. Org. Chem.*, **56**, 5991 (1991).
624. R. J. P. Corriu, G. F. Lanneau and D. Leclercq, *Tetrahedron*, **42**, 5591 (1986).
625. J. Jacques and C. Fouquey, *Org. Synth.*, **67**, 1 (1989).
626. N. Kato, *J. Am. Chem. Soc.*, **112**, 254 (1990).
627. J. Jankowska and J. Stawinski, *Synthesis*, 408 (1984).
628. K. C. Kumara Swamy, R. O. Day, J. M. Holmes and R. R. Holmes, *J. Am. Chem. Soc.*, **112**, 6095 (1990).
629. S. D. Burton, K. C. Kumara Swamy, J. M. Holmes, R. O. Day and R. R. Holmes, *J. Am. Chem. Soc.*, **112**, 6104 (1990).
630. D. A. Laidler and J. F. Stoddart, in *The Chemistry of Functional Groups*, Supplement E (Ed. S. Patai), Wiley, Chichester, 1980, pp. 1–57.
631. G. Coudert, M. Mpassi, G. Guillaumet and C. Selve, *Synth. Commun.*, **16**, 19 (1986).
632. Y. Nakatsuji, N. Kameda and M. Okahara, *Synthesis*, 280 (1987).
633. P. P. Castro, S. Tihomirov and C. G. Gutierrez, *J. Org. Chem.*, **53**, 5179 (1988).
634. S. T. Jolley, J. S. Bradshaw and R. M. Izatt, *J. Heterocycl. Chem.*, **19**, 3 (1982).
635. J. F. Stoddart, in *Topics in Stereochemistry*, Vol. 17 (Eds. E. E. Eliel and S. H. Wilen), Wiley, New York, 1987, pp. 207–288.
636. G. Mehta, K. S. Rao, N. Krishnamurthy, V. Srinivas and D. Balasubramanian, *Tetrahedron*, **45**, 2743 (1989).
637. E. Chapoteau, B. P. Czech, A. Kumar, A. Pose, R. A. Bartsch, R. A. Holwerda, N. K. Dalley, B. E. Wilson and J. Weining, *J. Org. Chem.*, **54**, 861 (1989).
638. R. S. Grewal and H. Hart, *Tetrahedron Lett.*, **31**, 4271 (1990).
639. C.-S. Chen, H.-E. Chao and S.-J. Wang, *Synth. Commun.*, **17**, 1431 (1987).
640. P. Zerr, M. Mussrabi and J. Vicens, *Tetrahedron Lett.*, **32**, 1879 (1991).
641. B. A. Jones, J. S. Bradshaw, P. R. Brown, J. J. Christensen and R. M. Izatt, *J. Org. Chem.*, **48**, 2635 (1983).
642. C. Erk, *Justus Liebigs Ann. Chem.*, 1083 (1991).
643. W. Worthy, *Chem. Eng. News*, **66**, 19 (1988).
644. D. A. Tomalia, A. M. Naylor and W. A. Goddard, III, *Angew. Chem., Int. Ed. Engl.*, **29**, 138 (1990).
645. A. B. Padias, H. K. Hall, Jr., D. A. Tomalia and J. R. McConnell, *J. Org. Chem.*, **52**, 5305 (1987).
646. G. R. Newkome, Z.-Q. Yao, G. R. Baker and V. K. Gupta, *J. Org. Chem.*, **50**, 2003 (1985).
647. G. R. Newkome, Z.-Q. Yao, G. R. Baker, V. K. Gupta, P. S. Russo and M. J. Saunders, *J. Am. Chem. Soc.*, **108**, 849 (1986).
648. M. N. Bochkarev, *Organomet. Chem. (USSR)*, **1**, 115 (1988).
649. C. J. Hawker and J. M. J. Fréchet, *J. Am. Chem. Soc.*, **112**, 7638 (1990).
650. K. L. Wooley, C. J. Hawker and J. M. J. Fréchet, *J. Am. Chem. Soc.*, **113**, 4252 (1991).
651. K. L. Wooley, C. J. Hawker and J. M. J. Fréchet, *J. Chem. Soc., Perkin Trans. 1*, 1059 (1991).
652. W. Buijs, P. van Elburg and A. van der Gen, *Synth. Commun.*, **13**, 387 (1983).
653. C. N. Barry and S. A. Evans, Jr., *J. Org. Chem.*, **48**, 2825 (1983).
654. C. N. Barry and S. A. Evans, Jr., *Tetrahedron Lett.*, **24**, 661 (1983).
655. X. Wang, *J. Chem. Soc., Chem. Commun.*, 1515 (1991).
656. M. Nakatsuka, J. A. Ragan, T. Sammakia, D. B. Smith, D. E. Uehling and S. L. Schreiber, *J. Am. Chem. Soc.*, **112**, 5583 (1990).
657. M. Shimizu, Y. Nakahara and H. Yoshioka, *Tetrahedron Lett.*, **26**, 4207 (1985).
658. A. P. Kozikowski, A. H. Fauq and J. M. Rusnak, *Tetrahedron Lett.*, **30**, 3365 (1989).
659. J. L. Offer, J. C. Metcalfe and G. A. Smith, *J. Chem. Soc., Chem. Commun.*, 1312 (1990).
660. A. P. Kozikowski, A. H. Fauq, G. Powis and D. C. Melder, *J. Am. Chem. Soc.*, **112**, 4528 (1990).
661. A. Pautard-Cooper, S. A. Evans, Jr. and W. R. Kenan, Jr., *Tetrahedron*, **47**, 1603 (1991).
662. T. Gajda, *Synthesis*, 1108 (1987).
663. C. Tschierske, H. Köhler, H. Zaschke and E. Kleinpeter, *Tetrahedron*, **45**, 6987 (1989).
664. D. G. Cleary, *Synth. Commun.*, **19**, 737 (1989).
665. A. M. Echavarren and J. K. Stille, *J. Am. Chem. Soc.*, **109**, 5478 (1987).

666. G. Martorell, A. Garcia-Raso and J. M. Saá, *Tetrahedron Lett.*, **31**, 2357 (1990).
667. T. Nakano, T. Terada, Y. Ishii and M. Ogawa, *Synthesis*, 774 (1986).
668. A. M. Maione and A. Romeo, *Synthesis*, 955 (1984).
669. D. Sparfel, J. Baranne-Lafont, N. K. Cuong, P. Capdevielle and M. Maumy, *Tetrahedron*, **46**, 793 (1990).
670. H. Firouzabadi, D. Mohajer and M. E. Moghaddam, *Synth. Commun.*, **16**, 211 (1986).
671. P. Capdevielle, D. Sparfel, J. Baranne-Lafont, N. K. Cuong and M. Maumy, *J. Chem. Soc., Chem. Commun.*, 565 (1990).
672. P. L. Anelli, S. Banfi, F. Montanari and S. Quici, *J. Org. Chem.*, **54**, 2970 (1989).
673. R. Siedlecka, J. Skarzewski and J. Mlochowski, *Tetrahedron Lett.*, **31**, 2177 (1990).
674. T. Inokuchi, S. Matsumoto, T. Nishiyama and S. Torii, *J. Org. Chem.*, **55**, 462 (1990).
675. M. F. Semmelhack, C. R. Schmid, D. A. Cortés and C. S. Chou, *J. Am. Chem. Soc.*, **106**, 3374 (1984).
676. M. F. Semmelhack, C. S. Chou and D. A. Cortés, *J. Am. Chem. Soc.*, **105**, 4492 (1983).
677. T. Inokuchi, S. Matsumoto and S. Torii, *J. Org. Chem.*, **56**, 2416 (1991).
678. Y. Sakata and Y. Ishii, *J. Org. Chem.*, **56**, 6233 (1991).
679. Y. Ishii, K. Yamawaki, T. Ura, H. Yamada, T. Yoshida and M. Ogawa, *J. Org. Chem.*, **53**, 3587 (1988).
680. K. Yamawaki, T. Yoshida, H. Nishihara, Y. Ishii and M. Ogawa, *Synth. Commun.*, **16**, 537 (1986).
681. K. Kaneda, Y. Kawanishi, K. Jitsukawa and S. Teranishi, *Tetrahedron Lett.*, **24**, 5009 (1983).
682. K. Yamawaki, T. Yoshida, T. Suda, Y. Ishii and M. Ogawa, *Synthesis*, 59 (1986).
683. B. M. Choudary, A. Durgaprasad and V. L. K. Valli, *Tetrahedron Lett.*, **31**, 5785 (1990).
684. H. Tomioka, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, **23**, 539 (1982).
685. S. Kanemoto, H. Saimoto, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, **25**, 3317 (1984).
686. R. V. Stevens, K. T. Chapman, C. A. Stubbs, W. W. Tam and K. F. Albizati, *Tetrahedron Lett.*, **23**, 4647 (1982).
687. K. S. Kim, Y. H. Song, N. H. Lee and C. S. Hahn, *Tetrahedron Lett.*, **27**, 2875 (1986).
688. M. Navarro, W. F. De Giovani and J. R. Romero, *Tetrahedron*, **47**, 851 (1991).
689. S. Matsumura, T. Kawamori and S. Yoshikawa, *Chem. Lett.*, 729 (1991).
690. T. Miyazawa and T. Endo, *J. Org. Chem.*, **50**, 3930 (1985).
691. L. Cottier, G. Descotes and J. Sabadie, *J. Mol. Catal.*, **7**, 337 (1980).
692. S. Murahashi, T. Naota, K. Ito, Y. Maeda and H. Taki, *J. Org. Chem.*, **52**, 4319 (1987).
693. C. W. Jefford and Y. Wang, *J. Chem. Soc., Chem. Commun.*, 634 (1988).
694. T. R. Beebe, R. Adkins, R. Baldridge, V. Hensley, D. McMillen, D. Morris, R. Noe, F. W. Ng, G. Powell, C. Spielberger and M. Stolte, *J. Org. Chem.*, **52**, 5472 (1987).
695. Y. Tamaru, Y. Yamada, K. Inoue, Y. Yamamoto and Z. Yoshida, *J. Org. Chem.*, **48**, 1286 (1983).
696. Y. Shvo, Y. Blum, D. Reshef and M. Menzin, *J. Organomet. Chem.*, **226**, C21 (1982).
697. T. Baba, K. Kameta, S. Nishiyama, S. Tsuruya and M. Masai, *Bull. Chem. Soc. Jpn.*, **63**, 255 (1990).
698. R. Berthon, A. Forestiere, G. Leleu and B. Sillion, *Tetrahedron Lett.*, **22**, 4073 (1981).
699. Y. Ishii, T. Yoshida, K. Yamawaki and M. Ogawa, *J. Org. Chem.*, **53**, 5549 (1988).
700. D. M. Hollinshead, S. C. Howell, S. V. Ley, M. Mahon, N. M. Ratcliffe and P. A. Worthington, *J. Chem. Soc., Perkin Trans. 1*, 1579 (1983).
701. S. Torii, T. Inokuchi and T. Sugiura, *J. Org. Chem.*, **51**, 155 (1986).
702. R. Bloch and C. Brillet, *Synlett*, 829 (1991).
703. M. P. Doyle and V. Bagheri, *J. Org. Chem.*, **46**, 4806 (1981).
704. Y. Ishii, K. Osakada, T. Ikariya, M. Saburi and S. Yoshikawa, *J. Org. Chem.*, **51**, 2034 (1986).
705. Y. Ishii, K. Suzuki, T. Ikariya, M. Saburi and S. Yoshikawa, *J. Org. Chem.*, **51**, 2822 (1986).
706. H. Tomioka, K. Takai, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, **22**, 1605 (1981).
707. M. P. Doyle, R. L. Dow, V. Bagheri and W. J. Patrie, *J. Org. Chem.*, **48**, 476 (1983).
708. Y. Takahashi, N. Yoneda and H. Nagai, *Chem. Lett.*, 1187 (1982).
709. K. P. Lok, I. J. Jakovac and J. B. Jones, *J. Am. Chem. Soc.*, **107**, 2521 (1985).
710. A. J. Bridges, P. S. Raman, G. S. Y. Ng and J. B. Jones, *J. Am. Chem. Soc.*, **106**, 1461 (1984).
711. D. Kyriacou and T. P. Tougas, *J. Org. Chem.*, **52**, 2318 (1987).
712. K.-H. Schwarz, K. Kleiner, R. Ludwig, E. Schrötter and H. Schick, *Justus Liebigs Ann. Chem.*, 503 (1991).
713. F. Gasparrini, M. Giovannoli, D. Misiti, G. Natile and G. Palmieri, *Synth. Commun.*, **18**, 69 (1988).

714. H. Firouzabadi, A. Sardarian and H. Gharibi, *Synth. Commun.*, **14**, 89 (1984).
715. H. Firouzabadi, N. Iranpoor, F. Kiaeezadeh and J. Toofan, *Synth. Commun.*, **14**, 973 (1984).
716. R. Schobert, *Synthesis*, 741 (1987).
717. C. M. Amon, M. G. Banwell and G. L. Gravatt, *J. Org. Chem.*, **52**, 4851 (1987).
718. T. T. Tidwell, *Synthesis*, 857 (1990).
719. T. T. Tidwell, *Org. React. (N.Y.)*, **39**, 297 (1990).
720. R. Cassis and J. A. Valderrama, *Synth. Commun.*, **13**, 347 (1983).
721. H. Firouzabadi, N. Iranpoor, H. Parham and J. Tootan, *Synth. Commun.*, **14**, 631 (1984).
722. A. Fischer and G. N. Henderson, *Synthesis*, 641 (1985).
723. D. H. R. Barton, A. G. Brewster, S. V. Ley, C. M. Read and M. N. Rosenfeld, *J. Chem. Soc., Perkin Trans. 1*, 1473 (1981).
724. H. Firouzabadi and N. Iranpoor, *Synth. Commun.*, **14**, 875 (1984).
725. F. Minisci, A. Citterio, E. Vismara, F. Fontana and S. De Bernardinis, *J. Org. Chem.*, **54**, 728 (1989).
726. C. López, A. González, F. P. Cossío and C. Palomo, *Synth. Commun.*, **15**, 1197 (1985).
727. S. Kajigaeshi, Y. Morikawa, S. Fujisaki, T. Kakinami and K. Nishihira, *Bull. Chem. Soc. Jpn.*, **64**, 336 (1991).
728. A. Pelter and S. Elgendy, *Tetrahedron Lett.*, **29**, 677 (1988).
729. M. Daumas, Y. Vo-Quang, L. Vo-Quang, L. Le Goffic, *Synthesis*, 64 (1989).
730. F. Ishii and K. Kishi, *Synthesis*, 706 (1980).
731. D. V. Pratt, F. Ruan and P. B. Hopkins, *J. Org. Chem.*, **52**, 5053 (1987).
732. T. Takata, R. Tajima and W. Ando, *J. Org. Chem.*, **48**, 4764 (1983).
733. J. K. Crandall, M. Zucco, R. S. Kirsch and D. M. Coppert, *Tetrahedron Lett.*, **32**, 5441 (1991).
734. Y. Tsuji, T. Ohta, T. Ido, H. Minbu and Y. Watanabe, *J. Organomet. Chem.*, **270**, 333 (1984).
735. E. Gutierrez and E. Ruiz-Hitzky, *Mol. Cryst. Liq. Cryst.*, **161**, 453 (1988).
736. E. Gutierrez, A. J. Aznar and E. Ruiz-Hitzky, in *Studies in Surface Science and Catalysis*, Vol. 41 (Eds. M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, C. Montassier and G. Pérot), Elsevier, Amsterdam, 1989, pp. 211–219.
737. E. Gutierrez and E. Ruiz-Hitzky, in *Pillared Layered Structures* (Ed. I. V. Mitchell), Elsevier, London, 1990, pp. 199–208.
738. E. Gutierrez, A. Loupy, G. Bram and E. Ruiz-Hitzky, *Tetrahedron Lett.*, **30**, 945 (1989).
739. A. Costa and J. M. Riego, *Synth. Commun.*, **17**, 1373 (1987).
740. G. A. Olah, P. S. Iyer and G. K. Surya Prakash, *Synthesis*, 513 (1986).
741. Á. Molnár and M. Bartók, *Helv. Chim. Acta*, **64**, 389 (1981).
742. Q. Wang and Z. Chen, *Kexue Tongbao*, **29**, 1130 (1984); *Chem. Abstr.*, **102**, 45280g (1985).
743. Á. Molnár, I. Bucsi and M. Bartók, *Acta Phys. Chem. Szeged*, **31**, 571 (1985).
744. Á. Molnár, I. Bucsi and M. Bartók, in *Studies in Surface Science and Catalysis*, Vol. 41 (Eds. M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, C. Montassier and G. Pérot), Elsevier, Amsterdam, 1989, pp. 203–210.
745. S. Sugiyama, S. Fukunaga, K. Ito, S. Ohigashi and H. Hayashi, *J. Catal.*, **129**, 12 (1991).
746. M. J. Pestchanker and O. S. Giordano, *Tetrahedron Lett.*, **31**, 463 (1990).
747. S. P. Joseph and D. N. Dhar, *Synth. Commun.*, **18**, 2295 (1988).
748. M. Bartók and Á, Molnár, *J. Chem. Soc., Chem. Commun.*, 1178 (1980).
749. Á. Molnár, G. Sirokmán and M. Bartók, *Acta Chim. Acad. Sci. Hung.*, **106**, 189 (1981).
750. G. Sirokmán, Á. Molnár and M. Bartók, *J. Mol. Catal.*, **19**, 35 (1983).
751. Á. Molnár, K. Felföldi and M. Bartók, *J. Mol. Catal.*, **11**, 225 (1981).
752. Á. Molnár, and M. Bartók, *Acta Chim. Acad. Sci. Hung.*, **89**, 393 (1976).
753. Á. Molnár and M. Bartók, *J. Catal.*, **72**, 322 (1981).
754. C. N. Barry and S. A. Evans, Jr., *J. Org. Chem.*, **46**, 3361 (1981).
755. G. A. Olah, A. P. Fung and R. Malhotra, *Synthesis*, 474 (1981).
756. J. Diab, M. Abou-Assali, C. Gervais and D. Anker, *Tetrahedron Lett.*, **26**, 1501 (1985).
757. D. Kotkar and P. K. Ghosh, *J. Chem. Soc., Chem. Commun.*, 650 (1986).
758. H. Neumann, *Chimia*, **23**, 267 (1969).
759. E. Palomino, A. P. Schaap and M. J. Heeg, *Tetrahedron Lett.*, **30**, 6797 (1989).
760. N. Ishizuka, *J. Chem. Soc., Perkin Trans. 1*, 813 (1990).
761. E. J. Corey and N. Raju, *Tetrahedron Lett.*, **24**, 5571 (1983).
762. P. L. Robinson and S. A. Evans, Jr., *J. Org. Chem.*, **50**, 3860 (1985).
763. J. W. Kelly, P. L. Robinson and S. A. Evans, Jr., *J. Org. Chem.*, **51**, 4473 (1986).

764. J. W. Kelly and S. A. Evans, Jr., *J. Org. Chem.*, **51**, 5490 (1986).
765. W. T. Murray and S. A. Evans, Jr., *J. Org. Chem.*, **54**, 2440 (1989).
766. P. L. Robinson, C. N. Barry, J. W. Kelly and S. A. Evans, Jr., *J. Am. Chem. Soc.*, **107**, 5210 (1985).
767. P. L. Robinson, C. N. Barry, S. W. Bass, S. E. Jarvis and S. A. Evans, Jr., *J. Org. Chem.*, **48**, 5396 (1983).
768. W. Szeja, *Synthesis*, 983 (1985).
769. M. K. Ellis and B. T. Golding, *Org. Synth.*, **63**, 140 (1985).
770. K. S. Bhat, P. L. Joshi and A. S. Rao, *Synthesis*, 142 (1984).
771. P. Picard, D. Leclercq, J.-P. Bats and J. Moulines, *Synthesis*, 550 (1981).
772. G. Carr and D. Whittaker, *J. Chem. Soc., Perkin Trans. 2*, 359 (1989).
773. G. Tagliavini, D. Marton and D. Furlani, *Tetrahedron*, **45**, 1187 (1989).
774. G. Tagliavini and D. Marton, *Gazz. Chim. Ital.*, **118**, 483 (1988).
775. D. Kotkar, S. W. Mahajan, A. K. Mandal and P. K. Ghosh, *J. Chem. Soc., Perkin Trans. 1*, 1749 (1988).
776. Á. Molnár, K. Felföldi and M. Bartók, *Tetrahedron*, **37**, 2149 (1981).
777. B. Mundryk and T. Cohen, *J. Org. Chem.*, **54**, 5657 (1989).
778. D. De, M. Seth and A. P. Bhaduri, *Synthesis*, 956 (1990).
779. P. F. Vlad and N. D. Ungur, *Synthesis*, 216 (1983).
780. T. Yamato, C. Hideshima, G. K. Surya Prakash and G. A. Olah, *J. Org. Chem.*, **56**, 3192 (1991).
781. L. A. Paquette and J. T. Negri, *J. Am. Chem. Soc.*, **113**, 5072 (1991).
782. H. Nishiyama, M. Sasaki and K. Itoh, *Chem. Lett.*, 1363 (1981).
783. F. Camus, B. Hasiak, M. Martin and D. Couturier, *Synth. Commun.*, **12**, 647 (1982).
784. K. Bock, C. Pedersen and H. Thøgersen, *Acta Chem. Scand., Ser. B*, **35**, 441 (1981).
785. A. Wisniewski, E. Skorupowa and J. Sokolowski, *J. Carbohydr. Chem.*, **10**, 77 (1991).
786. C. Montassier, J. C. Menezo, J. Moukolo, J. Naja, J. Barbier and J. P. Boitiaux, in *Studies in Surface Science and Catalysis*, Vol. 59 (Eds. M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, G. Pérot, R. Maurel and C. Montassier), Elsevier, Amsterdam, 1991, pp. 223–230.
787. C. Montassier, J. C. Ménézo, J. Moukolo, J. Naja, L. C. Hoang, J. Barbier and J. P. Boitiaux, *J. Mol. Catal.*, **70**, 65 (1991).
788. C. Montassier, J. C. Ménézo, L. C. Hoang, C. Renaud and J. Barbier, *J. Mol. Catal.*, **70**, 99 (1991).
789. D. Marton, P. Slaviero and G. Tagliavini, *Tetrahedron*, **45**, 7099 (1989).
790. I. Bucsi, A. Molnár and M. Bartók, in *Heterogeneous Catalysis Proc. 6th Int. Symposium*, Part 2 (Eds. D. Sopov, A. Andreev, A. Palazov and L. Petrov), Publishing House of the Bulgarian Academy of Sciences, Sofia, 1987, pp. 158–163.
791. D. V. Petrocine and R. Hametz, U. S. Pat 4.507.518; *Chem. Abstr.*, **102**, 220415d (1985).
792. G. Carr, C. Dean and D. Whittaker, *J. Chem. Soc., Perkin Trans. 2*, 351 (1988).
793. S. Abdel-Baky and A. Moussa, *Synth. Commun.*, **18**, 1795 (1988).
794. M. J. Ackland, J. F. Gordon, J. R. Hanson, B. L. Yeoh and A. H. Ratcliffe, *J. Chem. Soc., Perkin Trans. 1*, 2013 (1988).
795. C. A. Davis, R. Guillermo-Alvarez, J. R. Hanson and P. B. Hitchcock, *J. Chem. Soc., Perkin Trans. 1*, 1619 (1990).
796. W. Hartwig, *Tetrahedron*, **39**, 2609 (1983).
797. H. Redlich, W. Sudau and H. Paulsen, *Tetrahedron*, **41**, 4253 (1985).
798. W. P. Neumann, *Synthesis*, 665 (1987).
799. M. Orfanopoulos and I. Smonou, *Synth. Commun.*, **18**, 833 (1988).
800. Y. Ting, W. Verboom, L. C. Groenen, J.-D. van Loon and D. N. Reinhoudt, *J. Chem. Soc., Chem. Commun.*, 1432 (1990).
801. F. Grynszpan, Z. Goren and S. E. Biali, *J. Org. Chem.*, **56**, 532 (1991).
802. Z. Goren and S. E. Biali, *J. Chem. Soc., Perkin Tras. 1*, 1484 (1990).
803. D. Forster and G. F. Schaefer, *J. Mol. Catal.*, **64**, 283 (1991).
804. M. Marzi and D. Misiti, *Tetrahedron Lett.*, **30**, 6075 (1989).
805. E. J. Corey and P. B. Hopkins, *Tetrahedron Lett.*, **23**, 1979 (1982).
806. M. Ando, H. Ohhara and K. Takase, *Chem. Lett.*, 879 (1986).
807. B. M. Trost and A. G. Romero, *J. Org. Chem.*, **51**, 2332 (1986).
808. J. L. King, B. A. Posner, K. T. Mak and N.-C. C. Yang, *Tetrahedron Lett.*, **28**, 3919 (1987).
809. G. Solladié and J. Hutt, *J. Org. Chem.*, **52**, 3560 (1987).

810. G. Solladié, A. Girardin and G. Lang, *J. Org. Chem.*, **54**, 2620 (1989).
811. D. L. J. Clive, K. S. K. Murthy, C. Zhang, W. D. Hayward and S. Daigneault, *J. Chem. Soc., Chem. Commun.*, 509 (1990).
812. R. Dams, M. Malinowski, I. Westdorp and H. Y. Geise, *J. Org. Chem.*, **47**, 248 (1982).
813. B. E. Kahn and R. D. Rieke, *Organometallics*, **7**, 463 (1988).
814. P. Sarmah and N. C. Barua, *Tetrahedron*, **45**, 3569 (1989).
815. J. C. Sarma, N. C. Barua, R. P. Sharma and J. N. Barua, *Tetrahedron*, **39**, 2843 (1983).
816. Z. Liu, B. Classon and B. Samuelsson, *J. Org. Chem.*, **55**, 4273 (1990).
817. H. M. Walborski and M. P. Murari, *J. Am. Chem. Soc.*, **102**, 426 (1980).
818. K.-D. Gundermann and L. Schwandt, in *Methoden der Organischen Chemie (Houben-Weyl)*, Vol. E3, Thieme, Stuttgart, 1983, pp. 510–518.
819. P. S. Kalsi, P. P. Kaur, J. Singh and B. Chhabra, *Chem. Ind. (London)*, 394 (1987).
820. D. Y. Jackson, *Synth. Commun.*, **18**, 337 (1988).
821. T. R. Beebe, P. Hii and P. Reinking, *J. Org. Chem.*, **46**, 1927 (1981).
822. A. Cisneros, S. Fernández and J. E. Hernández, *Synth. Commun.*, **12**, 833 (1982).
823. A. Banerjee, B. Hazra, A. Bhattacharya, S. Banerjee, G. C. Banerjee and S. Sengupta, *Synthesis*, 765 (1989).
824. H. Firouzabadi, N. Iranpoor, G. Hajipoor and J. Toofan, *Synth. Commun.*, **14**, 1033 (1984).
825. T. Morimoto and M. Hirano, *J. Chem. Soc., Perkin Trans. 2*, 123 (1983).
826. D. H. R. Barton, J. P. Kitchin, D. J. Lester, W. B. Motherwell and M. T. B. Papoula, *Tetrahedron*, **37**, Supplement 1, 73 (1981).
827. C. Venturello and M. Ricci, *J. Org. Chem.*, **51**, 1599 (1986).
828. K. Kaneda, K. Morimoto, and T. Imanaka, *Chem. Lett.*, 1295 (1988).
829. M. Zviely, A. Goldman, I. Kirson and E. Glotter, *J. Chem. Soc., Perkin Trans. 1*, 229 (1986).
830. D. H. R. Barton, W. B. Motherwell and A. Stobie, *J. Chem. Soc., Chem. Commun.*, 1232 (1981).
831. D. H. R. Barton, J.-P. Finet, W. B. Motherwell and C. Pichon, *Tetrahedron*, **42**, 5627 (1986).
832. T. R. Felthouse, P. B. Fraundorf, R. M. Friedman and C. L. Schosser, *J. Catal.*, **127**, 393 (1991).
833. T. R. Felthouse, P. B. Fraundorf, R. M. Friedman and C. L. Schosser, *J. Catal.*, **127**, 421 (1991).
834. C. Sotiriou, W. Lee and R. W. Giese, *J. Org. Chem.*, **55**, 2159 (1990).
835. M. Floor, A. P. G. Kieboom and H. van Bekkum, *Recl. Trav. Chim. Pays-Bas*, **108**, 128 (1989).
836. R. de A. Epifanio, W. Camargo and A. C. Pinto, *Tetrahedron Lett.*, **29**, 6403 (1988).
837. Y. Ito, *J. Chem. Soc., Chem. Commun.*, 622 (1991).
838. L.-C. Yuan, T. S. Calderwood and T. C. Bruice, *J. Am. Chem. Soc.*, **107**, 8273 (1985).
839. R. I. Murray and S. G. Sligar, *J. Am. Chem. Soc.*, **107**, 2186 (1985).
840. T. Okamoto, K. Sasaki and S. Oka, *J. Am. Chem. Soc.*, **110**, 1187 (1988).
841. P. Mohr, M. Tori, P. Grossen, P. Herold and C. Tamm, *Helv. Chim. Acta*, **65**, 1412 (1982).
842. D. Bankston, *Org. Synth.*, **66**, 180 (1988).
843. C. Sheu, A. Sobkowiak, S. Jeon and D. T. Sawyer, *J. Am. Chem. Soc.*, **112**, 879 (1990).
844. A. J. Pandell, *J. Org. Chem.*, **48**, 3908 (1983).
845. A. Altamura, C. Fusco, L. D'Accolti, R. Mello, T. Prencipe and R. Curci, *Tetrahedron Lett.*, **32**, 5445 (1991).
846. C. A. A. van Boeckel, G. M. Visser and J. H. van Boom, *Tetrahedron*, **41**, 4557 (1985).
847. F. W. Lichtenthaler, P. Jarglis and K. Lorenz, *Synthesis*, 790 (1988).
848. J. S. Bradshaw, P. Huszthy, C. W. McDaniel, C. Y. Zhu, N. K. Dalley, R. M. Izatt and S. Lifson, *J. Org. Chem.*, **55**, 3129 (1990).
849. H. Ruholl and H. J. Schafer, *Synthesis*, 54 (1988).
850. M. A. Andrews and S. A. Klaeren, *J. Am. Chem. Soc.*, **111**, 4131 (1989).
851. E. S. Simon, G. M. Whitesides, D. C. Cameron, D. J. Weitz and C. L. Cooney, *J. Org. Chem.*, **52**, 4042 (1987).
852. D. K. Sohounloue, C. Montassier and J. Barbier, *React. Kinet. Catal. Lett.*, **22**, 391 (1983).
853. C. Montassier, D. Giraud and J. Barbier, in *Studies in Surface Science and Catalysis*, Vol. 41 (Eds. M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, C. Montassier and G. Pérot), Elsevier, Amsterdam, 1989, pp. 165–170.
854. C. Montassier, D. Giraud, J. Barbier and J. P. Boitiaux, *Bull. Soc. Chim. Fr.*, 148 (1989).
855. Á. Molnár and M. Bartók, *Acta Phys. Chem. Szeged*, **25**, 161 (1979).
856. M. Kato, Y. Tooyama and A. Yoshikoshi, *Bull. Chem. Soc. Jpn.*, **64**, 50 (1991).
857. S.-I. Murahashi, K. Kondo and T. Hakata, *Tetrahedron Lett.*, **23**, 229 (1982).
858. Y. Tsuji, K.-T. Huh and Y. Watanabe, *J. Org. Chem.*, **52**, 1673 (1987).

859. Y. Tsuji, K.-T. Huh, Y. Ohsugi and Y. Watanabe, *J. Org. Chem.*, **50**, 1365 (1985).
860. Y. Tsuji, Y. Yokoyama, K.-T. Huh and Y. Watanabe, *Bull. Chem. Soc. Jpn.*, **60**, 3456 (1987).
861. K. Felföldi, M. S. Klyavlin and M. Bartók, *J. Organomet. Chem.*, **362**, 193 (1989).
862. J. Runeberg, A. Baiker and J. Kijenski, *Appl. Catal.*, **17**, 309 (1985).
863. R. Vultier, A. Baiker and A. Wokaun, *Appl. Catal.*, **30**, 167 (1987).
864. L. Forni, G. Stern and M. Gatti, *Appl. Catal.*, **29**, 161 (1987).
865. L. Forni and S. Nestori, in *Studies in Surface Science and Catalysis*, Vol. 41 (Eds. M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, C. Montassier and G. Pérot), Elsevier, Amsterdam, 1989, pp. 291–298.
866. L. Forni and R. Miglio, in *Studies in Surface Science and Catalysis*, Vol. 59 (Eds. M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, G. Pérot, R. Maurel and C. Montassier), Elsevier, Amsterdam, 1991, pp. 367–376.

CHAPTER 19

Quinones: The present state of addition and substitution chemistry*

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*This chapter was intended to appear in an 'Update' volume on the addition and substitution chemistry of quinones. For various reasons it was decided to cancel the publication of further 'Update' volumes. Even so, the author and the editor believe that to present this new material is of considerable interest to the readers of the Functional Groups series, and we do so, albeit in a volume to which this chapter does not strictly belong.

Supplement E: The chemistry of hydroxyl, ether and peroxide groups, Vol. 2
Edited by S. Patai

I. INTRODUCTION

A. Quinones In Organic Chemistry

Art and elegance are central to the creative activity of designing novel routes to desirable molecular structures. From what fundamental palette does the organic chemist choose? A limited array of those structures we name are found in an intriguingly high percentage of successful syntheses. Of these, certainly the six-atom ring must be the peerless example. Since Wöhler and Liebig traced its course in oil of bitter almonds and

Kekulé proposed its atomic formulation, benzene has been granted its own half of the organic terrain. Cyclohexane, and various partially reduced versions, found in the terpenes and steroids affect the life of every species. Oxygen and nitrogen analogs dominate the carbohydrates and the alkaloids bringing life and death in hospitals and alleys.

A substantial claim to a portion of this centrality can be made by the derivative of the general class known as quinones. With their highly symmetrical pair of α,β-unsaturated carbonyls we find the quinones in dyes and pharmaceuticals, both natural and synthetic. Their varied roles in biochemical processes have only begun to be explored and an important future can be seen in the material sciences.

B. Objectives and Form of this Review

My goal in this, as in my previous studies[1,2], is to include the significant contributions and still keep the volume of material within reason. The subjective judgements thus demanded are bound to lead to an imperfect result. My hope is to provide detailed discussions of the major contributions to each area of chemical advancement coupled with enough leading references so that the interested chemist can follow any trail he/she wishes. In the current material I have linked my past reviews with the literature published in major reviews into the early 1990s.

C. A Brief History of the Quinone Addition Synthon

A century and a half ago the father of organic chemistry, Fredrich Wöhler, was intrigued by a certain collection of atoms, $C_6H_4O_2$. Six years earlier, in 1838, Woskressenski discovered 1,4-benzoquinone as an oxidation product[3]. Subsequent investigations showed that the compound is easily reduced. Wöhler, an expert in laboratory manipulation, turned his mind to the task of converting this reactive molecule into new and interesting modifications. Jean Baptiste Dumas's demonstration that chlorine reacts very well by replacing hydrogen in carbon compounds seemed a reasonable place to begin.

In fact Wöhler's discovery that hydrogen chloride adds easily to the quinone nucleus[4] opened one of the most productive single synthetic pathways in organic chemistry. It was to be sixty-five years before Arthur Michael showed that α,β-unsaturated carbonyl groups are attractive sites for the addition of a wide variety of nucleophilic materials[5]. While Michael's experiments with quinones are nearly lost in the vast number of synthetic studies he conducted personally, his name is still attached to this general reaction.

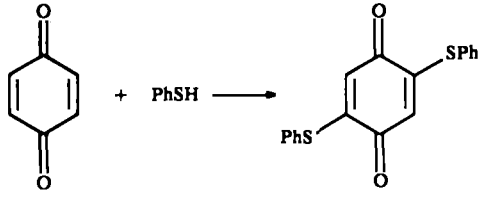
II. HETEROATOM CHEMISTRY

A. Sulfur Addition Reactions

1. Thiol addition kinetics and mechanisms

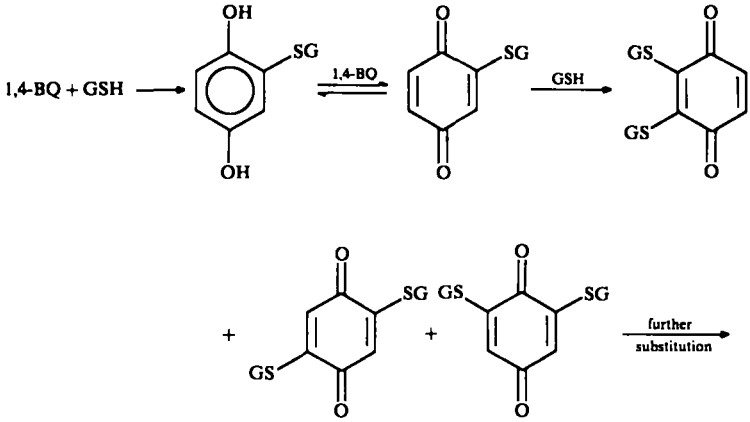
Michael actually carried out an early example of this class of additions in his search for understanding of valence (equation 1)[5]. Subsequently sulfur substituted quinones, like organosulfur chemistry itself, have proven fascinating to organic chemists with widely varying interests. In spite of their continuing effort I was forced in my past comments on sulfur addition (Reference 1, pp. 880–900; Reference 2, 539–551) to express a hope for kinetic studies of this important area; happily some have begun to appear.

Recognition of the thiol group's key role in important biochemical pathways has led



(1)

to several determinations of their rates of interaction with quinones. Monks and collaborators have studied the products formed from glutathione and 1,4-benzoquinone (1,4-BQ) under physiological conditions[6]. They were able to expand upon earlier mechanistic proposals by showing that all possible addition products are formed with this simplest quinone (equation 2). The presence of all three isomeric disubstituted thioethers is consistent with the elegant work of Gates and collaborators (Reference 1, pp. 884–885) and appears to be unique to the sulfide linkage. These studies are related to their earlier work on the role of quinone–thiol chemistry in the nephrotoxicity of bromobenzene (equations 3 and 4)[7,8].



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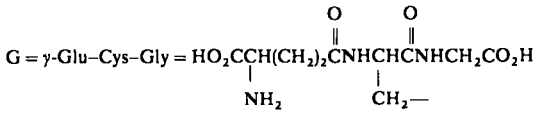

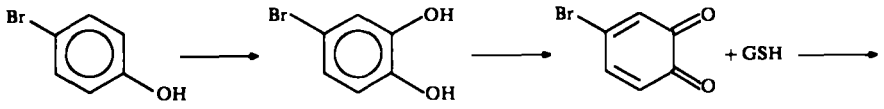

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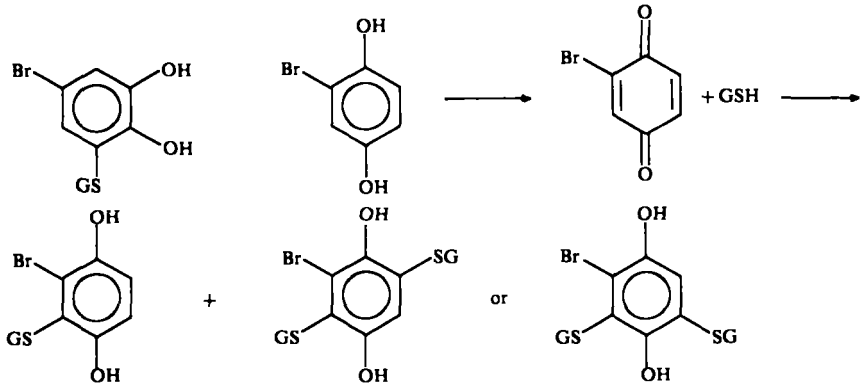
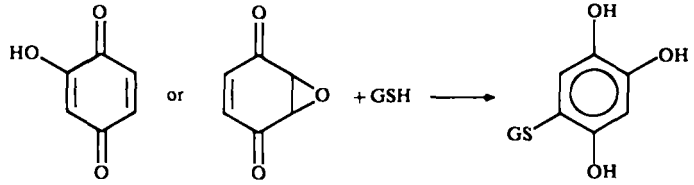


(4)

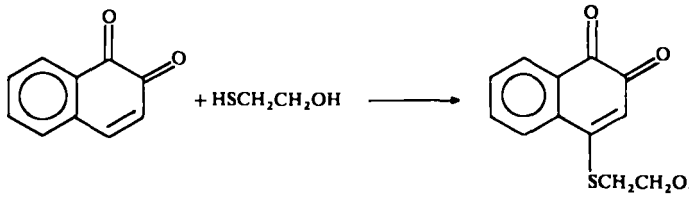
Also in 1988, Brunmark and Cadenas published a complementary investigation including additional examples of variously substituted quinones and rates of autoxidation for the glutathionyl substituted hydroquinone products[9]. Glutathione adds to either 2-hydroxy- or 2,3-epoxy-1,4-benzoquinone to produce 2-hydroxy-5-glutathionylhydroquinone (equation 5). This compound undergoes autoxidation 44 times faster than 2-glutathionylhydroquinone which in turn autoxidizes 8 times faster than hydroquinone. These authors



(5)

also studied the effects of methyl substitution on the addition of glutathione to 1,4-benzoquinone. Their results for 2-methyl- and 2,6-dimethyl-1,4-benzoquinone and the corresponding epoxides show a slight rate enhancement from the single methyl group and decreases whenever the sulfide is forced to be adjacent to it. These observations are consistent with earlier studies (Reference 1, p. 884).

1,2-Quinones derived from the powerfully carcinogenic polycyclic aromatic hydrocarbons may interact with cysteine and glutathione. The importance of such chemistry in detoxification has been investigated[10]. 1,2-Naphthoquinone was used as a model compound and 2-mercaptoethanol as a quinone trapping reagent (equation 6).



(6)

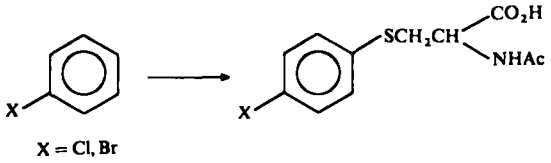
TABLE 1. Second-order rates of reactions of various nucleophiles with 1,2-naphthoquinone[10]

Nucleophile	$k(\text{min}^{-1}\,\text{M}^{-1})$
Potassium phosphate, pH 7.0	0.003
Tris-HCl, pH 9.0	0.32
Glycine, pH 9.0	3.7
NaOH, 0.001 M	182
2-Mercaptoethanol	107,500
Glutathione	164,500
L-Cysteine	342,000

The structure of the thioether, as 4- rather than 3-substituted, was established by NMR and is unlikely on mechanistic grounds. The same arguments apply to the thioether product of benzo[*a*]pyrene 7,8-quinone. Under pseudo-first-order conditions, used for buffer studies, the thiols react too rapidly to measure, and second-order rates were determined at low, equimolar concentrations. Table 1 shows that all three thiols react several orders of magnitude faster than the estimated second-order rates of buffers. The 7,8-quinone of benzo[*a*]pyrene reacted only with the thiols, and the spectral changes were too small to permit kinetic measurements.

A related study shows that a variety of polycyclic *o*-quinones are excellent substrates for 15-hydroxyprostaglandin dehydrogenase[11]. Their discovery that glutathione thioethers of menadione and toluquinone are potent inhibitors of prostaglandin B_1 oxidation provides new insight on the toxicity of such quinones.

The general subject of thioether hydroquinones or catechols and their relationship to toxicity was of interest to biochemists even before that field had its current name. Today we recognize the seriousness of exposure to benzene and its halogenated derivatives, but it was in 1879 when the first mercapturic acids were isolated from dogs whose diets included these compounds (equation 7)[12,13]. Hanzlik and students examined the various synthetic routes that might be used in the preparation of the isomeric bromomercapturic acids[14]. Direct Michael addition leads to complex mixtures unless an excess of quinone is present. Similar addition to 2-bromo-1,4-benzoquinone gives a mixture of the three isomeric mercapturic acids. Finally, addition to 4,5-dibromo-1,2-benzoquinone also gives the single possible catechol (equation 8). All of the compounds prepared are difficult to



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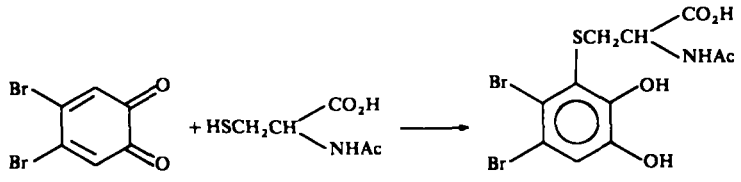
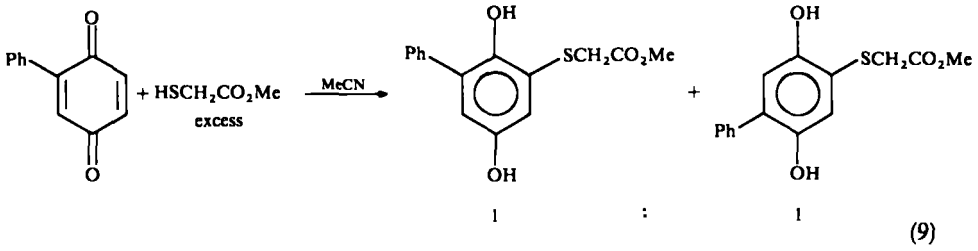
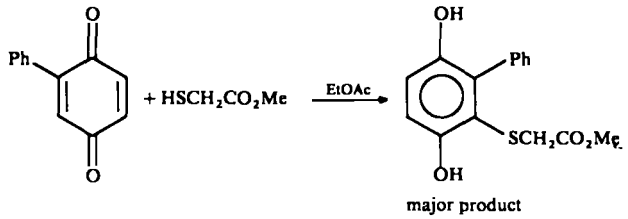


(8)

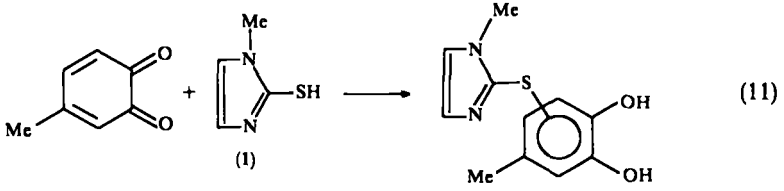
crystallize and no yields data are presented. It is important to note that bromine appears to be the only substituent other than sulfur which gives detectable amounts of all three isomeric thioether addition products in a single solvent.

The study of enzyme reactions has stimulated some fundamental studies of quinone–thiol addition chemistry as, for example, in the design of affinity label inhibitors for the reductive alkylation catalyst thymidylate synthase[15]. An examination of 5-*p*-benzoquinonyl-2′-deoxyuridine 5′-phosphate was undertaken using as models 2-phenyl-1,4-benzoquinone and methyl mercaptoacetate. This addition is strongly solvent-dependent (equations 9 and 10). Once again no indication of the product yields is provided, although an interesting question is raised about the relative yields. Much remains to be done in this area of growing importance.



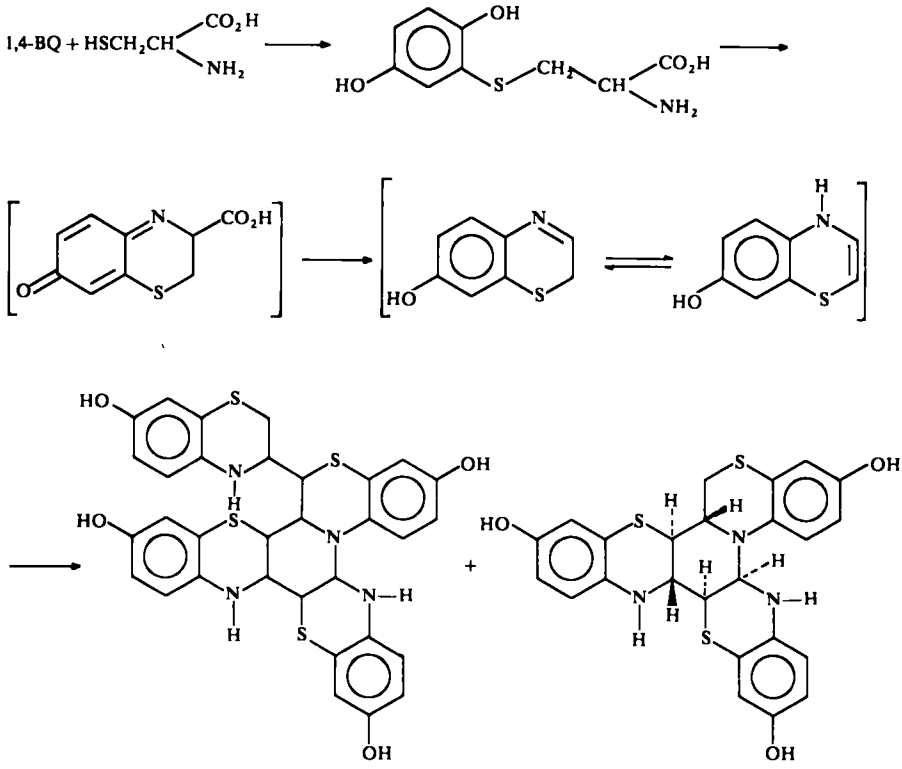


The oxidation of phenols is catalyzed by tyrosinase from mushrooms and is inhibited by thiols. Two recent studies support the importance of thioether formation in this chemistry. Andrawis and Kahn investigated the heterocycle methimazole (1) and isolated the addition product, but did not determine its structure (equation 11)[16]. McAllister and Campbell provided convincing evidence that coenzyme A inhibits by forming the corresponding thioether[17].



2. *Synthetic studies*

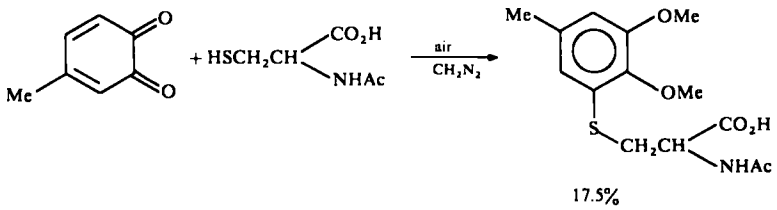
The addition of bidentate molecules to quinones has important implications in medical and industrial applications. One often-studied example is the addition of cysteine (Reference 1, p. 546) which has been reexamined[18]. When the reaction is carried out under



(12)

anaerobic conditions, a small amount of the postulated intermediate results. Undefined polymers and two polycyclic compounds which result from decarboxylation and polymerization of a cyclized intermediate are also found (equation 12). If the reaction is stopped in its early stages, other intermediates which support this mechanism are obtained.

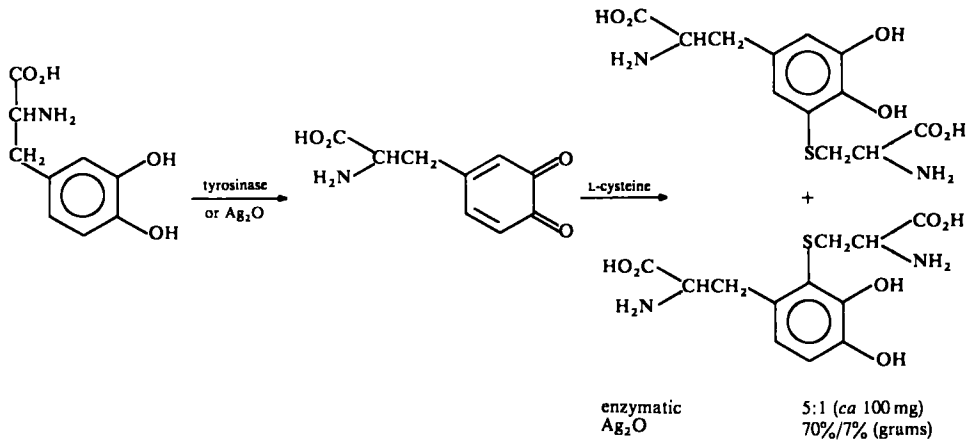
The related addition of cysteine to *o*-quinones has been the subject of several studies. Nkpa and Chedekel worked with 4-methyl-1,2-benzoquinone and *N*-acetylcysteine to resolve questions surrounding the surprising 1,6-addition to dopaquinone (equation 13)[19]. In the absence of oxygen no reaction was observed; they conclude that a radical mechanism without an anil intermediate must be involved.



17.5%

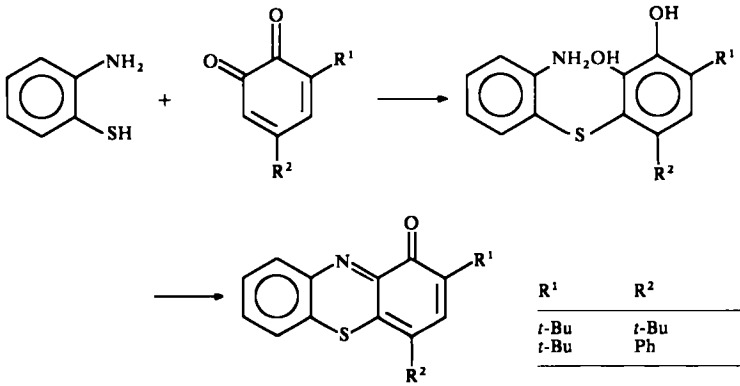
(13)

The corresponding thioethers of dopaquinone have been synthesized by the usual routes in the search for practical antitumor drugs (equation 14)[20]. These workers also studied the relationship of thioether formation from the oxidation of catechols by the mushroom enzyme tyrosinase, but from a product perspective as opposed to the kinetic treatments cited earlier[21,22]. The results are of limited direct synthetic significance since most products were not fully characterized, but excellent information on HPLC analysis is provided[21,23].



(14)

Another bidentate molecule with a long history of addition chemistry is 2-aminothiophenol, but its chemistry with *o*-quinones has been neglected. Thomson and collaborators have made a detailed study of this area and established the need for bulky groups in the quinonoid ring to prevent spontaneous cyclization[24]. The intermediate thioether was not isolated, but oxidized and cyclized directly (equation 15). Reaction with 1,2-naphthoquinone took place only at the 4-position and, when blocked, no useful product was obtained.



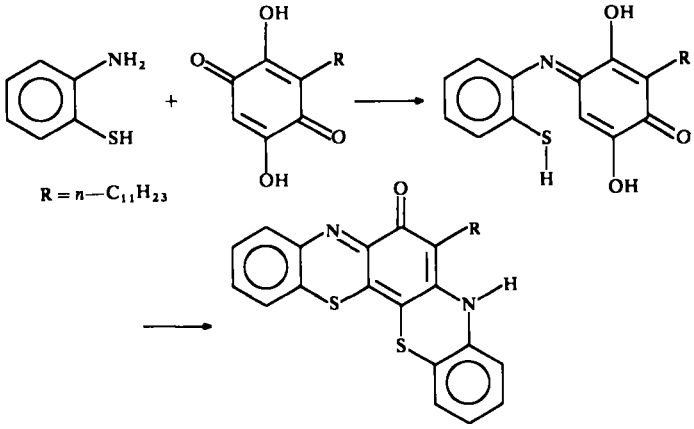
(15)

R^1	R^2	%
t-Bu	*t*-Bu	33
t-Bu	Ph	58

Rao and Rao have obtained similar compounds from embelin[25a]. For this 1,4-benzoquinone they postulate the formation of an anil prior to sulfur addition and find an interesting hydroxyl group substitution reaction (equation 16). The *S*-triazole relatives of *o*-aminothiophenol also add well to 1,4-benzoquinone and the intermediates cyclize to potentially important heterocycles (equation 16a)[25b].

The long-debated regiospecificity of thiol additions to juglone and its derivatives has come up once again and the answer is to avoid the whole issue and use substitution chemistry (see Section VII)[26]. Both addition compounds were obtained by fractional recrystallization (equation 17). We all agree that more than one pathway is involved; when will someone sort out the optimum conditions for each? Similar chemistry was reported in greater detail more than 35 years earlier (equation 18)[27].

A number of reports of purely synthetic procedures have appeared and serve to



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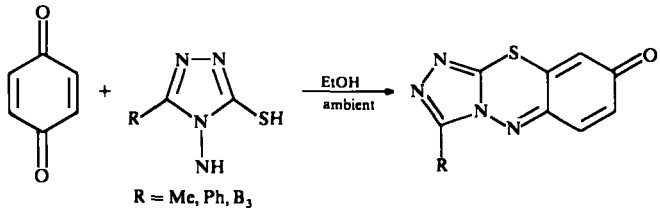
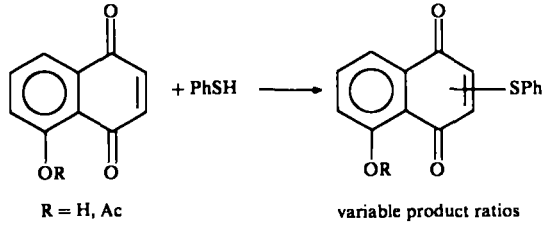


(16a)



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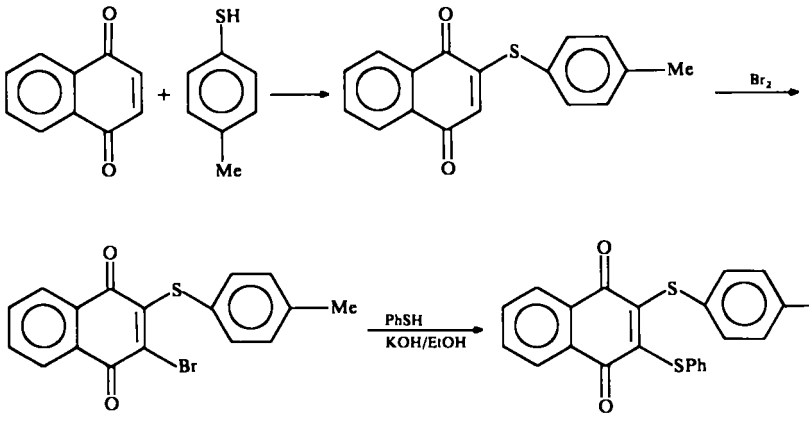

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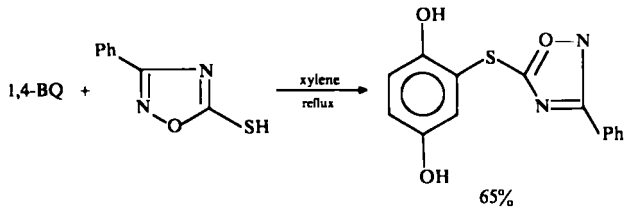

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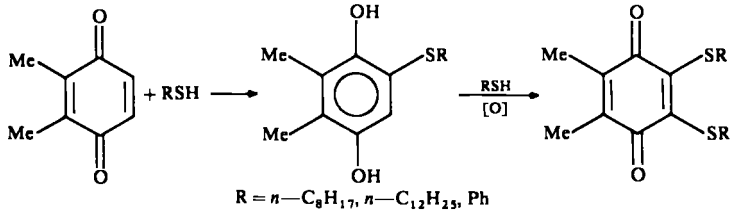


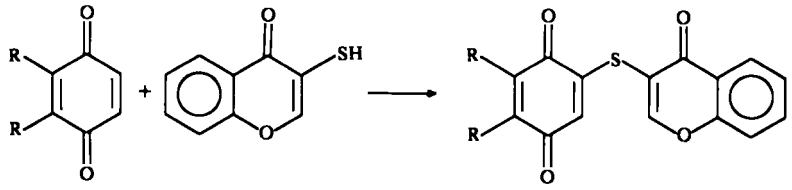
(20)

illustrate the variety of thiols which continue to find interested chemists to exploit their potentials. The heterocycle 3-phenyl-1,2,4-oxadiazole-5-thiol reacts smoothly with 1,4-benzoquinone (equation 19)[28].

A variety of 2,3-dimethyl-1,4-benzoquinones with one or two alkylthio or arylthio substituents have been prepared in fair yields by thiol addition followed by oxidation with Fremy's salt followed by a second addition (equation 20)[29].

Löwe and Kennemann have shown that a wide variety of interesting compounds can be prepared from 3-mercaptochromone including its addition in fair yields to 1,4-benzo- and 1,4-naphthoquinone (equation 21)[30].

Bittner and colleagues have prepared several phenylthio substituted 1,4-benzoquinones in conjunction with their studies of conducting organic materials. The 2,5- and 2,6-bis(phenylthio)-1,4-benzoquinones were prepared by simple addition in acetic acid and fractional recrystallization[31]. Of greater novelty is the synthesis of the three isomeric



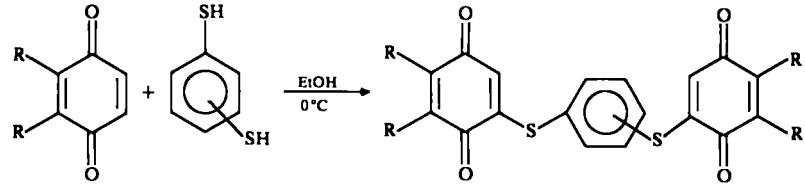
R = H, CH=CHCH=CH

63%, 53%

(21)

benzenedithiols and their addition in good yields to 1,4-benzo- and 1,4-naphthoquinones (equation 22)[32].

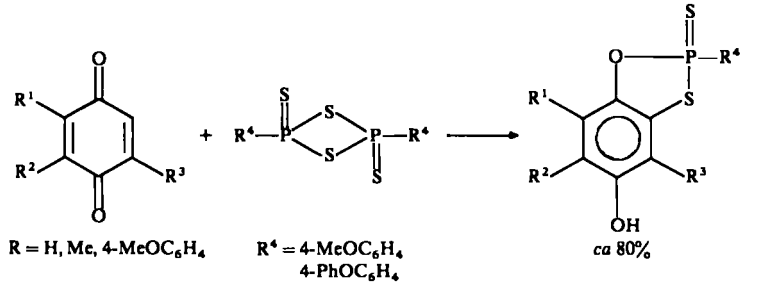
Interesting and potentially useful phosphorus–sulfur–oxygen heterocycles are formed from the addition of 1,3,2,4-dithiadiphosphetane-2,4-disulfides to a variety of 1,4-benzoquinones (equation 23)[33]. Complex bis-dithiophosphates also add to benzo- and



R = H, CH=CHCH=CH

70–80%

(22)



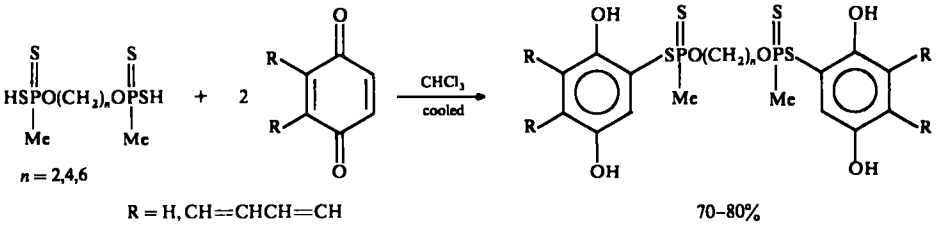
R = H, Me, 4-MeOC$_6$H$_4$ R^4 = 4-MeOC$_6$H$_4$, 4-PhOC$_6$H$_4$ *ca* 80%

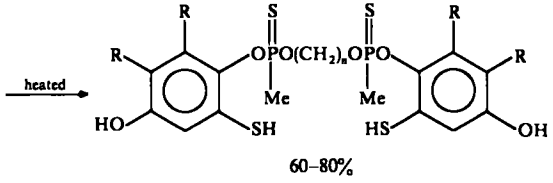
(23)

naphthoquinones, but on heating rearrange to the corresponding bis-arylethers (equation 24)[34].

In their search for photo-cross-linking polymers Cha, Tsunooka and Tanaka have prepared several 1,4-benzoquinones in which a diol or carboxylic acid function is attached to the quinone through a thioether linkage (equation 25)[35,36]. These monomers were subsequently converted to polyesters or polyurethanes.

When strong electron-withdrawing groups are present on a 1,4-benzoquinone, thiourea adds regiospecifically to give good yields of 1,3-benzoxathiol-2-ones (equation 26)[37]. This study nicely complements the work of Lau and subsequent workers (Reference 1, pp. 890–892; Reference 2, pp. 548–549).





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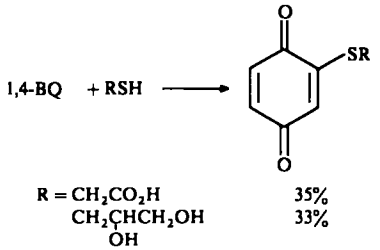

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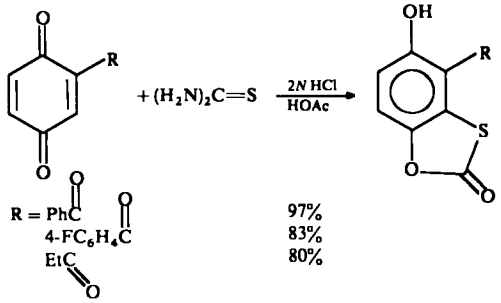


(26)

B. Nitrogen and Oxygen Addition

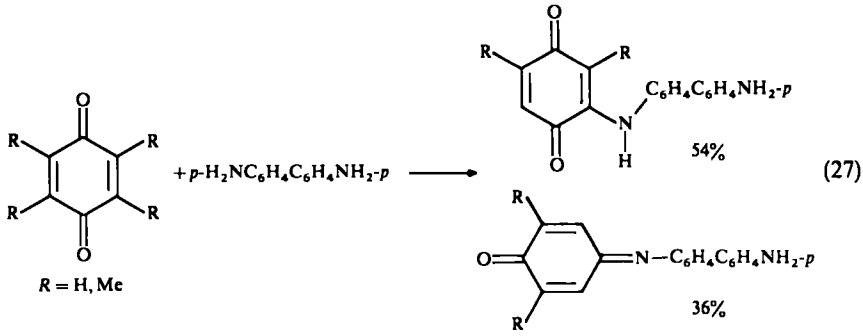
1. Nitrogen addition kinetics and mechanisms

Nitrogen addition chemistry has always stimulated a great deal of kinetic intrest, but as I reported in the past (Reference 1, pp. 900–916; Reference 2, pp. 552–572) it has often centered on electronic details of smaller interest to the organic chemist. However, the

biochemists are showing the way and providing some excellent new data. For example, Graveel and colleagues have examined the long-standing problem of the formation of the humic acids through the interaction of benzidine and some methyl-1,4-benzoquinones (equation 27)[38]. Their data show the presence of a rapid reversible imine formation followed by slow, irreversible addition. Product isolation showed the presence of both of these intermediates which readily polymerize. No evidence for the reaction of two equivalents of quinone with benzidine was presented.

In the development of an analytical method for sulfa drugs Iskander and collaborators determined the rates of eight such compounds with 1,4-benzoquinone (equation 28)[39]. Their product determinations are in agreement with many earlier studies and their own results with anilines[40].

Continued interest in the fate of 1,2-benzoquinones related to the enzymatic reactions of tyrosinase and L-dopa led Garcia-Carmona and associates to study the model system 4-methyl-1,2-benzoquinone and L-proline with rapid scanning spectrophotometry[41]. The rate of reaction of quinone with water was also determined and shown not to be involved in the nitrogen addition reaction. The structure of the product was assumed to be 5-methyl-4-*N*-prolyl-1,2-benzoquinone. While the structure does not change the kinetic conclusions, its contrast to the sulfur findings should be examined (equation 29).



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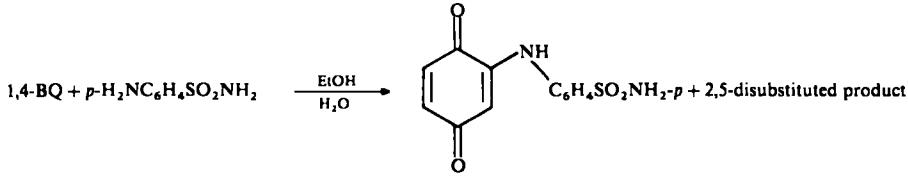

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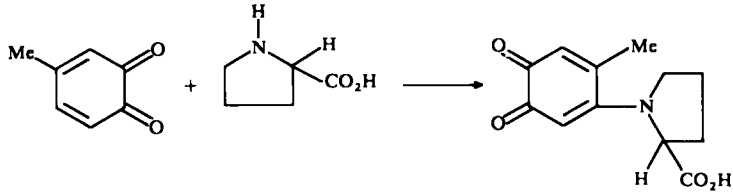
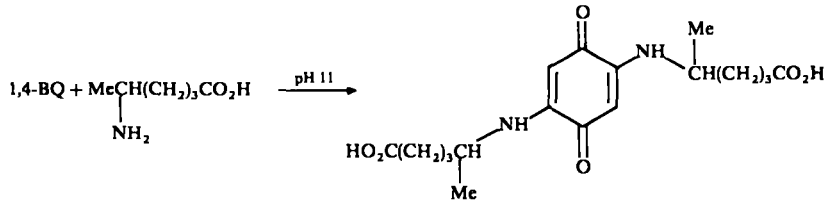


(29)

A study combining electrochemical and spectrophotometric techniques is, unfortunately, only available in Japanese[42]. The rates determined at unusually high pH are consistent with the usually accepted stepwise mechanism, but no product analyses are reported in the abstract (equation 30).

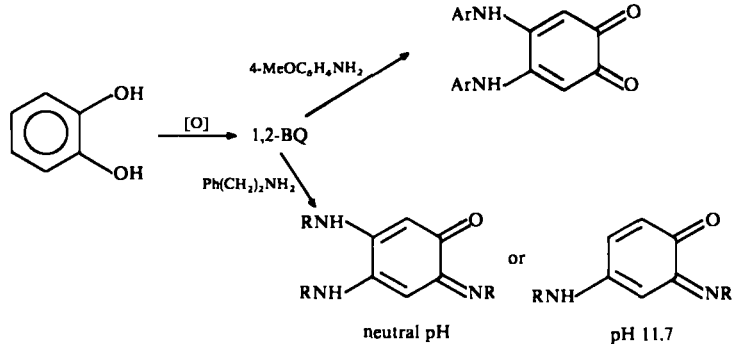


(30)

2. Synthetic studies with nitrogen

Truscott and students have made another heroic attempt to sort out the difficult addition of aliphatic amines to catechol oxidized *in situ* to 1,2-benzoquinone (1,2-BQ)[43]. They find, on the basis of extremely small product recovery, two distinct product types for aromatic and aliphatic amines (equations 31 and 32). The intervention of 2-hydroxy-1,4-benzoquinone was ruled out.

Forrester and Thomson have confirmed the unusual 2,3-addition of nitrosobenzene to 1,4-benzoquinone and presented evidence of a radical-anion mechanism (equation 33)[44].



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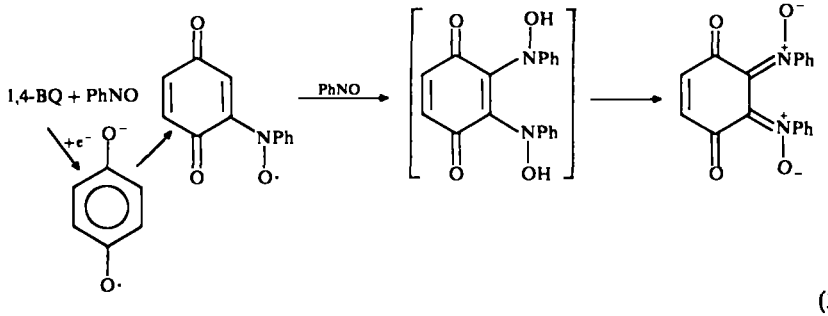

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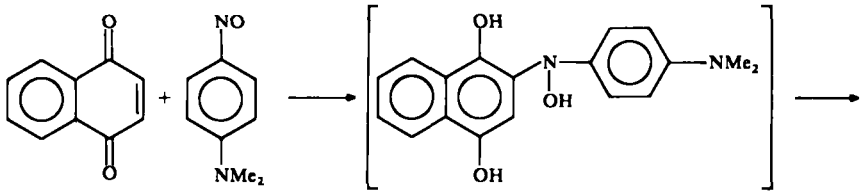

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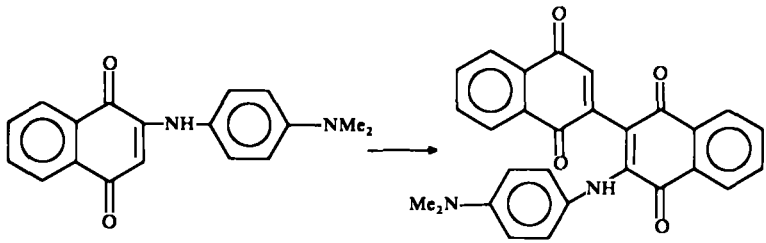
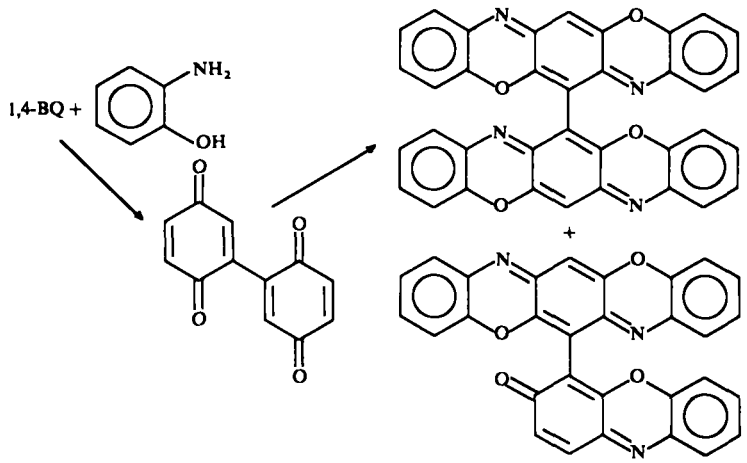


They find a different product with 1,4-naphthoquinone (equation 34) and suggest that a delicate balance of redox properties is probably the determining factor.

The search for more useful dyes produced interesting results in the addition of 2-aminophenol to 1,4-benzoquinone (equation 35)[45]. The authors suggest that dimerization of the quinone followed by reaction with the aniline accounts for the interesting polycyclic products.

In general aziridinyl quinones have been prepared by substitution chemistry, but the search for antimalarials has shown the utility of addition chemistry (equation 35a)[48b]. The naphthoquinones were tested as sulfonate and acylate esters.

Seeking fluorescent sodium indicators Minta and Tsien prepared a long series of 1,7-diaza crown ethers, including one example bearing two quinonoid structures (equation 36)[46]. This material was converted to several derivatives which show only limited promise.



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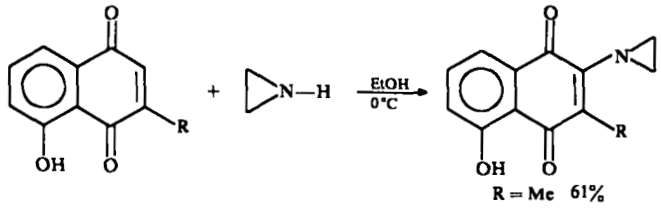

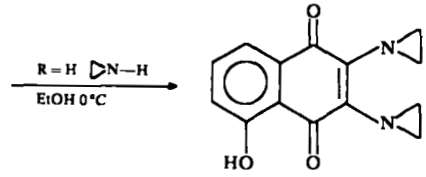

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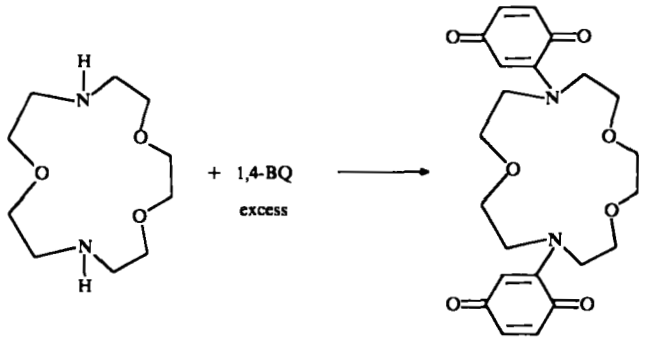

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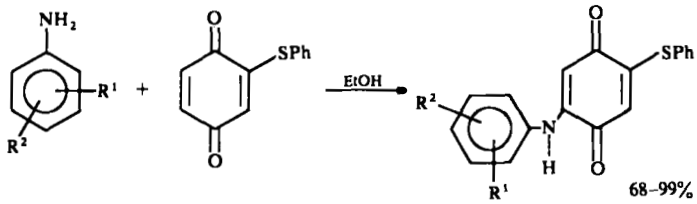
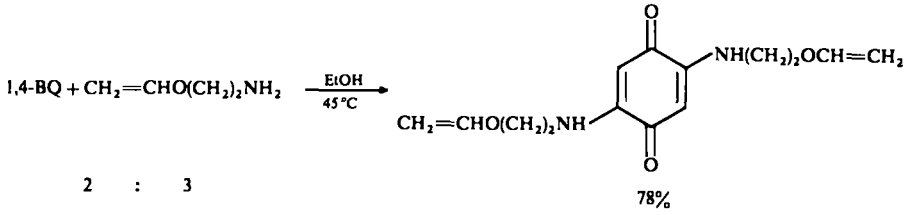


(36a)

$R^1 = H$ $R^2 = 2$-, 3- or 4-Me; 2- or 4-MeO
$R^1, R^2 = 3,4$-CH=CHCH=CH

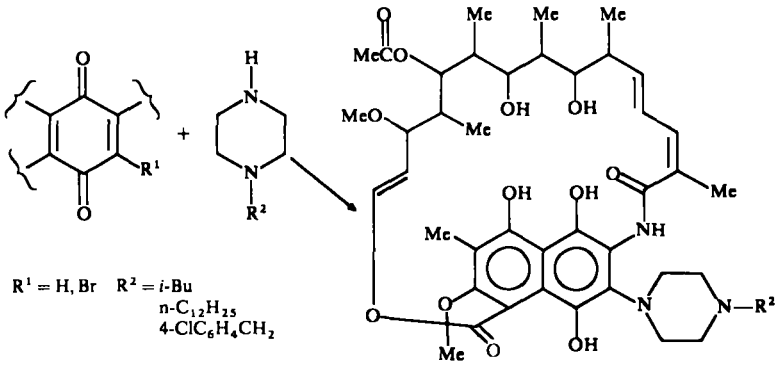
In an effort to obtain a reliable picture of ^{13}C chemical shift values a series of substituted 1,4-benzoquinones including several alkylamino derivatives were studied[47]. The standard addition procedure was used. Strangely no sulfur compounds were included. In similar chemistry several 2,5-bis(alkylamino)-1,4-benzoquinones have been prepared and examined for antitumor potential[48a]. Bittner and Krief have shown that the addition of substituted anilines to 2-phenylmercapto-1,4-benzoquinone takes place in good to excellent yield (equation 36a)[48c]. This observation is in marked contrast to the addition of a sulfur nucleophile to a quinone bearing a thioether linkage where important amounts of all three isomers are formed.



(37)

A report of a good yield of an interesting vinyl ether by standard addition has been made (equation 37)[49].

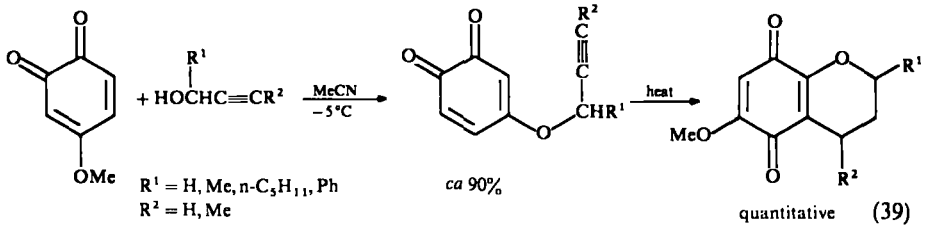
Finally, Traxler and colleagues have been able to separate the antibacterial and hypolipidemic activities of a rifamycin making use of addition and substitution chemistry in that series (equation 38)[50].



(38)

3. *Synthetic studies with oxygen*

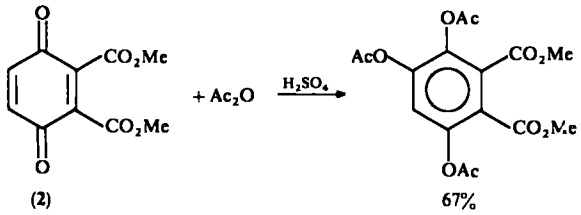
The addition of primary and secondary propargyl alcohols to 4-methoxy-1,2-benzoquinone takes place in good yield under mild conditions (equation 39)[51]. These products undergo a sequence of thermal isomerizations to give 2*H*-1-benzopyran-5,8-quinones in excellent yields and high regiospecificity. While this process represents an important new synthetic tool, the authors err in saying that benzopyran quinones have not been reported. Tišler's excellent review of heterocyclic quinones gives many examples[52].



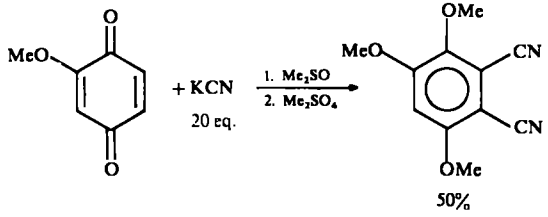
(39)

C. Thiele–Winter Acetoxylation

Two completely different approaches to the synthesis of the antitumor, antibiotic fredericamycin A involve the application of this synthon. Parker and students have investigated various routes to the trialkoxyphthalic acids as key intermediates in their prospective synthesis[53]. To introduce the required third oxygen in quinone **2** they used sulfuric acid catalyzed Thiele conditions which produced an acceptable yield (equation 40). In an alternative preparation they began with 2-methoxy-1,4-benzoquinone and KCN which gave poorer, but still useful amounts of product (equation 41).

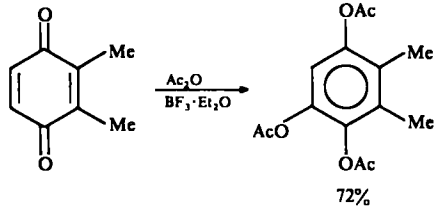


(2) 67% (40)



50% (41)

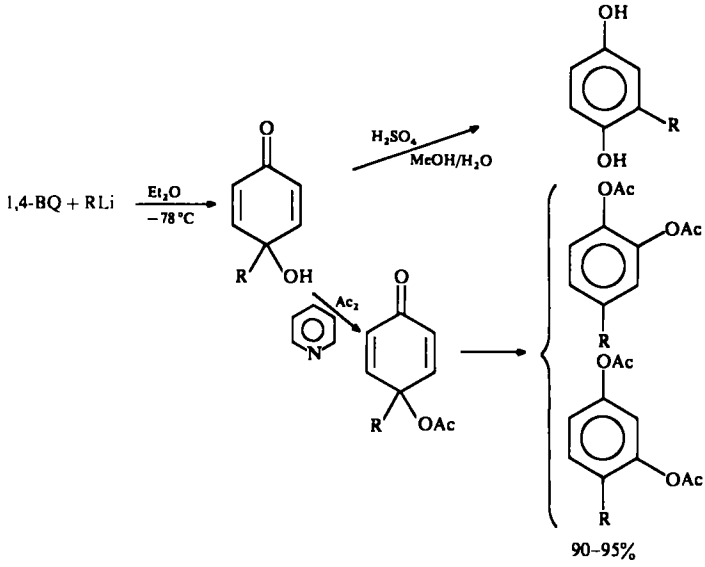
Bach and students proposed an entirely different approach, but it still required the introduction of a third oxygen function. They also solved the problem with reductive acetoxylation (equation 42)[54].



72% (42)

In synthesizing perfluoroalkyl resorcinols or hydroquinones the isomeric catechol product can also be obtained under the right conditions (equations 43–45)[55]. The total yields are excellent in all cases, but no way has yet been found to change the 1:1 ratio of rearranged products.

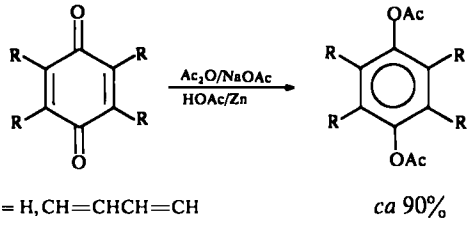
Reductive acetylation under basic conditions gives the hydroquinone esters as might be expected. One example is found in the study of model quinones in attempts to increase the solubility of coal (equation 46)[56].



(43)

(44)

(45)

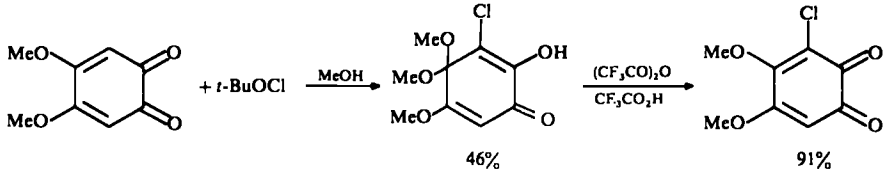


(46)

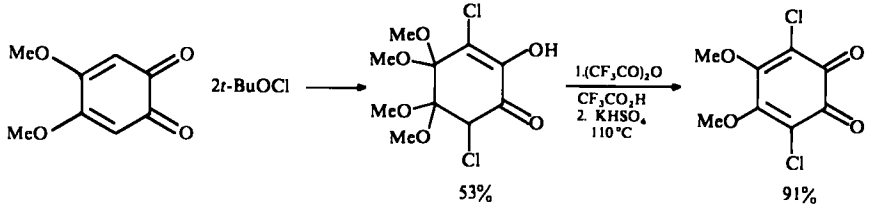
D. Inorganic Ion Additions

1. Halogens

In their elegant studies of quinone alkylation Moore and students found the need of a variety of halogenated 1,2-benzoquinones and they proposed a general route to these not readily available compounds[57]. The central reaction is 4,5-dimethoxy-1,2-benzoquinone with *t*-butyl hypochlorite (equation 47). The *bis*-form of the quinone ketal intermediate, which is subsequently converted to the 3,6-dichloroquinone product,



(47)

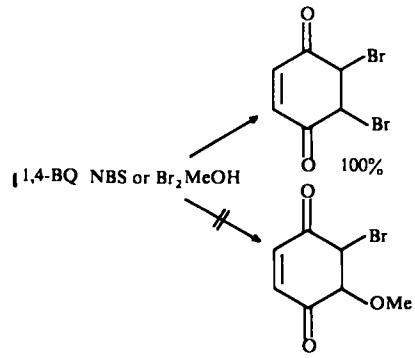


(48)

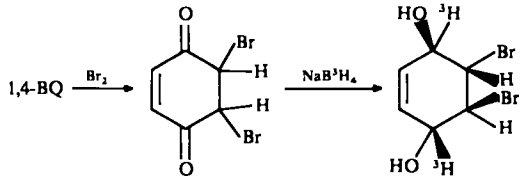
can be formed in good yield using two equivalents of hypochlorite (equation 48). Several other chloro and bromo *o*-quinones are examined.

Heasley and students have worked on the reaction between NBS and α,β-unsaturated ketones in methanol[58]. Their results are similar to those of de la Mare[59]. Perhaps their most interesting observation is that 1,4-benzoquinone, the only quinone included, fails to give methoxy bromide adduct either with or without NBS present (equation 49).

A tritium-labeled quinone epoxide involved in enzyme inhibition studies was synthesized using bromine addition (equation 50)[60a].



(49)

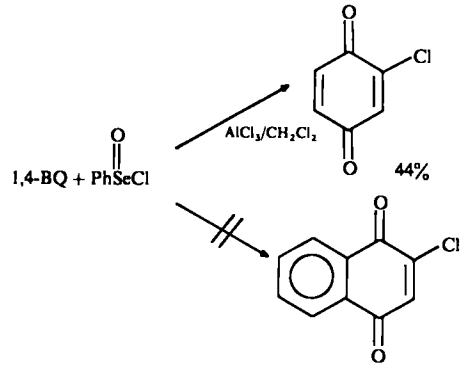


(50)

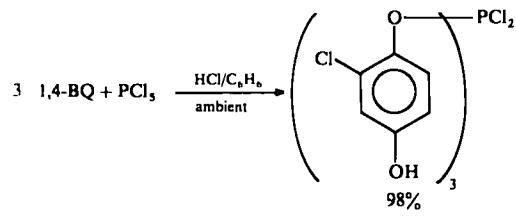
Zamarlik's group prepared siccayne in six stages, beginning with the bromination of 1,4-BQ[60b].

Benzeneseleninyl chloride is a useful vinylic chlorinating reagent for a variety of alkenes and α,β-unsaturated ketones[61]. Unfortunately, only 1,4-benzoquinone was successfully examined (equation 51).

The reductive addition of chlorine to quinones remains a reaction of limited synthetic value. A recent investigation of the direct reaction of phosphorus pentachloride shows that smooth, rapid, and clean reactions occur (equation 52)[62].



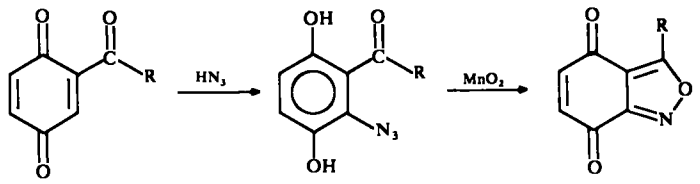
(51)



(52)

2. Azides

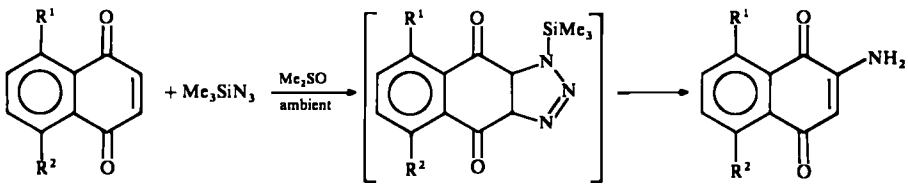
Valderrama and students continue to explore 1,4-benzoquinones bearing strong electron-withdrawing groups. They have shown that the 3-azido substituent reacts with manganese dioxide to produce good yields of 2,1-benzisoxazol-4,7-diones (equation 53)[63]. The cyclization products reported are unsubstituted in the quinone ring. No cyclization product was obtained in the phenyl substituted example, possibly for steric reasons.



(53)

R	%	%
H	66	52
Me	92	76
OMe	89	—
Ph	0	—

An important new reagent for the direct introduction of amino groups in 1,2- and 1,4-naphthoquinones, azidotrimethylsilane, has been explored by Tišler's group

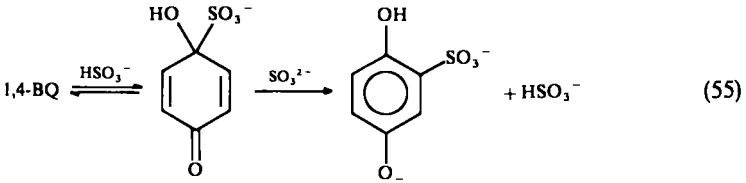


R^1, R^1 = H, OH, OMe, OAc 70–90% (54)

(equation 54)[64]. The yields are good, but not highly regiospecific. Proposed mechanisms involve possible 1,3-dipolar cycloaddition, or Michael addition, and by-products are explained on the basis of diazonium coupling with a second quinone molecule. Perhaps some of these questions can be resolved and isolation of intermediates realized.

3. *Inorganic sulfur*

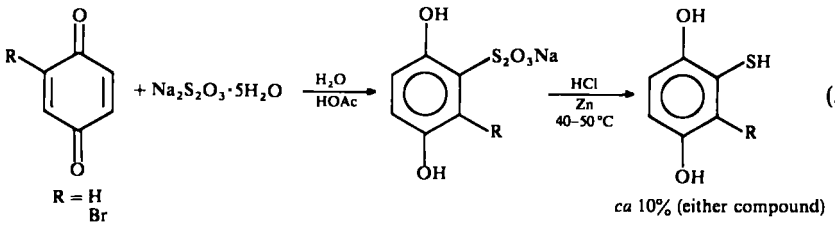
A significant concern of the photographic industry is still the interaction of sulfite and quinones. Youngblood reviewed the fairly extensive literature of such additions, based primarily on product studies, and added his own kinetic investigation[65]. The reactions were followed by stopped-flow ultraviolet techniques in the pH range 4.5 to 8.0. Both the appearance of hydroquinone product and the disappearance of quinone were examined. The latter experiment gives evidence of the rapid reversible formation of a 1,2-carbonyl adduct (equation 55).



(55)

The reaction rates were independent of the wavelength followed and demonstrated no general acid or basic catalysis. A small medium effect was noticed with increased phosphate concentration. The experimental data are consistent with a complicated rate equation. A reasonable mechanistic pathway is described. Evidence of greater complications at higher pH limited the usefulness of the study under those conditions. Youngblood concludes sadly that the mechanisms are still poorly understood. He expresses the hope that the work in the 'well-behaved' neutral region is valuable for future investigations. He has certainly provided the impetus.

In addition to their extensive studies of thiol addition to quinones Monks and colleagues[66] have developed an important modification of Alcalay's method for the synthesis of thiophenols from 1,4-benzoquinones (Reference 1, pp. 937–938)[66]. While the yields are small the simplicity of the method for preparing these reactive compounds is impressive (equation 56).



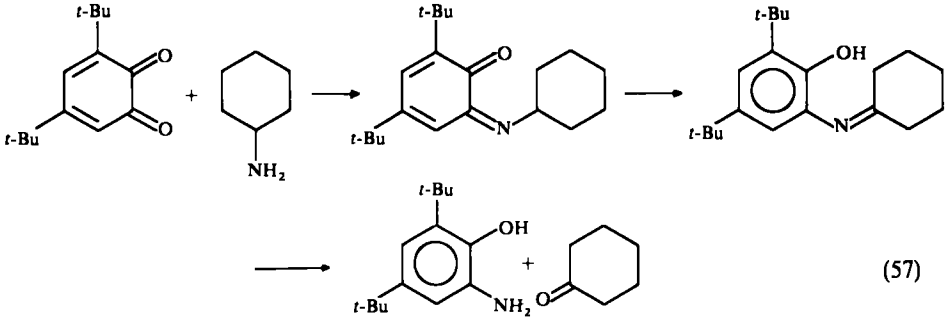
(56)

III. CARBONYL CHEMISTRY

As in my earlier reviews of quinone carbonyl chemistry (Reference 1, pp. 950–963; Reference 2, pp. 589–603) arbitrary assignments are prevalent here. I have attempted to select those reactions which uniquely effect the carbonyl bonds, but the divisions between cycloaddition and carbonyl chemistry, for example, are often fuzzy.

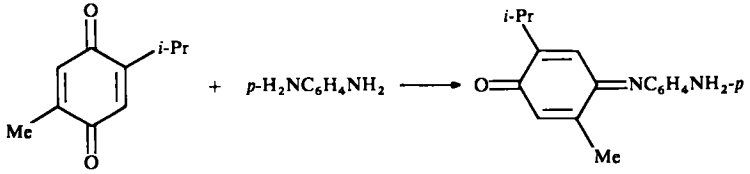
A. Nitrogen Chemistry

The demonstrated utility of 3,5-di-*t*-butyl-1,2-benzoquinone, often called Corey's Reagent, in deamination reactions has inspired a detailed look at the mechanism of this extraordinary reaction[67]. A combination of experimental and theoretical approaches lends strong support to the rearrangement of quinone imines to Schiff bases as shown in equation 57. The study also describes efforts to regenerate the quinone from the aminophenol by-product.



(57)

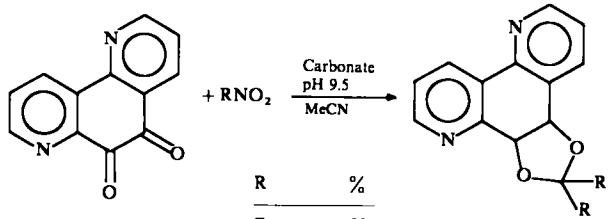
Kallmayer and Weiten have shown that the blue compound obtained from sulfanilamide and thymol in the presence of sodium hypochlorite (75%) can also be prepared from thymoquinone and *p*-phenylenediamine (equation 58)[68].



(58)

B. Cycloaddition to 1,2-Dicarbonyls

In experiments designed to investigate an enzymatic reaction involved in bacterial nitroalkane oxidations Ohshiro and students found an interesting cyclization (equation 59)[69]. Most of the complex quinones studied involve nitrogen heterocyclic systems, and the yields vary from moderate to good. The presence of an intermediate in the reaction is argued as well as proposals about the mechanism.

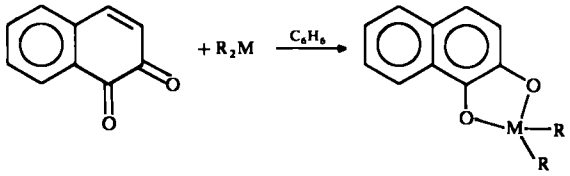


R	%
Et	88
n-Pr	70
i-Pr	67

(59)

C. Organometallic Cyclization

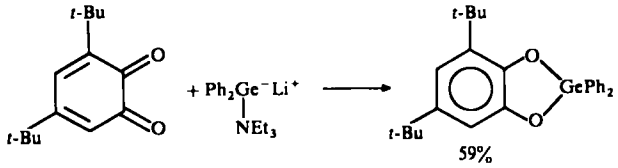
There has been an effort to examine in some detail the way in which germanium and tin compounds cyclize with 1,2-benzoquinones. Neumann and students have been active using both of these metals in the production of good yields of a wide variety of α-diketones as well as α,β-unsaturated ketones[70,71]. Several *o*-quinones are included in the latter catagory (equation 60). The compounds are well characterized and the mechanism of the addition studied. Possible applications in organic synthesis are left for the future.



(60)

M	R	%
Ge	Me	70
Sn	CH_2SiMe_3	—

Similar studies have been reported by Rivière and students. In addition to a variety of substituted germylenes, including halo and alkoxy substituted examples[72], they have examined the germyllithium organics (equation 61)[73]. Detailed studies of the cyclization reactions of 3,5-di-*t*-butyl-1,2-benzoquinone show little effect of solvent or catalyst[74]. Again we must await the development of synthetic applications.

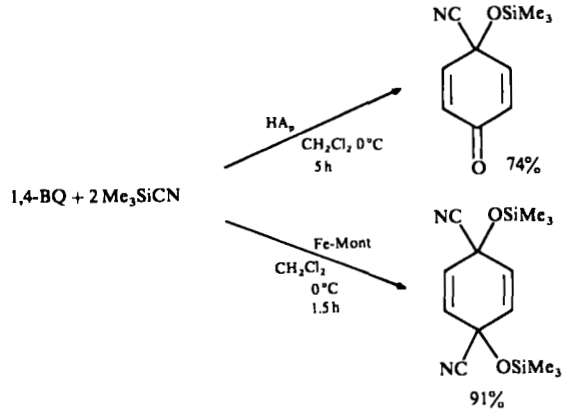


(61)

D. Silyl and Organolithium Additions

The important addition of cyanotrimethylsilane developed by Evans[75] (Reference 2, pp. 592–593) has been significantly expanded through the introduction of two efficient catalysts[76]. The yield obtained with a variety of carbonyl groups is near quantitative, and if two equivalents of reagent are used with 1,4-benzoquinone either the mono- or *bis*-adduct may be obtained (equations 62 and 63).

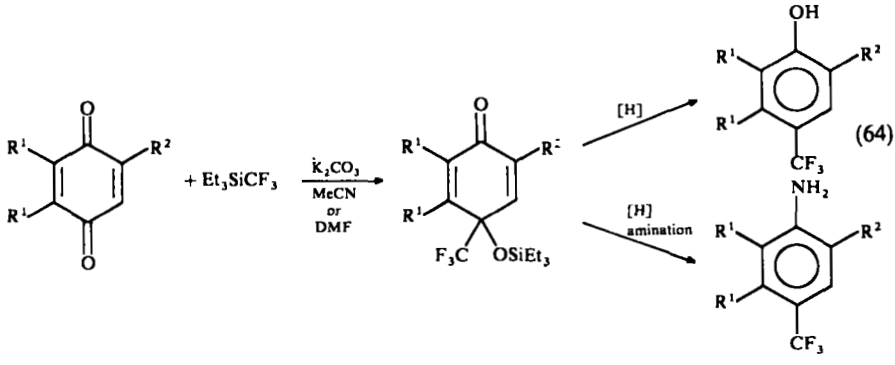
The increasing use of the trifluoromethyl group has created a need for improved synthetic methods. The evidence produced in the case of phenols and anilines prompted Stahly and Bell to report the addition of trialkyl(trifluoromethyl)silane to a variety of quinones[77]. The intermediate 1,2-addition product can be reduced to a phenol (equation 64) or reductively reduced to an aniline (equation 65) in most cases with satisfactory results.



(62)

(63)

HA_p = hydroxyapatite
Fe-Mont = Fe^{3+} ion-exchanged montmorillonite



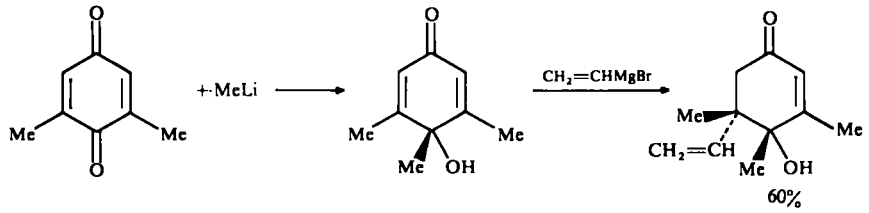
(64)

(65)

R^1	R^2	%
H	H	72
H, *t*-Bu	*t*-Bu	90
CH=CHCH=CH	H	44

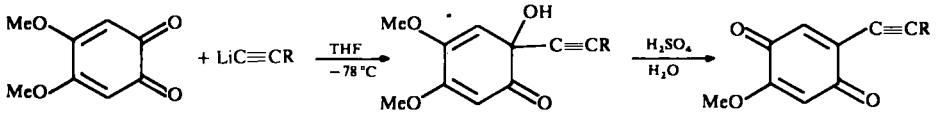
Liotta and collaborators continued their work in quinone and lithium chemistry by examining the fairly rare case of an alkoxide–metal complex exerting regio- and stereocontrol for a nucleophilic species[78]. Their approach involves 1,2-carbonyl addition of various organolithium reagents followed by a Grignard reaction. The important synthetic outcome is high regiospecificity coupled with miniminal steric hinderance (equation 66). The high yield reactions may be performed independently thus adding to their synthetic promise.

In a similar vein Moore and students have fully developed their studies of alkynyl quinone syntheses[79]. The main thrust of this synthetic project is the synthesis of alkynyl-



(66)

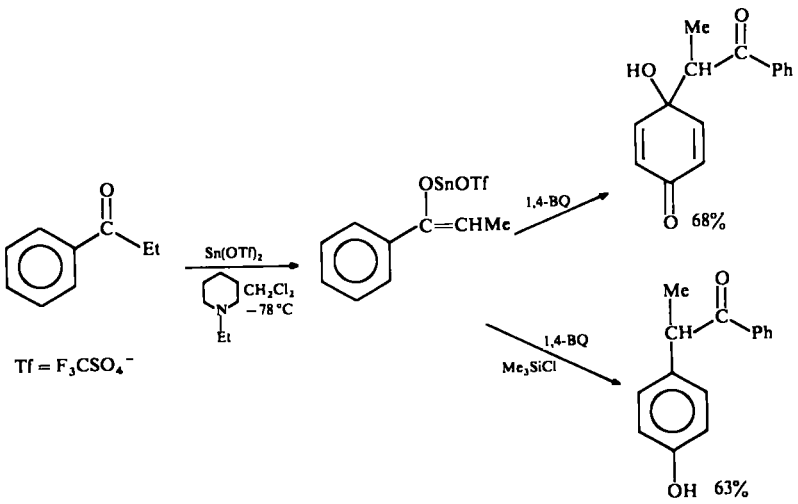
substituted 1,2-benzoquinones as a complement to the earlier work on 1,4-benzoquinones. The 1,2-addition of lithium acetylides to alkoxy substituted 1,2-benzoquinones was followed by acid hydrolysis to 2-alkynyl-5-methoxy-1,4-benzoquinones (equation 67). Many examples are given, all in excellent yield, concluding with specific illustrations of bioreductive alkylating agents as pro-drugs.



R	%	%
Ph	95	97
n-Bu	94	94
CO_2Et	92	94

(67)

The group of Mukaiyama reports the successful Michael addition of tin(II) enolates to 1,4-benzoquinone and its nitrogen analogs[80]. Through the use of chlorotrimethylsilane it is possible to obtain good yields of the reduced *p*-substituted phenol directly (equations 68 and 69). Detailed study of quinones and other α,β-unsaturated ketones reveals mechanistic details along with optimum conditions for obtaining either product[81].

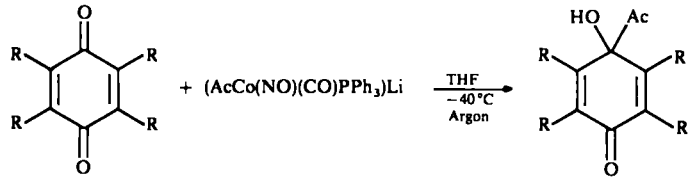


(68)

(69)

E. Carbon 1,2-Addition Chemistry

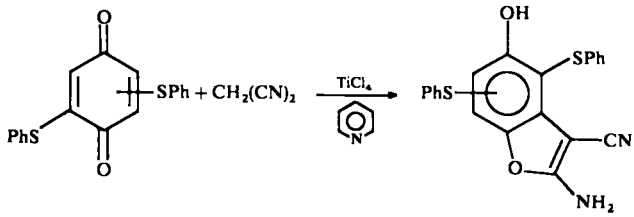
Hegedus and Perry prepared a stable cobalt tricarbonyl complex which reacts with a variety of organolithium reagents. The acylate complexes produced add, in moderated yields, to quinone carbonyl groups (equation 70)[82]. It was not possible to improve the yields and little regiospecificity was observed.



(70)

R	%
H	28
Me	29
2,6-Me_2	33

The synthesis of tetracyanoquinodimethanes has become a popular goal in recent years as the search continues for special types of conducting organic molecules. The use of titanium tetrachloride in pyridine, the Lehnert reagent, has proven useful. It happens that this method is not applicable to quinones bearing phenylthio substituents (equation 71)[83]. The modest yields of benzofurans should not retard continuing efforts to improve them and to extend the range of their synthesis. Compounds of this structure are often difficult to prepare by other means. A clue is provided in the observations that better yields are obtained using pyridine alone.



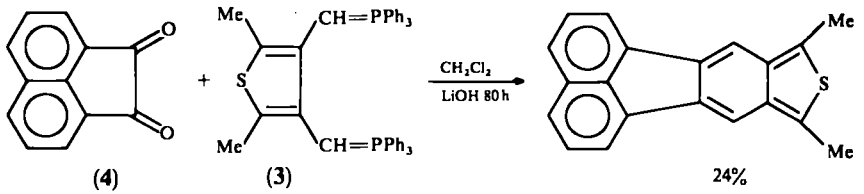
(71)

2,5-	32%
2,6-	35%

F. Notes

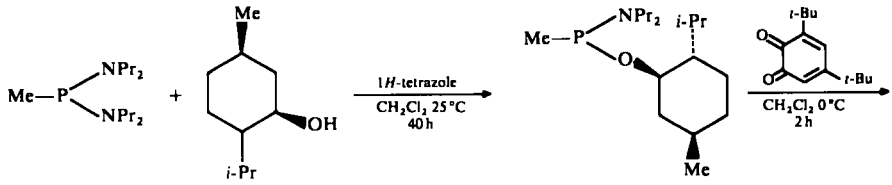
With renewed interest in the synthesis of polycyclic aromatic compounds Nicolaides and collaborators attempted to add a 1,4-bis-phosphonium salt (**3**) to several quinones and the α-diketone (**4**) which they, like many others, insist on calling a quinone (equation 72)[84a]. In this one instance they were able to obtain the Wittig product. Addition to one of the carbonyl groups was observed in two cases while *o*-chloranil produced a 1,3-benzodioxole. In all cases there was significant hydrolysis of the ylide.

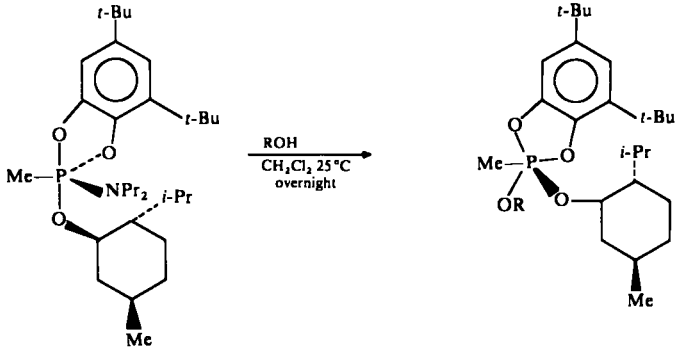
The lack of a general method for preparing phosphorus with five different groups attached has limited the stereochemical study of important enzyme reactions. Moriarty and students have used 3,5-di-*t*-butyl-1,2-benzoquinone to form a key intermediate in such a synthesis (equation 72a)[84b].



(4) (3)

(72)

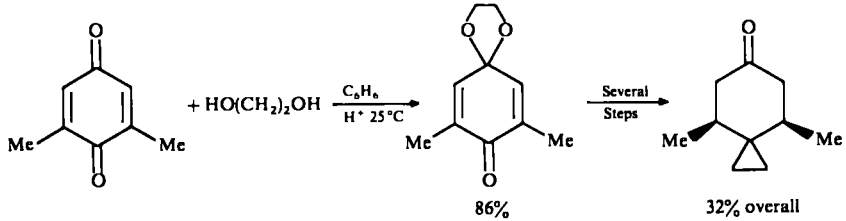




(72a)

R	%
Me	88
Et	94
c-C_6H_{11}	86
l-(−) menthyl	95
$(CH_2)_2SS$- 	100

Quinones often require the protection of the carbonyl function while other chemistry is carried out. This requirement of synthetic sequences is especially important and difficult



86% 32% overall

(73)

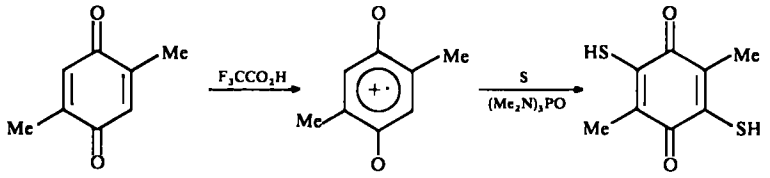
with the two carbonyls of quinones. Franck-Neumann and students took advantage of steric restraints to use the common protecting reagent ethylene glycol in the synthesis of a derivative of the antitumor–anti bacterial Illudine M (equation 73)[85].

IV. ALKYLATION, ARYLATION AND RADICALS

A. Radicals and Quinones

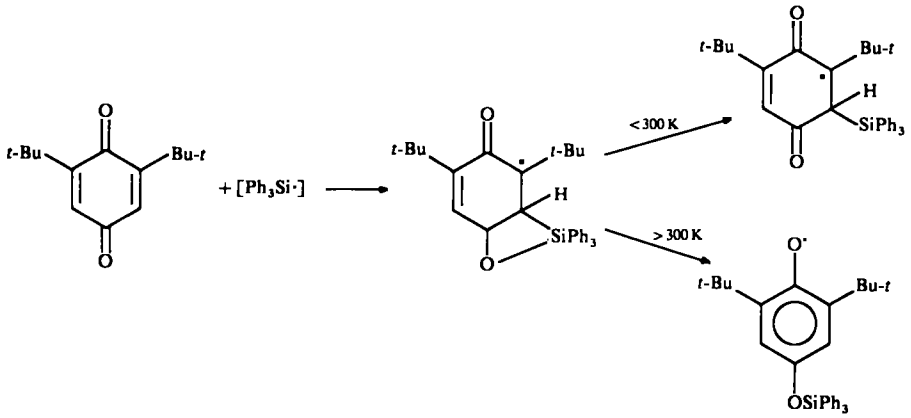
The study of radical and quinone interactions has centered on the synthetic applications and the formation of new carbon–carbon bonds (Reference 1, pp. 963–985; Reference 2, pp. 603–613). Recent reports deal with the introduction of noncarbon substitutents, intermediate detection and kinetic studies.

The Lawesson reagent does not seem to have been used in the sulfurization of quinones but Wan and students have shown that it succeeds with 2,6-dimethyl-1,4-benzoquinone and that the radical cation is an intermediate (equation 74)[86].



(74)

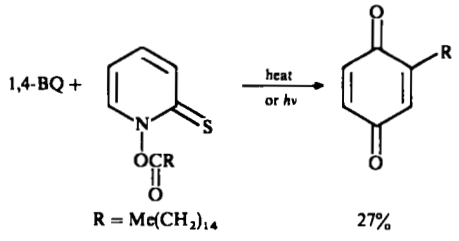
The observed products from the reaction of silyl radicals with 2,6-disubstituted-1,4-benzoquinones are temperature dependent[87]. At temperatures below 300 K addition takes place at the kinetically favored alkene; at higher temperatures only the thermodynamically more stable oxygen radicals are observed. Kinetic evidence shows internal rearrangement and structural variation consistent with a four-membered cyclic transition state (equation 75).



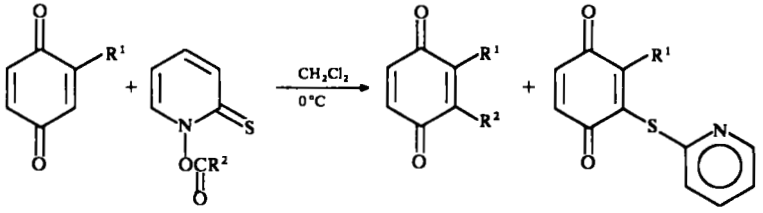
(75)

Barton and colleagues discovered a potentially important method of generating radicals under mild conditions in the decomposition of thiohydroxamic esters either thermally or photochemically. Their first study gave promise of facile alkylation of quinones (equation 76), but with disappointing yields[88]. They reasoned correctly that

lower temperatures should improve yields. Surprisingly, a new sulfur adduct resulted (equation 77)[89]. The synthetic utility of this new finding is apparent, and the yields of alkylation can be improved by varying the amounts of quinones. 1,4-Naphthoquinones are also reactive and a variety of sensitive functional groups can be involved in the decarboxylation reaction.



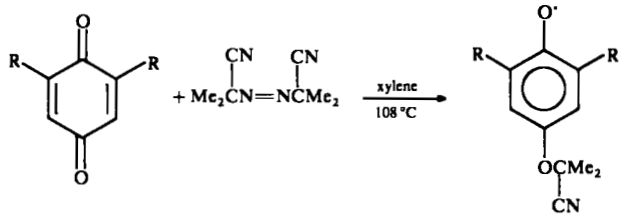
(76)



(77)

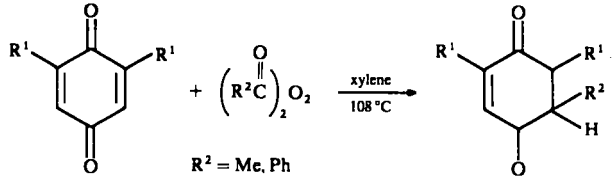
R^1	R^2	%	R^1	%
H	$Me(CH_2)_{14}$	10	H	77
Me	Ph_2CHCH_2	10		80
	$c\text{-}C_6H_{11}$	10		78
		15	—	71
		25	Me	60
		21		21

A study of the effect of carbon radical structure on the point of attack in 2,6-dialky-1,4-benzoquinone gives strong support to earlier studies[90]. The radicals cyanoisopropyl, polystyryl and poly-(α-methylstyryl) all show identical ESR spectra with alkylquinones of varying bulk, and all are consistent with attack at the oxygen atom (equation 78). On the other hand, radicals generated by the thermal decomposition of benzoyl or acetyl peroxides add to the alkene linkage of the quinone (equation 79).



(78)

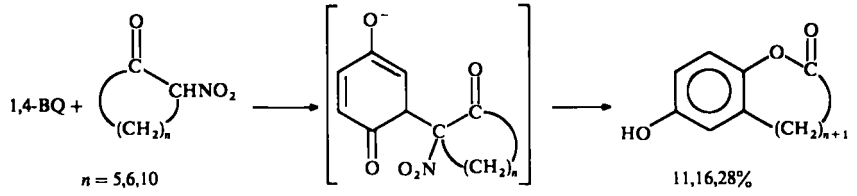
R = Me, Et, *i*-Pr, *s*-Bu



(79)

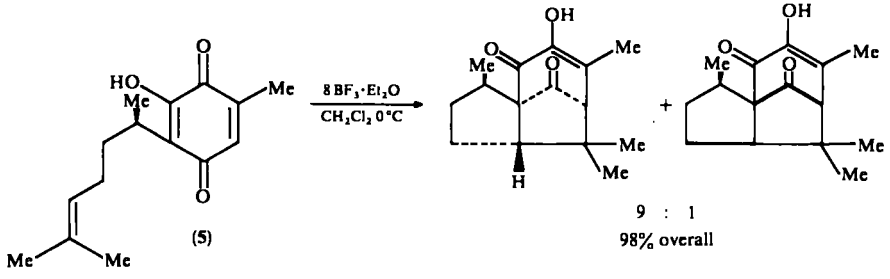
B. Michael Alkylation of Quinones

Many common reactions of quinones towards nucleophiles are classic examples of reductive Michael addition, and this name has also been applied to the alkylation process. Evidence for the utility of Michael alkylation is found in the addition of 2-nitrocycloalkanones to 1,4-benzoquinone and subsequent ring expansion to lactones (equation 80)[91].



(80)

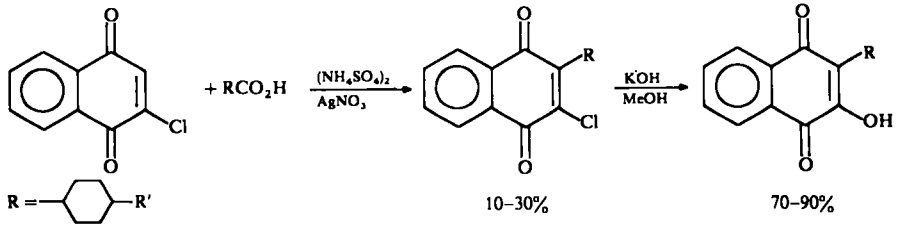
In their continuing studies concerning cyclization of perezone (5) Joseph-Nathan and students[92,93] have reviewed this chemistry (Reference 1, p. 1041) including the first demonstration of its mechanism[94]. Their most recent contribution is an important investigation of the stereochemistry of the boron trifluoride catalyzed mode of addition (equation 81)[95]. Their conclusion is that very small changes in the quinone structure cause large changes in the course of the cyclization.



(81)

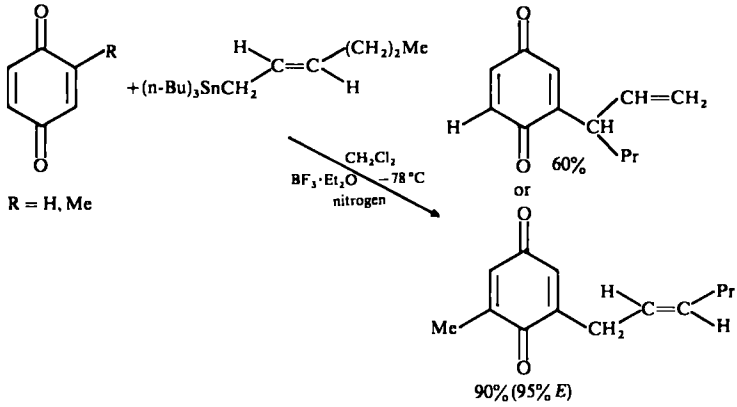
The decarboxylation of carboxylic acids using ammonium persulfate, as developed by Jacobsen and Torssell[96], is often the route to quinones which are otherwise difficult to obtain. For example, Hudson and collaborators have synthesized a series of cyclohexyl 3-hydroxy-1,4-naphthoquinones for antiparasitic testing (equation 82)[97]. More highly substituted quinones react with numerous acids in this chemistry[98,99]. Unfortunately the data given in the English abstracts are not helpful. What may be a related total

synthesis is even less useful in that the potentially interesting alkylation is not described[100].



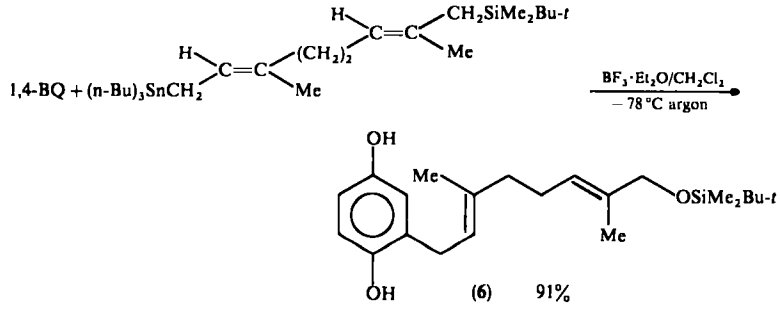
(82)

One effective way to promote carbon nucleophiles for addition to quinones is through organometallics. The allylstanyl reagents[101], so well developed by Naruta and collaborators (Reference 2, pp. 605–608), have been applied to (*Z*)-diastereomers which are found to react without complete retention of stereochemical configuration, in contrast to the (*E*)-isomer (equation 83)[102]. In general, the yields are high and steric effects important.



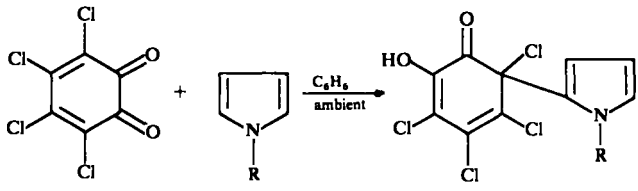
(83)

A key step in the synthesis of arnebintol, an interesting ansa-type molecule (**6**), involves the application of similar chemistry using a trimethylsilyloxy derivative of the tri-n-butylprenylstannane (equation 84)[103].



(84)

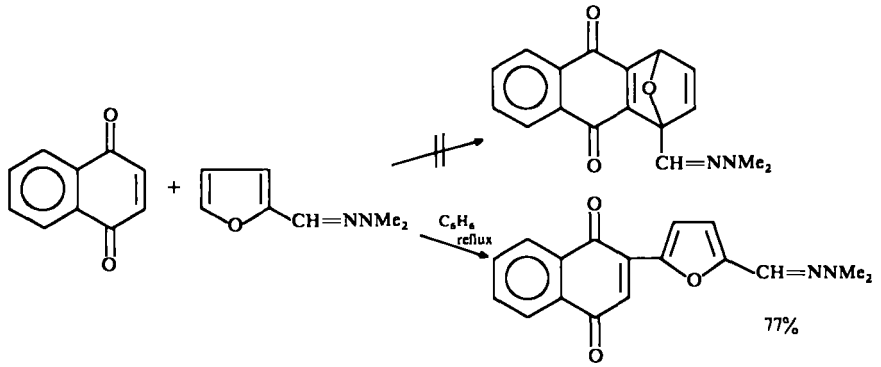
Studies of the addition of pyrroles to certain quinones shows Michael products in contrast to the cyclizations observed with azepine (equation 85)[104]. The yields are rather low although mild conditions are employed.



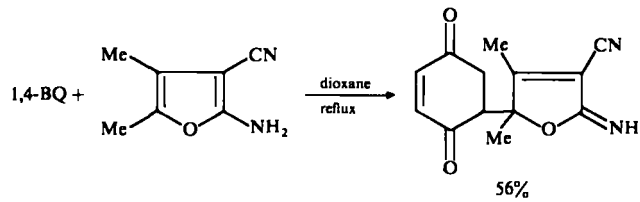
R	%
Me	25
Ph	14

(85)

Potts and Walsh attempted the expected Diels–Alder reaction of furfural dimethylhydrazone with 1,4-naphthoquinone and its aza derivatives but found a strong preference for Michael product (equation 86)[105]. Blanton and students observed similar chemistry with a highly substituted furan ring (equation 87)[106].



(86)

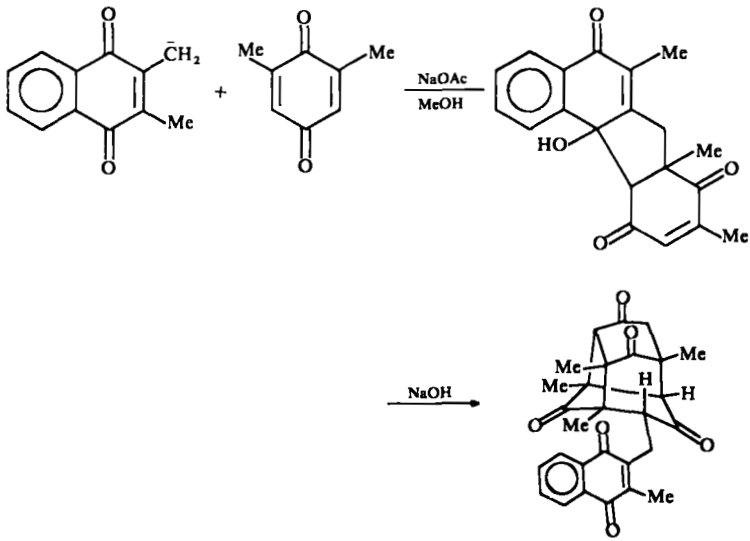


(87)

C. Arylation of Quinones

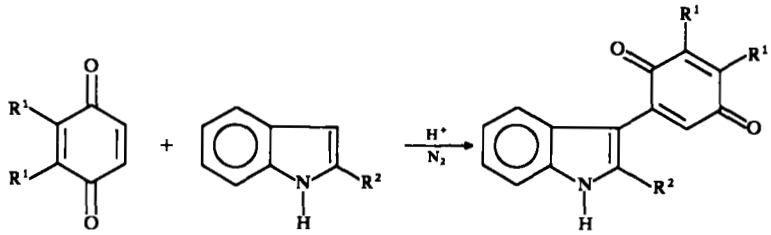
The linking of aromatic and quinonoid rings has been used in many synthetic circumstances (Reference 1, pp. 1043–1047; Reference 2, pp. 663–671) and continues to be of interest. A review by Tišler, though restricted to examples containing two naphthalene rings, provides examples involving quinones[107]. Some of his examples are related to the active methylene chemistry of quinones which are now less actively investigated (Reference 1, pp. 1047–1073; Reference 2, pp. 671–682).

In one report Dean and students studied the fascinating chemistry of cage formation in the anionic reactions of methylated 1,4-benzo- and naphthoquinones (equation 87a)[108]. In a closely argued investigation they conclude that charge-transfer complexes are required for the formation of these exotic and potentially useful molecules.



(87a)

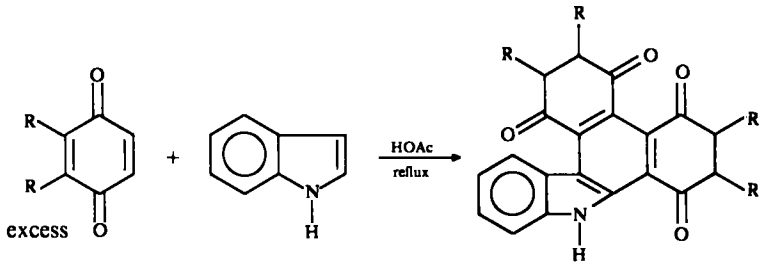
Prota and colleagues have reexamined earlier reports of simple reductive addition of indoles to 1,4-quinones[109,110]. They show that under anaerobic conditions it is possible to obtain good yields of the reported products (equation 88) while with excess quinone more complex Diels–Alder products are formed (equation 89). Some of this chemistry should be compared with studies involving cycloaddition of indoles and quinones (see Section V.C).



(88)

		$R^1 = H$	$R^1 = CH{=}CHCH{=}CH$
$R^1 = H$	$R^2 = H$	70%	62%
$CH{=}CHCH{=}CH$	Me	90%	78%

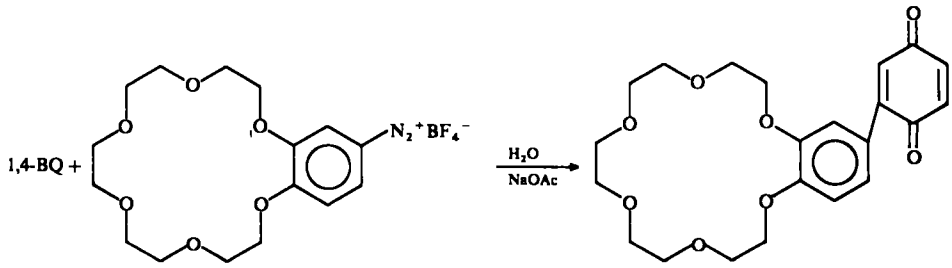
In contrast to earlier periods of quinone history little use of the classic Meerwein method using diazonium salts has been reported. One study involves the synthesis in low yield of a crown ether attached to a quinone for studies of enzyme catalysis (equation 90)[111]. A second effort describes the synthesis, in greater that 70% yields, of embelin derivatives for antibacterial screening (equation 91)[112].



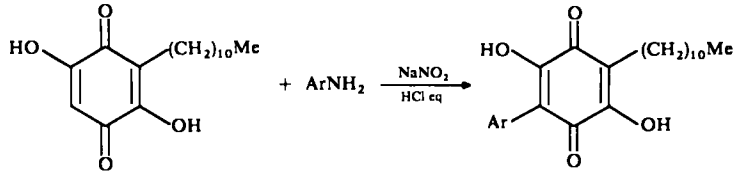
(89)

$R = H$;
$R^1 = CH{=}CHCH{=}CH$

65%
82%



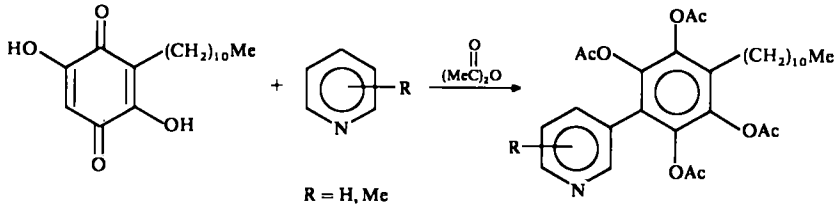
20% (90)



(91)

Ar = Ph, 2,3 or 4-ClC_6H_4
2,3 or 4-$NO_2C_6H_4$
2,4-$MeOC_6H_4$
2,3 or 4-MeC_6H_4

In another study of embelin chemistry pyridine and related heterocycles were found to add to the single unsubstituted position of the quinonoid ring. The reaction takes place in acetic anhydride and produces the reduced tetraacetates (equation 92)[113].



R = H, Me

(92)

V. CYCLOADDITION REACTIONS OF QUINONES

A. The Contributions of Quinones to Diels–Alder Theory

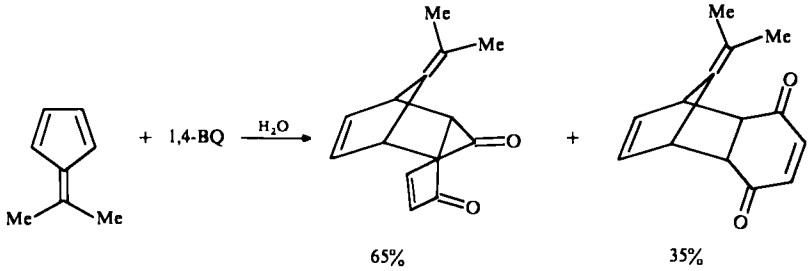
1. Rates and mechanisms

Few chemical reactions can claim such length and breadth of interest as the 'diene synthesis'. It is natural therefore to find a continuing series of high quality theoretical investigations associated with these cycloadditions. Quinonoid structures occur frequently in synthetically interesting molecules obtainable by Diels–Alder chemistry. Quinones are well represented in such studies because of the variety of active sites provided by their structure.

In the past few years the emphasis of physical-organic studies of Diels–Alder chemistry has centered on rates and stereochemistry. The introduction of new procedures, for example, Lewis acids or trimethylsilyloxy substituents, brought about dramatic changes.

With quinones, relative rate data for the disappearance of starting material are measured along with product yields. In spite of this inelegant approach the evidence shows that several unsuspected reaction conditions cause large changes in both the rate and stereochemistry of this synthon.

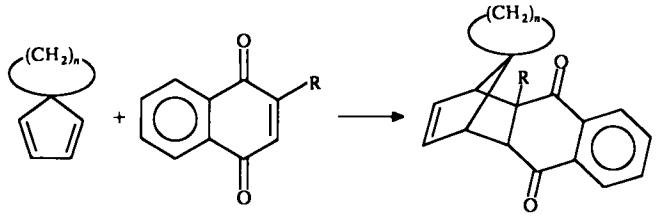
A specific example of this observation is found in Griesbeck's work on the addition of dimethylfulvene to 1,4-benzoquinone (equation 93)[114]. Examination of the reaction in a wide variety of solvents revealed important points. First, with the exception of water, there is very little change in rate. Second, the ratio of *endo/exo* product is essentially constant (1:1) for all solvents except water. In water the rate is 100-fold higher than in aprotic solvents and at least 20-fold that in protic solvents. The diastereomeric products were produced in a 2:1 ratio. Changes in the formal concentrations of nearly insoluble reactants in heterogeneous aqueous reaction media show an important trend. If the reactants are approximately millimolar, the *endo/exo* ratio is 1:9. At formal concentrations of 1.6 molar the diastereomers are formed in a ratio of 9:1. I found no report of further exploration of this effect.



(93)

Singh and students explored the use of micelles in aqueous media for the Diels–Alder addition of spirocyclopentadienes to 1,4-benzo- and naphthoquinones (equation 94)[115]. Their comparison of yields in boiling toluene versus ambient water containing cetyltrimethylammonium bromide shows an increase in yield in all cases. The example illustrated below could only be prepared in the aqueous micelles. Reaction times were of the order of 10–12 hours in toluene and approximately 3 hours in water.

This suggestion that molecular aggregation strongly influences reaction rates has been examined by Liotta and students[116]. In considering Diels–Alder reactions which fail in water, probably because of low solubility, they found that ethylene glycol provides substantial rate enhancements. One ought not to be surprised since the glycol not only



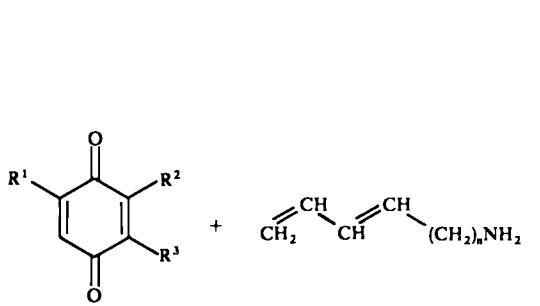
(94)

Micelle			Toluene		
n	R	%	*n*	R	%
0	H	68	0	H	50
0	Me	86	0	Me	0
2	H	75	2	H	53
2	Me	46	2	Me	40

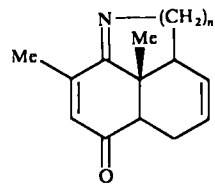
hydrogen bonds in networks nearly as well as water, but also provides a small hydrocarbon backbone which helps to solubilize the hydrophobic dienophiles.

As for asymmetric induction, it was found[117] that catalytic amounts of bovine serum albumin produce as much as a 38% enantiomeric excess in the addition of enol ethers or esters without changing the regiochemistry. The various 1,4-naphthoquinones studied showed substantial rate enhancements on changing from benzene to water.

Grieco and students have examined the effect of increased separation between the diene and the hydrophilic group rendering the system water soluble (equation 95)[118]. High yields of tricyclic imines were obtained under mild conditions. The relatively acidic solutions prevented the use of several of the usual dienophiles, e.g. acrolein and methyl acylate, but these too could be used when the sodium salt of *N*-dienyl succinamic acid was used in place of the ammonium chlorides. Evidence is presented comparing the times and yields for aqueous versus hydrocarbon solvents.

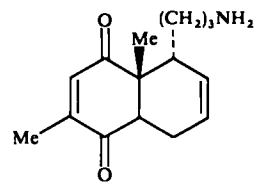


R^1	R^2	R^3
Me	Me	H
Me	H	Me
MeO	Me	H



n	%
1	98
2	99

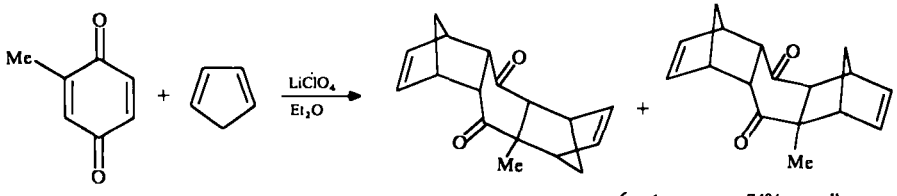
or



62%

(95)

In a more recent study Grieco and collaborators have shown that the system of 5 *M* lithium perchlorate in diethyl ether can produce greatly enhanced rates of Diels–Alder cyclization[119]. In some examples they were able to prepare adducts which had only been obtainable at high temperature and/or high pressure (equation 96). As the reason for these promising results, the idea of a high internal solvent pressure has been advanced. These observations add a new dimension to this chemistry by allowing the use of water-sensitive or insoluble reactants.



6 : 1 74% overall (96)

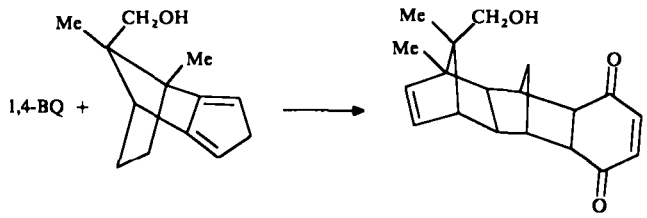
In a recent paper of Wilcox and students cycloocta[*def*]biphenylene-1,4-dione is not only compared with quinones, but actually called one in the title[120]. The rates of cyclization of these compounds are compared and fitted to a model involving substantial charge transfer in the transition state. The observations are interesting and may be relevant to quinone chemistry, although that subject is not discussed. The continued use of an inaccurate nomenclature is not helpful.

2. *Models and stereochemistry*

The widespread use of the Diels–Alder reaction in natural product synthesis is associated with its highly developed stereoselective properties. Since quinones are moderately active dienophiles it has been possible to exploit their functional flexibility. Most of this work has centered on the task of understanding the facial stereoselectivity of the newly formed bonds.

Paquette and students have studied cyclopentadienes containing a specifically oriented primary alcoholic group (equation 97)[121]. 1,4-Benzoquinone, along with several other common dienophiles, was chosen for its ability to participate in hydrogen bonding. The results show that steric effects far outweigh any stereochemical control by the heteroatom.

Some of the most important recent advances in Diels–Alder synthesis are associated with the use of Lewis acid catalysts as first recognized by Valenta and students[122] and employed by many researchers (Reference 2, pp. 619–625). This group has recognized the unique reactivity of 1,4-benzoquinone and the many recorded examples of changes of stereochemistry found in the total synthesis of steroids. They synthesized the bicyclic



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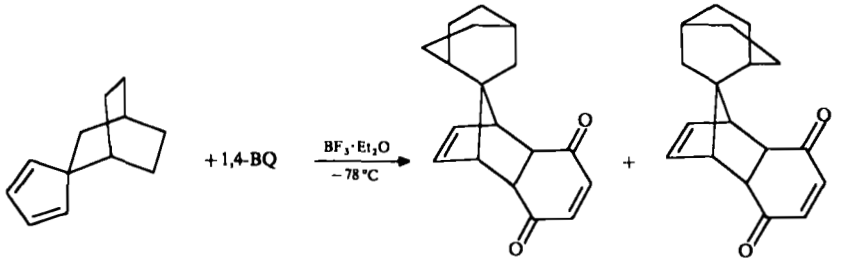
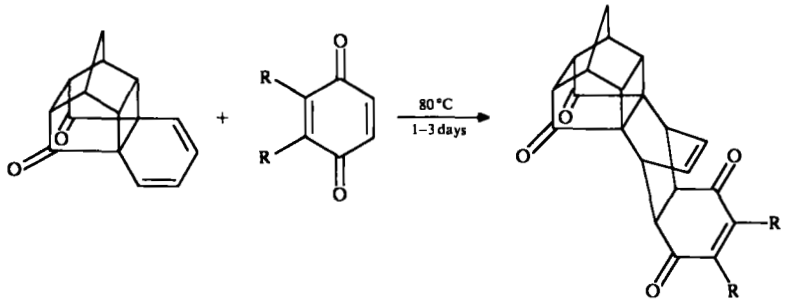


(98)

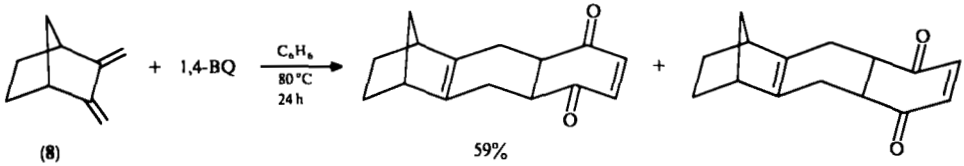
spirocyclopentadiene **7** and examined its chemistry (equation 98)[123]. They observed no significant difference in facial stereoselectivity between the thermal and boron trifluoride etherate catalyzed reactions. There is evidence that when steric interactions are important in the *exo*-region, the geometry of the transition state is constant and insensitive to dienophile reactivity. The product ratios were so constant that experiments were conducted to rule out the possibility of equilibration.

About the same time, another group working with an even more complex cyclic diene reported similar results. The observed selectivity was greater and the wider range of dienophiles revealed additional information about the reaction in general (equation 99)[124].



(99)

An earlier study by Vogel and collaborators shed light on the question of dienophiles of varied reactivity[125]. Their results with stereospecifically deuterated 2,3-dimethylidenebicyclo[2.2.1]heptane (**8**) are consistent with the later studies. They show 1,4-benzoquinone to react with a high preference for *endo*-face addition and to be subject to steric influences (equation 100).



(8)

59%

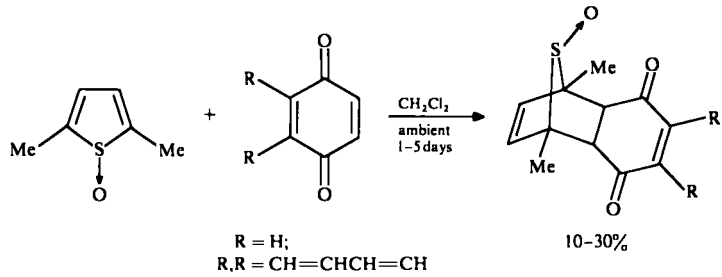
7 : 1

(100)

Detailed calculations for highly hindered spirocyclopentadienes correlate well with the experimental results and suggest strongly that, at least for these reactions, steric effects are important[126a]. They also postulate that the Lewis acid catalyzed reactions involve an earlier transition state.

Hendrickson and collaborators have re-examined the stereochemical outcome of the reaction between isoprene and 2-methoxy-6-methyl-1,4-benzoquinone[126b]. They find, as have others, little stereoselectivity. The importance of their work lies in the clear demonstration that the Lewis acid employed can alter the course of the reaction dramatically.

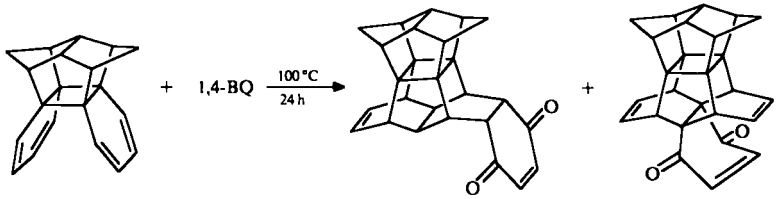
Three additional studies have approached these questions and produced meaningful results. Fabian, using intermolecular perturbation theory, was successful in predicting the regioselectivity of benzo- and naphthoquinones in reactions leading to biologically important molecules[127]. Fallis and students found that 2,5-dimethylthiophene oxide is not a very reactive diene, but with quinones it gives exclusively the *syn* adduct (equation 101)[128].



R = H; R,R = CH=CHCH=CH

10–30%

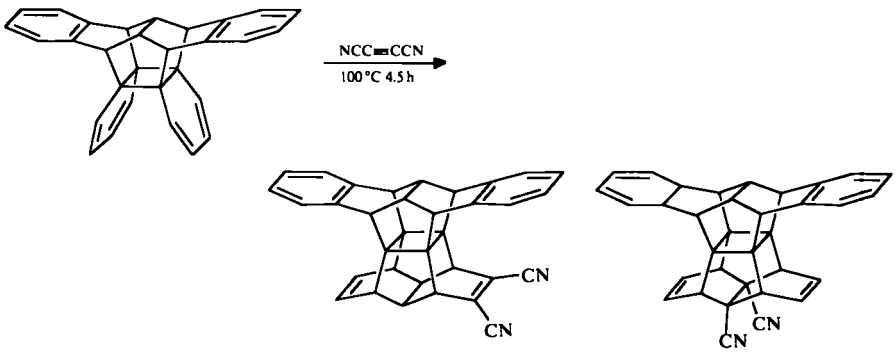
(101)



79%

0%

(102)



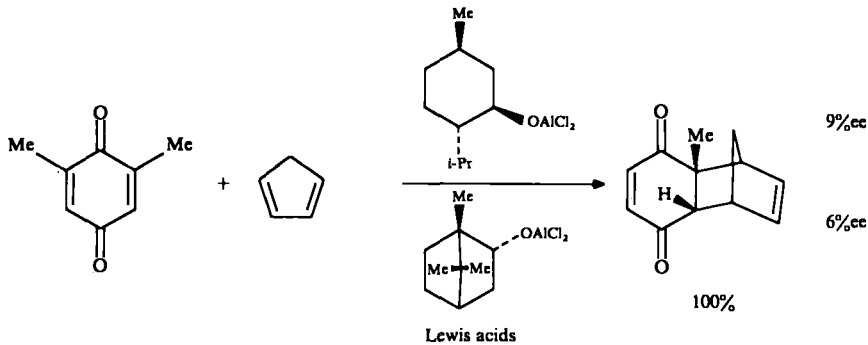
88:12

(102a)

Finally, Prinzbach and collaborators have examined perhaps the ultimate polycyclic dienes in their evaluation of the consecutive cycloadditions, referred to as domino, versus the inside capture pincer product (equation 102)[129]. 1,4-Benzoquinone gave good yields of exclusively domino products and significant amounts of pincer adduct were obtained only with dicyanoacteylene (equation 102a).

While the major interest in the stereochemical study of Diels–Alder reactions has centered on regiochemistry of diastereomers, chemists are beginning to examine questions involving chiral induction. Valenta and Northcott have reviewed the somewhat limited literature on this subject and presented an exciting new study in which 2,6-dimethyl-1,4-benzoquinone plays a central role[130]. Using chiral monoterpene alcohols in combination with alkyl aluminum halides as the Lewis acid, they have carried out the addition reaction with cyclopentadiene (equation 103). In all cases some enantiomeric excess was demonstrated, but it was always much less than that obtained in the addition of methacrolein. The s-*trans* dienophile quinone showed very little chiral induction suggesting that the terpene is too far away in the transition state.

Two additional studies of more limited scope are also of interest. Thornton and Siegel have achieved high stereoselectivity using the comercially available 1-(*O*-methylmandeloxy)-dienes (equation 104)[131a]. In reactions with boron trifluoride etherate less than 10% of



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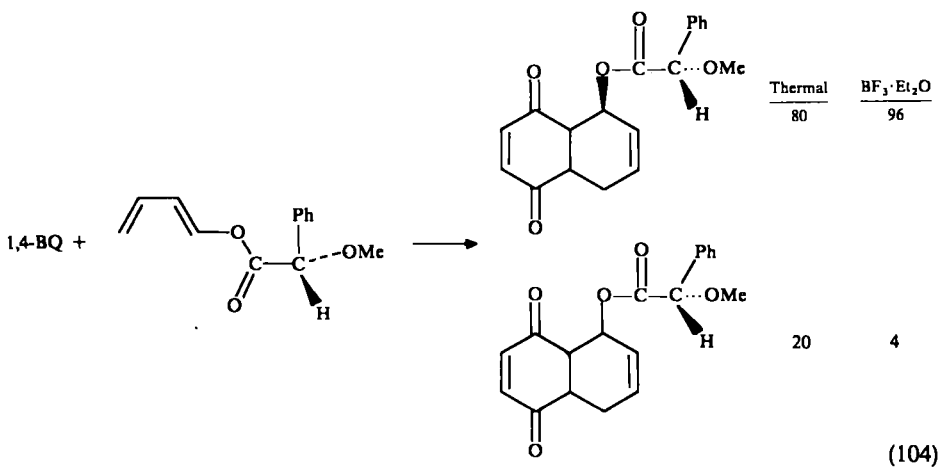
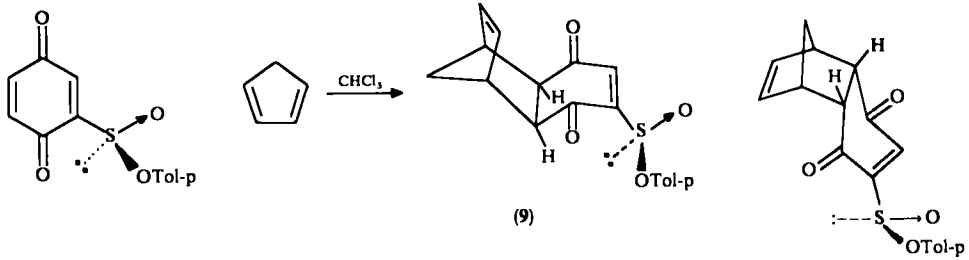


(104)

the minor product was obtained, and even the thermal reaction showed a 80:20 product ratio. Noting prior work of Trost and students[131b], the authors propose a radically different, perpendicular model, transition state based on X-ray structures for benzo- and naphthoquinone adducts. This model agrees so well with their data that further exploration seems warranted.

Using exactly the opposite approach, Carreño and coworkers[132] prepared the first simple chiral 1,4-benzoquinone (**9** in equation 105). Reactions with acyclic dienes produced only naphthoquinones, although desulfurated intermediates were detected in the NMR spectra. With cyclopentadiene, addition took place exclusively at the unsubstituted double bond. The ratio of *exo*:*endo* product is exactly reversed by using a Lewis acid catalyst. This new tool has yet to be used to its potential.

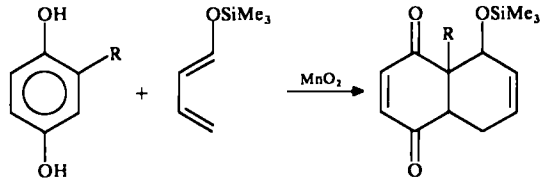


%					
Lewis acid	72	:	28	95	overall
without L.a.	10	:	90	89	

(105)

3. *Regiospecificity and activation*

Success of the Diels–Alder reaction in natural product syntheses often depends on the proper balance between reactive systems and high stereospecificity. Many studies therefore investigate delicate changes in the ability of the diene or dienophile to participate in the cyclization. Most have focused on the diene, since the quinonoid structure is often desired as a component of the final product or at least the controlling element in the synthesis. This generalization is not universal, however, as seen in the studies of Valderrama and coworkers (equation 106)[133].



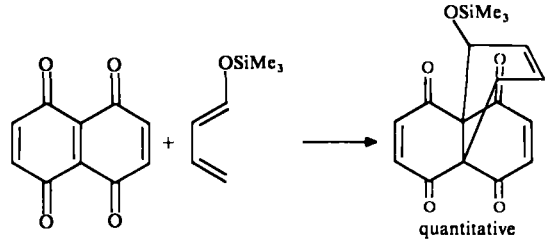
R	%
CHO	92
NO_2	96
COMe	89
CN	84

(106)

They have used the nascent quinone technique generating *in situ* extremely reactive quinones bearing electron-withdrawing groups. They have also activated their dienes with a trimethylsilyloxy group (equation 107). This scheme, coupled with their discovery of the utility of maganese dioxide, produced excellent yields of Diels–Alder adducts.

Fariña and colleagues have also been active in the synthesis of amino substituted anthracyclinones. They discovered a potentially useful *trans* cycloaddition reaction and were able to show that the chemistry also takes place in 1,3-dipolar additions (equations 108–110)[134]. The cycloaddition work has been extended and the alkoxy and silyloxy dienes show some regiospecificity[135]. This work resembles the highly oxygenated reduced anthraquinones synthesized by Krohn and collaborators[136].

The application of silyloxy dienes has a long and productive history (Reference 2, pp. 627–629) which has continued. The impetus for this effort is directly associated with the synthesis of polycyclic natural products of complicated stereochemistry. Brassard



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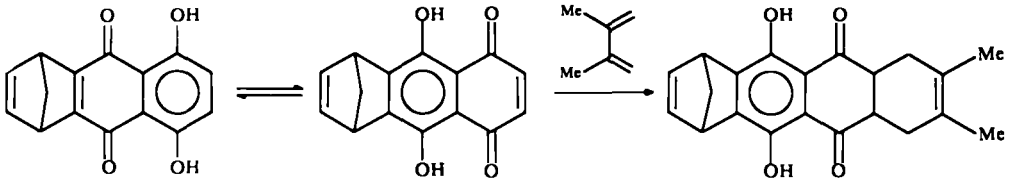

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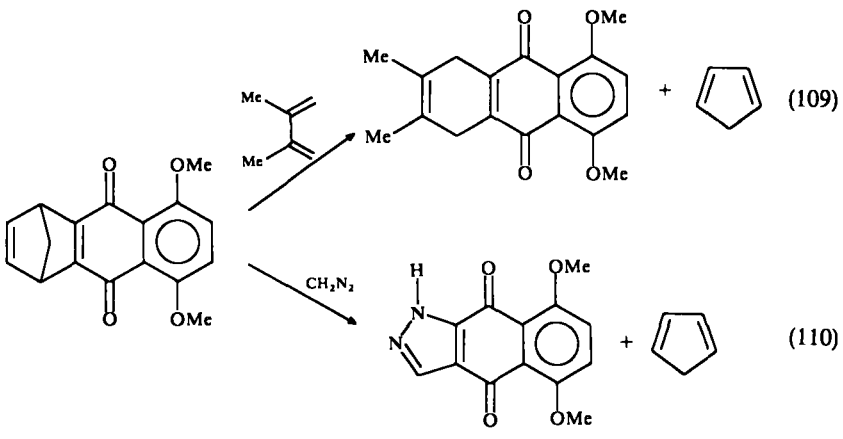
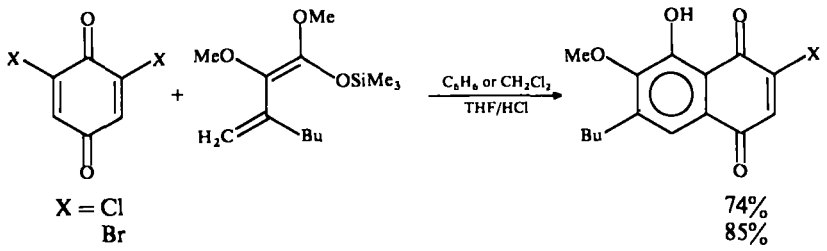


(109)

(110)

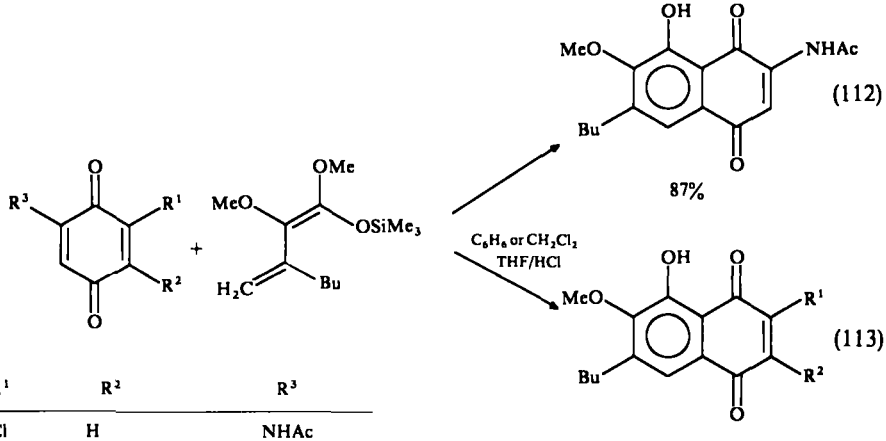


(111)

and students have played a leading role in this field since the mid-70s. Their effort to understand the structure of a degradation product of phomazarin, an azaanthraquinone pigment, is an example of an old problem showing new chemistry (equation 111). The high regiospecificity ultimately led to the synthesis of the degradation product. Of greater interest is the discovery of a previously unsuspected strong directive effect by the acetamido group (equations 112 and 113)[137a]. The combination of activated dienes and the directive effect of bromine shows excellent yields of highly stereoselective product (equations 113a and 113b)[137b].

A heterocyclic modification of these electron-rich dienes produces the thermodynamically less stable natural form of juglone derivatives such as ventiloquinones H and I (**10** and **11** in equation 114)[138].

The utilization of haloquinones in the above synthesis represents an approach often exploited by Brassard and colleagues, for example, their synthesis of the quinizarins or 1,4-dihydroxylated anthraquinones (equation 115)[139]. The haloquinones are relatively sluggish in cycloadditions but in the present study it was possible through careful selection of appropriate substrates to achieve reasonable reaction times and product yields. In

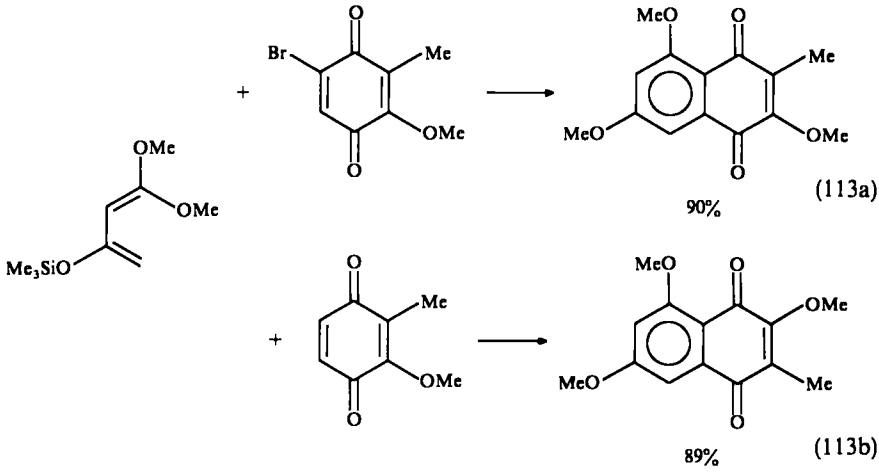


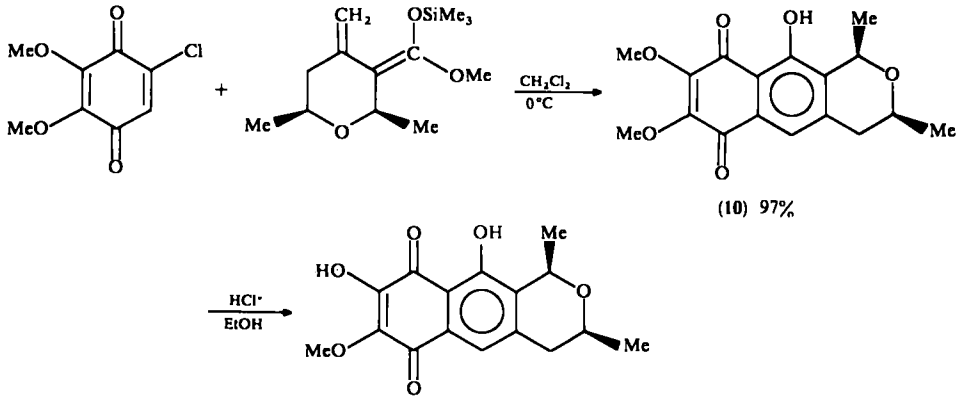
(112)

(113)

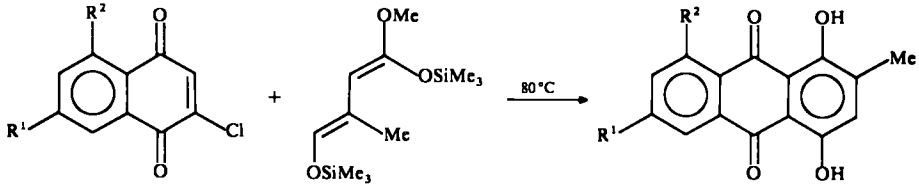
R^1	R^2	R^3
Cl	H	NHAc
H	NHAc	Cl

R^1	R^2	%
H	NHAc	27
NH_2	H	16





(114)



R^1	R^2	%
H	H	76
OMe	OAc	68
OMe	OMe	95

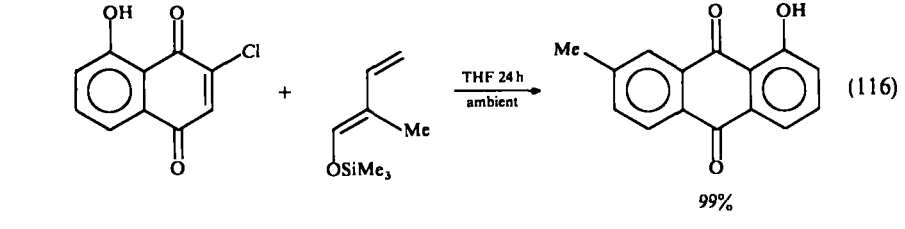
(115)

these and other studies erroneous structures from earlier reports are corrected and promising routes to future total syntheses described.

Brassard and Boisvert had reported much earlier that halo quinones react smoothly and regiospecifically even with monooxygenated dienes (equation 116)[140]. This work produced facile preparations of a number of important natural products. Significant too is the work by other research groups stimulated by Brassard's lead; for example, Cameron and students have used chlorinated benzoquinones and oxygenated dienes in the preparation of alizarin derivatives (equation 117)[141]. Grunwell and collaborators have shown that bromo-1,4-naphthoquinones can exhibit excellent regiospecificity, but fail to undergo Diels–Alder chemistry in the addition of electron-rich dienes (equation 118)[142].

Various groups have made contributions to the synthesis of anthraquinones and tetracyclic quinones using a wide variety of reactive alkoxy and silyloxy dienes[143–146].

An area closely related to activated dienes involves the synthesis of ketene acetals. Here too Brassard has taken the lead as, for example, in his work with Simoneau on the synthesis of the purpurins (equation 119)[147]. With the benzoquinones little Diels–Alder addition takes place, but an apparently clean 1,2-carbonyl reaction should lead to useful new possibilities. Addition also takes place in good yield with a variety of naphthoquinones. Krohn and colleagues have investigated similar chemistry involving a 1,2-quinonoid modification in the preparation of the tetracyclic anthracyclinones



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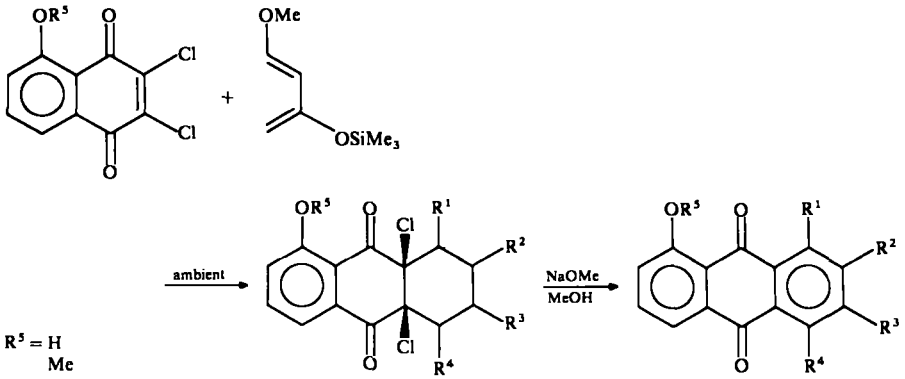
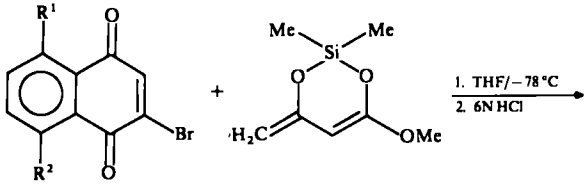


%	R^1	R^2	R^3	R^4	R^5
77	OMe	H	=O	H	H
81	H	=O	H	OMe	Me

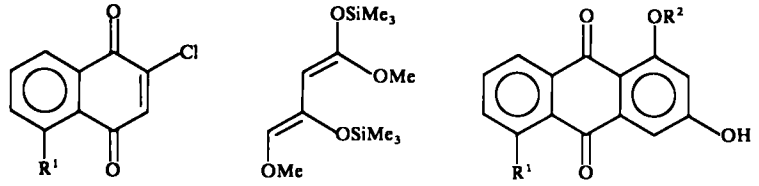
R^1	R^2	R^3	R^4	R^5	%
H	H	OH	H	H	95
OMe	OH	H	H	Me	82

(117)



R^1	R^2	%
OH	H	57
H	OH	71

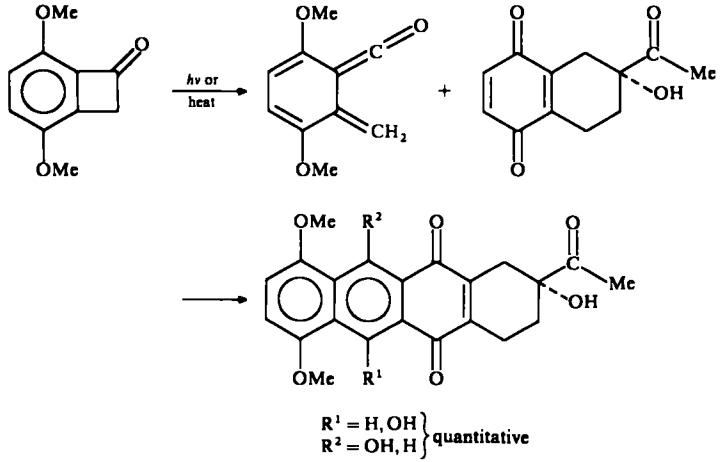
(118)



R^1 = H, OAc

R^1	R^2	%
H	H	48
H	Me	4
OH	H	50

(119)

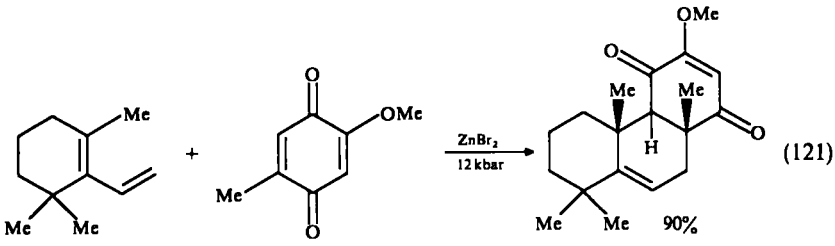


(120)

(equation 120)[148]. A note describing diethylphosphoryloxy dienes has appeared[149]. Compared to analogous silyloxy compounds this attractive new synthetic tool shows enhanced stability, higher yields and greater regiospecificity. Unfortunately, only 1,4-benzoquinone was included in this report.

4. *Lewis acids and high pressure*

In the Diels–Alder literature of the past decade the use of Lewis acids and high pressure stand out as major advances. Engler and students have combined these techniques[150] and applied them to the synthesis of a variety of di- and triterpenes[151,152]. They discovered that mild Lewis acids combined with high pressure produced accelerated reaction rates and improved stereoselectivity (equation 121). In some instances addition takes a different route when carried out at atmospheric pressure (equation 122). Certainly more intensive study is merited.



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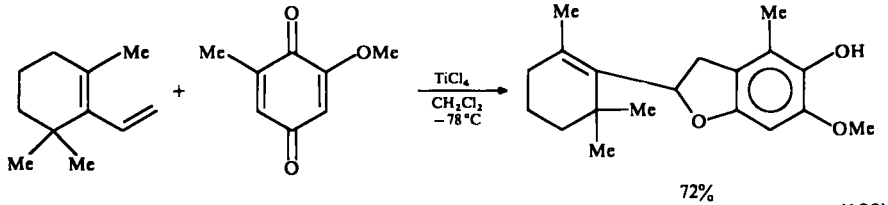


(122)

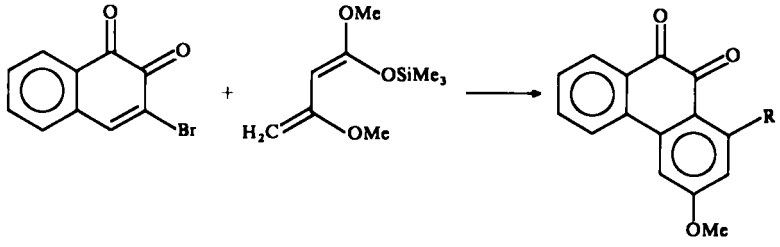
A curious observation made in the course of a study of 1,4-acetoxychlorination of 1,3-dienes was that 1,4-benzoquinone plays an essential role while its cycloaddition presents a bothersome competing reaction[153]. Further study of the mechanistic details could help our understanding of the transition state involved in Diels–Alder catalysis.

5. *Ortho-quinones*

Brassard and students also examined the reactions of 1,2-quinones[154]. A greater dependence upon substituents in either the quinone or the diene as a determining factor in product structure has been shown. The future utility of this study can be seen in an unprecedented example of complete change in product selectivity with a modest change of reaction conditions (equation 123).

The ability of 1,2-benzoquinones, especially such highly substituted examples as *o*-chloranil, to use their α-dicarbonyl groups in place of the diene is well known (Reference 1, pp. 1015–1018; Reference 2, pp. 643–645). Substituted oxazoles can act as dienophiles in such chemistry producing good yields of 1,4-dioxin derivatives with potentially useful patterns of ring structure and functionality (equation 124)[155].

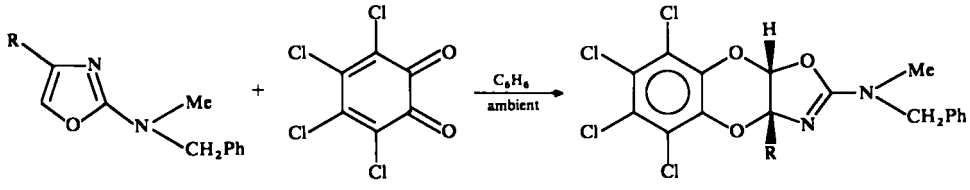
Following their studies of the addition of the highly substituted cyclobutadiene **12** to carbonyl compounds, Regitz and students have studied the details of addition to several *o*-quinones (equation 125)[156]. The intermediate shown was isolated or characterized by NMR.



THF/0 °C
C_6H_6/6 °C

R = OH 70%
R = OMe 57%

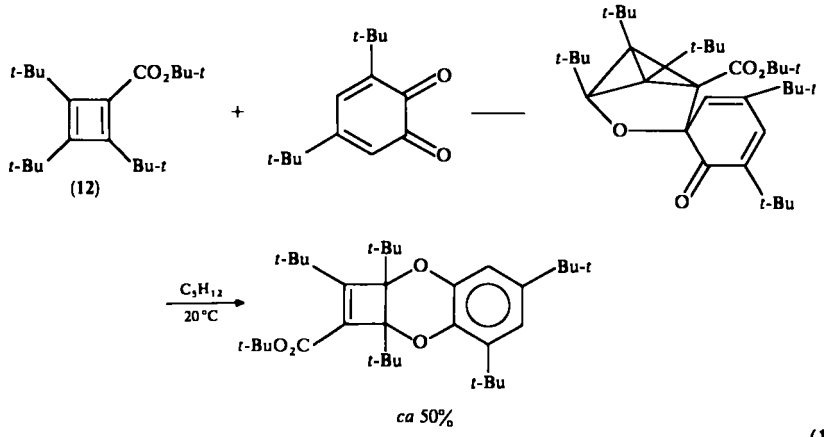
(123)



R = H
Me

87%
71%

(124)

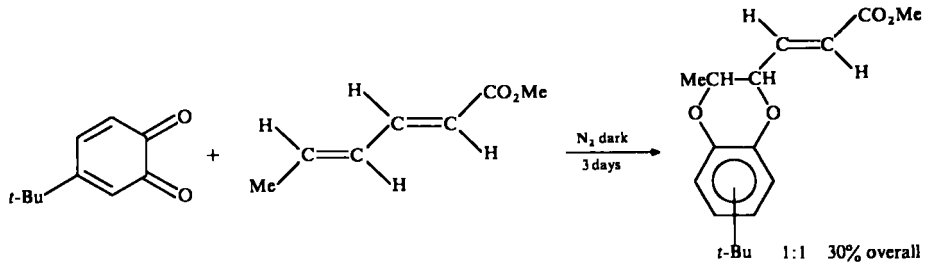


ca 50%

(125)

Seno and colleagues showed that alkenes add 4-*t*-butyl-1,2-benzoquinone at room temperature to give different products depending on the exact nature of the alkene[157]. Unlike the other three alkenes studied methyl sorbate lacks an active methylene group and its 1:1 product represents exclusive Diels–Alder addition (equation 126). In the other cases mixtures of oxygen and carbon addition were found and evidence is presented for a change in mechanism from hydride shift to radical hydrogen transfer.

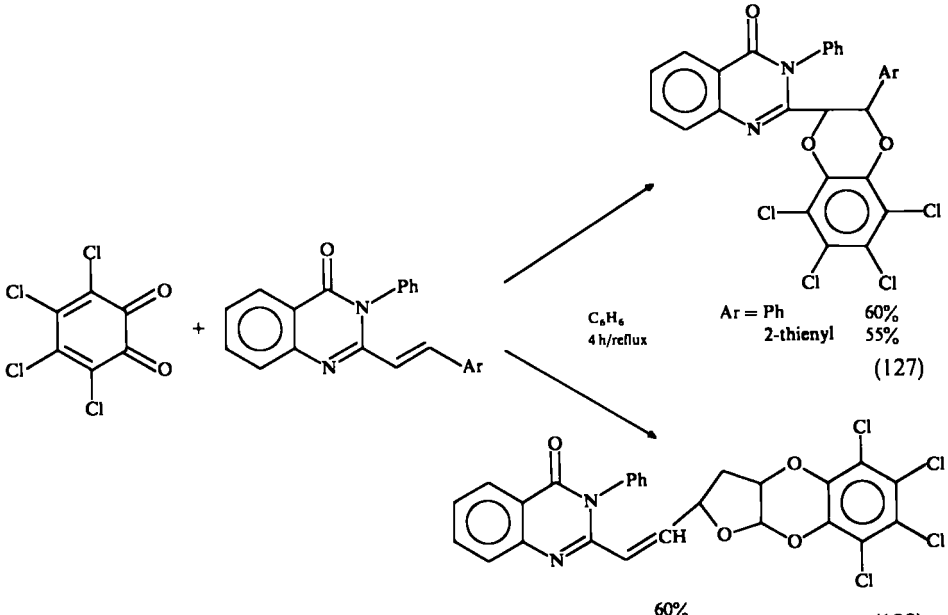
In somewhat similar chemistry 2-styrylquinazoline-4-ones yield heterocyclic adducts



(126)

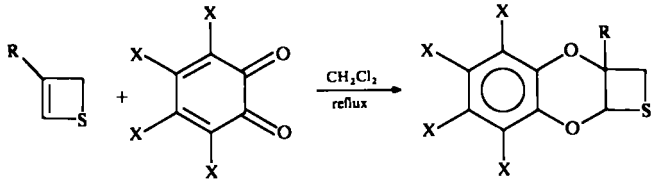
by reaction at either the styryl double bond (equation 127) or to a furane ring when present on the styrene (equation 128)[158].

Two interesting examples of the role sulfur can play in Diels–Alder chemistry involve *o*-quinones. Dittmer and students have examined thietes or thiacyclobutenes and found



(127)

(128)

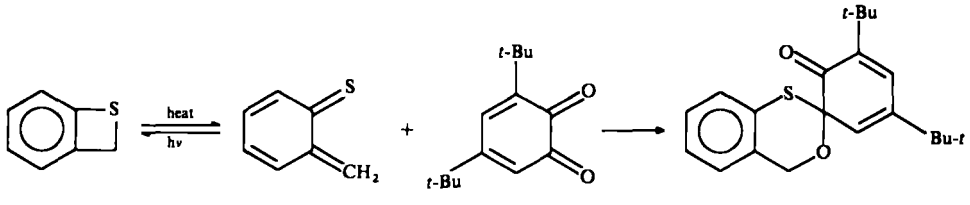


(129)

R = H, Ph, 2-naphthyl
X = Cl, Br

that, contrary to the general observation, these compounds retain their four-membered ring in such additions (equation 129)[159].

Meier and colleagues studied benzothiete, especially its thermal ring opening to the sulfur–methide quinone analog **13**. They found that 3,5-di-*t*-butyl-1,2-benzoquinone forms a spiro heterocycle through reaction at one carbonyl (equation 130)[160].



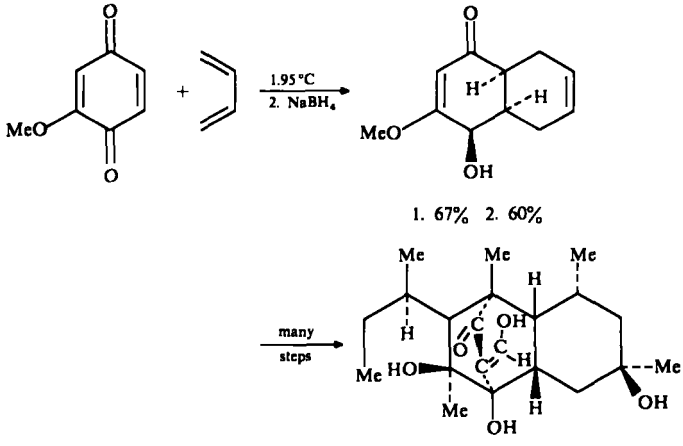
(13) 91% (130)

B. Synthetic Applications

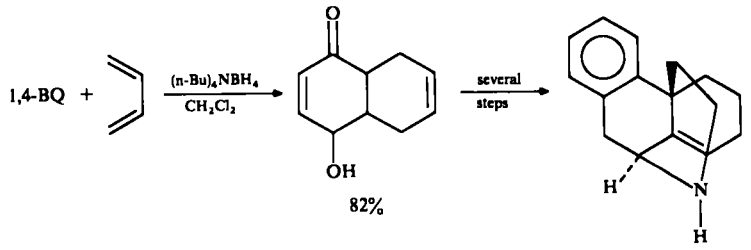
Diels–Alder reactions have recently dominated quinone chemistry. Their breadth merits noting, for the intellectual effort represented is the artistic key to appreciation of synthetic design. The following series of examples is hardly exhaustive. My first review of quinone Diels–Alder chemistry simply reported significant examples of the 1,4-benzoquinones (Reference 1, pp. 1000–1011) and the 1,2-benzoquinones (Reference 1, pp. 1011–1018). My second effort produced so many reported syntheses that I further subdivided the general structure of the nonquinonoid reactant (Reference 2, pp. 629–636). I have followed that practice here, although changing fashions have dictated a new series of subclasses.

1. *Simple dienes*

The simplicity of quinone Diels–Alder reactions should not obscure the fact that the quinonoid nucleus provides crucial future synthetic options[161–169]. An outstanding example is Hopkins and Pratt's work with the betaenones and their stereochemical complexity (equation 131)[170].



Betaenone B (131)

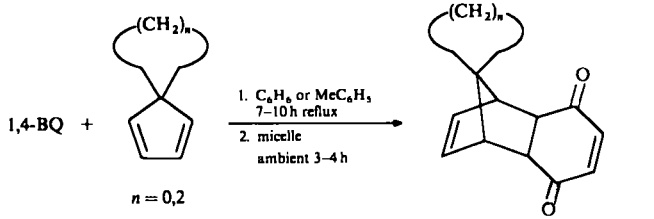


(132)

Tius and Thurkauf chose the ultimate in simplicity in beginning the study of morphinans (equation 132)[171].

2. *Cyclopentadiene derivatives*

These have been used in Diels–Alder chemistry more than any other single molecular type[172–179]. Thus, Mehta and coworkers employed the parent reaction to prepare the exotic dodecahedrane[180] and natural products containing three fused five-membered rings[181]. These addition reactions are useful because of their unique ability to undergo photochemical formation of cage compounds with demanding stereochemical restraints. So basic are these considerations that an undergraduate experiment has been described[182,183]. Spirocyclopentyl and spirocyclopropyl examples have been reported (equation 133)[184,185].



conditions	n = 0	2
1	60%	45%
2	66%	78%

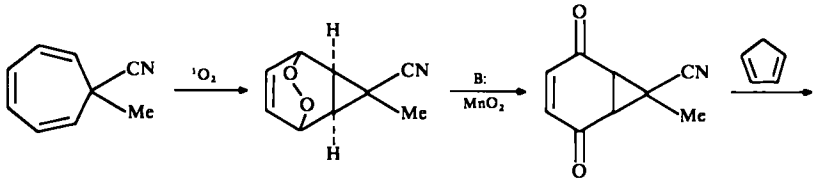
(133)

A report of a facile synthesis of homoquinones has opened possibilities for study and revealed lowered reactivity and significant stereoselectivity (equation 134)[186].

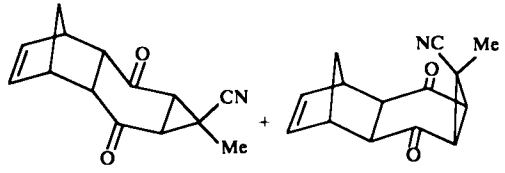
3. *Exocyclic dienes*

Synthetic routes to polycyclic ring systems continue to be studied. The union of a naphthoquinone and a cyclohexane-1,2-dimethylene with the proper stereochemical controlling substituents provides an efficient converging synthesis of members of the anthracycline family (equation 135)[187]. More highly saturated molecules offer attractive entries to the tetracyclines[188].

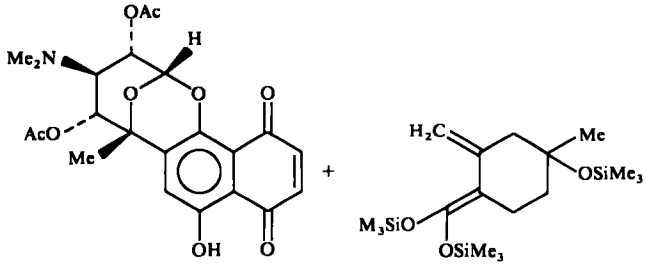
Müllen and students, searching for large molecules with exciting electrical properties, employed such novel systems as 1,2,5,6-tetra-*exo*-methylenecyclooctane (**11**) (equation 136)[189,190]. Charge transfer complexes were studied with molecules produced from Diels–Alder synthesis involving 1,2-quinodimethane (**15** in equation 137)[191]. A similar approach was employed in preparing 1,4-anthracenediones but gave only fair yields[192].

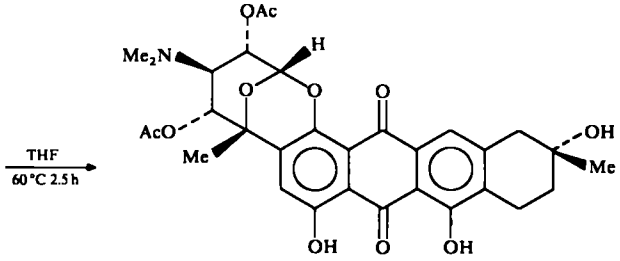


(134)



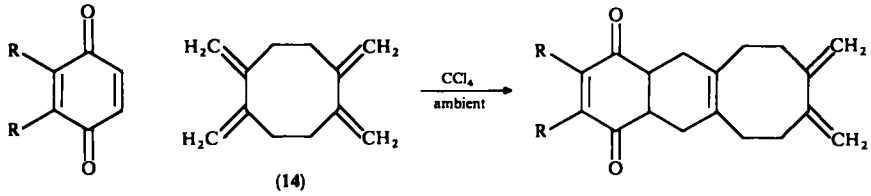
80% 20% 76% overall





50%

(135)

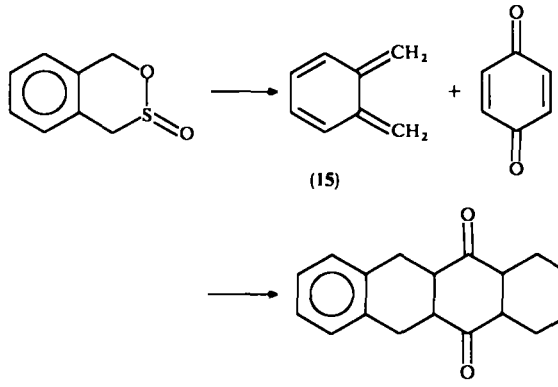


(14)

R = H
R,R = CH=CHCH=CH

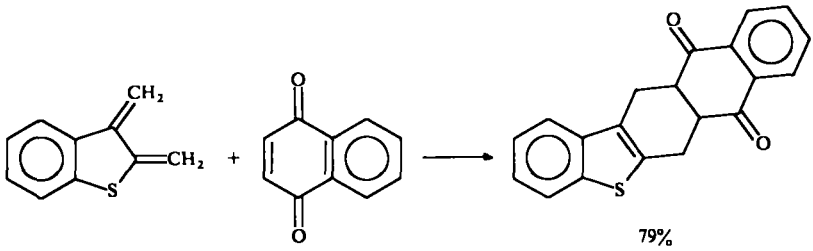
85%
75%

(136)



(15)

(137)



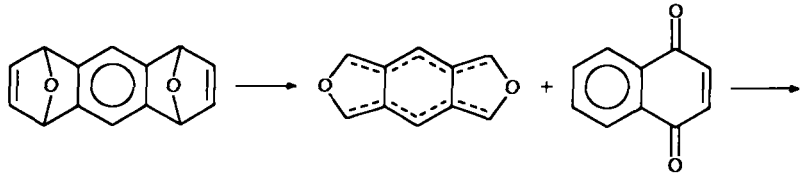
79%

(138)

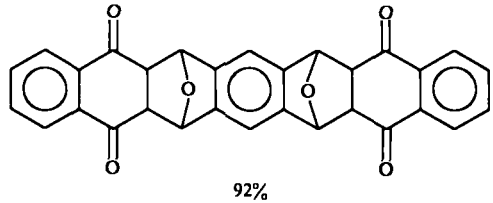
A heterocycle bearing an exocyclic diene system has been prepared and shown to react well with 1,4-naphthoquinone (equation 138)[193].

4. Oxygen and sulfur heterocyclic dienes

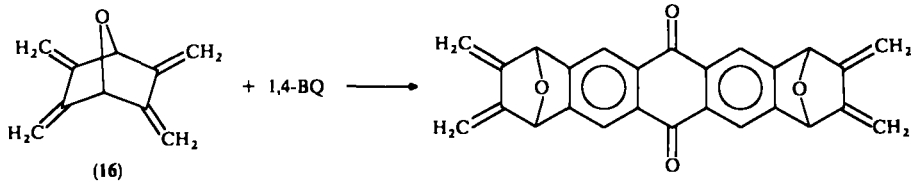
Several groups pursued the isobenzofurans and related compounds as routes to polycyclic molecules. The preparation of *bis*-isobenzofurans (equation 139)[194] and the



(139)



92%



(16)

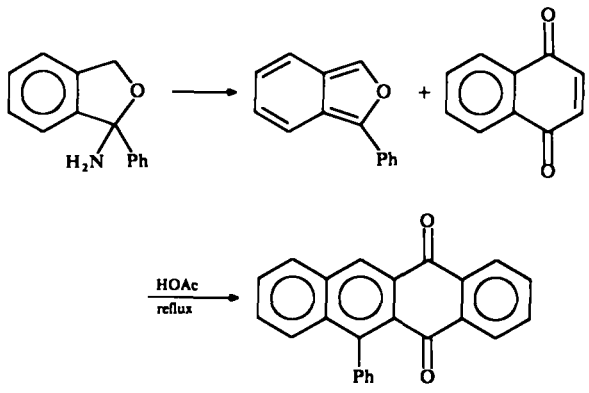
(140)

application of tetramethylidene-7-oxanorborane (**16**) in equation 140 represent important advances[195,196].

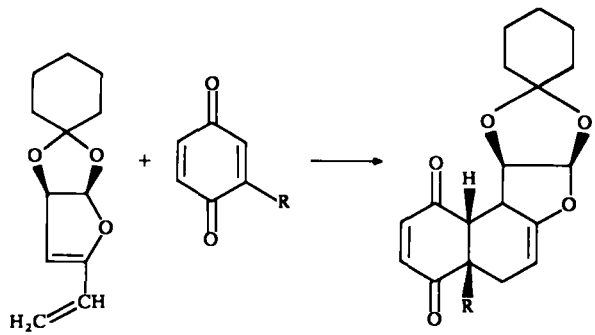
Smith and students continue exploring the phenyl substituted isobenzofurans and their cycloaddition reactions with a wide variety of dienophiles including various quinones (equation 141)[197,198].

1,4-Benzoquinones bearing electron-withdrawing groups are prepared *in situ* and react with an interesting diene derived from D-glucose (equation 142)[199].

There have been two reports from Diels–Alder chemistry with sulfur compounds. The dimethyl ester of tetrathiooxalic acid (**17**) reacts with 1,4-naphthoquinone and the adduct is spontaneously oxidized (equation 143)[200]. 1,4-Benzoquinone and 2-vinylbenzo[*b*]-thiophene react to the expected tetracyclic sulfur product[201].

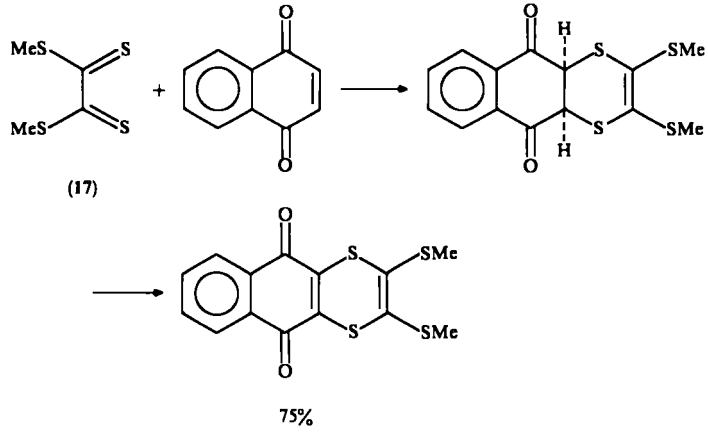


(141)



R = H, CHO, COMe, CO_2Me

(142)



(143)

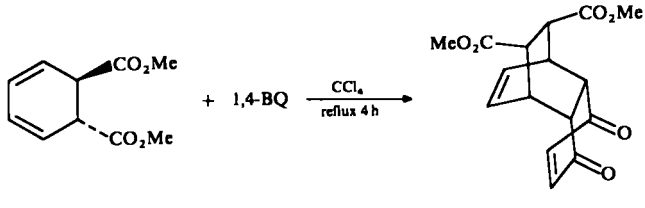
Isolated reports of heterocyclic oxygenated dienes, including furan silyl enol ethers[202], coumarins[203], vinyl pyranoids[204] and dioxenes[205], all hold promise.

5. *Endocyclic dienes*

Specific applications in this area are routine, but their ultimate direction is elegant and important. Cornforth and coworkers, using the varied functionality of the quinone nucleus, have continued investigating the stereochemistry of enzyme reactions[206]. Grimme, Warner and collaborators studied the mechanistic details of benzene extrusion from norcaradiene adducts[207]. Other examples have been used in photochemical studies[208] and natural product synthesis[209].

A modification of these schemes provides interesting stereochemical information (equation 144)[210]. Why the *cis*-ester and the anhydride fail to react requires study.

Finally, the diene **18** reacts smoothly with the standard dienophiles (equation 145)[211]. A



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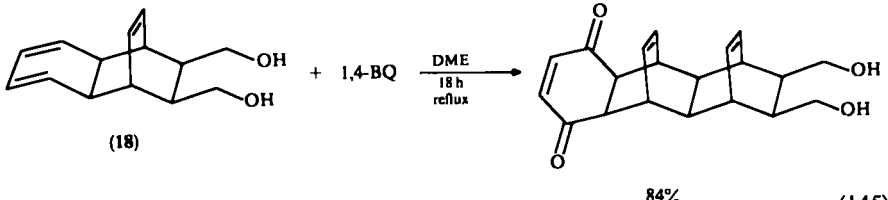
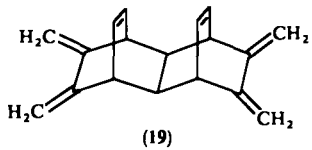


(145)

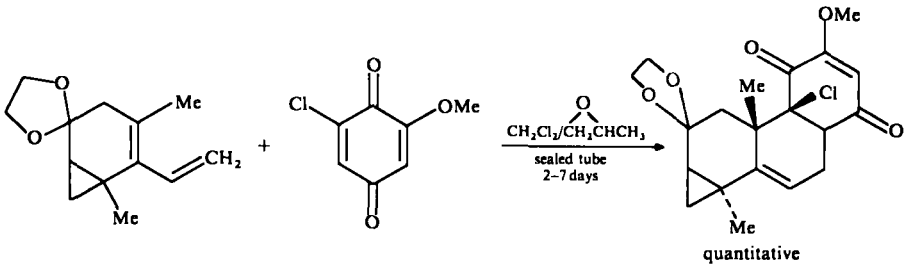
dibridged tetra-*exo*-cyclic diene (**19**) produced in this same study attains a new level of imagination in organic synthesis.



(19)

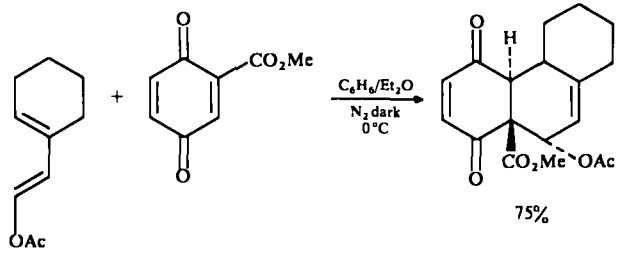
6. Vinyl cyclohexenes

These molecules aid in the synthesis of terpenoids through their ability to form a succession of fused six-membered rings with angular groups and specific stereochemistry. This approach often makes severe demands on both the diene and the dienophile. Several imaginative solutions of these and other problems have been reported. Meinwald has introduced the fused cyclopropane ring as an activating substituent and for its subsequent synthetic potential (equation 146)[212].



(146)

Pelizzoni and collaborators have continued their research of quinones bearing electron-withdrawing groups[213]. Both 1,4- and 1,2-benzoquinones reacted with 1- or 2-acetoxyvinyl cyclohexene rings (equation 147). The resulting stereochemistry has potential.

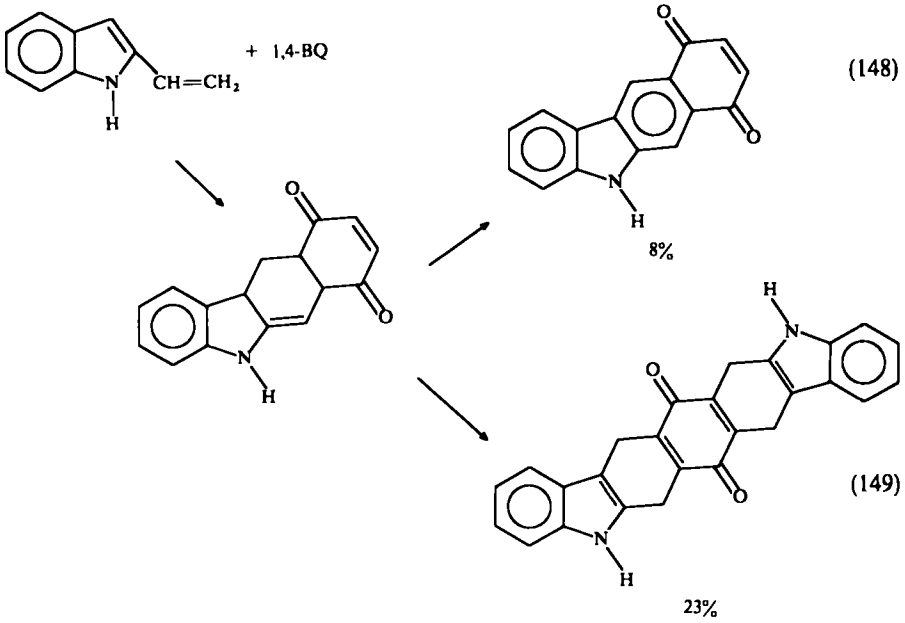


(147)

The directive effects of electron-donating groups in the quinone by either methoxy groups[214] or fused furan rings[215] should be noted.

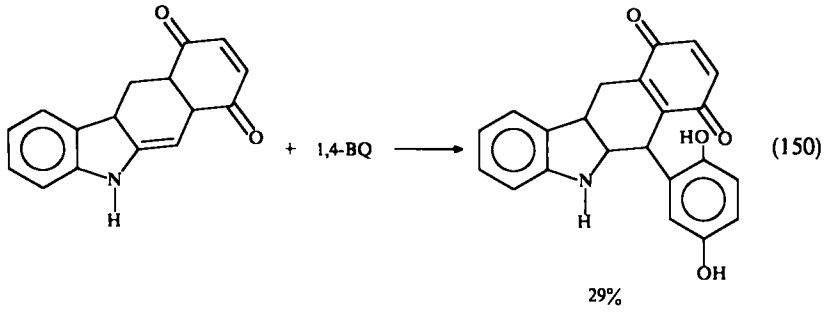
7. *Indole quinones*

Heterocyclic quinones have been studied by Pindur and students using Diels–Alder reactions of vinyl substituted indoles. They reported the first synthesis of 2-vinylindole and showed that it undergoes addition with either one or two molecules of 1,4-benzoquinone (equations 148 and 149)[216]. The intermediate associated with the first cycloaddition also reacts with the quinone in an ene reaction (equation 150)[217]



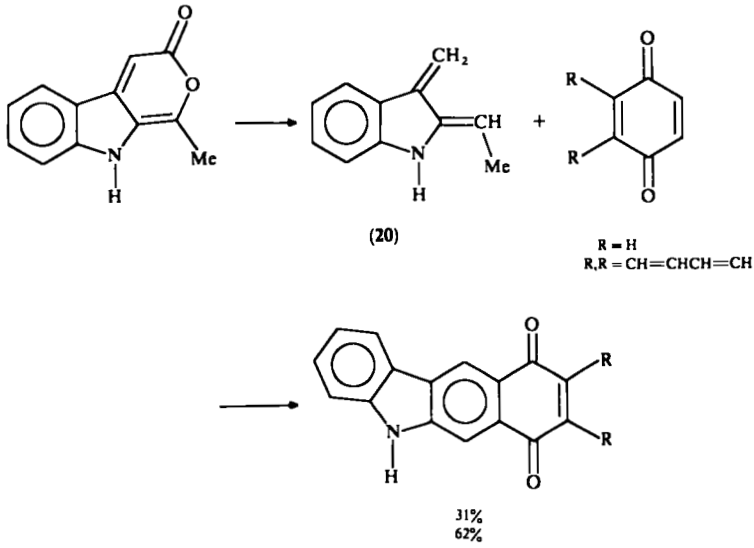
(148)

(149)



(150)

In another study Pindur's group prepared the synthetic equivalent of an indolo-2,3-quinodimethane (**20**) and showed it to be capable of smooth and exciting Diels–Alder quinone additions (equation 151)[218]. Other synthetic reports have appeared, including a significant contribution overlooked in both earlier reviews[219,220].

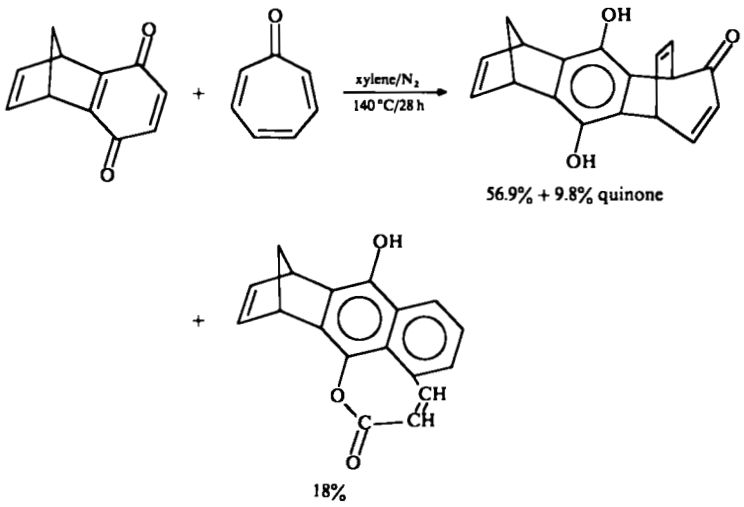


(151)

8. Aromatic and styryl dienes

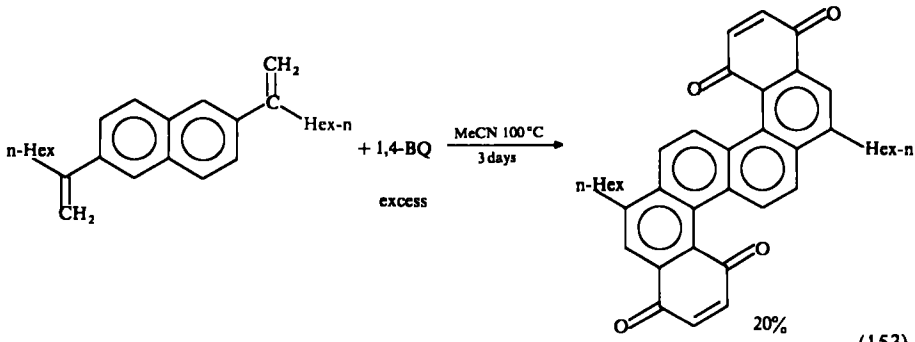
The Diels–Alder reaction of anthracenes with 1,4-benzoquinone has produced polycyclic aromatics of unusual structures involving skeletal rearrangement[221] or charge transfer[222]. In a different context Mehta and Karra have reexamined the reported inactivity of tropone with an unactivated 1,4-benzoquinone (equation 152)[223].

The synthesis of large molecules involving the preparation of *bis*-vinylnaphthalenes has produced positive results warranting study (equation 153)[224].



18%

(152)

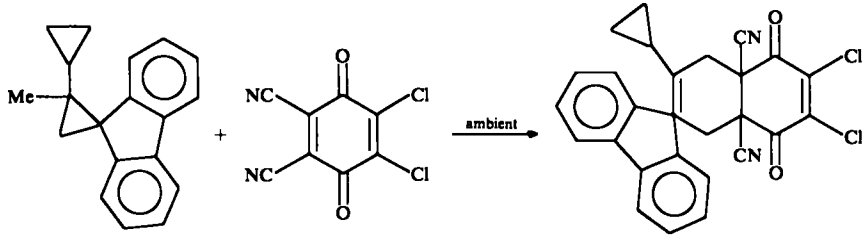


(153)

9. Activated dienes

An imaginative approach to the constant problem of activating dienes for synthetic purposes is the incorporation of cyclopropyl rings. Nishida and colleagues studied the chemistry of a spirocyclopropylfluorene (**21**) and found that it reacts well with the high-potential quinone 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (equation 154)[225]. In contrast 2,3,5,6-tetrachloro-1,4-benzoquinone showed no reactivity.

Kienzle and colleagues are seeking approaches to the diterpenoids using enol ether dienes activated with a cyclopropyl substituent (equation 155)[226]. The preparation of the dienes does not seem difficult, and the yields of cycloaddition products are uniformly high. This same group previously explored the activation of dienes using siloxy and enamine substituents with equally promising results[227].



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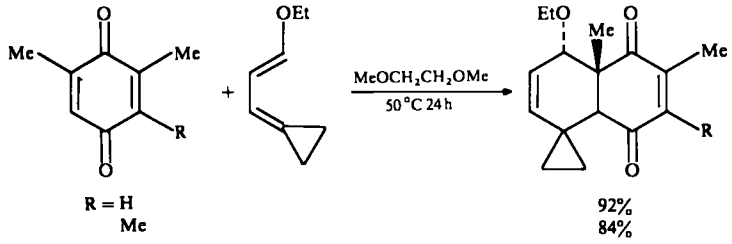
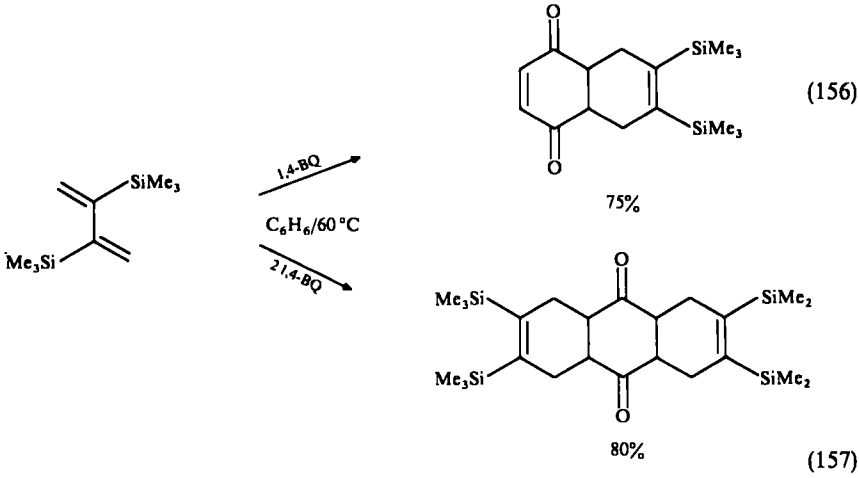


(155)

The synthesis of forskolin, an important diterpenoid, has led chemists to attempt both of the modifications just described. Thus, Snider and Kulkarni employed the cyclopropyl route[228] while Sih and colleagues have explored the application of siloxy enol ethers[229].

The chemistry of 2,3-*bis*(trimethylsilyl)-1,3-butadiene has been reported and deserves study and application (equations 156 and 157)[230].



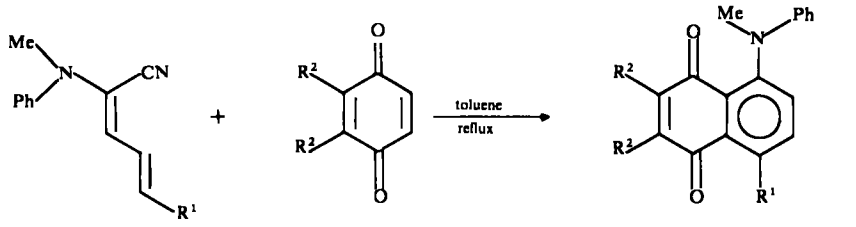
(156)

(157)

Attaching both a cyano and an anilino substituent to a diene presents a variety of synthetic possibilities. Fang and students prepared such compounds in very good yield and showed that they react well with 1,4-benzo- and 1,4-naphthoquinones (equation 158)[231]. Another approach involves a nitrodienamine (**22**) which gives moderate yields of substituted anthraquinones with a variety of juglones, but failed to react cleanly with 1,4-benzoquinone (equation 159)[232].

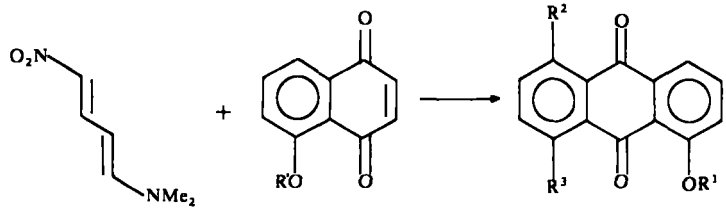
Chlorinated dienes have been studied less than other substrates, but two reports illustrate their promise. They involve the halogenated naphthoquinones as useful intermediates in the preparation of functional derivatives (equation 160)[233,234].

Kraus and colleagues have made an impressive, one-pot preparation of a key intermediate in the synthesis of pyranoquinones[235]. The combination of Diels–Alder and retro-Claisen reactions merits attention (equation 161).



R^1 = Me R^2 = H 67%
Et R^2 = CH=CHCH=CH 88%

(158)

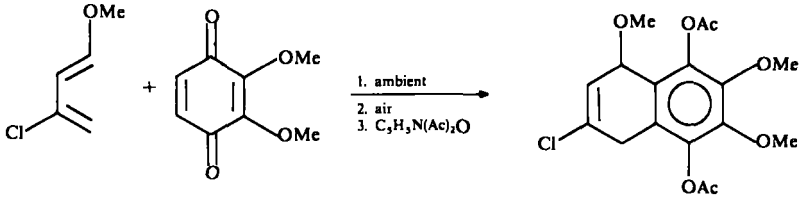


(22)

$R^1 = H$, Me

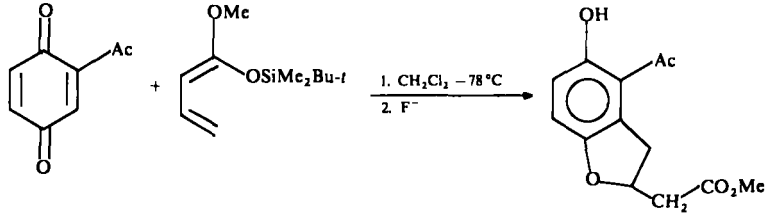
R^2	R^3	%
NO_2	H	37
H	H	4
H	NO_2	46

(159)



93%

(160)



91%

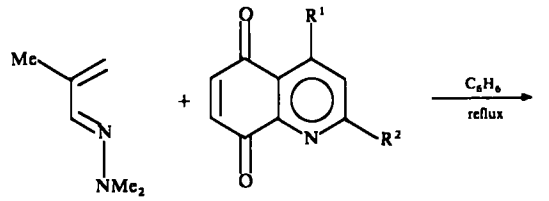
(161)

10. Aza dienes

In their search for azaanthraquinones, potentially important in cancer therapy, Potts and students explored the addition of dienes to azanaphthoquinones[236] and the addition of aza dienes to naphthoquinones (equation 162)[237]. In both approaches, results are promising with good yields and high regioselectivity. Fillion and colleagues applied this method successfully[238]. Shepherd approached the problem using heterocyclic-1,2-dimethylene compounds and 1,4-benzoquinone (equation 163)[239].

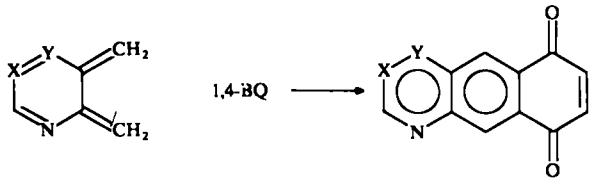
McKillop and Brown employed the disilyloxy-aza-diene (**23**) in a smooth and regiospecific synthesis of the antibiotic mimosamycin (equation 164)[240].

Oxazoles have been used to prepare isoquinolinediones in fair yield (equation 165)[241].



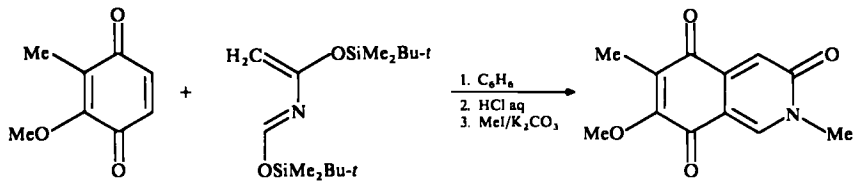
R^1	R^2	%
H	H	74
Me	Cl	70

(162)



X	Y	%
H	H	69
H	N	48
N	H	25

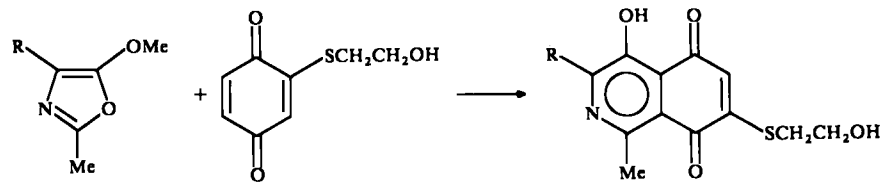
(163)



(23)

54%

(164)



R = Et
MeSCH$_2$CH$_2$

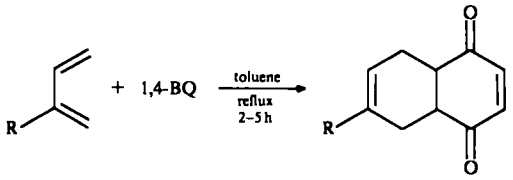
60%
45%

(165)

11. Organometallic substituents

Diels–Alder reactions can be activated by increasing their electron richness and by attaching organometallic substituents. Giering and students attached cyclopentadienyl iron carbonyl to various 1,3-butadienes and showed that while rapid addition occurs, there are problems of stability and poor regiospecificity[242].

Alternative approaches involve the tributyltin substituent which can be converted to the phenylseleno derivative (equation 166)[243,244]. Both of these compounds add well to 1,4-benzoquinone.



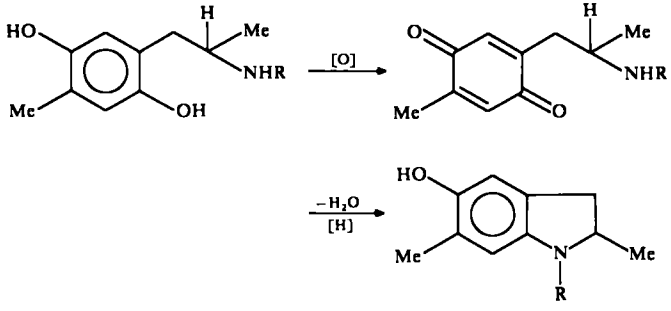
$R = Bu_3Sn$ 69%
PhSe 64%

(166)

C. Enamine Addition and the Nenitzescu Condensation

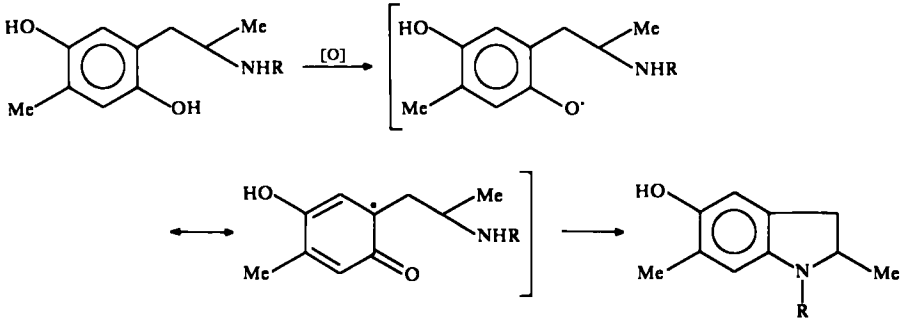
Interest in the synthesis of hydroxyindoles has created a steady flow of studies applying this remarkable synthon. For over 20 years Kuckländer and associates made successive contributions to our understanding of the mechanisms involved in both the original reaction and its modifications (see Reference 1, pp. 1028–1033 and Reference 2, pp. 645–649).

Besides studying the classical Nenitzescu indole synthesis this group has examined an intramolecular version[245] involving a nascent quinone (equation 167). This work, an important complement to Adams's reasearch[246] on dopamine and derivatives (see Reference 2, p. 541), has led to evidence for the critically important intermediacy of the semiquinone (equations 168 and 169)[247a,b]. A series of cycloalkanones bearing an exocyclic enamine group produced carbazoles suited to further cyclizations (equation 170)[248,249a]. The bridgehead nitrogen obtained was useful in synthesizing a new antidepressant. In the case of a cyclohexanone enamine, interesting polycyclic (**A**) and ring-expanded (**B**) products are observed (equation 171). The chemistry of both of these products has been examined[249b].

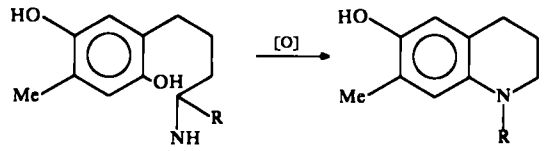


R	%
H	91
Me	85
Ph	85

(167)

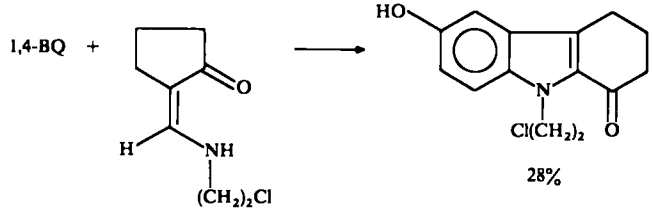


(168)



(169)

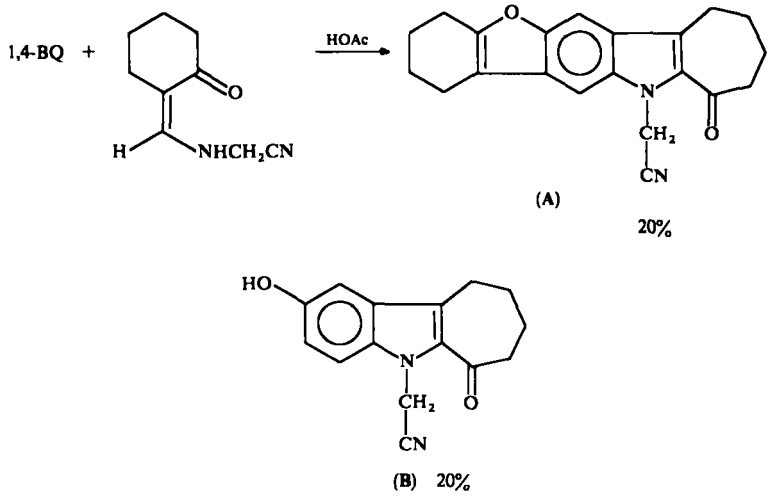
R	%
H	70
Me	44
Ph	64



(170)

R	%
H	57
Me	55

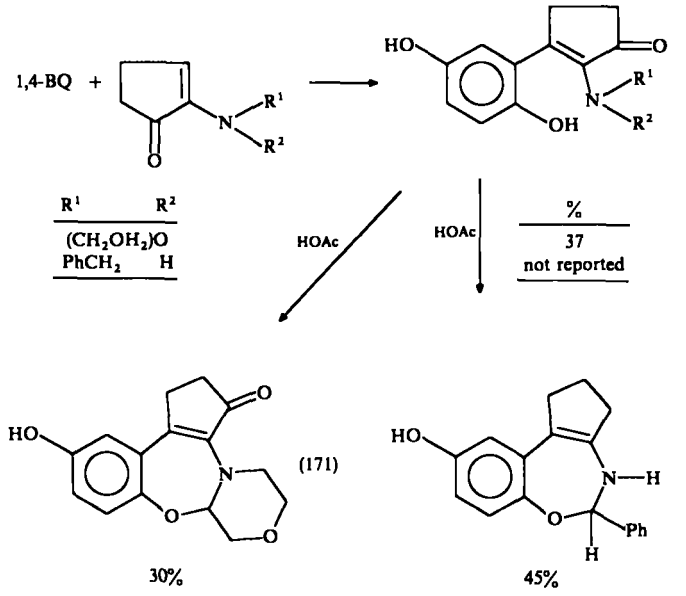
R	%
Ac	89
Me	90



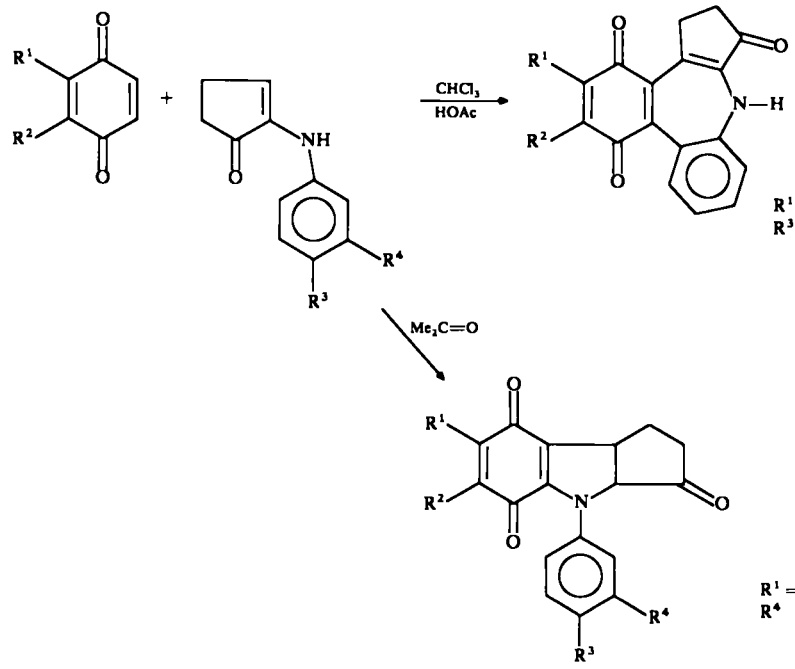
(171)

When the alkene linkage of the cycloalkanone enamine is within the ring carbazoles are not obtained. Studies of α-keto-enamines in a five-membered ring show that simple Michael addition products are intermediates in the path to unusual heterocycles, some of which include a quinonoid ring (equations 172–173a)[250,251].

More recently Kuckländer and students reexamined[252a] the addition of enols from β-dicarbonyls to 2-acetyl-1,4-benzoquinone, reported by Eugster in 1971 (see Reference 1, p. 1041). They have clarified the structures of the first intermediate and of the final products (equation 174). Regiospecificity has been demonstrated for the benzofuran

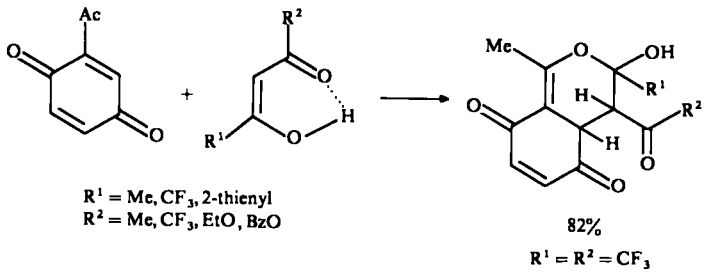


(172)


R1
R2
O
+
NH
R4
R3
CHCl3
HOAc
N—H
37%
R1 = R2 = Cl
R3 = R4 = H
Me2C=O
42%
R1 = H, R2 = Me
R4 R3

(173)

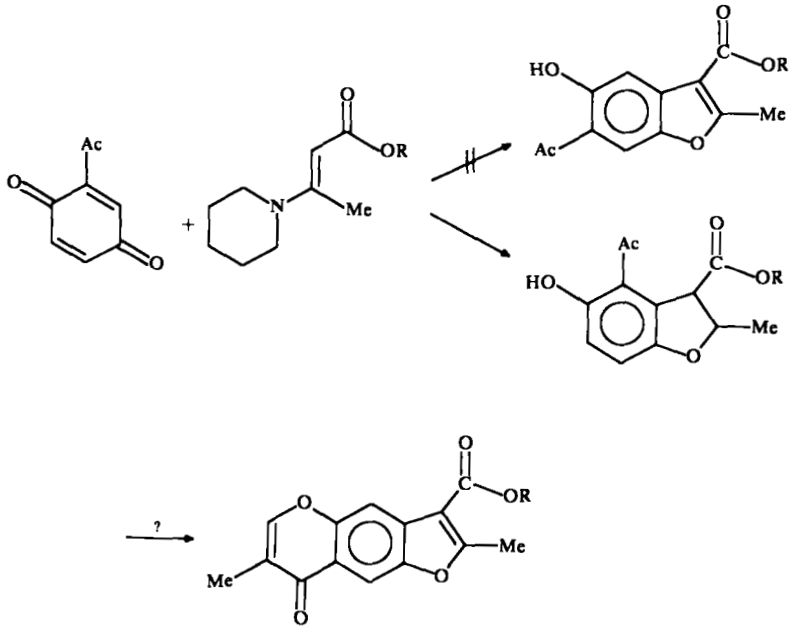
(173a)


Ac
R2
O
H
R1
Me
OH
82%
R1 = R2 = CF3
R1 = Me, CF3, 2-thienyl
R2 = Me, CF3, EtO, BzO
HO
R1
R2
40–70%

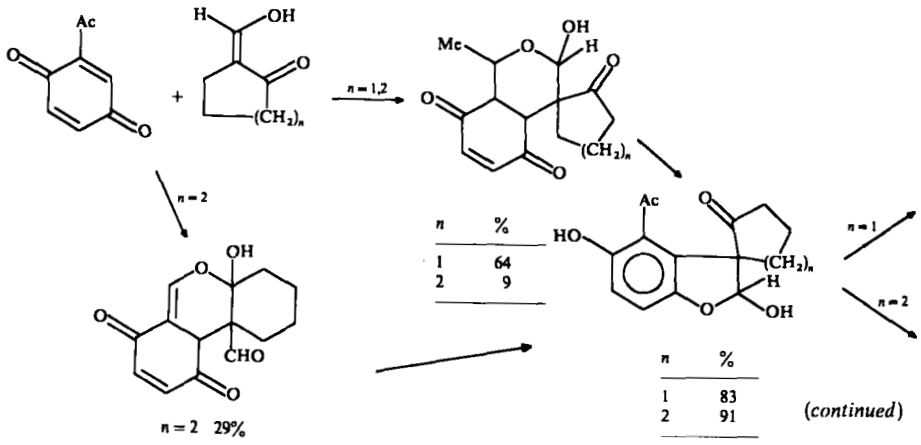
(174)

product, but the exact role(s) of benzofuranocoumarins is yet to be described (equation 175)[252b]. Later studies involving the nature of the intermediates have also expanded the range of enols employed, especially to α- and β-diketones and the corresponding enamines (equations 176, 176a, and 176b)[253].

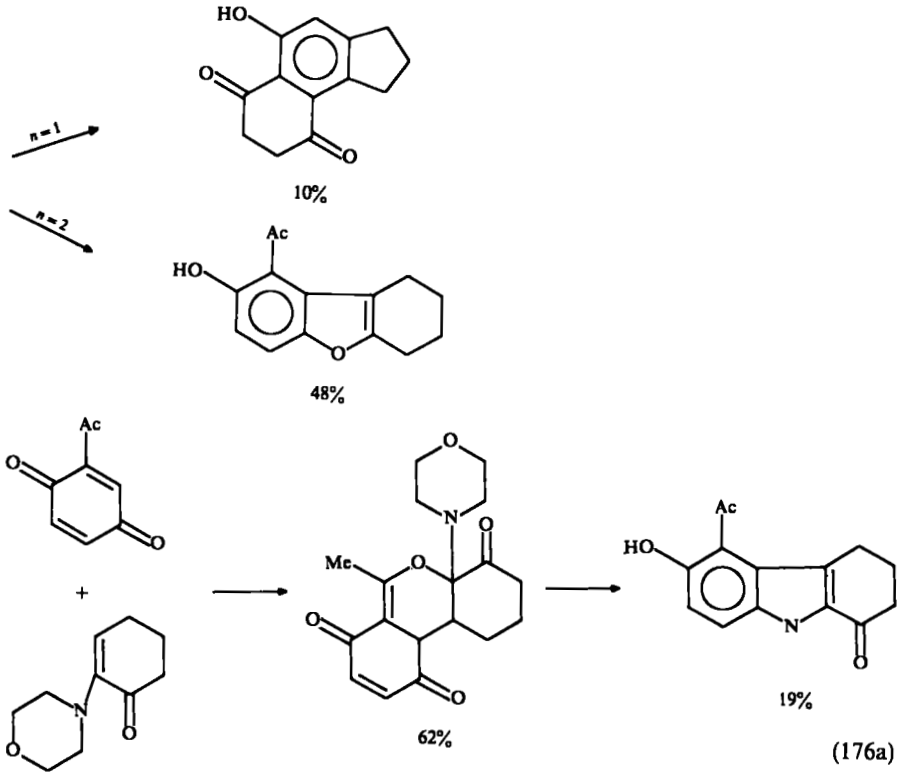
In the early 1980s Kozerski studied the addition of acylenamines to 1,4-benzoquinone



(175)



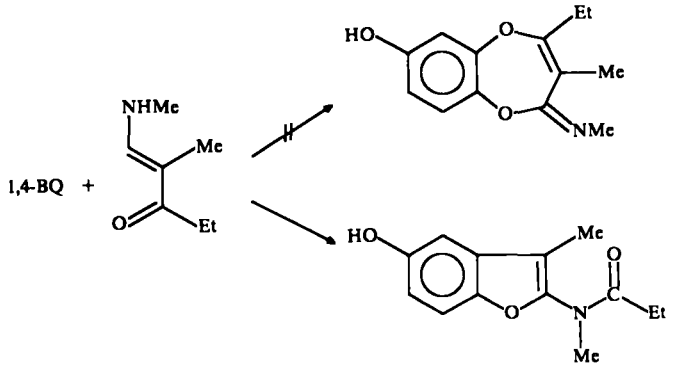
(176)

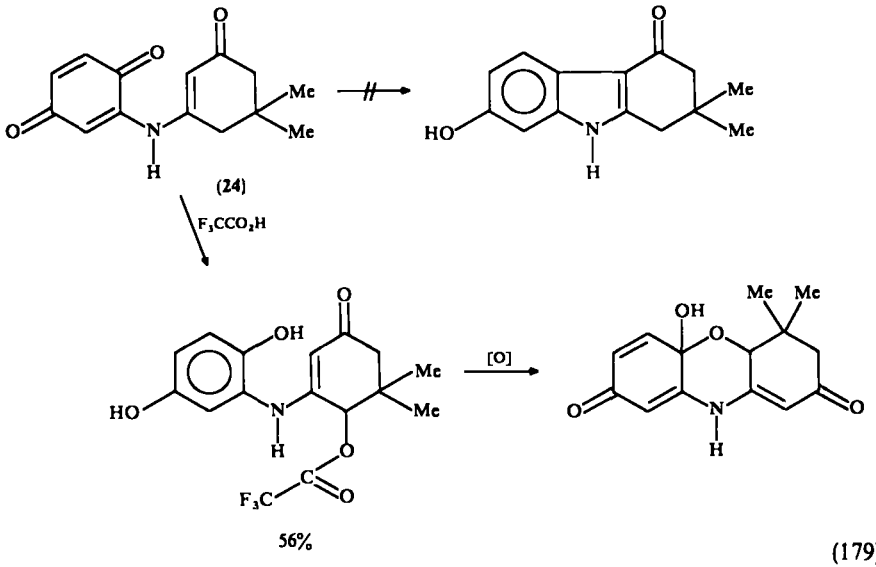

HO
O
O
n = 1
10%
n = 2
Ac
HO
O
48%
Ac
O
O
+
N
O
O
Me
O
N
O
O
O
62%
Ac
HO
N
O
19%
(176a)
Ac
O
O
+
H
N
(CH2)n
O
Me
HO
N
O
Me
5%
(176b)
Me
Me
N+
O
Cl−
HO
(CH2)n
OH

n	%
1	43
2	31

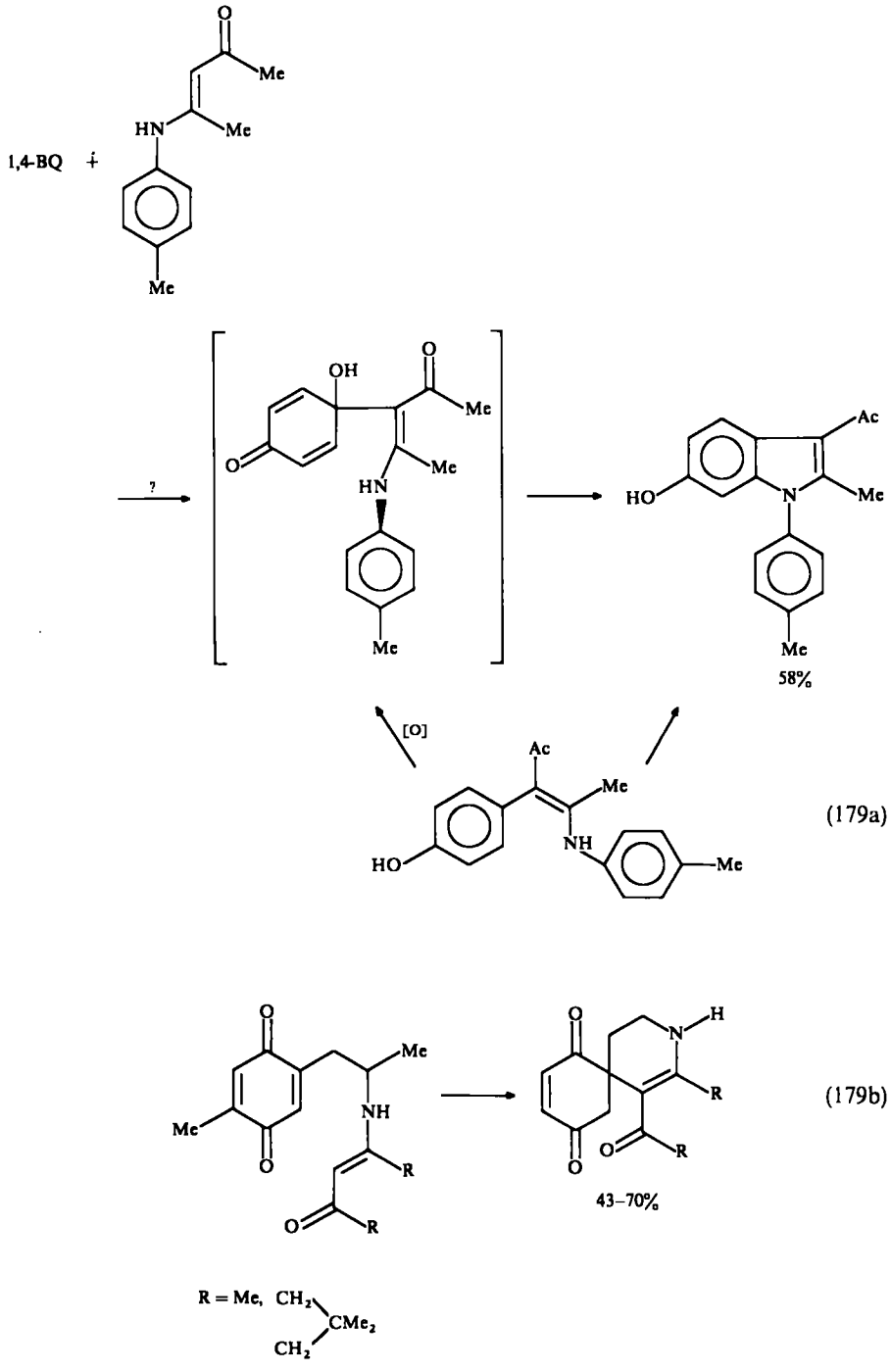
(see Reference 2, p. 648) and proposed 2*H*-1,5-benzodioxepin as the product structure. Subsequently he offered ^{13}CNMR as evidence. He argued on the same basis for the presence of 2,3-dihydrobenzofurans (equation 177)[254–256]. Kuckländer and Kuna have carefully reinvestigated the spectra of these unusual compounds. Their data show that neither of these structural proposals is satisfactory[257]. They find that the common non-Nenitzescu benzofurans are formed (equation 178). This variant pathway, well established for quinones containing strong electron-withdrawing groups, also obtains when such groups are present in the enamine.

Appropriately, Kuckländer and students have begun a series of experiments directed at the unresolved problem of the exact mechanism of this synthon. Their first contribution deals with the tricky question of intermediates. One proposed intermediate (**24**), after its unambiguous synthesis, failed to yield the Nenitzescu product (equation 179)[258a].



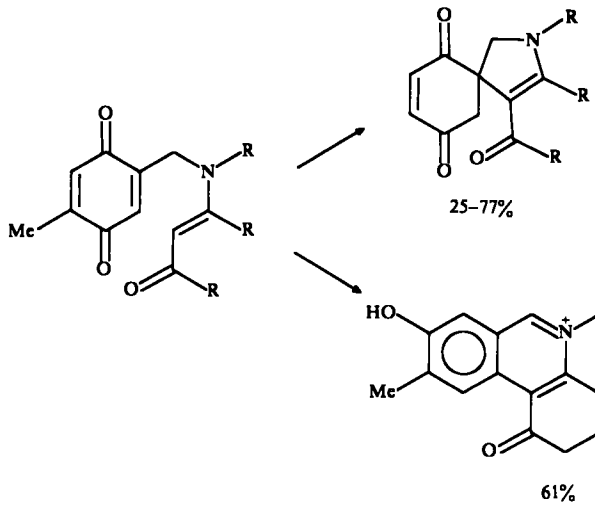


(179)

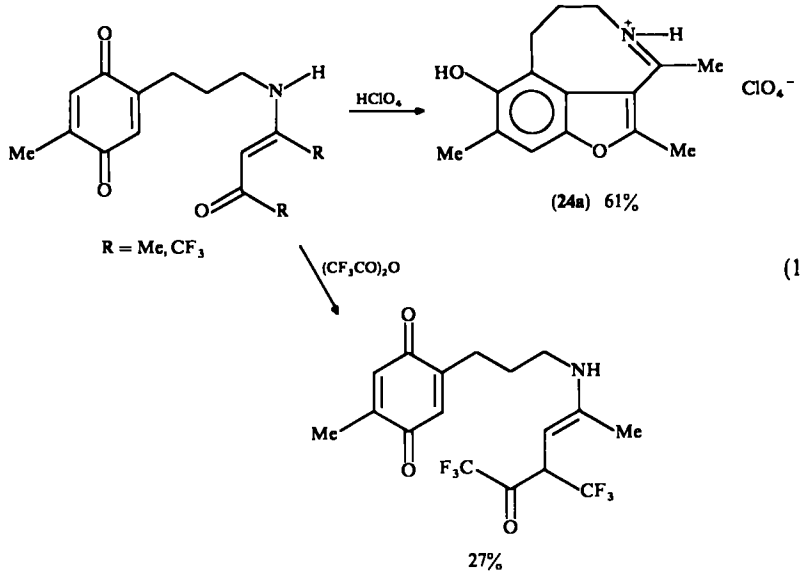


(179a)

(179b)



(179c)



(179d)

They have suggested, as an alternative, a 1,3-cycloaddition intermediate, consistent with the observed chemistry.

The generation of *N*-aryl-6-hydroxy-indoles under Nenitzescu conditions results from attack first of the enamine *β*-carbon atom on the quinone carbonyl (equation 179a)[258b]. This result was proven chemically and confirmed by molecular modeling.

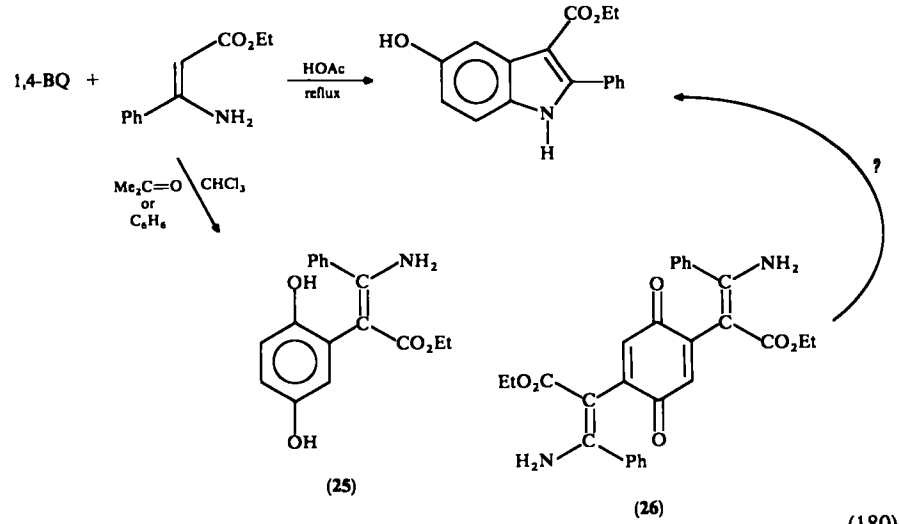
Continued study of the cyclization reactivity of variously substituted enaminones attached to 2-methyl-1,4-benzoquinone produced new spiro-derivatives (equations 179b, 179c)[258c] and benzazocin (**24a**, equation 179d)[258d].

These cleverly designed and elegantly executed studies show well the strong reactivity of the enamine-β-carbon as opposed to its nitrogen atom. While forcing conditions lead to phenanthridines resulting from quinone carbonyl reaction, it is clear that the higher primary reactivity resides in the quinonoid carbon–carbon double bond.

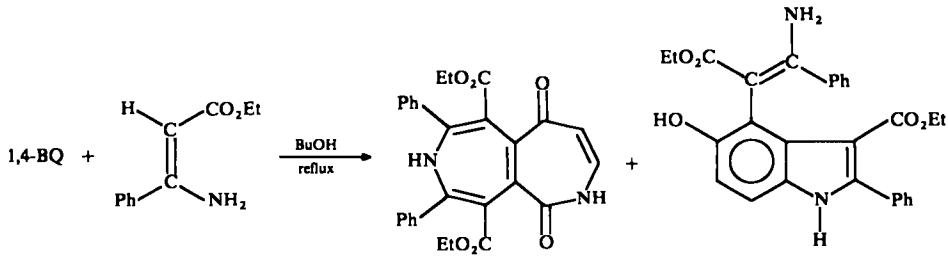
Other workers found that when a phenyl group is present in the enamine, the reaction is strongly solvent-dependent and succeeds only in refluxing acetic acid (equation 180)[259]. In the usual solvents the expected intermediate (**25**), the quinonoid bis-addition product (**26**) and hydroquinone are found. Finally, in alcohols two entirely unexpected cyclic products are obtained (equation 181). The complicated mechanistic proposal needs study.

Recently, efforts have been made to improve the yields and range of useful substituents, especially with thiol groups. The combination of methylthio and cyano groups does produce good yields in most cases (equation 182)[260]. The methyl substituent, which produced a poor yield, also produced some benzofuran by-product.

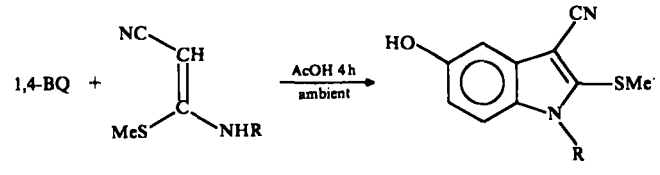
The use of aniline enamines without the cyano group produced only modest yields of benzofurans (equation 183)[261]. The addition of the amino-1*H*-2-pyridone (**27**)



(180)

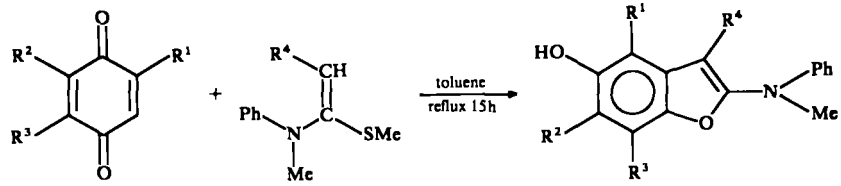


(181)



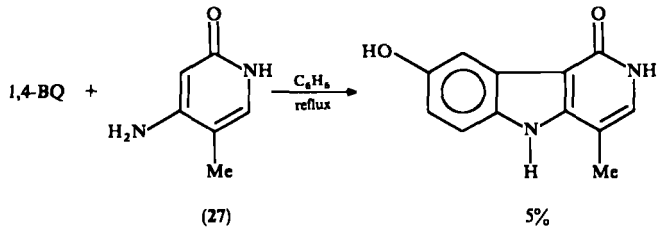
R	%
Me	40
Ph	79
4-ClC_6H_4	92
4-$MeOC_6H_4$	87
Bz	89

(182)



(183)

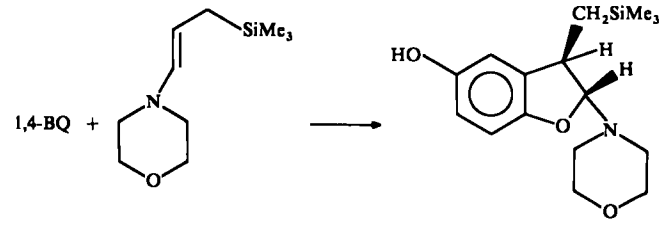
R^1	R^2	R^3	R^4	%
H	H	H	H	45
Cl	Cl	H	H	51
H	CN	CN	H(THF)	10
H	H	H	Me	38
Cl	Cl	H	Me	46



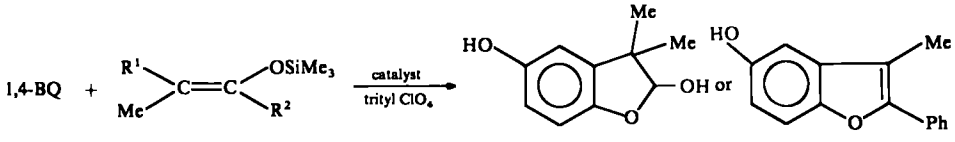
(27) 5%

(184)

produced the interesting heterocycle expected, but in very poor yield (equation 184)[262]. In contrast to these discouraging results the addition of a silyl substituted enamine introduces potentially useful functionality; again the benzofuran structure rather than the normal Nenitzescu indole is obtained (equation 185)[263]. The addition of silyl enol ethers also produces reasonable yields of reduced benzofurans (equation 186)[264]. The same reaction will occur with quinone monoimides yielding the 5-amino benzofuran. If imidoquinones are the starting point, good yields of indoles are obtained. Later the analogous chemistry of 1,2-benzoquinones was examined, and here the furans generally represent a by-product to the equally useful Michael additions (equation 187)[265].



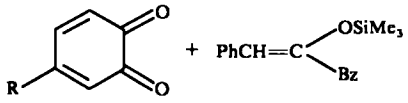
(185)

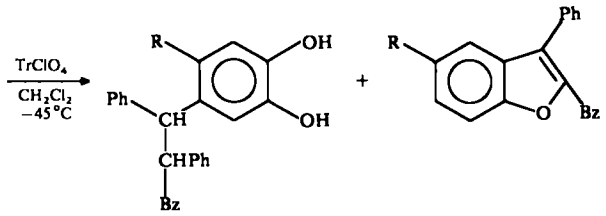


R^1 = Me, H, Me; R^2 = H, Ph

71% 65%

(186)





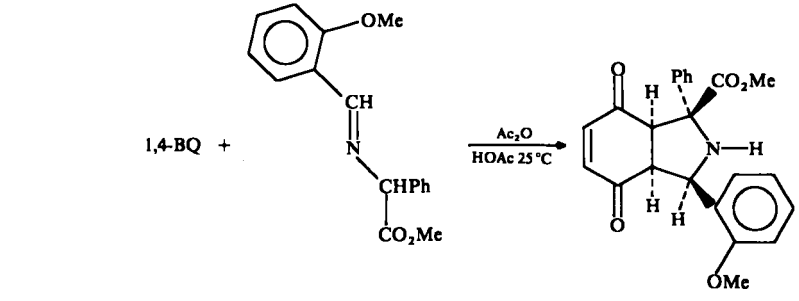
R = H	59%	0%
Me	61%	13%
t-Bu	16%	47%

(187)

D. 1,3-Dipolar Cycloaddition Reactions

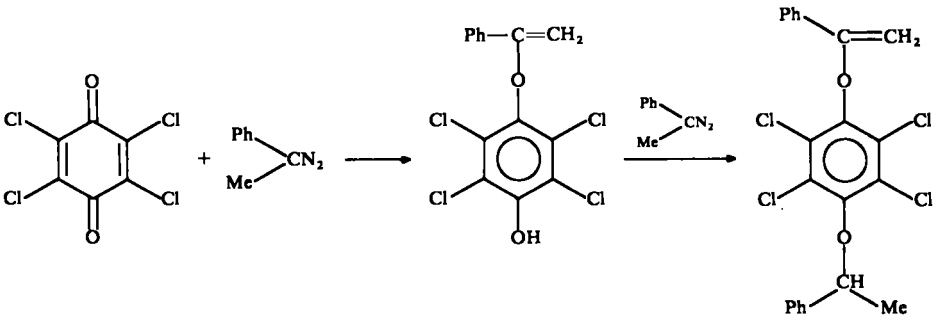
The catalytic effect of Bronsted and Lewis acids on 1,3-dipolar cycloaddition reactions has been studied, including only a single quinone example (equation 188)[266]. The rate enhancements are believed to be related to the pK_a of Bronsted acids and metallo-1,3-dipoles of Lewis acids.

Oshima and Nagai have continued their probing of the addition of diazo compounds showing that fully substituted 1,2- and 1,4-quinones react only at their carbonyl groups (equation 189)[267]. This and earlier results have been amplified with more highly structured diazo compounds and examples of a variety of chloro-1,4-benzoquinones[268,269]. The same addition patterns are observed as a function of increased substitution, and



68%

(188)



quantitative

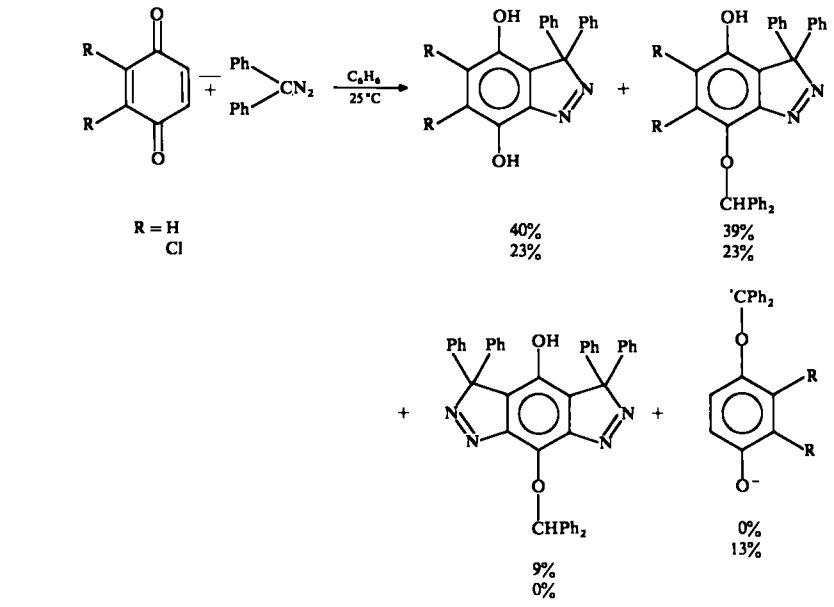
(189)

subsequent reactions of the 3*H*-indazoles and *bis*(3*H*-pyrazoles) have been reported (equations 190 and 191). There has been a detailed study of these decompositions in which the quinones play a major role, but in chemistry beyond the scope of this review[270].

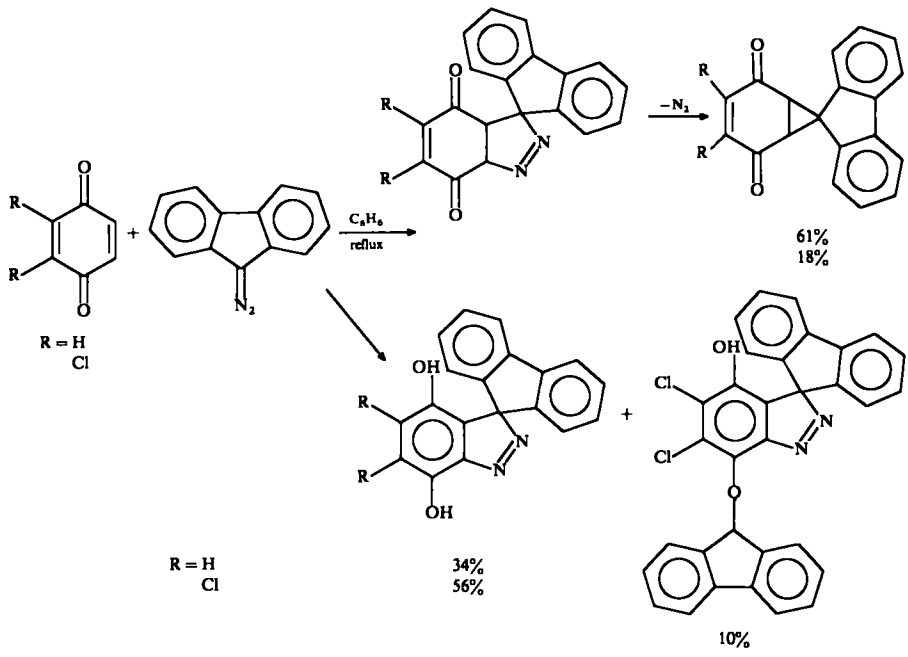
As part of their work on 1,3-cycloaddition[271] Padwa and students have prepared the azomethine ylide equivalent (**28**) and demonstrated its utility in addition to quinones by preparing an isoindole alkaloid (equation 192)[272]. In somewhat similar systems they have examined the reaction of oximino α-diazo ketones with rhodium(II) for the generation of azometine ylides, which react well with 1,4-benzoquinone to yield key intermediate skeletons for alkaloid syntheses (equation 193)[273].

The placement of bridgehead nitrogen in heterocyclic synthesis has led Schultz and colleagues to examine the intramolecular reactions of azido groups attached by carbon chains to 2,6-dimethyl-1,4-benzoquinone (equation 194)[274]. Although yields are low, the potential utility of the products makes attempts to improve them worthwhile. An aromatic ring in the chain changes the reaction outcome drastically and greatly improves the yield (equation 195).

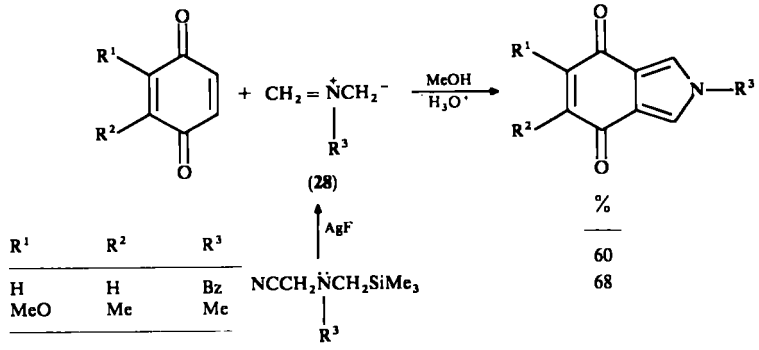
In another study this group has shown that nitrones generated from an aldehyde and *N*-methylhydroxylamine add well to 2,3- and 2,6-dimethyl-1,4-benzoquinone (equation 196))[275]. The change in product distribution caused by a small steric change coupled with the failure of intermolecular cyclization (equation 197) needs further study.



(190)

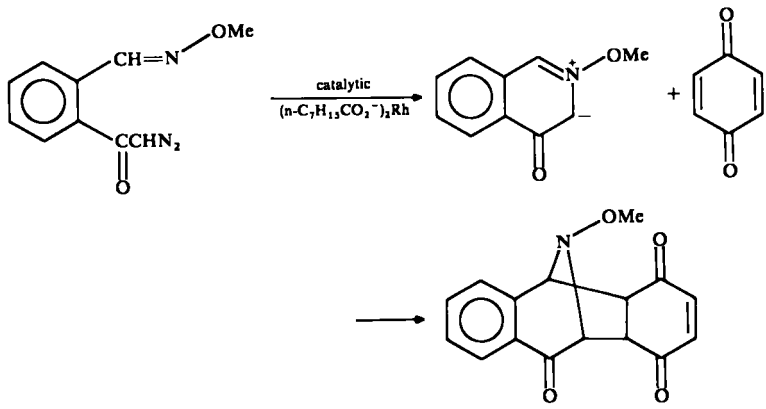


(191)



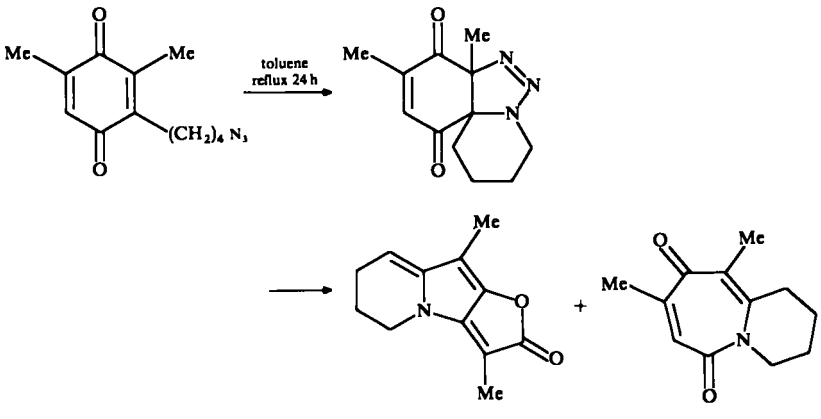
R^1	R^2	R^3
H	H	Bz
MeO	Me	Me

(192)



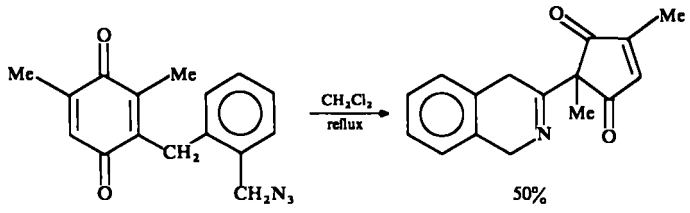
(193)

67% (as diacetate)

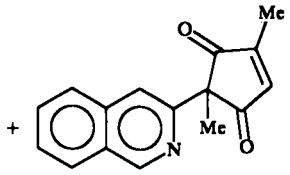


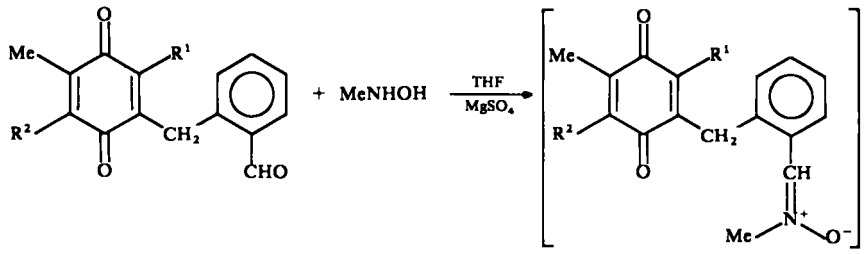
12% 7%

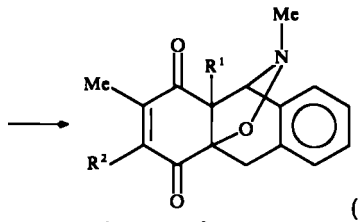
(194)



(195)

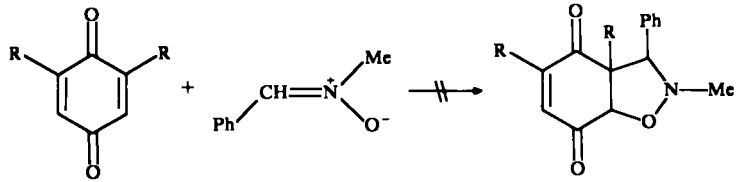






(196)

R^1	R^2	%
Me	H	81
H	Me	73



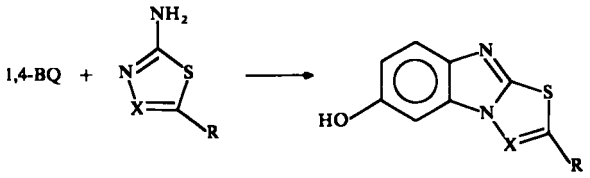
R = H
Me

(197)

A different approach to the synthesis of bridgehead nitrogen compounds involves the simple addition of aminoheterocycles to 1,4-benzoquinone (equation 198)[276]. These syntheses complement reactions of 2-chloropyridine.

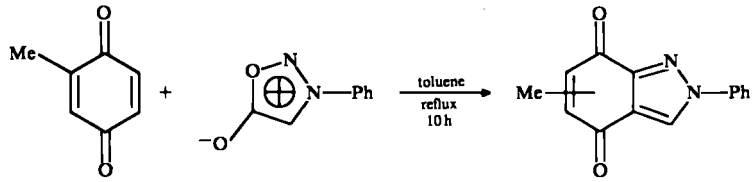
3-Phenylsydnone leads to products analogous to those obtained with diazomethanes, but with a phenyl substituent on a nitrogen (equation 199)[277]. The reaction gives only a modest yield and is completely nonstereospecific.

In continuing research on the anionic chemistry of quinones (see Section IV.C) Dean and students have studied the addition of 2-diazopropane to 2-methyl-1,4-naphthoquinone. They found that even at low temperatures the highly hindered spiro oxirane (**29**) is formed and that it is much more stable than any analogous compound in their experience (equation 200)[278].



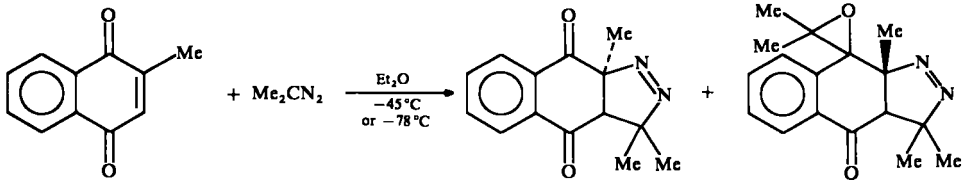
(198)

R	X
H	N
Ph	N
H	CH
H	CPh



42%

(199)



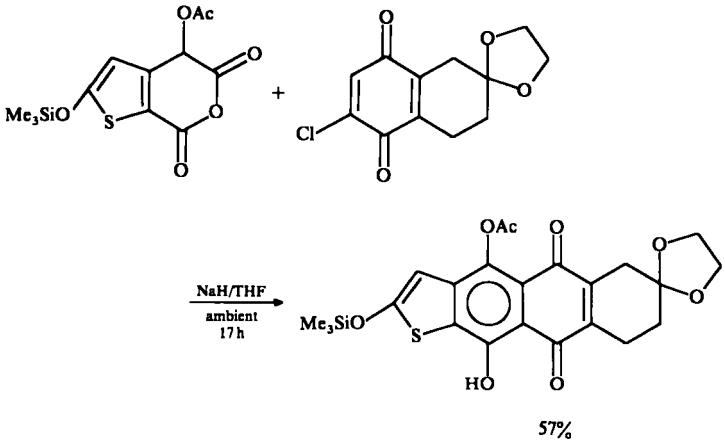
60%

(**29**) 12%

(200)

E. Homophthalic Anhydrides

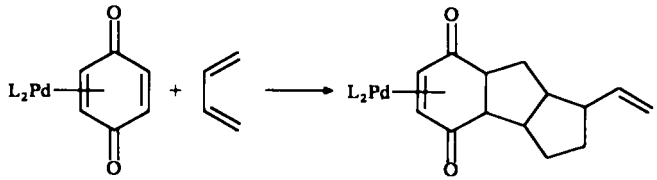
The exceptional work with homophthalic anhydrides conducted by Tamura and colleagues continues with the preparation of anthracyclinones[279]. Each has been obtained in high yield and excellent stereospecificity considering the complexity of the molecules sought. This synthon has been expanded to include the delicate thiophene ring in the total synthesis of compounds related to the antitumor agent daunomycin (equation 201)[280].



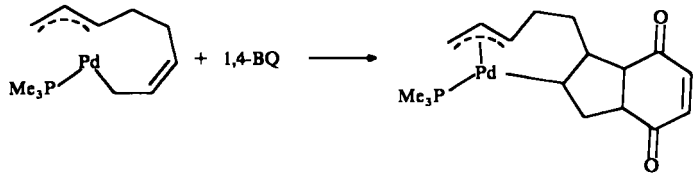
(201)

F. Metal Catalysis

Some mechanistic details have been found related to the cycloaddition of 1,3-butadiene and 1,4-benzoquinone which was complexed with palladium (equation 202)[281]. Reactions between η^1,η^3-octadienediyl-palladium complexes and 1,4-benzoquinone (equation 203) or 5-hydroxy-1,4-naphthoquinone emphasize the importance of intermediate palladium complexes. Work continues on developing a catalytic process.



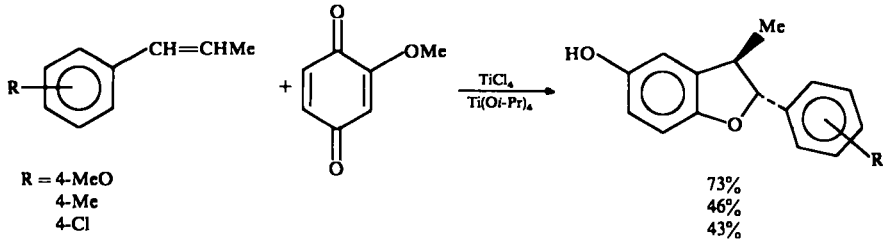
(202)



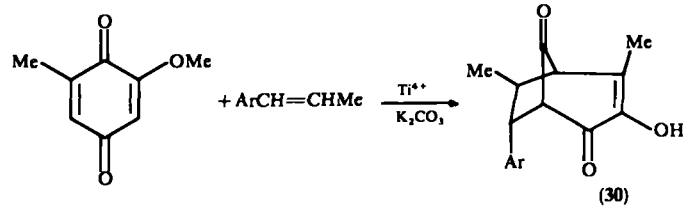
(203)

In addition to their work on the Diels–Alder reaction, Engler and students have made contributions to other cyclization procedures. They have found that both *cis*- and *trans*-β-methylstyrenes containing electron-withdrawing groups add to a variety of 1,4-benzoquinones to give good yields of *trans*-dihydrobenzofurans (equation 204)[282]. Intermediate 1,4-addition products can be isolated or converted to the final products. The exact nature of the titanium(IV) catalyst used has a marked effect on the product distribution. The reactions are all stereoselective, but with 2-methoxy-5-methyl-1,4-benzoquinone and *trans*-β-methylstyrenes the reaction was not regiospecific. The synthesis of an interesting natural product, kadsurenone, using this new chemistry is reported.

This addition chemistry has also been shown to involve the unusual bicyclic product (**30**), a formal 5 + 2 cycloadduct (equation 205)[283]. Mechanistic proposals are presented and further work promised.



(204)



(205)

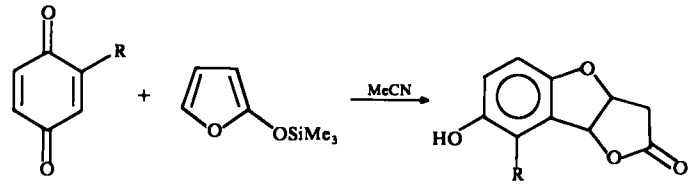
(**30**)

Ar	%
Ph	41
2-Tol	44
4-Tol	21
4-ClC_6H_4	27

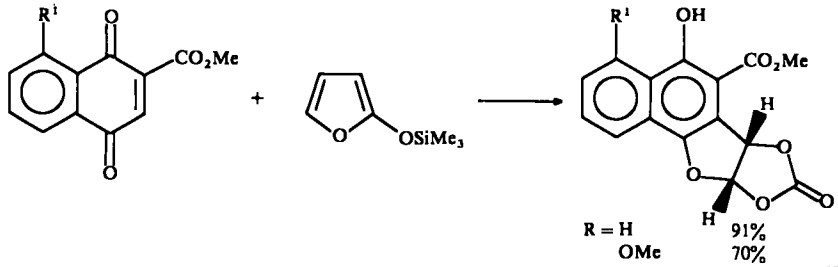
G. Furan and Indole Cycloaddition

The cycloaddition of these simple heterocycles to quinones represents a facile entry to several complex and potentially useful ring systems. With 1,4-benzo- and naphthoquinones bearing strong electron-withdrawing groups, 2-trimethylsilyloxyfuran adds in adequate to excellent yield (equations 206 and 207)[284].

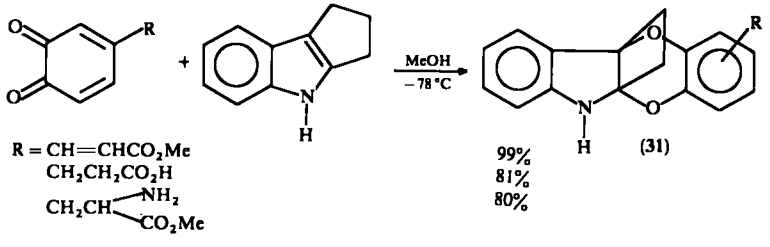
Indoles add to unactivated 1,2-benzoquinones to yield adducts like **31** (equation 208)[285]. With nascent 1,2-benzoquinones related to dopamine it is possible to trap the oxidation products in high yield using 1,2,3,4-tetrahydrocyclopent[*b*]indole (**32**, equation 209)[286].



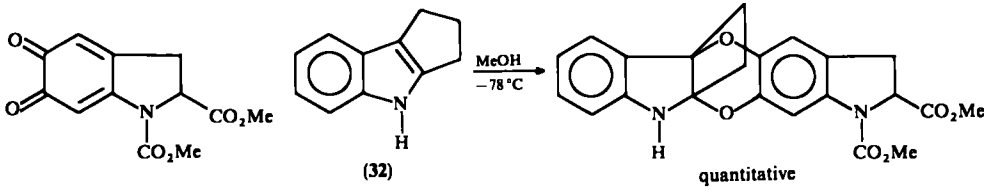
(206)



(207)



(208)



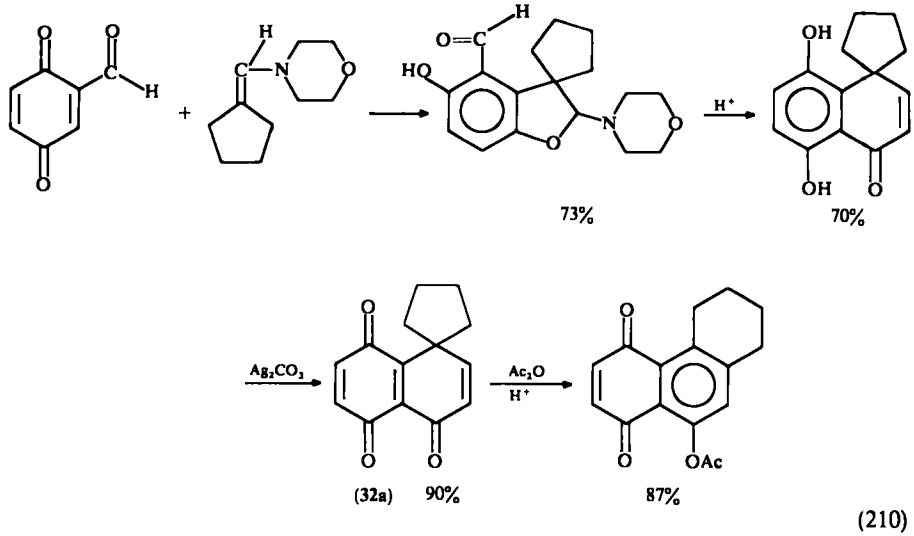
(209)

VI. TANDEM CHEMISTRY OF QUINONES

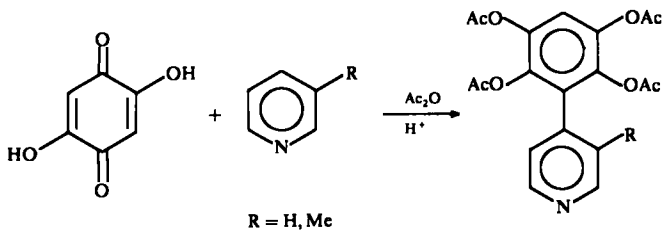
An exciting aspect of recent quinone chemistry has been the extent to which chemical transformations are carefully orchestrated in the search for an elegant and efficient synthesis. Here is a sample of syntheses in which the quinonoid nucleus was used in the efficient preparation of a complex molecule.

The failure of a well-established reaction to perform as expected sometimes presents

opportunities. The Thiele–Winter acetoxylation of the quinone **32a** reduces only the nonquinonoid carbonyl (equation 210)[287]. This Thiele–Winter reaction, in tandem with an arylation reaction, gives good yields of pharmacologically interesting heterocycles (equation 211)[288].



(210)

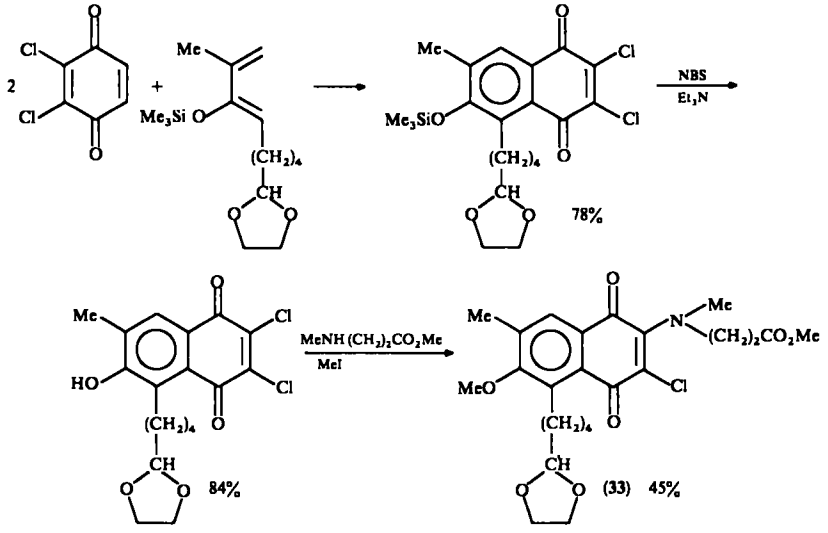


(211)

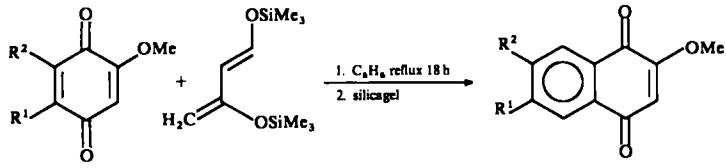
The quinone **33** related to an important series of ansamycin antibiotics, was prepared using Diels–Alder cyclization followed by a regiospecific substitution reaction (equation 212)[289]. In 1986 Brassard and Guay synthesized two new naphthoquinones which are important for biosynthesis[290]. Their well-developed activated diene Diels–Alder route (equation 213) was followed by a complex series of conversions. The result was a one-pot synthesis of the desired material (equation 214). A variation led to an adequate yield of the isomeric product (equation 215).

The synthesis of furano-*o*-benzoquinones has potential in medicine. Snyder and students prepared 3-methyl-4,5-benzofurandione (**34**) by two cyclization routes and then studied its Diels–Alder chemistry (equations 216–218)[291].

Antibiotics of the ravidomycin family were prepared by McKenzie and colleagues using a combination of Meerwein and Diels–Alder chemistry (equation 219)[292,293]. A thiol substitution reaction was employed for removal of the chlorine (equation 220).



(212)

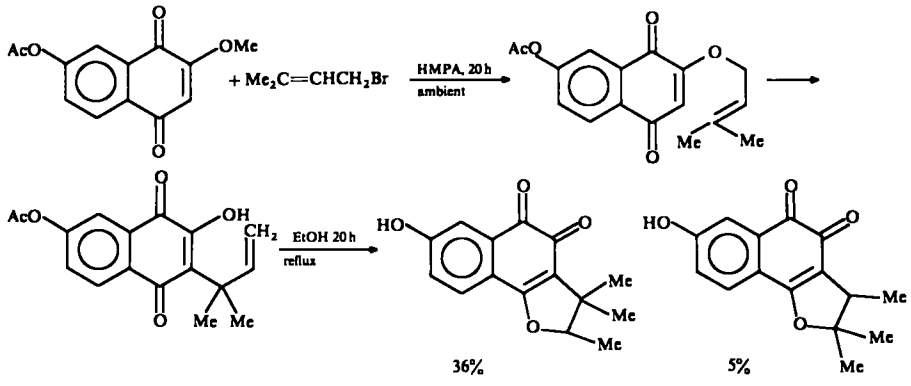


R^1	R^2
Cl	H
H	Cl

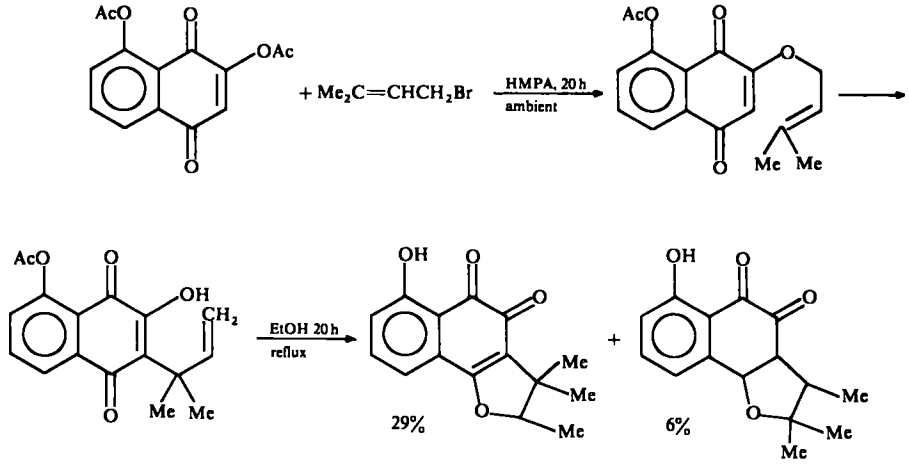
1. C_6H_6 reflux 18 h
2. silicagel

R^1	R^2	%
H	OH	99
OH	H	100

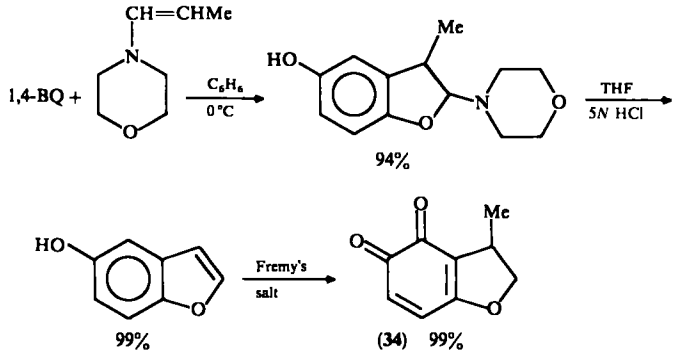
(213)



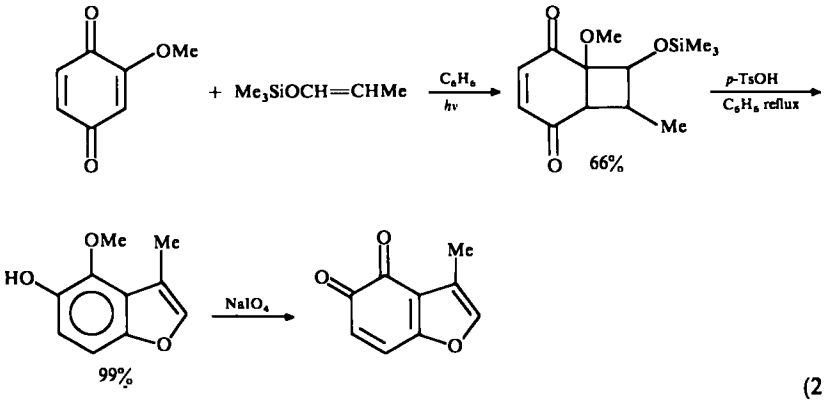
(214)


AcO
OAc
+ Me2C=CHCH2Br
HMPA, 20 h
ambient
Me Me
EtOH 20 h
reflux
OH
CH2
29%
6%

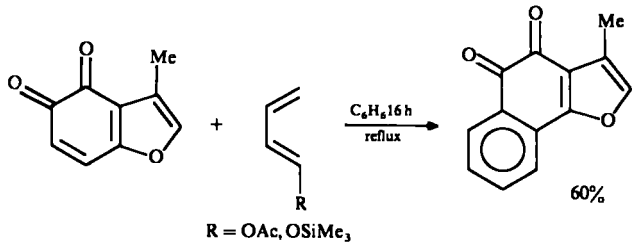
(215)


CH=CHMe
1,4-BQ +
C6H6
0 °C
HO
94%
THF
5N HCl
Fremy's
salt
99%
(34) 99%

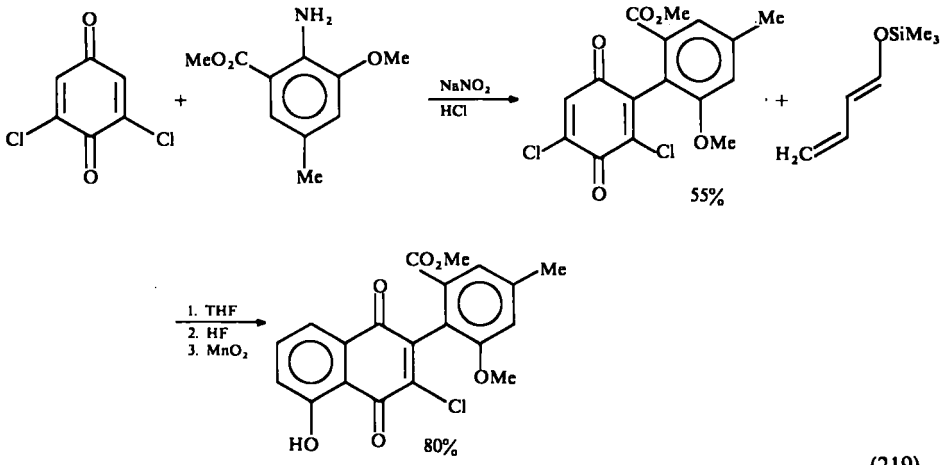
(216)


OMe
+ Me3SiOCH=CHMe
C6H6
hv
OSiMe3
66%
p-TsOH
C6H6 reflux
HO
NaIO4
99%

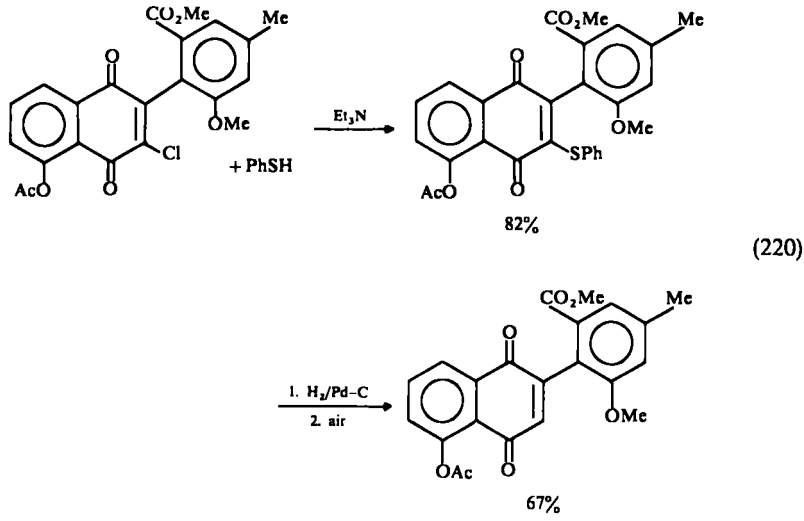
(217)


Me
O
O
O
R
R = OAc, OSiMe3
C6H6 16 h
reflux
Me
O
O
O
60%

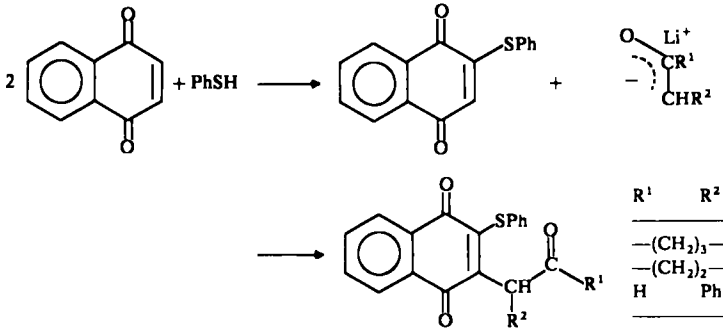
(218)


O
Cl
Cl
O
NH2
MeO2C
OMe
Me
NaNO2
HCl
CO2Me
Me
O
Cl
OMe
Cl
O
55%
OSiMe3
H2C
1. THF
2. HF
3. MnO2
CO2Me
Me
O
OMe
Cl
HO
O
80%

(219)

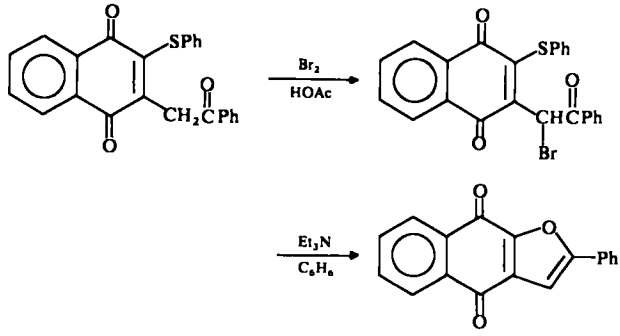

CO2Me
Me
O
OMe
Cl
AcO
O
+ PhSH
Et3N
CO2Me
Me
O
OMe
SPh
AcO
O
82%
1. H2/Pd-C
2. air
CO2Me
Me
O
OMe
OAc
O
67%

(220)

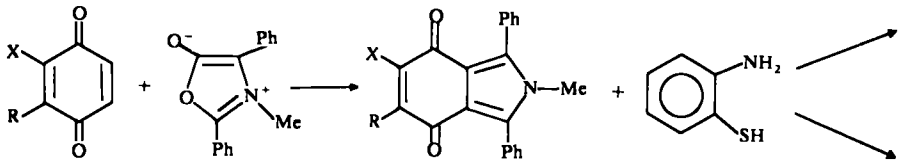


R^1	R^2	%
$-(CH_2)_3-$		76
$-(CH_2)_2-$		75
H	Ph	62

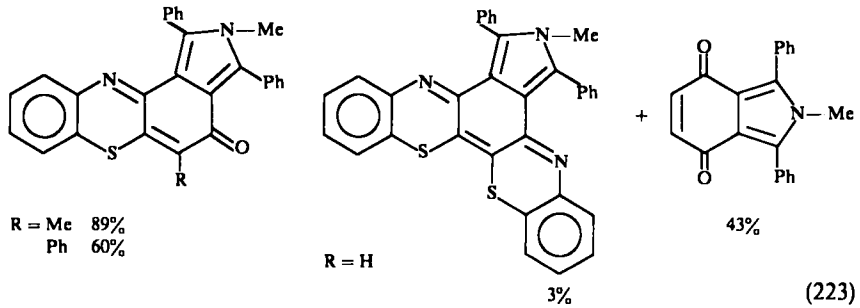
(221)



(222)



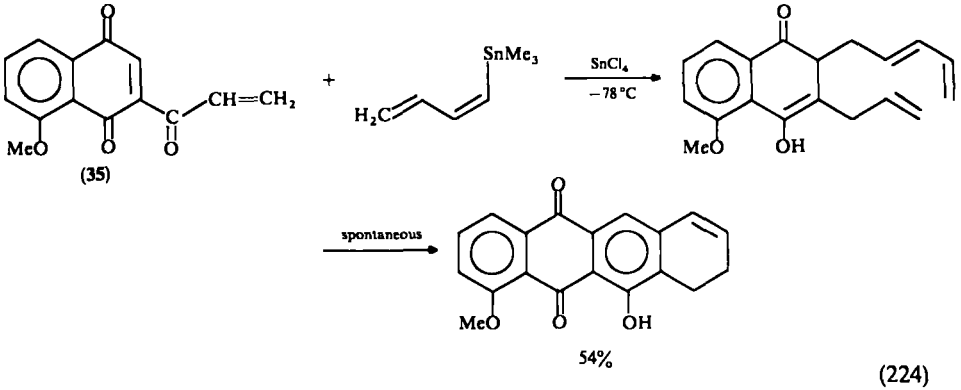
R	X	%
H	Br	31
Me	H	35
Ph	H	35



(223)

Ueno and colleagues began by placing the thiol substituent in a 1,4-naphthoquinone to take advantage of its regiochemical influence[294]. A series of lithium enolates were added in approximately 70% yield (equation 221). It is suggested, on one example, that such compounds can be smoothly converted to naphthofuran-4,9-diones (equation 222). The same group used heterocyclic reactions to prepare a variety of 4*H*-pyrrolo[3,4-*a*]-phenothiazin-4-ones (equation 223)[295]. Yields are modest, but their synthesis, being potentially important, is a major accomplishment.

Naruta, Nishigaichi and Maruyama appear to be the first to use the term tandem[296]. Searching for efficient routes to the structurally demanding anthracyclines, they used the 1,4-naphthoquinone (**35**) in a Michael reaction with the appropriate pentadienyltin followed by a spontaneous, intramolecular Diels–Alder cyclization (equation 224). The high regiospecificity is notable.

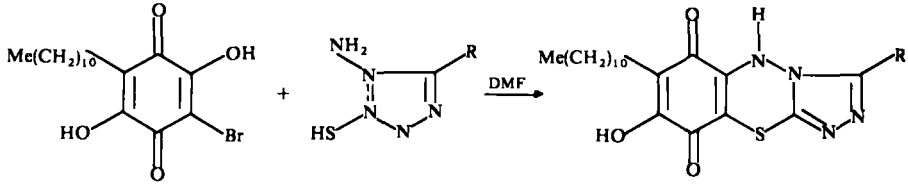


(224)

VII. SUBSTITUTION REACTIONS OF QUINONES

A. Sulfur

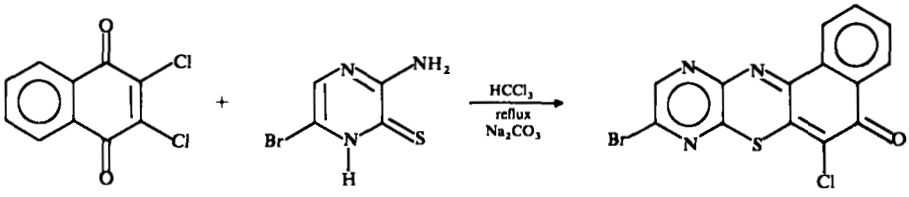
Unlike current sulfur addition chemistry there remains a lamentable shortage of mechanistic studies of substitution reactions. Some synthetic applications have been reported, for example Rao and collaborators obtained good yields of heterocyclic quinones related to embelin, a potentially useful family of drugs (see also Sections II.A and II.B)[297]. The bidentate heterocycle 4-amino-5-mercapto-*S*-triazole reacts with bromoembelin by an unusual double substitution reaction in which the hydroxy group is the leaving group (equation 225). One might expect an anil intermediate, but none was reported.



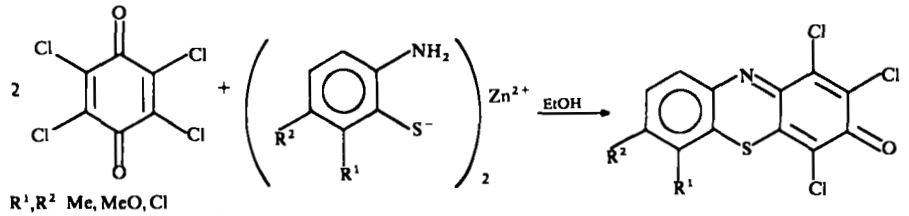
R = Me, Pr, Ph, 4-pyridyl, 4-ClC$_6$H$_4$

(225)

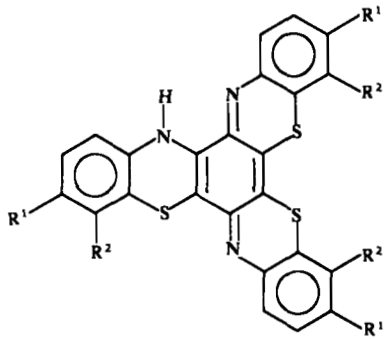
Evidence for an anil intermediate, however, is found in the analogous synthesis presented by Okafor and Okoro in their study of the diazaphenothiazine dyes[298]. The yield of the pyrazine derivative is only 48% but we still have the first example of an angular 1,4-diazaphenothiazine (equation 226). It should be noted that this reaction incorporates three separate steps, which in the pyrazine cases were carried out separately (equation 227). Chloranil will react with the zinc salt of various 5-substituted 2-aminothiophenols. Surprisingly good yields of a polycyclic dye (**36**), in which all chlorines have been replaced, are obtained[299].



(226)



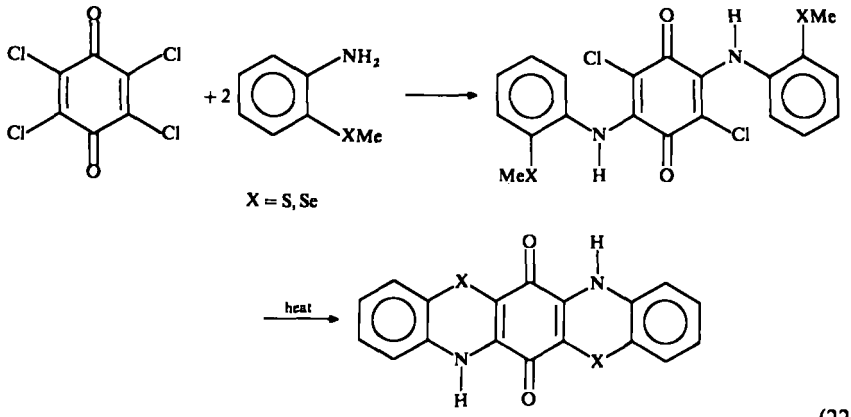
(227)



(36)

Kitahara and collaborators, have continued their search for optical recording material which absorb in the near IR; more recently they have prepared sulfur and selenium derivatives of polycyclic quinonoid dyes (equation 228)[300].

The successful synthetic efforts of d'Angelo and colleagues directed toward regiospecific chemistry in the juglone series relate to substitution as well as addition chemistry (equation 229)[26].



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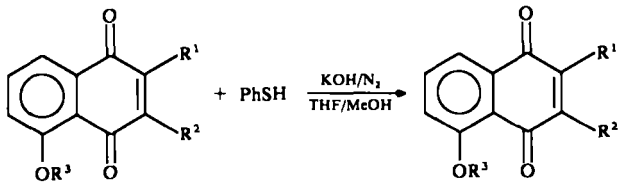
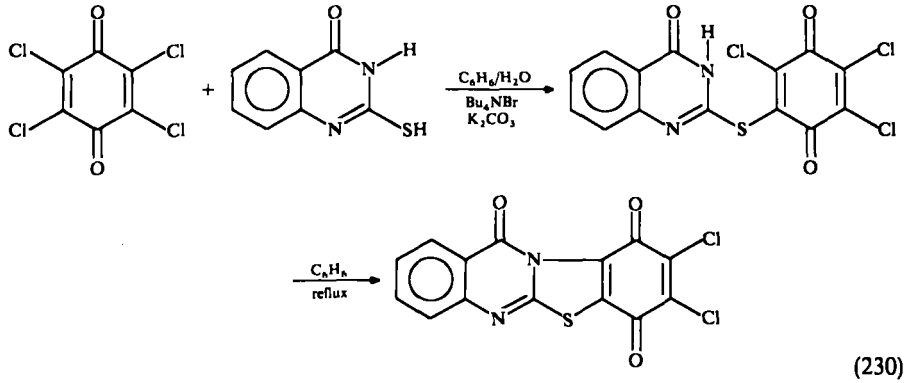


R1	R²	R³
Br	H	Ac
H	Br	Me

R¹	R²	%
PhS	H	75
H	PhS	82

(229)

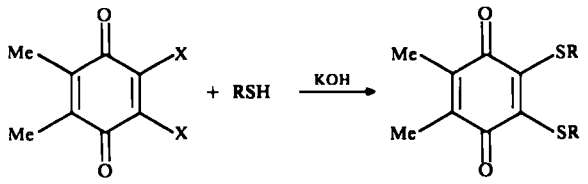
Another potentially important heterocyclic synthesis is disappointing. Only sketchy information, not even yields, are given. The use of phase transfer catalysis was shown to be highly useful for the preparation of sensitive organic compounds, for example, 2-mercapto-4-(3*H*)-quinazolinone was allowed to react with 2,3-dichloro-1,4-naphthoquinone in a two-phase solid–liquid system (equation 230)[301]. The benzene solution of the organic substances and the solid potassium carbonate were connected through



(230)

tetrabutylammonium bromide, which is unable to transfer carbonate into the organic phase. After mercaptan substitution it appears that bridgehead nitrogen linkages are formed, which is the most interesting part of this study. In the chloranil case, evidence for this sequence is found where the thioether is the only product. The final cyclization step could only be achieved by a conventional homogeneous, thermal reaction.

Wladislaw has reported modest yields for a variety of alkyl and aryl thiols with 2,3-dichloro- (or dibromo) 5,6-dimethyl-1,4-benzoquinones (equation 231)[302].



X = Cl, Br

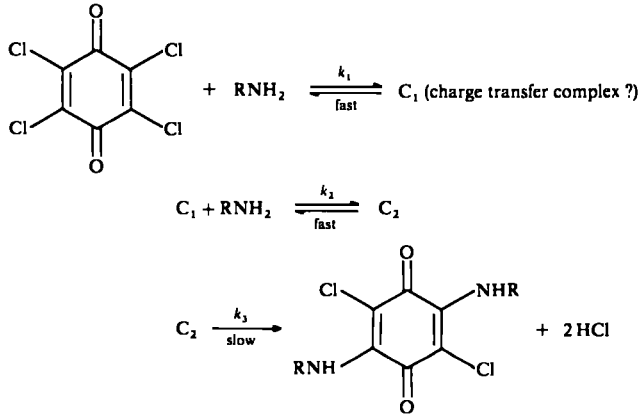
R	%
Me	65
Bu	30
Ph	47

(231)

B. Nitrogen

1. Kinetics and mechanisms

In 1988 there were two important studies involving the rates of displacement in chloroquinones by nitrogen functions. Valero and collaborators investigated the details of the reactions between n-butyl- and *sec*-butylamine and chloranil[303,304a]. A review of the literature complements the detailed kinetic study of their behavior in cyclohexane solution. The reported intermediates for this system differ in polar and nonpolar solvents. As might be expected consideration of the spectra, rate equations and thermodynamic parameters shows that the two systems behave similarly and leads to a common mechanism (equation 232). Both reactions were shown to be autocatalytic in the presence



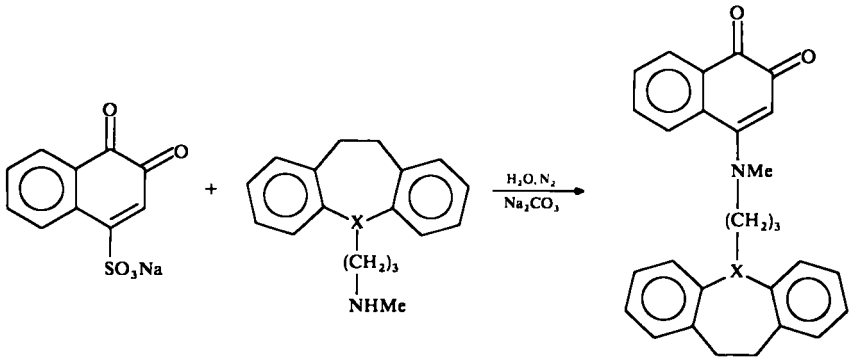
(232)

of excess amine. The application of scales of electronic and polar parameters allows a linear free energy relationship to be constructed for the reaction of 11 aliphatic amines with chloranil[304b].

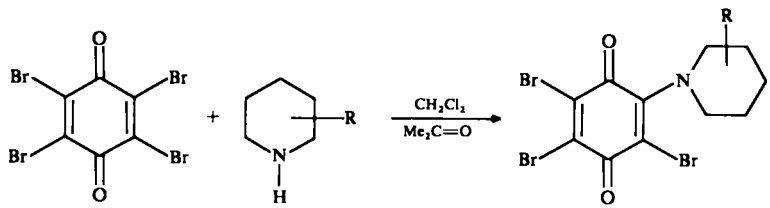
Thiomorpholine and chloranil form a 1:1 charge transfer complex in chloroform as indicated by a spectrophotometric study[305]. With excess thiomorpholine the 3,6-bis-substitution product is formed. Similar chemistry is observed with piperidines and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, but both mono- and disubstitution products are found[306].

2. *Synthesis*

Kallmayer has continued his interest in nitrogen substituted quinones related to the desipramin drugs, but has now utilized substitution rather than addition chemistry (equation 233)[307]. The spectral properties of these 1,2-naphthoquinones are compared with the 1,4-benzoquinones previously reported. In a later study, heterocyclic secondary amines were reacted with 2,3,5,6-tetrabromo-1,4-benzoquinone in moderate yields (equation 234)[308]. The 2,5-diamino product was identified as a minor product.



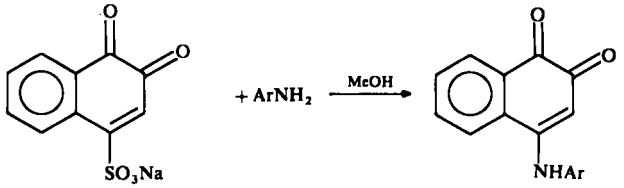
(233)



(234)

R	%
H	41
2-Me	34
3-Me	37
4-Me	50

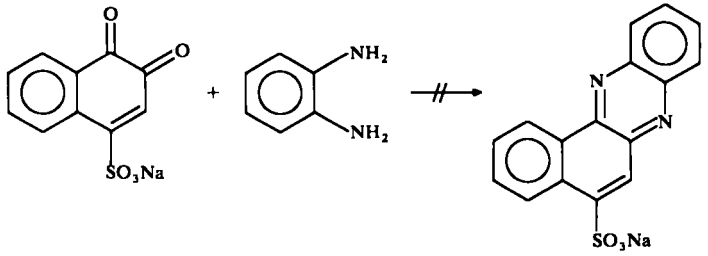
A series of anilines failed to displace the bromines in this chemistry, but were reactive towards 1,2-naphthoquinone-4-sulfonic acid sodium-salt (equation 235)[309]. These amino substituted quinones underwent the usual cyclization reaction with *o*-phenylenediamine, but the product heterocycles could not be prepared either through the reverse reaction sequence or from the 4-chloro precursor (equations 236 and 237).



(235)

Ar = Ph
4-$MeOC_6H_4$
4-BrC_6H_4
4-$NO_2C_6H_4$
2-$H_2NC_6H_4$

88%



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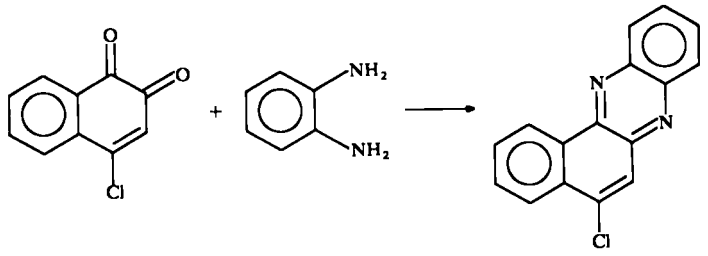
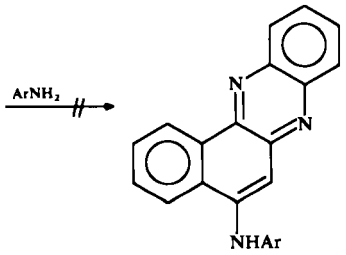
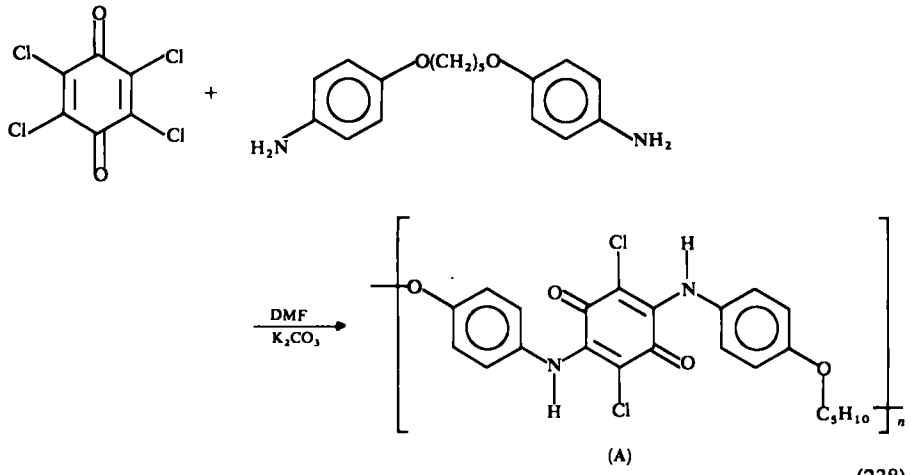


(237)

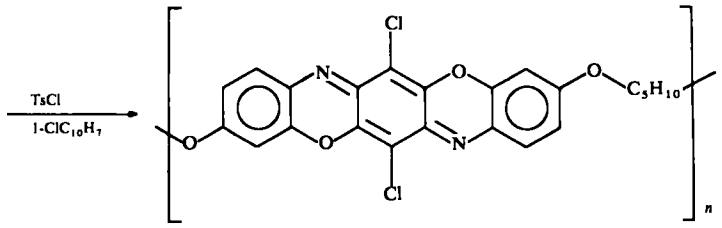


The search for polymers with useful optical properties led Dalton and Yu to prepare a prepolymer (**A**) involving a flexible-chain spacer (equation 238)[310]. It is possible, using the high-boiling solvent 1-chloronaphthalene and *p*-toluenesulfonyl chloride, to cyclize the prepolymer so that the final polymeric product contains a triphenodioazine rigid-rod segment (equation 239).

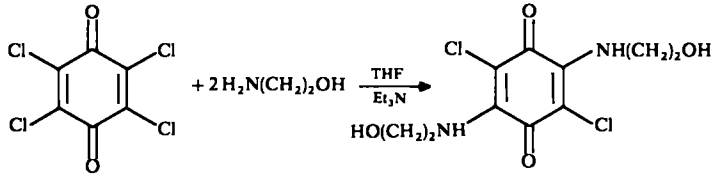


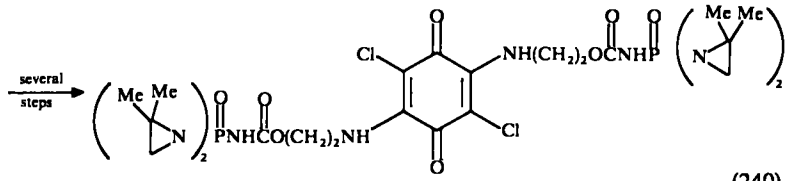
(A)

(238)



(239)

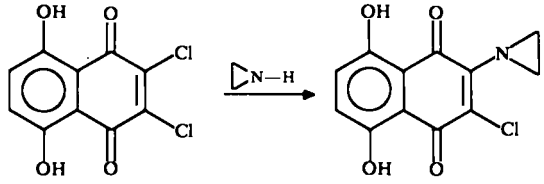




(240)

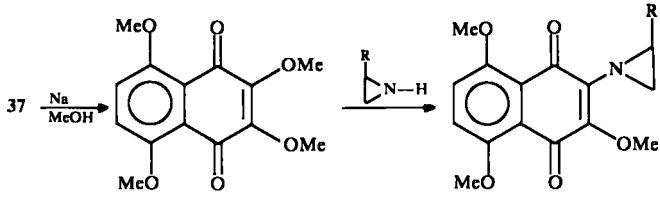
The known efficacy of both quinonoid and *bis*(2,2-dimethyl-1-aziridinyl)phosphinic esters as antineoplastic agents led Bardos and students to prepare a molecule containing both structures (equation 240)[311].

Aziridinyl groups attached directly to a quinone ring have a long and significant synthetic history (Reference 1, pp. 1101–1109); for example, 2,3-dichloro (or bromo) naphthazarins (**37**) react smoothly with aziridine to produce moderate yields of nitrogen products (equation 241)[312]. Sodium in methanol converts **37** to the 2,3-dimethoxy derivative (**38**) which also reacts with aziridine or 2-methylaziridine in somewhat improved yield. Both methoxy groups may be replaced (equation 242).



(37) 30%

(241)



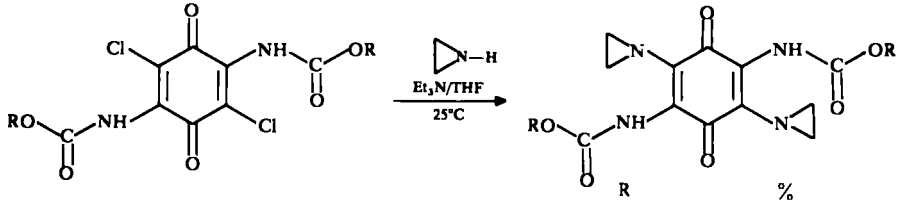
(38)

R = H 50%
Me 40%

(242)

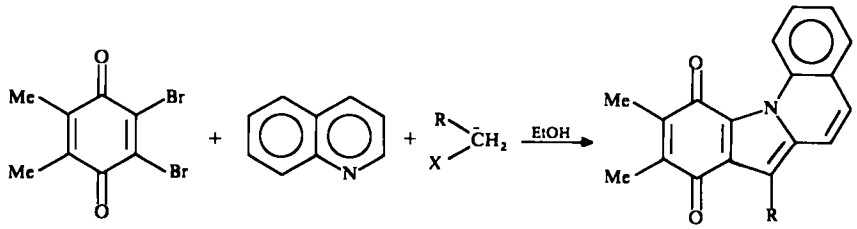
Excellent yields of 1,4-benzoquinones containing carbamic acid esters along with aziridinyl groups were realized by Dzielendziak and Butler (equation 243)[313].

2,3-Dibromo-5,6-dimethyl-1,4-benzoquinone reacts with quinoline or isoquinoline in the presence of active methylene compounds to produce interesting bridgehead nitrogen compounds (equations 244 and 245)[314,315]. Yields vary.



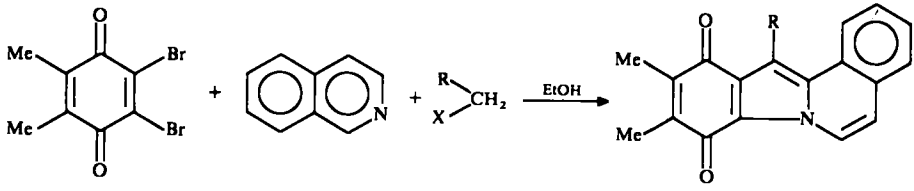
R	%
Me	78
Et	79
n-Pr	82
n-Bu	81
i-Bu	89

(243)



X	R	%
NO_2	H	11
NO_2	Me	19
Ac	CO_2Et	68
Ac	Ac	56
CO_2Et	CN	40

(244)

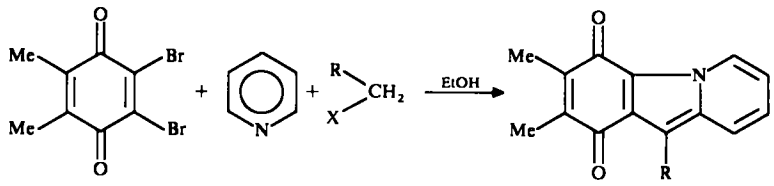


X	R	%
NO_2	H	13
NO_2	Me	21
Ac	Ac	46
CO_2Et	CN	50

(245)

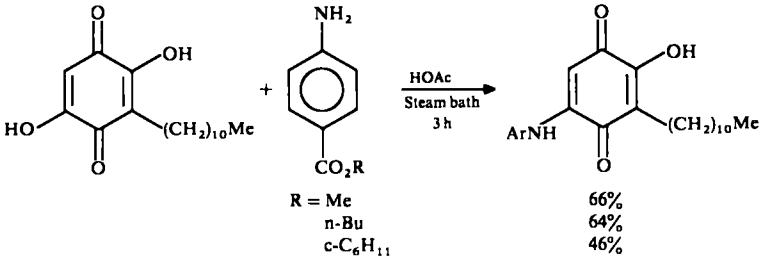
Nearly identical chemistry is found with pyridine and active methylene compounds in the presence of this 1,4-benzoquinone (equation 246)[316].

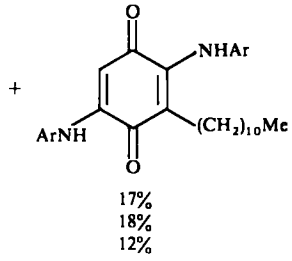
Rao and colleagues have continued their investigations of embelin by preparing a series 5-anilino and 2,5-*bis*(anilino) derivatives of a large number of 4-aminobenzoic acid esters (equation 247)[317]. The unusual nature of the hydroxyl leaving group is emphasized by their other studies on chloranilic acid (equation 248)[318].



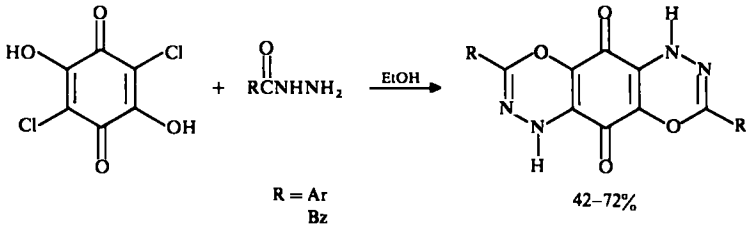
X	R	%
NO_2	H	13
NO_2	Ac	22
Ac	Ac	56
CO_2Et	CN	59

(246)





(247)

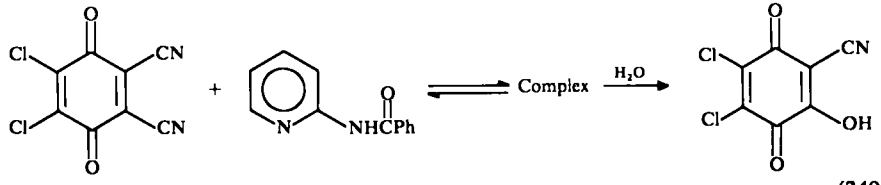


(248)

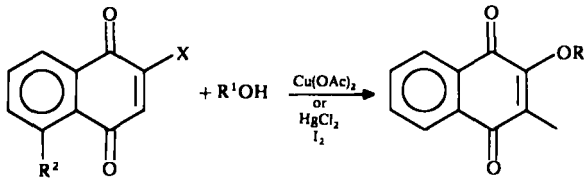
C. Oxygen

The presence of a trace of water leads to unusual oxygen substitution chemistry of the complex between 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and amidopyridines (equation 249)[319]. Attempts to form this product by hydrolysis lead only to the corresponding ammonium salt.

Methyl, ethyl and isopropyl alcohols can be attached, in fair yields, to 1,4-naphthoquinones either by addition or substitution in the presence of Hg(II) of Cu(II) salts (equation 250)[320]. Steric effects play a significant role in these ionic reactions.



(249)

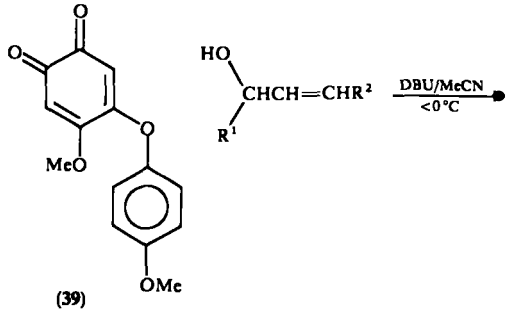


(250)

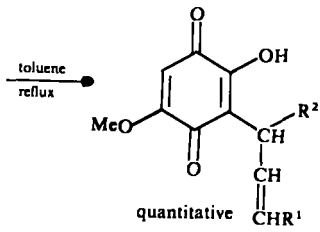
	R¹	R²	%
X = H	Me	H	60
Cl	Et	H	50
Br	i-Pr	H	40
H	Me	OH	50
Cl	Et	OH	40
Br	i-Pr	OH	30

Maumy and colleagues have applied the Claisen rearrangement to the synthesis of several natural products containing the 1,4-benzoquinone ring. They showed that *p*-methoxyphenyl substituted 1,2-benzoquinone (**39**) exchanges in generally excellent yield, with a variety of alcohols under basic conditions[321]. These intermediates may be isolated or thermally rearranged quantitatively. This completely stereospecific reaction enables us to prepare some difficultly available 1,4-benzoquinones (equation 251)[322]. This basic sequence has also been applied to the synthesis of benzofuranoquinones (equation 252)[323].

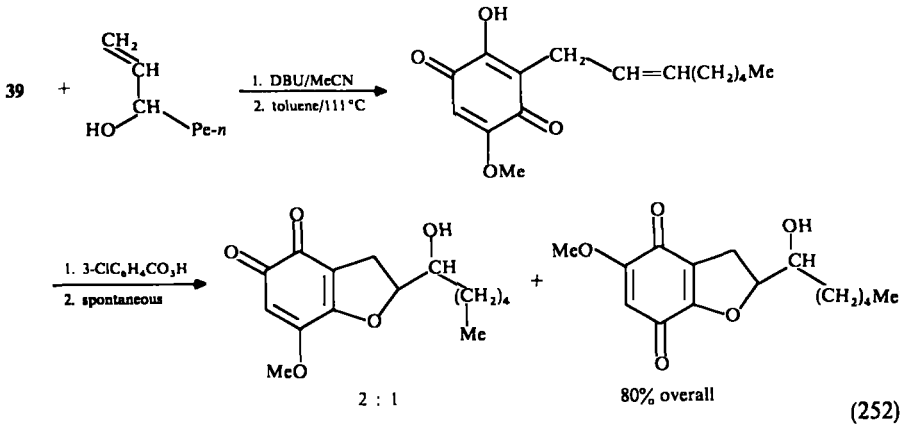
Oxygen substitution is the first step in the synthesis of a triphenodioxazine dye with nearinfrared absorption capabilities as reported by Renfrew[324]. The substitution of chloranil by *p*-phenylenediamine sulfonic acid produced the desired 2,5-disubstitution product which underwent acid cyclization (equation 253).



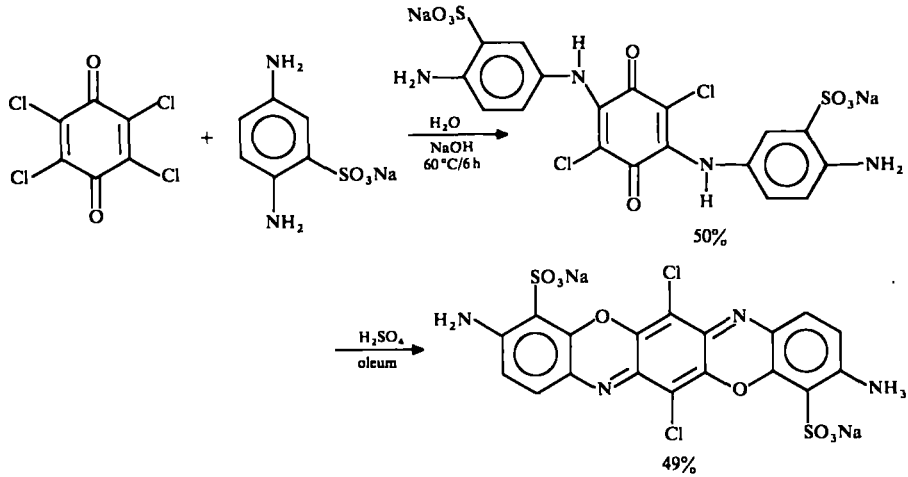
R¹	R²	%
H	H	95
H	Me	71
H	Ph	77
Me	H	90



(251)



(252)



(253)

VIII. ACKNOWLEDGMENT

It is with the greatest pleasure that I note the beautiful fishing village of Cassis, France, the warm people of the Midi and especially The Carmargo Fondation for the peace and tranquility in which to contemplate the beauty of quinones.

IX. REFERENCES

1. K. T. Finley, 'The addition and substitution chemistry of quinones', in *The Chemistry of Quinonoid Compounds* (Ed. S. Patai), Vol. II, Chap. 17, Wiley, London, 1974, pp. 877–1144.
2. K. T. Finley, 'Quinones as synthones', in *The Chemistry of Quinonoid Compounds* (Eds. S. Patai and Z. Rappoport), Vol. II, Chap. 11, Wiley, Chichester, 1988, pp. 537–717.
3. A. Woskressenski, *Justus Liebigs Ann. Chem.*, **27**, 268 (1838).
4. F. Wöhler, *Justus Liebigs Ann. Chem.*, **51**, 155 (1844).
5. A. Michael, *J. Prakt. Chem.* [2] **79**, 418 (1909) and **82**, 306 (1910).

6. S. S. Lau, B. A. Hill, R. J. Highet and T. J. Monks, *Mol. Pharmacol.*, **34**, 829 (1988).
7. T. J. Monks, S. S. Lau and R. J. Highet, *Drug Metab. Dispos.*, **12**, 432 (1984).
8. (a) T. J. Monks, S. S. Lau, R. J. Highet and J. R. Gillette, *Drug Metab. Dispos.*, **13**, 553 (1985). (b) K. G. Eckert, P. Eyer, J. Sonnenlichler and I. Zetl, *Xenobiotica*, **20**, 351 (1990).
9. A. Brunmark and E. Cadenas, *Chem.-Biol. Interact.*, **68**, 273 (1988).
10. T. S. Smithgall, R. G. Harvey and T. M. Penning, *J. Biol. Chem.*, **263**, 1814 (1988).
11. H. Chung, R. G. Harvey, R. N. Armstrong and J. Jarabak, *J. Biol. Chem.*, **262**, 12448 (1987).
12. E. Bauman and C. Preusse, *Chem. Ber.*, 806 (1879).
13. M. Jaffe, *Chem. Ber.*, 1092 (1879).
14. R. P. Hanzlik, P. E. Weller, J. Desai, J. Zheng, L. R. Hall and D. E. Slaughter, *J. Org. Chem.*, **55**, 2736 (1990).
15. M. K. Vadnere, L. Maggiora and M. P. Mertes, *J. Med. Chem.*, **29**, 1714 (1986).
16. A. Andrawis and V. Kahn, *Biochem. J.*, **235**, 91 (1986).
17. R. A. McAllister and E. H. G. Campbell, *IRCS Med. Sci.*, **14**, 1217 (1986).
18. O. Crescenzi, G. Prota, T. Schultz and L. J. Wolfram, *Tetrahedron*, **44**, 6447 (1988).
19. N. N. Nkpa and M. R. Chedekel, *J. Org. Chem.*, **46**, 213 (1981).
20. S. Ito, S. Inoue, Y. Yamamoto and K. Fujita, *J. Med. Chem.*, **24**, 673 (1981).
21. T. Kato, S. Ito and K. Fujita, *Biochim. Biophys. Acta*, **881**, 415 (1986).
22. S. Ito, T. Kato and K. Fujita, *Biochem. Pharmacol.*, **37**, 1707 (1988).
23. Y. Imai, S. Ito and K. Fujita, *J. Chromatogr.*, **420**, 404 (1987).
24. N. E. Mackenzie, S. Surendrakumar, R. H. Thomson, H. J. Cowe and P. J. Cox, *J. Chem. Soc., Perkin Trans. 1*, 2233 (1986).
25. (a) D. V. Rao, V. V. R. Rao, T. V. P. Rao and Y. V. D. Nageswar, *Sulfur Lett.*, **8**, 309 (1989). (b) B. R. Rani, M. F. Rahman and V. T. Balerao, *Org. Prep. Proced. Int.*, **23**, 157 (1991).
26. S. Laugraud, A. Guingant, C. Chassagnard and J. d'Angelo, *J. Org. Chem.*, **53**, 1557 (1988).
27. K. Miyaki, N. Ikeda and D. Mizuno, *J. Pharm. Soc. Jpn.*, **73**, 961 (1953).
28. A. El-Fotooh, G. Hammam, A. A. Gattas and N. M. Youssif, *Egyptian J. Chem.*, **27**, 515 (1984).
29. K. Mori, K. Takahashi, T. Kishi and H. Sayo, *Chem. Pharm. Bull.*, **35**, 1270 (1987).
30. W. Löwe and A. Kennemann, *Arch. Pharm. (Weinheim)*, **321**, 541 (1988).
31. J. Y. Becker, J. Bernstein, S. Bittner, E. Harlev, J. A. R. P. Sarma and S. S. Shaik, *New J. Chem.*, **12**, 875 (1988).
32. S. Bittner and E. Harlev, *Synthesis*, 868 (1989).
33. N. M. Yousif, R. Shabana and S.-O. Lawesson, *Bull. Soc. Chim. France*, 283 (1986).
34. G. A. Kutyrev, O. S. Korolev, E. G. Yarkova, O. E. Lebedeva, R. A. Cherkasov and A. N. Pudovik, *Zh. Obshch. Khim. (Engl. Transl.)*, **58**, 1145 (1988).
35. Y. Cha, M. Tsunooka and M. Tanaka, *J. Photochem.*, **35**, 93 (1986).
36. Y. Cha, M. Tsunooka and M. Tanaka, *J. Appl. Polym. Soc.*, **31**, 861 (1986).
37. R. Al-Hamdany, J. M. Al-Rawi, B. A. Ahmed and K. F. Al-Shahiry, *J. Prakt. Chem.*, **329**, 337 (1987).
38. A. I. Ononye, J. G. Graveel and J. D. Wolt, *Environmental Toxicology Chem.*, **8**, 303 (1989).
39. M. L. Iskander, H. A. A. Medien and S. Nashed, *Microchem. J.*, **39**, 43 (1989).
40. M. L. Iskander, H. A. A. Medien and S. Nashed, *Microchem. J.*, **36**, 368 (1987).
41. E. Valero, J. Escribano and F. Garcia-Carmona, *Phytochemistry*, **27**, 2055 (1988).
42. H. Kobayashi, K. Kobayashi, Y. Ohhara, Y. Kawashima, T. Ohno and S. Mizusawa, *Denki Kagaku oyobi Kogyo Butsuri Kagaku*, **57**, 1006 (1989); *Chem. Abstr.*, **112**, 177787u (1990).
43. M. K. Manthey, S. G. Pyne and R. J. W. Truscott, *Aust. J. Chem.*, **42**, 365 (1989).
44. A. R. Forrester and R. H. Thomson, *Z. Naturforsch.*, **40b**, 1515 (1985).
45. A. Bolognese, G. Scherillo and W. Schäfer, *J. Heterocycl. Chem.*, **23**, 1003 (1986).
46. A. Minta and R. Y. Tsien, *J. Biol. Chem.*, **264**, 19449 (1989).
47. I. Trifunović, D. Sladić, N. Dogović and M. J. Gašić, *J. Serb. Chem. Soc.*, **52**, 559 (1987).
48. (a) A. E. Mathew, R. K.-Y. Zee-Cheng and C. C. Cheng, *J. Med. Chem.*, **29**, 1792 (1986). (b) T.-S. Lin, L.-Y. Zhu, S.-P. Xu, A. A. Divo and A. C. Sartorelli, *J. Med. Chem.*, **34**, 1634 (1991). (c) S. Bittner and P. Krief, *Synthesis*, 350 (1990).
49. B. F. Kukharey, V. K. Stankevich and G. R. Klimenko, *Zh. Prikl. Khim. (Leningrad)*, **61**, 2715 (1988); *Chem. Abstr.*, **111**, 57172x (1989).
50. P. Traxler, W. Kump, K. Mueller and W. Tosch, *J. Med. Chem.*, **33**, 552 (1990).
51. O. Reinaud, P. Capdevielle and M. Maumy, *Synthesis*, 790 (1987).
52. M. Tišler, 'Heterocyclic Quinones', in *Advances in Heterocyclic Chemistry*, **45**, 37 (1989).

53. K. A. Parker, D. M. Spero and K. A. Koziski, *J. Org. Chem.*, **52**, 183 (1987).
54. J. C. Evans, R. C. Klix and R. D. Bach, *J. Org. Chem.*, **53**, 5519 (1988).
55. H. Suzuki, Y. Shiraishi, K. Shimokawa and H. Uno, *Chem. Lett.*, 127 (1988).
56. C. K. S. Nair, B. K. Kumari and M. Pardhasaradhi, *Fuel*, **68**, 127 (1989).
57. U. Wriede, M. Fernandez, K. F. West, D. Harcourt and H. W. Moore, *J. Org. Chem.*, **52**, 4485 (1987).
58. V. L. Heasley, T. J. Louie, D. K. Luttrull, M. D. Millar, H. B. Moore, D. F. Nogales, A. M. Sauerbrey, A. B. Shevel, T. Y. Shibuya, M. S. Stanley, D. F. Shellhamer and G. E. Heasley, *J. Org. Chem.*, **53**, 2199 (1988).
59. R. C. Atkinson, P. B. D. de la Mare and D. S. Larson, *J. Chem. Soc., Perkin Trans. 2*, 271 (1983).
60. (a) A. E. Gal and J. P. Voorstad, *J. Labelled Compd. Radiopharm.*, **24**, 397 (1987).
(b) M. Pinault, Y. Frangin, J. P. Genet and H. Zamarlik, *Synthesis*, 935 (1990).
61. N. Kamigata, T. Satoh and M. Yoshida, *Bull. Chem. Soc. Jpn.*, **61**, 449 (1988).
62. A. A. Kutyrew, S. G. Fomin and V. V. Moskva, *Phosphorus and Sulfur*, **39**, 19 (1988).
63. R. Cassis, M. Fernández, R. Tapia and J. A. Valderrama, *Synth. Commun.*, **17**, 1077 (1987).
64. B. Husu, S. Kafka, Z. Kadunc and M. Tišler, *Monatsh. Chem.*, **119**, 215 (1988).
65. M. P. Youngblood, *J. Org. Chem.*, **51**, 1981 (1986).
66. T. J. Monks, R. J. Highet, P. S. Chu and S. S. Lau, *Mol. Pharmacol.*, **34**, 15 (1988).
67. R. F. X. Klein, L. M. Bargas and V. Horak, *J. Org. Chem.*, **53**, 5994 (1988).
68. H. J. Kallmayer and J. Weiten, *Pharmazie*, **43**, 130 (1988).
69. S. Itoh, K. Nii, M. Mure and Y. Ohshiro, *Tetrahedron Lett.*, **28**, 3975 (1987).
70. E. Michels and W. P. Neumann, *Tetrahedron Lett.*, **27**, 2455 (1986).
71. K. Hillner and W. P. Neumann, *Tetrahedron Lett.*, **27**, 5347 (1986).
72. P. Rivière, A. Castel, J. Satgé and D. Guyot, *J. Organomet. Chem.*, **315**, 157 (1986).
73. P. Rivière, A. Castel, J. Satgé, D. Guyot and Y. H. Ko, *J. Organomet. Chem.*, **339**, 51 (1988).
74. A. Castel, P. Rivière, J. Stagé and Y. H. Ko, *J. Organomet. Chem.*, **342**, C1 (1988).
75. D. A. Evans and R. Y. Wong, *J. Org. Chem.*, **42**, 350 (1977).
76. M. Onaka, K. Higuchi, K. Sugita and Y. Izumi, *Chem. Lett.*, 1393 (1989).
77. G. P. Stahly and D. R. Bell, *J. Org. Chem.*, **54**, 2873 (1989).
78. M. Solomon, W. C. L. Jamison, M. McCormick, D. Liotta, D. A. Cherry, J. E. Mills, R. D. Shah, J. D. Rodgers and C. A. Maryanoff, *J. Am. Chem. Soc.*, **110**, 3702 (1988).
79. H. W. Moore, K. F. West, U. Wriede, K. Chow, M. Fernandez and N. V. Nguyen, *J. Org. Chem.*, **52**, 2537 (1987).
80. T. Mukaiyama, R. S. J. Clark and N. Iwasawa, *Chem. Lett.*, 479 (1987).
81. T. Mukaiyama, N. Iwasawa, T. Yura and R. S. J. Clark, *Tetrahedron*, **43**, 5003 (1987).
82. L. S. Hegedus and R. J. Perry, *J. Org. Chem.*, **50**, 4955 (1985).
83. J. Y. Becker, J. Bernstein, S. Bittner, E. Harlev and J. A. R. P. Serme, *J. Chem. Soc., Perkin Trans. 2*, 1157 (1989).
84. (a) D. N. Nicolaides, K. E. Litines and N. G. Argyropoulos, *J. Chem. Soc., Perkin Trans. 1*, 415 (1986).
(b) R. M. Monarty, J. Hiratake and K. Liu, *J. Am. Chem. Soc.*, **112**, 8575 (1990).
85. M. Franck-Neumann, M. Miesch and F. Barth, *Tetrahedron Lett.*, **30**, 3537 (1989).
86. M. T. Craw, M. C. Depew and J. K. S. Wan, *Phosphorus and Sulfur*, **25**, 369 (1985).
87. A. Alberti, C. Chatilialoglu, G. F. Pedulli and P. Zanirato, *J. Am. Chem. Soc.*, **108**, 4993 ((1986).
88. D. H. R. Barton, D. Crich and G. Kretzschmar, *J. Chem. Soc., Perkin Trans. 1*, 39 (1986).
89. D. H. R. Barton, D. Bridon and S. Z. Zard, *Tetrahedron*, **43**, 5307 (1987).
90. T. L. Simándi, A. Rockenbauer and F. Tüdös, *Eur. Polym. J.*, **25**, 501 (1989).
91. H. Stach and M. Hesse, *Helv. Chim. Acta*, **69**, 85 (1986).
92. F. Walls, J. Padilla, P. Joseph-Nathan, F. Giral, M. Escobar and J. Romo, *Tetrahedron*, **22**, 2387 (1966).
93. P. Joseph-Nathan, M. P. González, E. García, H. Barrios and F. Walls, *Tetrahedron*, **30**, 3461 (1974).
94. P. Joseph-Nathan, V. Mendoza and E. García, *Tetrahedron*, **33**, 1573 (1977).
95. (a) P. Joseph-Nathan, M. E. Garíbay and R. L. Santillan, *J. Org. Chem.*, **52**, 759 (1987).
(b) I. H. Sanchez, R. Yañez, R. Enriquez and P. Joseph-Nathan, *J. Org. Chem.*, **46**, 2818 (1981).
96. N. Jacobsen and K. Torssell, *Justus Liebigs Ann. Chem.*, **763**, 135 (1972).
97. A. T. Hudson, M. J. Pether, A. W. Randall, M. Fry, V. S. Latter and N. McHardy, *Eur. J. Med. Chem. Chim. Ther.*, **21**, 271 (1986).

98. L. Gu, Y. Zhong and J. Zhang, *Huaxue Xuebao*, **46**, 379 (1988); *Chem. Abstr.*, **110**, 94622u (1989).
99. L. Gu and Y. Zhong, *Youji Huaxue*, **9**, 239 (1989); *Chem. Abstr.*, **112**, 35379p (1990).
100. H. Zhang, B. Pan, Z. Tao and Q. Qin, *Huaxue Xuebao*, **47**, 896 (1989); *Chem. Abstr.*, **112**, 178453u (1990).
101. A. Takuwa, Y. Naruta, O. Soga and K. Maruyama, *J. Org. Chem.*, **49**, 1857 (1984).
102. A. Takuwa, O. Soga, T. Mishima and K. Maruyama, *J. Org. Chem.*, **52**, 1261 (1987).
103. K. Mori, M. Waku and M. Sakakibara, *Tetrahedron*, **41**, 2825 (1985).
104. K. Saito and Y. Horie, *Heterocycles*, **24**, 579 (1986).
105. K. T. Potts and E. B. Walsh, *J. Org. Chem.*, **53**, 1199 (1988).
106. H. Kooshkabadi, W. F. Schmidt, S. J. Cutler, F. M. El-Kabbani and C. D. Blanton, Jr., *Heterocycles*, **29**, 1221 (1989).
107. M. Tišler, *Org. Prep. Proced. Int.*, **18**, 17 (1986).
108. F. M. Dean, L. E. Houghton, G. H. Mitchell, R. Nayyir-Mashir and C. Thebtaranonth, *Tetrahedron*, **42**, 3663 (1986).
109. A. Napolitano, M. G. Corradini and G. Prota, *Tetrahedron*, **43**, 2749 (1987).
110. M. G. Corradini, C. Costantini, G. Prota and T. M. Schultz, *Gazz. Chim. Ital.*, **119**, 153 (1989).
111. P. S. Rao, K. V. P. Rao and K. P. Raju, *Fitoterapia*, **58**, 417 (1987).
112. G. Israel and K. Urban, *Z. Chem.*, **28**, 211 (1988).
113. S. M. Jain, R. Kant, A. N. Sarin, S. K. Dhar and K. L. Dhar, *Indian J. Chem., Sect. B*, **28B**, 790 (1989).
114. A. G. Griesbeck, *Tetrahedron Lett.*, **29**, 3477 (1988).
115. V. K. Singh, B. N. S. Raju and P. T. Deota, *Synth. Commun.*, **18**, 567 (1988).
116. T. Dunams, W. Hoekstra, M. Pentaleri and D. Liotta, *Tetrahedron Lett.*, **29**, 3745 (1988).
117. S. Colonna, A. Manfredi and R. Annunziata, *Tetrahedron Lett.*, **29**, 3347 (1988).
118. P. A. Grieco, P. Galatsis and R. F. Spohn, *Tetrahedron*, **42**, 2847 (1986).
119. P. A. Grieco, J. J. Nunes and M. D. Gaul, *J. Am. Chem. Soc.*, **112**, 4595 (1990).
120. C. F. Wilcox, Jr., K. R. Lassila and C. E. Young, *J. Org. Chem.*, **54**, 5035 (1989).
121. L. A. Paquette, C. Vanucci and R. D. Rogers, *J. Am. Chem. Soc.*, **111**, 5792 (1989).
122. R. A. Dickinson, R. Kubela, G. A. MacAlpine, Z. Stojanac and Z. Valenta, *Can. J. Chem.*, **50**, 2377 (1972).
123. D. J. Burnell, H. B. Goodbrand, S. M. Kaiser and Z. Valenta, *Can. J. Chem.*, **65**, 154 (1987).
124. J. M. Coxon, M. J. O'Connell and P. J. Steel, *J. Org. Chem.*, **52**, 4726 (1987).
125. P.-A. Carrupt, F. Berchier and P. Vogel, *Helv. Chim. Acta*, **68**, 1716 (1985).
126. (a) F. K. Brown, K. N. Houk, D. J. Burnell and Z. Valenta, *J. Org. Chem.*, **52**, 3050 (1987).
(b) J. B. Hendrickson, A. M. Haestier, S. G. Stieglitz and B. M. Foxman, *New J. Chem.*, **14**, 689 (1990).
127. W. Fabian, *Monatsh. Chem.*, **117**, 1057 (1986).
128. A. M. Naperstkow, J. B. Macaulay, M. J. Newlands and A. G. Fallis, *Tetrahedron Lett.*, **30**, 5077 (1989).
129. W.-D. Fessner, C. Grund and H. Prinzbach, *Tetrahedron Lett.*, **30**, 3133 (1989).
130. C. J. Northcott and Z. Valenta, *Can. J. Chem.*, **65**, 1917 (1987).
131. (a) C. Siegel and E. R. Thornton, *Tetrahedron Lett.*, **29**, 5225 (1988).
(b) B. M. Trost, D. O'Krongly and J. L. Belletire, *J. Am. Chem. Ser.*, **102**, 7595 (1980).
132. M. C. Carreño, J. L. G. Ruano and A. Urbano, *Tetrahedron Lett.*, **30**, 4003 (1989).
133. J. A. Valderrama, F. Fariña and M. C. Paredes, *Synth. Commun.*, **19**, 3301 (1989).
134. F. Fariña, M. C. Paredes and V. Stefani, *Tetrahedron*, **42**, 4309 (1986).
135. F. Fariña, M. C. Paredes and V. Stefani, *J. Chem. Res. (S)*, 296 (1988).
136. K. Krohn, H. Markus, H. P. Kraemer and W. Frank, *Justus Liebigs Ann. Chem.*, 1033 (1988).
137. (a) V. Guay and P. Brassard, *Synthesis*, 294 (1987).
(b) M. E. Botha, R. G. F. Giles and S. C. Yorke, *J. Chem. Soc., Perkin Trans. 1*, 85 (1991).
138. M. Blouin, M.-C. Béland and P. Brassard, *J. Org. Chem.*, **55**, 1466 (1990).
139. B. Simoneau and P. Brassard, *Tetrahedron*, **44**, 1015 (1988).
140. L. Boisvert and P. Brassard, *J. Org. Chem.*, **53**, 4052 (1988).
141. D. W. Cameron, G. I. Feutrill and P. L. C. Keep, *Tetrahedron Lett.*, **30**, 5173 (1989).
142. J. R. Grunwell, A. Karipides, C. T. Wigal, S. W. Heinzman, J. Parlow, J. A. Surso, L. Clayton, F. J. Fleitz, M. Daffner and J. E. Stevens, *J. Org. Chem.*, **56**, 91 (1991).
143. S. H. Bell, D. W. Cameron, G. I. Feutrill, B. W. Skelton and A. H. White, *Tetrahedron Lett.*, **26**, 6519 (1985).

144. D. W. Cameron, G. I. Feutrill, G. B. Gamble and J. Stavrakis, *Tetrahedron Lett.*, **27**, 4999 (1986).
145. A. Hosomi, Y. Sakata and H. Sakurai, *Tetrahedron Lett.*, **26**, 5175 (1985).
146. N. Takeuchi, J. Ohki and S. Tobinaga, *Chem. Pharm. Bull.*, **36**, 481 (1988).
147. B. Simoneau and P. Brassard, *Tetrahedron*, **42**, 3767 (1986).
148. K. Krohn, H. Rieger, E. Broser, P. Schiess, S. Chen and T. Strubin, *Justus Liebigs Ann. Chem.*, 943 (1988).
149. H.-J. Liu and W. M. Feng, *Synth. Commun.*, **17**, 1777 (1987).
150. T. A. Engler and S. Naganathan, *Tetrahedron Lett.*, **27**, 1015 (1986).
151. T. A. Engler, S. Naganathan, F. Takusagawa and D. Yohannes, *Tetrahedron Lett.*, **28**, 5267 (1987).
152. T. A. Engler, U. Sampath, S. Naganathan, D. V. Velde and F. Takusagawa, *J. Org. Chem.*, **54**, 5712 (1989).
153. J.-E. Bäckvall, J.-E. Nyström and R. E. Nordberg, *J. Am. Chem. Soc.*, **107**, 3676 (1985).
154. J. Paquet and P. Brassard, *Can. J. Chem.*, **67**, 1354 (1989).
155. A. Dondoni, M. Fogagnolo, A. Mastellari, P. Pedrini and F. Ugozzoli, *Tetrahedron Lett.*, **27**, 3915 (1986).
156. J. Fink, G. Maas and M. Regitz, *J. Org. Chem.*, **50**, 3839 (1985).
157. M. Takada, R. Oshima, Y. Yamauchi, J. Kumanotani and M. Seno, *J. Org. Chem.*, **53**, 3073 (1988).
158. K. A. M. El-Bayouki, H. H. Moharram, A. S. El-Sayed, H. M. Hosney and M. A. Hamid, *Oriental J. Chem.*, **4**, 84 (1988).
159. S. Marinuzzi-Brosemer, B. H. Patwardhan, K. A. Greenberg and D. C. Dittmer, *Heterocycles*, **26**, 969 (1987).
160. M. Schmidt, H. Meier, H.-P. Niedermann and R. Mengel, *Chem. Ber.*, **123**, 1143 (1990).
161. R. V. Stevens and A. P. Vinogrodoff, *J. Org. Chem.*, **50**, 4056 (1985).
162. R. V. Stevens, S. R. Angle, K. Kloc, K. F. Mak, K. N. Trueblood and Y.-X. Liu, *J. Org. Chem.*, **51**, 4347 (1986).
163. C. A. Barron, N. Khan and J. K. Sutherland, *J. Chem. Soc., Chem. Commun.*, 1728 (1987).
164. A. V. R. Rao, D. R. Reddy, G. S. Annapurna and V. H. Deshpande, *Tetrahedron Lett.*, **28**, 451 (1987).
165. B. Tarnchompoo, C. Thebtaranonth and Y. Thebtaranonth, *Tetrahedron Lett.*, **28**, 6671 (1987).
166. D. Bender and K. Müllen, *Chem. Ber.*, **121**, 1187 (1988).
167. D. J. Brecknell, R. M. Carman and R. C. Schumann, *Aust. J. Chem.*, **42**, 511 (1989).
168. L. Larsen and J. K. Sutherland, *J. Chem. Soc., Chem. Commun.*, 784 (1989).
169. R. R. Al-Hamdany and A. N. Ali, *J. Iraqi Chem. Soc.*, **12**, 45 (1987).
170. D. V. Pratt and P. B. Hopkins, *J. Org. Chem.*, **53**, 5885 (1988).
171. M. A. Tius and A. Thurkauf, *Tetrahedron Lett.*, **27**, 4541 (1986).
172. K. Hayakawa, K. Kido and K. Kanematsu, *J. Chem. Soc., Chem. Commun.*, 268 (1986).
173. L. A. Paquette, M. Gugelchuk and M. L. McLaughlin, *J. Org. Chem.*, **52**, 4732 (1987).
174. R. A. Pascal, Jr. and D. Van Engen, *Tetrahedron Lett.*, **28**, 293 (1987).
175. S. P. Douglas, J. F. Sawyer and P. Yales, *Tetrahedron Lett.*, **26**, 5955 (1985).
176. P. Yates, S. P. Douglas, S. K. Datta and J. F. Sawyer, *Can. J. Chem.*, **66**, 2268 (1988).
177. H. Hart and T. Ghosh, *Tetrahedron Lett.*, **29**, 881 (1988).
178. T.-C. Chou, K. S. Chuang and C.-H. Lee, *J. Org. Chem.*, **53**, 2835 (1988).
179. A. G. Griesbeck, *Chem. Ber.*, **123**, 549 (1990).
180. G. Mehta and M. S. Nair, *J. Am. Chem. Soc.*, **107**, 7519 (1985).
181. G. Mehta, A. N. Murthy, D. S. Reddy and A. V. Reddy, *J. Am. Chem. Soc.*, **108**, 3443 (1986).
182. G. S. Ling, A. S. Zektzer, G. E. Martin, A. P. Marchand and J.-W. Jin, *J. Org. Chem.*, **53**, 2647 (1988).
183. A. P. Marchand, V. Vidyasagar, M. B. Buckner and P. O. Holman, *J. Chem. Educ.*, **64**, 642 (1987).
184. V. K. Singh, B. N. S. Raju and P. T. Deota, *Synth. Commun.*, **16**, 1731 (1986).
185. V. K. Singh, P. T. Deota and B. N. S. Raju, *Synth. Commun.*, **17**, 593 (1987).
186. W. Adam, U. Kliem, V. Lucchini, E.-M. Peters, K. Peters and H. G. von Schnering, *Chem. Ber.*, **121**, 1063 (1988).
187. M. Kawasaki, F. Matsuda and S. Terashima, *Tetrahedron*, **44**, 5727 (1988).
188. A. Hosomi, K. Otaka and H. Sakurai, *Tetrahedron Lett.*, **27**, 2881 (1986).

189. M. Wagner, W. Wohlfarth and K. Müllen, *Chimia*, **42**, 377 (1988).
190. G. Krummel and K. Müllen, *Tetrahedron Lett.*, **29**, 2809 (1988).
191. N. Martin, R. Behnisch and M. Hanack, *J. Org. Chem.*, **54**, 2563 (1989).
192. S. Askari, S. Lee, R. R. Perkins and J. R. Scheffer, *Can. J. Chem.*, **63**, 3526 (1985).
193. G. Dyker and R. P. Kreher, *Chem. Ber.*, **121**, 1203 (1988).
194. J. Luo and H. Hart, *J. Org. Chem.*, **53**, 1341 (1988).
195. W. C. Christopfel and L. L. Miller, *J. Org. Chem.*, **51**, 4169 (1986).
196. L. L. Miller, A. D. Thomas, C. L. Wilkins and D. A. Weil, *J. Chem. Soc., Chem. Commun.*, 661 (1986).
197. J. G. Smith and G. Kruger, *J. Org. Chem.*, **50**, 5759 (1985).
198. J. G. Smith, D. E. Fogg, I. J. Munday, R. E. Sandborn and P. W. Dibble, *J. Org. Chem.*, **53**, 2942 (1988).
199. A. Mukhopadhyay, S. N. Suryawanshi and D. S. Bhakuni, *Indian J. Chem., Sect. B*, **26B**, 501 (1987).
200. T. Gillmann and K. Hartke, *Chem. Ber.*, **119**, 2859 (1986).
201. A. Ghosh, S. B. Maiti, A. Chatterjee and S. R. Raychaudhuri, *Indian J. Chem., Sect. B*, **28B**, 724 (1989).
202. L. Camici, A. Ricci and M. Taddei, *Tetrahedron Lett.*, **27**, 5155 (1986).
203. J. Reisch and A. Bathe, *Justus Liebigs Ann. Chem.*, 543 (1988).
204. B. H. Lipshutz, S. L. Nguyen and T. R. Elworthy, *Tetrahedron*, **44**, 3355 (1988).
205. M. Fétizon, P. Goulaouic, I. Hanna and T. Prangé, *J. Org. Chem.*, **53**, 5672 (1988).
206. N. H. Buttrus, J. Cornforth, P. B. Hitchcock, A. Kumar and A. S. Stuart, *J. Chem. Soc., Perkin Trans. 1*, 851 (1987).
207. A. Bertsch, W. Grimme, G. Reinhardt, H. Rose and P. M. Warner, *J. Am. Chem. Soc.*, **110**, 5112 (1988).
208. P. L. M. Beckwith, E. L. Ghisalberti, P. R. Jefferies, C. L. Raston and A. H. White, *Aust. J. Chem.*, **41**, 351 (1988).
209. P. A. Wender, T. W. von Geldern and B. H. Levine, *J. Am. Chem. Soc.*, **110**, 4858 (1988).
210. F. Jordache, M. Dănilă, A. Schiketanz, M. Gheorghiu and F. Badea, *Rev. Roumaine Chim.*, **33**, 903 (1988).
211. C.-T. Lin and T.-C. Chou, *J. Org. Chem.*, **55**, 2252 (1990).
212. M. Sakaino and J. Meinwald, *Tetrahedron Lett.*, **28**, 3201 (1987).
213. M. Forte, F. Orsini, F. Pelizzoni and G. Ricca, *Gazz. Chim. Ital.*, **115**, 41 (1985).
214. B. Chenera, U. Venkitachalam, D. Ward and W. Reusch, *Tetrahedron*, **42**, 3443 (1986).
215. J. X. Shen, P. Z. Zhang and M. Qiao, *Yaoxue Xuebao*, **23**, 545 (1988); *Chem. Abstr.*, **110**, 114544a (1989).
216. U. Pindur and M. Eitel, *Helv. Chim. Acta*, **71**, 1060 (1988).
217. M. Eitel and U. Pindur, *Heterocycles*, **27**, 2353 (1988).
218. U. Pindur and H. Erfanian-Abdoust, *Justus Liebigs Ann. Chem.*, 803 (1988).
219. B. Saroya and P. C. Srinivasan, *Synthesis*, 748 (1986).
220. W. E. Noland and R. J. Sundberg, *J. Org. Chem.*, **28**, 884 (1963).
221. G. Yamamoto and M. Oki, *Chem. Lett.*, 2181 (1987).
222. N. Kitaguchi, *Bull. Chem. Soc. Jpn.*, **62**, 800 (1989).
223. G. Mehta and S. R. Karra, *J. Org. Chem.*, **54**, 2975 (1989).
224. K. Blatter, A.-D. Schlüter and G. Wegner, *J. Org. Chem.*, **54**, 2396 (1989).
225. S. Nishida, M. Murakami, H. Oda, T. Tsuji, T. Mizuno, M. Matsubara and N. Kikai, *J. Org. Chem.*, **54**, 3859 (1989).
226. F. Kienzle, J. Stadlwieser and I. Mergelsberg, *Helv. Chim. Acta*, **72**, 348 (1989).
227. F. Kienzle, I. Mergelsberg, J. Stadlwieser and W. Arnold, *Helv. Chim. Acta*, **68**, 1133 (1985).
228. Y. S. Kulkarni and B. B. Snider, *Org. Prep. Proced. Int.*, **18**, 7 (1986).
229. G. Bold, S. Chao, R. Bhide, S.-H. Wu, D. V. Patel, C. J. Sih and C. Chidester, *Tetrahedron Lett.*, **28**, 1973 (1987).
230. P. J. Garratt and A. Tsotinis, *Tetrahedron Lett.*, **27**, 2761 (1986).
231. J.-M. Fang, C.-C. Yang and Y.-W. Wang, *J. Org. Chem.*, **54**, 477 (1989).
232. N. Takeuchi, J. Ohki and S. Tobinaga, *Chem. Pharm. Bull.*, **36**, 481 (1988).
233. D. L. Flynn and D. E. Nies, *Tetrahedron Lett.*, **27**, 5075 (1986).
234. G. H. Jones, M. C. Venuti, J. M. Young, D. V. K. Murthy, B. E. Loe, R. A. Simpson, A. H.

Berks, D. A. Spires, P. J. Maloney, M. Kruseman, S. Rouhafza, K. C. Kappas, C. C. Beard, S. H. Unger and P. S. Cheung, *J. Med. Chem.*, **29**, 1504 (1986).
235. G. A. Kraus, J. Shi and D. Reynolds, *J. Org. Chem.*, **55**, 1105 (1990).
236. K. T. Potts, D. Bhattacharjee and E. B. Walsh, *J. Org. Chem.*, **51**, 2011 (1986).
237. K. T. Potts, E. B. Walsh and D. Bhattacharjee, *J. Org. Chem.*, **52**, 2285 (1987).
238. M. Chigr, H. Fillion and A. Rougny, *Tetrahedron Lett.*, **29**, 5913 (1988).
239. M. Shepherd, *J. Chem. Soc., Perkin Trans. 1*, 1495 (1986).
240. A. McKillop and S. P. Brown, *Synth. Commun.*, **17**, 657 (1987).
241. G. A. Tolstikov, E. E. Shul'ts and G. F. Vafina, *Zh. Org. Khim.*, **25**, 2249 (1989); *Chem. Abstr.*, **113**, 6126u (1990).
242. P. S. Waterman, J. E. Belmonte, T. E. Bauch, P. A. Belmonte and W. P. Giering, *J. Organomet. Chem.*, **294**, 235 (1985).
243. M. Taddei and A. Mann, *Tetrahedron. Lett.*, **27**, 2913 (1986).
244. G. S. Bates, M. D. Fryzuk and C. Stone, *Can. J. Chem.*, **65**, 2612 (1987).
245. U. Kuckländer and U. Henze, *Arch. Pharm. (Weinheim)*, **317**, 394 (1984).
246. Y.-O. Liang, P. M. Plotsky and R. N. Adams, *J. Med. Chem.*, **20**, 581 (1977).
247. (a) U. Kuckländer and U. Bastian, *Z. Naturforsch.*, **42b**, 1567 (1987).
(b) U. Kuckländer and U. Bastian, *Arch. Pharm. (Weinheim)*, **322**, 213 (1989).
248. U. Kuckländer and K. Kuna, *Arch. Pharm. (Weinheim)*, **320**, 677 (1987).
249. (a) U. Kuckländer, H. Töberich and K. Kuna, *Arch. Pharm. (Weinheim)*, **320**, 308 (1987).
(b) U. Kuckländer, H. Töberich and K. Kuna, *Arch. Pharm. (Weinheim)*, **320**, 312 (1987).
250. U. Kuckländer and B. Schneider, *Chem. Ber.*, **119**, 3487 (1986).
251. U. Kuckländer and B. Schneider, *Chem. Ber.*, **121**, 577 (1988).
252. (a) U. Kuckländer, U. Herweg-Wahl, W. Massa and G. Baum, *Chem. Ber.*, **120**, 1791 (1987).
(b) U. Kuckländer and K. Kuna, *Arch. Pharm. (Weinheim)*, **322**, 183 (1989).
253. (a) U. Kuckländer, U. Herweg-Wahl, W. Poll and L. Rickerich, *Chem. Ber.*, **121**, 1841 (1988).
(b) U. Kuckländer, U. Herweg-Wahl, K. Kuna and A. Steigel, *Arch. Pharm (Weinheim)*, **324**, 11 (1991).
(c) U. Kuckländer, K. Kuna, B. Schneider, A. Steigel and B. Mayer, *Chem. Ztg.*, in press.
254. L. Kozerski and Z. Urbanczyk-Lipkowska, *Bull. Pol. Acad. Sci. Chem.*, **32**, 159 (1984).
255. L. Kozerski, *J. Mol. Struct.*, **75**, 95 (1981).
256. L. Kozerski, *Magn. Reson. Chem.*, **23**, 988 (1985).
257. U. Kuckländer and K. Kuna, *Chem. Ber.*, **120**, 1601 (1987).
258. (a) U. Kuckländer, P. Ulmer, K. Kuna and H. Töberich, *Chem. Ber.*, **122**, 209 (1989).
(b) U. Kuckländer, U. Herweg-Wahl and K. Kuna, *Arch. Pharm (Weinheim)*, **324**, 7 (1991).
(c) U. Kuckländer, P. Ulmer and G. Zerta, *Chem. Ber.*, **122**, 1493 (1989).
(d) U. Kuckländer, K. Kuna, G. Zerta and W. Poll, *Z. Naturforsch. B*, in press.
259. M. Palaghită and D. Răileanu, *Rev. Roumaine Chim.*, **33**, 953 (1988).
260. M. Yokoyama, S. Watanabe and H. Hatanaka, *Synthesis*, 846 (1987).
261. H. Takahata, A. Anazawa, K. Moriyama and T. Yamazaki, *J. Chem. Soc., Perkin Trans. 1*, 1501 (1987).
262. C. H. Nguyen and E. Bisagni, *Tetrahedron*, **43**, 527 (1987).
263. L. Birkofer and W. Quittmann, *Chem. Ber.*, **119**, 257 (1986).
264. T. Mukaiyama, Y. Sagawa and S. Kobayashi, *Chem. Lett.*, 2169 (1987).
265. Y. Sagawa, S. Kobayashi and T. Mukaiyama, *Chem. Lett.*, 1105 (1988).
266. R. Grigg, H. Q. N. Gunaratne and V. Sridharan, *Tetrahedron*, **43**, 5887 (1987).
267. T. Oshima and T. Nagai, *Tetrahedron Lett.*, **26**, 5317 (1985).
268. T. Oshima and T. Nagai, *Bull. Chem. Soc. Jpn.*, **61**, 2507 (1988).
269. T. Oshima and T. Nagai, *Bull. Chem. Soc. Jpn.*, **62**, 2580 (1989).
270. Y. Nakano, M. Hamaguchi and T. Nagai, *J. Org. Chem.*, **54**, 1135 (1989).
271. A. Padwa (Ed.), *1,3-Dipolar Cycloaddition Chemistry*, Vols. 1 and 2, Wiley–Interscience, New York, 1984.
272. A. Padwa, Y.-Y. Chen, W. Dent and H. Nimmesgern, *J. Org. Chem.*, **50**, 4006 (1985).
273. A. Padwa and D. C. Dean, *J. Org. Chem.*, **55**, 405 (1990).
274. A. G. Schultz, W. G. McMahon, R. R. Staib and R. K. Kullnig, *Tetrahedron Lett.*, **28**, 4929 (1987).
275. A. G. Schultz, W. G. McMahon and R. K. Kullnig, *J. Org. Chem.*, **52**, 3905 (1987).

276. M. Sahu, J. K. Sahu and A. Nayak, *Indian J. Chem., Sect. B*, **25B**, 1266 (1986).
277. S. Nan'ya, K. Katsuraya, E. Maekawa, K. Kondo and S. Eguchi, *J. Heterocycl. Chem.*, **24**, 971 (1987).
278. M. F. Aldersley, F. M. Dean and B. E. Mann, *J. Chem. Soc., Perkin Trans. 1*, 2217 (1986).
279. Y. Tamura, M. Sasho, S. Akai, A. Wada and Y. Kita, *Tetrahedron*, **40**, 4539 (1984).
280. Y. Tamura, M. Kirihara, J. Sekihachi, R. Okunaka, S. Mohri, T. Tsugoshi, S. Akai, M. Sasho and Y. Kita, *Tetrahedron Lett.*, **28**, 3971 (1987).
281. R. Benn, G. Gabor, P. W. Jolly, R. Mynott and B. Raspel, *J. Organomet. Chem.*, **296**, 443 (1985).
282. T. A. Engler, K. D. Combrink and J. E. Ray, *J. Am. Chem. Soc.*, **110**, 7931 (1988).
283. T. A. Engler, K. D. Combrink and F. Takusagawa, *J. Chem. Soc., Chem. Commun.*, 1573 (1989).
284. M. A. Brimble, J. J. Gibson, R. Baker, M. T. Brimble, A. A. Kee and M. J. O'Mahony, *Tetrahedron Lett.*, **28**, 4891 (1987).
285. K. C. Joshi, V. N. Pathak and R. Gupta, *J. Fluorine Chem.*, **38**, 153 (1988).
286. Y. Omote, A. Tomotake and C. Kashima, *J. Chem. Res. (S)*, 10 (1987).
287. R. Cassis, M. Scholz, R. Tapia and J. A. Valderrama, *Tetrahedron Lett.*, **26**, 6281 (1985).
288. N. Farfán, E. Ortega and R. Contreras, *J. Heterocycl. Chem.*, **23**, 1609 (1986).
289. A. P. Kozikowski and Y. Xia, *J. Org. Chem.*, **52**, 1375 (1987).
290. V. Guay and P. Brassard, *J. Natural Products*, **49**, 122 (1986).
291. J. Lee, J. Tang and J. K. Snyder, *Tetrahedron Lett.*, **28**, 3427 (1987).
292. T. C. McKenzie, W. Hassen and S. J. F. Macdonald, *Tetrahedron Lett.*, **28**, 5435 (1987).
293. S. J. F. Macdonald, T. C. McKenzie and W. D. Hassen, *J. Chem. Soc., Chem. Commun.*, 1528 (1987).
294. W.-B. Kang, S. Nan'ya, T. Toru and Y. Ueno, *Chem. Lett.*, 1415 (1988).
295. S. Nan'ya, T. Tange, E. Maekawa and Y. Ueno, *J. Heterocycl. Chem.*, **23**, 1267 (1986).
296. Y. Naruta, Y. Nishigaichi and K. Maruyama, *J. Org. Chem.*, **53**, 1192 (1988).
297. M. S. Rao, V. R. Rao and T. V. P. Rao, *Sulfur Lett.*, **4**, 19 (1985).
298. C. D. Okafor and U. C. Okoro, *Dyes and Pigments*, **9**, 427 (1988).
299. H. Nishi, T. Furukawa and K. Kitahara, *Nippon Kagaku Kaishi*, 522 (1984); *Chem. Abstr.*, **101**, 38414e (1984).
300. H. Nishi, S. Minami and K. Kitahara, *J. Heterocycl. Chem.*, **26**, 875 (1989).
301. A. K. El-Shafei and A. M. El-Sayed, *Rev. Roumaine Chim.*, **33**, 291 (1988).
302. B. Wladislaw, *Phosphorous Sulfur*, **33**, 173 (1987).
303. A. Codoñer, I. S. Monzó, J. Palou and R. Valero, *J. Chem. Soc., Perkin Trans. 2*, 221 (1988).
304. (a) I. S. Monzó, J. Palou, J. Roca and R. Velero, *J. Chem. Soc., Perkin Trans. 2*, 1995 (1988).
(b) H. S. Randhawa, R. Sachdeva and S. K. Suri, *Z. Phys. Chem. (Leipzig)*, **27**, 189 (1990).
305. M. Krishnamurthy, K. S. Babu and U. Muralikrishna, *Indian J. Chem., Sect. A*, **27A**, 669 (1988).
306. U. Muralikrishna and M. Krishnamurthy, *Indian J. Chem., Sect. A*, **25A**, 949 (1986).
307. H.-J. Kallmayer, *Pharm. Acta Helv.*, **62**, 2 (1987).
308. H.-J. Kallmayer and W. Fritzen, *Arch. Pharm. (Weinheim)*, **320**, 769 (1987).
309. H.-J. Kallmayer, *Pharm. Acta Helv.*, **63**, 242 (1988).
310. L. Yu and L. R. Dalton, *J. Am. Chem. Soc.*, **111**, 8699 (1989).
311. S. Zhang, J. Earle, J. MacDiarmid and T. J. Bardos, *J. Med. Chem.*, **31**, 1240 (1988).
312. B. Horowska, Z. Mazerska, A. Ledochowski, G. Cristalli, P. Franchetti and S. Martelli, *Eur. J. Med. Chem.*, **23**, 91 (1988).
313. A. Dzielendziak and J. Butler, *Synthesis*, 643 (1989).
314. D. Al-Sammerral and Z. S. Sallh, *J. Chem. Eng. Data*, **32**, 390 (1987).
315. D. Al-Sammerral and F. Al-Sammerral, *J. Chem. Eng. Data*, **33**, 70 (1988).
316. D. Al-Sammerral and Z. S. Salih, *Indian J. Chem., Sect. B*, **26B**, 180 (1987).
317. D. V. Rao, V. V. R. Rao, J. P. Rao and B. Subrahamaniyam, *Indian J. Pharm. Sci.*, **48**, 37 (1986).
318. M. S. Rao, V. R. Rao and T. V. P. Rao, *Indian J. Chem., Sect. B*, **28B**, 178 (1989).
319. P. Bruni, G. Tosi and G. Valle, *J. Chem. Soc., Chem. Commun.*, 1022 (1988).
320. R. N. Khanna, K. P. Singh, S. K. Yadav and S. Srinivas, *Synth. Commun.*, **19**,3151 (1989).
321. O. Reinaud, P. Capdevielle and M. Maumy, *Tetrahedron*, **43**, 4167 (1987).
322. O. Reinaud, P. Capdevielle and M. Maumy, *Synthesis*, 293 (1988).
323. O. Reinaud, P. Capdevielle and M. Maumy, *Tetrahedron Lett.*, **28**, 4675 (1987).
324. A. H. M. Renfrew, *J. Soc. Dyers Colour.*, **105**, 262 (1989).

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