The Chemistry of The Hydroxyl Group: Part 1
Edited by Saul Patai

The chemistry of
the hydroxyl group

THE CHEMISTRY OF FUNCTIONAL GROUPS

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The chemistry of the hydroxyl group

Edited by

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Foreword

The present volume of the series 'The Chemistry of the Functional Groups' is again organized according to the general plan as described in the Preface to the series, printed on the following pages.

Only one of the originally planned chapters did not materialize, that on 'Oxidation and Reduction of Alcohols'.

Jerusalem, March 1970 SAUL PATAI

The Chemistry of the Functional Groups
Preface to the series

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

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

With these restrictions, it is realized that no plan can be devised for a volume that would give a *complete* coverage of the subject with *no* overlap between chapters, while at the same time preserving the read-

ability of the text. The Editor set himself the goal of attaining *reasonable* coverage with *moderate* overlap, with a minimum of cross-references between the chapters of each volume. In this manner, sufficient freedom is given to each author to produce readable quasi-monographic chapters.

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

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

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

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

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

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

This plan entails that the breadth, depth and thought-provoking

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

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

The Chemistry of the Alkenes (*published in two volumes*)
The Chemistry of the Carbonyl Group (*published in two volumes*)
The Chemistry of the Ether Linkage (*published*)
The Chemistry of the Amino Group (*published*)
The Chemistry of the Nitro and the Nitroso Group (*published in two parts*)
The Chemistry of Carboxylic Acids and Esters (*published*)
The Chemistry of the Carbon–Nitrogen Double Bond (*published*)
The Chemistry of the Cyano Group (*published*)
The Chemistry of the Amides (*published*)
The Chemistry of the Hydroxyl Group (*published in two parts*)
The Chemistry of the Carbon–Halogen Bond (*in preparation*)
The Chemistry of Carbonyl Halides (*in preparation*)
The Chemistry of the Azido Group (*in preparation*)
The Chemistry of the Carbon–Carbon Triple Bond
The Chemistry of Imidoates and Amidines
The Chemistry of the Thiol Group
The Chemistry of the Quinonoid Compounds
The Chemistry of the Hydrazo, Azo and Azoxy Groups
The Chemistry of the SO, —SO_2, —SO_2H and —SO_3H Groups
The Chemistry of the —OCN, —NCO and —SCN Groups
The Chemistry of the —PO_3H_2 and Related Groups

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 started, let alone continued, without the support of many persons. First and foremost among these is Dr. Arnold Weissberger, whose reassurance and trust encouraged me to tackle this task, and who continues to help and

advise me. The efficient and patient cooperation of several staff-members of the Publisher also rendered me invaluable aid (but unfortunately their code of ethics does not allow me to thank them by name). Many of my friends and colleagues in Jerusalem helped me in the solution of various major and minor matters, and my thanks are due especially to Prof. Y. Liwschitz, Dr. Z. Rappoport and Dr. J. Zabicky. Carrying out such a long-range project would be quite impossible without the non-professional but none the less essential participation and partnership of my wife.

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CHAPTER 1

Theoretical aspects of the chemistry of the hydroxyl group

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I. INTRODUCTION

A. A Density Approach to Chemical Binding

This chapter is concerned with the quantum mechanical prediction and interpretation of the properties of the hydroxyl group as a radical, as an ion, either positively or negatively charged, or as a functional group. The theoretical description of the electronic structure is given in terms of molecular orbital theory and all quantitative results are based on self-consistent field (SCF) calculations at or near the Hartree–Fock limit. The results of such calculations are known to yield good representations of molecular charge distributions and in this chapter the attempt is made to relate the chemistry of the hydroxyl group directly to the properties of the spatial distribution of electronic charge in the molecule.

The molecular charge distribution describes the manner in which the electronic charge is distributed throughout real space. Thus the properties of a system may be given a direct *physical* description and interpretation when they are related to the charge distribution. A discussion of the properties in terms of the spatial details of the wavefunction ψ does not yield a direct physical picture because of the multidimensional nature of the wavefunction for a many-electron system.

The function ψ for an N-electron system is a function of the space and spin coordinates of all the electrons. The instantaneous *simultaneous* probability of each electron being in some particular small region of space with a given spin is given by the product

$$\psi^*\psi \, d\tau_1 \, d\tau_2 \ldots d\tau_i \ldots d\tau_N$$

where $d\tau_i$ denotes both an infinitesimal volume element in the space of electron i and a definite spin component either α or β. The integration of this product over *all* the spins (thereby changing each $d\tau_i$ into a spatial volume element dx_i) and over the spatial coordinates of all the electrons but one, say electron 1,

$$dx_1 \int \psi^*\psi \, dx_2 \, dx_3 \ldots dx_N \tag{I-1}$$

yields a function which describes the probability of finding one of the electrons in some particular region of its cartesian space; i.e., it yields a single-electron probability distribution in three-dimensional space. Since all N electrons are equivalent and indistinguishable, a consequence of the antisymmetry requirements imposed on ψ by the Pauli exclusion principle, the *total* probability of finding negative charge in a given region of space is N times the one-electron probability given in equation (I-1)

$$dx_1 \, N \int \psi^*\psi \, dx_2 \, dx_3 \ldots dx_N \tag{I-2}$$

The three-dimensional distribution function $\rho(x)$

$$\rho(x) = N \int \psi^*\psi \, dx_2 \, dx_3 \ldots dx_N \tag{I-3}$$

is the total electronic charge density or total electronic charge distribution, a function in three-dimensional space.

The charge distribution $\rho(x)$ determines all of the electrical moments of the system (dipole, quadrupole, etc., and fields and field gradients at the positions of the nuclei). The charge distribution also determines the 'size' and 'shape' of a molecule in its nonbonded

interactions with other systems, and is responsible for the scattering observed in X-ray and electron diffraction experiments. Electron and X-ray diffraction results provide in principle a method for the experimental determination of molecular charge distributions. Reviews of such attempts, mainly in the field of X-ray crystallography, have been given by Brill[1] and by O'Connell, Rae and Maslen[2]. Kohl and Bartell[3, 4] have reported electron diffraction results for small-angle scattering on gas phase molecules which suggest that electron scattering techniques now in development should be able to provide information about the charge distribution of the bonding electrons.

Hohenberg and Kohn[5] have presented a theorem which shows that in principle even the energy of the system may be expressed as a function of the charge distribution. The function $\rho(x)$ therefore contains all the information necessary for a complete physical description of a system.

The increase in our understanding and prediction of chemical phenomena may be related to the increase in our understanding of how the electronic charge is distributed in a molecule and of how these distributions change during a chemical reaction. Concepts such as ionic-covalent character and electronegativity[6] are outstanding examples of earlier attempts to determine empirically how the total charge is partitioned between the atomic components of a molecular system. With the advent of relatively good quantum mechanical calculations, we are now able to determine and relate chemical phenomena to the actual distribution of charge throughout three-dimensional space.

In addition to its use in the direct calculation of physical properties, the charge distribution may be analysed in terms of the total amount of charge which is found in different regions of space, for example, the amount of charge in the 'binding region' between the nuclei, or in the regions normally pictured as occupied by 'lone pairs'. Related to the total density maps are the *density difference* maps which are obtained by subtracting the density distributions of the constituent atoms from the total molecular density. Such maps provide a picture of the redistribution of charge which results in the formation of a chemical bond. The density difference maps show patterns which are characteristic of and distinct for limiting types of bonds ionic and covalent[7]. The density and density-difference maps can therefore serve as the basis for definitions of distinct bond types.

The physical picture provided by the charge distribution may be carried even further through the use of the Hellmann–Feynman

theorem which relates in a rigorous manner the forces acting on the nuclei to the distribution of charge in the molecule[8, 9]. Because of the essentially classical nature of the connexion between the forces and the electronic charge distribution, a study of the forces exerted on the nuclei can provide a physical basis for the interpretation of chemical binding.

Since the results which follow lean so heavily on Hartree–Fock wavefunctions, a brief discussion of the ultimate accuracy and limitations of these functions is given in the following section.

B. Hartree–Fock Wavefunctions

A Hartree–Fock wavefunction is by definition the best possible single determinantal wavefunction for a system. Such a wavefunction consists of an antisymmetrized product of one-electron functions, the orbitals. The antisymmetrization of the wavefunction is a necessary consequence of the Pauli principle and has the result of correlating the motions of electrons with identical spins. The motions of electrons with different spins are, however, completely uncorrelated because the probability function for all such pairs of electrons is given simply as a product of the individual probabilities, i.e., the electrons act independently. For this reason the difference between the true energy of the system and that predicted by the Hartree–Fock wavefunction is called the correlation energy[10]. (There is also a correction for the neglected relativistic effects but these are very small for atoms in the first two rows of the Periodic Table.)

The orbitals are obtained as solutions to the Hartree–Fock equations*

$$\left[-\tfrac{1}{2}\nabla_1^2 - \sum_\alpha \frac{Z_\alpha}{r_{1\alpha}}\right]\mu_i(x_1) + \left[\sum_j \int \mu_j^*(x_2)\frac{1}{r_{12}}\mu_j(x_2)\,d\tau_2\right]\mu_i(x_1) - \sum_j\left[\int \mu_j(x_2)\frac{1}{r_{12}}\mu_i(x_2)\,d\tau_2\right]\mu_j(x_1) = \varepsilon_i\mu_i(x_1) \quad \text{(I-4)}$$

there being one such equation for each spin-orbital μ_i, i.e., a space orbital ϕ_i multiplied by an α or β spin function. For a closed-shell system of N electrons there will be $N/2$ occupied and distinct space orbitals. The summations in equation (I-4) are over all N of the occupied spin-orbitals.

The first bracketed term in equation (I-4) represents the kinetic

* Atomic units are used throughout this chapter: length, 1 au $= a_0 = 0{\cdot}52917$ Å; energy, 1 au $= e^2/a_0 = 6{\cdot}2771 \times 10^2$ kcal/mole; force, 1 au $= e^2/a_0^2 = 8{\cdot}2377 \times 10^{-3}$ dynes; charge density, 1 au $= e/a_0^3 = 6{\cdot}749\, e^-/\text{Å}^3$.

energy and the potential energy in the field of the nuclei of an electron in the orbital μ_i. The summation $\sum_j \mu_j^*(x_2)\mu_j(x_2)$ in the second term, called the coulomb term, represents the *total* electronic charge density at each point in space, and the integral of this quantity over the operator $1/r_{12}$ gives the repulsive field exerted on the electron in μ_i by the total charge distribution (including a contribution from the electron in μ_i). The third bracketed term, the exchange term, arises from the antisymmetry conditions imposed on the wave-function, and is different from zero only for those spin-orbitals possessing the same spin as μ_i. This term removes all contributions to the total repulsive field experienced by the electron in μ_i at the position x_1 from other electrons with the same spin as that of the electron in μ_i. The exchange charge density when integrated over all space yields one electronic charge and hence its presence in equation (I-4) decreases the total number of electronic charges exerting a repulsive force on the electron in μ_i by unity. The exchange term may, therefore, be interpreted as providing a correction to the coulomb term which includes a contribution from the electron in μ_i exerting a repulsive force on itself[11].

Equation (I-4) replaces the actual instantaneous repulsions between pairs of electrons by an average interaction, one which describes each electron separately interacting with the average field of the remaining electrons. The exchange term effectively correlates the motions of electrons with parallel spins by removing from the immediate vicinity of a given electron all charge density arising from electrons with similar spin. The same electron, however, experiences only the average field exerted by electrons with opposite spin, and this is the origin of the so-called correlation error in the total energy.

The total energy of the system in terms of the orbital energies ε_i is

$$E = \sum \varepsilon_i - \sum_{i<j} \{[ii|jj] - [ij|ji]\} \qquad \text{(I-5)}$$

where the terms in square brackets represent the coulomb and exchange integrals respectively.

Equation (I-4) for the one-electron orbital energies is derived by demanding that the functions μ_i give the *lowest possible energy* for the system. This particular set of orbitals, the Hartree–Fock orbitals, provide the best one-electron approximation to the system. A set of N equations of the form I-4 are too involved to solve directly, since the solution of each equation demands a knowledge of the solutions for the remaining $(N - 1)$ equations. This is a consequence of the

fact that the average field exerted by the remaining $(N - 1)$ electrons as expressed by coulomb and exchange terms is known only when all the remaining μ_i are known.

To overcome this difficulty Roothaan[12] has devised a self-consistent field method for solving the Hartree–Fock equations for a system based on the expansion of each μ_i in terms of a linear combination of much simpler functions[13]. The set of simpler functions, called the basis set, is finite in number and usually consists of Slater or Gaussian type atomic orbitals centred on the various nuclei in the molecule.

The SCF equations of Roothaan may be solved for a basis set containing only $\sim N$ distinct atomic orbitals for an N-electron problem. While the molecular orbitals obtained from such a minimal size basis set are self-consistent, they are poor approximations to the true Hartree–Fock orbitals. Only by including a large number of atomic orbitals in the basis set can the expansion be made flexible enough adequately to describe the Hartree–Fock molecular orbitals. Ideally the Hartree–Fock result represents the limiting case of an expansion in terms of an infinite basis set. However, experience has shown that the Hartree–Fock limit may be reached for all practical purposes using basis sets of reasonable size. For example, the basis set required to approximate the Hartree–Fock orbitals for the OH radical[14] to an accuracy of about 0·001 consisted of 24 Slater type orbitals (STO's) with the following composition: centred on oxygen, two $1s$, two $2s$, four $2p\sigma$ and four $2p\pi$, two $3d\sigma$ and one $3d\pi$, one $4f\sigma$ and one $4f\pi$; and centred on hydrogen, two $1s$, one $2s$, one $2p\sigma$ and one $2p\pi$.

Our primary use of the Hartree–Fock results will be to obtain molecular charge distributions. With regard to this use, there is a very important theorem which can be proved for a Hartree–Fock wavefunction. The theorem itself is due to Brillouin[15] and, as a consequence of this theorem, we can show that the charge density and its dependent properties obtained from a Hartree–Fock wavefunction are correct up to the second-order. (The interested reader is referred to Ref. 16 for a discussion of this theorem which is relevant to the calculation of charge distributions.) Thus we may expect the Hartree–Fock charge distribution (a one-electron property) and the properties determined by the charge distribution to be relatively insensitive to the correlation error (a property of the two-electron probability distribution) inherent in the Hartree–Fock wavefunction. To test this assumption we have listed in Table I-1 the

TABLE I-1. A comparison of experimental and Hartree–Fock results[a].

Molecule	Term	μ (Debyes)		Forces on nuclei		D_e[b] (e.v.)		R_e (au)		ω_e (cm^{-1})	
		Calc.	Exp.	on proton	on heavy nucleus	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.
LiH	$X^1\Sigma^+$	−6·002	−5·882	−0·003	−0·002	1·49	2·52	3·034	3·015	1433	1406
CH	$X^2\Pi_r$	1·570	1·46	−0·014	−0·053	2·47	3·65	2·086	2·124	3053	2869
OH	$X^2\Pi_i$	1·780	1·660	−0·024	−0·074	3·03	4·63	1·795	1·8343	4062	3735
HF	$X^1\Sigma^+$	1·942	1·8195	−0·026	−0·075	4·38	6·12	1·696	1·7328	4469	4139
NaH	$X^1\Sigma^+$	−6·962	—	+0·0002	−0·582	0·932	2·3	3·617	3·566	1187	1172
HCl	$X^1\Sigma^+$	1·197	1·12	−0·0108	+0·1833	3·48	4·616	2·389	2·4087	3181	2990
H_2O	X^1A_1	1·955	1·85	+0·002	+0·080	6·80	9·49				

[a] The calculated and experimental data for the diatomic hydrides are from Ref. 14 and for H_2O from Ref. 17.

[b] These are 'rationalized' dissociation energies calculated by subtracting the Hartree–Fock estimate of the molecular energy from the Hartree–Fock estimate of the energy of the atoms. By this method a large fraction of the correlation error in D_e is cancelled. Only the *change* in the correlation energy in passing from the molecule to the dissociated atoms remains in the estimate of D_e.

values of the dipole moments and forces acting on the nuclei calculated from Hartree–Fock wavefunctions for a number of hydride molecules. In addition to the one-electron properties just cited we have also included calculated values of some energy quantities and spectroscopic constants. The values of the one-electron properties are indeed in good agreement with experiment, the dipole moments exhibiting an average error of about 0·12 Debyes and the forces on the nuclei which should be zero at the equilibrium bond length, indicating only slight departures from electrostatic equilibrium. Brillouin's theorem holds strictly only for closed-shell molecules but the calculated properties of the open-shell systems included in Table I-1, OH and CH, do not exhibit any sudden deterioration in quality.

The electronic contribution to the dipole moment is determined primarily by the spatial details of the charge distribution in its outer regions while the forces are most sensitive to the properties of the charge distribution in regions close to the nuclei. While the dipole moment and the forces offer tests of different moments of the charge distribution, they are still averages over the complete distribution. A test of the accuracy of the actual spatial distribution of charge predicted by a Hartree–Fock wavefunction can be made only by comparing the distribution with one obtained from a more extended calculation. Such comparisons have been made for H_2 and Li_2 [18], using the wavefunctions of Das and Wahl[19] which yield a large fraction of the correlation energy. It was concluded that no noticeable error is introduced when a Hartree–Fock density distribution is used to portray the molecular charge distribution. In the case of Li_2 a plot of the difference density distribution between the extended and the Hartree–Fock results yielded no values greater than 1×10^{-4} au, a number smaller by a factor of 20 than the outer contours used to determine the nonbonded sizes of molecules.

The data in Table I-1 indicate that while the correlation error is appreciable for the energy (a quantity directly determined by the two-electron probability distribution) it is much less significant for the one-electron charge distribution and its dependent properties.

II. A STUDY OF THE O–H BOND IN OH^+, $OH^\cdot$ AND OH^-

A. The Molecular Charge Distributions

The introductory discussion of the electronic structure of the hydroxyl group will be concerned with the molecular charge distri-

butions and mechanism of binding of the proton in the diatomic species OH^+, $OH^\cdot$ and OH^-.

The molecular orbital configurations and ground state symmetries for these molecules are

$$\begin{array}{ll} OH^+ & 1\sigma^2 2\sigma^2 3\sigma^2 1\pi^2;\ {}^3\Sigma^- \quad ({}^1\Delta,\ {}^1\Sigma^+) \\ OH^\cdot & 1\sigma^2 2\sigma^2 3\sigma^2 1\pi^3;\ {}^2\Pi \\ OH^- & 1\sigma^2 2\sigma^2 3\sigma^2 1\pi^4;\ {}^1\Sigma^+ \end{array}$$

The hydroxide ion possesses a closed-shell electronic structure and hence a singlet, symmetric ground state. The radical $OH^\cdot$ possesses both orbital and spin degeneracy. The half-filled π configuration in OH^+ results in three distinct states, ${}^3\Sigma^-$, ${}^1\Delta$ and ${}^1\Sigma^+$. To first-order the energies of these states differ because of different contributions from the repulsive energies between the electrons. The state of highest multiplicity, the ${}^3\Sigma^-$ state, is lowest in energy. Certain energy values and other physical characteristics of these molecules are listed in Table II-1. The bond strengths, with respect to the appropriate separated atom or ion states, decrease in the order OH^-, $OH^\cdot$, OH^+, and the bond lengths increase in the same order.

TABLE II-1. Physical properties of OH^+, $OH^\cdot$ and OH^- *.

AH	Term	R_e (au)	D_e (ev)	Electron affinity (ev)	Ionization potential (ev)	ω_e (cm^{-1})
OH^+	$X^3\Sigma^-$	1·944	(>4·4)			
$OH^\cdot$	$X^2\Pi$	1·8342	4·63	1·83	13·36	3735·2
OH^-	$X^1\Sigma^+$	(1·81)	(>3·48)			(3773)

* Data from P. E. Cade. *J. Chem. Phys.*, **47**, 2390 (1967).

The total molecular charge distributions for the OH species are shown in Figure 1 in the form of contour maps in the plane of the nuclei*. Bader, Keaveny and Cade[20] have presented an interpretation of the binding in the first-row neutral diatomic hydrides based upon the molecular charge distribution and the forces which it exerts on the nuclei. On this basis the binding in LiH is classified as ionic and that in BH → HF as covalent. The binding in BeH is

* The Hartree–Fock wavefunctions used to calculate the charge densities were obtained from P. E. Cade and W. Huo, *J. Chem. Phys.*, **47**, 614 (1967) for $OH(X^2\Pi_i)$, $CH(X^2\Pi_r)$ and $LiH(X^1\Sigma^+)$; unpublished wavefunctions of P. E. Cade were employed for $OH^-(X^1\Sigma^+)$ and $OH^+({}^3\Sigma^-)$.

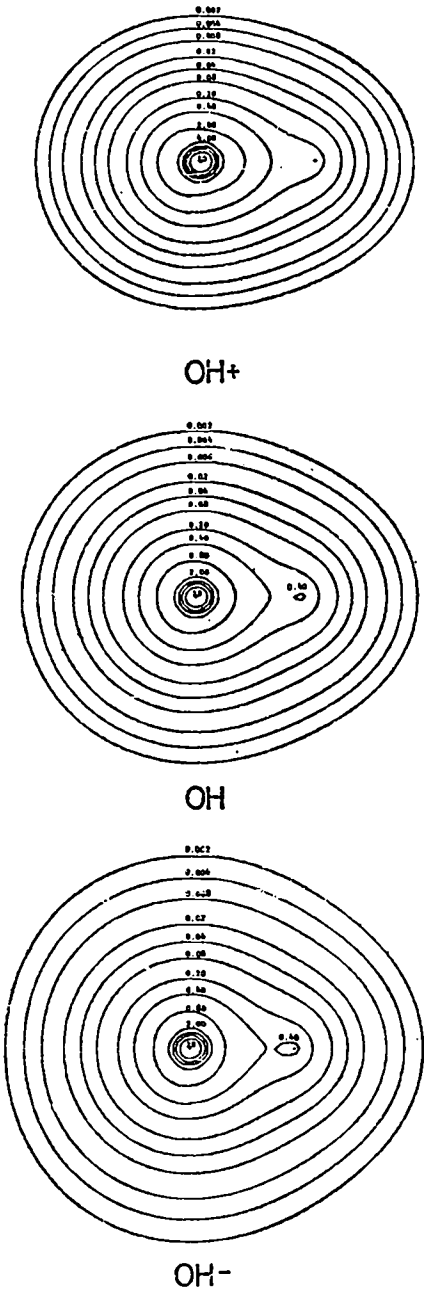
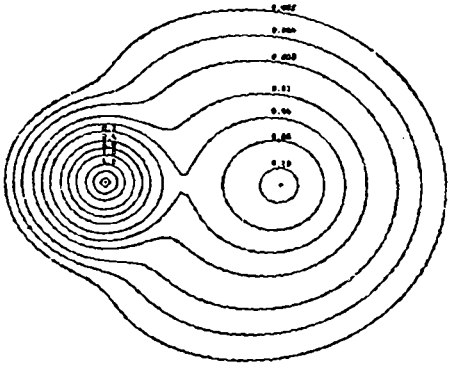
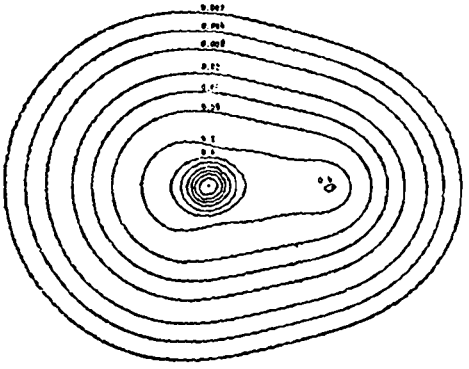


FIGURE 1. Contour maps of the total molecular charge distributions of diatomic hydrides in their electronic ground states. The proton is represented by the dot on the right-hand side in each contour map.



LiH



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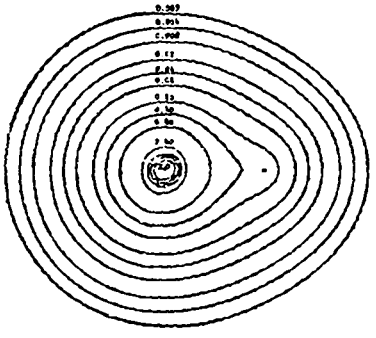


HF

Figure 1 continued

transitional between the limiting classifications ionic and covalent. Comparative studies play an important role in our understanding of chemistry and for this reason the charge distributions of LiH, CH and HF are also displayed in Figure 1. The charge distribution in LiH provides an example of the extreme localization of the valence charge density which does occur in ionic binding. The properties of the charge distributions of CH and HF bracket those of OH• and provide gauges for measuring the extent of charge reorganization when an electron is added to or removed from the neutral OH• species.

The valence charge density becomes increasingly diffuse through the series $OH^+ \rightarrow OH^-$ with an accompanying increase in the amount of charge density in the region of the proton. The outermost density contour shown in each diagram (equal to 0·002 au) defines a volume in space which encloses over 95% of the total electronic charge of the system. For molecules able to exhibit nonbonded interactions, the molecular length and width as determined by this particular contour agree well with the sizes of molecules determined by nonbonded interactions in both the gaseous and solid states[7]. The lengths (L) reported in Table II-2 provide at least a relative measure of the size and extent of the charge distributions of the hydride molecules.

TABLE II-2. Properties of the molecular charge distributions of diatomic hydrides[a]

AH	μ (Debyes)	L	r_A Molecule	r_A Atom or ion	r_H Molecule	Nonbonded charges on[b] A	H
OH^+		6·4	2·8	2·6	1·7	3·84 (3·5)	0·24
OH•	1·780	6·7	3·0	2·9	2·0	4·23 (4·0)	0·36
OH^-		7·1	3·1	3·1	2·2	4·68 (4·5)	0·51
LiH	−6·002	7·7	1·7[c]	3·2	2·9	1·09 (1·5)	0·71
CH	1·570	7·9	3·5	3·2	2·3	3·21 (3·0)	0·49
HF	1·942	6·3	2·7	2·8	1·9	4·72 (4·5)	0·30

[a] All lengths are in au.
[b] Values in parentheses are free separated atom or ion values.
[c] The value of r_{Li^+} is 1·8 au.

The distance measured from either nucleus along the bond axis to the outermost (0·002) contour provides a measure of the nonbonded radius of the 'atom' in the molecule. The contribution of the non-

bonded density on both H and O to the length of the molecule increases as the number of electrons is increased. The value of r_H for the free atom is 2·5 au. Relative to this value the nonbonded radius of H is considerably decreased in all three molecules. The removal of an electron from OH^* causes an overall tightening of the charge distribution and a shift in the values of the nonbonded radii towards values characteristic of HF. In fact the amount of charge density in the region of the proton in OH^+ is less than in HF. Similarly the addition of an electron to OH^* results in an expansion of the charge distribution and in a set of nonbonded radii close in value to those for the preceding neutral hydride NH ($r_N = 3{\cdot}2$, $r_H = 2{\cdot}1$ au).

The electron population of any spatial region may be obtained by integrating the charge density over the corresponding restricted volume in space. Table II-2 lists such populations for the nonbonded regions of A and H, the nonbonded regions being defined by the volume of space on the nonbonded side of a plane perpendicular to the bond axis, and passing through the A or H nucleus. The nonbonded charge on oxygen exceeds that of the parent oxygen ion or atom in each of the three molecules. The nonbonded population on hydrogen is essentially unchanged from the free atom value in OH^- but decreased from this value in OH^* and still more so in OH^+.

The changes in the nonbonded charges on O and H upon ionization of or electron attachment to OH again reflect a shift in the properties of the charge distribution towards those characteristic of HF or NH respectively. The increase in the nonbonded charge on O and its decrease for H (compared to O^+ and H) in OH^+ indicate the presence of a greater degree of charge polarization than is found in HF. While the total nonbonded charge on O in OH^- is similar in value to that on F in the isoelectronic molecule HF, the nonbonded charges on H differ greatly in the two cases. OH^- falls into sequence when one compares the values of the nonbonded charges in the molecule with those of the parent species O^- and H. Such a comparison shows that the valence charge density is democratically delocalized over both nuclei in a manner similar to that found for the less polar central member of the hydride series CH.

A more detailed view of the differences in the charge distributions of OH^* and OH^- is given in Figure 2. The Figure portrays a density difference map obtained by subtracting the molecular charge density of OH^* from that of OH^- calculated at the equilibrium bond length of OH^*. The map thus shows the instantaneous change in the charge density when an electron is captured by the OH^* molecule. (The

density difference map for the ionization of $OH^{\bullet}$ is similar in all its spatial features to Figure 2 but the signs of the contours are reversed and their magnitudes larger than those for the electron attachment.)

In the orbital approximation the added electron enters the 1π molecular orbital. A glance at Figure 5 indicates that the 1π orbital

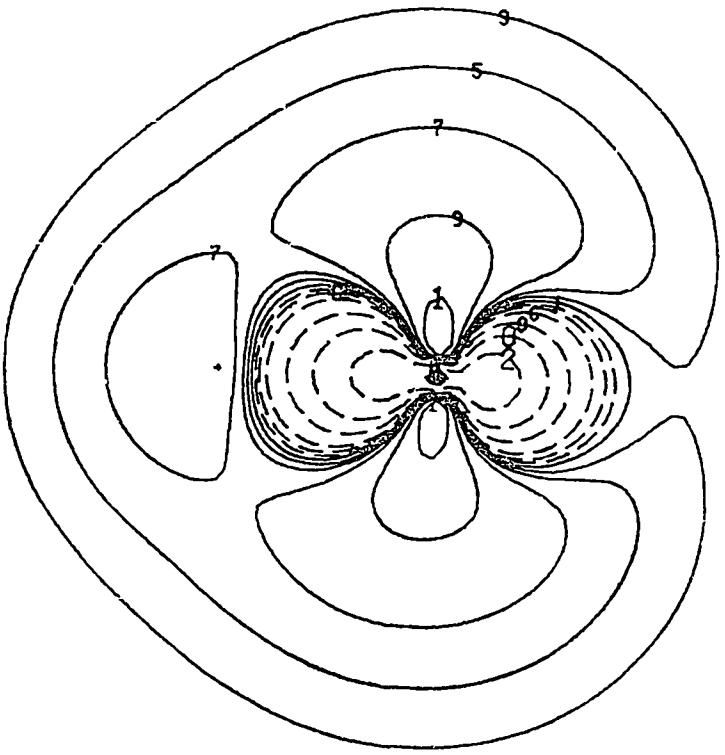


FIGURE 2. A density difference map showing the change in the molecular charge distribution when an electron is captured by the neutral OH species. Solid contour lines (odd numbered contours) denote an increase in charge density, dashed lines (even numbered contours) denote a decrease. The key relating the values of the contours to their numerical labels is given in Table II-7. The proton is on the left-hand side in this diagram.

density in all three of the OH species is highly localized on the O nucleus with a distribution very close to that of a $2p\pi$ atomic orbital on oxygen. In view of this, the enhancement of the charge density in the region of the proton in OH^- is surprising. In addition, there is a region of charge deficiency along the bond axis in the region of the oxygen nucleus corresponding to a *loss* of almost 0·1 charges to other

regions when the electron is added to OH^*. If the molecular orbitals remained unchanged during ionization or electron attachment (an assumption which is frequently employed) Figure 2 would reduce to a density plot of the 1π molecular orbital. The pattern of charge shift actually obtained indicates that all the orbitals undergo a substantial change when the number of electrons or the electron configuration is altered. Thus, in spite of the fact that the 1π orbital is atomic-like in both OH^* and OH^- (with zero density at the proton), the presence of the extra electron leads to changes in the σ orbitals of the system via the coupling provided by the exchange and coulomb integrals in the Hartree–Fock equations. The use of rigid or virtual orbitals will thus lead to incorrect assumptions regarding the changes in the charge distribution caused by the addition, removal or excitation of an electron[21].

One further point of interest regarding the total charge distribution is its insensitivity to changes in the spin multiplicity when these changes correspond to transitions between different electronic states arising from the same configuration[21]. For example, the molecular charge distributions for the three states of OH^+, $^3\Sigma^-$, $^1\Delta$ and $^1\Sigma^+$, all of which arise from the same $1\pi^2$ open-shell configuration, are indistinguishable to the accuracy to which they are portrayed in the present article. It should be stressed that completely separate and distinct Hartree–Fock calculations are made for each state. Thus the differences in the chemistry observed for such states of different multiplicity cannot be accounted for in terms of differences in their charge distributions. Instead, the difference in their chemistry must be related to the ability of the systems with nonzero spin to induce a spin polarization in the reacting system and in this manner follow a different reaction coordinate.

A detailed picture of the net reorganization of the charge density of the separated atoms accompanying the formation of a molecule may be obtained by subtracting the superimposed densities of the component (undistorted) atoms separated by R_e from the molecular charge density, also evaluated at $R = R_e$. This density difference distribution when illustrated in the form of a contour plot in the plane of the nuclei will be designated $\Delta\rho_{SA}(x,y)$. The density distribution which results from the superposition or overlap of the undistorted atomic densities does not place sufficient charge density in the 'binding region' to balance the forces of nuclear repulsion[22]. The regions of charge increase in the density difference maps are, therefore, the regions to which charge is transferred relative to the separated atoms

to obtain a state of electrostatic equilibrium and a stable chemical bond. In this sense the charge density differences may be interpreted as pictures of the 'bond density'.

It is natural to use the location of this charge increase relative to the positions of the nuclei to characterize the bond[7]. Thus, if the density difference map exhibits a region of net accumulation of negative charge symmetrically placed between and behind the nuclei, as is the case for the homonuclear diatomic molecules, the bond is classified as covalent. If, at the other extreme, the net accumulation of negative charge is distinctly localized in the region of only one of the nuclei, as exemplified in LiH or LiF, the bond is classified as ionic. The mutually shared charge density binds the nuclei in the covalent case, while in the ionic case they are bound by the density increase localized on one nucleus.

The density difference maps for the OH species and LiF, CH and HF are illustrated in Figure 3. The contours in these maps represent the increase or decrease in the amount of charge density present in the molecules relative to the distribution obtained by the overlap of the undistorted atom or ion densities. The principal features of the $\Delta\rho_{SA}(x,y)$ maps are similar for all three of the OH species. There is an accumulation of charge density in both the bonded and nonbonded regions of the oxygen which is concentrated along the internuclear axis. The charge increase on the bonded side encompasses the proton. These charge accumulations are a result of a charge removal from the region behind the proton and from a belt-like region perpendicular to the bond at the position of the oxygen nucleus. The concentration of charge density along the axis and its removal from a torus-like region perpendicular to the axis represents a *quadrupole polarization*. The same type of quadrupolar polarization is present in the regions of the F and C nuclei in HF, CH and LiF. The simple *dipolar polarization* depicted in the $\Delta\rho_{SA}(x,y)$ maps in the vicinity of the proton or the Li, a deficiency of charge density on one side and an accumulation on the other, is typical of the charge rearrangements found for atoms which employ principally *s* orbitals in their binding. However, *for atoms which employ principally* p-*type orbitals, the reorganization of the charge density accompanying bond formation is quadrupolar in character*, regardless of the bond type[7, 20, 23].

The chemically important feature of the quadrupolar polarization is that it results in a charge increase in the antibinding region, the region normally ascribed to lone pair or unshared electron density. Thus polarization accounts for the increase in electronic charge

found in the nonbonded regions of the A nuclei. Note that the region of charge removal in the vicinity of the heavy nuclei is largely confined to the binding region.

The $\Delta\rho_{SA}$ map for OH^- is most similar to that for CH as judged by a comparison of the extent of charge removal from the nonbonded region of the proton, of the positioning and extent of the charge increase in the binding region relative to the position of the proton and of the spatial extent of the torus-like region of charge removal from the region of the oxygen or carbon. The tightening of the charge distribution accompanying the ionization of $OH^\bullet$ to yield OH^+ results in a shift of the characteristics of the $\Delta\rho_{SA}$ map towards those of HF.

The nonbonded radius of the Li in LiF (and in LiH) is the same as for a Li^+ ion. Since the valence density of the Li atom is extremely diffuse, only a single negative contour appears in the $\Delta\rho_{SA}$ map to signify its essentially complete transfer to the F. The slight accumulation of charge density on the nonbonded side of the Li nucleus is the result of a polarization of the $1s$ core density, the significance of which is discussed below. It has been previously[24] shown that a plot of just the sigma density increase around F in LiF (that is, from 1σ, 2σ, 3σ and 4σ molecular orbitals) is almost coincidental to a single occupied $2p\sigma$ density on F. Thus the $\Delta\rho_{SA}$ pattern obtained in LiF can be viewed as the equivalent of filling a $2p\sigma$ orbital vacancy and characteristic of the ionic case. This limiting pattern is most closely approached here by HF and OH^+. None of the hydrides illustrated in Figure 3, however, attains the ionic limit. Instead the proton, unlike the Li nucleus in LiF, is encompassed by the density increase on A, one which in the hydrides may be associated with the *partial* filling of an asymmetrically distorted $2p\sigma$ orbital on A. The density increase binding the nuclei is thus shared by both nuclei, and the binding in these molecules is therefore covalent. The extent and details of sharing the charge increase, however, change markedly through the series. In CH and OH^- the density increase in the binding region is a maximum at the proton and results from a sharing of density centred on both nuclei. The remaining members of the series, OH, OH^+ and HF, give $\Delta\rho_{SA}$ diagrams which progressively give the appearance of an unsymmetrical $2p\sigma$ atomic orbital centred on A with a proton embedded at its extremity.

There is another feature of the $\Delta\rho_{SA}$ maps which indicates that the extent of charge transfer is not as great in the hydrides, OH^+ and HF for example, as in the ionic cases of LiH or LiF. The extreme

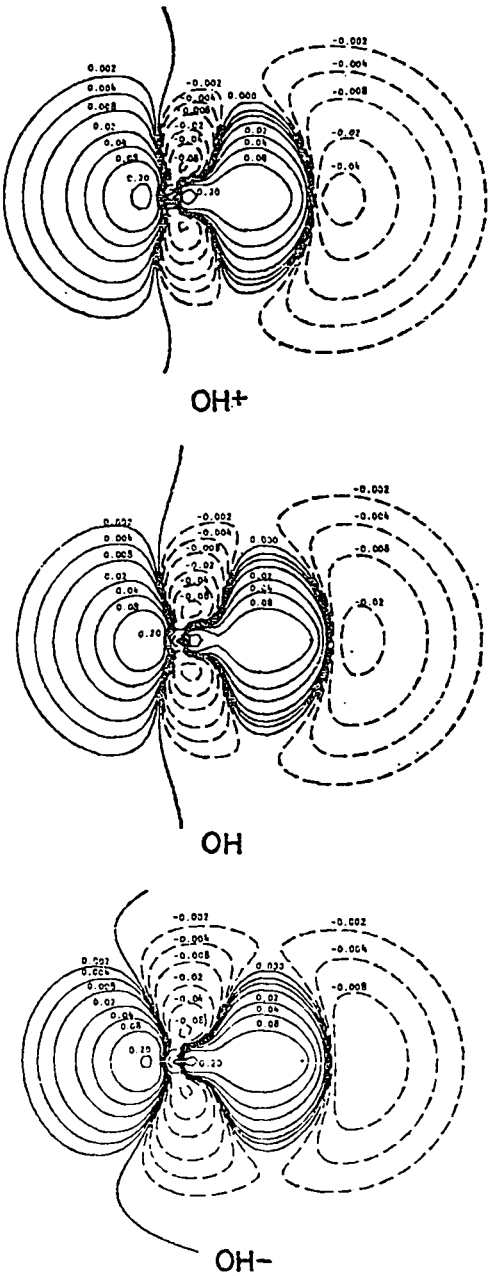


FIGURE 3. Contour maps of the density difference distributions $\Delta\rho_{SA}$ (molecular minus atomic) for diatomic hydrides and LiF in their ground electronic states. The atomic densities of the A nuclei used in the construction of these maps correspond to a configuration which places a single electron in their $2p\sigma$ orbital.

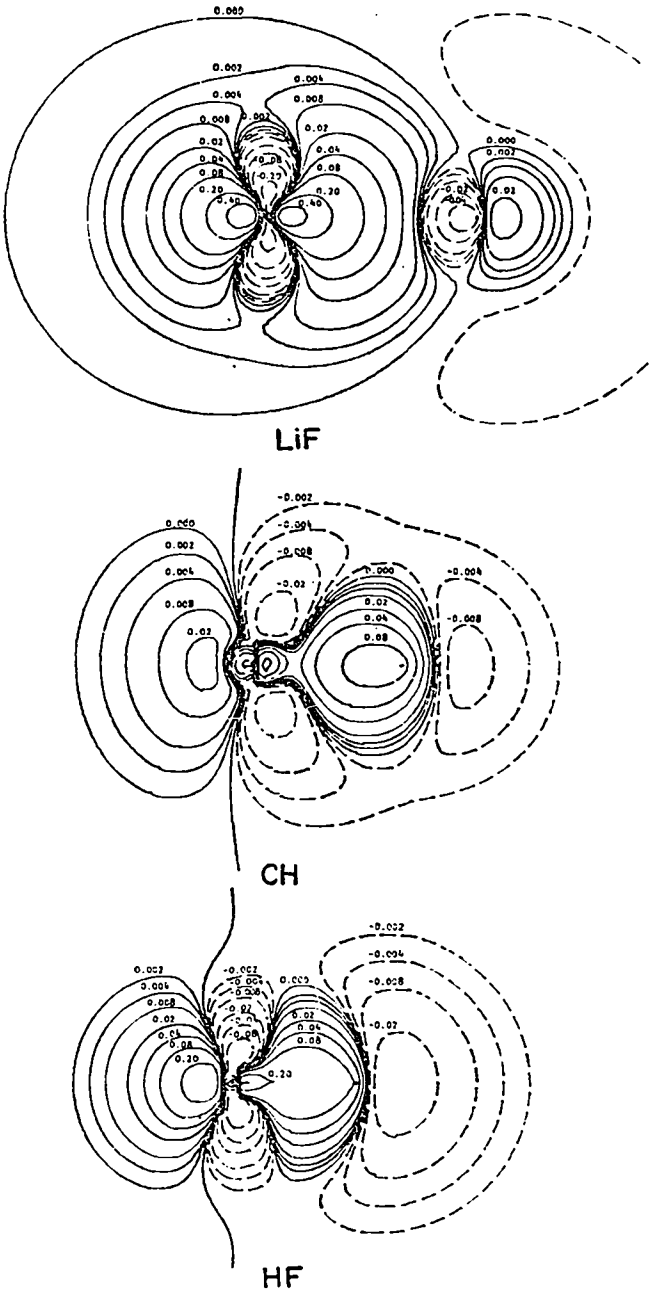


Figure 3 continued

The remaining $2p$ electrons are averaged over the $2p\pi$ orbitals. The proton is on the right-hand side in these maps.

localization of the charge density on H and F in LiH and LiF places a restriction on the direction of polarization of the density localized on H and on F (i.e., like H^- and F^-) and of the density remaining on Li (i.e., like Li^+). It is clear that the transfer of charge to a region which is localized on F and which effectively excludes the Li nucleus will lead to the creation of a net negative electric field at the Li nucleus and attraction (just coulombic attraction). Furthermore, if the localized charge were symmetric about the F nucleus, then it would experience a net positive electric field, or repulsion, originating from the Li^+-like core. Thus, to achieve electrostatic equilibrium in the presence of such pronounced charge transfer, the density distribution localized on the F must be polarized along the bond, that is, towards the Li. Such an inwards polarization exerts a force on the anionic nucleus which counterbalances the net force of repulsion due to the positive electric field. Similarly, the density in the immediate vicinity of the Li nucleus must be polarized away from the F to counterbalance the net force of attraction exerted by the density transferred to this atom, and hence come to equilibrium. The localized density on F is indeed polarized along the bond axis and that on the Li is back-polarized as required. The same polarizations are evident in a $\Delta\rho_{SA}$ map for LiH (see Ref. 20). The polarization of the density increase in the vicinity of each nucleus in a direction opposite to that of the dipole as found in LiH and LiF is characteristic of the ionic case.

The $\Delta\rho_{SA}$ maps for the hydrides shown in Figure 3 indicate that the charge increases on both A and H are polarized in the *same* direction as the dipole or, alternatively, in the same direction as the direction of the charge transfer. Thus the amount of charge transferred to the A nuclei in these cases is not sufficient to cancel the nuclear field on A and exert a net negative field at the position of the proton.

The quadrupolar and dipolar polarizations are not unique to diatomic molecules. As discussed below, the same polarizations are found to characterize the charge rearrangements in polyatomic molecules as well. Nor are the polarizations unique to the $\Delta\rho_{SA}(x,y)$ distributions. Instead, they represent the primary response of a charge distribution to an electric field, be it internal or external, static or dynamic. For example, a displacement of the nuclei during a vibrational motion changes the internal field exerted on the charge distribution causing it to change or 'relax'. Figure 4 illustrates that a bond extension of the O–H radical *diminishes* both the quadrupole polarization of the charge density in the vicinity of the O nucleus

and the dipolar polarization in the region of the proton. A corresponding density difference map for a bond contraction is the same as that shown in Figure 4 with all signs reversed. Thus, as the bond is contracted the polarizations are *enhanced* and charge density is removed from the belt-like region perpendicular to the bond axis and concentrated along the axis.

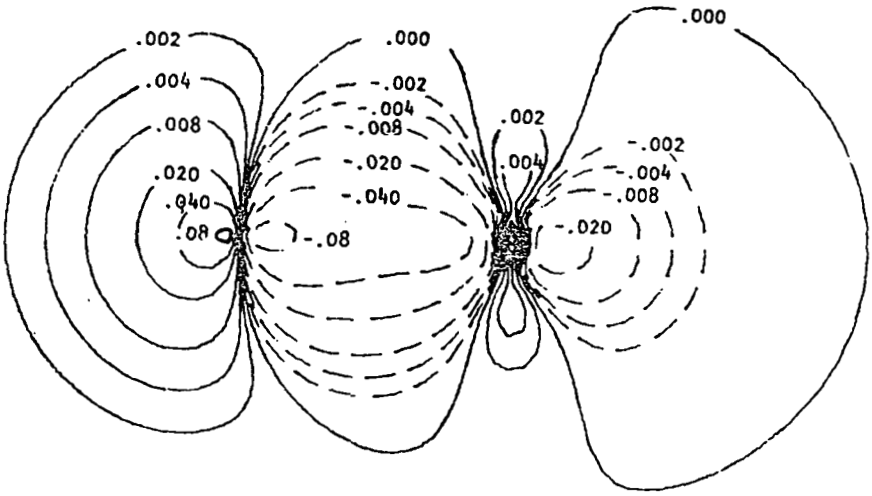


FIGURE 4. A density difference map showing the change or relaxation of the charge density in the OH molecule when the bond length is increased by 0·166 au. The oxygen nucleus is held stationary. For a bond contraction the algebraic signs of the contours are reversed.

Stevens and Lipscomb[25] have presented density difference maps which illustrate the change in a molecular charge density caused by an externally applied field. The density difference maps given by these authors

$$\Delta\rho(x,y) = \rho(\text{molecule in field}) - \rho(\text{unperturbed molecule})$$

illustrate the same polarizations of the charge density as are found in the $\Delta\rho_{SA}(x,y)$ maps. For example, the results of Stevens and Lipscomb for the hydrogen fluoride molecule show that when the direction of the positive field is from the proton to the fluorine, charge is removed from a torus-like region perpendicular to the axis at the position of the F nucleus and transferred to both the binding and antibinding regions of the F nucleus along the internuclear axis. Thus the polarizations evident in the $\Delta\rho_{SA}(x,y)$ maps, which show the response of the atomic charge densities to a field resulting from

the close approach of nuclei, are identical in form with the response of a system to an externally applied field.

The same polarizations are also evident in the approach of two molecules in a chemical reaction. For example, the change in the charge distributions of the HF molecule and the F^- ion as they approach one another to form the $(FHF)^-$ ion[26] indicate that the field of the fluoride ion causes a removal of charge from the region of the proton, enhancing the positive field directed at the fluorine nucleus in the HF molecule. This increased field, in complete analogy with the results of Stevens and Lipscomb[25], enhances the quadrupole polarization already present in the region of the fluorine nucleus in HF with the result that still more charge is transferred from the perpendicular belt-like region to the binding and antibinding regions of the fluorine nucleus along the internuclear axis.

B. *An Interpretation of the Binding in Terms of the Forces Exerted on the Nuclei*

According to the theorem of Hellmann and Feynman[8, 9] the force on any nucleus in a system of nuclei and electrons is just the classical electrostatic force exerted on the nucleus in question by the other nuclei and by the electron density distribution. The important feature of this theorem is that the force is determined by the distribution of charge in real three-dimensional space, an observable property of the system. It is for this reason that a discussion of the binding in a molecule in terms of the forces exerted on the nuclei may be given a classical interpretation.

The theorem itself is easily derived. The X-component of the force on nucleus A in a system with fixed nuclei is given by

$$F_{X_A} = \partial E/\partial X_A = (\partial/\partial X_A)\langle\psi^* |H| \psi\rangle$$
$$= \langle\psi^*|\partial H/\partial X_A|\psi\rangle + \langle\partial\psi^*/\partial X_A|H|\psi\rangle + \langle\psi^*|H|\partial\psi/\partial X_A\rangle \quad \text{(II-1)}$$

For the exact wavefunction

$$H\psi = E\psi$$

and the two final terms on the right-hand side of equation (II-1) may be reduced to

$$E\frac{\partial}{\partial X_A}\int \psi^*\psi \, d\tau = 0$$

Hence

$$F_{X_A} = \langle\psi|\partial H/\partial X_A|\psi\rangle \quad \text{(II-2)}$$

When ψ and the electronic coordinates are expressed in terms of a space-fixed coordinate system a further simplification occurs. Under

these conditions the only terms in the Hamiltonian operator H which depend on the nuclear coordinates are the internuclear separations R_{AB} and the nuclear-electron attraction terms. For example in a diatomic molecule AB

$$\partial H/\partial X_A = \frac{\partial}{\partial X_A}\left(\frac{Z_A Z_B}{R_{AB}} - Z_A \sum_i \frac{1}{r_{iA}}\right) = \frac{Z_A Z_B}{R_{AB}^2} - Z_A \sum_i \frac{\cos\theta_{Ai}}{r_{iA}^2}$$

where θ_{Ai} and r_{Ai} are polar coordinates centred on nucleus A defining the position of electron i. The only term involving the electronic coordinates, the last term, is a one-electron operator, and thus a knowledge of the full N-electron probability distribution as given by

$$\psi^*\psi \, dx_1 \, dx_2 \ldots dx_N$$

is unnecessary. Instead it is necessary to have only the probability distribution for a single electron multiplied by N, i.e., the molecular charge density

$$\rho(x) = N\int \psi^*\psi \, dx_2 \ldots dx_N \qquad \text{(I-3)}$$

Thus

$$F_{X_A} = \frac{Z_A Z_B}{R_{AB}^2} - Z_A \int \frac{\cos\theta_A}{r_A^2}\rho(x)\, dx \qquad \text{(II-3)}$$

The Hellmann–Feynman theorem holds for the exact wavefunction and a certain class of approximate functions (those which have been fully optimized with respect to the nuclear coordinates) which includes the Hartree–Fock function[27]. In the Hartree–Fock case the electron density or charge distribution assumes a particularly simple form. Since the molecular orbitals form an orthogonal set of functions

$$\rho(x_\mu) = \sum_i N_i \phi_i^*(x_\mu)\phi_i(x_\mu)$$

where N_i is the occupation number of the molecular orbital $\phi_i(x_\mu)$. The total electronic contribution to the force can therefore be equated to a sum of orbital contributions. For interpretative purposes it is convenient to go one step further and rewrite equation (II-3) as

$$F_{XA} = (Z_A/R^2)\,[Z_B - \sum_i f_{iA}] \qquad \text{(II-4)}$$

where f_{iA} is the force exerted on nucleus A by the charge density in the ith molecular orbital multiplied by R^2

$$f_{iA} = R^2 N_i \int \phi_i^*(x_\mu)\frac{\cos\theta_{\mu A}}{r_{\mu A}^2}\phi_i(x_\mu)\, dx \qquad \text{(II-5)}$$

The f_{iA} may be either attractive or repulsive and thus their values can be used as a quantitative gauge of the binding or antibinding characteristics of the ith molecular orbital using a significant reference standard. The reference standard is based on the contributions to the force on A as $R \to \infty$, where $F_A = 0$; that is, the reference state is that of the component separated atoms. Clearly, at large R the unperturbed atom A possesses a centre of symmetry and exerts a zero net force on nucleus A. One may interpret the vanishing of the force at large R as resulting from each electron on B screening one of the nuclear charges on B from nucleus A. Thus the limiting value at $R \to \infty$ of the sum of the f_{iA} values for the force on nucleus A is the total electronic charge on atom B and

$$\sum_i f_{iA}^{(\infty)} = \sum_l N_l = Z_B \qquad \text{(II-6)}$$

where the sum over l refers to a sum over the *atomic* orbitals on B.

The f_{iA} have the dimensions of electronic charge. Each f_{iA} is numerically equal to the number of point charges which, when placed at the B nucleus, exert the same field at the A nucleus as does the density in the ith molecular orbital. The electronic contribution to the force on the A nucleus at any value of R may, therefore, be equated to an effective number of charges situated at the B nucleus, this number being the sum of the partial forces. At R_e the system is in electrostatic equilibrium, $F_A = 0$ and again one obtains the condition

$$\sum_i f_{iA}(R_e) = Z_B$$

At intermediate internuclear distances the sum of the effective charges exceeds Z_B, corresponding to a net force of attraction, and for large values of R it reduces to the number of electronic charges which correlate with the separated B nucleus, e.g. equation (II-6). This suggests that the limiting value of each individual f_{iA} should be taken as the number of electrons in the ith molecular orbital which correlate with the B atom for large values of R, N_{iB}

$$f_{iA}(R \to \infty) = N_{iB} \quad (= 0, 1 \text{ or } 2)$$

The partial forces provide an absolute measure of the binding ability of an orbital density in terms of the number of point charges at the B nucleus which produce a field at A equivalent to that exerted by the actual density distribution. A measure of the binding ability of a molecular-orbital charge distribution relative to the separated atoms as the reference standard is given by a comparison of the value

of $f_{i\mathrm{A}}(R_e)$ with $N_{i\mathrm{B}}$. This compares the charge equivalent (in terms of a number of charges on B) of the electric field exerted by a pair of electrons in the molecule with the charge equivalent of the field exerted by the ancestral pair of electrons in the separated atoms. This latter number is simply the number of electrons which correlate with B, since the electrons which correlate with A exert no field at the A nucleus as $R \to \infty$. In general $f_{i\mathrm{A}}(R_e)$ may be greater than, equal to or less than $N_{i\mathrm{B}}$ leading to the three definitions listed below:

$$\begin{aligned} f_{i\mathrm{A}}(R_e) &> N_{i\mathrm{B}} \quad \text{binding MO} \\ f_{i\mathrm{A}}(R_e) &\sim N_{i\mathrm{B}} \quad \text{nonbinding MO} \\ f_{i\mathrm{A}}(R_e) &< N_{i\mathrm{B}} \quad \text{antibinding MO.} \end{aligned}$$

To allow for a more detailed understanding of the variations in the $f_{i\mathrm{A}}$ or $f_{i\mathrm{H}}$ values, each is expressed in terms of the separate contributions which arise from the atomic populations on A and H and the overlap population. These separate contributions to the f_is are easily determined since the basis set in the expansions of the present wavefunctions consists of Slater-type atomic functions centred on both A and H. Thus equation (II-5) is written as

$$f_{i\mathrm{A}} = [f_{i\mathrm{A}}^{(\mathrm{AA})} + f_{i\mathrm{A}}^{(\mathrm{AH})} + f_{i\mathrm{A}}^{(\mathrm{HH})}] \tag{II-7}$$

for the A nucleus in A–H, and as

$$f_{i\mathrm{H}} = [f_{i\mathrm{H}}^{(\mathrm{HH})} + f_{i\mathrm{H}}^{(\mathrm{AH})} + f_{i\mathrm{H}}^{(\mathrm{AA})}] \tag{II-8}$$

for the proton. For example, $f_{i\mathrm{A}}^{(\mathrm{AA})}$ ($\equiv$ atomic force) denotes the contribution to the partial force on nucleus A from the atomic charge population on A; $f_{i\mathrm{A}}^{(\mathrm{AH})}$ ($\equiv$ overlap force) is the corresponding contribution from the overlap charge density, and $f_{i\mathrm{A}}^{(\mathrm{HH})}$ ($\equiv$ screening force) is the contribution to the partial force on the A nucleus from the atomic charge density centred on the proton. The screening force is a measure of the electronic shielding of the proton from the nucleus A by the electrons situated on H. The screening force provides the sole contribution to the f_i values for large values of R, i.e.,

$$f_{i\mathrm{A}}(\infty) = f_{i\mathrm{A}}^{(\mathrm{HH})}(\infty) = N_{i\mathrm{H}} \quad \text{and} \quad f_{i\mathrm{H}}(\infty) = f_{i\mathrm{H}}^{(\mathrm{AA})}(\infty) = N_{i\mathrm{A}}$$

The atomic, overlap, and screening contributions to the partial forces provide more information than do the population figures themselves. As important as the amount of charge in determining the binding in a molecule is the exact disposition of the charge, its polarization and whether it is diffuse or concentrated. There are certain limiting cases for which the screening contribution to a

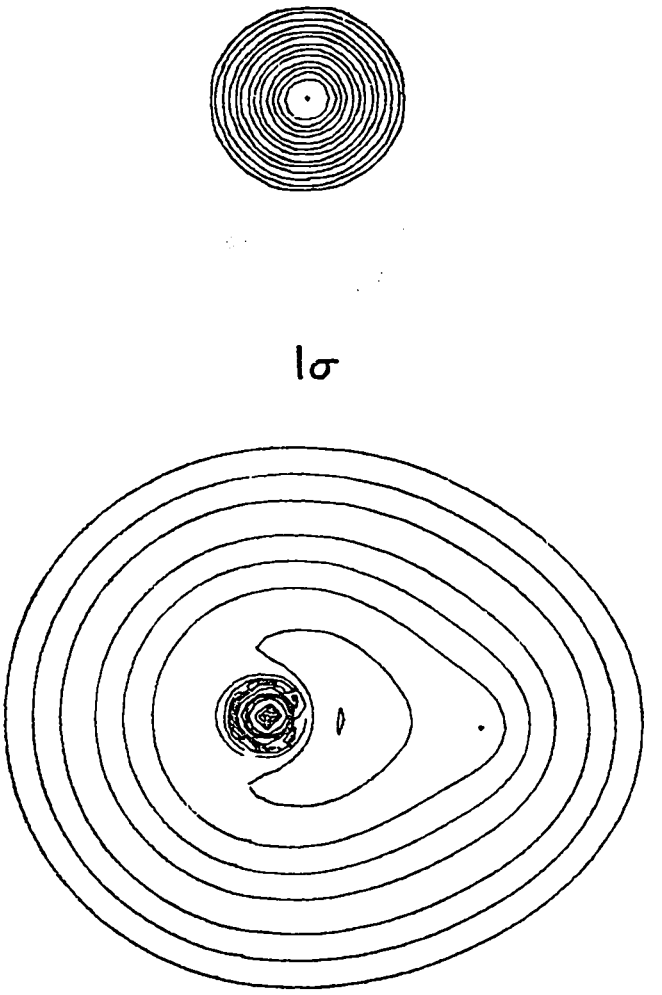
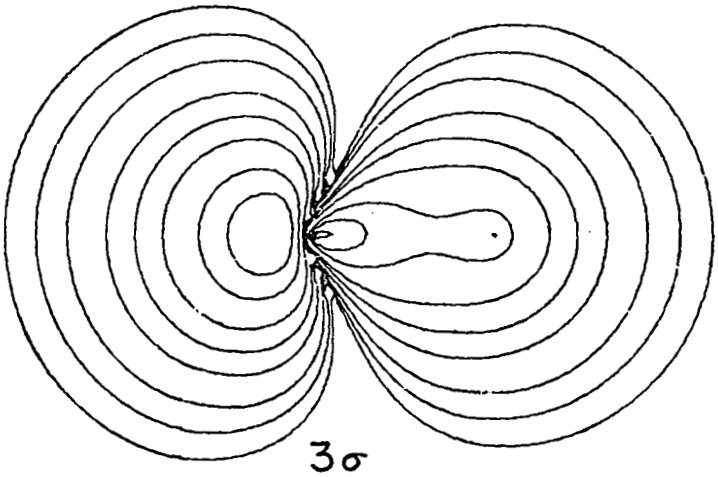


FIGURE 5. Contour plots of the molecular orbital charge densities of the OH^- ion. The values of the contours are obtained by numbering them consecutively starting with the outer contour and using the key given in Table II-7. There is a near circular node encompassing the closely spaced contours centred on the oxygen nucleus in the 2σ orbital density. The 3σ and 1π densities possess nodes which are nearly perpendicular to and along the OH bond axis respectively.



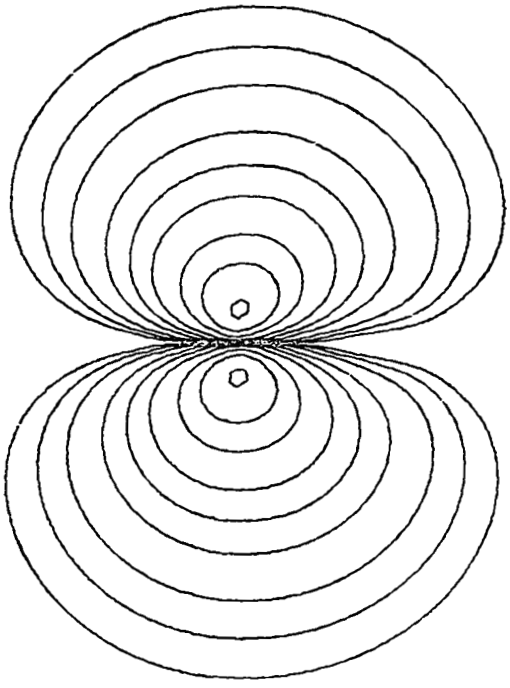


Figure 5 continued

partial force on the proton, for example, is numerically equal to the actual number of electrons on A. This equivalence occurs at large values of R and in the case of a tightly bound spherical inner-shell density centred on nucleus A in the molecule. In general, however, the screening contribution to the force on the proton will differ from the actual atomic population on A as the charge density on A may be diffuse and hence be partially penetrated by the proton at R_e or it may be polarized either towards or away from the proton. Similarly, the magnitude of the overlap force contribution is dependent upon whether the overlap charge density is diffuse in nature or concentrated along the internuclear axis. Any inequality in the sharing of the overlap charge density by the nuclei in a heteronuclear molecule is made evident by a difference in the forces which the overlap density exerts on two nuclei.

The molecular orbitals for the OH^- ion are illustrated in Figure 5 in the form of their charge density contributions. The general characteristics of the orbital densities are similar for all three of the OH diatomic species. The forces which these orbital densities exert on the O and H nuclei are given in Tables II-3–6 in terms of the charge equivalents f_{iO} and f_{iH} and their components.

Aside from a slight polarization, the 1σ molecular orbital is very close in appearance and properties to the inner shell $1s$ orbital on oxygen. The value of $f_{1\sigma,H}(R_e)$, the charge equivalent of the force on the proton, is 2 for all the OH molecules. The whole of this contribution arises from a screening contribution, i.e., from an atomic charge density on oxygen. The 1σ density simply screens two units of the nuclear charge on oxygen from the proton. This same screening effect is obtained at all internuclear distances greater than R_e including the case of the separated atoms. The value of $f_{1\sigma,H}$ is left unchanged by the formation of the molecule,

$$f_{1\sigma,H}(R_e) = N_{1sO}$$

and the 1σ density is classed as *nonbinding* with respect to the proton.

The 1σ density, while localized on oxygen as an inner-shell atomic density, is slightly polarized and exerts a small attractive atomic force on the oxygen nucleus in each case. The degree of polarization decreases as the number of electrons in the OH system increases. The limiting value of $f_{1\sigma,O}$ for large values of R is zero as the 1σ density correlates with a $1s$ density on oxygen, which does not exert a force on the oxygen nucleus. The 1σ charge density is therefore, slightly *binding* for the oxygen nuclei.

TABLE II-3. Forces exerted on the nuclei by the 1σ density.

	Forces on the proton					Forces on the O nuclei			
	$f_{1\sigma,H}$	Atomic	Overlap	Screening		$f_{1\sigma,O}$	Atomic	Overlap	Screening
OH^+	2·001	0·000	0·000	2·001	OH^+	0·291	0·290	0·001	0·000
$OH^\cdot$	2·000	0·000	0·000	2·000	$OH^\cdot$	0·247	0·245	0·002	0·000
OH^-	2·000	0·000	0·000	2·000	OH^-	0·214	0·213	0·001	0·000

TABLE II-4. Forces exerted on the nuclei by the 2σ density.

	Forces on the proton					Forces on the O nuclei			
	$f_{2\sigma,H}$	Atomic	Overlap	Screening		$f_{2\sigma,O}$	Atomic	Overlap	Screening
OH^+	2·428	0·026	0·222	2·180	OH^+	0·967	0·825	0·131	0·011
$OH^\cdot$	2·317	0·040	0·383	1·894	$OH^\cdot$	0·905	0·581	0·292	0·032
OH^-	2·214	0·047	0·423	1·744	OH^-	0·862	0·481	0·339	0·043

TABLE II-5. Forces exerted on the nuclei by the 3σ density.

	Forces on the proton					Forces on the O nuclei			
	$f_{3\sigma,H}$	Atomic	Overlap	Screening		$f_{3\sigma,O}$	Atomic	Overlap	Screening
OH^+	2·094	0·099	0·578	1·417	OH^+	−0·377	−1·341	0·832	0·132
$OH^\cdot$	1·684	0·068	0·475	1·141	$OH^\cdot$	−0·344	−1·430	0·915	0·169
OH^-	1·385	0·066	0·380	0·939	OH^-	−0·305	−1·473	0·959	0·209

TABLE II-6. Forces exerted on the nuclei by the 1π density.

	Forces on the proton					Forces on the O nuclei			
	$f_{1\pi,H}$	Atomic	Overlap	Screening		$f_{1\pi,O}$	Atomic	Overlap	Screening
OH^+	1·558	0·001	0·024	1·533	OH^+	0·166	0·141	0·024	0·001
$OH^\cdot$	2·084	0·001	0·044	2·039	$OH^\cdot$	0·226	0·180	0·045	0·001
OH^-	2·413	0·001	0·058	2·354	OH^-	0·242	0·177	0·063	0·002

The ancestral relationship of the 2σ molecular orbital to a $2s$ atomic orbital on oxygen is readily discernible in the form of its charge density contours. The lack of contours encircling only the proton indicates that the distribution of the 2σ charge density is determined primarily by the field of the oxygen nucleus. The density is however, strongly perturbed by the proton and charge density is accumulated in the region between the nuclei. The localization of the 2σ charge density in the region of the oxygen nucleus decreases through the series in the order OH^+, $OH^\bullet$, OH^-.

The 2σ molecular orbital correlates with the doubly occupied $2s$ orbital on oxygen. For large internuclear separations the correlated $2s$ density will exert no force on the oxygen nucleus and a screening force on the proton equivalent to that of two negative charges: $f_{2\sigma,O}(\infty) = 0$ and $f_{2\sigma,H}(\infty) = 2$. Thus when compared to the separated atoms, the 2σ charge density is *binding* for both the proton and the oxygen in all three molecules. The binding of the proton, which is measured by the amount by which $f_{2\sigma,H}$ exceeds 2, is primarily the result of the force exerted by the overlap density in OH^- and $OH^\bullet$. The decrease in the overlap contribution and the increase in the screening contributions to $f_{2\sigma,H}$ through the series from OH^- to OH^+ indicate that the 2σ charge density becomes increasingly contracted towards the oxygen as the total number of electrons in the system decreases. The 2σ atomic population on oxygen in OH^+ which is necessarily less than 2, is strongly polarized towards the proton with the result that the force which it exerts on the proton is equivalent to placing $\sim$2·2 electronic charges at the position of the oxygen nucleus.

The binding of the oxygen nucleus by the 2σ density, like that of the proton, decreases through the series from OH^+ to OH^-. The binding of the oxygen nucleus in OH^+ is primarily the result of the atomic population on oxygen being polarized towards the proton, while in OH^- the atomic and overlap contributions are almost equally important.

The 3σ orbital density resembles a $2p\sigma$ atomic orbital on oxygen with the lobe on the bonded side of the nucleus strongly contracted along the internuclear axis. However, in the immediate vicinity of the oxygen nucleus there is a larger amount of charge density accumulated in the nonbonded than in the bonded lobe. The 3σ orbital densities for $OH^\bullet$ and OH^+ are similar to that for OH^-, but, as for the 2σ density, become progressively more contracted towards the oxygen nucleus as the total number of electrons in the system decreases.

The 3σ orbital correlates with the singly occupied H $1s$ and O $2p\sigma$ atomic orbitals. In the limit of large internuclear distances the values of both $f_{3\sigma,\mathrm{H}}$ and $f_{3\sigma,\mathrm{O}}$ approach unity as the correlated atomic densities screen one nuclear charge on each nucleus. The values of $f_{3\sigma,\mathrm{H}}(R_e)$ indicate that the 3σ density is *binding* with respect to the proton and becomes progressively more so in the order OH^-, $OH^\bullet$, OH^+. For example, in OH^+ the force exerted on the proton by the 3σ density is equivalent to placing $\sim 2{\cdot}1$ electronic charges at the oxygen nucleus as opposed to the separated atom equivalent of one electronic charge. The number of charges which are effective in binding the proton is doubled in the formation of the 3σ orbital in OH^+. In both OH^+ and $OH^\bullet$ the proton is bound primarily by the 3σ charge density, while in OH^- the 2σ and 3σ charge densities are comparable in this respect.

The 3σ charge density exerts an *antibinding* force on the oxygen nucleus in spite of a large overlap contribution because of an even larger negative atomic force term. The negative values for $f_{3\sigma,\mathrm{O}}$ indicate that the 3σ density is antibinding in the absolute sense as it exerts a force which tends to pull the oxygen nucleus away from the proton. This pattern of overlap and atomic force contributions is characteristic of any orbital charge density which involves a significant $p\sigma$ component. It is the increase in the 3σ density on the oxygen and its extreme back-polarized form which are responsible for the characteristic pattern of the $\Delta\rho_{\mathrm{SA}}$ maps and for the increase in non-bonded charge densities of the oxygen atoms in the OH species.

The screening of the proton by the 3σ charge density is uniformly low throughout the series reflecting the relative localization of the 3σ charge density on the oxygen nuclei.

The molecules OH^+ to OH^- possess two to four π electrons, respectively. The 1π orbital correlates with the $2p\pi$ orbitals on the oxygen, and it is evident from Figure 5 that the 1π molecular orbital retains its basic atomic orbital character. The 1π orbital density is in each case centred on the oxygen with contours characteristic of a $2p\pi$ atomic density slightly polarized in the direction of the proton.

The 1π density screens two to four nuclear charges on oxygen from the proton in the separated atom case. Thus

$$f_{1\pi,\mathrm{H}}(\infty) = N_{p\pi}$$
$$f_{1\pi,\mathrm{O}}(\infty) = 0$$

The values of $f_{1\pi,\mathrm{H}}(R_e)$ listed in Table II-6 are less than the orbital occupation number in each case. The 1π density is, therefore,

antibinding with respect to the proton in the relative sense that in the molecule it does not screen an equivalent number of nuclear charges on the oxygen. This antibinding effect is a direct consequence of the π density being concentrated around the internuclear axis, rather than along it (where it has a node). The small value of the overlap and atomic force contributions to $f_{1\pi,H}$ illustrate that no significant π bond is present in these molecules and the 1π molecular densities are best described as inwardly polarized atomic densities on the oxygen nuclei.

The binding–antibinding properties exhibited by the molecular orbitals in the OH species are characteristic of Hartree–Fock orbitals regardless of the system in which they are found, if they have either a common correlated atomic orbital or a common major orbital component they exhibit similar binding properties. For example, a Hartree–Fock orbital which correlates with a $2s$ atomic orbital on the most electronegative atom in a molecule [the 2σ orbital in the hydrides AH (A = B → F), the $2\sigma_g$ orbital in homonuclear diatomics, or the 3σ orbital in BeO, BF, CO or LiF] is always *binding* for both nuclei. The molecular orbital density in the region of the nucleus with which it correlates is *polarized into the bond* and exerts an attractive force on this nucleus. In addition, the overlap charge density exerts almost equal forces on both nuclei in the heteropolar examples. These are the binding characteristics of an orbital which correlates with $2s$ atomic orbital on the most electronegative atom in the molecule whether the bond is covalent, polar or ionic.

Similarly a Hartree–Fock orbital which exhibits (or correlates partially with) a $2p\sigma$ component on a given nucleus (the 3σ orbital in AH, A=C → F, the $3\sigma_g$ in homonuclear diatomics or the 4 orbital in BF, CO, LiF and BeO) is strongly polarized into the antibinding region of that nucleus and exerts an antibinding force on it. It is the polarization associated with such an orbital which is responsible for the charge increase in the lone pair or nonbonded region of the charge distribution. The forces exerted by the overlap charge density in these same orbitals are, for the heteronuclear cases, approximately twice as large for the nucleus on which the $2p\sigma$ component is centred as they are for the second nucleus.

The Hartree–Fock π molecular orbitals, whether they are delocalized as in CO or strongly localized on a single nucleus in OH, are inwardly polarized and exert nearly equal overlap forces on both nuclei.

TABLE II-7. Key to density and density difference maps.

Density maps		Density difference maps	
Contour No.	Value of contour (in au)	Contour No.	Value of contour (in au)
1	0·002	1	0·000
2	0·004	2	−0·002
3	0·008	3	0·002
4	0·02	4	−0·004
5	0·04	5	0·004
6	0·08	6	−0·008
7	0·20	7	0·008
8	0·40	8	−0·02
9	0·80	9	0·02
0	2·00	0	−0·04
1	4·00	1	0·04
2	8·00	2	−0·08
3	20·00	3	0·08
4	40·00	4	−0·20
		5	0·20
		6	−0·40
		7	0·40
		8	−0·80
		9	0·80

III. THE MOLECULAR CHARGE DISTRIBUTIONS OF CH_3OH AND CH_2FOH

This section presents a discussion of the total molecular charge distributions and their orbital components for the polyatomic systems methanol and fluoromethanol. The wavefunctions for these polyatomic systems, which are close to Hartree–Fock accuracy, were obtained by Csizmadia, Tel and Wolfe[28] using a basis set of Gaussian-type atomic orbitals (GTO's) centred on the nuclei. The basis set consisted of fifty-six orbitals for methanol and seventy-two for fluoromethanol. Contracted basis functions were formed by taking linear combinations of the GTO's on the various centres as suggested by Huzinaga[29]. The twenty GTO's centred on oxygen, for example, were combined to give ten contracted basis functions. The energy minimization in the SCF calculation is obtained by varying only the linear coefficients of the contracted sets of basis orbitals, the composition of each contracted set remaining fixed. The use of contracted sets of orbitals makes feasible (in terms of computing time)

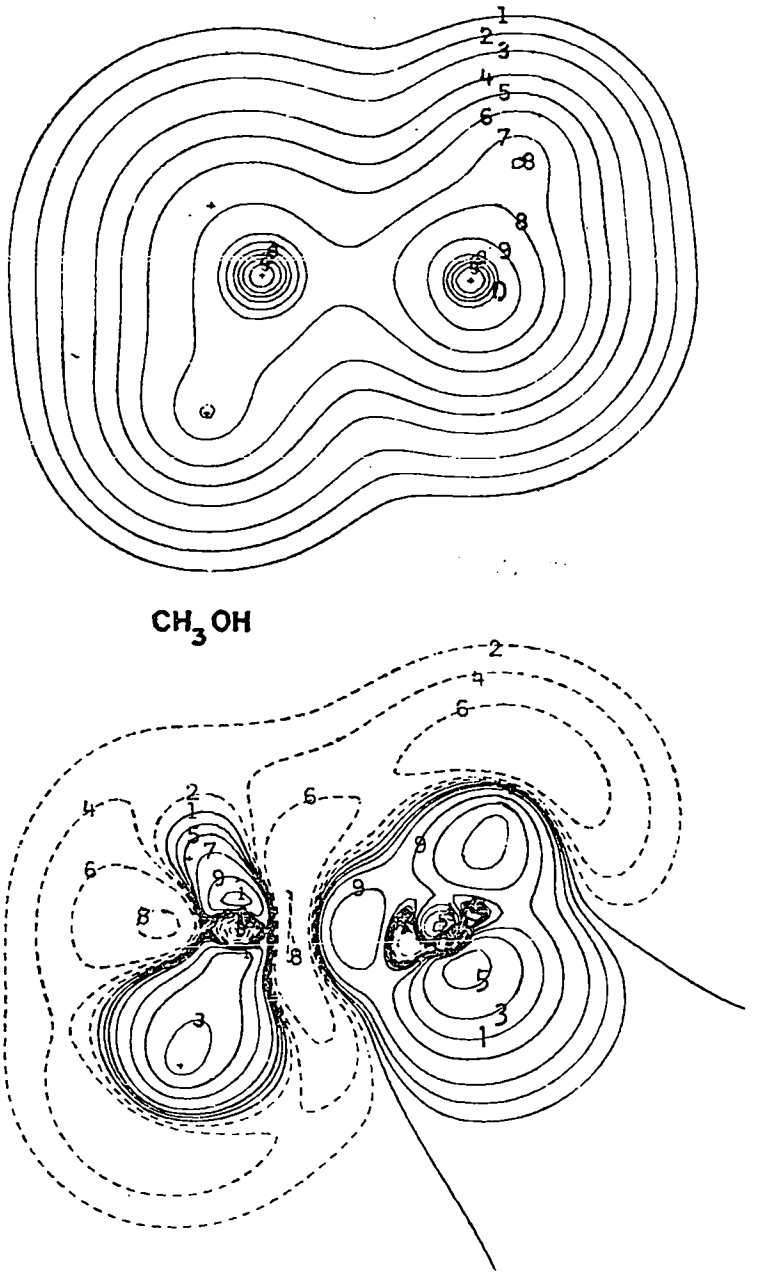
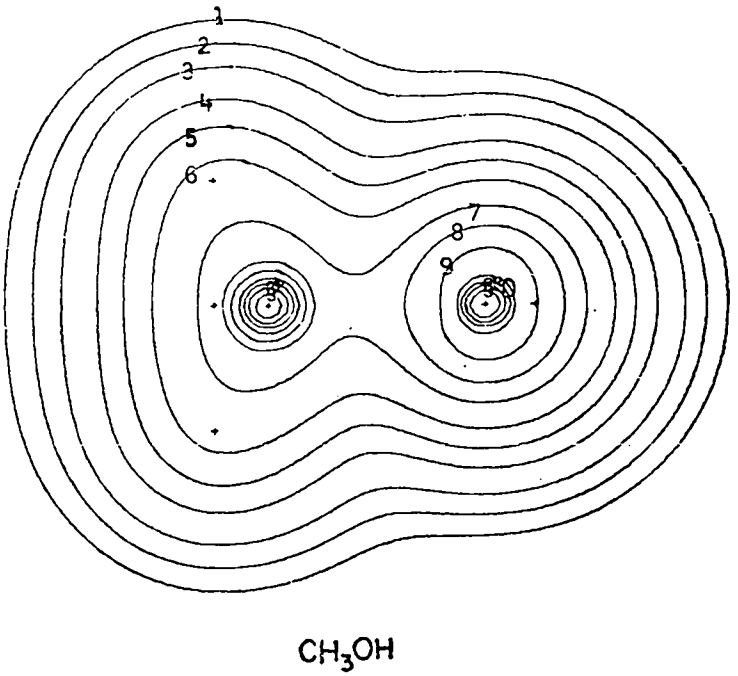


FIGURE 6. Contour maps of total molecular charge distribution in methanol in the staggered conformation. The plot on the left is in the plane of the HCOH nuclei and that on the right is in the plane perpendicular to this. Beneath each



CH_3OH

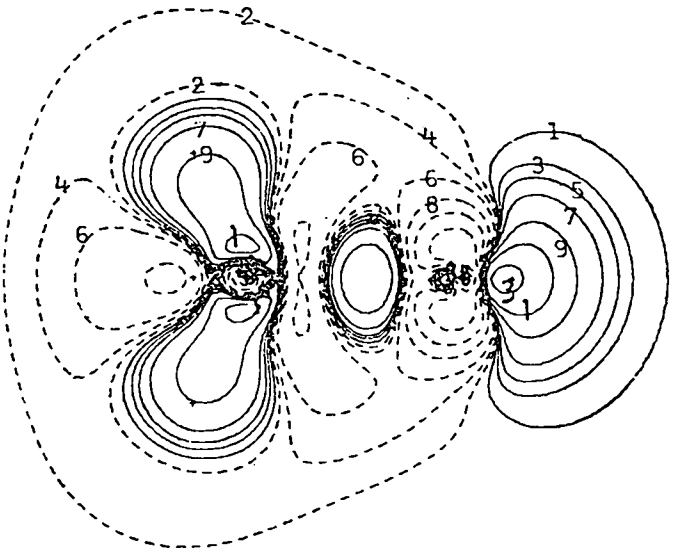


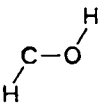
Figure 6 continued

total density plot is the corresponding $\Delta\rho_{SA}$ map. The key for the values of the contours of the total and density difference maps is given in Table II-7.

the use of a very extended basis set with only a minimal sacrifice in the flexibility which could be obtained if the coefficients of all the GTO's were separately and independently varied in the energy minimization. SCF calculations for relatively large polyatomic systems are now carried out using such contracted basis sets of GTO's[17, 30, 31].

A. The Molecular Charge Distribution of CH_3OH

The total charge distribution of methanol in the staggered conformation is depicted in Figure 6. Two contour maps of the charge distribution are shown; one in the plane of the nuclei and the other



in a plane perpendicular to this one, through the carbon and oxygen nuclei. The relative positions of nuclei not in the plane of a given diagram are indicated by vertical projections of their positions on to the plane in question. A tetrahedral geometry is assumed about the carbon, and the COH bond angle is also set at the tetrahedral value. The bond lengths employed are (in Å); O–H, 0·96; C–O, 1·428; C–H, 1·091; C–F, 1·375.

The SCF calculation predicts the staggered conformation for methanol illustrated in Figure 6 to represent the energy minimum with respect to rotation about the C–O bond axis. The barrier height for internal rotation, the energy difference between the eclipsed and staggered forms of methanol is calculated[28] to be 1·44 kcal/mole. The experimental value for the barrier is 1·07 kcal/mole[32]. The barrier in methanol has also been determined by Fink and Allen[33] and by Pedersen and Morokuma[34] within the SCF–Roothaan framework using Gaussian basis sets. Their calculated values for the barrier are 1·06 and 1·59 kcal/mole respectively. Fink, Pan and Allen[35] have compared the computed and experimental barrier values for a number of molecules and, in general, the agreement between experiment and theory is as noted above for methanol.

A comparison of Figures 1 and 6 illustrates that the principal features of the charge distributions of the O–H and C–H bond fragments in methanol are remarkably similar to the molecular charge distributions of the corresponding diatomic species OH($^2\Pi$) and

CH($^2\Pi$). The nonbonded radii on hydrogen and oxygen in methanol are identical with the values found in the OH molecule while the nonbonded radii of carbon and of the hydrogen in the CH bond differ from those of the CH molecule by only 0·1 au, the nonbonded charge density being slightly more contracted in the molecular fragment than in the diatomic molecule. The complete outer envelopes of the charge densities of the fragments in methanol are similar in all respects to those for the diatomic species. Thus the shape and size of the charge distribution in methanol can be predicted from the appropriate bond lengths and bond angles together with the nonbonded radii and general shapes of the charge distributions of the CH and OH diatomic species.

The nonbonded charge density on oxygen exhibits a pronounced polarization whose direction undergoes a continuous change in each of the planes obtained by a rotation about the C–O bond axis. In the plane of the H–C–O–H nuclei the nonbonded charge density on oxygen is concentrated along an axis which bisects the COH bond angle. In the plane perpendicular to this, the charge density centred on oxygen is concentrated along a line perpendicular to the C–O bond axis.

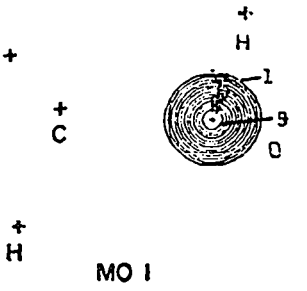
The polarization in the plane containing the four nuclei is particularly evident in the density difference map (molecular density minus the overlapped atomic distributions) also shown in Figure 6. Because of its tetrahedral environment the atomic density of carbon has been sphericalized in the construction of this $\Delta\rho_{SA}$ map. The atomic density on oxygen corresponds to the configuration $1s^2\ 2s^2\ 2p_x\ 2p_y^2\ 2p_z$ where the y-axis is perpendicular to the plane containing the four nuclei. This results in spherical contours for the oxygen atom charge distribution in this plane and corresponds to the valence bond description of the two unpaired electrons on oxygen forming single bonds with the carbon and hydrogen atoms. The $\Delta\rho_{SA}$ map indicates that the charge distribution of the oxygen atom, which is initially spherical in this plane, is strongly polarized along the line which bisects the COH bond angle, into both its bonded and nonbonded regions, but particularly into the latter. The charge density is not accumulated directly along either the O–H or O–C bond. There is a region of charge removal at the oxygen which is perpendicular to the principal line of polarization. Thus the $\Delta\rho_{SA}(X)$ map exhibits a quadrupolar polarization in the region of the oxygen similar to that found in the diatomic molecules. In the COH system, however, the polarization is with respect to an axis which bisects the

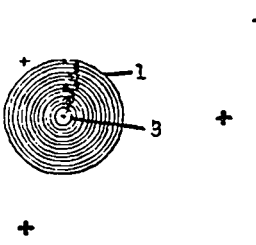
directions of the C–O and O–H bond directions. The same quadrupolar polarization is found in a $\Delta\rho_{SA}(X)$ map for the water molecule in the plane of the nuclei[36]. In this case the polarization is directed along the C_2 symmetry axis which bisects the HOH bond angle and the charge removal occurs from a belt-like region perpendicular to this axis at the position of the oxygen nucleus. The quadrupolar polarization also persists in the perpendicular plane of the methanol system.

The charge density in the region of the carbon also exhibits a quadrupolar polarization. In this case the charge accumulation is understandably concentrated in a belt-like region perpendicular to the C–O bond axis to encompass the protons while the region of charge removal occurs along the axis, to the extent of causing a partial depletion of the atomic densities between the carbon and oxygen nuclei. A comparison of the $\Delta\rho_{SA}(X)$ map for methanol with that for the CO molecule[23] indicates that even the sigma bond charge density (which is the only density to contribute to the charge density on the C–O axis) is greatly reduced in the polyatomic system. In contrast to this, the $\Delta\rho_{SA}(X)$ map indicates that the extent of charge accumulation between the C and H and the O and H nuclei in methanol is very similar to that found in the density difference maps for the corresponding diatomic species.

The molecular orbital charge densities for methanol in the staggered conformation are illustrated in Figure 7. They are numbered in order of increasing energy. This particular configuration possesses a plane of symmetry (the one containing the H–C–O–H nuclei) and every molecular orbital must be either symmetric or antisymmetric with respect to it. For this reason density contour maps of the antisymmetric orbitals, numbers six and nine (which have a node in the plane of symmetry), are illustrated in the plane perpendicular to the symmetry plane.

The molecular orbitals numbers one and two are $1s$ atomic-like orbitals centred on the oxygen and carbon nuclei respectively and hence are similar to the 1σ orbitals in CH or OH or to the 1σ and 2σ orbitals in CO. The major component of molecular orbital number three is from the $2s$ orbital on oxygen. Thus it strongly resembles the 2σ orbital in the diatomic hydrides (see Figure 5) or the 3σ orbital in CO. In all three cases the orbital density is strongly polarized towards the nuclei bonded to the oxygen as indicated by the contour with the shape of a half-moon. A similar pattern of contours appears again in molecular orbital number four, this time localized on the





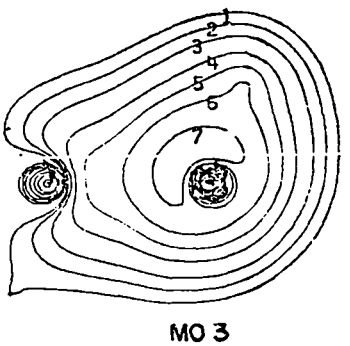
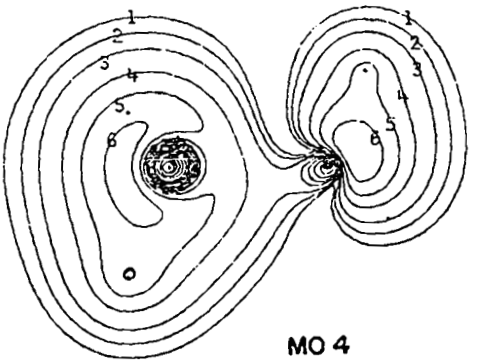
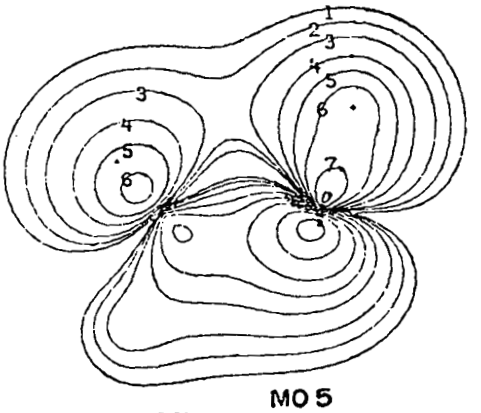
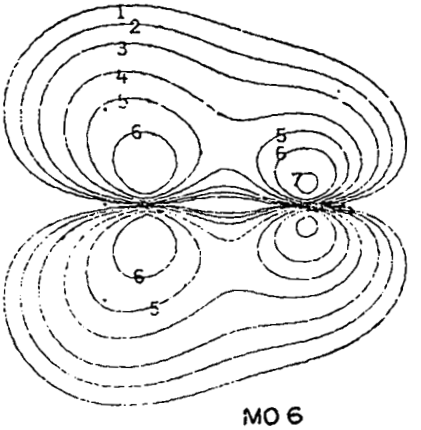


FIGURE 7. Contour plots of the molecular orbital charge densities for methanol in the staggered configuration. The maps for orbitals six and nine (overleaf) are shown in a plane perpendicular to plane containing the HCOH nuclei.







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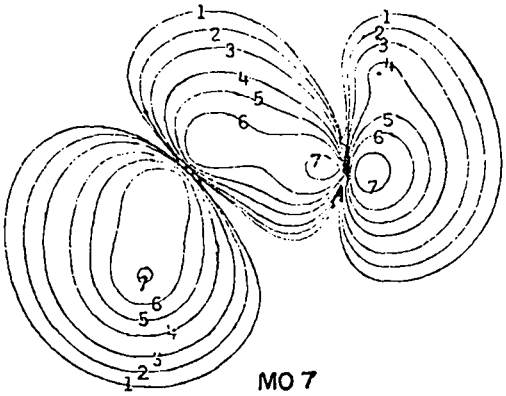
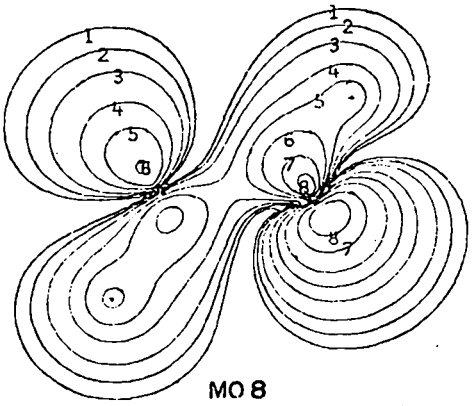




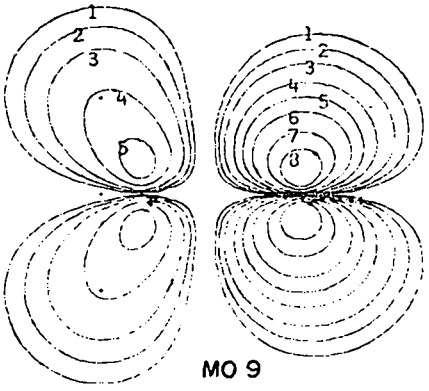


Figure 7 continued

carbon and binding the protons in the methyl group. This orbital is, however, less strongly localized than is the preceding one. In general, the extent of delocalization of the orbitals increases as their energy increases.

Although the 4σ orbital in CO correlates with a doubly occupied $2s$ orbital on carbon in the separated atoms, the formation of the CO molecule results in a transfer of charge to oxygen and the resulting molecular orbital exhibits a large $2p\sigma$ component centred on the oxygen nucleus. The 4σ orbital density in CO is characterized by an accumulation of charge density between the carbon and oxygen nuclei and by an even larger accumulation in the nonbonded region of the oxygen[23, 37]. It is clear from Figure 7 that in methanol the field of the three methyl protons rather than that of the oxygen dominates the form of the 4σ orbital to the extent that the density distribution is now largely localized on carbon on the side of the protons with the characteristics of a large $2s$ atomic component on carbon. While the orbital still exhibits a nodal structure at oxygen characteristic of a $2p\sigma$ distribution, the amount of charge in the antibinding region of the oxygen and in the CO bond region is greatly reduced from that found in CO. The weakening of the sigma bond structure in CO by the addition of hydrogens is evident in the sharing of the polarization density in orbital number three between the carbon and the proton bonded to the oxygen and in the complete reversal of the polarization in orbital number four.

Molecular orbital number five may be considered to be derived from one of the components of the doubly degenerate π orbitals in CO. The density is mostly concentrated in the region of the OH bond and the density in this fragment strongly resembles the 3σ orbital of the diatomic hydrides (see Figure 5) to the point that spatially related contours in the two maps have identical values. There is a strong back-polarization of the charge density on oxygen (away from the proton) indicating a large $2p\sigma$ component, the characteristic feature of the 3σ densities in the hydrides. Molecular orbital number six which is concentrated in a plane perpendicular to the one containing the OH bond, represents the second component of the bonding π orbital in CO. It is less perturbed from this form than is orbital number five but shows a larger concentration of charge density on carbon than is found in CO[37].

The 5σ orbital is the orbital of highest energy occupied in the ground state of CO. In this diatomic species the orbital is largely concentrated in the nonbonded region of the carbon (characteristic

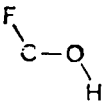
of an orbital with a large $p\sigma$ component on one centre) and exhibits two nodes perpendicular to the bond axis at the positions of the carbon and oxygen nuclei. This same nodal structure is evident in molecular orbital number seven of methanol but the charge density in this case is strongly delocalized over the entire system and contributes to the bonding of the protons on oxygen and carbon as well as to the bonding between the two heavy nuclei.

There are four more electrons in methanol than in CO and the two final molecular orbitals in methanol, particularly orbital number nine, are closely related to the doubly degenerate 2π antibonding orbital of CO. The 2π orbital is unoccupied in the ground state of CO. Since the 1π orbital in CO is heavily localized on the oxygen, the antibonding 2π orbital is concentrated in the region of the carbon. In methanol, however, the presence of the three methyl protons reverses this behaviour. The bonding π-like orbital, orbital number six, is more democratically shared and slightly favours the carbon. Consequently, the second π-like orbital in methanol, orbital number nine, is localized to a considerable extent in the region of oxygen.

Csizmadia et al[28] have also determined the wavefunction and molecular energy of the methoxide ion. The value predicted for the proton affinity of the methoxide ion using the molecular energies of CH_3OH and CH_3O^- is -420 kcal/mole. Hopkinson et al[38] have found the correlation between experimental and calculated proton affinities to be excellent when extensive basis sets are employed in the determination of the calculated values. These authors noted that both the experimental and calculated proton affinities fall into definite groups characterized only by their charge, e.g., dinegative ions have proton affinities between -500 and -700 kcal/mole; all mononegative species between -320 and -450 kcal/mole and the neutral species between -70 and -220 kcal/mole. The value for the methoxide ion falls within the range of values for the mononegative ions.

B. The Charge Distribution in CH_2FOH

The total molecular charge distribution for fluoromethanol is illustrated in the plane of the



nuclei in Figure 8. The charge density in the region of the oxygen

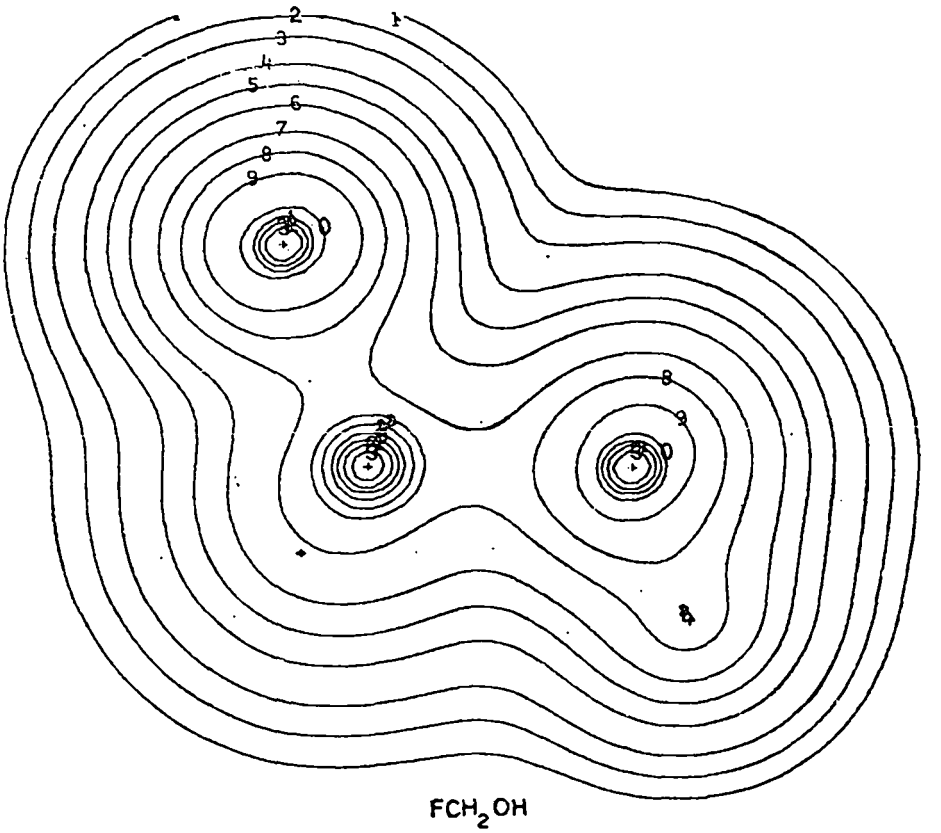


FIGURE 8. Contour plots of the total density and density difference distributions for the fluoromethanol molecule.

exhibits the same polarization as in methanol and the nonbonded radii of the OH bond fragment are essentially unchanged in value. The nonbonded charge density on carbon is slightly more contracted than it is in methanol, all the outer contours being displaced in closer to the carbon nucleus by approximately one-tenth of an au. The nonbonded radius on fluorine is 2·8 au, the same as that found in the CF diatomic molecule and close to the value of 2·7 in HF.

A much more detailed comparison of the effect which fluoro substitution has on the charge distribution of methanol may be obtained by comparing the $\Delta\rho_{SA}$ maps for CH_3OH and CH_2FOH (Figures 6 and 8). The inductive effect of the fluorine on the CO bond is very evident in such a comparison. The contours defining the region of charge increase between the C and O nuclei are increased in magnitude and extent, while those defining the charge deficit are similarly

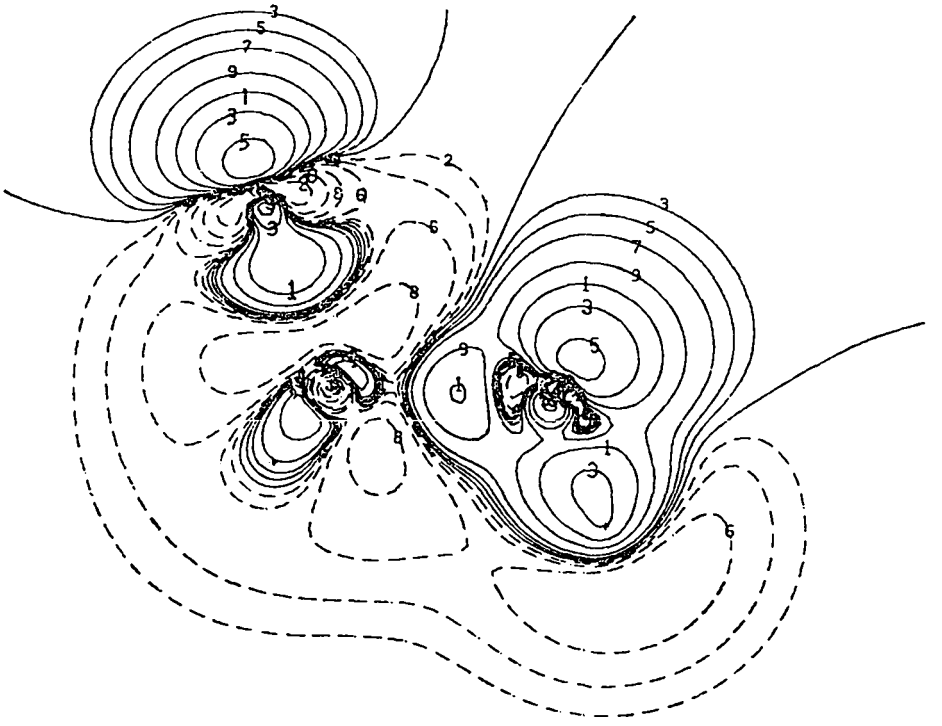


Figure 8 continued

decreased. A detailed comparison of the two $\Delta\rho_{SA}$ maps indicates that the whole of the charge increase in the vicinity of the oxygen nucleus and the proton is shifted slightly towards the carbon in CH_2FOH compared to CH_3OH. The charge increase at the position of the proton in the OH bond is slightly decreased. Aside from these effects the pattern of charge increase and decrease in the vicinity of the oxygen and hydrogen is the same as is found in CH_3OH, with a strong quadrupole polarization along the axis bisecting the COH bond angle. The regions of charge increase in the immediate vicinity of the carbon nucleus are directed along the axis which bisects the FCO bond angle. The pattern of the density difference map for the C–F bond fragment is very similar to that obtained for the CF diatomic molecule. Both maps exhibit a similar region of charge deficit in the binding region adjacent to the carbon nucleus, indicating a considerable degree of charge transfer to the region of the fluorine. The fluorine exhibits a quadrupole polarization typical of diatomic molecules.

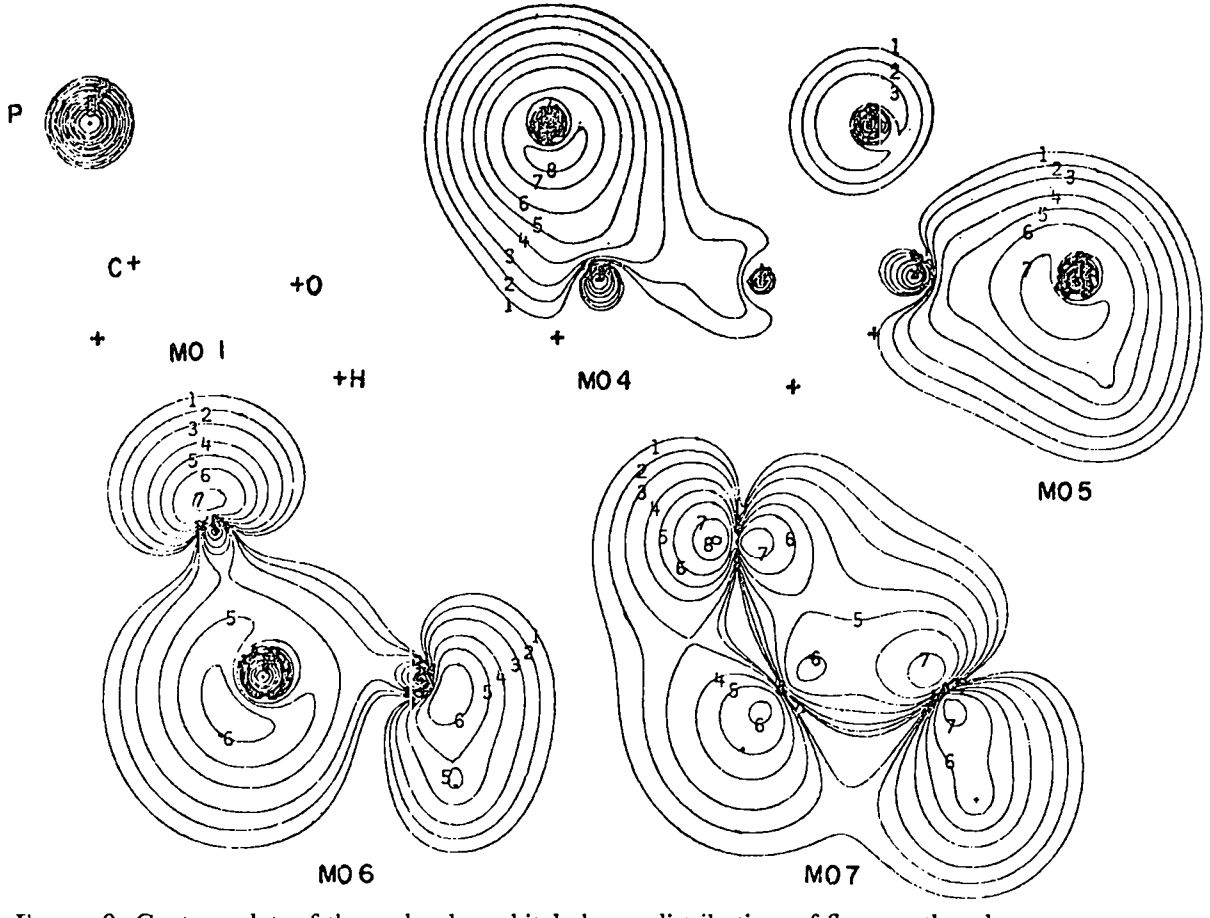


FIGURE 9. Contour plots of the molecular orbital charge distributions of fluoromethanol.
Only the densities of the orbitals symmetric with respect to the plane of the FCOH nuclei are shown.

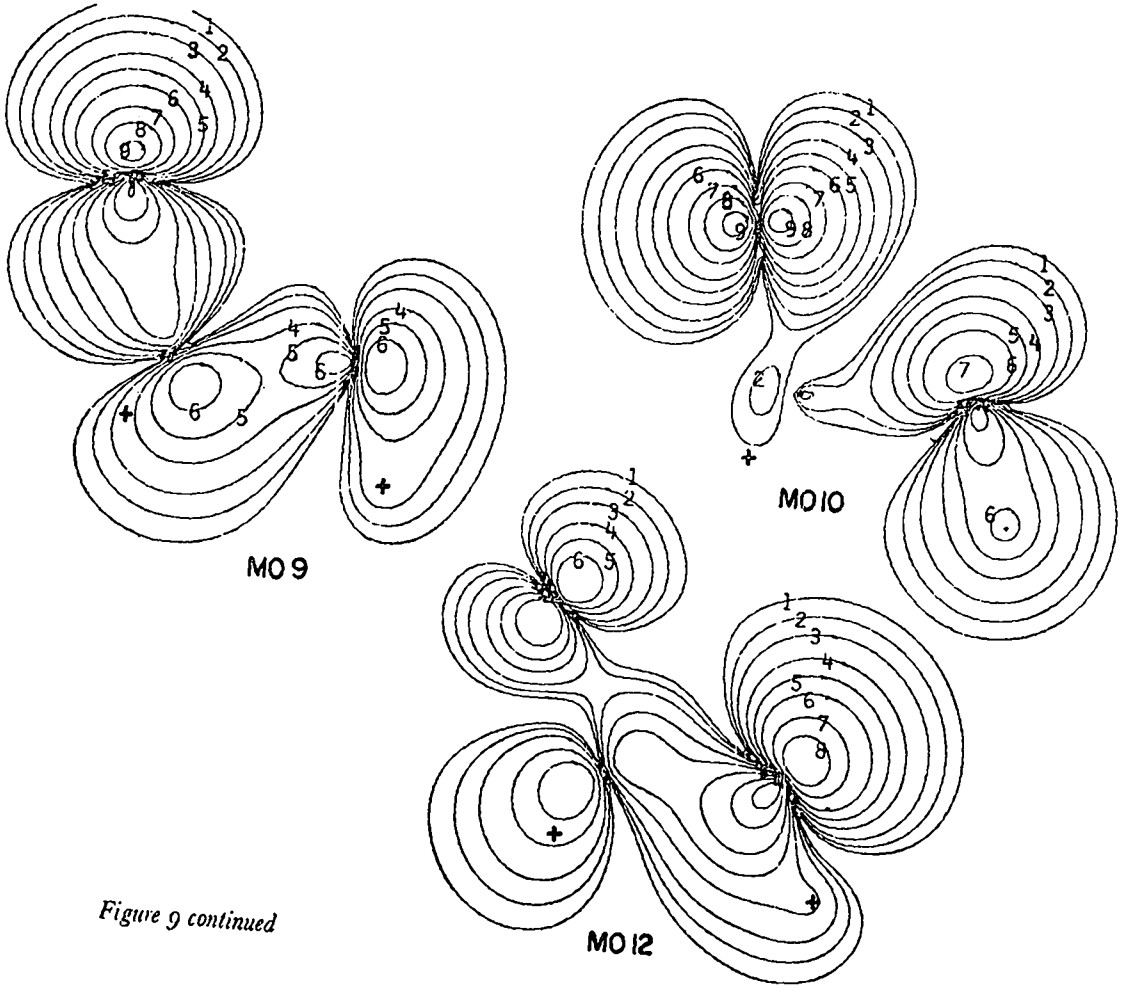


Figure 9 continued

The large increase in and expansion of the charge density into the nonbonded regions of the heavy nuclei, which occurs on bond formation as a result of the quadrupole type polarization, plays a dominant role in determining the relative stability of the various possible conformers. This question of relative stability is of particular interest in the case of CH_2FOH since Csizmadia et al[28] predict the staggered configuration as illustrated in Figure 8 to be the one of maximum relative energy. A rotation of the CH_2F fragment by 120° about the CO bond axis decreases the potential energy of the system by 12·60 kcal/mole. This gives the most stable conformation of the CH_2FOH molecule, one in which the proton in the OH group is in a staggered position relative to one of the methyl protons. A barrier of intermediate height (8·25 kcal/mole) is obtained by a further rotation of 60°, which results in an eclipsing of the fluorine with the proton of the OH bond.

The configuration of maximum energy thus corresponds to one in which the fluorine eclipses the nonbonded charge on oxygen rather than to one in which it eclipses the hydroxyl proton. In the alcohol molecules, the axis of principal polarization of the nonbonded charge density on oxygen forms an angle with the CO bond almost identical with the COH bond angle. The spread of the nonbonded charge density out from its axis of polarization is, however, much greater than is the spread of the bonded density along the OH bond axis. Consequently the nonbonded interactions between the FH_2C- and $HO-$ charge distributions are a maximum when the fluorine eclipses the nonbonded charge density on the oxygen. Similarly, the nonbonded interactions between the H_3C- and $HO-$ groups in methanol are a maximum when the nonbonded charge densities on carbon and oxygen are eclipsed.

The charge distributions of the molecular orbitals in CH_2FOH which are symmetric with respect to the plane containing the FCOH nuclei are shown in Figure 9. The density distributions of the antisymmetric orbitals are very similar to their symmetric counterparts in terms of the extent of their localization on the fluorine, carbon and oxygen nuclei. Molecular orbitals numbers one, two and three are $1s$ atomic-like distributions centred on the fluorine, oxygen and carbon nuclei respectively. The density plots of orbitals two and three are not shown in the diagram since they are the same as the corresponding orbital plots in Figure 7 for methanol.

Molecular orbital number four is, aside from a small tail to the oxygen, similar to the 3σ orbital in the diatomic CF species. The

contours exhibit the shape characteristic of a strong $2s-$ component, in this case centred on fluorine and polarized towards the carbon. Orbitals five and six are primarily polarized $2s$ components on oxygen and carbon respectively, and, with the exception of the tails extending to fluorine, resemble very closely the corresponding orbitals, numbers three and four, in methanol.

Similarly, orbitals seven and eight resemble the π-like bonding orbitals five and six of methanol, but the distributions in CH_2FOH encompass the fluorine as well. The antibonding π-like pair of orbitals, numbers ten and eleven, are concentrated almost exclusively on the fluorine and oxygen nuclei, and more so on the former than on the latter nucleus. The final pair of orbitals, twelve and thirteen, are concentrated in the region of the oxygen.

IV. ACKNOWLEDGMENTS

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CHAPTER 2

Nucleophilic attack by hydroxide and alkoxide ions

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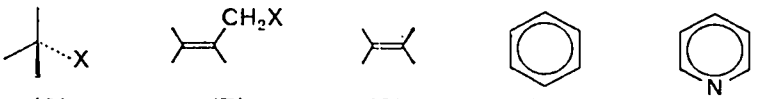
I. INTRODUCTION

In reactions involving nucleophilic attack by hydroxide $(OH)^-$ and alkoxide $(OR)^-$ ions, a critical feature is the rather obvious observation that the former contains a second ionizable proton. The loss of this proton can give rise to further reaction after the initial nucleophilic attack by the hydroxide ion. This possibility does not arise in the case of the analogous alkoxide ions, and most of the general kinetic data on the nucleophilic attack by these two species come from investigations involving alkoxide ions.

The further reaction referred to above can manifest itself either in the form of side reactions, or in some cases, as will be shown in later sections, by complete further reaction giving rise to products entirely different from those in the corresponding alkoxide reactions. In these cases, the reactions involving attack by the simpler alkoxide ions provide excellent models for the initial products of the attack by hydroxide ion.

The reactions involving attack by these ions represent an enormous field of study, and any review must be restricted to some extent in its choice of subject material. The purpose of the present review is to present the reactions resulting from the attack of hydroxide and alkoxide ions on the range of carbon skeletons represented by (**A**—**E**) below*.

* The major omissions in this approach are the attacks on functional groups. The most important of these, attack on the carbonyl grouping, has recently been reviewed[1].



(A) (B) (C) (D) (E)

It is hoped to illustrate the change in the reactions of the ions with these substrates and also the general trend in the mechanism of their substitution reactions which changes from a synchronous one-step reaction to a two-step reaction involving an intermediate. Both of these changes are determined by the presence of π-electron systems, and the activating groups which these require for nucleophilic attack to occur.

Substitution reactions at saturated carbon atoms have been extensively investigated and reviewed. Because of this, these particular alkoxylation and hydroxylation reactions are presented in outline only, for comparison with those in later sections. In general, the emphasis in the chapter is placed strongly on mechanistic aspects; papers of a preparative nature are normally referred to only where they are relevant to a discussion of the mechanism. (This is not a severe restriction, as most of the reactions are rather obvious from a preparative point of view, involving either substitution of an activated group, or addition at a specifically activated position.)

One important aspect which is not considered here, as it does not usually affect the overall mechanisms which are the main subject of the chapter, but which is common to all the reactions, is the role of the solvent—in particular the use of dipolar aprotic solvents as reaction media. These generally enhance the rate of substitution reactions involving an ionic species and a neutral substrate which involve a transition state containing both moieties (which includes all the reactions considered here), and are of both preparative and theoretical interest. This aspect has been treated in reviews by Parker[2-4], Reichard[5] and in other publications[6-11].

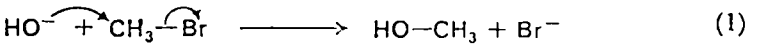
Finally, the particular reactions and mechanisms which are presented here are only part of a much larger field of study, and references which are review articles or which contain a large amount of general data are marked with an asterisk (*) in the reference section to facilitate additional reading.

II. ATTACK AT SATURATED CARBON

A. Bimolecular Reactions Involving Hydroxide and Alkoxide Ions

Kinetically, the displacement of bromide ion from methyl bromide

by hydroxide ion in aqueous alcohol[12] (equation 1) is found to be second-order, first-order in both reactant and substrate, as are the



(1)

reactions of simple alkyl bromides with ethoxide ions in ethanol solution[13]. These are typical of the reactions of simple *n*-alkyl halides with these two ionic species.

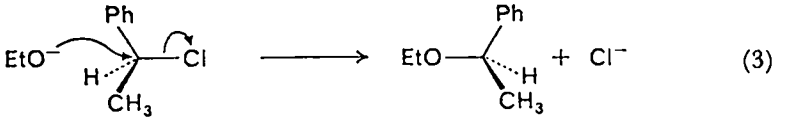
The reaction is considered [14–17] to involve attack by the ion on the carbon atom from the side opposite the group to be displaced (equation 2). The reaction begins with the attachment of the nucleo-

(2)

Transition state

phile to the smaller lobe of the sp^3 orbital by which the group to be displaced is attached to the carbon atom and proceeds through a transition state, where both nucleophiles are attached to the opposite lobes of a *p* orbital while the remaining orbitals are sp^2 hybridized and lie in a plane at right angles to these groups. It terminates by the re-establishment of sp^3 hybridization of the carbon orbitals with the attacking nucleophile now attached to the carbon.

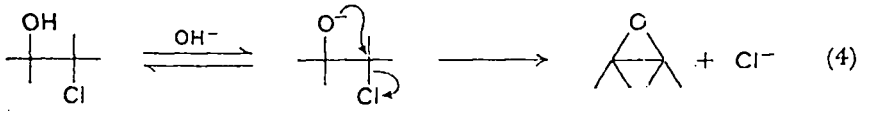
It is implicit in the above equation (2) that there is inversion of the configuration of the attached groups in the product. If the reaction is carried out with an optically active substrate, one should obtain the enantiomer from the reaction. Thus, treatment of the optically active α-phenylethyl chloride with ethoxide ion in ethanol yields[18] almost pure, optically active inverted product (equation 3). Similar results are found for other substitutions involving the highly reactive alkoxide or hydroxide ions.



(3)

In general, the S_N2 mechanism is favoured for these strongly basic ions. One particular case of the S_N2 mechanism involving alkoxide ions which is of synthetic importance is the base-catalysed formation of epoxides from chlorohydrins[19]. The reaction is considered to in-

volve an internal S_N2 displacement of chloride ions by initially formed alkoxide ion (equation 4).



(4)

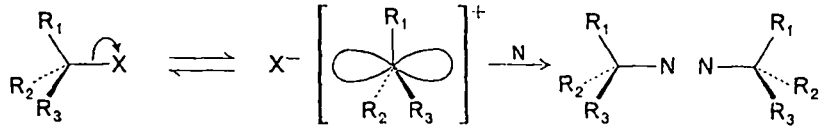
B. *Unimolecular Reactions*

Although, as indicated above, the S_N2 type of reaction is favoured for displacements involving the highly reactive alkoxide or hydroxide ions, under certain conditions substitution can occur by a unimolecular mechanism to give products which have arisen from formal replacement of X by OR or OH. This mechanism is favoured for solvolysis reactions involving actual attack by OH_2 and ROH. The reaction under these conditions is considered to involve an initial ionization to yield a carbonium ion (**1**) which is then attacked by the nucleophilic solvent (equation 5). Because the conditions favour-

(5)

(1)

able for this mode of reaction are often those involving solvolysis, kinetic evidence cannot be used to determine the molecularity of the reaction, and this decision must be made from other considerations. Very important is the stereochemistry of the reaction. Thus, implicit in the formation of the carbonium ion **1** in equation (5) is the idea that, since the carbonium ion is planar, nucleophilic attack can occur from either side to give a product which is a racemic mixture, irrespective of the stereochemistry of the reactant (equation 6).

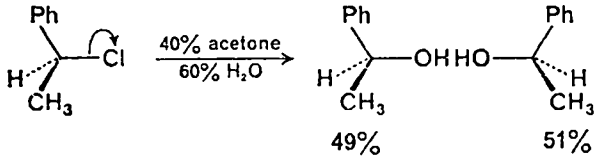


(6)

(1)

Indeed, when optically active α-phenylethyl chloride reacts under

solvolysis conditions to give the alcohol, the product is almost* 100% racemized[18] (equation 7).

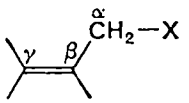


(7)

Thus the overall substitution by hydroxide and alkoxide ions at saturated carbon atoms can be considered as proceeding via two possible extreme modes of substitution.

III. ATTACK ON ALLYLIC SYSTEMS

In both structure and reactions[20, 21] the allylic system 2 occupies a place intermediate between saturated and alkene systems. In some reactions, both the point of attack and the mechanism are those



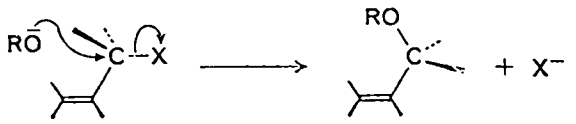
(2)

discussed above for reactions at saturated carbon atoms, and the main point of interest is how the presence of the C=C bond affects the rates of the reactions. In other reactions, however, attack can occur at the alkene double bond to give quite different products.

A. Bimolecular Substitution Reactions

1. Involving attack at the α-carbon atom

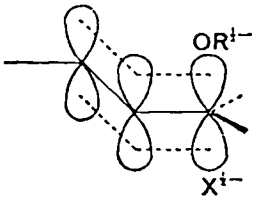
This mode of reaction is exactly analogous to the S_N2 reactions of saturated systems, the nucleophile attacking the saturated carbon atom at the side remote from the substituent X which is displaced in a concerted process (equation 8).



(8)

* Absolutely unambiguous results are rare. For a discussion of the complicating features see Refs. 14–17.

The most significant feature of the reaction is the effect of the alkene moiety on the rate of the reaction compared with that of the corresponding aliphatic substrate. In general, much faster reactions are observed, the increase in rate being reflected (Table 1) in a decrease in the activation energy of the reaction. This is considered



(3)

to be due to stabilization of the transition state by overlap of the π orbitals of the double bond with the p orbital formed on the α-carbon atom in the transition state (3). The conjugation over the three atoms which is now possible lowers the overall energy of the system. The effect of substituents on the reactivity of these compounds has been reviewed[21].

TABLE 1. Relative rates and activation energies for the reaction of allylic halides and the corresponding saturated halides with ethoxide ion in ethanol solution at 44·6°C[a].

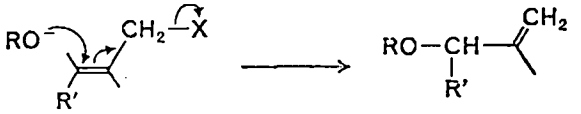
Substrates	$\frac{k_2(\text{allyl})}{k_2(\text{alkyl})}$	E_a (kcal mole^{-1})
$CH_2{=}CHCH_2Cl$	~27	20·6
$CH_3CH_2CH_2Cl$		21·1
$CH_3CH{=}CHCH_2Cl$	~88	20·5
$CH_3CH_2CH_2CH_2Cl$		21·2
$CH_2{=}C(CH_3)CH_2Cl$	~340	20·5
$CH_3CH(CH_3)CH_2Cl$		22·4

[a] C. A. Vernon, *J. Chem. Soc.*, 4462 (1954).

2. Involving attack on the alkene moiety

A second possible mode of bimolecular substitution is available in allyl systems because of the double bond. This attack can take place at the γ-carbon atom (equation 9) to give, for any substituted alkene which is unsymmetrical with respect to the transition state,

a different product from that described in section I above. This mode of displacement is usually called S_N2' and, in general, will



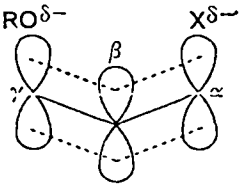
(9)

be promoted relative to the normal S_N2 reaction where there are substituents on the α-carbon atom which tend to inhibit the normal S_N2 reaction by either steric or inductive effects.

Several reactions of this type have been documented for alkoxide ions, although this mode of reaction is not as favoured for charged as for uncharged nucleophiles.

Thus, although α-methylallyl chloride with ethoxide ion in ethanol yields only a small quantity of the abnormal product[22], *t*-butylallyl chloride forms substantial amounts of 'abnormal' product with both ethoxide[23] and phenoxide ions[24], and α,α-dichloroallyl chloride gives exclusively the abnormal product with ethoxide ion[25].

The reaction is considered[21] to proceed in an analogous manner to the S_N2 mechanism, i.e., via a one-step mechanism involving synchronous bond breaking and formation with a transition state such as **4** where there is stabilization from the overlap of the (β) *p*-orbital with the (α) and (γ) 'pseudo' *p*-orbitals. However, the ex-



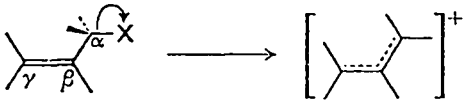
(4)

perimental evidence on this point is not completely conclusive. Bordwell and co-workers[26] have shown that the rates of reaction of 3-halomethylbenzothiophene 1,1-dioxides with thiourea in methanol were very dependent on the halogen atom, and had the same ratio of halogen activities as normal S_N2 reactions with the same nucleophile. However, although this eliminates mechanisms for this reaction in which the carbon–halogen bond fission is not the rate-determining step, it is equally in accord with a two-step mechanism where the second step is rate-determining (some cases of aromatic substitution are known where this is so). However unlikely this

might be considered for relatively unactivated substrates, the mechanism could be altered by the presence of strongly electronegative substituents on C_β (e.g. CN, NO_2, Ph, NO_2) which would not only facilitate attack on C_γ, but would also tend to stabilize the possible resultant ion.

B. *Unimolecular Substitution Reactions*

The first step in allylic unimolecular reactions is similar to that in the aliphatic series (section II) in so far as it involves ionization to yield a carbonium ion (**5**) (equation 10).



(10)

(**5**)

However, the carbonium ion formed is now mesomeric by virtue of the initial double bond, and attack by the second nucleophile can now occur at either end to give, in the case of an unsymmetrical carbonium ion, different products. For example, the solvolysis of $(CH_3)_2C{=}CHCH_2Cl$ in acetic acid–silver acetate yields the two possible products (equation 11). That the isomeric $(CH_3)_2CClCH{=}CH_2$

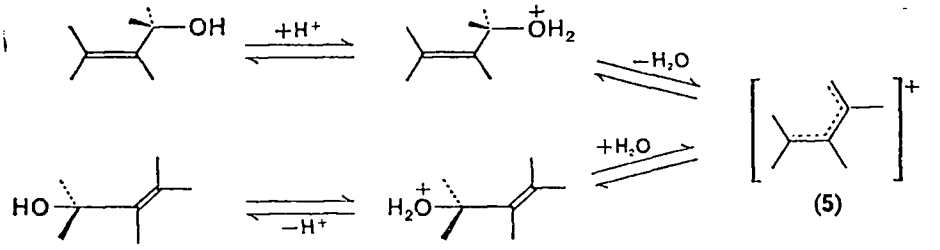
$$(CH_3)_2C{=}CHCH_2Cl \xrightarrow[CH_3COOAg]{CH_3COOH} \underset{55\%}{(CH_3)_2C{=}CHCH_2OH} + \underset{45\%}{(CH_3)_2\overset{\overset{OH}{|}}{C}{-}CH{=}CH_2} \quad (11)$$

which should yield the same intermediate carbonium ion, in fact gives the same mixture of products[27] is good evidence for the S_N1 mechanism. Electron-releasing substituents at the α and γ positions stabilize the intermediate (**5**) and lower the activation energy, thereby increasing the rate[28]. The effect of monosubstitution by an alkyl group in these positions in allyl chloride increases the rate by a factor of (2–5) $\times$ 10^3. Two alkyl substituents are roughly twice as effective as one in a given position. A phenyl substituent is somewhat more activating than a methyl group[21].

However, most of the data pertinent to this reaction come from solvolysis reactions such as that described above, and, in these cases, kinetic evidence for the molecularity of the reaction is missing. As the solvent is one of the reactants, 'first-order' kinetics will be shown

by both unimolecular and bimolecular reactions. Care must therefore be taken in the interpretation of the data in these systems, and the molecularity of the reactions decided from other factors. A complete discussion of these is given by DeWolfe and Young[21].

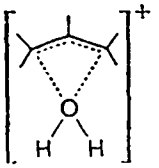
A particularly interesting case of the above reaction is the solvolysis of allylic alcohols. In the case where the attack is at the end of the carbonium ion where the initial ionization took place, the starting material is regenerated. If, however, attack takes place at the other end of the carbonium ion, the net result is isomerization of the allylic alcohol (equation 12). Although the reaction is acid-catalysed, it comes within the scope of the present chapter because of the nucleophilic attack of OH_2 which actually represents the isomeriza-



Isomerization (12)

tion process. The reaction can also be described in terms of an S_Ni mechanism involving a cyclic intermediate of type **6**.

Although the reaction is again of the solvolysis type, and inferences as to the molecularity of the reaction must be made from sources other than kinetic ones, the evidence favours the intermediacy of a carbonium ion such as **5** or **6**, and not a concerted bimolecular process.



(6)

In some cases, a decision between the S_N1 and the intramolecular S_Ni reaction can be made by using ^{18}O-labelled alcohol where, if the reaction is of the S_Ni type, the ^{18}O should be retained in the product. In the isomerization of α-phenylallyl alcohol in acidic 60% aqueous dioxane[29] and in 40% dioxane–aqueous perchloric acid[30],

the rearranged alcohol contains little of the ^{18}O of the starting alcohol, and the mechanism is considered to be S_Ni.

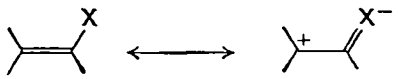
However, a similar study[31] of the isomerization of *cis*- and *trans*-5-methyl-2-cyclohexene showed that although the *trans*-isomer reacted by the S_Ni mechanism, the *cis*-isomer isomerized mainly by the intramolecular S_Ni mechanism.

IV. ATTACK ON CARBON-CARBON MULTIPLE BONDS

A. General Comments on C=C Bonds

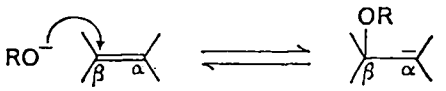
The very high electron density in the double bond system of ethylenes makes direct nucleophilic attack unfavourable, unless there are one or more electronegative groups present which can lower the electron density at the carbon atoms. Common activating groups are NO_2, CN, COR.

For such electronegative groups, the resonance structures of the molecule are:



(7)

The contribution of structure **7** depends on the nature of X, the net effect being the lowering of the electron density at the carbon atom β to the electronegative group, and nucleophilic attack will normally take place at this position. In general, the attack of alkoxide and hydroxide ions on C=C bonds can be rationalized[32, 33] in terms of a general first equilibrium reaction in which an anion **(8)** is formed by the attack of the nucleophile on the β-carbon atom of the double bond (equation 13). According to the nucleophile and



(8) (13)

the conditions, the further reaction of **8** can give rise to a whole variety of products. For hydroxide and alkoxide ions, reactions involving addition, decomposition and substitution are the most important and these will be discussed separately. As will be seen below, it is in some cases critical whether the nucleophile is hydroxide or alkoxide ion, the presence of the ionizable hydrogen on the former

giving rise to a quite different reaction path, although the initial reaction is similar in both cases.

B. Attack on C=C Bonds

1. Attack by alkoxide ions: addition of alcohols

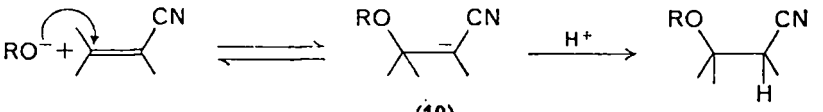
In 1905, Meisenheimer[34] found that sodium methoxide or sodium ethoxide added instantaneously and at room temperature to β-nitrostyrene with the formation of an alkoxy derivative (9).

$$C_6H_5CH{=}CHNO_2 \xrightarrow[CH_3ONa]{CH_3OH} C_6H_5\underset{\displaystyle OCH_3}{\underset{|}{CH}}{-}CH_2NO_2$$

(9)

This is found to be a general reaction of arylnitroalkenes[35] and other activated double bonds[33].

The kinetics of the cyanoethylation reaction between cyanoethylene and various alkoxides in their parent alcohols have been investigated by Feit and Zilkha[36]. Their kinetic analysis showed that the alkoxide ions and not the alcohols were acting as nucleophiles. The reaction was first-order in both cyanoethylene and alkoxide ion and proceeded according to the scheme below (equation 14). The



(10) (14)

first step in the reaction, the formation of the intermediate **10**, is a particular case of reaction (13). Feit and Zilkha also found that the rate of the reaction was independent of the counterion for a given alkoxide, and within a series of alkoxides, was in the order $OMe^- < OEt^- < n\text{-}PrO^- < n\text{-}BuO^- < i\text{-}PrO^-$, reactivity inversely proportional to the acidity of the alcohol.

The same relative reactivities of alkoxides was found by Ferry and McQuillin[37] for their reaction with $CH_2{=}CHCOCH_3$. The butenone was formed in an initial, very fast reaction of the methobromide of 4-dimethylaminobutan-2-one with base (equation 15a). The rate-determining step (equation 15b) is second-order, first-order in both base and substrate, and is thought to proceed in an analogous manner to equation (14) above. A similar mechanism (equation 16) was proposed by Crowell and co-workers[38] for the basic methanolysis

$$Me_3\overset{+}{N}CH_2CH_2COCH_3 \xrightarrow[\text{fast}]{OR^-} CH{=}CHCOCH_3 \qquad (15a)$$

$$CH_2{=}CHCOCH_3 \underset{}{\overset{ROH}{\rightleftharpoons}} RO{-}CH_2CH_2COCH_3 \qquad (15b)$$

of dibenzoylethylene. They found that a linear Hammett relation

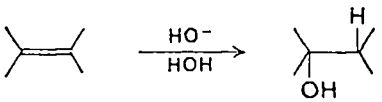
$$PhCOCH{=}CHCOPh \overset{OCH_3^-}{\rightleftharpoons} PhCO\bar{C}H{-}\underset{\displaystyle OCH_3}{\underset{|}{CH}}{-}COPh \xrightarrow[HOCH_3]{fast} PhCOCH_2{-}\underset{\displaystyle OCH_3}{\underset{|}{CH}}{-}COPh \qquad (16)$$

existed between the rates and the sum of the σ-values of the *para*-substituents in both rings.

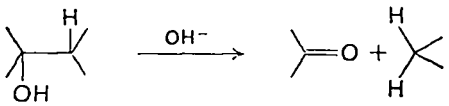
Although the stereochemical course of the reaction has not been investigated in detail, one can envisage different products depending on the lifetime of the intermediate ion **9**. Thus, if the addition of H^+ was very fast, giving a short lifetime to the intermediate, the addition of the alcohol would approximate to a concerted reaction, and one would obtain a product in which the elements of the alcohol were orientated *trans*. If, however, the intermediate ion **9** had a finite lifetime longer than the time for rotation about the C_α-C_β bond, one would obtain a range of configurations.

2. Attack by hydroxide ion or H_2O: cleavage reactions

Attack by OH^- to yield a simple hydration of the double bond (equation 17a) is in accord with the attack by alkoxide ions discussed in the previous section. However, the product (**11**) formed in



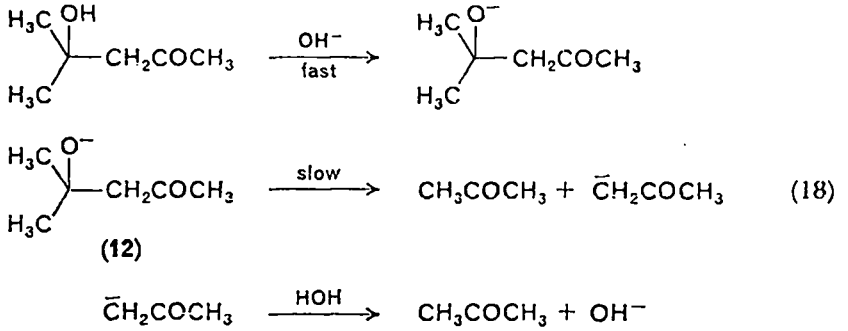
(11) (17a)



(11) (17b)

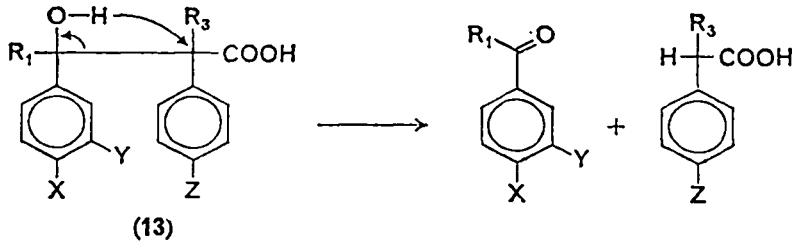
this case differs from the corresponding alkoxy product in that it contains an ionizable hydrogen and, in general, further reaction occurs (equation 17b), giving cleavage to the corresponding carbonyl and active methylene compounds. There is no reported case of cleavage caused by alkoxides alone. Steps (17a) and (17b) are essentially the reverse equilibria of the condensation reactions commonly used to prepare alkenes[39].

Reactions corresponding to step (17b) above can be investigated independently of the initial stages (equation 17a) in the above reaction mechanism[40, 41]. Thus, Westheimer and Cohen[40] studied the dealdolization of diacetone alcohol and found the reaction to be base-catalysed and to follow the reaction equation (18), with the rate-determining step the decomposition of the ion **12**.



(18)

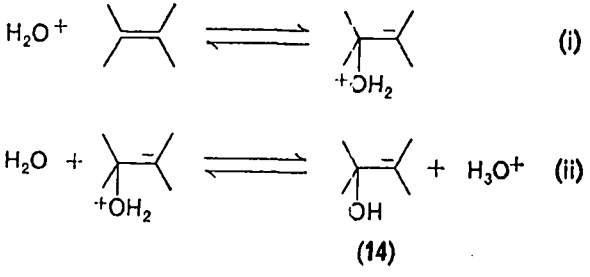
In contrast, Rondestvedt and Rowley[41] found that, in the cleavage of β-hydroxy acids and esters of general formula **13**, the results were best correlated in terms of a concerted mechanism in which the breaking of the C_α–C_β bond in **13** was essentially simultaneous with the breaking of the O–H bond (equation 19), there being no significant build-up of an intermediate corresponding to **12**. The



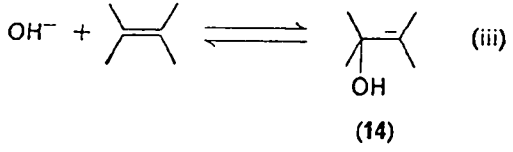
(13) (19)

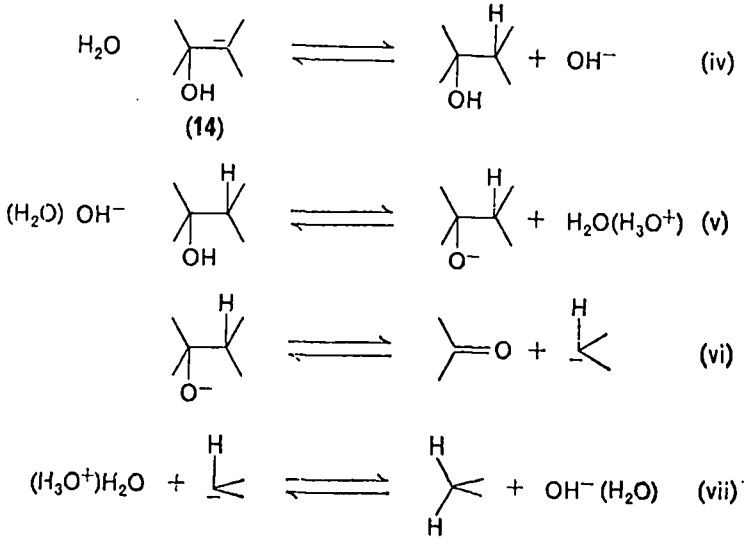
competition between hydrolysis and alkene formation in similar systems has also been investigated[47].

Attack by OH_2 (20a)



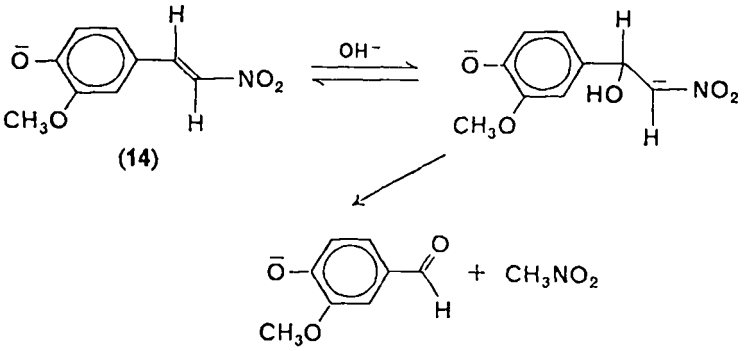
Attack by OH^- (20b)





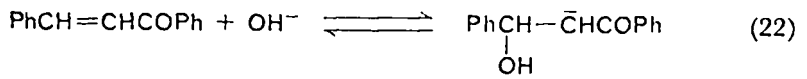
The kinetics of several complete hydrolyses have been investigated[42–47]. The results can all be accommodated by the expansion of the reactions (17a, b) into the general scheme below, where the initial attack can either be by hydroxide ions or water molecules to form the ion **14**. From this point, the two schemes are equivalent.

Thus Stewart[42] found that the yellow phenolate (**14**) of 4-hydroxy-3-methoxy-β-nitrostyrene loses its colour in basic solvent owing to hydration. The kinetic analysis pointed to attack by hydroxide ion (equation 21).



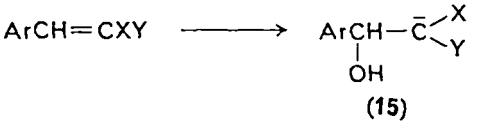
(14) (21)

Similarly, Walker and Young[43] found that the base-catalysed decomposition of mononitrochalcones in aqueous alcohol was second-order, the rate $= k'$[chalcone] $= k$[chalcone][NaOH], suggesting initial attack by OH^- (equation 22).



(22)

Patai and Rappoport[44, 45] found that the hydrolysis of arylmethylene malononitriles could follow either equation (20a) by attack of hydroxide ions, or equation (20b) by attack of water, depending on the reaction conditions. Thus the base-catalysed hydrolysis in 95% ethanol[44] indicated initial attack by hydroxide ion to form the intermediate ion (**15**) directly as in equation (20b) (equation 23). When the same hydrolysis was carried out in 95%



(15) (23)

ethanol in the absence of base, the reaction scheme followed was equation (20a), the rate-determining step being the relatively slow

initial attack by H_2O to give the ion **16** which then reacted to give **15** as in equations (24a, b). Evidence for this reaction scheme was

$$ArCH{=}CXY + H_2O \rightleftharpoons ArCH(^+OH_2)-\bar{C}XY \quad (24a)$$

(16)

$$ArCH(^+OH_2)-\bar{C}XY + H_2O \rightleftharpoons ArCH(OH)-\bar{C}XY + H_3O^+ \quad (24b)$$

(15)

that the rate depression by acids was dependent[45] on the concentration of the substrate.

A similar dependence of mechanism on the reaction conditions was found by Crowell and Francis[46] in the hydrolysis of substituted β-nitrostyrenes in aqueous solution. At pH 0·8—6·0, they found two consecutive, pseudo-first-order reactions, the first of which showed general base catalysis, and the second of which was pH-dependent, in agreement with equations (25a, b), involving attack by H_2O.

$$ArCH{=}CHNO_2 + OH_2 \rightleftharpoons ArCH(^+OH_2)-\bar{C}HNO_2 \quad (25a)$$

$$ArCH(^+OH_2)-\bar{C}HNO_2 + OH_2 \rightleftharpoons ArCH(OH)-\bar{C}HNO_2 + H_3O^+ \quad (25b)$$

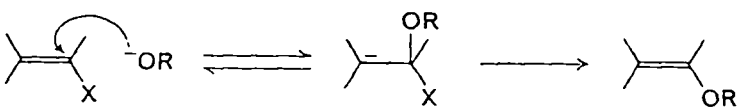
(17)

At higher pH, the cleavage occurred at an enhanced rate, and at pH 11, the primary step changed, attack being by OH^- to form the ion (**17**) directly.

3. Substitution reactions

If there is a labile group attached directly to the double bond, a replacement reaction can occur after the initial attack by the anion (equation 26), by an 'addition–elimination' mechanism.

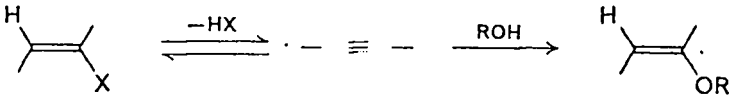
There are several other routes which can give the substitution



$$+ X^- \quad (26)$$

Addition-Elimination **(18)** **(19)**

product (**19**). The most important of these is the 'elimination–addition' mechanism shown in equation (27) in which an acetylene is formed initially which then adds the elements of the alcohol (see section IV.C) to give **19**.



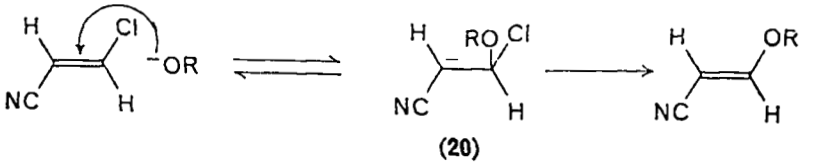
Elimination–Addition **(19)** (27)

The reactions (26) and (27) differ in several significant aspects which can, in principle, be used to distinguish between them. Thus in route (26) there should be no deuterium exchange with the solvent, but (27) should give complete exchange. Stereochemically, one might also hope to differentiate between the two reactions: (27) will give no relationship between the stereochemistry of the two isomers, as both *cis*- and *trans*-isomers will give the same intermediate acetylene. In equation (26), however, there is the possibility that the stereochemistry of the starting material will influence that of the product: thus if the ion **18** has a relatively long lifetime, there will be a distribution of the isomeric products depending on their thermodynamic stability, but if **18** is very short lived, approaching in the limit a concerted reaction, then one might expect a reaction where the stereochemistry of the reactant is retained in the product. However, it is seldom that a clear-cut distinction can be made between the two schemes (which may, of course, occur simultaneously), owing to complicating features such as the possible *cis–trans*-isomerization and further addition to the double bond (section B.1 above) which can obscure differences in stereochemistry.

In general, mechanism (26) will be favoured for compounds with a low electron density on the β-carbon atom to provide the initial attack. Mechanism (27) will be especially favoured in *cis*-isomers where there is a favourable *trans*-disposition of the elements of HX (where X is the leaving group) to promote the elimination reaction. For a given substrate, the occurrence of the elimination–addition mechanism will depend on the proton basicity of the nucleophile. Since alkoxide ions are highly basic with respect to protons, in many instances, reaction (27) will compete with reaction (26).

Thus, although the *cis*- and *trans*-isomers of β-chlorocrotonate undergo substitution by thiophenoxides with retention of configuration, only the *trans*-isomer is obtained in substitution by alkoxides[48].

However, both the *cis*- and *trans*-isomers of β-chloro-α-cyanoethylene react with alkoxides to give products of the same stereochemistry as the starting materials[49], and the reaction can be formulated as in equation (28) with the restriction that the intermediate ion (**20**) must have a very short lifetime, or that the reaction proceeds in a concerted manner.

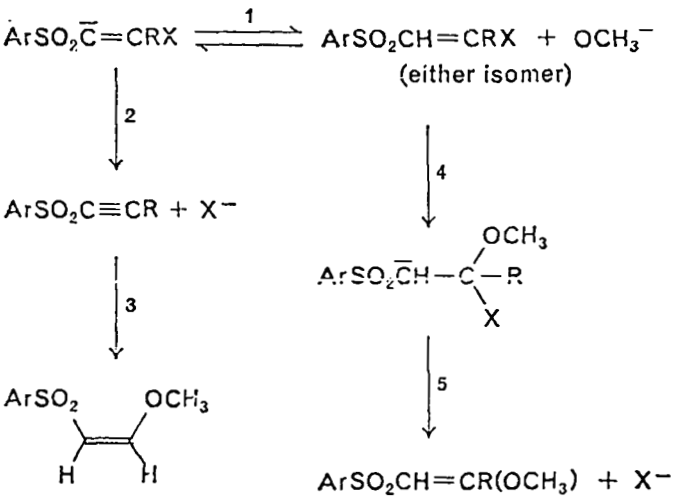


(20) (28)

The competition between the two possible mechanisms for substitution has been investigated in detail for the reactions of arylsulphonylhaloethylenes (**21**) with methoxide ion by Modena and co-workers[50–54].

$$RC_6H_4SO_2CR^1{=}CR^2X$$

(21)



(29)

Their results, some of which are summarized in Table 2, are discussed[54] in terms of the reaction scheme (29). The addition–elimination mechanism 1, 4, 5, under the restrictions discussed above, could give retention of configuration of both isomers, whereas both isomers would give the *cis*-product by the elimination–addition mechanism (steps 2 and 3 in equation 29), as both would give the acetylene and the stereochemistry of step 3 is known[50, 54] to give

the *cis*-product. There is retention of configuration in the *trans*-isomers, indicating that these react via 1, 4, 5, and the lack of any element effect in two series of *trans*-compounds (Table 2) suggests that the breaking of the C–Hal bond is not rate-determining, in accordance with $k_4 < k_5$. A critical case is compound IV (Table 2) where α-elimination is not possible and reaction must be by addition–elimination. There is now no difference, either in rates or in activation energies, between the four isomers.

The *cis*-isomers behave quite differently, showing both greatly enhanced rates of reaction and also very strong element effects (Table 2). The large differences in the rates of reaction between compound IV (*cis*), where no elimination is possible, and the other

TABLE 2. Rate coefficients $k_2 \times 10^3$ (l m^{-1} sec^{-1}) of reactions of substituted arylsulphonylethylenes (**21**) with methoxide ion in methanol solution

				X = Br		X = Cl		
R	R^1	R^2	Temp.	*cis*	*trans*	*cis*	*trans*	Ref.
p-NO_2 I	H	H	0°C	—	—	280	168	50
p-Me II	H	H	0°C	1780	5·35	9·6	6·4	51
H III	H	H	0°C	2600	8·8	18	10·5	51
p-NO_2 IV	Me	H	(25°C)	5·05	5·26	5·40	6·22	52
p-NO_2	H	Me	(25°C)	7850	—	71·9	—	53

TABLE 3. Kinetic and thermodynamic parameters for the elimination–addition (subscript e) and addition–elimination (subscript a) reactions of *cis* arylsulphonyl chloroethylenes[65].

RC_6H_4—SO_2CH=CHCl with methoxide ion in methanol[a].

R	Temp.	k_e/k_a	E_e (kcal/mole)	E_a (kcal/mole)
H	0	1·1	24	17
	13	2·2	—	—
	25	3·0	—	—
p-CH_3	0	0·8	—	—
	13	1·0	24	20
	25	1·4	—	—

[a] The estimated errors are ca 10% for the rate coefficients and ±1 kcal/mole for the activation energies.

cis-isomers suggests the occurrence of the competing addition–elimination reaction (steps 2 and 3 in equation 29) which would be favoured in the case of the *cis*-compounds by a facile *trans*-elimination of HX.

Retention of configuration in the case of the *cis*-isomers is ambiguous, as both routes would give the same stereochemistry (equation 29). The exact relationship between the two mechanisms in the case of the *cis*-isomers has recently been studied in detail[55]. Direct evidence was found for the occurrence of the elimination–addition mechanism (steps 2 and 3) in the detection of the intermediate acetylene, both by isolation in cases of suitable kinetics, and by infrared spectroscopy in others. In a detailed examination of the kinetics, it was found possible to separate the kinetic parameters for the two processes. These are summarized in Table 3. The activation energy for the elimination–addition mechanism is larger than for the addition–elimination mechanism and the elimination mechanism becomes more important at higher temperatures. It was found to be significant at room temperature in all the cases studied.

An extreme case of the difference in the reaction of *cis*- and *trans*-isomers, due to the tendency of the *cis*-isomer to react by elimination, is found in the reactions of the isomers of 4-nitro-β-bromostyrene[56, 57, 58a] and 2,4-dinitro-β-bromostyrene[58a] with alkoxides. The *cis*-isomers react by a *trans*-elimination of HBr to form the corresponding acetylenes (equation 30). It has been suggested that

$$RC_6H_4CH{=}CHBr \xrightarrow{OCH_3} RC_6H_4C{\equiv}CH + HOCH_3 + Br^- \qquad (30)$$

TABLE 4. Rate coefficients and thermodynamic parameters for the reaction of bromostyrenes of general formula ArCX=CHBr with methoxide ion in MeOH solution[58a a].

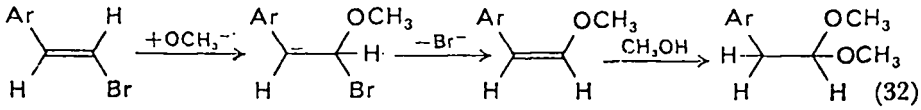
Compound	Ar	X	Temp. (°C)	$k \times 10^3$ (l m^{-1} sec^{-1})	E^a (kcal mole^{-1})	ΔS_{25}° (e.u.)
I *cis*	4-nitro	H	25	0·71	25	+8·8
II *cis*	4-nitro	D	25	0·32	—	—
III *trans*	4-nitro	H	78·25	0·97	25·1	−2·8
III *trans*	4-nitro	D	78·25	0·98	—	—
IV *cis*	2,4-dinitro	D	25	1070	19·9	+6·3
V *trans*	2,4-dinitro	H	25	720	18·9	−7·1

[a] Similar results are obtained from the corresponding chloro-compounds[58b].

the elimination is by a concerted mechanism[59]. However, the *trans*-isomers react much more slowly to form the acetals as indicated in equation (31). The addition of the OCH_3 groups to the β-carbon

$$RC_6H_4CH{=}CHBr \xrightarrow[CH_3OH]{^-OCH_3} RC_6H_4CH_2CH(OCH_3)_2 + Br^- \qquad (31)$$

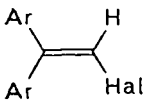
atom is in accord with the occurrence of the addition mechanism with subsequent addition of MeOH as in equation (32).



(32)

That equation (30) was not important in the case of the *trans*-isomers was shown[58a] by studies on the α-deuterated compounds (Table 4). There is no isotope effect, and no exchange of deuterium with the solvent, eliminating equation (30). The isotope effect shown by the *cis*-isomers is in accord with the reaction proceeding completely by elimination. By contrast, nucleophiles which are much less hydrogen-basic react with both the *cis*- and *trans*-isomers of these systems to give products with retention of configuration, indicating an addition–elimination mechanism for both isomers[58, 60]. Very similar results have recently been reported for the reactions of the corresponding chloro compounds[58b].

1,1-*diphenylethylenes*. The possibility of α-hydrogen abstraction is removed in the case of 2-halo-1,1-diphenylethylenes, and these would seem to be ideally suited for kinetic investigations of alkene nucleophilic substitution reactions. However, 1,1-diphenyl-2-chloro- or -2-bromoethylenes react with basic alcoholic solutions to give, in addition to substitution of the halogen by alkoxide ions, or, in some cases, instead of this substitution, rearrangement by α-elimination to give diphenylacetylenes as in equation (33) (Fritsch rearrange-

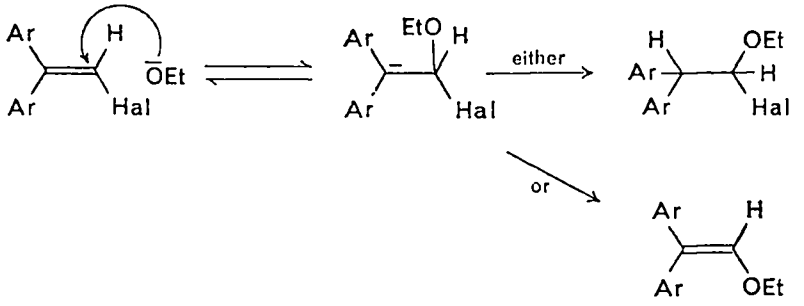


$$\xrightarrow{OCH_3^-} \underset{(21)}{Ar{-}C{\equiv}C{-}Ar} + CH_3OH + Hal^- \qquad (33)$$

ment[61, 62]). When t-BuO^- is used as base, only α-elimination occurs[63], while other alkoxides give mixtures of the two mechanisms[64]. Replacement of the α-hydrogen with a methyl group does not give a clean substitution reaction[65].

However, some suitably substituted derivatives do give clean

substitution reactions. Thus, Silversmith and Smith[66] found that 1,1-diphenyl-2-fluoroethylene reacted with OEt^- in ethanol to give 1,1-diphenyl-2-ethoxethylene. The reaction was first-order with respect to both reactants, and the authors concluded that the results were consistent with an addition–elimination mechanism in which the first step was the formation of an ionic intermediate [(equation 34), with Ar = C_6H_5 and Hal = F].



(34)

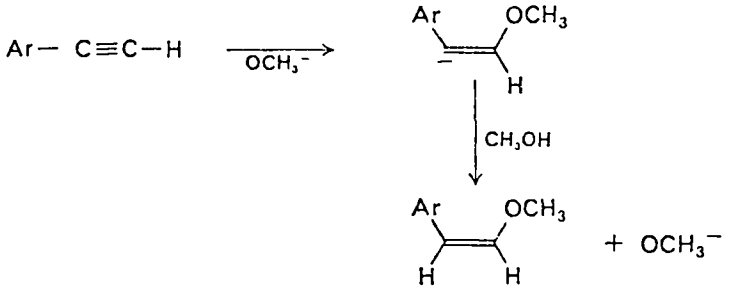
Similarly, Beltrame and co-workers[67] found that *p*-nitro substitution in the phenyl rings gave simple alkoxydehalogenation of the chloro- and bromo-derivatives. The reactions were again first-order with respect to each reactant, and the results can be accommodated in equation (34) above (with Ar = p-$NO_2C_6H_4$ and Hal = Cl, Br). The rates of reaction were 10^6 × those of the unsubstituted compounds, and a correlation between the rates of reaction for a series of *p,p*-disubstituted derivatives and the sum of the Hammett parameters for the two substituents was found. A discussion of the theoretical approach of these authors to this reaction will be given in section IV.D.

C. Attack on C≡C Bonds: Addition of Alcohols

The addition of alcohols and phenols to acetylenes can be catalysed by both alkoxides[68] and tertiary amines[69]. As with alkenes, reaction is greatly facilitated by the presence of electron-withdrawing substituents. The addition is generally[68, 70] considered to proceed by a *trans* mechanism.

Thus Miller[68] found that the reaction of phenylacetylene with sodium methoxide in methanol solution gave only one isomer, considered to be the *cis*-form. The mechanism (35) (Ar = Ph) was suggested to account for this.

Similarly, Modena and co-workers[71, 72] have shown that the

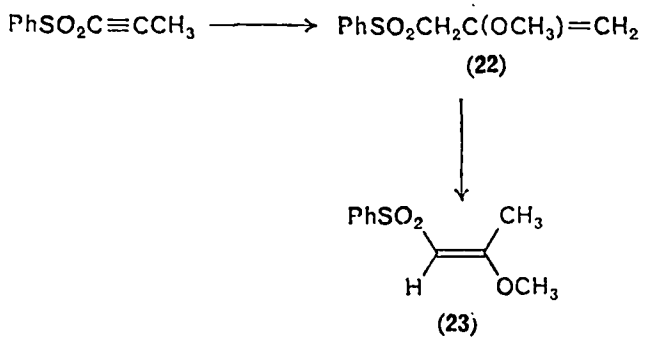


(35)

methoxide-catalysed addition of methanol to *p*-tolylsulphonylacetylene gives the *cis*-2-alkoxy-1-*p*-tolysulphonylethylene [equation (35), Ar = *p*-tolyl·SO_2].

The reaction, measured by the rate of disappearance of the acetylene by measurement of the C≡C infrared stretching frequency, was found to obey a first-order kinetic equation, as the alkoxide concentration does not change with time, but the rate depends on the first power of the alkoxide concentration as required by equation (35). As judged by the second-order rate constants for the reaction, ethoxide ion reacts faster than methoxide ion. The activation energies for the addition of MeOH and EtOH are very similar: E_a(MeOH) = 16·4 kcal mole^{-1}, E_a(EtOH) = 17·6 kcal mole^{-1}.

Although substitution of the acetylene hydrogen by a methyl group does not alter the kinetics of the reaction significantly[73], it alters the course of the reaction[74], giving 2-methoxy-3-phenylsulphonylpropene (**22**) as the kinetic product which then isomerizes to *trans*-2-methoxy-1-phenylsulphonylpropene (**23**) as in equation (36).



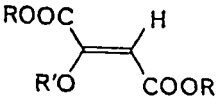
(36)

(22)

(23)

The addition of alcohols to disubstituted acetylenes has been investigated by Winterfeldt and co-workers[69, 70, 75, 76]. In general, the rule of *trans*-addition is borne out. Thus, addition of alcohols to

acetylene dicarboxylate gives mainly the compound **24**, although additions at high temperatures lead to the *cis*-derivative. With dicyanoacetylene, however, the *cis*-isomers predominate, even although the reactions were performed at room temperature.



(24)

In general, alkoxide-catalysed additions to triple bonds will be complicated by the possibility of the base-catalysed isomerization of the resulting alkene(s). Arguments regarding the stereochemistry of the reaction which are based on product analysis will be more valid when the thermodynamically less stable alkene predominates.

D. Investigations Involving Intermediates

In 1885, Friedlander[77] found that *p*-nitro-*β*-nitrostyrene formed a complex which he formulated as **25** when it was treated with an alcoholic solution of potassium hydroxide (equation 37). The salt decomposed rapidly in the free state yielding the original components. This compound does not seem to have been investigated further, but recently intermediates corresponding to those postulated

$$p\text{-}NO_2C_6H_4CH{=}CHNO_2 \xrightarrow[EtOH]{OEt^-K^+} p\text{-}NO_2C_6H_4\underset{\displaystyle OEt}{\underset{|}{CH}}{-}CH{=}NOO^-K^+ \quad (37)$$

(25)

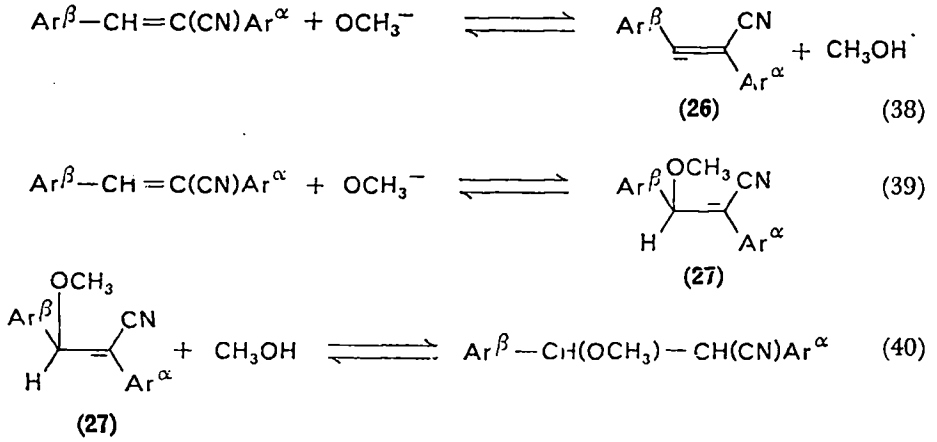
TABLE 5. Wavelengths (mμ) and extinction coefficients (l m^{-1} cm^{-1}) of the positions of maximum absorption of substituted α-cyanostilbenes in basic DMSO–ethanol mixtures[78].

	Stilbene	λ_{max}	ε
I	4-nitro	547	42,600
II	3′-chloro-4-nitro	547	43,700
III	4,4′-dinitro	553	42,100
IV	4-cyano	402	47,400
V	3′-chloro-4-cyano	402	47,200
VI	4′-nitro-4-cyano	393	44,000
VII	3-cyano	363	28,800

as the product of initial attack by alkoxide ions o. general formula **9** have been completely characterized in activated stilbene systems[78–80].

Thus, the interaction between alkoxide ions and a large number of substituted stilbenes in DMSO–methanol mixtures has been investigated by Stewart and Kroeger using u.v. spectroscopy for the purpose of establishing an H_- scale[78, 79]. The u.v.–visible spectra of these solutions (Table 5) are quite different from those of the parent stilbenes and show trends which are indicative of the nature of the species formed.

Of the possible reactions (38–40), it was considered that[48], under



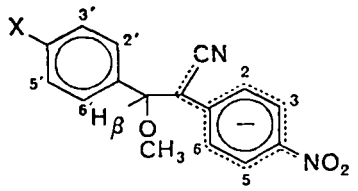
the conditions of the experiment, the contribution from equation (40) would not be significant. From the similarity in shape and position between the u.v. spectra of the species formed from α-cyano-4-nitrostilbene and the anion of 4-nitrobenzyl cyanide, it was concluded that the colour-producing species was **27** and not **26** which could be formed by proton abstraction. Further support for the colour-producing reaction being one of methoxide addition, rather than proton abstraction, comes from the general effect of substituents in the two rings, both on the position of the u.v.–visible maximum[78] (Table 5) and the equilibrium constant for the reaction[79]. In general, substituents in the β-phenyl ring (I—III and IV—VI) have much less effect than substituents in the α-phenyl ring (I, IV, VII; II, V; III, VI) as would be expected from structure **27**, whereas **26** would give exactly the opposite trend.

The interactions of anhydrous sodium methoxide with a series of α-cyano-4-nitro-4′-X-stilbenes have also been studied by n.m.r.[80], and the intermediates formed in these cases characterized unam-

biguously. Because of the lack of abstractable hydrogens in the system, reaction (40) cannot occur.

The n.m.r. spectra of the products of reactions corresponding to equations (38) and (39) for α-cyano-4-nitro-4′-X-stilbenes would be expected to be quite different and diagnostic: Thus the product (**28**) one would expect to have an n.m.r. spectrum consisting of a 'normal' aromatic spectrum for the β-phenyl ring and a spectrum closely corresponding to the spectrum of the anion of 4-nitrophenylacetonitrile (**30**) for the α-phenyl ring, but showing some variation with both nucleophile and substituents. There should be a large change in the chemical shift of H_β from an alkene hydrogen at low field to a hydrogen attached to an sp^3 carbon atom at higher field, whose chemical shift would be dependent on the nature of the nucleophile.

The spectrum of compound **29** would be quite different, a critical feature being the complete lack of an absorption corresponding to the abstracted alkene proton H_β. If hydrolysis occurred due to small traces of water, then the α-phenyl ring should show exactly the spectrum of the anion of 4-nitrophenylacetonitrile (**30**) with the methylene hydrogen at high field, and the β-phenyl ring the spectrum of 4-X-benzaldehyde, with the aldehydic proton at low fields and independent of the nucleophile.



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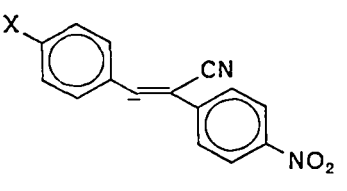

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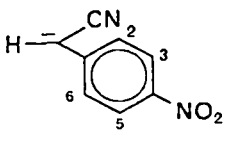


(30)

The addition of anhydrous sodium methoxide to a DMSO solution of α-cyano-4-nitro-4′-methoxystilbene gives an intense violet-pink coloration (λ_{max} 550 mμ) and causes the broadening and eventual disappearance of the spectrum of the stilbene and the appearance of a new spectrum at higher fields (Figure 1). The new spectrum consists of an AA′XX′ pattern centred at $\delta = -6{\cdot}95$ (rel. intens. 4), two multiplets centred at $\delta = -7{\cdot}34$ (doublet, rel. intens. 2) and $\delta = -6{\cdot}38$ (approximately a triplet with further splitting, rel. intens. 2), and a sharp singlet at $\delta = -5{\cdot}01$ (rel. intens. 1). The spectrum is consistent with the formation of the intermediate **28** (X = OCH_3), as shown in Figure 1.

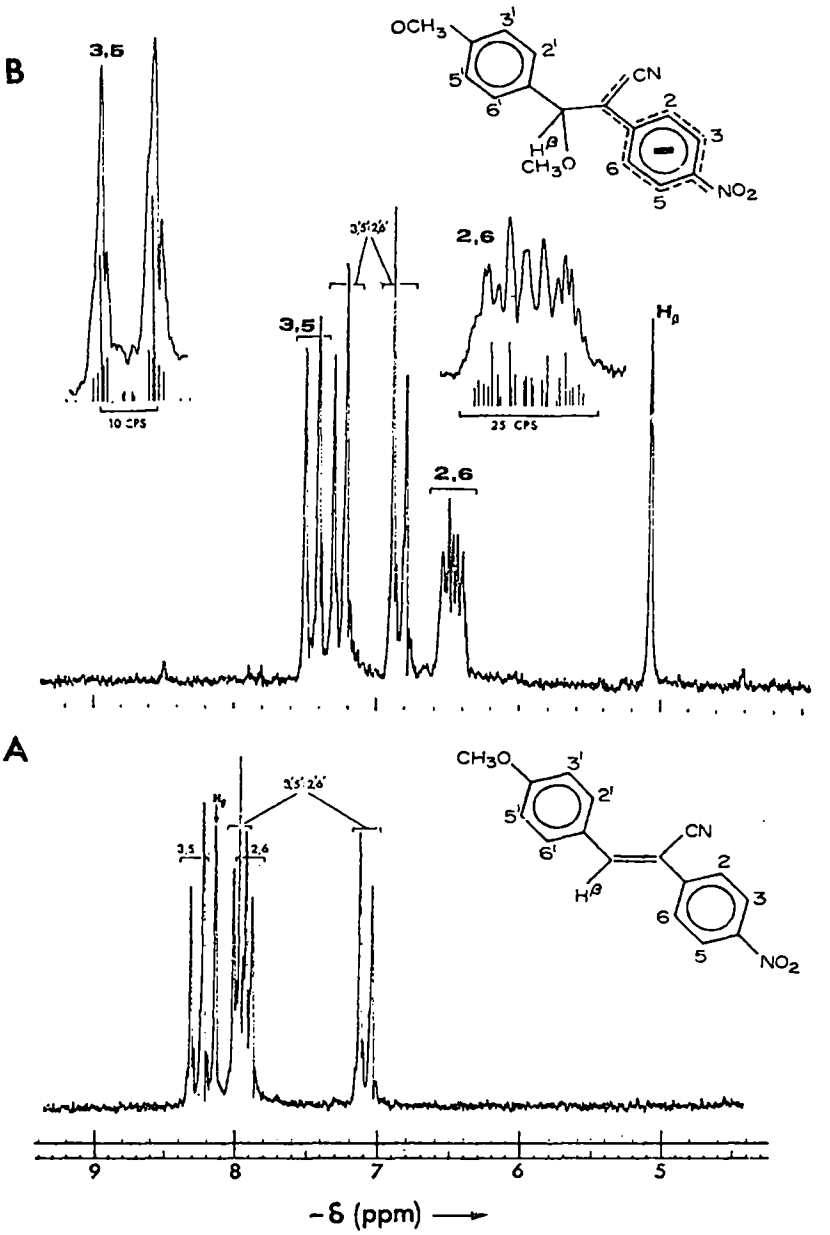


FIGURE 1. 100 MHz n.m.r. spectra of (A) X-cyano-4-nitro-4′-methoxystilbene in DMSO solution and (B) this solution after the addition of anhydrous sodium methoxide.

It is inconsistent with either hydrolysis or the occurrence of reaction (38). Thus the AA'XX' pattern can be assigned to the four hydrogens on the β-phenyl ring and the singlet at $\delta = -5{\cdot}01$ to the H_β proton. The shifts of the other two multiplets correspond very closely to those observed for the ring hydrogens of 4-nitrophenylacetonitrile anion (Table 6), although the multiplet structures are different, and can be assigned to the four hydrogens of the α-phenyl ring. That they do not form a simple AA'XX' system suggests that, as in the case of the 4-nitrophenylacetonitrile anion[81], there is restricted rotation around the α-phenyl–C_α bond, the complexity of the resonance at $\delta = -6{\cdot}38$ arising because $J_{23} \sim \gamma_0\delta_{2,6}$. This, and the very large changes in the chemical shifts of the α-phenyl resonances, suggest very substantial delocalization of the negative charge into the α-phenyl ring, so that the anion is probably more properly formulated as in **28**, rather than with the negative charge localized on the α-carbon atom as is usually done. This is thought to be the case for all the compounds studied. Such a delocalization would be favoured by a planar rather than a tetrahedral configuration at the α-carbon atom, and it is possible that this is the case for stilbenes with very electronegative groups in the 4-position.

The sharpness of the H_β proton would suggest that there is free rotation round the C_α–C_β bond as required for such intermediates to take part in the *cis–trans* isomerization of alkenes. The solutions are quite stable for several days.

Similar conclusions can be drawn regarding the structures of the intermediates formed from a whole series of α-cyano-4-nitro-4'-X-stilbenes. The n.m.r. parameters (Table 6) are in close agreement with those described above, but show small differences which rule out the formation of **30**, as identical spectra for the α-phenyl ring would be obtained in this case. In general, the complexes seem to be quite stable (at least in solution). The n.m.r. spectra reveal that, whereas there is free rotation about the β-phenyl–C_β and C_α–C_β bonds, there is restricted rotation around the α-phenyl–C_α bond in all the complexes and delocalization of the negative charge into the α-phenyl ring, suggesting perhaps the favouring of a planar configuration at this carbon atom. Although the above effects will, in general, be very dependent on the nature and position of substituents in the α-phenyl ring, it is thought that the results obtained from these more activated substrates may be of somewhat general applicability.

Both the *cis*- and *trans*-isomers of α-cyano-4-nitrostilbene give rise to the same n.m.r. spectrum on treatment with base.

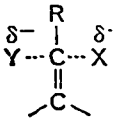
TABLE 6. Chemical shift data ($-\delta$, ppm), coupling constants (cps) and chemical shift differences (cps) from the 100 MHz n.m.r. spectra of compounds of general formula **28** and **30** in DMSO solution[a].

	X	H_β	$H_{2,6}$[b]	$\nu_0\delta_{2,6}$	$J_{2,6}$	$J_{2,3}\ J_{5,6}$	$J_{3,5}$	$\nu_0\delta_{3,5}$	$H_{3,5}$[b]	β-Phenyl ring
28	OCH_3	5·01	6·38	5·0 ± 0·5	2·5 ± 0·4	9·5 ± 0·5	1·8 ± 0·3	0·0 + 0·5	7·34	AA'XX' system
28	CH_3	5·09	6·44	8·5 ± 0·5	2·1 ± 0·3	9·5 ± 0·5	1·8 ± 0·3	0·0 + 0·5	7·45	AA'BB' system
28	NO_2[c]	5·36	6·56	18.0 ± 0·5	—	10·0 ± 0·5	—	—	7·50	AA'XX' system
28	H	5·16	6·51	9·5 ± 0·3	2·3 ± 0·3	10·0 ± 0·3	1·8 ± 0·3	0·5 ± 0·4	7·47	Unresolved multiplet
30	—	—	6·27	19·0 ± 0·3	2·3 ± 0·2	9·0 ± 0·2	2·6 ± 0·2	13·0 ± 0·3	7·39	—

[a] C. A. Fyfe, *Can. J. Chem.*, **47**, 2331 (1969).
[b] Denotes multiplet centre.
[c] Owing to radical-exchange broadening, only the major splittings were properly resolved.

E. Theoretical Approaches

In 1953, Gold[82] discussed alkene nucleophilic substitution reactions in terms of the possible intermediates or transition states **31** and **32**. In **31**, attack by the nucleophile occurs in the plane of the alkene so that in the transition state, the groups C,Y,R and X are all coplanar. Such a mode of displacement would give a change of configuration, and more recent work has eliminated this. The second possibility (**32**) where the attacked carbon atom assumes a



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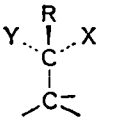
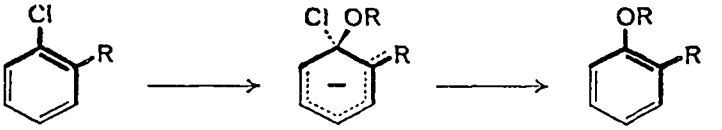


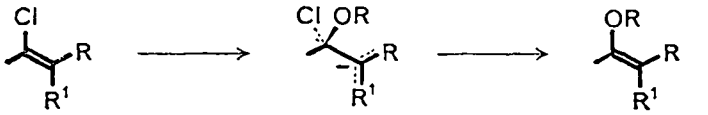
(32)

tetrahedral configuration, is more in accord with the experimental evidence. **32** could range from approximating to the transition state in a one-step mechanism to being a relatively stable carbanion.

In fact, the analogies between aromatic and alkene nucleophilic substitutions are very strong. The activation energies and the effect of substituents in both cases are very similar, and during the reaction the attacked carbon atom must change its configuration from sp^2 to sp^3, either in a transition state or intermediate complex (equation 41). In both cases, the existence of stable intermediates from suitably activated substrates can be demonstrated.



(41a)



(41b)

(R is an electronegative group)

It should be possible directly to extend the semi-quantitative approach of Miller[203] for aromatic substitution (see section V), using the same data, to, for example, the alkoxy dehalogenation of 2-(*p*-nitrophenyl)-1-haloethylenes. The transition states and intermediate complexes could be represented as I—V in Figure 2. By analogy with the aromatic system (see on), these would give rise in

the general case to curves of the types A—C in Figure 2. Thus a useful qualitative guide could be got as to the activation energies and also to the life-time of the intermediate complex, and hence the occurrence of essentially concerted reaction and possible retention of stereochemistry (curve C) or formation of the thermodynamically more stable isomer (curve A).

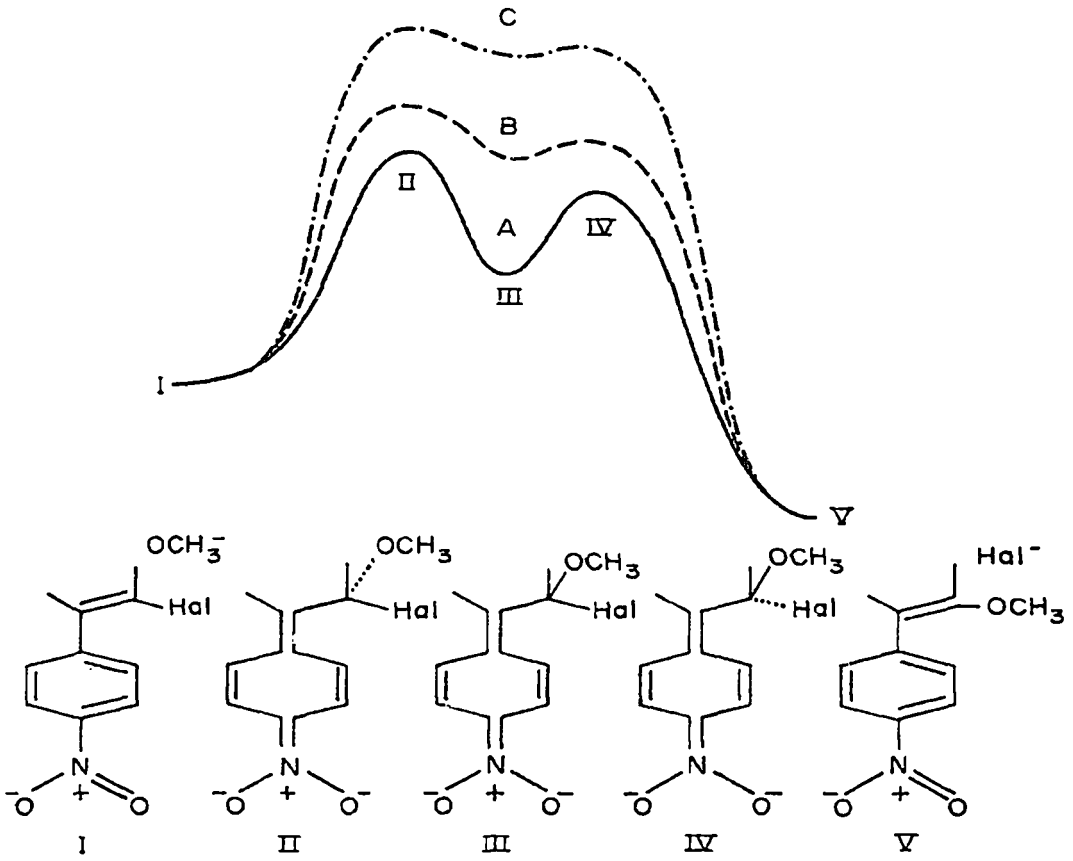
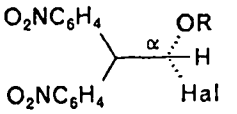


FIGURE 2. Possible energy profiles of a bimolecular, 'two-step' alkene substitution reaction.

Although there is this close analogy with aromatic substitutions, there has been little attempt to accommodate alkene substitutions within the general theoretical approaches to aromatic substitutions. Recently, however, Simonetta and co-workers[6,7] have extended their delocalization approach (see section V) to the alkoxy dehalogenation of 1,1-di-*p*-nitrophenyl-2-haloethylenes. They considered the attacking alkoxide group to approach from above the plane of the

alkene and to form a transition state of type **33** by attack at the α-carbon atom.



(33)

The leaving and attacking groups were considered together as a 'pseudo-atom' bonded to the residue by a 'quasi-σ' bond to the α-carbon atom and by interaction with the π-electrons of the residue via a 'quasi-π' orbital and two electrons just as in the aromatic case (see on). On this model, differences in π-electron energies in the initial substrates and the transition states (**33**) were calculated. A correlation was obtained between experimental ΔG values and calculated $\Delta E\pi$ values, but the authors considered that the fact that the parameters which had to be chosen for the pseudo-atom were different from the corresponding ones in the aromatic and aza-aromatic series gave rise to doubts as to the applicability of the method to alkene substitutions.

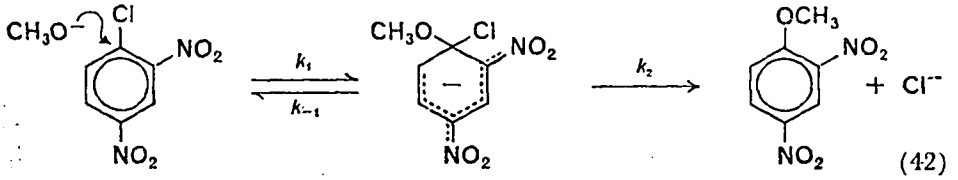
V. ATTACK ON AROMATIC SYSTEMS

A. General Comments

Because of the high electron density of the aromatic system, as with alkenes, nucleophilic substitution usually occurs only where there are one or more suitable electronegative groups (e.g. NO_2, CN, COR) oriented *ortho* and/or *para* to the position of substitution. Thus, although the Dow process for the direct conversion of chlorobenzene into phenol by Na_2CO_3 requires copper as catalyst and temperatures in excess of 300°C, *ortho*- and *para*-nitrohalobenzenes undergo relatively facile reaction with base.

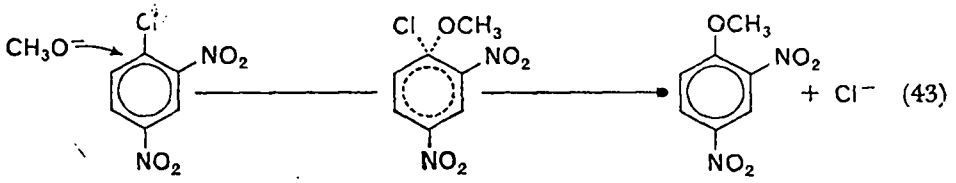
In general, the reactions are kinetically second-order, first-order with respect to both nucleophile and substrate, and are usually discussed[83–88] in terms of the 'two-stage' mechanism introduced by Bunnett[83, 85] (equation 42). In this scheme, the displacement of, for example, chloride ion from 2,4-dinitrochlorobenzene by methoxide ion is thought to proceed via an intermediate (**34**) of finite stability. In **34** both leaving and attacking groups are covalently bonded to the carbon atom at the point of attack which is now of sp^3 hybridization, and the negative charge from the attacking alkoxide ion is

delocalized round the residue of the aromatic ring and on to the two nitro groups. The energy profile of the reaction will have a minimum corresponding to the complex **34**.



(34) (42)

However, an alternative mechanism has been considered[89–91] (equation 43). In this, the reaction proceeds in one step, with synchronous bond making and breaking in an analogous manner to the aliphatic S_N2 reaction discussed in section II. There is *no* intermediate in this mechanism, and no dip in the energy profile of the reaction*.



Transition state (43)

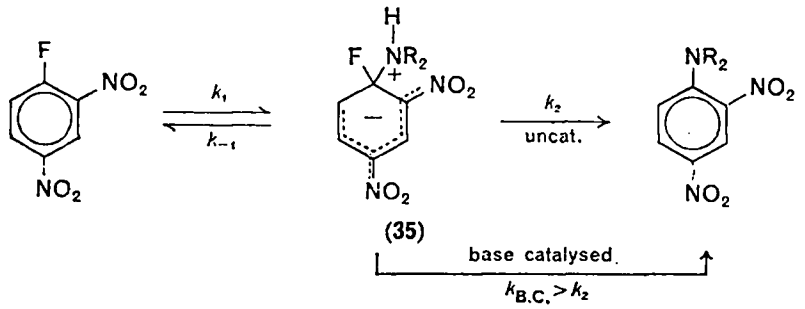
There are several general pieces of kinetic evidence in favour of the two-step mechanism: (i) In reactions where the fission of a carbon–halogen bond is a rate-determining step, the order of the rates of reaction is F < Cl < Br ~ I. In many aromatic substitution reactions involving halogens, the observed order is F ≫ Cl ~Br ~I[85]. This can be accounted for in terms of the two-stage mechanism with $k_2 < k_1$ in equation (42), but is difficult to explain on the basis of equation (43). The reverse order[89, 92] can also occur, and can also be accommodated in the two-stage mechanism with $k_2 > k_1$ in equation (42).

(ii) It is found[85] that the rates of reaction of a whole series of 1-X-2,4-dinitrobenzenes with piperidine are within a factor of five of one another, i.e., independent of the strength of the C–X bond.

* The structure assigned to the transition state in equation (43) should not be taken too literally as it is not entirely clear what type of structure is envisaged by those who have suggested this mode of reaction.

This again can be explained in terms of equation (42) with $k_2 < k_1$, but like (i) above is difficult to interpret in terms of the 'one-step' reaction scheme.

(iii) Very convincing kinetic evidence for the existence of an intermediate is the general base catalysis observed under certain conditions when amines are the nucleophiles. In terms of the intermediate complex theory (equation 44), the intermediate **35** will have a labile proton on the nitrogen atom. Any process which can facilitate the loss of this proton will increase the rate of conversion of **35** into products, as NR_2 is a much poorer leaving group than $^+NHR_2$. In the presence of a base, there will be the 'normal' conversion of the intermediate into products, and the faster 'base-catalysed' conversion, the overall effect being an increase in the reaction rate.



(44)

Since the catalysis involves the decomposition of the intermediate into products, it should only be observed in systems where the decomposition of the intermediate is the rate-determining step, i.e., $k_1 > k_2$, and will therefore be favoured by the presence of relatively poor leaving groups, and its occurrence and magnitude will vary as these groups are changed. In fact, base catalysis has been observed[93–97] in a variety of systems, and the general trends predicted[93] by the two-stage mechanism are found. Particularly incisive is the observation of a variable $^{16}O/^{18}O$ isotope effect in the substitution of 2,4-dinitrophenyl phenyl ether by piperidine, when catalysed by varying concentrations of hydroxide ion[97]. The general mechanism for the base catalysis is considered[94, 95] to involve a fast proton transfer, followed by a rate-determining removal of the leaving group by the moiety BH^+ [98].

Although any one particular case of catalysis could be accounted for in terms of the one-step theory by the postulate that the base intervened in the transition state, the differences observed with the

variation of substrate and nucleophile cannot reasonably be accommodated in this fashion, and the above observations provide the strongest kinetic evidence for the 'two-step' mechanism.

However, the cases which can kinetically be unambiguously assigned to the bimolecular mechanism are relatively few (and must obviously involve amines), and the general acceptance of the 'two-step' mechanism is to some extent due to its more flexible character, and to the inferences which can be drawn from other studies (see on).

B. Substitutions Involving Alkoxide and Hydroxide Ions

1. 'Activated' substrates

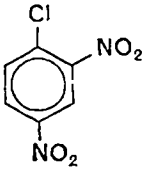
Displacement reactions involving attack by alkoxide and hydroxide at activated centres have been widely investigated. Typical of these are the displacement reactions involving halogens, some illustrative examples of which are given in Table 7. Activation by substituents is generally in the order *para* > *ortho* when alkoxide or hydroxide ions are the nucleophiles, both when judged by rates of reaction and by activation energies. The main effect of the substituents is seen in the very large lowering of the activation energy from that of the unactivated substrate.

The activating effects are not however additive (Table 7). Thus the introduction of a second nitro group lowers the activation energy by a much smaller amount than the introduction of a single group in either the *ortho* or *para* position.

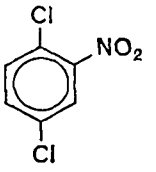
The relative activating effects of various substituents have been found[83, 85] to be in the order

$$-N_2^+ > -NO_2 > -SO_2CH_3 > -NMe_3^+ > -CN > -CF_3$$

In general, the effects of substituents will be shown in the ground state, the transition state, and in the intermediate complex, all of which may determine the kinetic pattern of the reaction. Correlations can be obtained with the variation of one or more substituents within a series of closely related compounds, which may allow inferences to be drawn regarding the mechanism. For example, Norman



(36)



(37)

and co-workers[99] found that in the bimolecular reactions of both 1-chloro-2,4-dinitrobenzene (**36**) and 1,4-dichloro-2-nitrobenzene (**37**) with a series of substituted phenoxide ions, the rates correlated with the σ-values of the phenoxide ion substituents, suggesting that in the transition state the phenoxide ion is appreciably bound. The parallel nature of the correlations for the two series suggested[99] that the transition states for the two were similar, even though the reactivities were very different.

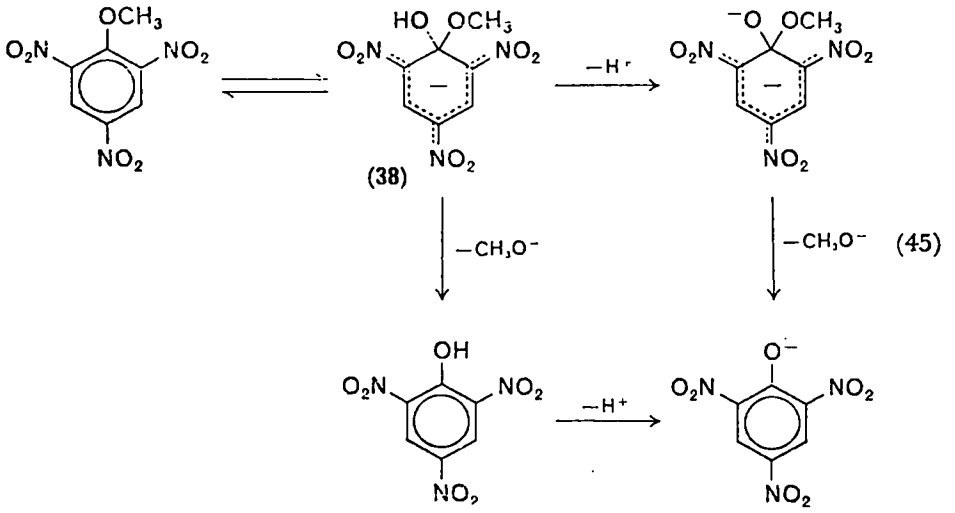
TABLE 7. Second-order rate coefficients ($l\ m^{-1}\ sec^{-1}$) and activation energies (kcal $mole^{-1}$) for the reactions of alkoxide ions with some nitro-activated halobenzenes.

Substrate	Conditions	k_2	E_a	Ref.
Chlorobenzene	OMe^-|MeOH (200°)	—	40·0	105b
2-chloronitrobenzene	OEt^-| EtOH (90°)	$3{\cdot}97 \times 10^{-4}$	22·2	218
4-chloronitrobenzene	OEt^-| EtOH (90°)	$9{\cdot}63 \times 10^{-4}$	20·1	218
4-chloronitrobenzene	OMe^-|MeOH (0°)	$8{\cdot}9 \times 10^{-9}$	24·0	204
4-chloro-1,3-dinitrobenzene	OMe^-|MeOH (0°)	$2{\cdot}0 \times 10^{-3}$	17·5	204
Fluorobenzene	OMe^-|MeOH (200°)	—	34·9	[a],
4-fluoronitrobenzene	OMe^-|MeOH (0°)	$6{\cdot}26 \times 10^{-6}$	21·2	[a], 207
4-fluoro-1,3-dinitrobenzene	OMe^-|MeOH (0°)	$1{\cdot}74 \times 10^{0}$	13·5	[a], 207

[a] B. A. Botto, M. Liveris and J. Miller, *J. Chem. Soc.*, 750 (1956).

As shown above, groups *ortho* and *para* to nitro groups undergo facile displacement by hydroxide and alkoxide ions. This is true of nitro groups, and the *ortho*- and *para*-isomers of dinitrobenzene as well as higher homologues are subject to ready displacement of one group by base. In accord with the general characteristics of nitro-activated substrates, the relative rates are *para* > *ortho*, and the reaction proceeds faster with ethoxide than with methoxide ions[100].

In substitutions involving hydroxide ions[100a, 101–104], the product obtained is not the phenol, but the phenate ion. A typical example is the reaction of trinitroanisole with hydroxide ion. Gold and Rochester[104] examined its rate of decomposition in weakly basic phosphate buffer solutions and considered that the kinetics were consistent with the rate-determining step being the attachment of the hydroxide ion to form the intermediate **38** (equation 45). There are two pathways by which the phenate ion can now be formed from the complex. In general, it will be very difficult to distinguish between them.

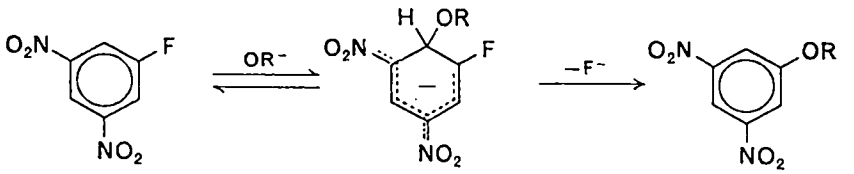


(45)

2. Non-activated substrates

Discussion of nucleophilic aromatic substitution normally centres on the reactions of the so-called 'activated' substrates discussed above, where the activating groups are orientated *ortho* and/or *para* to the reaction site, and can stabilize excess negative charge in the ring in both transition state and intermediate complex. However, if 'activation' is judged by the rates and activation energies of the reaction, then there is considerable activation in substrates where the activating groups are orientated *meta* to the site of reaction. Thus, although the rate of reaction of *m*-nitrofluorobenzene is approximately 10^{-4} that of the *ortho*- or *para*-isomers, there is a considerable increase compared with the unactivated substrate[22]. If there are two nitro groups present (to give 1-fluoro-3,5-dinitrobenzene), then the decrease in activation energy (cf. fluorobenzene) is equal to that effected by a nitro group in the *ortho*- or *para*-position. Since there can be no direct delocalization of charge into the nitro groups in this displacement, an intermediate of finite stability is unlikely and reaction probably proceeds in one step. However, these reactions can be considered within a general formalism* involving an intermediate corresponding to those of the two-stage mechanism (equation 46). If the reaction involved the intermediate, then a considerably smaller activation energy might be required than if the reaction proceeded directly from the aromatic substrate. The

* Of which the reaction of trinitrobenzene with methoxide ion is a special case.



(46)

(39)

reaction between trinitrobenzene and methoxide ion (see below) where there is some evidence of the intermediacy of a complex corresponding to **39** is a special case of this general scheme where the displaced group is a nitro group. In fact, intermediates corresponding to **39** for a variety of halogen substituents can be observed in basic DMSO solution[106], and it may be possible to investigate their possible role in the reaction mechanism.

C. Investigation of Attack by OR^- and OH^- leading to the Formation of Intermediates

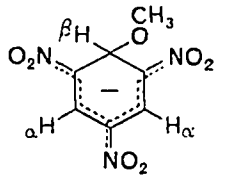
Under certain conditions, attack by hydroxide or alkoxide ions can lead to the formation of intermediates in large enough concentration for their detection, characterization and possibly isolation[88, 107]. This is achieved if the two-stage mechanism is stopped at the intermediate complex, effectively making the substitution reaction an equilibrium reaction involving the reactants and intermediate complex. The two common methods are (a) by the direct attack of alkoxide or hydroxide ion on an 'unsubstituted' nitroaromatic, where further reaction of the intermediate involves the energetically unfavourable elimination of H^- and the reaction effectively stops at this point and (b) by attack of alkoxide ion on a nitroanisole so that the complex is symmetrical with respect to both the attached groups, and any subsequent reaction must lead to the formation of the original reactants. Equilibria established under conditions (a) or (b) above, are then altered in favour of the complex by the use of dipolar aprotic solvents such as dimethyl sulphoxide or dimethylformamide.

1. Attack on nitro- and polynitro-aromatics

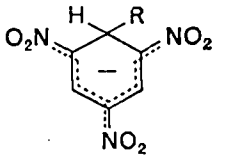
a. Attack on 1,3,5-*trinitrobenzene**. The interaction between TNB and alkoxides was investigated by several authors[108–111] before the end of the last century. In 1895 Lobry de Bruyn and Van Leent[108c] described the isolation of a solid complex by the action of KOH on

* Hereafter referred to as TNB.

a methanolic solution of TNB. Similar observations were made by other workers[109, 110]. De Bruyn showed that it was formed only in the presence of alcohol and had the empirical formula $C_6H_3(NO_2)_3.CH_3OK$. The formulation **40** was suggested by analogy



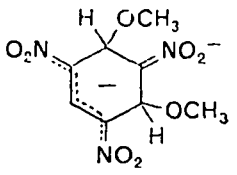
(40)



(41)

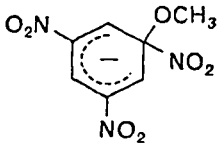
with the suggestions of Meisenheimer for the corresponding complex with trinitroanisole (see on). More recently, the visible[112] and infrared[113] spectra of this complex have been shown to correspond closely to those of the dialkoxy Meisenheimer compounds. A very elegant confirmation that the compound has structure **40** was given by Crampton and Gold[114]. The three equivalent protons in TNB give rise to a single sharp absorption at $\delta = -9{\cdot}21$ in DMSO solution, but the isolated product from the action of methanolic KOH on TNB shows two absorptions; a doublet at $\delta = -8{\cdot}42$ of relative intensity 2 ($J \sim 1$ cps) and a triplet at $\delta = -6{\cdot}14$ or relative intensity 1. These are in excellent agreement with those expected from H_α and H_β respectively in **40**. The large upfield shift in the resonance ascribed to H_β is caused by the change from sp^2 to sp^3 hybridization in the ring carbon atom, and chemical shifts in the range $\delta = -6{\cdot}0$ to $-6{\cdot}5$ are characteristic of this environment[107]. A product analogous to **40** is formed by the action of ethoxide ion on TNB[115]. Solutions of **40** undergo very facile exchange reactions with ketones[115, 116], amines [117] and aliphatic nitro compounds[118] to form the corresponding compounds **41** (R = CXYCOR′, NR′R″, $CXYNO_2$ respectively) by treatment of a DMSO solution of **40** with the reacting species. N.m.r. measurements have also been made on the 'in situ' formation of **40**. If increasing amounts of methoxide are added to a solution of TNB in DMSO, the n.m.r. spectrum shows first the formation of **40**[115, 119, 120], followed by changes at higher methoxide concentrations which may be indicative[115, 120] of the formation of **42**.

Quantitative spectrophotometric studies have been made on the interaction between TNB and alkoxides in alcoholic solution[121, 122]. Gold and Rochester found a value of $K = 15\,l\,m^{-1}$ for the equili-



(42)

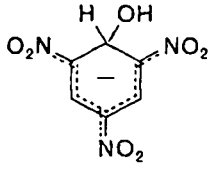
brium constant at 28°. Caldin and co-workers[122] studied the rate of formation of the ethoxy analogue of **40** and the rate of its decomposition by acids between −70° and −100°C. They found the activation energies for the forward and back reactions to be very similar, indicating considerable stability for the complex. At high ratios of alkoxide to TNB it has been suggested that complexes of stoichiometry 2 : 1 and 3 : 1 are formed[123, 124]. Solutions of **40** in methanol are known to be unstable[108, 121, 124–126], a slow irreversible reaction yielding mainly 3,5-dinitroanisole and nitrite ion taking place. The reaction is first-order in the complex **40**[121] but this does not necessarily mean that it is an intermediate in the reaction. The reaction would seem to proceed through a *transition state* (**43**). Such a



(43)
Transition state

species would have a very low stability, as there could be no delocalization of the negative charge by the nitro groups by a mesomeric effect, and it must be emphasized that *no* evidence has been found for a stable species corresponding to **43** in *any* system.

Attack by hydroxide ion on TNB in DMSO solution yields



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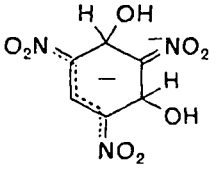

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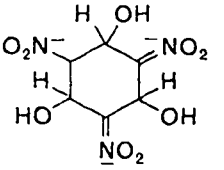


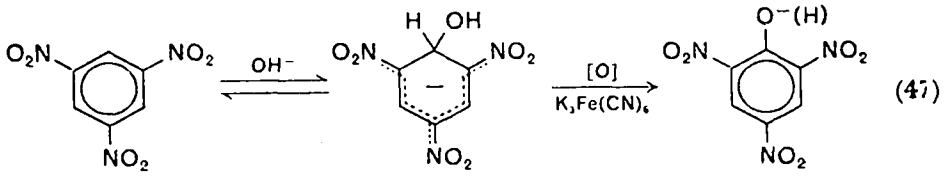
(46)

44[119, 127]. The n.m.r. spectrum of **44** is very similar to that of **40**, showing absorptions of $\delta = -8{\cdot}2_0$ (rel. intens. 2) and $\delta = -6{\cdot}1_5$ (rel. intens. 1). Compound **44** can also be made by treating a DMSO

solution of **40** with H_2O[127], giving an equilibrium mixture of **40** and **44***. Compound **44** can be isolated as its sodium salt in quantitative yield by addition of a large excess of H_2O to a DMSO solution of **40**. The u.v. and i.r. spectra of **40** and **44** are very similar, and **44** undergoes all the replacement reactions described above for **40**.

The formation of **44** by the action of aqueous alkali on TNB has been investigated spectrophotometrically by several workers[128–134]. General agreement is found with an equilibrium constant of $K \sim 2{\cdot}7$ l m^{-1} when determined spectrophotometrically, but this differs greatly from the value of 347 l m^{-1} found by a polarographic method[135]. At high ratios of hydroxide ion to TNB, it has been suggested that complexes **45** and **46** are formed[131, 135]. Again, solutions of complex **44** are unstable, slowly yielding 3,5-dinitrophenol and nitrite ion with traces of 3,5,3′,5′-tetranitroazoxybenzene. Gold and Rochester[129, 130] found the reaction to be light-sensitive, the apparent quantum yield increasing with the concentration of hydroxide ion and the rate being dependent on the wavelength of light used, the excitation causing reaction being at the longest wavelength absorption of the complex **44**. These observations suggest strongly that **44** is in fact involved in the reaction which presumably proceeds via a transition state analogous to **43**.

Another reaction which probably involves intermediates analogous to **44** is the alkaline oxidation of nitro compounds to nitrophenols[136]. Thus trinitrobenzene is oxidized to picric acid when boiled with alkaline potassium ferrocyanide (equation 47).



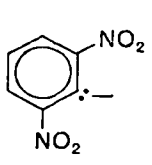
(44) (47)

The reaction can be formulated as involving the oxidation of the intermediate **44**. Apart from differences in formal charge, (equation (47) is analogous to reaction scheme (86) suggested for the alkaline oxidation of pyridinium ions to pyridones in section VI.B.1.

b. Attack on other nitroaromatics. In basic DMSO solution, 1,3-dinitrobenzene undergoes isotopic exchange, mainly in the 2-position. The

* In fact, the spectrum of **44** formed by reaction of **40** with traces of H_2O in DMSO solution was wrongly assigned a structure involving attack by the DMSO[115].

solutions also show a characteristic red colouration. From a detailed examination of the kinetics of the methoxide-induced tritium exchange in DMSO solution, Crampton and Gold[137] concluded that the colour-producing species was not **47** formed by proton abstrac-



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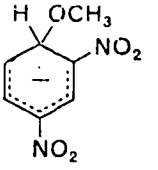

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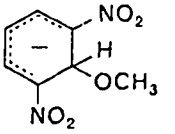
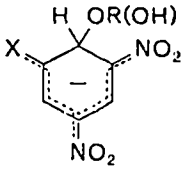


(49)

tion, a possibility considered by Pollitt and Saunders[138], but was due to a complex of dinitrobenzene which was inactive in the tritium exchange. These properties would be expected from the adduct **48**[137]. The formulation of the adduct as **48** rather than **49**, where attack has taken place between the two nitro groups, is suggested by the close correspondence of the visible spectrum (λ_{max} = 576 mμ) compared to that of the corresponding compound from 2,6-dinitroanisole (λ_{max} = 584 mμ). However, several workers have tried without success to measure the n.m.r. spectrum of **48**. The difficulty is at least partly caused by the extreme ease with which anion-radicals are formed in this system[139]. These can exchange with the unreacted dinitrobenzene and through this possibly affect the spectrum of the adduct. This effect is greatly reduced when the dinitrobenzene is present in relatively low concentration, so that as large a proportion as possible is present in the form of the adduct[106]. The n.m.r. spectrum is consistent with the formulation **48** with H_1, $\delta = -8{\cdot}36$; H_2, $\delta = -5{\cdot}43$; H_4, $\delta = -5{\cdot}35$, $J_{2,3} = 10$ cps and $J_{3,4} = 4{\cdot}5$ cps, in good agreement with the corresponding acetone adduct which has recently been reported[140], but it is inconsistent with the formulation **49** which would show only the three multiplets of an AB_2X spectrum.

Investigations have also been carried out on 1,3-dinitrobenzene systems which contain an electronegative group in the 5-position, making them more analogous to the case of 1,3,5-trinitrobenzene. However, there are now two possibilities for attack, namely **50** and **51**. Pollitt and Saunders[141] noted that the visible absorption spectra of a number of 1,3-dinitro-5-X-benzenes in DMSO solution in the presence of certain nucleophiles showed a series of two absorption maxima, and concluded that species analogous to both **50** and



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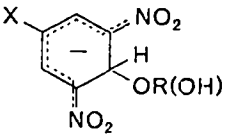


(51)

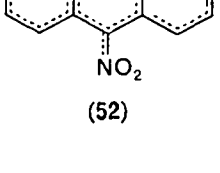
51 were present, each giving rise to a single absorption maximum. However, complex **40** formed from TNB where only one isomer is possible shows two maxima, and n.m.r. measurements [142] on 3,5-dinitrobenzonitrile and 3,5-dinitrobenzotrifluoride show only absorptions which can be attributed to complexes **50** (X = CN and X = CF_3 respectively) (Table 8). A similar situation is found with

TABLE 8. N.m.r. chemical shift parameters ($-\delta$, ppm) for the ring proton absorptions of complexes of general formula **50** in DMSO solution.

X	OR	H_α	H_β	H_γ
NO_2[114]	OCH_3	8·42	8·42	6·14
[127]	OH	8·20	8·20	6·15
CN[142]	OCH_3	8·08	7·35	5·40
	OH	8·21	7·52	5·50
CF_3[142]	OCH_3	8·02	7·13	5·44
	OH	8·15	7·31	too weak
H[106]	OCH_3	8·36	6·96	5·35
(δ = −5·43)				

3,5-dinitropyridine (section VI). However, although the non-observation of species rules out the possibility that they contribute to the absorption it does not exclude the possibility that they are formed in the initial attack and then isomerize very quickly to the more stable isomers (**50**).

N.m.r. studies suggest that stable adducts are also formed in nitropolycyclic aromatics[143]. Thus 9-nitroanthracene adds one equivalent of methoxide ion in DMSO solution to form the adduct **52**, and 1,3-dinitronaphthalene similarly gives **53**. The adducts **52**



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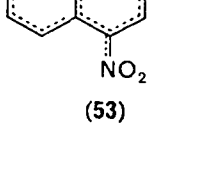
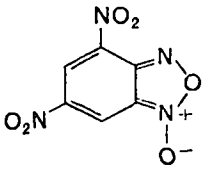


(53)

and **53** again undergo all the replacement reactions described in section IV.C.1a for the methoxy-adduct of TNB.

c. Attack on 4,6-dinitrobenzofuroxan. The formation of salts by the action of hydroxides on 4,5-dinitrobenzofuroxan (**54**) was described by Drost[144] in 1894, and investigated by several early workers[144–147]. Drost considered that a compound such as **55** was formed by proton abstraction (a similar suggestion had been made in the case of TNB[109]). Jackson and Earle[153a] suggested a structure of type **56** or **57** involving attack by the base. Recently, the simultaneous publication of results from three different research groups has unambiguously determined the structure of the species formed[148–150]. Thus no deuterium incorporation was found [148–150] on treating the



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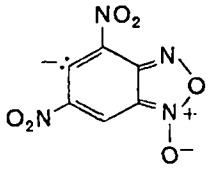
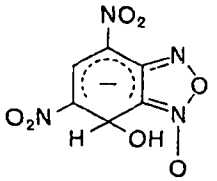


(55)

potassium salt with D_2SO_4, eliminating structures of type **55**, and no ^{18}O exchange with $^{18}OH_2$ [150], eliminating structures of type **58** where the heterocyclic ring has opened. The n.m.r. spectrum[148–150] of the salt formed by hydroxide addition shows doublet absorptions



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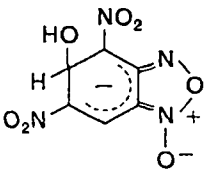

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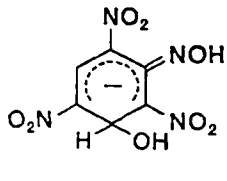


(58)

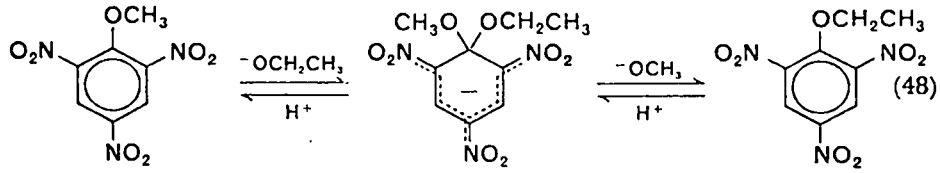
at $\delta = -8{\cdot}73$ and $\delta = -5{\cdot}94$ in agreement with structure **56** *or* **57**, but does not differentiate between them. However, Brown and Keys[148] synthesized the 4,6-dinitrobenzofuroxan with 50% deuterium in position 5. The n.m.r. spectrum of the hydroxide salt from this substrate shows a decrease in the low field absorption, hence H_5 is not attached to the sp^3 carbon atom, and the salt must have structure **56**.

2. Attack on nitro- and polynitro-anisoles

a. Attack on trinitroanisole and homologues.* The interaction between

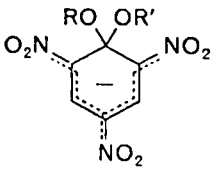
*Referred to as TNA.

TNA and alkoxide ions is one of the most amenable systems and has been the subject of intensive study from the early investigations of Meisenheimer[151] and Jackson and co-workers[152, 153] up to the present day. In an early definitive study[151], Meisenheimer isolated red solid salts by treating trinitroanisole with potassium ethoxide and trinitrophenetole with potassium methoxide. Both salts gave the same mixture of trinitroanisole and trinitrophenetole on treatment with mineral acid, and Meisenheimer concluded that they were in fact identical and had structure **59***, representing the reaction as (48).



(59)

More recent work has completely vindicated Meisenheimer's formulation, and complexes of this type are often referred to as 'Meisenheimer complexes' (or adducts, or salts). Compounds of the general type **60** have several characteristic properties. The absorption spectra show two maxima in the visible region at ca 420 mμ



(60)

and 500 mμ due to the trinitrocyclopentadienide residue[154–156] (Table 9, Figure 3). There is little variation within a series, and the absorption may be considered characteristic of these systems. In fact, the spectra of the different compounds are so similar that the observation of identical u.v. spectra from the two adducts originally isolated by Meisenheimer is not proof that they are identical, as has been suggested, since the other possibility, that an equimolar mixture of **60** (R = R′ = CH_3) and **60** (R = R′ = Et) is formed, would in fact give rise to an identical absorption spectrum (Table 9).

* Although formulated slightly differently with the charge localized on one nitro group.

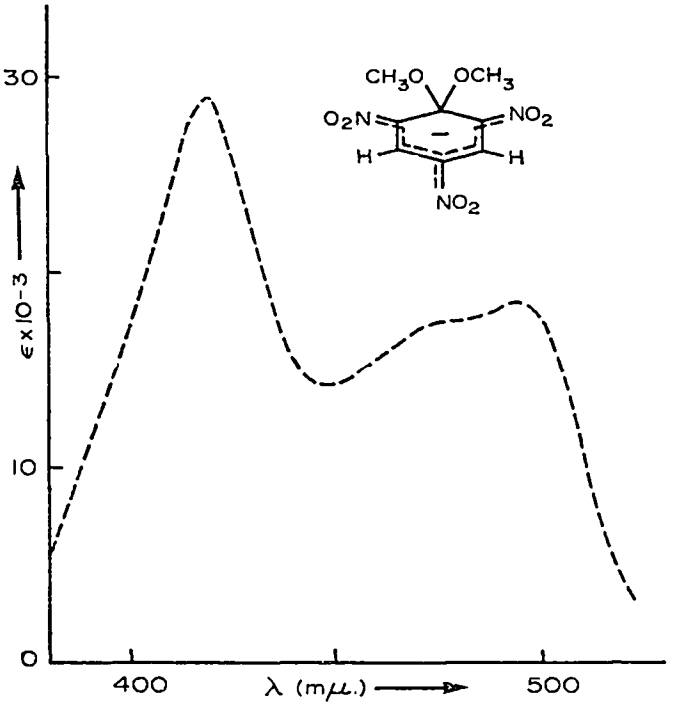


FIGURE 3. U.v.–visible absorption spectrum of compound **60** (OR = OR′ = OCH_3) in acetone solution.

The solid complexes also show characteristic i.r. spectra[157, 158] which are quite different from those of the parent ethers, and are in agreement with the general formulation **60**. Thus, the increased negative charge on the nitro groups leads to a lowering of the N–O stretching frequencies from 1552 cm^{-1} to 1513 or 1489 cm^{-1} on complex

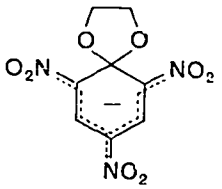
TABLE 9. U.v. spectral parameters of compounds of general formula **60** in acetone solution.

OR	OR′	λ_1 (mμ)	ε_1 ($l\ m^{-1}\ cm^{-1}$)	λ_2 (mμ)	ε_2 ($l\ m^{-1}\ cm^{-1}$)	Ref.
OCH_3	OCH_3	420	29,000	494	19,000	169
OCH_3	OCH_2CH_3	421	29,000	495	19,000	169
OCH_2CH_3	OCH_2CH_3	422	30,000	495	19,000	169
OCH_2CH_2O		414	30,500	490	22,200	160

formation. There is also a strong broad absorption between 1040 cm^{-1} and 1225 cm^{-1}. Data on the crystal structures of the

caesium and potassium salts of **60** (R = R′ = CH_2CH_3) have been presented[193].

A very direct demonstration of the covalent nature of these compounds and the essential correctness of formulation **60** is obtained from the n.m.r. spectra of the isolated compounds[159–161]. Thus the complex **60** (R = R′ = CH_3) shows only two sharp absorptions at $\delta = -8{\cdot}64$ (rel. intens. 1) and $\delta = -3{\cdot}03$ (rel. intens. 3). The relative intensities are in agreement with structure **60** in which both the two methoxyl groups and the two ring protons are equivalent. The methyl proton resonance occurs at a value corresponding to that of an aliphatic ether rather than an aromatic ether which would absorb $\delta = -4{\cdot}0$ indicating the change in hybridization at the carbon atom to which it is attached. The position of the ring proton resonance is characteristic[107] of the trinitrocyclopentadienide system. Similarly, the 'spiro' compound **61** [160, 162] shows only a single sharp absorption for the dioxolan ring protons[160] indicat-



(61)

ing the equivalence expected from structure **61**. Many investigations by n.m.r. have also been carried out on complexes generated in situ[115, 116, 119, 143, 159, 161–166] from the parent picryl ethers. The most incisive are those of Servis[164, 165]. The addition of sodium methoxide to a solution of TNA in dimethyl sulphoxide causes the disappearance of the TNA resonances and the appearance of two doublets of equal intensity at $\delta = -6{\cdot}17$ and $\delta = -8{\cdot}42$ ($J \sim 2$ cps) and a sharp resonance at $\delta = -8{\cdot}90$ (Figure 4). With time, the single resonance increases in intensity at the expense of the two doublet absorptions until these eventually disappear. The single resonance corresponds to the ring proton absorption in **62**, and Servis accounted for the spectral changes in terms of initial attack by methoxide ion at the unsubstituted 3-position to yield **63** which then isomerizes to give the thermodynamically more stable isomer (**62**) as in equation (49). The resonance at $\delta = -6{\cdot}17$ ascribed to H_β in **62** occurs at a position characteristic of protons attached to sp^3 hybridized carbon atoms in these systems. Since then, similar

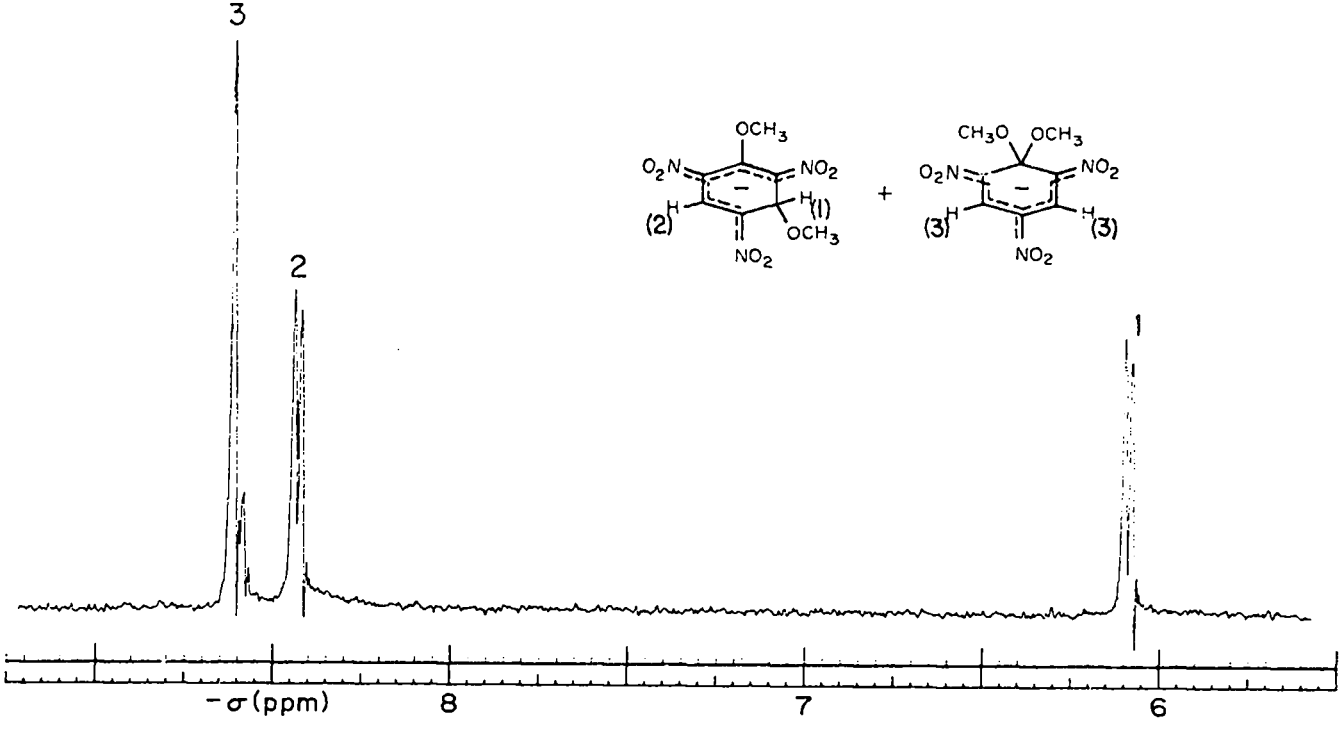
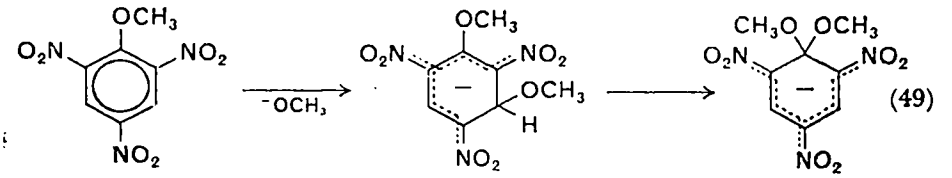


FIGURE 4. 100 MHz n.m.r. spectrum of a 1M solution of TNA in DMSO, 3 minutes after the addition of anhydrous sodium methoxide.



(63) (62) (49)

observations have been made on complexes from 1,3-dimethoxy-2,4,6-trinitrobenzene[143] and other systems (see below), and it appears that isomerizations of this type may be quite general. Ainscough and Caldin[167, 168] had investigated the kinetics of the attack by $^{-}OC_2H_5$ on TNA at low temperatures, and found two kinetic processes; a very fast initial reaction, and then a relatively slow reaction to form **60** (R = CH_3, R′ = C_2H_5. The initial fast reaction was interpreted[167, 168] as the formation of a charge-transfer or ion–dipole complex, but the absorption spectrum at low temperatures is characteristic of a Meisenheimer compound[170], and Servis[164] has pointed out that the results are in accord with equation (49).

Investigations of the interaction using u.v. spectroscopy have been made by several workers[169–172]. At high concentrations of methoxide ion in methanol solution, picryl ethers show an alteration in the visible absorption spectrum, which is attributed[169] to the presence of 1 : 2 and 1 : 3 complexes. (There is n.m.r. evidence[165] for the formation of a 1 : 2 complex in the case of TNA + $^{-}OCH_3$.) The spectrum becomes that of a normal 1 : 1 Meisenheimer compound on dilution, and acidification of fresh solutions yields the picryl ether. On standing, irreversible changes take place[169].

Estimates for the equilibrium constant for the formation of the 1 : 1 complex of trinitroanisole and methoxide ion in methanol solution (equation 50) vary considerably. Abe[171] and co-workers report a value of $K = 2{\cdot}26 \times 10^3$ l m^{-1} and $\varepsilon(410\ m\mu) = 3{\cdot}45 \times 10^4$ cm^2 m^{-1} and Gold and Rochester[170] report values of $K = 7{\cdot}70 \times 10^3$ l m^{-1} and $\varepsilon = 2{\cdot}42 \times 10^4$ cm^2 m^{-1}. The latter value receives support from the values of the extinction coefficients quoted by other workers[166, 169]. Fendler and co-workers[172] report a value of $K = 1{\cdot}7 \times 10^4$ l m^{-1}, but note that, at methoxide concentrations of

$$K^+OCH_3^- + TNA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} TNA.OCH_3^-K^+ \qquad (50)$$

10^{-2} M, the effect of increasing methoxide concentration is to increase k_1 and hence K*, so that differences in the values found by

* A similar effect was found by Bernasconi[173] in the action of methoxide on 2,4-dinitroanisole.

various workers may be due to differences in concentration ranges. All the values are, however, very much larger than the value found for the attack of methoxide ion on trinitrobenzene (section IV.1a above). In this system, the isomerization equilibrium found by Servis for TNA cannot occur, and the much larger equilibrium constant in the latter system may be due to the measurement being of two consecutive equilibria. The equilibrium has also been investigated by measurement of the methoxide-catalysed loss of ^{13}C from $2,4,6\text{-}(NO_2)_3C_6H_2O^{13}CH_3$ [174]. The rate-determining step in the isotopic exchange was found to be the unimolecular heterolysis of the complex, rather than the bimolecular formation of it, indicating that the complex is more stable than the starting ether, in agreement with the thermodynamic results from

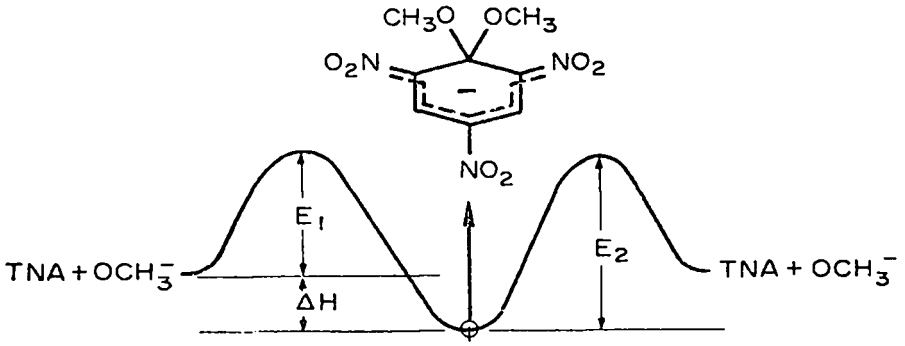


FIGURE 5. Energy profile for the reaction of TNA with methoxide ion in methanol solution.

optical measurements. (The technique of isotopic labelling has also been employed by Gitis and co-workers[175], but no equilibrium or rate measurements were made.)

There is general agreement between the thermodynamic parameters obtained from a whole variety of methods (Table 10, Figure 5). The main feature is that the complex formed is in fact not only stable, but more stable than the original substrate, by 2—7 kcal/mole.

Solutions of trinitroanisole in the presence of methoxide are unstable when irradiated at the wavelength of the absorption of the 1 : 1 complex, reacting by loss of a nitro group[176].

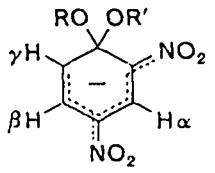
b. Attack on dinitro- and substituted dinitroanisoles. From both intuitive and theoretical[177] points of view, complexes from dinitroanisoles might be expected to be less stable than the trinitro-analogues. Although this has been verified experimentally, in fact it has still

TABLE 10. Thermodynamic parameters (kcal mole^{-1}) for the attack of methoxide ion on TNA in methanol solution (Figure 5) as determined by various methods.

System	Method	E_1	E_2	ΔH	Ref.
TNA + OEt^-	low T. kin. (u.v.)	13 kcal	—	—	167, 168
TNA + OCH_3^-	u.v.	10·0	12·0	−2·0	171
TNA + OCH_3^-	$O^{13}CH_3$	12[a]	19·4	−7·15	174
TNA + OCH_3^-	u.v.	13·5	19·0	−5·5	172
TNA + OCH_3^-	Miller	14·0	16·0	−2·0	203

[a] Not determined directly; value by subtraction.

been possible to observe and verify the structure of a large number of these compounds. Pollitt and Saunders[141] investigated the optical absorption spectra of a series of 2,6-dinitro-4-X-anisoles and 2,4-dinitro-6-X-anisoles. By analogy with the trinitro-derivatives, they concluded that the complexes formed were of the structures **64** and **65**.



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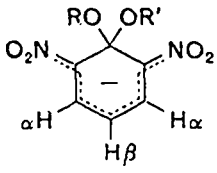
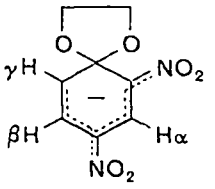


(65)

There is also a close correspondence between the absorptions of the adduct of 2,4-dinitroanisole and methoxide ion of suggested structure **64** and that of 1-(2′-hydroxyethoxy)-2,4-dinitrobenzene where it is thought[141] that the spiro compound **66** is formed. Measure-



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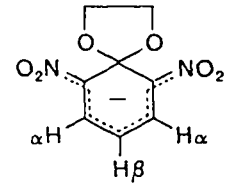


(67)

ments of the n.m.r. spectrum of **64** generated in situ in DMSO solution by the addition of sodium methoxide fully support the

structure suggested by Pollitt and Saunders. The ring proton absorptions occur at $\delta = -8{\cdot}52$, H_α; $\delta = -7{\cdot}90$, H_β; $\delta = -5{\cdot}36$, H_γ. There is (Table 11) a close similarity between the different homo-

TABLE 11. N.m.r. absorptions ($-\delta$, ppm) of ring protons of σ-complexes of dinitrophenyl ethers in DMSO solution.

Structure	OR	OR′	H_α	H_β	H_γ	Ref.
2,4-dinitroanisole	OCH_3	—	8·75	8·57	7·64	
64	OCH_3	OCH_3	8·68	7·26	5·09	107, 143, 119
64	OCH_3	OCH_2CH_3	8·70	7·20	5·10	107, 143, 119
64	OCH_2CH_3	OCH_2CH_3	8·68	7·19	5·10	107, 143
66	OCH_2CH_2O		8·52	6·90	5·36	107, 143, 180, 181
2,6-dinitroanisole	OCH_3	—	8·31	7·58	—	
65	OCH_3	OCH_3	7·93	5·02	—	107, 143
65	OCH_3	OCH_2CH_3	7·84	4·98	—	107, 143
67	OCH_2CH_2O		7·67	5·09	—	107, 143, 180, 181

logues of **64** and the spiro compound **66**, confirming the assignment.

Similarly, complex **65** can be generated by the addition of methoxide ion to DMSO solutions of 2,6-dinitroanisole. The ring protons give rise to an AX_2 system consistent with formulation **65**. The resonances occur at $\delta = -5{\cdot}0_2$, H_β and $\delta = -7{\cdot}93$, H_α, with $J_{H_\alpha\text{-}H_\beta} = 8$ cps, the large upfield shift in H_γ occurring because it is *meta* to both nitro groups. Again (Table 11), the spectra of homologues of **65** are very similar to those of the spiro compound **67**, giving added proof of the structure. In both cases, there is eventual decomposition to the dinitrophenate ion (this is true to some extent for the picryl compounds also). This may be due to reaction with trace amounts of H_2O in the DMSO solvent, but there is growing evidence[188] that phenate ion formation can occur by an S_N2 displacement on the methoxyl carbon atom (equation 51), so that at

(51)

least traces of phenate ions might be expected to be present in *all* solutions containing intermediates of these types*. Complexes of

* An analogous displacement involving an amine is an alternative explanation of the results of Servis[120] on the action of triethylamine on TNA.

type **64** have also been isolated as solid compounds[178, 179]. Originally they were obtained in a mixture with the phenate ion and were considered unstable[178], but recently Griffin and co-workers[179] have isolated them in a pure form, and demonstrated that they show considerable stability. This stability has been estimated quantitatively by several workers from kinetic investigations. The results are given in Table 12 and illustrated in Figure 6. Although experimentally difficult to estimate an accurate value of the equilibrium

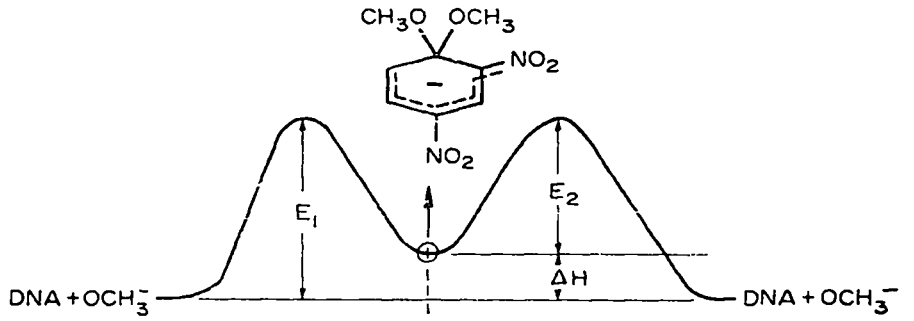


FIGURE 6. Energy profile for the reaction of 2,6-dinitroanisole with methoxide ion in methanol solution.

TABLE 12. Thermodynamic parameters (kcal/mole) for the attack of methoxide ion on 2,4-dinitroanisole in methanol solution as determined by various methods.

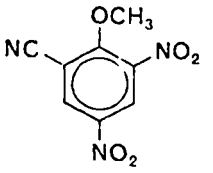
Method	E_1	E_2	ΔH (kcal/mole)	Ref.
^{13}C Isotopic exchange	(16·8)	—	—	174
Temp. jump.	(16·1—16·8)	(11·20—13·0)[a]	(5·6—3·1)[a]	173
Miller	19·5	12·5	7·0	203

[a] Value dependent on OCH_3^- concentration.

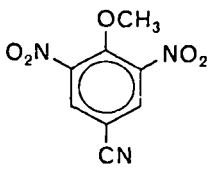
constant for complex formation[179], it is thought to be several thousand times less than that for the corresponding complex from trinitroanisole. Fendler[174] found that the rate of complex formation was the rate-determining step in the methoxyl exchange of ^{13}C-labelled 2,4-dinitroanisole, indicating that, unlike the case of trinitroanisole, the complex was less stable than the substrate. The activation energy (E_1) for this process was found to be 16·8 kcal/mole. Using the 'temperature-jump' technique, Bernasconi[173] found a value of $11{\cdot}8 \pm 0{\cdot}5$ kcal/mole for the decomposition (E_2) of the complex,

compared with a value of 12·5 kcal/mole predicted by Miller (see below).

Several workers have investigated the complex formation of 2-cyano-4,6-dinitroanisole (**68**)[182–184] and 4-cyano-2,6-dinitroanisole (**69**)[166, 183, 184].

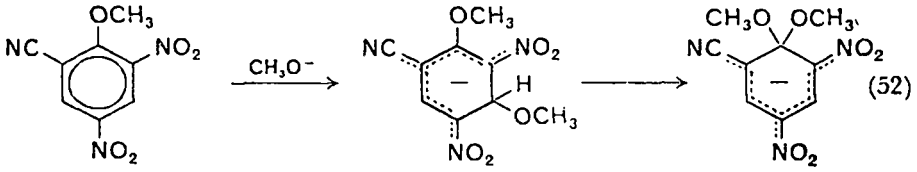


(**68**)



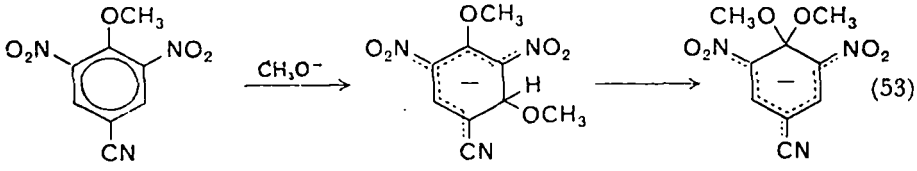
(**69**)

The n.m.r. spectrum of the stable isolated complex formed from 2-cyano-4,6-dinitroanisole indicated that it had structure **70**[182–184], but Griffin and co-workers[183, 184] showed that a rearrangement similar to that found by Servis in the case of trinitroanisole took place, the thermodynamically less stable isomer (**71**) being formed first which then rearranged to **70** (equation 52). They found a



(**68**) (**71**) (**70**) (52)

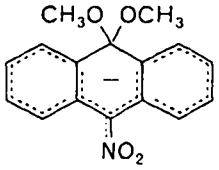
similar rearrangement in the case of 4-cyano-2,6-dinitroanisole (equation 53), and were also able to isolate the complexes **70** and **72** as stable solids.



(**69**) (**73**) (**72**) (53)

In a detailed examination of the kinetics of formation of **70** and **72** compared with the corresponding complex **62** from trinitroanisole, Griffin and co-workers[184] found that the replacement of a nitro by a cyano group in trinitroanisole caused a 6·5-fold decrease for

replacement in the 2-position. These parallel exactly the relative activating effects found for *ortho*- and *para*-nitro groups in the methoxydechlorination of nitrochlorobenzenes[189]. N.m.r. investigations[143] of the addition of methoxide ion to a solution of 9-nitro-10-methoxyanthracene confirm the suggestion of Meisenheimer[151] that attack takes place at the 10-position to yield the complex **74**. Similarly, attack takes place at the 1-position in 1-methoxy-2,4-dinitronaphthalene to yield the complex **75**[143, 186]. The correspond-



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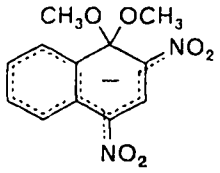


(75)

ing spiro compounds to **74**[187] and **75**[186, 187] can also be made. Measurements on the kinetics of the formation of **75** in methanol solution indicate that the complex is more stable than the anisole substrate[186]. The presence of the second aromatic ring causes an increase of approximately 250 times in the equilibrium constant for the formation of the complex compared with the analogous complex of 2,4-dinitroanisole, although the complex is still considerably less stable than the corresponding complex from trinitroanisole. The activation energy for the formation of **75** is 13·8 kcal/mole[186] which is ~3 kcal/mole less than that found[173, 174] for the complex from 2,4-dinitroanisole and reflects exactly the trend found for methoxy-dechlorinations of nitrochlorobenzenes and naphthalenes[189].

3. Relation of the observation of intermediates to the mechanism of substitution reactions

In general, intermediates of the general type above which are postulated in the two-stage mechanism are not normally observed (as judged by colour formation) in normal replacement reactions involving hydroxide or alkoxide ions. As has been stressed[87, 88], there is no direct logical connexion between the observation of intermediates in equilibrium processes as described above and their possible participation in kinetically controlled substitution reactions, and any inferences must be made with caution. However, even if one were able to detect the intermediates in these reactions, and determine kinetically that the reaction was first-order with respect to the intermediate, the concentration of the intermediate could be

re-expressed in terms of those of the reactants using the first equilibrium, and the participation of the intermediate in the reaction would always be an inference (however reasonable).

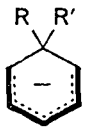
The general acceptance of the two-stage mechanism has been effected to some extent by the observation of intermediates of the same structural type and electronic configuration as those postulated in the S_NAr2 mechanism. This 'association' of the two has become somewhat more valid in recent years with the observation and characterization of intermediates from less activated substrates as discussed above, and the parallels found in the trends shown by the activation energies for complex formation and replacement reactions for similar changes in substrate. Also the work of Miller (see below) has included both processes in a general treatment with considerable success.

One promising possibility in the future may be the observation of intermediates in low concentrations and short lifetimes during reactions by use of pulsed n.m.r. and flow systems.

D. Theoretical Approaches

Several authors[190–200, 244] have performed molecular orbital calculations to obtain parameters which can be related to the structure and reactivity of the transition states and intermediate complexes of these substitution reactions. Most calculations employ the 'Wheland model'[190] for the intermediate **76** where the structure of the intermediate is that discussed in section C above.

The carbon atom at the point of attack is removed from the calculation, only the residue (shown in dark lines) and any groups attached to it contributing to the π-electron energy of the system.



(76)

Caveng and Zollinger[191] have employed this model and method of calculation to calculate π-electron densities in a whole series of intermediates formed from polynitroanisoles and the parent substrates, and have compared their results with those of the n.m.r. studies discussed in section C. Their calculations suggest that the negative charge in these complexes is mostly localized on the nitro

groups, and that there is relatively little increase in the π-electron density at the ring carbon atoms, a slight *decrease* being found in some cases.

Very recently, however, Hosoya, Hosoya and Nagakura[244] have disagreed with both the results and the method of calculation used in this study. They consider that nitro compounds are beyond the limit of the HMO treatment, and have calculated the π-electron structures of the 1,3,5-trinitro-, 1,3-dinitro-, 1,5-dinitro-, 2,4-dinitro-, and 3-nitro-pentadienyl anions by the 'method of composite molecules'. In this method, the electronic structure of the substituted pentadienyl anion is considered in terms of charge-transfer interaction between the MOs of the pentadienyl anion and those of the nitro groups. A 'Pariser–Parr–Pople' type self-consistent field molecular orbital calculation with configuration interaction was also made for the 1,3,5-trinitropentadienyl anion for purposes of comparison. In contrast to the results of Caveng and Zollinger[191], they found that both methods predicted a net negative charge in the ring in the 1,3,5-trinitropentadienyl complex. The electronic transitions of the anions were considered as due to charge-transfer from the pentadienyl group to the nitro group, and the calculated values of both the transition energies and the extinction coefficients were in good agreement with available experimental values.

One very important aspect considered by Caveng and Zollinger, but often neglected in calculations, is the possibility of distortion of the *ortho*-nitro groups from the plane of the ring, thus lessening their capacity for delocalizing the negative charge. In fact, molecular models indicate that steric interactions[166] can occur, and this will affect the substrate, transition states and intermediate complex. The non-coplanarity of the nitro groups with the ring can in fact be introduced very simply into the HMO calculation, and Caveng and Zollinger[191] performed their calculations for rotations of the nitro group from the plane of the ring of 0°, 30° and 60° in cases where distortion was possible.

Direct estimates of this distortion can now be made in the picryl series from the recently published X-ray structures of trinitrophenetole[192] and its ethoxy complex (**62**)[193]. In the case of the adduct **62** no significant distortions of the two *ortho*-nitro groups were found[193], and steric interaction in the case of the intermediate must be minimal. However, very considerable steric interactions were indicated in trinitrophenetole, the two *ortho*-nitro groups being rotated by 30° and 60° from the plane of the aromatic ring[192]. Since the

structure of the transition state will lie somewhere between these two extremes the possibility of distortion by steric interactions in this case will remain, to some extent at least, an unknown factor in calculations.

Correlation of parameters from molecular orbital calculations with activation energies from kinetic measurements is not so direct, however, as the MO calculations are based on a Wheland type structure which represents an *intermediate*, and the kinetic parameters depend on the energy of a *transition state*. The justification for this approach will depend on how closely the structure of the transition state resembles that of the intermediate complex*. The activation energy calculated (E_{MO}) is related to the difference in atom localization energies (A_n) of the substrate and intermediate (equation 54). The term Δ includes differences in solvation energies of the

$$E_{MO} = A_n\beta_{cc} + \Delta \qquad (54)$$

substrate and intermediate. Equation (54) also assumes that ΔS is a constant.

Murto[194] found reasonable agreement using this method of calculation with the experimentally determined activation energies for a series of methoxydehalogenations of nitrohaloaromatics. He also found a correlation between the logarithm of the rate constants and the electron densities at the position of substitution, indicating the importance of the charge density as a rate-determining factor in the reactions considered. Abe[177] has used the same model introducing a 'reaction parameter' by which the values of the resonance integrals can be changed during the course of substitution. His results suggest that Meisenheimer intermediates are more easily formed, and are more stable, with increasing number of nitro groups, in agreement with the trend found experimentally (section C). However, where direct comparisons can be made with experimental results, the agreement is only qualitative.

An alternative to the Wheland representation has been given by Simonetta and Carra [195, 196] as an extension of their treatment of the Fritsch rearrangement reaction[195]. In this representation, the sp^3 hybridized carbon atom and its substituents are not removed from the calculation, and the leaving and attacking groups (e.g. Cl and $^-OCH_3$) are considered together as a 'pseudo atom'. The orbitals of the oxygen and chlorine atoms of these groups can be combined

* Some guide to the validity of this approximation is given in the calculations of Miller (see below).

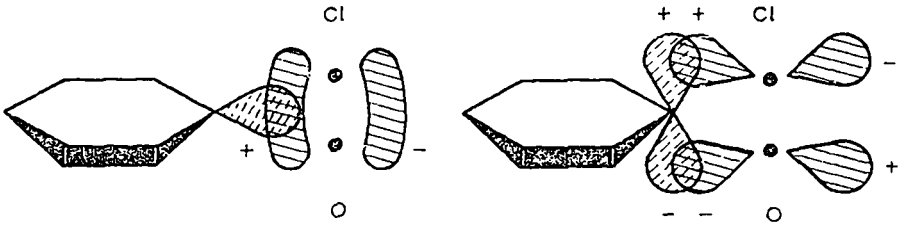
together to give a bonding orbital, resembling a σ orbital, which is symmetric with respect to the plane of the ring (equation 55a),

$$\psi_\sigma = (1/\sqrt{2})(\psi_{Cl} + \psi_O) \tag{55a}$$

and an antibonding orbital which is antisymmetric with respect to the plane of the ring, resembling a Π orbital ψ_π (equation 55b).

$$\psi_\pi = (1/\sqrt{2})(\psi_{Cl} - \psi_O) \tag{55b}$$

The 'sigma' orbital ψ_σ can combine with the sp^2 orbital of the attached carbon atom (Figure 7a) and the 'π' orbital with its p_z orbital (Figure 7b). This model is much more flexible than the



(a) (b)

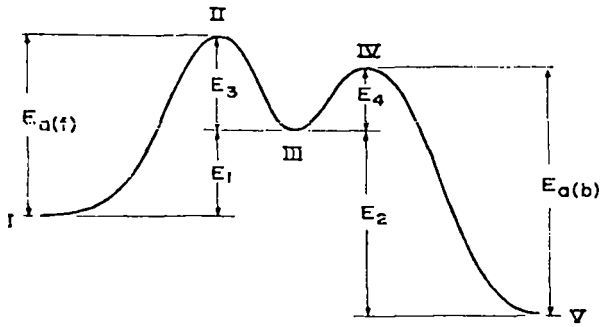
FIGURE 7. Bonding and antibonding molecular orbitals of the 'pseudo atom' in an aromatic nucleophilic substitution reaction.

Wheland one, in that the total bond order between the pseudo atom and the bonded carbon can be greater than 1. In fact the parameters for the pseudo atom are evaluated from some experimental results, and, in this sense, the calculations may be thought of as applying to a transition state, although it may be difficult to obtain a physical idea of this from the parameters found. Carra and Simonetta have applied this method to methoxy- and amino-dehalogenation reactions of benzene and naphthalene derivatives[196], and have obtained excellent correlations between experimental activation energies and calculated values of ΔE_π. The agreement is considerably better than that obtained for the same reactions using either π-electron densities, or the Wheland intermediate. Some idea of the relation of the transition state to the intermediate complex is given in the calculations of Nagakura[198]. From a consideration of the relative electron affinities and ionization potentials of substrate and reagents[197], Nagakura formulated the substitution process within the framework of the general theory of charge-transfer interactions introduced by Mullicken[201]. Thus the reaction is seen as a progressive transfer of charge from the reagent to the substrate, and a larger contribution

of the charge-transfer form $\psi_{R\text{-}S^-}$ to the total wavefunction ψ_{TOT}

$$\psi_{TOT} = a\,\psi_{R^-,S} + b\,\psi_{R\text{-}S^-} \qquad (56)$$

(equation 56). In this context, in the initial state, $a \gg b$, and in the intermediate complex, $b \gg a$. The transition state is thought of as the point where there is almost equal contribution from both $\psi_{R^-,S}$ and $\psi_{R\text{-}S^-}$ to the total wavefunction[202], and can be considered as the point where the whole system transfers from the no-bond to the charge-transfer structure. (A similar treatment has been given by Brown[199, 200] for electrophilic aromatic substitution reactions.)



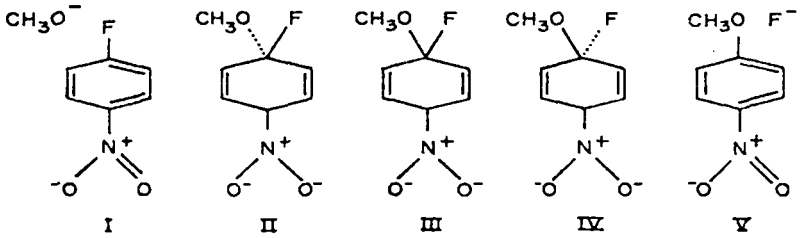


FIGURE 8. Energy for a bimolecular nucleophilic substitution proceeding via a 'two-step' mechanism.

A different approach, and one which is of very wide applicability, is that developed by Miller and co-workers[203–207]. The reaction (e.g. between methoxide ion and *p*-nitrofluorobenzene below) is thought of as proceeding according to the two-stage mechanism via structures I—V (Figure 8) where III is the intermediate complex in the Wheland representation. The energy levels of the reactants and products relative to the intermediate complex (E_1 and E_2 in Figure 8) are calculated by taking into account changes in bonding, electron affinity, solvation and delocalization energies in the dissociation of the intermediate complex to either the reactants or products[203].

Where possible, known thermodynamic values are used for these terms, but some must be approximated to, and others estimated. (See Ref.[203] for a full discussion of the approximations involved.) At this stage in the calculation one has obtained the same information as from the HMO calculations based on the Wheland model for the intermediate.

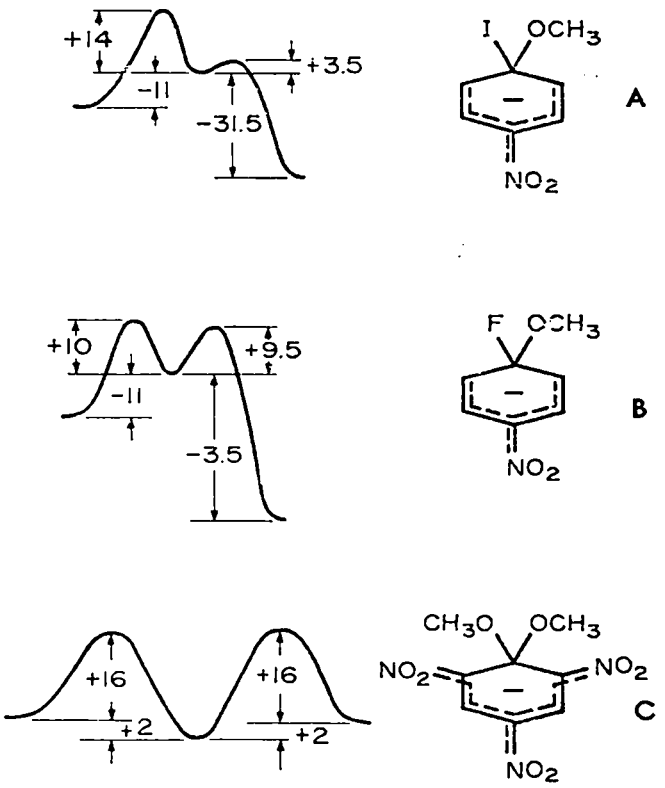


FIGURE 9. Energy profiles for aromatic nucleophilic substitution reactions involving the intermediates shown; from the calculations of J. Miller[203].

However, as discussed above, the kinetically measured activation energies are $E_{a(f)}$ or $E_{a(b)}$ in Figure 8. Miller[203] has calculated the activation energies E_3 and E_4 for the activation of the intermediate complex to the transition states for its decomposition by employing a semi-empirical correlation between % bond-dissociation energies and the exothermicity of the dissociation reaction*. Thus E_3 will

* Although semi-empirical, the correlation is not arbitrary. If one accepts a connexion between activation energies and reaction thermicity, the application in the range encountered in these reactions does not involve large errors.

be a percentage of the C–OCH_3 bond energy depending on the energy difference E_1, and E_4 a percentage of the C–F energy depending on the energy difference E_2. In this way, the kinetic activation energies $E_{a(f)}$ and $E_{a(b)}$ can be calculated. The approach is quite generally applicable to all substitution reactions for which the relevant bond-dissociation energies are known, and it would be quite reasonable to justify the method solely on the basis of being a general qualitative interpretation. However, in spite of the approximations involved, the agreement between calculated and experimental activation energies is *extremely* good (e.g. Table 13). Some representative schemes are shown in Figure 9. In no case is the Wheland intermediate a very good representation of the energy of the transition state. Of special note is the case of the stable complex (case C), discussed in section C. The method of Miller provides a strong direct link between these observable intermediates, and the general kinetic case.

The generally very good agreement with experimental activation energies provides justification not only for the method of calculation, but also for the model of the two-stage mechanism involved in it.

TABLE 13. Comparison of experimental activation energies with values calculated by the method of Miller[203] for the methoxydehalogenation of some activated halobenzenes[a].

Substrate	E_a(calc.) (kcal)	E_a(exp.) (kcal)	Ref.
1-F-4-nitrobenzene	21	21	203
1-Cl-4-nitrobenzene	24	24	203
1-I-4-nitrobenzene	25	25	203
1-F-2,4-dinitrobenzene	15	13·5	203
1-Cl-2,4-dinitrobenzene	16·8	18	194
1-I-2,4-dinitrobenzene	19	19	203
1-F-2,4,6-trinitrobenzene	8	10·5	194
1-Cl-2,4,6-trinitrobenzene	11·6	13·5	194

[a] See also Tables 11, 12.

VI. ATTACK ON AZA-AROMATIC SYSTEMS

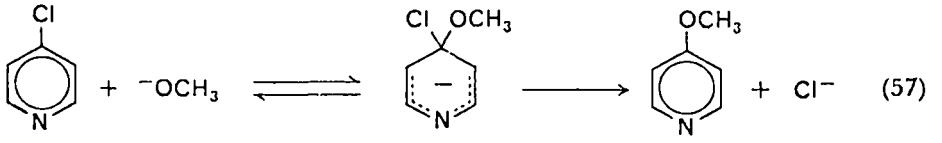
A. Pyridine and Homologues

1. Kinetics and mechanism

a. General. Nucleophilic substitution reactions in aza-aromatic systems proceed much more readily than in the corresponding benzene analogues owing to the activating effect of the ring nitrogen

atom. For example, 2- and 4-halopyridines react readily with alkoxides to yield the corresponding alkoxypyridines[208], and with hydroxide ion to yield the corresponding pyridones[209].

In general, second-order kinetics (first-order in both alkoxide and substrate) are found, and the reactions are usually discussed[210, 211] in terms of the intermediate complex theory introduced by Bunnett for aromatic substitution (section V). Thus the reaction of 4-chloropyridine would be represented as in equation (57).



(57)

However, despite the extensive investigations of Chapman and other workers, much of the internal kinetic evidence for the S_NAr2 mechanism proposed for aromatic systems is missing in the heterocyclic series, and discussions on nucleophilic heterocyclic substitutions [210, 211] have relied heavily on mechanistic evidence from the benzenoid series. There is also a lack of kinetic data on the reaction of alkoxides with simple aza-substrates.

The discussion is restricted to consideration of the simpler nitrogen heterocycles, particularly pyridines, to make comparison with earlier sections as direct as possible (the facile hydration of polyazaheterocycles has been reviewed[212, 213]). The main points of interest in the kinetic investigations, apart from the establishing of the bimolecular nature of the reaction, have been the quantitative investigation of the activating effect of the aza-nitrogen, both at various positions in the ring system and compared with the commonly used nitro activating group in the benzenoid series.

b. Activating effect of the aza group. The activating effect of the aza-nitrogen has been investigated in simple pyridine systems of several authors[214–216, 218–222]. Some relevant data[214–217] are given in Table 14. In general, the activating effect in the 4-position is somewhat larger than that in the 2-position, giving larger rates of reaction and smaller activation energies for the replacement of halogens by alkoxide ions. The activation energies for halogen replacement in unactivated aromatic hydrocarbons are considered[105, 214, 216] to be in excess of 30 kcal/mole, and the activating effect of the aza-nitrogen relative to the unsubstituted hydrocarbon is reflected in the lower activation energies observed in these cases, the introduction

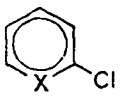
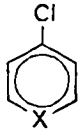
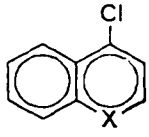
of an azine nitrogen lowering the activation energy by roughly 10 kcal/mole. A direct comparison of the rates of reaction can be made in the case of 2-chloro-naphthalene where the introduction of an aza-nitrogen in the 1-position (to give 2-chloroquinoline) increases the rate of reaction with methoxide ion by a factor of $6{\cdot}9 \times 10^9$ and the introduction of an aza-nitrogen in the 3-position (to give 3-chloroisoquinoline) by a factor of $1{\cdot}3 \times 10^5$. Other, less direct, comparisons can be made by comparing the effect of the insertion of an aza-nitrogen at various positions in a substrate already activated by an aza or nitro group[218–222]. In general, the aza group gives a very large increase in reactivity compared with the corresponding hydrocarbon. The activation at various positions is in the order *para* > *ortho* > *meta*.

TABLE 14. Kinetic and thermodynamic parameters for the alkoxydechlorination of chloropyridines.

Substituent	Conditions	$k \times 10^6$ ($l\ m^{-1}\ sec^{-1}$)	E_a (kcal $mole^{-1}$)	ΔS (e.u.)	Ref.
2-Cl	OMe^-, MeOH, 50°	$3{\cdot}31 \times 10^{-2}$	28·9	−5·3	217
3-Cl	OMe^-, MeOH, 50°	$1{\cdot}09 \times 10^{-5}$	32·9	−9·2	217
4-Cl	OMe^-, MeOH, 50°	$8{\cdot}9 \times 10^{-1}$	25·2	−10·4	217
2-Cl	OEt^-, EtOH, 20°	$2{\cdot}2 \times 10^{-3}$	26·8	−9·2	214, 215
4-Cl	OEt^-, EtOH, 20°	$8{\cdot}7 \times 10^{-2}$	20·9	−22·3	214, 216

The activating effect of the aza-nitrogen is often compared with the effect of the nitro group in benzenoid systems, and the two are very similar both in the preferred activation of positions *ortho* and *para* to the group and also in the magnitude of their effect.

Direct comparisons have been made in some simple systems by several authors[223–225]. The relative ratios for alkoxydechlorination in the simplest systems are shown below, where X = N or C–NO_2.

			
approx. ratio $\frac{k_{2\ nitro}}{k_{aza}}$	10	15·1	8·4
conditions	90°/OEt^-	60°/OEt^-	60°/OEt^-
reference	214, 224a	214, 224b	214, 224c

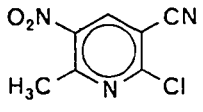
A large amount of data is also available in systems containing more than one activating group[225]. Although the exact relation between the two groups will depend on both the substrate and nucleophile, some generalizations can be made. Firstly, the difference between the two groups is often within an order of magnitude which is a small difference compared with the very large effect of either relative to the unsubstituted aromatic hydrocarbon. Secondly, in reactions with alkoxide ions, the relative activating effect of NO_2 compared with N is larger in the *ortho* than in the *para* position. These observations are in substantial agreement with the early qualitative study of Mangini and Frenguelli[223].

2. Evidence for intermediate complexes

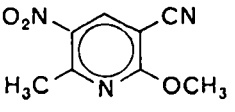
The detection of intermediates in the nucleophilic additions of alkoxides to activated substrates in the benzenoid series is considered an important piece of evidence in favour of the more general applicability of the two-stage mechanism for attack by alkoxides and hydroxides (section V).

The large activating effect of the aza group compared both with the unsubstituted hydrocarbon and with the C–NO_2 grouping (section VI.A.1) could suggest that the stabilization of some intermediates in the pyridine series might be high enough to allow for their detection.

In the conversion of 2-chloro-3-cyano-6-methyl-5-nitropyridine (**77**) into the corresponding alkoxy compound (**78**), Mariella and Hyalik[226] noted that an intense colour was produced. A similar observation was made by Fanta and Stein[227] in the treatment of 2-chloro-3-cyano-5-nitropyridine with methoxide ion. In further



(77)



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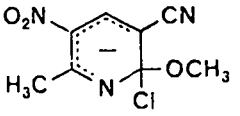


(79)

studies Mariella and co-workers[228] concluded that both 2-chloro and 2-alkoxy pyridines containing powerful electron-attracting groups in the 3- and 5-positions reacted with bases to produce intense colours, and that a probable explanation was the formation of a quinoid system analogous to the benzene series, for example, **79**, for the colour-producing species formed in the interaction of **77** with base. Although more recent research in the benzene series might suggest alternative explanations for some of their observations, the

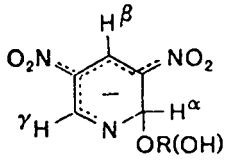
essence of their conclusions is undoubtably correct, and more recently intermediates of this type have been characterized by the n.m.r.[166, 229, 230]. The n.m.r. and u.v. spectral characteristics of these systems are collected in Table 15.

TABLE 15. N.m.r. and u.v. spectral parameters of pyridine σ-intermediates in DMSO solution.

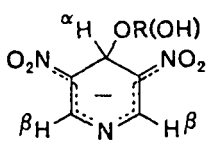
Structure	OR	X	$H_\alpha(-\delta)$	$H_\beta(-\delta)$	$H_\gamma(-\delta)$	λ_{max} (mμ)	Ref.
80	OCH_3	H	6·08	8·30	8·62	487	229
82a or **82b**[a]	OCH_3	NMe_2	6·05	8·20	—	448	229
	OCH_3	OCH_3	5·99	8·59	—	455	230
83	OCH_2CH_2O	H	—	8·35[b]	—	462	229
84	OCH_3	H	—	8·78	—	455	230, 166

[a] Assignment can be made in terms of either structure.
[b] Multiplet centre.

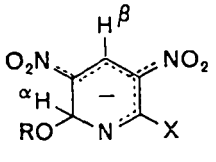
Thus the addition of sodium methoxide to a solution of 3,5-dinitropyridine in DMSO gives a bright red colouration and causes the disappearance of the 3,5-dinitropyridine resonances at 0·27 and 0·86τ and the appearance of three new resonances of equal intensity at 1·38, 1·70 and 13·92τ ascribable to the intermediate **80** (OR = OCH_3)[229]. The shift to higher fields has been found to be characteristic of the cyclopentadienide system, and the resonance at 3·92τ ascribed to the hydrogen atom on the sp^3 carbon atom is in good agreement with those found in benzenoid aromatic systems (section V). There is no evidence for the formation of the second possible isomer (**81**) (OR = OCH_3) and the solutions are quite stable with time. The corresponding hydroxyl compound can be made either directly by the addition of KOH, or by solvolysis of **80** (R = OCH_3). Both of these compounds undergo replacement reactions with diethylamine and acetone[229]. When there is a substitu-



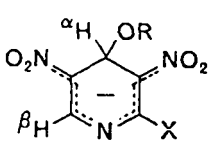
(80)



(81)



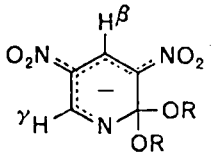
(82a)



(82b)

ent in the 2-position, e.g. NMe_2, then the intermediate is formed by attack at either position 4 or 6, giving either **82a** or **82b** (X = NMe_2),

but it is not possible to distinguish between these two structures on the basis of the n.m.r. spectrum alone[229]. Similarly, Illuminati and



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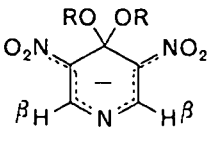


(84)

Stegel[230] found that the initial product of the action of base on 2-methoxy-3,5-dinitropyridine was a complex of the general type **82** (X = OCH_3, OR = OCH_3). Again it is impossible to establish the point of attack from the n.m.r. spectrum alone. Further possible reaction to form the dimethoxy intermediate **83** (OR = OCH_3) was obscured by a demethylation reaction. A complex of this type is, however, formed by the action of base on 2-(2′-hydroxycthoxy)-3,5-dinitropyridine where the complex **83** (OR, OR≡OCH_2CH_2O)[223] is formed. The dialkoxy intermediate **84** (OR = OCH_3) is formed by the action of methoxide on 4-methoxy-3,5-dinitropyridine[166, 230]. It is not clear whether this is the initial point of attack or not. The complex can be isolated[166, 230] and shows the general characteristics expected of a structure of this type (section V).

Intermediates have also been found in the pyrimidine series[230, 231]. Illuminati and Stegel[230] reported that attack by methoxide ion on the 2- and the 4-methoxy-5-nitropyrimidines occurs at a CH position, but it is not clear whether rearrangement occurs to the more stable dialkoxy intermediates or not.

Although the extension of the above observations of intermediates in highly activated systems to a consideration of the general applicability of the two-stage mechanism must be treated with the same reservations as in the benzenoid series, there is nevertheless a strong inference that this may be the case, at least in activated systems.

3. Theoretical approaches

All the different approaches outlined for aromatic systems (section V) are, in principle, applicable to heterocyclic systems, but not as much work has been done in this field. Particularly interesting would be a comparison of results calculated by Miller's semi-empirical method with experimental values. Recently, however, Simonetta and co-workers[232] have compared the calculated parameters for several different theoretical approaches to the alkoxy-

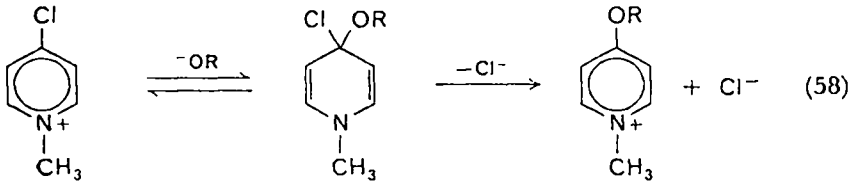
dechlorination of a large number of halo–aza compounds with experimental activation energies.

The methods used were the isolated molecule, localization and their own delocalization approach as described in section V. The different parameters used were the π-electron density at the carbon atom at the site of attack, the Wheland localization energy, and the difference in π-electron energy in the transition and initial states. When the activation energies were correlated, the delocalization method gave the best results and the isolated molecule the poorest. When the free energy changes were used, the delocalization method again gave the best fit, though not as good as with the activation energies. Again, the lack of suitable kinetic data for the alkoxydehalogenation of simpler aza aromatics is a serious limitation.

B. Pyridinium Ions

1. Kinetics and mechanism

A ready replacement of halogen by alkoxide occurs in the 2- and 4-positions of 1-alkylpyridinium salts[217, 233]. Kinetically, the reactions are first-order in both alkoxide and substrate and are thought of as proceeding according to equation (58), involving an intermediate complex (**85**). The activating effect of the quaternary



(85) (58)

nitrogen can be seen in a comparison of the rates of alkoxydechlorination of isomeric chloropyridines and chloropyridinium ions[217, 233] (Table 16). In fact the activating effect of the quaternary nitrogen is so much greater than the aza-nitrogen that a direct comparison with a common alkoxide is not possible, the rates of reaction of the 2- and 4-chloropyridinium ions with methoxide being too fast to measure, even at −15°C. Some idea of the difference can be obtained from the fact that even the rates of reaction of the pyridinium ions with the *p*-nitrophenoxide ion are still much larger than those of the corresponding pyridines with the very much stronger methoxide ion. The greater activating effect of the quaternary nitrogen, which has been estimated at $\times 10^7$ to $\times 10^{13}$ depending on position, is also

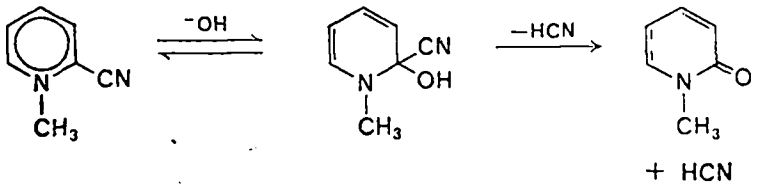
reflected in very much lower activation energies. The activating effect is in fact larger than that of the NO_2 group, the kinetics of the reaction of 2- and 4-chloronitrobenzene with methoxide ion being quite measurable at 50°.

In the pyridinium ions, the relative activation at different positions is $2 > 4 \gg 3$. The activation energies for the 2- and 4-positions are very similar, and the reversal in relative rates compared with the pyridines is mainly due to a much higher activation energy for the 2-chloropyridinium ion.

TABLE 16. Kinetic parameters for the alkoxydechlorination of isomeric chloropyridines and chloropyridinium ions in methanol solution at 50°C[217, 233].

Isomer	Reagent	Pyridium ion		Pyridine	
		$k \times 10^6$ (l m^{-1} sec^{-1})	E_a (kcal/mole)	$k \times 10^6$ (l m^{-1} sec^{-1})	E_a (kcal/mole)
2-Cl	$-OCH_3$	very fast		$3{\cdot}3 \times 10^{-2}$	28·9
	$-OC_6H_4NO_2$	$1{\cdot}39 \times 10^7$	18·6		
3-Cl	$-OCH_3$	ca. 1×10^2		$1{\cdot}09 \times 10^{-5}$	32·9
	$-OC_6H_4NO_2$	0·28	30·2		
4-Cl	$-OCH_3$	very fast		0·89	25·2
	$-OC_6H_4NO_2$	$4{\cdot}6 \times 10^5$	17·6		

Pyridone formation proceeds readily by the replacement of alkoxy, halogen and cyano groups in the 2- and 4-positions in pyridinium salts[234]. The reaction is thought to proceed as shown in equation (59)

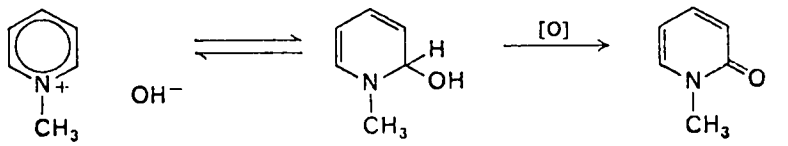


(59)

by a scheme analogous to equation (58) above, except that the final product is now a neutral species.

Pyridone formation also proceeds readily by the action of hydroxide ion on pyridinium ions without a readily replaceable group if the reaction is carried out in the presence of an oxidant[235–237]. Commonly used is potassium ferricyanide[238]. Although the pyridinium hydroxide salts can be prepared by the action of moist silver oxide on the pyridinium halides, they are normally generated in situ

by performing the reaction in alkaline solution. A very important feature of the reaction is its specificity to the 2-position, no report ever having been made of the formation of a 4(γ)-pyridone. The mechanism proposed[239] for the reaction (equation 60) is analogous



(60)

(86)

to those suggested for the replacement of labile groups (58 and 59) and requires the formation of a 'pseudo'- or 'carbinol'-base (**86**) which is then oxidized to the pyridone. This mechanism is analogous to that suggested for TNB (equation 47). However, the mechanism does not really give a complete picture of the reaction, as it does not account for the absence of the 4-pyridone while the activating effect of the quaternary nitrogen is of the same magnitude in both the 2- and 4-positions. The explanation may possibly lie in the actual mode of oxidation (see also below). Pyridinium ions substituted in the 3-position can give rise to isomeric products. Nicotinamide methiodide[240] gives both the 2- and 6-pyridones, as does 3-ethylpyridine[241], but nicotinic acid yields only the 6-isomer[242].

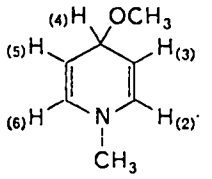
2. Investigations of intermediates

The equilibrium between a pyridinium hydroxide or alkoxide and a pseudo-base formed by attack of the ion in the 2- or 4-position of the pyridinium ring represents the first step in equations (58—60) above. In the case of unsubstituted pyridinium salts (equation 60), further reaction requires elimination of the very high energy hydride ion, which will be energetically unfavourable, and, in the absence of an oxidant, the reaction will not proceed further than the initial equilibrium. Investigation of this equilibrium should provide a model for the other two reactions.

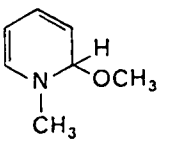
Such an equilibrium gives rise to a neutral species whose presence should be detectable by conductivity measurements. This approach has been used[243, 236], but no change in conductivity which might indicate the formation of complexes corresponding to **86** was found on basification of pyridinium salts with hydroxide. It was concluded that the oxidation must proceed through a very small quantity of pseudo-base.

However, an equilibrium of this type will be very dependent on the solvating properties and dielectric constant of the solvent, and pseudo-base formation can be observed with alkoxide ions in DMSO solution[106]. The pseudo-bases are quite stable under the conditions of the experiment, and the isomers observed are very dependent on substitution in the ring.

Thus the addition of anhydrous sodium methoxide to a DMSO solution of pyridinium methiodide causes the disappearance of the resonances of the pyridinium ring, and the appearance of two new multiplets at much higher fields, consisting of a doublet $\delta = -5{\cdot}84$ and a multiplet $\delta = -4{\cdot}34$. The latter can be resolved from the overlapping absorption of the methyl group of the pyridinium salt by the use of *N*-trideuteromethylpyridinium iodide. These absorptions can be assigned to the 2,6 and 3,4,5 protons in the adduct **87**.



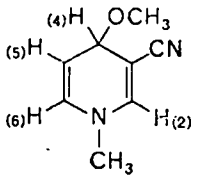
(87)



(88)

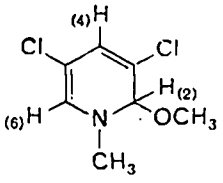
There are no resonances at any stage attributable to the isomeric complex **88**.

Similarly, the addition of methoxide to 3-cyanopyridinium methiodide yields the adduct (**89**) formed by attack in the 4-position and a small amount of another isomer.

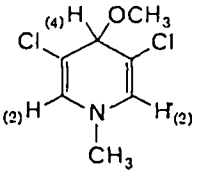


(89)

The relationship between adducts formed by attack at the 2- and at the 4-positions can be seen from the results on 3,5-dichloropyridinium methiodide. Addition of methoxide to this pyridinium salt in DMSO gives rise initially to three resonances of equal intensity at $\delta = -6{\cdot}79$, $\delta = -6{\cdot}51$, $\delta = -5{\cdot}45$ attributable to $H_{(6)}$, $H_{(4)}$ and $H_{(2)}$ respectively in **90**, and two other less intense resonances at



(90)



(91)

$\delta = -6{\cdot}86$ (rel. intens. 2) and $\delta = -4{\cdot}94$ (rel. intens. 1) corresponding to $H_{(2,6)}$ and $H_{(4)}$ in the small amount of the isomeric complex **91** present. With time the composition of the mixture changes in favour of the thermodynamically more stable 4-isomer (Figure 10).

The above observations suggest that the 'pseudo-base' adducts of

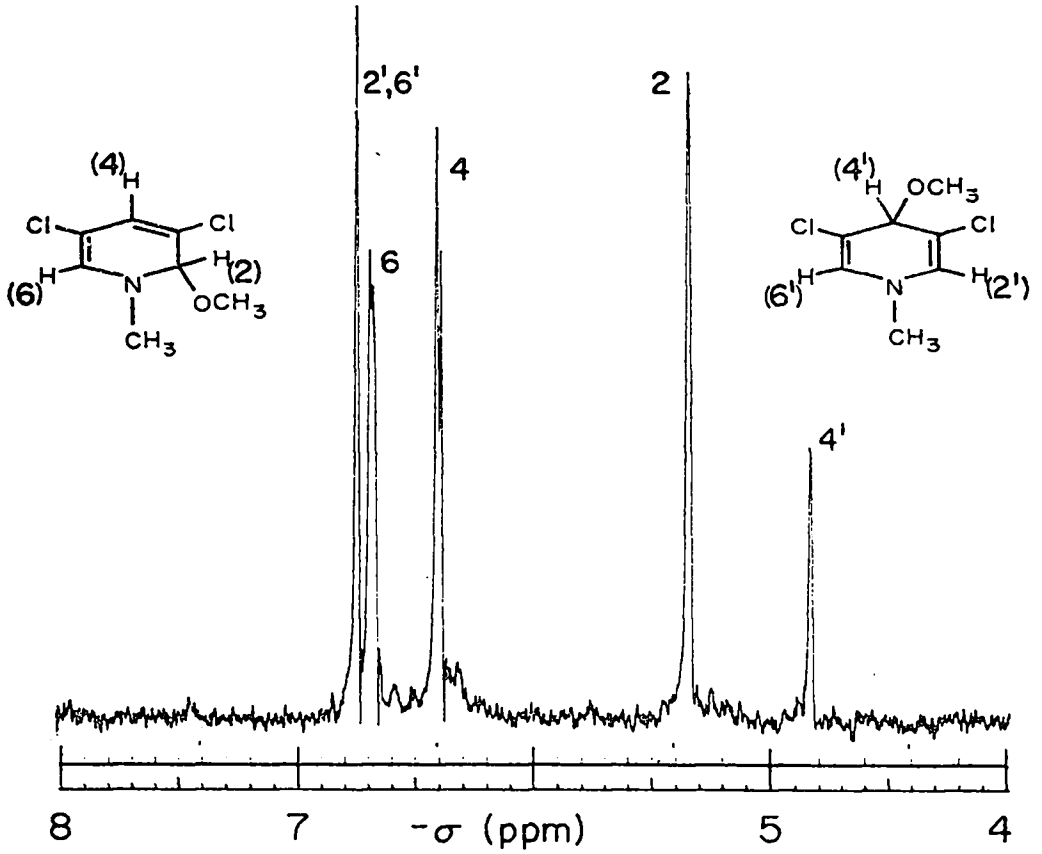


FIGURE 10. 100 MHz n.m.r. spectrum of a solution of 3,5-dichloropyridinium methiodide plus anhydrous sodium methoxide after 30 minutes.

this general type are quite stable species and can be produced quantitatively, at least in a very basic solvent. However, the factors governing which isomer is formed in a given case are not so clear. In the case of 3,5-dichloropyridinium methiodide it seems clear that it is the 2-isomer which is formed initially and then rearranges to the thermodynamically more stable 4-isomer. One could not argue from this, however, that this is the general case, as the factors which give the 2-isomer its stability (electronegative groups in the 3- and 5-positions) could also cause the attack in this position in the first place. The experimental non-observation of 4-pyridones is in agreement with either the very fast oxidation of a preferentially formed 2-adduct before it can rearrange to the 4-isomer, or the very specific preferential oxidation of the 2-adduct (perhaps by participation of the ring nitrogen in the oxidation step), even though it may be present in only a relatively small concentration. More experimental work is required to settle these points.

VII. ACKNOWLEDGMENTS

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CHAPTER 3

Free radical and electrophilic hydroxylation

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I. GENERAL

Some important indirect methods of introducing a hydroxyl group into a molecule involve attack by an electrophilic reagent as one of many steps in the synthesis. However, in this chapter only the direct hydroxylation of organic compounds by free radical and electrophilic reagents is considered. In common with many electrophilic reagents, the reactions with aromatic compounds have been the most extensively and intensively investigated.

The attacking reagents are uncharged or positively charged hydroxyl or hydroperoxyl entities[1a] and they may be free or complexed to a metal ion. They may be produced chemically by reaction between two reagents, photochemically by ultraviolet light or radiolytically by high energy ionizing radiation.

In recent years, the use of flow systems to produce a stationary state concentration of short-lived species in the cavity of electron paramagnetic resonance equipment has led to a greater understanding of the action of the chemical reagents. In many cases the short-lived transient intermediate species have been characterized. At the same time, application of pulse radiolysis techniques has enabled the early radiolytic species to be identified and their reactions to be followed. The development of sensitive separation and identification techniques, has made possible the identification of the products.

Direct electrophilic hydroxylation is not favoured as a synthetic method. In unsaturated compounds, free radicals can initiate side reactions such as polymerization or hydrogen abstraction. In aromatic compounds, the phenolic products are further attacked—particularly at the activated *ortho*- and *para*-positions—giving secondary products.

The reaction mechanism must therefore be studied under conditions where a small fraction of the original material is converted into products. The use of dilute solutions is a further simplification. These conditions are not satisfactory for practical synthetic methods.

The attacking species is known and well characterized for radiolytic hydroxylation by high energy ionizing radiation and for photolytic hydroxylation by ultraviolet light. On the other hand, rather complex interactions are involved for the chemical hydroxylating reagents. Much more is known about radiolytic hydroxylation so this method will be considered first*.

* The impact of recent research in radiation chemistry on the study of organic reaction mechanisms has been reviewed by Fendler and Fendler[323].

Quantities will, in general, be expressed in S.I. (Système International) units as well as the more familiar units. I.U.P.A.C. recommended abbreviations are used.

1 eV (electron volt) = 0·16 aJ (attojoule = 10^{-18} J)

mole/litre is used in preference to M to denote solution concentration.

1 nm (nanometre) = 1 mμ (millimicron) = 10 Å (Ångström unit)

Molar decadic (logarithm base 10) extinction coefficient (ε) is derived from the equation $\varepsilon.l.c = \lg (I_0/I)$, where l is the optical path length and c is the concentration of solute reducing light of intensity I_0 to intensity I. The units of ε are 10 M^{-1} cm^{-1} = 1 m^2/mole.

lg = common logarithm or $\log_{10}$

s = second

Second-order rate constant, k, is in units, M^{-1} s^{-1} or litre $mole^{-1}$ s^{-1} ≡ dm^3 $mole^{-1}$ s^{-1}.

II. RADIOLYTIC HYDROXYLATION

A. Introduction

Hydroxyl products result when aqueous solutions of certain organic solutes are exposed to high energy ionizing radiation—γ-rays, X-rays, β-particles, α-particles, etc.

The following[1] will assist readers not familiar with some of the radiation chemistry terms used in this section.

The extent of chemical reaction in any system exposed to ionizing radiation depends on the dose—the energy absorbed by unit weight of the material. A dose of one *rad* corresponds to the absorption of 100 erg per gramme of material ($6{\cdot}242 \times 10^{13}$ eV/g or 10^{-2} J/kg).

The amount of material changed, of reactive species produced, or of product separated is usually expressed as the radiation chemical yield or G-value—the number of molecules altered for every 100 eV (16 aJ) of energy absorbed. It follows that one Megarad (1 Mrad or 1000 krad, which is equivalent to 2·4 calories/g) makes a change of $G \times 1{\cdot}04 \times 10^{-3}$ mole/kg irradiated. G lies between 0·1 and 10 for many reactions.

Many products are formed within a millisecond. Those which are present a few minutes after the end of the irradiation are called 'prompt products'. Those that appear subsequently without further exposure to ionizing radiation are called 'post-irradiation products'. A wavy arrow is often used to indicate a radiation chemical reaction.

It should be noted that some of the literature references are to reports, etc., produced by or on behalf of Atomic Energy Commissions. Most of these are listed in *Chemical Abstracts* or *Nuclear Science Abstracts* and are available from libraries of corresponding authorities.

I. The reactive species

To date the main task in aqueous radiation chemistry has been to determine what are the primary species formed during the radiolysis of water and how much of each of these species is produced for a given input of energy. This task has proved to be a very difficult one, and even now that the main features appear to be clear, some details are incomplete.

The primary species are the hydrated electron, the hydrogen atom, the hydroxyl radical, molecular hydrogen, molecular hydrogen peroxide and the hydronium ion.

$$H_2O \rightsquigarrow e^-_{aq},\ H^{\bullet},\ OH^{\bullet},\ H_2,\ H_2O_2,\ H_3O^+ \qquad (1)$$

Radical species will generally be indicated by a dot ($R^{\bullet}$).

In Table 1 the experimental radiation chemical yields (*G*-values) are given. The amounts of the reducing radical species (e_{aq} and $H^{\bullet}$) available in acid or in alkaline solution are greater than in neutral solution.

TABLE 1. Radiation chemical yields (*G*-values) for primary species in aqueous solution.

	G-value (molecules per 100 eV)		
pH	0–2	4–11	13–14
e_{aq}	3·65	2·7	3·1
$H^{\bullet}$		0·55	0·5
$OH^{\bullet}$	2·95	2·8	2·9
H_2	0·45	0·45	0·45
H_2O_2	0·8	0·7	0·7

Accounts of these species and of their reactions are given in general textbooks on radiation chemistry[1,2]. Some of the older texts[3–5] give excellent accounts of earlier theories and of experimental results but were written before the discovery of the solvated electron[6]. The interpretations advanced in these texts must be modified accordingly.

The primary radiation chemical species undergo reaction with

solutes (sometimes called 'scavengers') to give the observed products. Thus, except in concentrated solution, the radiation does not act directly on the solute. The action is indirect via the solvent water.

While the essential nature and amount of the primary species was being established, and especially during recent years, radiation chemists have investigated the reactions of these species.

2. The hydroxyl radical

It has been shown that the primary oxidizing species formed in the radiolysis of aqueous solutions is uncharged[7] and is identical with that formed in the photolysis of hydrogen peroxide[8]. Hydroxyl groups have been found in the polymer produced by irradiation of acrylonitrile in aqueous solution[9]. The electron paramagnetic resonance spectrum of hydroxyl radicals has been found in irradiated ice[10]. It seems certain that the chemical entity involved is the hydroxyl radical ($OH^{\bullet}$).

The radiation chemical yield of hydroxyl radicals can be almost doubled by dissolving nitrous oxide in the solution before irradiation. The hydrated electrons which might otherwise interfere with the course of hydroxyl radical reactions are converted and then participate in those reactions.

$$e_{aq} + N_2O \longrightarrow N_2 + OH^{\bullet} + OH^- \qquad (2)$$

Similarly, in hydrogen peroxide solutions the reducing primary radical species (e_{aq} and $H^{\bullet}$) may be converted into oxidizing radicals.

$$H_2O_2 + e_{aq}, H \longrightarrow OH^{\bullet} + OH^-, H_2O \qquad (3)$$

In these ways and under suitable conditions, ionizing radiation is a 'clean' way of making hydroxyl radicals. Their reactions may be studied with relative freedom from interfering species.

3. The hydroperoxyl radical

The hydroperoxyl radicals ($HO_2^{\bullet}$) or their ionized form ($O_2^{\bullet -}$) are secondary products formed by reaction between hydrogen atoms or hydrated electrons and molecular oxygen dissolved in water which is exposed to air or an atmosphere of oxygen.

$$H^{\bullet} + O_2 \longrightarrow HO_2^{\bullet} \qquad (4)$$

$$e_{aq} + O_2 \longrightarrow O_2^{\bullet -} \qquad (5)$$

$$HO_2^{\bullet} \longrightarrow H^+ + O_2^{\bullet -} \qquad pK_a = 4{\cdot}4 \qquad (6)$$

Hydroperoxyl radicals are also formed by reaction between hydroxyl radicals and hydrogen peroxide. This reaction can become important when solutions of hydrogen peroxide are irradiated.

$$H_2O_2 + OH^{\bullet} \longrightarrow HO_2^{\bullet} + H_2O \qquad (7)$$

Although their identity has been established[11–14], the reactions of radiolytic hydroperoxyl radicals with organic solutes have not been extensively studied. In general, they are much less reactive than hydroxyl radicals and often react with each other to give a radiation chemical yield of hydrogen peroxide greater than the primary molecular yield ($G = 0{\cdot}7$).

$$2\,HO_2^{\cdot} \longrightarrow H_2O_2 + O_2 \qquad (8)$$

They must not be overlooked in any discussion of hydroxylating species.

4. Pulse radiolysis

Since much of our detailed knowledge of the early radiation chemical reactions comes from the application of pulse radiolysis, a brief outline of this technique will be given.

Pulse radiolysis[14–16] is the radiation chemical analogue of flash photolysis. Briefly, high energy electrons in a very short pulse (microseconds or nanoseconds) at over a million volts are fired from an electron accelerator into the chemical system under study. The chemical species present after the pulse are followed by detection methods with fast response times.

Although polarographic, conductometric and electron spin resonance detectors have been used, the ones most frequently used are spectrophotometric. A beam of light is passed through the chemical system and into a monochromator. The changes in intensity, as registered by a photoelectric cell, are displayed on a cathode ray tube. In this way, the appearance and change in concentration of an absorbing species can be followed with time. Also, the absorption spectrum of such a species can be found. Thus its kinetic behaviour can be followed and some idea of its nature or identity can be obtained.

B. *Hydroxyl Radical Reactions*

Hydroxyl radicals have been shown to undergo four different types of reaction with organic compounds—addition, hydrogen abstraction, electron transfer and displacement reactions.

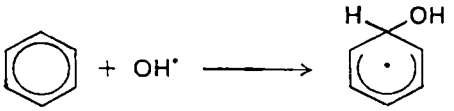
1. Benzenoid compounds

a. Early studies. Weiss, Stein and co-workers[17–24] studied the radiation chemistry of aqueous solutions of benzene[17, 18], benzoic acid[17, 22], nitrobenzene[20, 21] and chlorobenzene[24]. One result was to demonstrate that the oxidizing species was the hydroxyl radical

in that its reactions resembled those of the reactive entity in Fenton's reagent (ferrous ion and hydrogen peroxide—see section IV.B.). It was proposed that hydroxyl radicals abstracted ring hydrogens from the solute aromatic molecules to give the corresponding phenyl radicals ($XC_6H_4^{\bullet}$). Association of two of these radicals gave substituted biphenyls which had also been isolated from Fenton's reaction. Alternatively, each phenyl radical was thought to add another hydroxyl radical yielding the range of isomeric hydroxy compounds (phenols) which were found among the products of the radiolysis. Subsequent workers[25–56], using improved methods of product separation and identification, made more refined measurements, irradiating aqueous solutions of various aromatic compounds, but mostly benzene.

It was clear that in aerated solutions the yield of phenolic products was greater than half the G_{OH} value. (It is now known that hydroxyl radicals react so rapidly with the solute that under the conditions used it is extremely unlikely that the short-lived radicals, which are present at very low steady state concentrations, will react with a second hydroxyl radical as required by the proposed mechanism.) Further, oxygen isotopic studies showed that all the incorporated oxygen came from radiolysis of water. It was therefore proposed by several workers[26, 32, 33, 41], particularly Russian workers[34–40, 47, 52], that the $OH^{\bullet}$ radical must first add to the aromatic ring in the same way as many other organic substituting reagents which give a benzenium structure. Acceptance of this mechanism had to await its proof[57, 58] by pulse radiolysis techniques.

b. The definitive experiment. Using pulse radiolysis techniques, Dorfman, Taub and Bühler[58] were able to show in a strikingly direct way that the hydroxyl radical added to the aromatic ring of benzene



(9)

(1)

(equation 9) to give an absorption spectrum with a maximum at 313 nm corresponding to the hydroxycyclohexadienyl radical **1**. The identity of **1** was further established by showing that the rate constant for reaction (9) was greater than that for any hydrogen abstraction reaction. This would have given $C_6H_5^{\bullet}$. Furthermore, one would expect hydrogen abstraction by hydroxyl radicals from

fully deuterated benzene to take place at about one third the rate of that from C_6H_6. Experimentally, no such kinetic isotope effect was observed when C_6D_6 in aqueous solution was irradiated.

The fate of this radical depended on whether molecular oxygen was present in the solution. In deaerated solution, **1** disappeared by second-order processes giving dimers which slowly decomposed to biphenyl ($G = 0{\cdot}3$ molecules/100 eV), phenol ($G = 0{\cdot}23$) and other products (equations 10 and 11).

$$2\ HOC_6H_6^{\bullet} \longrightarrow \text{dimers} \longrightarrow C_6H_5C_6H_5 + 2\ H_2O \qquad (10)$$

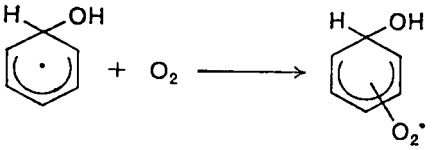
$$2\ HOC_6H_6^{\bullet} \longrightarrow C_6H_5OH + C_6H_5OH \qquad (11)$$

The adduct $C_6H_7^{\bullet}$, which had been formed by reaction between benzene and the hydrogen atom, also reacted with **1** (equation 12).

$$HOC_6H_6^{\bullet} + C_6H_7^{\bullet} \longrightarrow 2\ C_6H_6 + H_2O \qquad (12)$$

Also mentioned was the possibility of **1** reacting with solute benzene to give dimer hydroxylated products but these were not sought by analysis.

In aerated solution, **1** reacted (equation 13) with oxygen giving a spectrum with a maximum at a lower wavelength which could be attributed to the peroxy derivative **2**. The final product was



(13)

(2)

phenol, with an immediate radiation yield of $G = 1{\cdot}9$ (equation 14). Fifteen weeks after removal from the radiation field, G (phenol) was found to be 2·3. The additional amount was thought to have been formed from the decomposition of unstable products such as peroxides.

$$HOC_6H_6O_2^{\bullet} \longrightarrow HOC_6H_5 + HO_2^{\bullet} \qquad (14)$$

$$2\ HO_2^{\bullet} \longrightarrow H_2O_2 + O_2 \qquad (8)$$

At high pulse intensities, **2** disappeared by second-order processes in competition with reaction (14), presumably giving peroxides or hydroperoxides:

$$2\ HOC_6H_6O_2^{\bullet} \longrightarrow \text{peroxides} \qquad (15)$$

$$HOC_6H_6O_2^{\bullet} + HO_2^{\bullet} \longrightarrow \text{hydroperoxides} \qquad (16)$$

The yield of phenol decreased with increasing pulse intensity, i.e., with increasing concentration of **2**. High concentration favoured

second-order reactions (equations 15 and 16) rather than reaction (14). At the highest pulse intensity used, where the maximum concentration of **2** was 9×10^{-5} mole/litre, G(phenol) was 0·19. Post-irradiation production of phenol with $G = 0{\cdot}3$–$0{\cdot}5$ was observed.

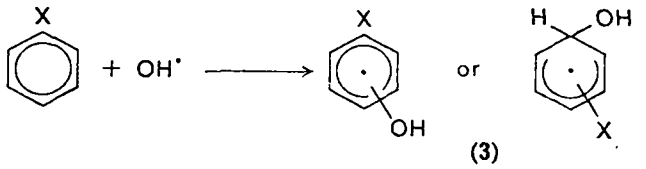
c. Transient species. Spectra similar to that of **1** were obtained for substituted **1** formed following the pulse radiolysis of aqueous solutions of chlorobenzene, bromobenzene, iodobenzene, toluene, phenol[58], benzoic acid[59], benzoate[60], nitrobenzene[61], etc.[62].

Although the transient species can be followed for but a fraction of a millisecond, their absorption spectra resemble closely[60] those of the carbonium ions formed when aromatic compounds are ring-protonated by concentrated sulphuric acid or by Lewis acid–hydrogen halide complexes.

The molar decadic extinction coefficient has been estimated in several cases. For **1** it is 3500 M^{-1} cm^{-1} (350 m^2/mole)[58]. For the benzoate–O^- adduct at pH 13 it is 3100 [60].

d. Kinetics of OH addition. Because the hydroxyl radical absorbs weakly[63–66] in the short ultraviolet region ($\varepsilon = 530$ M^{-1} cm^{-1} or 53 m^2/mole at about 230 nm with another broad maximum below 200 nm[66]), it is not possible to determine second-order rate constants for its reactions with solutes by following its rate of disappearance as can be done for reactions of the hydrated electron[6, 14, 16]. Nevertheless, a considerable body of data is available[67] from the application of competition methods[68–74] and from following the appearance of the transient adducts **1** [59, 75–77].

The rate constants for the reactions expressed by equation (17) have been reported by Neta and Dorfman[77] to range between



(3) (17)

$1{\cdot}4 \pm 0{\cdot}3 \times 10^{10}$ M^{-1} s^{-1} (dm^3 $mole^{-1}$ s^{-1}) for phenol (X = OH)[75] and $3{\cdot}2 \pm 0{\cdot}4 \times 10^9$ M^{-1} s^{-1} for nitrobenzene (X = NO_2). An independent determination[76] of the rate of formation of the nitrobenzene–hydroxyl radical adduct gave a value $4{\cdot}7 \pm 0{\cdot}5 \times 10^9$ M^{-1} s^{-1}. Further, the values determined[77] for benzoate (X = COO^-) show a slight downward trend with increasing benzoate concentration. Further study is needed.

Using a series of rate constants obtained by competition methods

for reaction between hydroxyl radicals and substituted benzenes, Anbar, Meyerstein and Neta[72] showed that there was a reasonably good correlation using Hammett's[78] $\sigma\rho$ relationship for electrophilic substitution (equation 18).

$$\lg[k_{(OH+C_6H_5X)}/k_{(OH+C_6H_6)}] = \sigma\rho \qquad (18)$$

σ denotes the Hammett substituent constant and ρ the reaction constant. Since data on the isomeric yields were not available for the whole range of compounds measured, it was not possible to evaluate the reaction rate constants for attack at positions *meta* or *para* to the substituent. As a near approach to the problem the overall reaction rate constant was used in equation (18) in conjunction with both σ_{para} and σ_{meta} values for deactivating substituents and σ_{para} values only for other substituents. (It has been established that there is little or no attack *meta* to *ortho-para* directing substituents as would be expected from such an electrophilic reagent as the hydroxyl radical.)

The value found for the series of substituted benzenes, $\rho = -0{\cdot}41$, was the same as that found when rate constants for $OH^{\bullet}$ reaction with *para*-substituted benzoate ions were plotted in a similar fashion. The σ values in disubstituted benzenes are therefore additive. This value of ρ is much lower than that for most other electrophilic reagents and this is attributed to the high reactivity of hydroxyl radicals, which makes them less susceptible to the directing influences of substituent groups and, incidentally, also makes them less selective. Using the absolute rate constants determined from pulse radiolysis, Neta and Dorfman[77] obtained a value $\rho = -0{\cdot}5$ in good agreement with that obtained from competition rate data.

The total reaction rate constants which have been used in these linear free energy correlations include contributions from $OH^{\bullet}$ reaction with the side chain, elimination of substituent groups and addition at the *ortho* position as well as the additions at *meta*- and *para*-positions. The partial rate constants for additions at each of these two positions should be separated from the overall reaction rate constant in order to test whether they reflect the electron distribution in the aromatic compound as expressed by the σ functions. The chemistry of the side reactions which affect the yields of isomeric products must be studied before this can be done. On the data now available[81, 85, 126] it would appear that the electron distribution in the ring is perturbed on the approach of the strong dipole of the hydroxyl radical.

e. Spectral correlations. The spectra of a number of **3** structures have been determined by pulse radiolysis techniques. Chutny[79] has shown that there are good correlations between these spectra and those of the corresponding aromatic compounds. The relative bathochromic shift of the primary band absorption maximum caused by substitution can be expressed as $(\nu_{C_6H_5OH} - \nu_{C_6H_4OHX})/(\nu_{C_6H_5OH})$. ν is the frequency of the absorption maximum. This was compared with the relative shift due to the same substituent in benzene. This ratio was found to lie between 0·71 and 1·12 and to be on the average 0·92. An exception was the benzoate–OH$^{\bullet}$ adduct (**3** where X = COO^-) for which the ratio was 0·48 and this was attributed to the influence of the negative charge on the substituent group.

The constancy indicates that the transient species have similar structure and the correlations may be used to predict absorption spectra of unknown species. Neta and Dorfman[77] have determined the spectra of other OH$^{\bullet}$ adducts, including those derived from some disubstituted benzenes, and have found fair agreement with Chutny's results.

Since it is probable that the hydroxyl group is attached to the cyclohexadienyl structure by sigma bonds (see section II.B.1.h) the observed spectrum in each case is an envelope of the contributions of the possible isomeric structures and of the various fragments remaining from side chain and substituent group elimination.

f. Reactions of the transient species. The rates of reaction of **3** with oxygen (equation 19) and with itself (equation 20) have been

$$XC_6H_5OH^{\bullet} + O_2 \longrightarrow \underset{(4)}{XC_6H_5(OH)O_2^{\bullet}} \qquad (19)$$

$$2\,XC_6H_5OH^{\bullet} \longrightarrow \text{products} \qquad (20)$$

measured by Cercek[80] for various substituents X. He found that, except for the adducts with benzene, toluene and ethylbenzene, the linear free energy relationship[77] of equation (21) held for reaction with oxygen.

$$\lg \frac{k_{(HOC_6H_5X^{\bullet}+O_2)}}{k_{(HOC_6H_6^{\bullet}+O_2)}} = \sigma\rho + C \qquad (21)$$

$$\rho = -1{\cdot}0 \quad \text{and} \quad C = -1{\cdot}4$$

A corresponding relationship held for $k_{(2HOC_6H_5X^{\bullet})}$ where $\rho = -0{\cdot}75$ and $C = 0{\cdot}3$. Activation energies for the second-order decay (equation 20) were also determined. The activation energy (kcal mole^{-1}) was found equal to $(5\sigma + 2{\cdot}5)$ for electron-withdrawing substituents and $(7\sigma + 5{\cdot}5)$ for electron-donating substituents.

This difference can be explained by assuming that electron-donating substituents give rise to a greater dipole repulsion between the two aromatic rings in the activated complex. Once again, the three aromatic hydrocarbon adducts did not correlate well but lay between the two groups. Since it seems unlikely that these react in a way fundamentally different from that of the other adducts, an explanation was sought in entropy effects. These may be caused by the absence of a lone pair of electrons in the side chains $-CH_3$ and $-C_2H_5$. This would inhibit hydrogen bonding with the water molecules. The result is that these adducts are twenty times more likely to react with oxygen and one fourth as likely to undergo biradical dimerization or disproportionation as would be expected from their σ constants.

Once again, such linear free energy correlations can be used to draw together and explain data and to predict rate constants. They could be refined if it were possible to separate the contributions from individual isomers. It is known for instance that of the three adducts formed during radiolysis of aqueous nitrobenzene solutions, that giving finally *o*-nitrophenol behaves quite differently from that giving *meta*- and *para*-products[81].

g. Formation of hydroxyl products. In deaerated solutions of benzene, the radiolysis products contain in addition to biphenyl (equation 10), bicyclohexadienyl compounds[58] ($G \sim 1$)[36] formed by diradical reactions (equations 22 and 23).

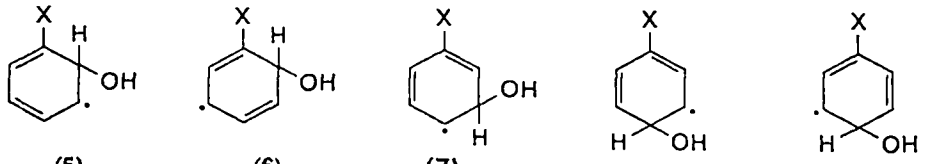
$$2\ HOC_6H_6^{\cdot} \longrightarrow (HOC_6H_6)_2 \qquad (22)$$

$$HOC_6H_6^{\cdot} + C_6H_7^{\cdot} \longrightarrow HOC_6H_6C_6H_7 \qquad (23)$$

At low dose rates, i.e., in steady radiolysis where the radical concentrations are much lower than in pulse radiolysis, **1** might react with the benzene substrate giving hydroxyphenylation products[58]. It should be noted that these diradical reactions are speculative as there is no report of a complete analysis of the radiolytic products from any aqueous aromatic solutions. Sitharamarao (quoted in Ref. 82) has found dihydroxybiphenyl ($G = 0{\cdot}8$) from irradiation of deaerated salicylate solution at pH 6·3 and no other hydroxylation products. In acid and alkaline solutions he found other products—dihydroxy-benzoic acids, benzoic acid, phenol and catechol[68].

Cercek[80] has considered the possible structures of **3** and concludes that one need only consider the structures shown overleaf.

Structure **7** is not applicable when X is an electron-donating substituent. Reactions between these species would be expected to give



(5) (6) (7)

products containing two aromatic rings joined together predominantly at the *meta* position relative to the original substituent.

In aerated solution of most aromatic solutes, reactions are thought[58] to follow equations (17), (19) and (24), giving a phenol. The amount

$$XC_6H_5(OH)O_2^{\cdot} \longrightarrow XC_6H_4OH + HO_2^{\cdot} \qquad (24)$$

of hydrogen peroxide found ($G = 2{\cdot}2$) in neutral solution can be accounted for by such a scheme in conjunction with equation (8) but more detailed evidence is lacking.

When $X = NO_2$, the peroxy derivatives of structures **5** and **6** are stabilized against unimolecular decomposition (equation 24) by forming a six-membered ring by hydrogen bonding between the out-of-plane hydroxyl radical in the *ortho* position and an oxygen of the nitro group[81]. At moderately high dose rates (10 krad per minute and higher) the diradical reaction (equation 25) predominates[81, 83–85].

$$2\,O_2NC_6H_5(OH)O_2^{\cdot} \longrightarrow O_2NC_6H_4OH + O_2NC_6H_5 + H_2O + 2\,O_2 \qquad (25)$$

The yield of *o*-nitrophenol is half that at very low dose rates or that in the presence of 0·2 mmole/litre dichromate ion which presumably acts as a one-electron oxidizing agent.

Land and Ebert[75] showed that, when the substrate is a phenol, **3** (X = OH) is able to eliminate water in a unimolecular reaction, giving a phenoxyl radical, $C_6H_5O^{\cdot}$. A special case is hydroquinone which gives a semiquinone radical $HOC_6H_4O^{\cdot}$ [86]. Fendler and Gasowski[85] suggest that this may be a general reaction leading to the elimination of substituent groups, NO_2, Cl, OMe from the ring.

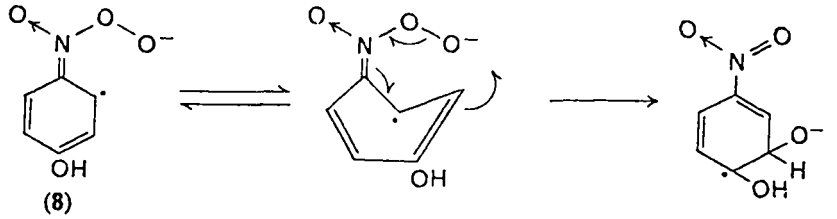
Cercek and Ebert[87] have shown that the hydroxyl radical does not attack the ring of *p*-nitrophenol. Since G(2-hydroxy-4-nitrophenol) = 2·95 in good agreement with G_{OH}, one would not have suspected from steady radiolysis studies[88, 89] that anything unusual was happening.

The nitro group is strongly electron-withdrawing and is assisted by the phenolic hydroxyl group which is an electron donor to *ortho*- and *para*-positions. Hence the nitro group in this compound is more

than usually electron-rich and is attacked by the hydroxyl radical in preference to the ring.

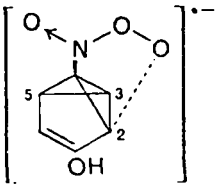
$$HOC_6H_4NO_2 + OH^{\bullet} \longrightarrow \underset{(8)}{HOC_6H_4NO_3H^{\bullet}} \qquad (26)$$

8 was found to have an absorption maximum at 295 nm whereas a maximum would be expected at about 420 nm if the ring were attacked to give a substituted **3** structure[87]. **8** is a weak acid ($pK_a = 5{\cdot}3$) and ionizes in neutral solution giving $HOC_6H_4NO_3^{-\bullet}$. In deaerated solution this species undergoes an interesting first-order rearrangement (equation 27) whereby the hydroxyl group is transferred to the aromatic ring giving a species absorbing at 400 nm. The rate constant for this rearrangement (k_{27}) was found to be $14 \pm 2\ s^{-1}$.

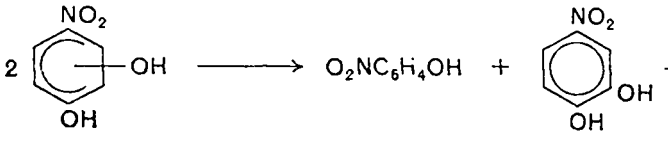


(27)

A cyclohexadienyl structure would enable the OH group to migrate from the nitro group of the *p*-nitrophenol–$O^{-\bullet}$ adduct to the 2-position without having to pass via the electron-deficient 3-position. In the benzvalene form positions 2, 3 and 5 can be depicted as equidistant from position 4. A cyclohexadienyl intermediate which provides a six-membered cyclic transition state for the oxygen transfer would therefore appear more likely than a benzvalene intermediate.



Two of these species disproportionate to give *p*-nitrophenol and the hydroxylated product. In aerated solution, **8** also disappeared



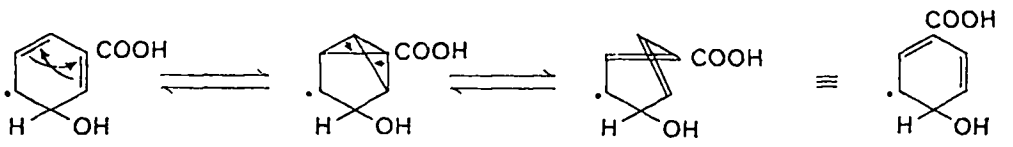
(28)

by a first-order process but 160 times faster than by reaction (27). Each hydroxyl radical gave one molecule of hydroxylated product[88].

Other examples have been found of compounds whose aromatic ring is not attacked by hydroxyl radical or only to a minor extent. In the case of nitrosobenzene[90] and phenylhydroxylamine[91] there is no subsequent transfer to the ring and no hydroxylation. Compounds in which the side chain is hydroxylated will be considered in section II.B.2.b.

h. Isomeric yields. The yields of possible isomeric products following aromatic substitution reactions do not necessarily reflect faithfully the proportion of reaction at the respective positions of the aromatic ring. Apart from various side reactions such as have been noted for the hydroxyl adducts with nitrobenzene and phenol, there is always the possibility of a rearrangement resulting in migration of the OH group to another position on the ring.

Volkert and Schulte-Frohlinde[92] irradiated benzoic acid in nitrous oxide-saturated solution and measured a yield of G(hydroxybenzoic acids) = 5·3. This total remained constant when ferricyanide ion was present during irradiation but the G(*ortho*) : G(*meta*) : G(*para*) yields changed from 1·6 : 1·7 : 1·9 at zero to 2·3 : 2·0 : 1·1 at 2 mmole/litre of ferricyanide ion and above. Allowing for enhancement by the addition of N_2O, the ratio of yields is comparable with that of 0·74 : 0·42 : 0·33 found in aerated solution[43, 51]. The change in the relative proportions of the three isomers must be due to tautomerism between the possible structures. It was suggested[92] that the $OH^{\cdot}$ radical might form a charge-transfer complex as has been observed for Cl-atoms[93]. This seems unlikely as does the possibility of **3** (X = COOH) remaining, or reverting to, a π-complex. There is the possibility of a prismane or benzvalene structure being formed[94–98] although these are usually associated with some form of excitation[97] in the case of substituted benzenes. Cercek[80] discounted the possibility of formal bonds between non-neighbouring carbon atoms on the grounds that this required a greater amount of energy than the other structures **5**, **6**, **7**, etc. Nevertheless, **3** is already non-planar and formation of one of these structures may be easier for cyclohexadienyl radicals than for benzenes. Rearrangement from *ortho* adduct to *para* precursor can be explained by either invoking a Dewar-type structure or by assuming that the hydrogen atom associated with the hydroxyl group on $C_{(2)}$ can ionize allowing the $C_{(1)}$–$C_{(2)}$ bond to be broken by rearrangement through a prismane or similar intermediate. Conversion from *meta* to *para* precursor is



(28a)

readily explained via a benzvalene intermediate. The phenomenon may not be general. There appears to be no rearrangement in the case of the nitrobenzene–$OH^{\bullet}$ adduct. Here the *ortho* adduct is relatively long-lived[81] and would be expected to have time to rearrange before reacting with oxygen[80] if such rearrangement were favoured.

It seems that, with a sufficiently high concentration of oxidizing agent present—ferricyanide ion[92], dichromate ion[81], molecular oxygen, etc.—there are fewer uncertainties. The isomeric ratios determined in aerated solution are usually considered to reflect the position of attack on the ring[99, 100]. By careful choice of the right mixture of nitrous oxide and oxygen, it is possible to eliminate interference by the hydrated electrons, to increase the available amount of hydroxyl radicals and to obtain oxidized product ratios reflecting the initial positions attacked. Further, $O_2^{-\bullet}$, H_2O_2, and other species which might interfere are not introduced in significant amounts. This gives a clean source of hydroxyl radicals indeed.

Until recently, there has been some doubt whether nitrous oxide and hydrated electrons do give hydroxyl radicals on reaction (equation 2). There is no physical evidence that $N_2O^{-\bullet}$ has a finite existence but $O^{-\bullet}$ might have to react with H_2O to give $OH^{\bullet}$ before reacting with many solutes. Nakken, Brustad and Hansen[101] have measured the *G*-values for the yields of isomeric hydroxy acids from the radiolysis of benzoate solution and of the 3-hydroxy and 5-hydroxy derivatives from anthranilic acid. They found differences between oxygen, nitrogen and nitrous oxide-saturated solutions and conclude that nitrous oxide on reaction with hydrated electron gives a species similar to, but not identical with, the hydroxyl radical. A complete chemical study and a full product analysis might be necessary to decide this point. The author has carried out some competition experiments with *para*-aminobenzoic acid and has been unable to find evidence for a separate species[102].

Some unexpected results were obtained by Nakken and coworkers[101] when hydrogen peroxide was added before irradiation. Hydrogen peroxide also increases the amount of available hydroxyl radical (equation 3) but introduces other reactions (equation 7). A more complete chemical study is required.

In most illustrations of peroxy radical structure, **2** or **4**, the O_2 from aerated solution is drawn attached to the ring location of the radical spot or is represented as attached to any reasonable location. There is the possibility of its being in a transannular position as has often been found in photochemical attachments.

Zhikharev and Vysotskaya[103], using oxygen-18 isotope, found that the water was the source of most of the oxygen in the phenol formed by radiolysis of aqueous benzene solution[52]. A small amount originated from the dissolved oxygen, but, since the dose used was a high one for mechanistic studies (2·1 Mrad), it is probable that all, or very nearly all, the oxygen was incorporated in the phenol via hydroxyl radical attack and originated from the solvent water.

p-Nitrosodimethylaniline has a strong absorption band with a maximum at 440 nm. The effect of added solutes on the bleaching of this absorption has been used in the determination of a wide range of hydroxyl radical–solute reaction rate constants using competition methods [69, 72, 73, 104–106]. One of the main products of $OH^{\cdot}$ reaction with this compound is the nitro derivative[106] as would be expected from studies with nitrosobenzene[90] but some hydroxy isomers could also be formed[106].

In the early days of radiation chemistry the radiation bleaching of aqueous solutions of very many dyes was investigated in the search for a radiation dosimeter[3, 107, 108]. Pulse and steady state radiolysis studies have continued[109–118] but although hydroxylation of the aromatic ring is probably involved in some of these, the actual products have not been identified for certain.

In addition to the studies already described, benzene[119–122], benzoate[123] or benzoic acid[124], *p*-aminobenzoic acid[125], anisole[126], fluorobenzene[127, 128] and compounds related to tyrosine (*p*-hydroxyphenylalanine)[129–131] have been investigated recently in aerated aqueous solution and the isomeric yields determined at the low to moderate dose rates of steady state radiolysis. In some cases, dose rate, pH and other effects have been studied in order to arrive at a better understanding of detailed reaction mechanisms. The yields in aerated or oxygenated solutions probably reflect the ratio of attack at the possible isomeric positions, and hence partial rate constants can be calculated. In deaerated solutions or those containing nitrous oxide (but no oxygen) different ratios are found. These may be attributed to differences between the rates of diradical reactions (equations 22 and 23) for the different isomeric forms of **3**.

The general reaction scheme outlined above and the exceptions

described explain most of the phenomena observed in the radiolytic hydroxylation of aromatic biochemical compounds[129–131].

i. Effect of additives. If ferrous ion is added to benzene solution before irradiation the *G*-value for phenol production is increased to 6 [34, 36, 45] or, under favourable conditions, to 14 [132–133a]. This indicates a chain reaction involving reduction of **2** (equation 13) by ferrous ion to a hydroperoxyl derivative $HOOC_6H_6OH$ which is further reduced to $OC_6H_6OH^{\bullet}$ (**9**). This can then react (equation 29) giving phenol and more **1** to continue the chain.

$$\underset{\textbf{(9)}}{OC_6H_6OH^{\bullet}} + C_6H_6 \longrightarrow \underset{\textbf{(1)}}{C_6H_6OH^{\bullet}} + C_6H_5OH \qquad (29)$$

$HO_2^{\bullet}$ and H_2O_2 are also made available as oxidizing agents by reaction with ferrous ion. $G(Fe^{3+})$ was found to be 65. Substantial post-irradiation production of ferric ion, phenol and mucondialdehyde was found. In the presence of ferrous ion, the isomeric ratio *G*(*ortho*) : *G*(*meta*) : *G*(*para*) hydroxy benzoic acids was 1·9 : 3·1 : 1·6 (compare section II.B.1.h) in irradiated benzoic acid solution[134].

These high yields of phenol from benzene have attracted attention to the industrial possibilities of the process because a chain reaction often has potential for increasing yields even further. Studies have been made in the presence of ferrous ion or cupric ion or inorganic oxides and at high temperatures (up to 200°C or so)[135–152]. It is thought that at high temperatures above 130°C, a chain reaction sets in. Also $HO_2^{\bullet}$ becomes effective as a hydroxylating agent even in the absence of metal ions. *G*(phenol) is more than 30. This has a bearing on the autocatalytic decomposition of aqueous solutions of benzene or toluene at high temperatures[149–152].

Irradiation of naphthalene[153] produced predominantly 1-naphthol with an apparent $G = 1{\cdot}44$ up to 130°C. Beyond 140°C the yield of 1-naphthol decreased whereas that of 2-naphthol increased. Once again it was thought $HO_2^{\bullet}$ became an effective hydroxylating agent beyond 140°C, thus giving a different distribution of the isomeric phenolic products.

Irradiation of benzene dissolved in aqueous solution containing 0·5—1·0 mole/litre nitrate ion gave nitration as well as hydroxylation[154, 155]. At pH 2, *G*(*o*- and *p*-nitrophenol) totalled 1·5 and *G*(phenol) = 1·5. At higher pH lower yields were found. Higher yields were found when oxygen was excluded. Similar effects have been found in radiolysis of other organic compounds in nitrate solutions[125, 156]. No detailed mechanism has been proposed for this

hydroxylation–nitration process. The absence of *m*-nitrophenol in the products suggests that phenol is formed first and is then nitrated.

j. Other conditions. In alkaline solutions the hydroxyl radical is ionized (equation 30)[157–159].

$$OH^{\bullet} + OH^{-} \leftrightharpoons O^{-\bullet} + H_2O \quad (pK = 11{\cdot}9) \tag{30}$$

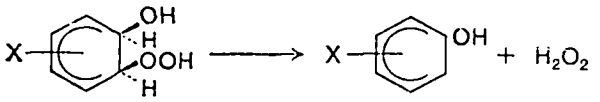
Very little study has been made of the reactions of $O^{-\bullet}$ with organic compounds[158] but it appears to be relatively unreactive towards benzoate[102], chlorobenzene[47] or benzene[103]. It combines with oxygen to give $O_3^{-\bullet}$ [12, 160, 161].

Irradiation of a gaseous mixture of benzene and oxygen gave phenol but no chemical mechanism was established[162]. Hydroxyl radicals are well known in gas phase radiolysis but little is known about their reactions with organic compounds. A novel form of hydroxylation occurred when a mixture of benzene and nitrous oxide was irradiated[163]. The nitrous oxide captured electrons to give $O^{-\bullet}$ which attacked the benzene to give phenol with G = 23·6.

k. Conclusions. To summarize, the early steps in the reaction between hydroxyl radicals and benzenoid compounds are fairly well understood. The final reactions in solutions containing an oxidizing agent such as oxygen, particularly those reactions going from **4** to the stable phenolic product, remain to be elucidated. The most probable course might be that represented by equations (31)—(36), as an alternative to equation (24). The disappearance of $HO_2^{\bullet}$ (or $O_2^{-\bullet}$) by reaction (8) is slow enough to enable a reasonable concentration to be built up.

$$\underset{\textbf{(4)}}{XC_6H_5(OH)O_2^{\bullet}} + O_2^{-\bullet} \longrightarrow \underset{\textbf{(10)}}{XC_6H_5(OH)O_2^{-}} + O_2 \tag{31}$$

This is similar to the reaction proposed by Daniels, Scholes and Weiss[32] and Loeff and Stein[121] except that in equation (31) the reducing agent is not $H^{\bullet}$ or e_{aq} but the much more probable $HO_2^{\bullet}$ or $O_2^{-\bullet}$ formed by their reaction with oxygen (equations 4 and 5). Although $HO_2^{\bullet}$ and $O_2^{-\bullet}$ are stoichiometrically identical, they may react at different rates with **4** or with its protonated form. Compound **10** or its protonated (un-ionized) form might react in different ways depending on what its substituent group X is and according to conditions. Equations similar to (32) and (33) can be written for the ionized form (**10**). Equation (32) is the general one giving equivalent amounts of the phenol. The hydrogens can be considered as in the *cis* configuration. In the *trans* configuration, equation (33)



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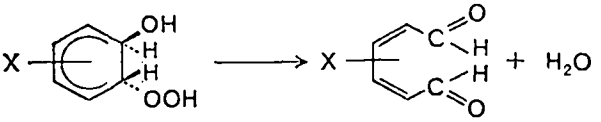


(33)

gives mucondialdehyde which has been found in irradiated benzene solutions[121]. $G = 1{\cdot}5$ in acid and 0·8 in neutral solutions but see Ref.163a.

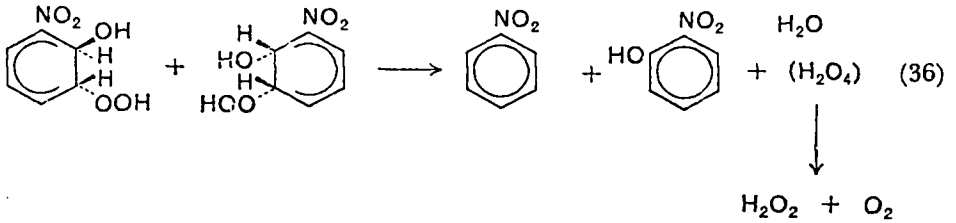
These equations cannot apply to radiolysis in the presence of a mixture of N_2O and O_2 of such proportions that almost all the electrons are captured by the N_2O. Here there is no $O_2^{-\cdot}$ available for reduction according to equation (31). At both high and low dose rates nitrobenzene gives the expected yield of *o*-nitrophenol[102]. This indicates that $O_2^{-\cdot}$ is not necessary for the reaction to proceed in that particular system.

In the presence of a one-electron oxidizing agent (Ox), phenols are formed (equation 34 and, less probably, equation 35).

$$XC_6H_5(OH)O_2^{\cdot} + Ox \longrightarrow XC_6H_4OH + HOx + O_2 \qquad (34)$$

$$XC_6H_5(OH)O_2H + Ox \longrightarrow XC_6H_4OH + HOx + HO_2^{\cdot} \qquad (35)$$

In the case of the precursors of *o*-nitrophenol, an alternative to equation (25) is equation (36).



(36)

Table 2 lists values for the hydroxylation products from radiolysis of aerated aqueous solutions of selected aromatic solutes. The isomeric distributions can be considered as reflecting most nearly the attack by OH radicals at the respective ring positions. However, account must be taken of side reactions following $OH^{\cdot}$ addition to the ring, such as that producing mucondialdehyde ($G = 0{\cdot}8$) from benzene[121]. The differences in each case between G_{OH} which is 2·8 (Table 1) and the total G (isomeric phenolic products) are due to

reactions of OH radicals with the side chains or at the substituted carbon atoms or other reactions at ring positions which do not yield isomeric phenolic products.

TABLE 2. Isomeric yields and reaction rate constants for radiolytic hydroxylation in neutral aerated solution.

Solute	G-values			Refs.	Reaction rate constants		
	o	*m*	*p*		Absolute $l\ mole^{-1}\ s^{-1}$	Relative	Refs.
Benzene		2·3		58	$7·8 \times 10^9$		77
		1·9		121		1·1	102
Benzoate	0·67	0·37	0·37	48	6·0		77
	0·62	0·32	0·26	123		1	68, 102
	0·49	0·31	0·39	101			
	0·66	0·34	0·31	102			
Nitrobenzene	1·03	0·48	0·51	81	4·7		76
					3·2		77
						0·5	102
Anisole	0·19	0	0·32	126	12		77
Fluorobenzene	0	0·2	0·32	128			
Chlorobenzene						1·1	68

Values for overall absolute and relative rate constants for the reactions (solute + $OH^{\cdot}$) are also given in Table 2. Partial rate constants for reaction leading to an isomeric product can be obtained by multiplying the overall rate constant by the ratio $G(\text{isomer}) : G_{OH}$.

2. Non-benzenoid compounds

a. Saturated compounds. The rates of reaction of hydroxyl radicals with aliphatic compounds have been measured by Anbar, Meyerstein and Neta[104]. In parallel with aromatic compounds, the $\sigma\rho$ correlation shows that the attack is electrophilic. The predominant reaction is hydrogen abstraction which leads to dimerization or peroxy, hydroperoxy or aldehyde compounds. In the case of aerated aqueous solutions of acetic acid a small yield ($G = 0·1$) of glycollic acid, $CH_2(OH)COOH$, has been found[164]. The radiolysis of solutions of amines gave oximes[165] with a G-value about 0·4. Aqueous solutions of cyclohexane gave cyclohexanol and cyclohexanone[165a].

b. Unsaturated compounds. With organic chemical compounds con-

taining a double bond, $OH^{\bullet}$ addition reactions predominate over the slower hydrogen abstraction reactions. For aqueous solutions of ethylene[166–175] the following reaction scheme (equations 37–40) has been proposed for deaerated solutions[170, 172, 174].

$$CH_2{=}CH_2 + OH^{\bullet} \longrightarrow HOCH_2CH_2^{\bullet} \quad (37)$$

$$2\,HOCH_2CH_2^{\bullet} \longrightarrow CH_3CHO + C_2H_5OH \quad (38)$$

$$HOCH_2CH_2^{\bullet} + C_2H_4 \longrightarrow HOC_4H_8^{\bullet} \quad (39)$$

$$2\,HOC_4H_8^{\bullet} \longrightarrow C_3H_7CHO + C_4H_9OH \quad (40)$$

$G(C_2H_5OH)$ and $G(C_4H_9OH)$ were both about 0·5.

The radiolytic hydrogen atoms also add to ethylene to give ethyl radicals[174] which do not result in any hydroxylation products.

$$CH_2{=}CH_2 + H^{\bullet} \longrightarrow CH_3CH_2^{\bullet} \quad (41)$$

Some of the radicals were able to initiate a polymerization chain.

$$HOCH_2CH_2^{\bullet} + nC_2H_4 \longrightarrow HOCH_2(CH_2)_{2n+1}^{\bullet} \quad (42)$$

Reaction (43) also occurred to a small extent.

$$OH^{\bullet} + C_2H_4 \longrightarrow C_2H_3^{\bullet} + H_2O \quad (43)$$

In aerated solution[171, 173]

$$HOCH_2CH_2^{\bullet} + O_2 \longrightarrow \underset{\textbf{(11)}}{HOCH_2CH_2O_2^{\bullet}} \quad (44)$$

$$CH_2{=}CH^{\bullet} + O_2 \longrightarrow CH_2CHO_2^{\bullet} \quad (45)$$

$$CH_3CH_2^{\bullet} + O_2 \longrightarrow CH_3CH_2O_2^{\bullet} \quad (46)$$

and $HO_2^{\bullet}$ also appeared able to add on to ethylene.

$$CH_2{=}CH_2 + HO_2^{\bullet} \longrightarrow HOOCH_2CH_2^{\bullet} \xrightarrow{O_2} \underset{\textbf{(12)}}{HOOCH_2CH_2O_2^{\bullet}} \quad (47)$$

Compound **11** corresponds to **2**, which is formed in the case of benzene. Interactions between the four peroxy compounds gave the observed product yields: G(glycollaldehyde) = 2·4, G(formaldehyde) = 2, G(acetaldehyde) = 1 and G(hydrogen peroxide) = 2·6. At very low doses G(glycollaldehyde) was about 30 and the reason for this is unknown.

The early parts of the reaction scheme have been confirmed by pulse radiolysis measurements[171, 175]. The reaction rate constants measured are $k_{37} = 1 \times 10^9\ M^{-1}\,s^{-1}$ (1 mole^{-1} s^{-1}), $k_{38} = 6{\cdot}3 \times 10^8$ and $k_{44} = 6{\cdot}6 \times 10^9$. The last value is about ten times that measured for the corresponding reaction for benzene[58, 80] (equation 13).

In parallel with aromatic solutes, ferrous ion was found to increase the product yield—in this case, formaldehyde and acetaldehyde. The system is complex but the species, $HOCH_2CH_2O^{\bullet}$ which corresponds to **10** for aromatic solutes has been proposed[174] as formed by a

similar reaction. Another possibility is that ferric ion is present in two complexed forms which react differently[171].

$$HOCH_2CH_2^{\cdot} + FeSO_4^{+} \longrightarrow CH_3CHO + Fe^{2+} + HSO_4^{-} \quad (48)$$

$$HOCH_2CH_2^{\cdot} + Fe(OH)^{2+} \longrightarrow HOCH_2CH_2OH + Fe^{2+} \quad (49)$$

Various other unsaturated compounds have been investigated. Propylene and allyl alcohol have been found to give mainly organic peroxides incorporating a hydroxyl group[176, 177]. Acrylamide also adds $OH^{\cdot}$ at the double bond[178]. Styrene and α-methylstyrene are attacked mainly at the aromatic ring but 20—40% and 15—30% respectively of the $OH^{\cdot}$ radical adds on at the side chain double bond[175, 179].

Acetylene in aerated aqueous solution gave glyoxal in yields indicating a chain reaction under some conditions[180].

The double bonds of olefinic acids are hydroxylated[181].

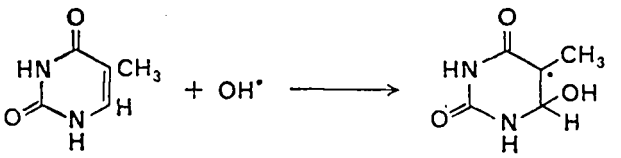
c. Biochemical compounds. The rates of reaction of hydroxyl radicals with a number of organic chemical compounds found in living organisms have been measured[67, 70, 71, 74].

(1) *DNA bases*

Identification of the site of radiation damage to the cell nucleus has led to the study of the radiolytic behaviour of the components of DNA. The pyrimidine and purine bases have been found to undergo hydroxylation[182–183a] in aqueous solution.

Pulse radiolysis techniques have now been applied in these studies[184–188a] and some of the reaction rate constants are known.

In neutral solution thymine (pK 9·8) is in the undissociated form. Hydroxyl radicals add on at the 6-position (equation 50)[189, 190], although there is also the possibility of addition at position 5 (the C atom to which the CH_3 group is attached)[186].

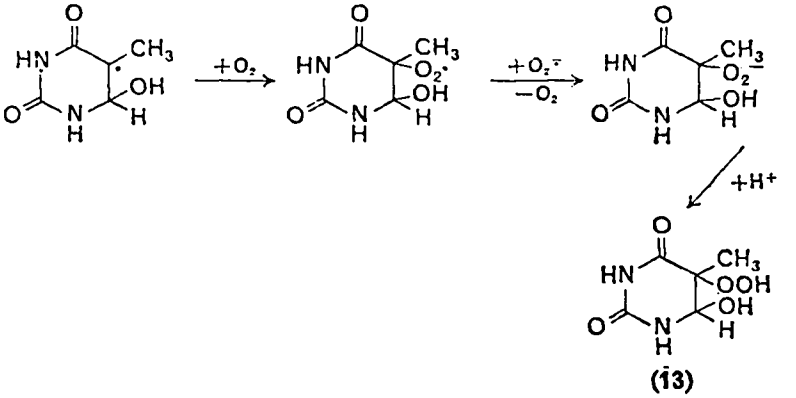


(50)

The overall rate for the (thymine + $OH^{\cdot}$) reaction has been measured[186] as $7{\cdot}4 \times 10^9$ l mole^{-1} s^{-1}. Even allowing for other reactions, this is high for attack at one position only and comparable to the rate constant for (benzene + $OH^{\cdot}$) where all π electrons are available. This double bond is a chromophoric group so its destruc-

tion is easily followed in either pulse radiolysis or steady radiolysis studies $G(-\text{double bond}) = 1{\cdot}9$.

Oxygen, if present, then adds on at the 5-position. The radical is reduced by $O_2^{-\cdot}$.



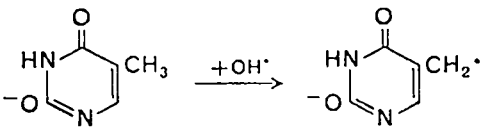
(51)

(13)

In this case the 6-hydroxy-5-hydroperoxythymine (**13**) is stable enough to be isolated[177]. $G = 1{\cdot}05$. **13** is formed with a lower yield below pH 5. Perhaps $HO_2^{\cdot}$ (pK 4·4) is not as effective as $O_2^{-\cdot}$ as a reducing agent or, alternatively, one of the intermediates is less stable in acid solution.

In neutral solution, $OH^{\cdot}$ adds to either the 5- or the 6-position at the double bond of uracil. In aerated solution, uracil and dimethyluracil also give hydroxyhydroperoxides. However, the cytosine hydroperoxide, though detectable at low pH, decomposes in neutral solution and is not stable enough to be isolated. This suggests that a hydroperoxide of this form may be an intermediate between the aromatic solute–hydroxyl radical–oxygen adduct (**4**) and the final product, a phenol. In the case of aromatic solutes, as for cytosine, the hydroperoxides might be unstable and decompose giving hydrogen peroxide and hydroxylated product. Between cytosine and uracil there may be compounds of structure like **13** which have a gradation of stabilities. Neutral aerated irradiated solutions of pyrimidine bases on acidification give 5,6 diols probably from the decomposition of **13**.

At pH 11, thymine is in the singly ionized form and the site of attack is changing to the methyl group itself (equation 52), despite there being two conjugated double bonds in the compound. $G(-5,6$ double bond$) = 1{\cdot}3$. Since uracil has not a methyl group there is no corresponding change in its reactions as the pH is increased.



(52)

At still higher pH, the ionization of the hydroxyl radical to $O^{-\bullet}$ is manifest and there is no longer any electrophilic hydroxylation.

At the highest pH studied, thymine is doubly ionized ($pK_2 > 13$) and the pyrimidine ring is aromatic. The reaction is hydrogen abstraction from the methyl group and the identified hydroxylation products are not formed directly.

The purine bases adenine and guanine appear to be more resistant to radiation than are the pyrimidine bases[182, 183]. Hydroxyl radicals appear to add at the 4,5 central double bond but no hydroxylation products have been found.

In the double helix conformation the DNA bases are protected somewhat from attack[191]. At physiological pH, the major reaction is $OH^{\bullet}$ attack on the pentose part of DNA.

(2) *Steroids, vitamins, etc.*

The effects of radiation on aerated aqueous solutions of other biochemicals have been summarized by Swallow[3]. In some of the earlier investigations no attempt was made to distinguish between the reactions and interactions of the various primary radiolytic species. The action, if any, of the hydroxyl radical, alone and without interfering reactions, is usually apparent in dilute aerated solution at low doses up to 30 krad. In the light of subsequent investigations with simpler model compounds, one must doubt the validity of reaction schemes in which the solute–$OH^{\bullet}$ adducts react with $HO_2^{\bullet}$. It is far more likely that they will first react with oxygen which is present at higher concentrations.

3. Use in synthesis

There are very few examples of the radiolytic hydroxyl radical being used in organic synthesis. Merger and Grässlin[192, 192a] have reported the synthesis of the hitherto unknown 1,2,3,4-tetrahydroxynitrobenzene with $G = 1{\cdot}41$ by irradiation of aqueous 4- or 5-nitropyrogallol. Davison[193] prepared the *o*-, *m*- and *p*-hydroxybenzoic acids from benzoic ^{14}C-acid. The *meta* derivative, in particular, is more difficult to prepare by conventional methods.

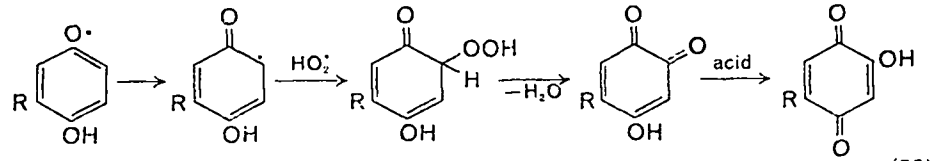
C. Hydroperoxyl Radical Reactions

1. General

The radiolytic production, spectra and subsequent reactions of the hydroperoxyl radical, $HO_2^{\bullet}$, and its ionized form, $O_2^{-\bullet}$ (pK_a 4·4) have been characterized (see section II.A.3) [11–13, 194, 195]. It is almost always formed in dilute aerated aqueous solutions and its rate of disappearance is low ($k_{HO_2^{\bullet}+HO_2^{\bullet}} = 0{\cdot}7 \times 10^6$, $k_{HO_2^{\bullet}+O_2^{-\bullet}} = 3{\cdot}0 \times 10^7$ and $k_{O_2^{-\bullet}+O_2^{-\bullet}} = 1{\cdot}2 \times 10^7$ l mole^{-1} s^{-1}) [195] compared with some other reactions. Therefore it can reach significant concentrations, and figures in many reaction schemes described in section II.B particularly in reaction with other radicals. Virtually no studies have been made of its reactions with organic solutes.

2. Hydroquinones

In general, $HO_2^{\bullet}$ abstracts hydrogen from the hydroxy group of a hydroquinone and no hydroxylation results[196, 197]. Hydroxylation of the ring has been observed on irradiation of 1,2,4-trihydroxybenzene, *p*-hydroquinone, toluhydroquinone and monochloroquinone[198, 199]. Such hydroxylation did not occur in the absence of oxygen but it was not established that ring attack was initiated by $HO_2^{\bullet}$. More recently, Bielski and Allen[199] have found that $HO_2^{\bullet}$ adds to the ring of semiquinone radicals, which have been formed either by hydrogen abstraction or by $OH^{\bullet}$ attack on the ring followed by water elimination[86].



(53)

The *G*-value for production of **14** depended on the oxidation reduction potential of the hydroquinone. Where R = Cl, $G(\mathbf{14}) = 1{\cdot}41$.

Phenols probably undergo a similar reaction but the product remains in the *o*-quinone form.

3. Ethylene

Basson and du Plessis consider that $HO_2^{\bullet}$ radicals add to ethylene (equation 47)[173].

Compound **12** forms a ring peroxide which, in acid solution, is converted into glycollaldehyde.

$$2HOOCH_2CH_2O_2^{\bullet} \xrightarrow[-H_2O_2]{-O_2} 2 \begin{matrix} CH_2{-}CH_2 \\ | \quad | \\ O{-}{-}O \end{matrix} \longrightarrow 2 \begin{matrix} CH_2CHO \\ | \\ OH \end{matrix} \qquad (54)$$

4. Dyes

Schulte-Frohlinde and co-workers[200] have shown that some dyes are bleached by $HO_2^{\bullet}$ radicals. No product analysis was carried out.

III. PHOTOLYTIC HYDROXYLATION

A. Production

If an aqueous solution of hydrogen peroxide is exposed to light of wavelength 370 nm or less, hydroxyl radicals are formed[201, 202].

$$H_2O_2 + h\nu \longrightarrow 2\ OH^{\bullet} \qquad (55)$$

Hochanadel[8] showed that the species formed was identical with the radiolytic primary oxidizing radical and was $OH^{\bullet}$ uncontaminated by other species. Quantum yields (molecules changed per quantum of light absorbed) as high as 80 have been reported[202]. Obviously a chain reaction is involved. At higher light intensities the quantum yield falls to a steady 1·0—1·4 [203]. Further reaction of $OH^{\bullet}$ with hydrogen peroxides produces $HO_2^{\bullet}$ (equation 7) so in that sense it is a mixed system[204]. At wavelengths less than 242 nm the photodissociation of water becomes energetically possible (equation 56)[205].

$$H_2O + h\nu \longrightarrow H^{\bullet} + OH^{\bullet} \qquad (56)$$

The hydroxyl radicals produced by photolysis can hydroxylate benzenoid, olefinic and heterocyclic compounds. In some cases the hydroxyl radicals can be prepared free of other interfering species. Sometimes the organic solute is raised to an excited state by the light and can then react with water adding, for example, H and OH groups to a double bond[183a]. The final product is often a hydroxyl compound but, because a free radical mechanism is not involved, this type of hydroxylation reaction will not be considered in this chapter.

Another system involves photoexcited electron transfer in the $Fe^{3+}OH^{-}$ complex in aqueous solutions of ferric ion. It was considered that free hydroxyl radicals were produced[206, 207] (equation 57).

$$Fe^{3+}OH^{-} \xrightarrow{h\nu} Fe^{2+}OH \longrightarrow Fe^{2+} + OH^{\bullet} \qquad (57)$$

Similarly the hydroxy ion, OH^{-}, on illumination releases an electron leaving a hydroxyl radical (equation 58).

$$OH^{-} \xrightarrow{h\nu} e_{aq} + OH^{\bullet} \qquad (58)$$

B. Benzenoid Compounds

Compounds related to naphthalene were irradiated in aqueous hydrogen peroxide solution with ultraviolet light by Boyland and Sims[208]. Phenols were the main products found. Benzoic acid, for example, gave the three isomeric hydroxybenzoic acids. The *ortho* : *meta* : *para* ratio was 2 : 1 : 1 approximately.

Loeff and Stein[48] studied the photodecomposition of hydrogen peroxide solutions at various concentrations with benzene as a solute. Phenol, mucondialdehyde and pyrocatechol were found to be the major products.

Jefcoate, Lindsay Smith and Norman have recently investigated the photolysis of hydrogen peroxide–toluene and hydrogen peroxide–benzene mixtures[208a].

Norman and Radda[209] found that anisole under ultraviolet irradiation gave *ortho* : *meta* : *para* derivatives in the ratio 84 : 0 : 16 whereas fluorobenzene gave the ratio 37 : 18 : 45.

Omura and Matsuura[210] found that ultraviolet-irradiated mixtures of phenols and hydrogen peroxide in aqueous solutions gave predominantly *o*-dihydroxy compounds. Smaller quantities of *para*-derivatives were also formed but there was no substitution *meta* to the existing OH group. *p*-Carboxy- and *p*-methoxy-phenols gave hydroquinones in addition to the usual catechol derivatives.

The percentage conversions of starting materials were rather too high in these experiments for firm conclusions to be drawn regarding the detailed mechanisms. The proposed attack of a second hydroxyl radical on each phenoxyl radical ($XPhO^{\bullet}$) to give the phenolic product cannot be considered the general mode of formation of the phenols.

Pacifici and Straley[210a] have observed hydroxylation of the aromatic nuclei of polyesters exposed to ultraviolet light.

C. Unsaturated Compounds

Milas and co-workers[201] studied the photolysis of mixtures of unsaturated compounds and hydrogen peroxide. Allyl alcohol gave glycerol, crotonic acid gave dihydroxybutyric acid, maleic acid or diethyl maleate gave mesotartaric acid and ethylene gave diethylene glycol or, in oxygenated solution, aldehydes[210b].

Kraljic[73] has used the bleaching of *p*-nitrosodimethylaniline[69] by the photolytic hydroxyl radical as a basis for determining relative rate constants for reaction of solutes with $OH^{\bullet}$. The agreement with

rate constants measured for radiolytic OH$^{\bullet}$ is said to be satisfactory. Fluorescein is also bleached[210c].

The results obtained in all these cases can be explained readily in terms of the reactions described for the radiolytic hydroxyl radical (equations 17, 19, 24, etc.).

The photolysis of hydrogen peroxide has been used as a source of hydroxyl radicals for electron paramagnetic resonance studies[211, 212]. Because of the technical difficulties encountered when liquid water is introduced into the e.p.r. cavity, many of these studies have been conducted in frozen aqueous solution at low temperatures or with strong hydrogen peroxide added to an organic liquid. Ultraviolet light is directed into the cavity itself. Although product determination does not normally form part of such investigations, valuable information regarding intermediate species is obtained. Strangely, allyl alcohol[211–212a] does not add hydroxyl radicals but undergoes hydrogen abstraction giving $^{\bullet}CH_2CHCHOH$. Oxygen, if present, adds to the radicals giving peroxy radicals.

D. Irradiation of Complexes

Bates, Evans and Uri[206] showed that 300—400 nm ultraviolet irradiation of ferric complexes such as $Fe^{3+}OH^-$, $Fe^{3+}Cl^-$ and $Fe^{3+}F^-$ gave a species which hydroxylated aromatic compounds. Benzoic acid gave the *o*-, *m*-, and *p*-hydroxybenzoic acids in the statistical ratio 2 : 2 : 1 [207]. Saldick and Allen[213] showed that the hydroxylating species was definitely the free radical OH$^{\bullet}$ and not an activated complex, such as ($Fe^{3+}OH$). With benzoic acid present as substrate the products were the hydroxybenzoic acids[207] which were further attacked on continued exposure[213].

Benzene solutions were studied by Baxendale and Magee[214]. They found that Fe^{3+} ions could be replaced by Cu^{2+} ions.

Solutions containing ($UO_2^{2+}H_2O$) and (Ce^{4+} OH^-) have been reported by Stein and Weiss[215] as giving free OH$^{\bullet}$ capable of hydroxylating aromatics. Richardson[216] has investigated aqueous Ce(IV) solutions. Yandell and Stranks[217] have shown that the action of light on ($Tl^{3+}OH^-$) solutions liberates hydroxyl radicals. This list is by no means exhaustive.

Hydroxyl radicals have also been reported[218] as being formed by the action of the radical cation of 9,10-anthraquinone-2-sulphonate (A). The radical cation is formed from a photo-excited state (equation 59).

$$A^* + A \longrightarrow A^{\bullet -} + A^{\bullet +} \xrightarrow{OH^-} A + OH^{\bullet} \qquad (59)$$

E. Gas Phase

Photolysis of water vapour and of hydrogen peroxide vapour also gives hydroxyl radicals but very little is known about their reactions[219–221a].

F. Conclusions

To summarize, hydroxyl radicals produced by the action of ultraviolet light on water, hydrogen peroxide or metal–hydroxy complexes appear capable of hydroxylating aromatic or olefinic compounds in the same way as do radiolytic hydroxyl radicals. Very little work has been done on these systems. The better experimental techniques now available and the better understanding of the general reactions suggest that considerable progress would ensue from a renewed attack on the problems of the system.

IV. CHEMICAL FREE RADICAL HYDROXYLATION

A. Introduction

The study of chemical methods of generating radicals capable of hydroxylating organic substrates has received considerable impetus from the similarities of the products found to those formed during metabolic hydroxylation in biological processes. The reactive entities in vivo are one-electron oxidizing agents and demonstrate the same electrophilic character combined with lack of selectivity attributed to free radicals. Hydroxyl and perhydroxyl radicals have both been considered possibilities.

There are broadly two types of systems[222, 223]. The first, based on hydrogen peroxide together with a metal ion of variable valency, is typified by Fenton's reagent (ferrous ion and H_2O_2), titanous ion and H_2O_2 and Hamilton's system (ferric ion, catechol and H_2O_2).

$$M^{n+} + H_2O_2 \longrightarrow M^{(n+1)+} + OH^- + OH^{\cdot} \qquad (60)$$

The second type is based on oxygen and is typified by Udenfriend's reagent[224, 225]. In the presence of ferrous ion, EDTA (ethylenediaminetetraacetic acid) and ascorbic acid, molecular oxygen is able to hydroxylate many compounds. Initially, it was thought that hydrogen peroxide is formed first as an intermediate. Evidence now shows that this is not so.

Udenfriend's reagent behaves as a 'mixed-function oxidase'[226] and is therefore considered to resemble closely in many details the processes obtaining in biological systems. Expressed simply—a mixed

function oxidase is able to reduce molecular oxygen and to convert it into a form so that one atom of each molecule of oxygen is reduced and the other appears in the product in a new hydroxyl group (in the cases we will consider).

Two further reactions (equations 7 and 61) can give rise to $HO_2^{\bullet}$ radical.

$$M^{(n+1)+} + H_2O_2 \longrightarrow M^{n+} + H^+ + HO_2^{\bullet} \quad (61)$$

The evidence for the radical nature of the active species and reviews of their reactions are given in papers by Norman and co-workers[222–222b] and by Staudinger and co-workers[223]. It should be pointed out that not all authors agree that these species are the free $OH^{\bullet}$ or $HO_2^{\bullet}$ radicals. Some consider $OH^{\bullet}$ and $HO_2^{\bullet}$ are complexed to the metal ions.

Each of these reagent types is now considered in turn followed by peracids and the other methods of hydroxylation which have been used.

B. Fenton's Reagent

1. General

Fenton's reagent, a mixture of ferrous ion and hydrogen peroxide, has been known since 1894[227]. Haber and Weiss[228] proposed a series of reactions in which the hydroxyl radical was the reactive species. Baxendale and co-workers[229–231] and Kolthoff and Medalia[232, 233] proposed some modifications to the original scheme but $OH^{\bullet}$, and to a minor extent $HO_2^{\bullet}$, remained as essential features (equations 62—65).

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^{\bullet} + OH^- \quad (62)$$

$$OH^{\bullet} + Fe^{2+} \longrightarrow OH^- + Fe^{3+} \quad (63)$$

$OH^{\bullet}$ and hydrogen peroxide react giving $HO_2^{\bullet}$ (equation 7).

$$Fe^{3+} + H_2O_2 \longrightarrow HO_2^{\bullet} + H^+ + Fe^{2+} \quad (64)$$

$$HO_2^{\bullet} + Fe^{3+} \longrightarrow O_2 + H^+ + Fe^{2+} \quad (65)$$

The kinetics of the system were recently investigated by Grinstead[234]. The arguments for the radical nature of the reagent are summarized by Norman and Lindsay Smith[222, 235].

By adding EDTA[236] or other chelating agents[235, 237, 238] to the system, the ferric ion is complexed. This means that the reagent may then be used over a far greater pH range. Kraljic[73] has found that the radiolytic $OH^{\bullet}$ radical reacts about as readily with EDTA as it does with benzene and other aromatics. This could complicate the reaction scheme considerably. Ascorbic acid[236, 239] also increases

the yield presumably by reducing the ferric ions to ferrous ions. Ascorbic acid reacts with OH• radical. The rate constant at pH 1 is listed[67, 70] as $7{\cdot}2 \times 10^9$ l mole^{-1} s^{-1}.

The relative rates of reaction of Fenton's OH• with a variety of solutes were measured by Merz and Waters[240–242]. In the light of present knowledge, the values they obtained for aromatic (non-chain reaction) compounds must be doubled to allow for a modification to their reaction scheme[68]. Uri[202] criticized Merz and Waters' treatment on other grounds. Kraljic[73] has used *p*-nitrosodimethylaniline to evaluate some relative rate constants. Norman and Radda[209] have also measured the relative rates of some reactions by a competitive method.

2. Benzenoid compounds

Hydroxylation of the aromatic ring by Fenton's reagent was found for benzene[222, 235, 242, 245], nitrobenzene[20, 242, 244], benzoic acid or benzoate[236, 239, 242, 246, 247], benzamide[242], phenylacetic acid[242], dimethylaniline[242], chlorobenzene[24, 235, 242, 244], fluorobenzene[222, 244], phenol[23, 246], anisole[244], *p*-cresol[248], naphthalene[207], toluene (also some hydrogen abstraction from the side chain)[235, 244] and acetanilide[223, 236].

The course of reactions is considered to be the same as for the radiolytic OH• radical and equation (7), followed by equation (19), has been applied under aerated conditions. Since there is a rather higher concentration of radical **3** than in steady radiolysis and a greater likelihood of anaerobic conditions, there is a greater chance of biphenyls (equation 10) being formed. Lindsay Smith and Norman[235] showed that **3** was oxidized by ferric ion to phenol (equation 66).

$$XC_6H_5OH^{\bullet} + Fe^{3+} \longrightarrow XC_6H_4OH + Fe^{2+} + H^+ \qquad (66)$$

A lower amount of phenol was formed if the ferric ion was removed by complexing it with fluoride ion or by replacing Fe^{2+} with Ti^{3+} which gives Ti^{4+}, a weaker oxidizing agent than Fe^{3+}. More phenol was formed if an excess of ferric was added. Alternatively, **3** reacts with oxygen (equation 19). Another possibility advanced was reaction with a second OH• radical. On competition kinetic grounds, this can be discounted for small conversions of starting material.

Although no isotope effect could be detected in the formation of **3** there was an isotope effect when chlorobenzene was present. Less

phenol was formed from deuterated benzene than from protobenzene. This was explained by a crossed disproportionation between the two adducts present in the solution (equations 67 and 68—compare equation 11).

$$C_6D_6OH^{\cdot} + ClC_6H_5OH^{\cdot} \longrightarrow C_6D_5OH + ClC_6H_5DOH \quad (67)$$

$$C_6D_6OH^{\cdot} + ClC_6H_5OH^{\cdot} \longrightarrow ClC_6H_4OH + C_6D_6HOH \quad (68)$$

Reaction (67) will be slower than for the corresponding proto compound because a deuterium atom must be transferred.

3. Effect of additives

Staudinger and co-workers[223] related the greater effectiveness of certain metal ions (Cu^+ or V^{3+} in place of Fe^{2+}) with their redox potential and the speed of their reactions with molecular oxygen. EDTA, then, increases the phenol yield because it lowers the Fe^{2+}/Fe^{3+} redox potential. Ascorbic acid reduces the oxidized Fe^{3+}. Other reducing agents, such as ene-diols, would also be effective provided that they were not radical traps. These authors also gave consideration to the role of $HO_2^{\cdot}$ radicals. It was not appreciated at that time that these are considerably more stable and less reactive than are $OH^{\cdot}$ radicals.

Grinstead[247] has suggested $OC_6H_4COO^{-\cdot}$ as an intermediate in the attack of Fenton's reagent on salicylate ion. This corresponds to the phenoxyl radical found in the pulse radiolysis of phenols (section II.B.g)[75, 86]. Consequently the subsequent reactions with either O_2, H_2O_2 or $OH^{\cdot}$ to give the products 2,3- and 2,5-dihydroxybenzoic acids cannot be taken as necessarily applicable to the action of Fenton's reagent on aromatics in general.

4. Olefinic compounds

Baxendale, Evans and Park[229] showed that the Fenton's radical added on to either side of the double bond of acrylonitrile and methyl methacrylate. Because of its industrial application as a redox initiator for olefin polymerization, there was considerable interest in Fenton's reagent in about the year 1950. Most of these investigations do not throw much light on its behaviour as a hydroxylating agent.

5. Heterocyclic compounds

The literature on the action of Fenton's reagent on heterocyclic compounds has been reviewed by Norman and Radda[249].

Hydroxylation of furans has been investigated recently[253a].

Scholes and Weiss[250] studied the degradation of nucleic acids and

DNA bases by Fenton's reagent. Breslow and Lukens[239] showed that quinoline gave 3-hydroxyquinoline. Cier, Nofre and co-workers[251–253] used Fenton's reagent modified by addition of pyrophosphate to complex the ferrous ion, to study purine and pyrimidine bases. In recent years emphasis has shifted to Udenfriend's and similar reagents as more nearly resembling enzymic action.

6. Fenton-type reagents

Almost any metal ion of variable valency may be used in place of ferrous ion in a Fenton-type reagent and much the same series of reactions will be found. One of these, titanous ion, has been so useful that sufficient investigations have been done on it to merit separate treatment. Ceric ions will also be dealt with separately because the reactive species behaves quite differently from that in Fenton's reagent.

Other metal ions which have been studied in a mixture with hydrogen peroxide are listed by Walling[254]. The energetics of $OH^{\bullet}$ radical production is discussed by Uri[202]. An interesting one is cupric ion[222b, 244, 246] which increases the radiation chemical yield of hydroxylated products (section II.B.1.i). Ferrocyanide has also been used[254a].

The osmium tetroxide-catalysed addition of a hydroxyl group on each side of the double bond of an olefin (Milas reaction) has recently been reinvestigated by Norton and White[255]. The main product is the glycol.

C. *Titanous System*

1. General

Titanous ion reacts with hydrogen peroxide by a one-electron reaction (equation 69) and has been reported as proceeding more readily than the corresponding reaction of ferrous ion[223, 256] (Fenton's reagent).

$$Ti^{3+} + H_2O_2 \longrightarrow Ti^{4+} + OH^- + OH^{\bullet} \qquad (69)$$

Dixon and Norman[257, 258] found this sytem superior to the Fenton's ferrous system in flow experiments whereby the radicals could be observed in the cavity of an electron spin resonance spectrometer less than 0·02 second after the reactants were mixed. This technique has since been used extensively on many chemical compounds. Generally studies have been confined to e.s.r. spectra measurements. Being in a liquid system much greater resolution can be obtained

than in a solid. (Ultraviolet irradiation of a low temperature glass of the compound mixed with hydrogen peroxide is another way of trapping transient radical species so that they can be studied.) From such spectra the structure of the radicals formed can be deduced and quantitative ideas on the distribution of the unpaired electron can be obtained[222b].

2. Benzenoid compounds

Using such a flow system with benzene as the substrate Dixon and Norman[259] were able to show unequivocally the presence of **1** formed by reaction (9) and to resolve the question of the primary step in the action of hydroxyl radical on the aromatic ring. Thermodynamic calculations had indicated that the elimination of water from $XC_6H_5OH^{\bullet}$ was quite probable. They demonstrated convincingly that this adduct was, in fact, reasonably stable. This left no doubts as to the validity of Dorfman, Taub and Bühler's[58] conclusions arrived at from pulse radiolysis studies (section II.B.1.b).

Dixon and Norman[258] found that phenol gave the phenoxyl radical, $PhO^{\bullet}$, and concluded that hydrogen abstraction from the OH group was more facile than from CH. Pulse radiolysis studies[75] have shown that in a two-stage reaction the hydroxyl radical adds to the ring and then water is eliminated (section II.B.1.g).

Lindsay Smith and Norman[235] showed that the titanous system and Fenton's reagent behaved similarly in the hydroxylation of aromatic compounds such as fluorobenzene and chlorobenzene, and was unaffected by the addition of EDTA. Armstrong and Humphreys[260] found that the titanous system gave a bigger yield of radicals from reaction with amino acids but otherwise behaved similarly. For both reagents, addition of EDTA made no difference.

The radicals formed by attachment of $OH^{\bullet}$ to a number of aromatic compounds have been characterized[208a, 259, 261–263].

3. Olefinic compounds

Dixon and Norman[258] showed that allyl alcohol gave a spectrum corresponding mainly to $HOCH_2CH^{\bullet}CH_2OH$ and a weaker one, corresponding to $HOCH_2CH(OH)CH_2^{\bullet}$. This is in accordance with the greater reactivity of the unsubstituted methylene group in an olefin $CH_2{=}CHX$, as compared with the substituted carbon atom. Smith and co-workers[264, 265] observed the same phenomenon also for acrylate esters. Oximes add an $OH^{\bullet}$ radical to the carbon atom of the C=N bond[266, 267] but lose a hydrogen atom to give a nitroxide.

Malcic acid, fumaric acid and crotonic acid add OH· at the double bond[268]. The reagent demonstrates electrophilic character[268a].

4. Heterocyclic compounds

Pyridine does not react with this reagent[266].

Ormerod and Singh[269] found that the titanous reagent did not react with purines but attacked pyrimidine bases to give results in good agreement with radiation chemical results. At pH 1, OH· added to the 6-position of thymine six times more readily than to the 5-position. Surprisingly, with EDTA present at pH 2, there is no addition at position 6 and the concentration of radicals with OH in position 5 is enhanced $2\frac{1}{2}$ times. Myers and co-workers[186] have also studied this system.

Furans are hydroxylated at position 5 or 4[253a].

D. Hamilton's System

Hamilton and co-workers[269–274], during an investigation of Udenfriend's reagent, tried the effect of replacing ascorbic acid by other ene-diols. They found that catalytic amounts of catechol, (10^{-4} mole/litre) or other 1,2-dihydroxy- or 1,4-dihydroxy-aromatics and of ferric ion or less efficiently cupric ion enabled H_2O_2 to hydroxylate aromatic compounds.

Using competition kinetic methods the ratio of the rate constants anisole : benzene : chlorobenzene : nitrobenzene was found to be 1·4 : 1 : 0·6 : 0·6 which agrees fairly well with that for the radiolytic OH· radical. The isomeric distributions do not agree so well.

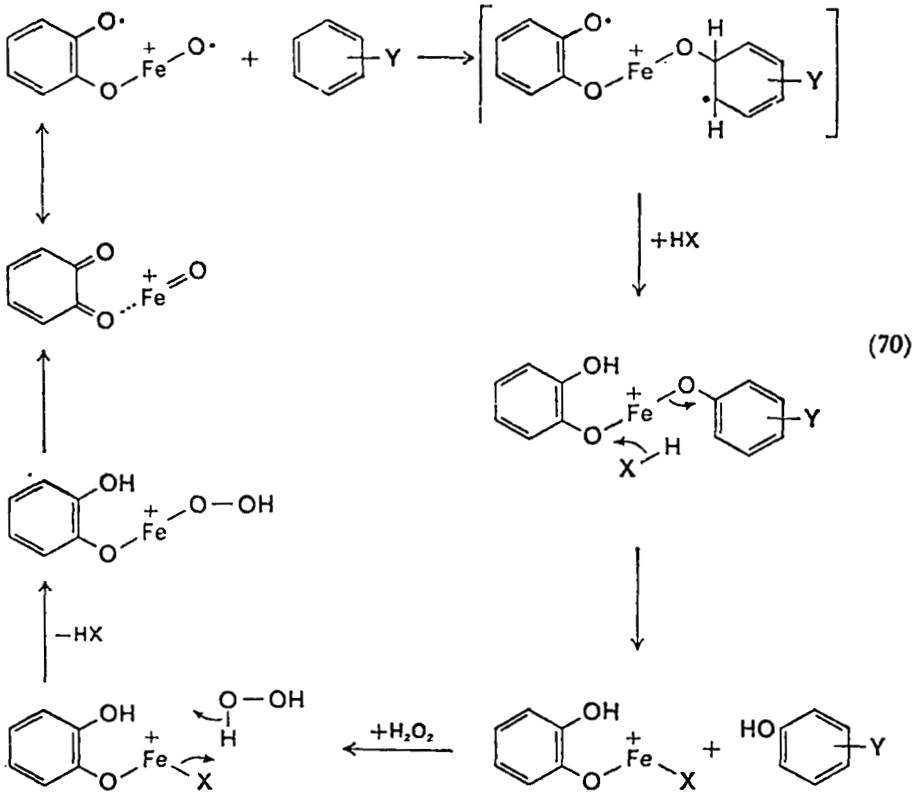
The scheme on the following page was proposed where HX is perchloric acid and C_6H_5Y is the substrate which is hydroxylated to HOC_6H_4Y. The reagent is regenerated.

The system has been shown to be capable of hydroxylating a number of aromatic compounds. An attractive feature is the low concentration of catechol or other catalyst and of ferric iron that is necessary. This introduces less interpretative complications than are found in some other systems.

E. Udenfriend's Reagent

1. Mechanism

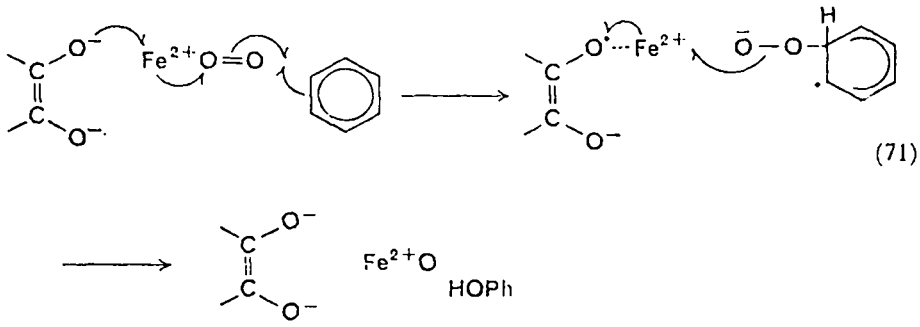
The best known of the systems that employ an electron donor to make dissolved molecular oxygen available as a hydroxylating agent is that proposed by Udenfriend and co-workers[224, 225]. The reagent



(70)

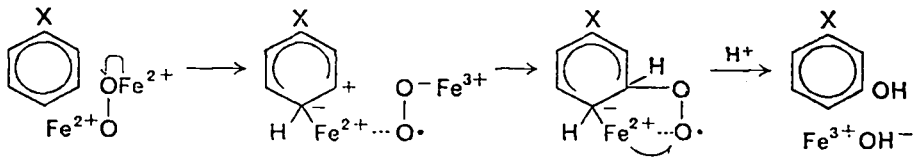
consists of ferrous ion, EDTA, ascorbic acid and oxygen. It was suggested that the oxygen was first reduced to hydrogen peroxide which then formed hydroxyl radicals. Norman and Radda[209] showed that the distribution of isomers following attack on anisole and chlorobenzene was different from that of Fenton's reagent. $HO_2^{\bullet}$ had been proposed as the radical in Udenfriend's reagent but by itself this reagent is not reactive enough. The attacking species is more selective than the radiolytic hydroxyl radical and is also electrophilic. In all, it is considered to be a better model for biological processes than any of the other systems.

Norman and Lindsay Smith[222] reported that the system is complex, and they have experienced difficulties in unravelling the mechanism. The molecular oxygen adds to the ferrous ion to give an ion, $Fe^{2+}O_2$, which is much more effective if EDTA is present. This acts as a bridge for electron transfer between the ascorbic acid and the aromatic ring and back again, being reduced itself in the process (equation 71).



(71)

In high concentrations of metal ion, $Fe^{2+}O_2Fe^{2+}$ is formed and this gives a preponderance of *meta*-substitution, presumably because Fe is first attached to the activated *ortho*- or *para*-position and thereby the *meta*-position is made more accessible to nucleophilic attack by oxygen (equation 72). Fluorobenzene gives a high proportion of



(72)

meta substituent even at low ferrous ion concentrations. Catechol and quinol are also found.

2. Systems

Some alternative complexing agents, but not all of them, and other metal ions such as titanous and copper ions[275–276a] can be used in place of ferrous ion, and other reversible electron donors can be used in place of ascorbic acid. An ascorbic acid to ferrous ion ratio of about six is an optimum, but hydroxylation will proceed very slowly even in the absence of an electron donor.

These studies have a bearing on the mechanisms obtaining in the autoxidation of aromatic compounds and, in particular, that of phenol. They are therefore of some technological significance.

Among the compounds studied with Udenfriend's reagent are a number of biochemicals and these are often hydroxylated if they are benzenoid, olefinic or heterocyclic compounds[276b,276c].

Smith and Hays[277] have recently compared the effect of X-radiation on uracil with that of ascorbic acid–$FeSO_4$. They found many similarities.

F. Ceric System

Baer and Stein[278] showed that ceric ion reacted with hydrogen peroxide to give the hydroperoxyl radical (equation 73).

$$H_2O_2 + Ce^{4+} \longrightarrow HO_2^{\cdot} + H^+ + Ce^{3+} \quad (73)$$

$HO_2^{\cdot}$ reacted with an excess of Ce^{4+} giving oxygen (equation 74)

$$HO_2^{\cdot} + Ce^{4+} \longrightarrow O_2 + H^+ + Ce^{3+} \quad (74)$$

The kinetics of these reactions were investigated by Baxendale[279], Sigler and Masters[280], and Czapski, Bielski and Sutin[281]. They found that equation (73) was reversible. Anbar[282] proposed that an intermediate complex Ce^{III}–OOH was formed and existed for a finite time.

Using a flow system Saito and Bielski[283] determined the electron paramagnetic resonance spectrum of the radical $HO_2^{\cdot}$. In the presence of an excess of cerous ion, there was a significant decrease in signal strength. There was good agreement with the spectra of $HO_2^{\cdot}$ obtained by other methods[283]. Bains, Arthur and Hinojosa[284] found that addition of Ti^{4+} ions produced a narrower stronger signal, indicating that the radical species produced in the ceric system was less stable than its titanic analogue.

The radical species does not appear to hydroxylate benzene[235] and is generally not very reactive. In these respects it resembles the radiolytic hydroperoxyl radical.

G. Peracids

1. General

Peracids can undergo either homolysis giving free hydroxyl radicals:

$$RCO\text{–}O\text{–}OH \longrightarrow RCOO^{\cdot} + OH^{\cdot} \quad (75)$$

or heterolysis giving hydroxyl cations:

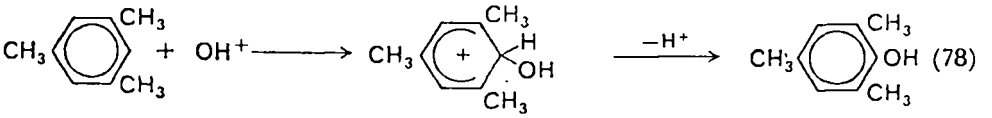
$$RCO\text{–}O\text{–}OH \longrightarrow RCOO^- + OH^+ \quad (76)$$

Both of these species appear to be capable of acting as electrophilic hydroxylating agents.

Uri[202] calculated that there should be a small amount of OH^+ present in equilibrium in hydrogen peroxide solution:

$$H_2O_2 + H^+ \rightleftharpoons H_2O + OH^+ \quad (77)$$

Derbyshire and Waters[285] chose mesitylene to demonstrate this. Mesitylene on hydroxylation with hydrogen peroxide in acetic acid–sulphuric acid mixtures gave mesitol. In this compound the positions activated by the OH group were blocked against further attack by more reagent so complications due to secondary reactions were minimized.



(78)

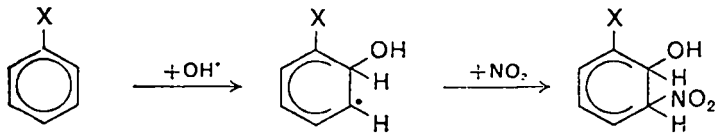
A Lewis acid such as boron trifluoride may be used in place of the acetic acid–sulphuric acid mixture[286].

2. Pernitrous acid

Pernitrous acid is formed when nitrous acid and hydrogen peroxide are mixed (equation 79). It is unstable.

$$H_2O_2 + HNO_2 \xrightarrow{-H_2O} ONOOH \longrightarrow ONO^{\cdot} + OH^{\cdot} \qquad (79)$$

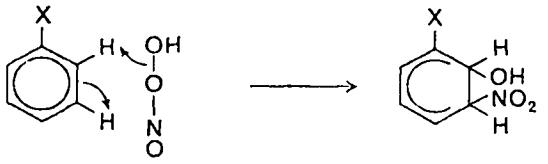
Halfpenny and Robinson[287, 288] concluded that the $OH^{\cdot}$ radical added almost always *ortho* or *para* to any existing substituent group in the benzene ring. This was followed by nitration in the *meta*-position giving either 1-hydroxy-2-nitro or 2-nitro-3-hydroxy derivatives. The incoming groups occupied adjacent positions in all the products found, probably because in **1** the unpaired electron was localized in that position (equation 80). Compound **15**, which is



(80)

not unlike **4**, was thought to decompose by elimination of either water, nitrous acid or hydrogen or the substituent as HX.

The products found from benzene are nitrobenzene, *o*-nitrophenol and smaller quantities of biphenyl, *p*-dinitrobenzene, phenol, other nitrophenols and some tar. Several other benzoid compounds were investigated but the presence of tar and dimers among the products casts doubt on the validity of deductions from the isomeric distributions of the products. It is always possible that the pernitrous acid does not dissociate until it reacts with the aromatic compound.



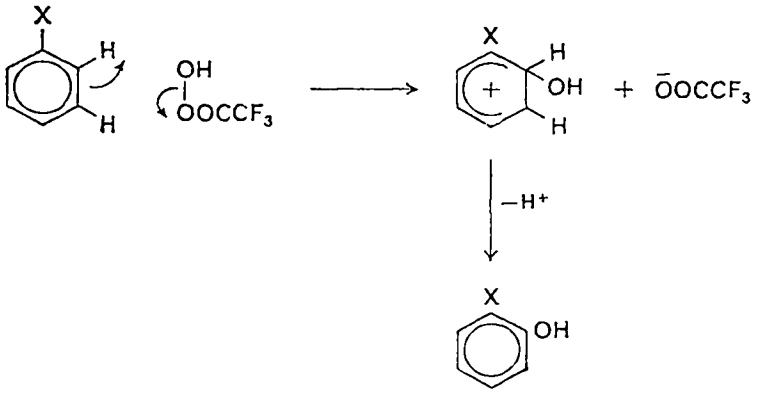
(81)

3. Trifluoroperacetic acid

a. General. Derbyshire and Waters[285] suggested that other peracids might give OH^+. The hydroxylating action of perbenzoic and peracetic acids was known but owing to secondary reactions giving quinones this action was not always recognized. In trifluoroperacetic acid (**16**) the fluorine atoms attract electrons from the O–O bond thus facilitating the fission of this bond[289]:

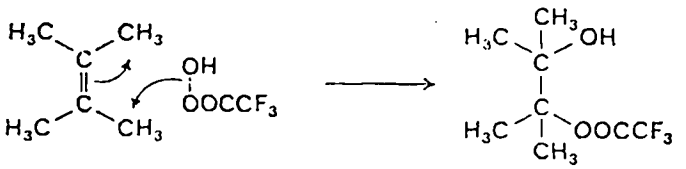
$$\underset{\textbf{(16)}}{\overset{\delta-}{CF_3COO}-\overset{\delta+}{OH}} \longrightarrow CF_3COO^- + OH^+ \qquad (82)$$

Once again decomposition does not necessarily[290] take place giving free OH^+. The reagent may act as in equation (83).



(83)

Evidence that **16** may decompose in this way is given by the reaction[291] with tetramethylethylene (equation 84).



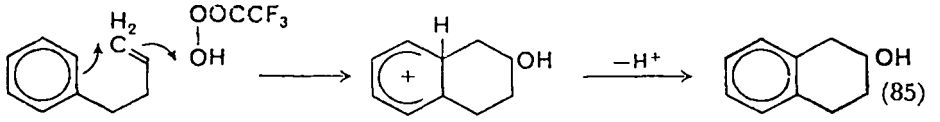
(84)

The reactions of **16** are described in several texts and reviews[222, 292, 293]. It has proved to be a very useful electrophilic hydroxylating agent.

b. Benzenoid compounds. The reaction with some aromatics has been studied by Davidson and Norman[294]. The isomeric distributions obtained were quite different from those obtained with Fenton's reagent. More importantly, published values for radiolytic hydroxyl radical reactions[126, 128] show quite a different distribution. The conditions are not strictly comparable but there seems little doubt that the attacking species is not the hydroxyl radical[294a]. The reagent can be considered as an electrophile of low selectivity but more selective and less reactive than the OH$^{\bullet}$ radical.

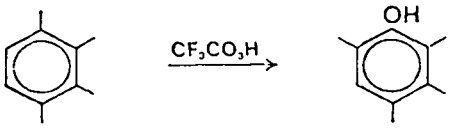
The presence of a substituent nitro group in an aromatic compound does appear to inhibit the attack of **16**; although, since considerable amounts of tar were formed, the evidence is not clear[291]. In radiolytic hydroxylation nitro compounds are attacked quite readily (section II.B).

Oxidative cyclization can also be the result of attack by **16** (equation 85)[294].

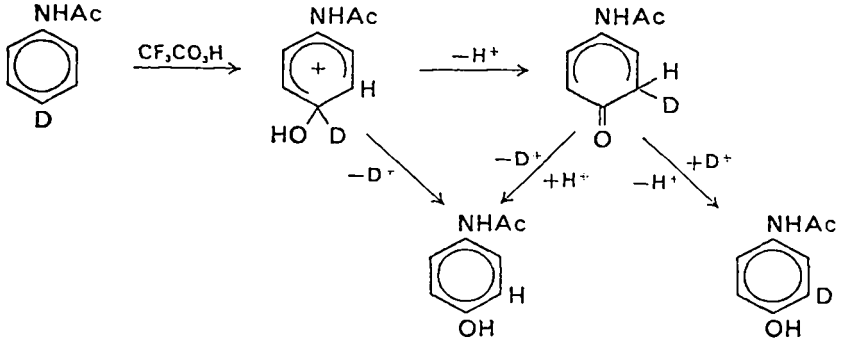


(85)

Attack at a ring carbon on which there is already a substituent sometimes induces methyl migration by a Wagner–Meerwein rearrangement. Prehnitene gives a variety of products including isodurenol[291] (equation 86).



(86)



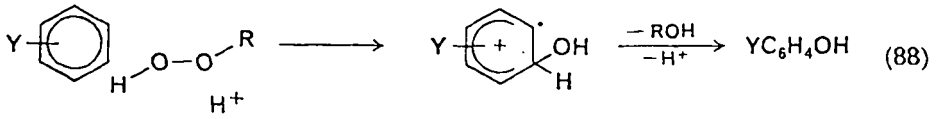
(87)

An analogous rearrangement has been observed for deuterated acetanilide[295] (equation 87). 7·5% of the product is that deuterated in the 3-position. It is suggested that hydrogen migration might be a common reaction for phenolic cations.

c. Effect of additives. Usually hydrogen peroxide and trifluoroacetic acid are mixed to prepare **16** in situ. The effectiveness of **16** may be increased by carrying out the reaction in methylene chloride. Also effective is addition of boron trifluoride, a Lewis acid, which has been used by Hart, Buehler and Waring[291] to obtain high yields of products. The Lewis acid coordinates with one of the oxygens not used in the hydroxylation and thus facilitates decomposition. Iodine in conjunction with **16** has been used by Hey and co-workers[296] to hydroxylate steroids.

4. Other peracids

Hydroxylation has been reported following the action of peracetic acid, perbenzoic acid and persuccinic acid[297, 297a]. The presence of acid assists reaction[293] (equation 88). Smith and Fox[268] found that



(88)

Ti^{3+} and peracetic produce a species which reacts like the OH• radical.

Inorganic peroxy acids such as persulphuric acid and peroxychromic acid have been observed to effect hydroxylation[298] but hydroxyl radicals are not necessarily involved.

5. Peresters

Diisopropyl peroxydicarbonate has been shown by Kovacic and Morneweck[243] and by Kovacic and Kurz[244] to give a reasonably good yield (about 50%) in the hydroxylation of aromatic compounds to produce phenols. Reaction was carried out in the presence of a Friedel–Crafts catalyst and gave essentially no undesirable side reactions. This is a considerable advantage over those methods involving hydroxyl radicals. The initial electrophilic attack was thought to be by an oxonium cation to give a phenol ester–aluminium chloride complex which resists further attack by the reactant. On hydrolysis this yields the phenol.

H. Other Systems

There are other systems in which the action of hydroxyl radicals has been postulated in order to explain the results obtained.

Benzene is converted into *o*-nitrophenol by the Baudisch reaction (hydrogen peroxide, hydroxylamine hydrochloride and cupric ion). The first step involves hydroxylation[299, 300].

In the analogous system morpholine, copper salt and oxygen, phenols are oxidized to quinones[301]. Since known scavengers have no effect, $OH^{\bullet}$ radicals are most probably not involved.

Heckner, Landsberg and Dalchau[302] concluded that alkaline permanganate oxidized toluic acid and malonic acid through an intermediate $OH^{\bullet}$ radical which existed in equilibrium in solution[303] (equation 89).

$$MnO_4^- + OH^- \rightleftharpoons MnO_4^{2-} + OH^{\bullet} \quad (89)$$

Relative reaction rates were determined and agreed well with pulse radiolysis values[77, 90].

Powdered silica has some OH groups on the surface. If an organic compound is ground up with it, some hydroxylation results[304]. It would be interesting to know the isomeric distribution for the product from some monosubstituted benzenes.

An electrical discharge in water vapour produces $OH^{\bullet}$ radicals[305]. This should be a worthwhile source of such radicals. If an electrodeless discharge is used then no contaminants or catalytic metals are introduced. Hydroxyl radicals are also produced from hydrogen peroxide vapour[305a].

Hydrogen atoms are readily produced in the gas phase. By reaction with oxygen, $HO_2^{\bullet}$ radicals are produced[306].

Hydrogen peroxide can be homolysed by pyrolysis. Hydroxyl radicals result.

Ultrasonic waves can break up water, and one of the products is the $OH^{\bullet}$ radical[321, 322].

V. COMPARISON OF REAGENTS

A. Identity of Species

Except where there is clear evidence to the contrary, the hydroxylating species produced by chemical reagents have been called hydroxyl radicals in each case throughout this chapter. Nevertheless, since the hypothesis was first advanced in 1934 there has been speculation whether the hydroxyl radical is, in fact, formed by

Fenton's reagent. This speculation continues today and is also applied to the other reagents.

It was hoped that the e.s.r. spectra of the species would resolve these questions, but either the spectra are not exactly what would be expected on theoretical grounds for the free radicals or the radicals are perturbed in some ways by the components of the reagent system. Methods are now available[307] for finding the e.s.r. spectra of short-lived radiolytic species so these points may soon be resolved.

There is now reasonable agreement that the radiolytic and photolytic species are free $OH^{\bullet}$ radicals and are electrophilic reagents. However, only recently have techniques been available to study them without interference from other species and other reactions. The chemically produced species are undoubtedly similar in their behaviour. Some investigators have suggested that the reactive species may be complexes containing metal ions. Identification of a reactant with a known species can only follow when both kinetic data and product distribution are seen to vary together over a range of changing conditions.

Frequently one finds a categorical statement in the chemical or biological literature that one or other of the chemically generated species is known to be the hydroxyl radical. On tracing back one finds that such statements are based on the authority of a hypothesis put forward before the hydroxyl radical had been discovered for certain and its properties and reactions investigated. Furthermore, the necessary experimental equipment and techniques had not been developed at that time. At the present time, there is insufficient evidence to decide which, if any, of the chemically produced species are free $OH^{\bullet}$ radicals. Some of the considerations that must be taken into account will be summarized. In many cases conditions are different and the chemistry not understood.

B. Some Discrepancies

Livingston and Zeldes[211, 212] found that photolysis of allyl alcohol–H_2O_2 mixtures gave a spectrum quite different from that obtained by Dixon and Norman[259] using the flow system. Atkins and Symons[308] pointed out that since $OH^{\bullet}$ reacts so readily with H_2O_2 giving $HO_2^{\bullet}$, a more stable radical, it is difficult to be sure what species one is studying in ultraviolet-irradiated hydrogen peroxide solutions. Similarly, they consider $HO_2^{\bullet}$ or possibly $(TiOO^{\bullet})^{4+}$ to be the active species formed from titanous salts and hydrogen peroxide.

From product yields using the competitive method, Norman and Radda[209] have found relative rates for Fenton's radical in the ratio anisole: benzene: chlorobenzene: nitrobenzene of 6·35:1:0·55:0·14. This should be compared with the radiolytic values 1·5:1:1:0·4 [68, 77].

Myers and co-workers[186] found that the radiolytic OH$^{\bullet}$ added to carbon atom 6 of thymine whereas the titanous radical also added to position 5 on the other side of the double bond. Ormerod and Singh[269] noted a difference in site of attack between pH 1 and 2.

There is plenty of evidence that ferrous ion forms complexes with many anions[309, 310]. This influences its rate of reaction with H_2O_2. There appears to be no reason why OH$^{\bullet}$ should not remain complexed to the iron. Shiga[311] found that Fenton's reagent attacked the hydrogens on the ω carbon atoms of alcohols whereas the titanous reagent attacked the α position. The radiolytic and photolytic OH$^{\bullet}$ radical attack the α position. He concludes that Fenton's radical may be a complex, such as Fe–EDTA–H_2O_2. In a subsequent publication Shiga and co-workers[312] distinguished between the electrophilic titanous reagent and nucleophilic (sic) Fenton's reagent. On the other hand Smith and Wood[313] found that by varying the concentrations of the reactants it was possible to obtain radicals corresponding to hydrogen atom abstraction from all sites of the alkyl part of alcohols.

Staudinger[223] found different isomeric ratios for the hydroxylation products resulting from the action of Fenton's reagent and titanous system respectively on acetanilide. The reactions with cellulose are different for the two reagents[313a].

Chiang and co-workers[315] and Armstrong and Humphreys[260] consider that in the titanous system a complex $[Ti(H_2O)_4OH$ (substrate)$]^{4+}$ is formed. To react, a substrate must be able to form this complex. If this is so, the dependence of yields on pH should differ from that in the radiolytic system. Norman[314] states that it is now apparent that the titanous reagent is far more complex than was at first thought.

Turkevich and co-workers[315], Fischer[316], Florin, Sicilio and Wall[317] and Mickewich[318], have considered the e.s.r. spectra of the titanous radical as well as its growth and decay. They conclude that it is some form of complex, perhaps $(TiOO)^{3+}$ which is essentially a complexed $O_2^{-\bullet}$. Such a complex does not necessarily behave like $O_2^{-\bullet}$.

The difficulty in finding an e.s.r. spectrum for OH$^{\bullet}$ radical

in Fenton's system may be due to its very short life vis-à-vis dimerization ($k_{OH+OH} = 5 \times 10^9$ l mole^{-1}s^{-1}). When scavengers are present the time scale is very short in terms of most experimental techniques and thus the species is not readily detectable. During pulse radiolysis experiments in the presence of 1 mmole l^{-1} benzoate all hydroxyl radical reactions are more than 99% complete in $\approx$1 microsecond[60].

Sicilio, Florin and Wall[319] and Takakura and Rånby[320] were able to resolve two peaks in the e.s.r. spectrum of the titanous reagent. These were attributed to $HO^{\cdot}$ and $HO_2^{\cdot}$ and both were thought to be coordinated with Ti(IV) ions and possibly other species.

Bains, Arthur and Hinojosa[284] mixed H_2O_2 with pairs of metal ions (Fe^{2+}, Ti^{3+} and Ce^{4+}). From the changes of the e.s.r. spectra with relative concentrations they deduced that Ti^{4+} forms stable complexes with the radical species generated in these systems but Fe^{3+} and Ce^{3+} do not.

There are sufficient discrepancies between results for doubts to arise. Some of these discrepancies are due to making comparisons between experiments conducted under quite different conditions. For example, in most comparative tables one finds listed the pioneering radiation chemical results of Weiss, Stein and co-workers[17–24] obtained twenty years ago; both experimental and interpretative techniques have advanced greatly since then. It is interesting that only recently did new information appear, published by three independent groups[68, 76, 85, 90], on the aqueous radiation chemistry of solute nitrobenzene—a key compound in the study of directive effects of substituents in the benzene ring. It is quite apparent that a greater understanding of the chemistry of the systems is necessary before valid comparisons can be made.

The systems are complicated—much more complicated than the simpler radiolytic or photolytic ones—and only very recently has the understanding of these model systems progressed to a point of reasonably universal agreement. The species are very reactive, so their existence is transitory and special methods must be used to detect and identify them and to follow their reactions. They react to give other very reactive species, and several reaction steps may occur before the formation of a stable product which can be separated. Often there is a chain reaction so that results are difficult to replicate and there is uncertainty regarding what reaction is affected by a given change in experimental conditions. Further, these difficulties are compounded by the variety of the substances added in the

practical systems. These substances may increase the yields of desired products but do not necessarily increase the chances of being able to sort out the mechanistics of even the basic processes. Without this knowledge the practical system is unapproachable.

C. Important Factors

Radiation chemical studies have demonstrated the importance of oxygen, low conversions, solute concentration and dose rate in some cases[321]. Addition of ferrous or copper ions introduces a chain reaction and increased yields result. Radiation chemical studies have an advantage over photochemical studies in that, within limits and certainly for dilute solutions, the rate of production and amount of hydroxyl radicals can be controlled with fair accuracy while other conditions are varied over a wide range. It should be possible to derive kinetic data for the interaction of many of the species. These data can be used, by means of computer programmes, to calculate product yields which can be compared with experimental values. Only when an evaluation has been made of a reactant's kinetic behaviour as well as the isomeric distribution of its products, can its identity be established with any certainty.

In the meantime, even without this knowledge, the practical chemist can still make use of these reagents to effect electrophilic hydroxylation in a single step.

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The Chemistry of The Hydroxyl Group: Part 1
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CHAPTER 4

Formation of hydroxyl groups via oxymetallation, oxidation, and reduction

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I. INTRODUCTION: OXYMETALLATION AND OXIDATION

The first parts of this review are concerned with reactions which introduce the hydroxyl group into organic compounds and in which at least one major stage is oxidative. Knowledge of mechanisms of

oxidation has increased markedly in recent years and excellent texts giving extensive coverage are available (e.g., see References 1—4). The subject matter of these occasionally coincides with material in this chapter and it is for this reason that the topics here have received consideration in proportion to the extent to which they are inadequately treated in secondary sources elsewhere. Additional considerations have been the actual or potential synthetic utility and theoretical importance of the reactions.

A. The Formation of OH Groups at Saturated Carbon

The most direct method of inserting a hydroxyl group at saturated carbon is by autoxidation. This is essentially a homolytic chain reaction between triplet ground state, molecular oxygen and the substrate preferably in the presence of an initiator to counter the poor radical properties of molecular oxygen. Hydroperoxides are normally formed in the first instance but these are easily reduced, e.g., by lithium aluminium hydride, to alcohols. Although this appears to constitute a most general method of forming alcohols by oxidation it is limited in synthetic use to those examples where the desired reaction site is also the most reactive towards radicals. Alkanes are much less active than allylic and benzylic positions and reactivity generally parallels bond dissociation energies. Radicals which promote autoxidation may be generated by thermal or photochemical disruption of an initiator, photochemically via a 'sensitizer', e.g., benzophenone, or by direct homolysis of bonds in the substrate by high energy irradiation. The area is generally well served with reviews of the synthetic scope and mechanisms of the reactions (e.g., see References 5—7). Asymmetric synthesis has been observed in the autoxidation of DL-3-*p*-menthene in the presence of the optically active catalysts manganese D(−)- and -L(+)-mandelate[8].

Many carbon acids, e.g., tri-*p*-nitrophenylmethane, are quite inert towards attack by molecular oxygen but react readily in the form of their carbanions to yield hydroperoxides. Examples of these and the proposed mechanisms appear in section III.B.

Photoinitiated autoxidation of hydrocarbons proceeds via a homolytic chain process; quite different in its characteristics is the dye-photosensitized oxygenation of olefins to allylic hydroperoxides and cyclic conjugated dienes to *endo*-peroxides. These latter oxygenations find analogy in those effected by singlet oxygen, and the evidence is probably conclusive that the dye-photosensitized oxygenations also

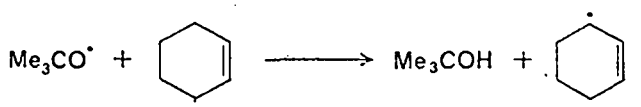
proceed via oxygen in this form. The evidence for this important development is reviewed in section III.A.

Of considerable interest are the autoxidations of organometal compounds, particularly boron and aluminium trialkyls, which find technical use in the manufacture of aliphatic alcohols and of peroxides as polymerization catalysts. The mechanistic features of these reactions appear in section III.C.

Formally resembling the autoxidation is the oxidation of trialkylboranes with hydrogen peroxide, alkyl hydroperoxides and peroxy acids. Trialkylboranes, which may be formed by hydroboration of alkenes, are oxidized by alkaline hydrogen peroxide to alcohols which correspond to an anti-Markownikoff hydration of the alkene[9, 10]. This very useful procedure continues to be extended, and amongst the developments one may note its use for the preparation of optically active alcohols with H–D asymmetry[11] and the stereoselective syntheses of alcohols via cyclic hydroboration of dienes with 2,3-dimethyl-2-butylborane[12].

Peresters undergo a copper-catalysed reaction of homolytic type with alkenes to introduce an ester group at the allyl position[13], e.g., *t*-butyl perbenzoate when heated with cyclohexene and a catalytic amount of cuprous bromide produces 73% of 3-benzoyloxycyclohexene. The mechanism of these reactions is probably as follows[14–16], e.g.. for cyclohexene:

$$PhCOO{-}OCMe_3 + Cu^{I} \longrightarrow PhCOOCu^{II} + Me_3CO^{\bullet} \qquad (1)$$



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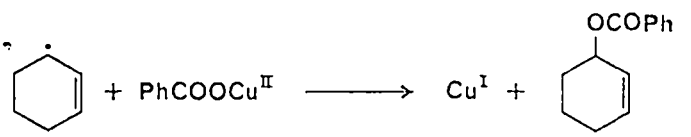


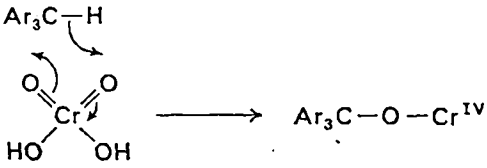
(3)

There is evidence that equation (3) involves a carbonium ion[15]. Unsymmetrical alkenes yield mixtures of isomeric products which may result from a mesomeric allylic radical, terminal alkenes produce mostly an unrearranged product. Appropriate reagents are able to effect the conversion of cumene into 3-acetoxycumene in 30% yield[16] and tetralin into 1-benzoyloxytetrahydronaphthalene in 15% yield[17]. The reagents are also able to introduce an ester group

into other compounds containing active carbon–hydrogen bonds, e.g., ethers and thioethers[13]. The method offers a convenient route for the synthesis in particular of allyl alcohols.

Chromium compounds are capable of oxidizing tertiary alkanes to tertiary alcohols and alkenes to allylic alcohols but usually in poor yield. Further oxidation results in carbonyl compounds and carboxylic acids and the method has limited synthetic value. The mechanism of the chromic acid oxidation of triaryl alkanes to carbinols probably involves either the homolytic route (equation 4) or the cyclic transition state (equation 5):

$$Ar_3CH + Cr^{VI} \longrightarrow Ar_3C^{\bullet} + Cr^{V} \qquad (4)$$



(5)

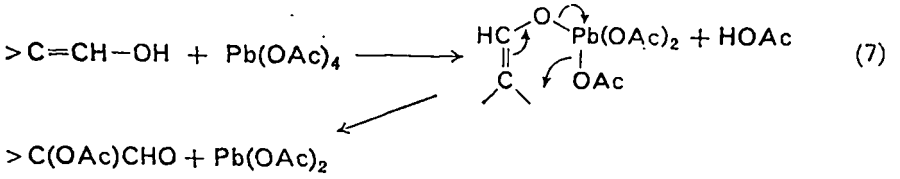
the fate of the radical in equation (4) is probably conversion into a chromium ester. Oxidation with chromium compounds has been reviewed recently[18–20], and the possible use of these in synthesis, e.g., of *t*-butyl chromate[21] and chromyl chloride[22], continues to be explored.

The limitations in the use of potassium permanganate for the oxidation of hydrocarbons to alcohols are similar to those of chromic acid. Further oxidation of the alcohols to carbonyl compounds and carboxylic acids is frequent, and an additional drawback is the low solubility of the oxidant in many organic solvents. The use of triphenylmethylarsonium permanganate which is soluble in chloroform has been described[23]. Potassium permanganate will effect the oxidation of tertiary hydrocarbon groups to carbinol as in branched chain carboxylic acids and in arylalkanes, and finds here synthetic use. The suggested mechanism for these oxidations involves permanganate ion abstraction of a hydrogen atom from the tertiary position giving a radical pair in a solvent cage. Recombination within the cage produces an alkyl hypomanganate:

$$R_3CH + MnO_4^- \longrightarrow [R_3C^{\bullet}MnO_4H^-] \longrightarrow R_3COMnO_3H^- \qquad (6)$$

The ester may decompose by several routes; these mechanisms and other features have been reviewed recently[24].

Lead tetraacetate is able to effect acetoxylation at carbon–hydrogen bonds and thus affords a possible stage to the overall introduction of a hydroxyl group. The synthetic use of the method is limited by the occurrence of additional reactions and the reagent's ability to attack readily only those carbon–hydrogen bonds which are adjacent to carbonyl, phenyl, alkenyl or ether groups. The reaction with carbonyl compounds probably proceeds via a heterolytic mechanism involving the decomposition of an intermediate ester of the enol with lead tetraacetate:



(7)

The mechanism of the acetoxylation of ethers, and allylic and benzylic acetoxylations is not yet clear. There is evidence of homolytic routes but the reactions do not appear to be accompanied by products arising from dimerization or chain transfer of radicals, although dimers have been characterized in the boron trifluoride-catalysed oxidation of benzene derivatives[25]. Lead tetraacetate whilst fairly inactive towards benzene will effect several reactions including acetoxylation of certain aromatic and heteroaromatic compounds. The reactions of this reagent have been reviewed recently[26]. Of considerable interest is the report of the use of lead tetra(trifluoracetate) which effects the trifluoroacetoxylation of hydrocarbons such as benzene and heptane. Trifluoroacetoxylation may be followed by hydrolysis and the four compounds investigated gave alcohols in 45 ± 10% yields[27]. The mechanism is not yet known.

Apart from lead tetraacetate, the acetates of Hg(II) and Tl(III), together with Pd(II) salts and selenium dioxide in acetic acid, also effect allylic acetoxylation. In so far as acetoxylation may be regarded as a route to the oxidative introduction of a hydroxyl group these reactions are described in sections II.A—D.

B. The Formation of OH Groups at Unsaturated Carbon

The direct introduction of a hydroxyl group on olefinic carbon by autoxidation is very restricted in scope and at present of little value in synthesis. The limitations are, first, that removal of allylic hydrogen is energetically preferred to the homolytic addition of oxygen

and, secondly, if oxygen does add then it results in a peroxy radical which is more likely in these circumstances to add to more olefin, producing after further repetitions a polyperoxide, than it is to abstract a hydrogen atom to become a hydroperoxide. It has been observed that it is those olefins which polymerize readily which also autoxidize and that this process of autoxidation becomes equivalent to copolymerization[5]. At elevated temperatures, the addition of oxygen to many olefins increases at the expense of allylic attack and becomes a competing process. The dye-photosensitized addition of oxygen to conjugated dienes is reviewed in section III.A.

The compounds chromic acid, chromyl acetate and chloride find little use in the synthesis of alcohols from alkenes. Chromyl acetate may oxidize alkenes to epoxides but in most cases several products are formed with the epoxide in small proportion[18].

The dihydroxylation of alkenes by aqueous permanganate in basic solution is well known. The oxidation also takes place readily with periodate and catalytic amounts of permanganate in neutral solution (the Lemieux and von Rudloff reagent). Permanganate is the oxidant and is continuously regenerated by periodate[24]. Similar in mechanism and product are dihydroxylations with osmium tetroxide[28, 29]. Whereas these two methods produce *cis* glycols, the Prevost reagent—a solution of iodine in carbon tetrachloride together with an equivalent of silver acetate or benzoate—under anhydrous conditions yields the diacyl derivative of a *trans*-glycol via neighbouring acetoxy participation[30, 31]. A comparison of the mechanisms of acetoxylation by the Prevost reagent and lead tetraacetate has been reported recently[32].

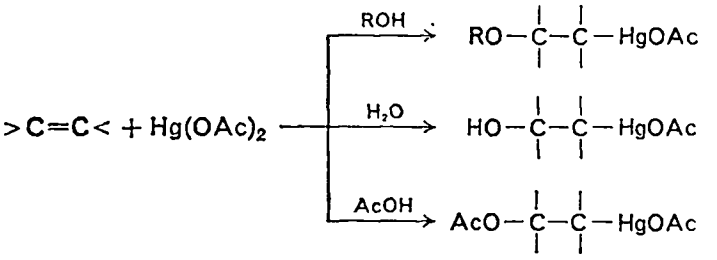
The epoxidation of alkenes with peracids offers another useful route to the synthesis of *trans*-1,2-diols[13]. The formation of the epoxide is a stereospecifically *cis*-addition, the subsequent ring opening usually proceeds with inversion of configuration at the carbon atom attacked resulting in an overall *trans*-addition to the double bond[33]. Epoxides are easily converted by lithium aluminium hydride into monohydric alcohols, the reaction is of S_N2 type and the rigid epoxides of multi-ring systems such as steroids yield axial alcohols.

Lead tetraacetate reacts with alkenes in a variety of ways and yields some 1,2-diacetoxy derivative. The mechanism of the reaction is not known, the addition does not appear to be stereospecific and the reaction has little preparative value at present[26]. The reactions of alkenes with compounds of Hg(II), Tl(III), and Pd(II) are dealt with in sections II.A—C.

II. THE INTRODUCTION OF OH GROUPS VIA CERTAIN OXYMETALLATION AND ACETOXYLATION PROCEDURES

A. *Mercury(II) Salts*

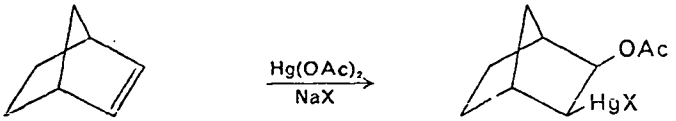
Alkenes undergo electrophilic addition reactions with mercuric salts under mild conditions in solvents with nucleophilic activity to produce organomercury adducts of the type:



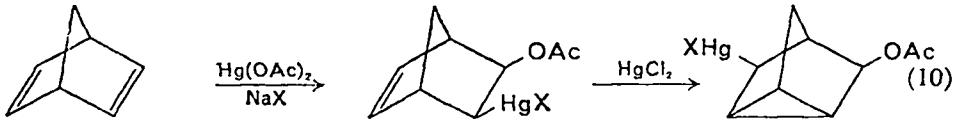
(8)

These reactions are not new and earlier work has been reviewed[34, 35]. Whereas many alkenes may be induced to react in the manner shown by equation (8), a change in reaction conditions, particularly temperature or solvent, often leads to the formation of other products. For example, in acetic acid as solvent Hg(II) acetate oxidizes cyclohexene to the allylic acetate and, in a water-suspension, to the allylic alcohol and cyclopentyl aldehyde[36].

The formation of the adduct by electrophilic addition does not appear to proceed by free carbonium ions or those involving neighbouring carbon participation. Both norbornene[37] (**1**) and norbornadiene[38] (**3**) react to give unrearranged *cis*-2,3-*exo*-mercuration products (**2** and **4**), although **4** undergoes $HgCl_2$-catalysed isomerization to the nortricyclenic oxymercurial **5** [38]:



(1) (2) (9)

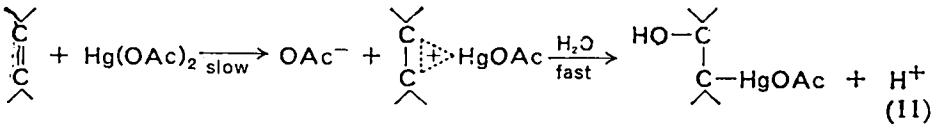


(3) (4) (5) (10)

Similarly, both *endo*- and *exo*-dicyclopentadienes undergo oxymercuration in water and methanol without rearrangement to give *exo,cis*-addition products[39]. The results imply that the formation of initial products is under kinetic control but that lengthy reaction times may yield products of greater thermodynamic stability arising from a consecutive rearrangement of carbonium ions formed by heterolysis of the Hg–carbon bond[38, 40].

The stereochemistry of this addition reaction depends upon the structural features of the alkene taking part. There are two main divisions: the hydroxymercuration of acyclic and monocyclic alkenes is a *trans*-addition, whereas that of bicyclic alkenes in which the double bond is sterically hindered to *endo*-attack is a *cis*-addition.

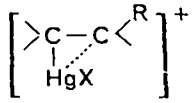
The *trans*-addition of Hg(II) acetate in aqueous solution is considered to proceed via a Hg(II)–olefin π-complex (mercurinium ion) which is then *trans*-solvolysed:



(II)

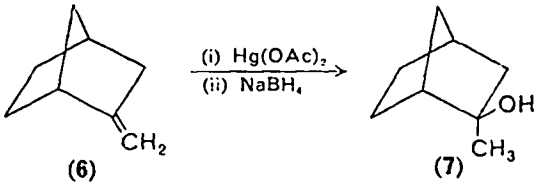
Evidence for this scheme rests on the kinetics of formation of the adduct, the observed stereochemistry of the products, and kinetic studies of dehydroxymercuration which is the acid-catalysed reversion of hydroxymercuration[34, 35, 41–44]. A relevant illustration of the latter is that α-2-methoxycyclohexylmercury(II) chloride, in which the substituents may assume a *trans*-diaxial conformation, undergoes perchloric acid-catalysed dehydroxymercuration ca 10^6 times faster than the β-diastereoisomer[35]. Recently a *trans*-solvolysed mercurinium intermediate has been used to rationalize the occurrence of partial asymmetric synthesis in the methoxymercuration of α,β-unsaturated esters, namely, (−)-menthyl crotonate, cinnamate and β-methyl cinnamate[45].

The symmetrical structure assigned to the mercurinium intermediate has been disputed by Halpern and Tinker[46] who report the kinetics of the hydroxymercuration of many acyclic alkenes and cyclohexene with Hg(II) perchlorate in aqueous perchloric acid solution. They observed that the rate constants for hydroxymercuration of eight alkenes give a good log k versus σ^* plot of slope $\rho^* = -3{\cdot}3$. Consequently they suggest that the rate-determining step is the formation of an intermediate which has a high degree of positive charge localization, approaching carbonium ion character, on the carbon atom adjacent to the substituent R:



There is an interesting comparison here with the mercuric acetate cleavage of substituted phenylcyclopropanes to yield an adduct, which has $\rho^+ = -3{\cdot}2$, and may involve an intermediate of similar structure[47]. In contrast, evidence of a σ-bridged mercurinium ion has been reported for the methoxymercuration of allenes[48]. The direct demonstration of kinetic nonparticipation of solvent molecule has yet to be made. The unsymmetrical π-complex has been favoured by other authors (e.g., see Reference 37) to account for features of the reaction and it lends itself readily to an explanation of the observation that the oxymercuration–demercuration procedure leads to a Markownikoff hydration of hydrocarbon alkenes.

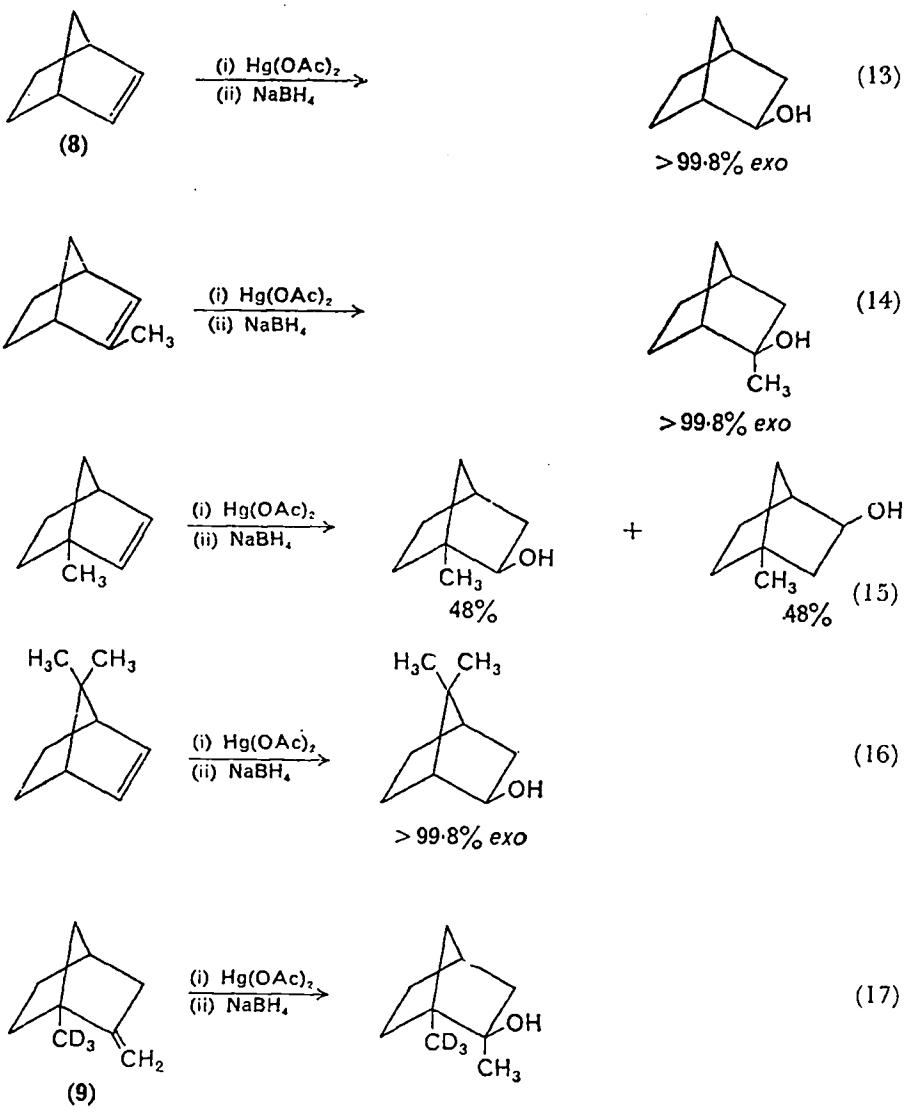
It is the synthetic utility of this feature which has been returned to by H. C. Brown and co-workers[49, 51]. They have shown that oxymercuration combined with reduction of the oxymercurial adduct by sodium borohydride in situ provides a convenient, mild method to achieve Markownikoff hydration of carbon–carbon double bonds without rearrangement. The method complements the anti-Markownikoff hydration effected by the hydroboration–oxidation of alkenes and is considered superior to the procedure whereby the *exo*-alcohol of a bicyclic alkene is obtained via epoxidation and metal hydride reduction. A representative selection of alkenes have been hydrated in good yield by this method. The hydration of bicyclic alkenes takes place on the least hindered side resulting in *exo*-alcohols, e.g., 2-methylene-norbornane (**6**) yields 2-methyl-*exo*-norbornanol (**7**) in 99·5% yield:



(6) (7) (12)

In a series of molecules whose structures offer increasing steric hindrance to *endo*-approach there is an increasing preference for the formation of the *exo*-alcohol. The effect is similar to that observed in the lithium aluminium hydride reduction of hindered ketones[50]. The oxymercuration–demercuration procedure shows a high degree of

stereoselectivity in effecting substantially *exo*-hydration of norbornene (**8**) and related compounds as the following examples illustrate (total yields $\geqslant 84\%$)[51]:

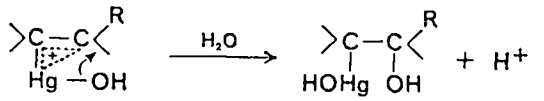


In common with the oxymercurations mentioned earlier, these proceed without skeletal rearrangements, or without scrambling as indicated particularly by equations (15) and (17).

Whereas the mechanism of *trans*-hydration of a mercurinium-type

intermediate is reasonable for alkenes free from steric-controlling effects, the structure of the transition state leading to *cis*-addition is not yet clear. As yet there are no rate measurements for the hydroxymercuration of bicyclic olefins; however, the results of Brown and coworkers[49, 51] indicate that *cis*-oxymercuration is not handicapped by slower reaction rates than *trans*-oxymercuration. That of norbornene (**8**) is amongst the fastest and that of 7,7-dimethylnorbornene (**9**) is considerably slower.

cis-Additions commonly arise from cyclic intermediates, and in the case of hydroxymercuration this would require the replacement of acetoxy from the mercurinium intermediate by hydroxyl. The reaction could then be represented by:



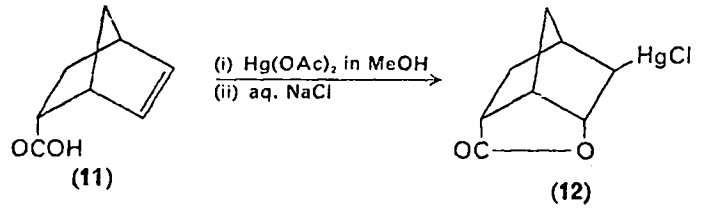
(10) (18)

Structure **10** would also be present during *trans*-addition to unhindered olefins but here the intramolecular transfer of hydroxyl would have to compete with intermolecular rearwards attack by solvent. This model has been developed by Traylor[52] who envisages competitive S_N2 and S_Ni processes. Traylor has also suggested that ring strain rather than steric hindrance may be responsible for the *cis*-oxymercuration of norbornene via a mercurinium ion which itself is more reactive because of rigidity and strain than in the case of cyclohexene. In this connexion he has demonstrated that bicyclo-[2,2,2]octene undergoes both *cis*- and *trans*-oxymercuration.

Stereochemically anomalous reaction products may arise when substituents near to the carbon–carbon double bond undergo prior coordination with mercury. There are a number of examples in the literature[35] and Sung Moon and Waxman[53] have adapted the observations of Henbest and Nicholls[54] for 4-substituted cyclohexenes, to the stercospecific synthesis of *trans*-1,3-diols of six-, seven- and eight-membered rings by the oxymercuration–demercuration of cycloalk-2-en-1-ols.

Certain areas of the subject seem to be particularly beset by conflicting stereochemical claims, e.g., Jensen and Miller[55] report that the oxymercuration of 5-norbornene-2-*endo* carboxylic acid (**11**) with Hg(II) acetate yields 94% of the α-5-chloromercurilactone **12** as a consequence of *trans*-addition and not the mixture of *endo*- and *exo*-compounds reported earlier by other authors[56]. This example is

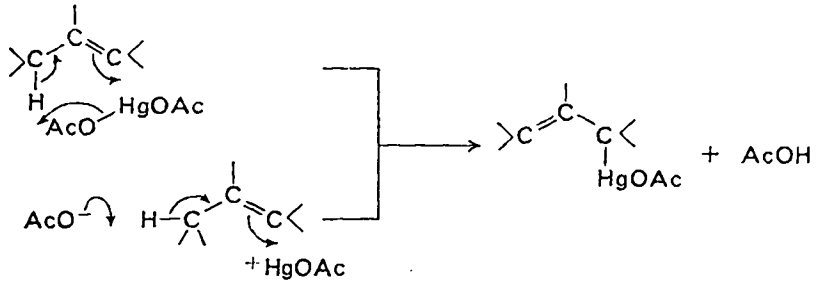
also of interest in being one of a number in which a *trans*-intramolecular nucleophilic attack on the mercurinium intermediate takes place:



(11) (12) (19)

The reaction of Hg(II) acetate in acetic acid with olefins at elevated temperatures commonly effects allylic acetoxylation[57-59] from which alcohols may be obtained by hydrolysis. The acetoxylations and ring contractions of cyclic olefins strongly resemble those produced by Pb(IV) acetate, and it is probable that similar mechanisms occur. A feature of the Pb(IV) acetate oxidations is the frequency of Wagner–Meerwein rearrangements[60]. Not all reactions of Pb(IV) acetate with olefins, however, are ascribed a heterolytic route. For example, the reagent reacts with styrene to give several products, one of these, PhCH(OAc)Et, is considered to result from a radical chain reaction, and another, $PhCH(OAc)CH_2OAc$, by two concurrent reactions of homolytic and heterolytic character[60, 61]. In addition, of considerable interest is the report that molecular oxygen inhibits the benzylic acetoxylation of toluene by scavenging the short-lived free radical intermediates such as $PhCH_2^{\bullet}$ or $Pb(OAc)_3^{\bullet}$, occurring in a radical chain process[62].

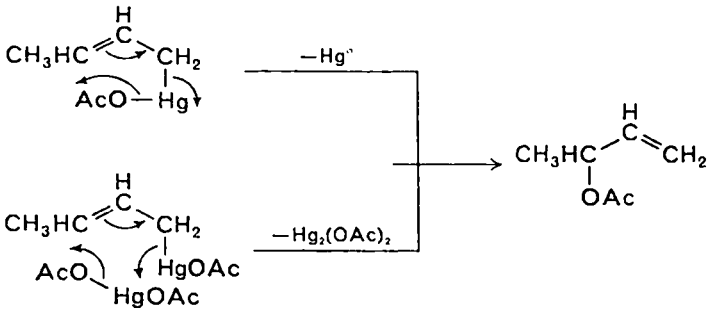
Whereas the oxymercuration adduct has been suggested by some authors as an intermediate in the acetoxylation reaction, Winstein and co-workers have implied the possibility of the direct formation of an allylic mercurial, envisaged mechanistically as of S_Ei' (equation 20) or S_E2' (equation 21) type[63]:



(20)

(21)

These processes may be regarded generally as the reversion of the reported S_Ei' or S_E2' demercurations of butenylmercuric acetate in acetic acid which yield 99·5% of the secondary allylic acetate. The demercuration is slow at 25° but greatly increased in the presence of Hg(II) acetate and the following S_Ei' (equation 22) and S_E2' (equation 23) schemes have been suggested[64]:



(22)

(23)

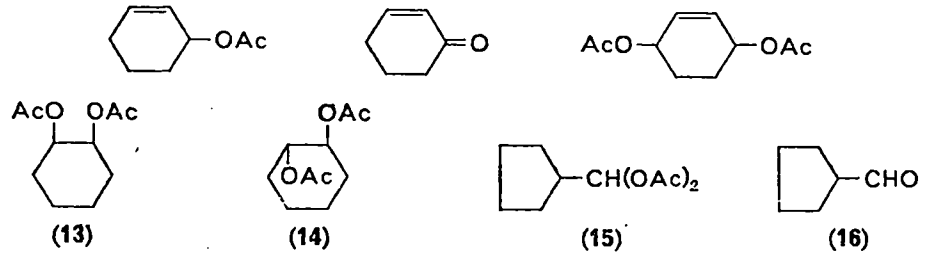
Examination of butenylmercuric acetate by n.m.r. has shown that under conditions of rapid allylic equilibration (induced by HgX_2 salts) the equilibrium is far on the side of the primary butenyl structure as in the case of the analogous Grignard and PdCl compounds[65]. In terms of acetoxylation, this implies that the secondary acetate may be anticipated to be the product from the allylic oxidation of both 1- and 2-butene as any secondary mercurials initially formed isomerize rapidly to the primary structure. The expectation has been borne out by an examination of the acetoxylation of a number of 1- and 2-alkenes (C_5—C_8) with Hg(II) acetate in acetic acid at 75° [63]. However, the proportion of secondary allylic acetate diminishes with reaction time particularly with 2-olefins owing to $Hg(OAc)_2$-catalysed isomerization of the allylic acetates; olefin isomerization also occurs. The exclusive formation of secondary allylic acetates in these particular examples is, therefore, based essentially on the unique demercuration process and is not consistent with normal carbonium ion or free radical behaviour. The general applicability of the rationalization is not known and it may not apply to olefins of widely different structural type.

A completely different approach to the problem has been made by Wiberg and Nielsen[66] who investigated the stereochemistry of the allylic acetoxylation of a number of cyclic olefins with Hg(II) acetate at elevated temperatures for prolonged periods. They consider that the results, e.g., the formation of racemic carvotanacetol acetate from (+)-carvomenthene, require the intermediacy of a symmetrical,

allylic carbonium ion. This arises from the heterolysis of the Hg–carbon bond of an allylmercuric acetate which is itself formed via electrophilic addition and elimination of a proton from the mercurinium-type intermediate.

B. Thallium(III) *Salts*

Although the reactions have been less well investigated it is apparent that Tl(III) salts react with olefins in a manner similar to that of Hg(II) salts and Pb(IV) acetate. Acyclic olefins are oxidized to glycols and carbonyl compounds by Tl(III) salts in aqueous solution[67] and the kinetics of oxidation of certain of these have been examined[68]. Cyclohexene in acetic acid solution is oxidized to the following products[36, 67, 69-71]:



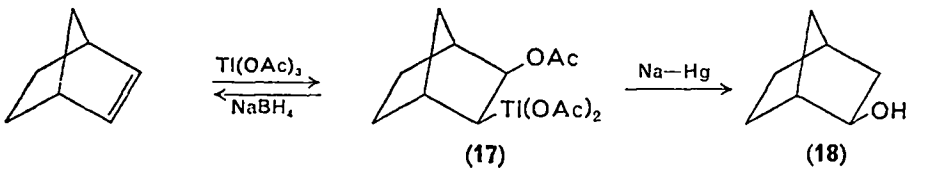
(13) (14) (15) (16)

and the glycol monoacetates of **13** and **14**; products **13**—**16** are often formed in high proportion. There is little work reported on the stereochemistry of the cyclohexane diacetates (**13** and **14**) but one study has shown that mainly the *trans*-isomer is formed in dry acetic acid and mainly the *cis*-isomer in the moist solvent[36]. Both isomers are considered to have a common precursor in the *trans*-oxythallation adduct which undergoes metal–carbon bond heterolysis with acetoxy participation to yield an acetoxonium ion. Solvolyses in which the stereochemistry of the product depends upon the medium and particularly the presence of water are a feature of acetoxonium compounds[36]. The ring-contracted products are presumably also the consequence of carbonium ions but on this occasion with neighbouring carbon participation.

Features such as the multi-component nature of the product, the degree of incidence of allylic attack and presence of ring-contracted products suggests that oxidations with Tl(III) salts stand nearer to the behaviour of those of Pb(IV) acetate than those of Hg(II) salts. Both Hg(II) and Pd(II) acetates oxidize cyclohexene to the allylic acetate exclusively[36]. Comparisons should be treated with caution as solvent

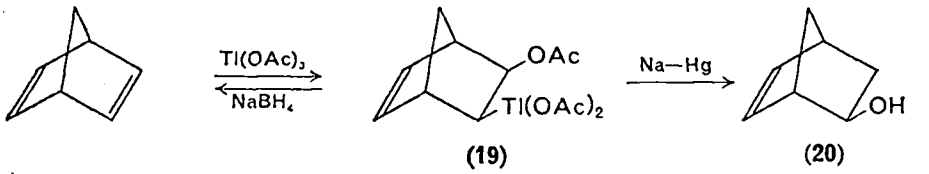
and temperature have an important role in deciding what products form. However, it is probable that carbonium ions resulting from metal–carbon bond cleavage have a more prominent part in the reactions of Tl(III) salts and Pb(IV) acetate with olefins than do Hg(II) salts. The mechanisms of allylic oxidation and acetoxylation have received little direct attention.

Oxythallation adducts have been isolated from styrene, *o*-allylphenol[71], norbornene and norbornadiene[38]. For the latter two compounds, confirmation of expected *cis,exo*-oxythallation was obtained by an application of the nuclear Overhauser effect in their double resonance n.m.r. spectra; the single resonance n.m.r. spectra are complicated by large proton–thallium coupling constants[72]. On treatment with sodium borohydride in ether–methanol both the norbornene and norbornadiene oxythallation adducts (**17** and **19** respectively) undergo reductive deoxythallation to regenerate the parent olefin exclusively. On the other hand, the norbornene adduct (**17**) is reduced by sodium amalgam in aqueous suspension to a high yield of *exo*-norborneol (**18**). Similar treatment of the norbornadiene adduct **19** and reacetylation of the product leads to a high yield (ca 95%) of the acetates of *exo*-5-norborneol (**20**) (ca 85%) and nortricyclanol (**21**) (ca 15%)[38]:



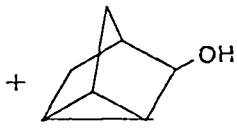
(17) (18)

(24)



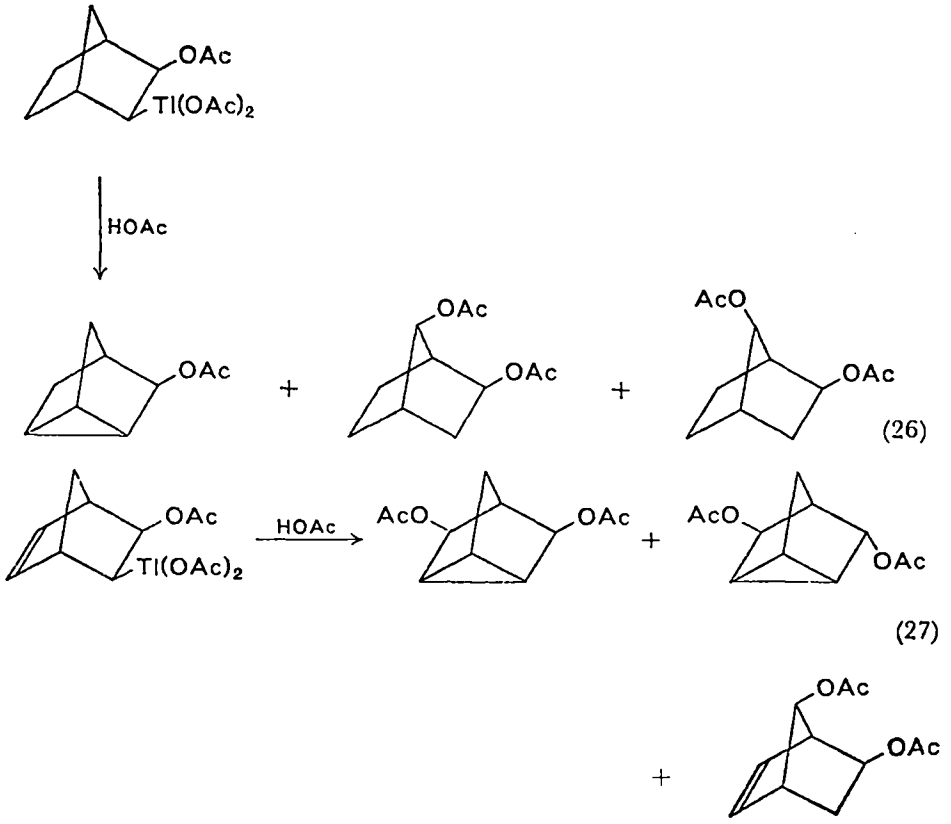
(19) (20)

(25)



(21)

The oxythallation adducts of norbornene and norbornadiene undergo rearrangements analogous to that of the oxymercuration adduct of norbornadiene noted earlier. However, there appear to be differences in that a greater variety of products is obtained fairly rapidly on acetolysis at room temperature and identical products are also obtained by direct treatment of norbornene and norbornadiene with Tl(III) acetate in acetic acid[38]—some examples follow:



The ease of Wagner–Meerwein rearrangement accompanying dethallation in acetic acid illustrates the importance of distinguishing whether the formation of products has been kinetically or thermodynamically controlled.

The effect of structure upon rate of reaction in the aqueous Tl(III) oxidation of simple olefins qualitatively parallels that observed in the acid-catalysed hydration of olefins[68, 73]. This observation has been offered as further evidence of carbonium ion character for the activated complex involved in oxythallation. The difference in

degree of carbonium ion character of the reactive intermediates in oxythallation and oxymercuration has been ascribed to the effect of the higher charge of thallium reducing the size of the *d*-orbitals and hence the *d–p* overlap necessary for strong π-bonding. The decomposition of the mercury intermediate by nucleophiles is envisaged as essentially S_N2 (one might add also S_Ni) whereas that of the thallium intermediate is S_N1[68, 73]. However, the unequivocal demonstration of the stereochemistry of oxythallation has yet to be reported.

Oxythallation combined with reductive dethallation under aqueous conditions does not yet appear to have been exploited in the manner of the mercury analogue for the synthesis of alcohols from olefins.

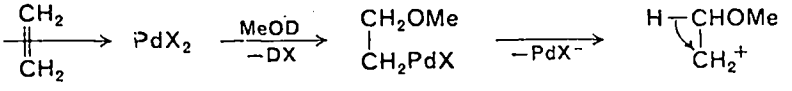
C. Palladium(II) Salts

The oxidation of olefins with Pd(II) chloride in aqueous solution is the basis of a most useful technical preparation of carbonyl compounds, particularly when Cu(II) chloride is used as a redox system to make the reaction catalytic in Pd(II)[74, 75]. 1- and 2-Olefins are oxidized to methyl ketones in high yield and in certain respects oxidations with Pd(II) resemble those of Tl(III)[68, 73, 76], in which saturated ketones and glycols are produced, more than those of Hg(II)[77, 78] in which, e.g., propene gives mainly acrolein. On the other hand, the small dependence of rate of oxidation to carbonyl compounds by Pd(II) upon olefin structure is unlike that of Hg(II) or Tl(III) oxidations and suggests little carbonium ion character in the transition state. This feature has been rationalized by a concerted, nonpolar, four-centre addition mechanism leading to an oxypalladation adduct[79].

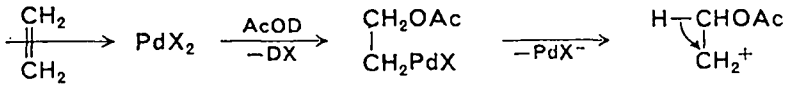
Oxidation of olefins with Pd(II) salts in the presence of acetic acid produces vinyl and allyl acetates in a manner generally similar to Hg(II), Tl(III) and Pb(IV) acetate acetoxylations[80, 81]. The reaction of Pd(II) with olefins is considered to proceed via a preliminary PdX_2–olefin complex to an oxypalladation adduct[80–86]. Such adducts have not yet been characterized and have at the moment the status of reactive intermediates. Questions prompted by results gained in related fields as to the kinetics and stereochemistry of their formation are generally unanswered. Winstein and co-workers have studied the acetoxylation of acyclic 1- and 2-olefins (C_3—C_5) with Pd(II) acetate at 25° in acetic acid[80] and compared the results with those obtained with Hg(II) acetate[63] mentioned earlier. There is a striking contrast in that 1-olefins give mainly enol acetate while 2-olefins give mainly

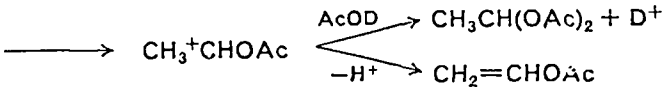
allylic acetate. In addition, the small amount of allylic acetate formed from a 1-olefin is mainly primary, whereas the allylic acetate from a 2-olefin is mainly secondary. The proportion of enol to allyl acetate is sensitive to solvent. Product distributions were measured early in the reaction to obtain values close to kinetic control proportions as it was observed during lengthy reaction periods that product isomerization occurred. The data were rationalized by a sequence in which an oxypalladation adduct with preferred Markownikoff orientation eliminates the elements HPdOAc with the preferred formation of an allylic acetate. The oxypalladation adduct of a 1-olefin with Markownikoff orientation can lead only to an enol acetate[80].

The detailed manner of the decomposition of the oxypalladation adducts to give products is not clear. One suggestion, based on isotopic labelling, is that the Pd–carbon bond heterolyses to a carbonium ion which rearranges and solvolyses, or loses proton[83]:



and





The absence of deuterium in the saturated products precludes the possibility of their having been formed by addition of solvent molecule to a vinyl intermediate. An acceptable mechanism also has to preclude enolic intermediates which tautomerize to products. A variation of the mechanism is a Pd-assisted hydride shift followed by, or synchronously with, proton loss from an adjacent carbon atom. Differences between this and the carbonium ion mechanism outlined above are in the timing of the stages and the required *cis*-arrangements of the palladium group and the hydrogen atom involved in assisted hydride transfer. This mechanism, also incorporating the suggestion of an adduct with *cis*-orientation, has been used by Haszeldine and co-workers[86] to interpret the acetoxylation of cy-

clohexene with Pd(II) chloride in acetic acid (containing sodium acetate at 20°) which produced cyclohex-2-enyl acetate (76%) and cyclohex-3-enyl acetate (24%). These authors have also demonstrated that the π-allylic complex di-μ-chloro-bis(cyclohexenyl) dipalladium(II) is not a precursor in the acetoxylation of cyclohexene.

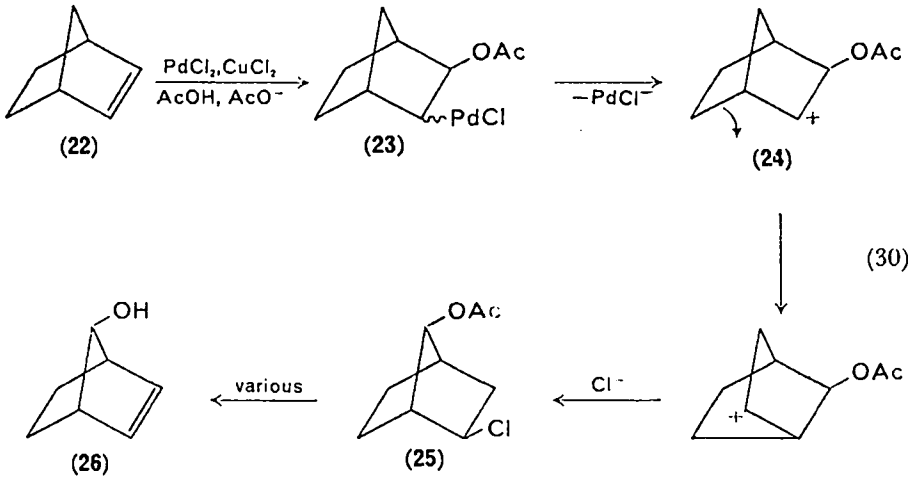
A new variation on the use of Pd(II) and Cu(II) combinations has been reported by Henry[81]. Whereas Cu(II) alone has no oxidative activity towards olefins, when present in high concentration with Pd(II), the reaction of Pd(II) takes a different course. Little vinyl acetate is formed and the product consists of saturated compounds, e.g., from ethylene, 2-chloroethyl acetate and ethylene glycol mono- and di-acetate; homologues of ethylene undergo similar reactions. *cis*- and *trans*-2-Butene give comparable quantities of both 2,3- and 1,3-isomers and this is ascribed to a prior rearrangement of the oxypalladation adduct. The results have been rationalized by a mechanism in which Cu(II) chloride successfully competes with elimination of HPdCl from the oxypalladation adduct by reacting directly with it, but the precise nature of this reaction has yet to be made clear. As with the mentioned results of Winstein and co-workers[80], the product distributions in this new reaction are best explained by preferential Markownikoff oxypalladation[81].

Norbornene (**22**) is oxidized in acetic acid solution by a mixture of Pd(II) and Cu(II) chlorides, with the latter in high concentration, to 50—84% yields of *exo*-2-chloro-*syn*-7-acetoxynorbornane (**25**). This was converted into the difficultly accessible *syn*-7-norbornenol (**26**). The formation of **25** was explained as due to heterolysis of the Pd–carbon bond in the oxypalladation adduct (**23**) to yield a norbornyl cation (**24**) which undergoes rearrangement and then nucleophilic attack as set out in equation (30)[87]. In view of the report by Henry[81] mentioned earlier it is interesting that here no special function was ascribed to Cu(II) chloride.

The quantity and range of results reported so far in these acetoxylation studies by Pd(II) do not permit a general mechanism to be established. The importance of reaction conditions such as temperature and solvent, and the structure of the olefin is such that inferences drawn from results gained under one set of conditions may not be exactly applicable to another.

D. Acetoxylation with Selenium Dioxide in Acetic Acid

Selenium dioxide is best known for its ability to oxidize ketones



via enol selenite esters to α,β-diketones[3]. The reagent when used in acetic acid medium will also effect allylic acetoxylation. These reactions have been less fully studied than the ketone oxidations, and the mechanism is far from clear. It was formerly thought to be homolytic and involve hydrogen atom abstraction from the alkene in the manner of allylic bromination with *N*-bromo amides and autoxidation[88], but more recently heterolytic mechanisms have been suggested[66, 89]. A feature of these and related allylic acetoxylations by metal acetates are the relatively high temperatures and lengthy reaction periods required[66] in comparison with those for the formation of oxymetallation adducts with, e.g., Hg(II) and Tl(III) salts. The question as to whether the allylic acetoxylations proceed via these adducts is not yet settled.

The competitive allylic acetoxylation of nuclear substituted 1,3-diphenylpropenes (**27**) by SeO_2 in organic solvents of differing acidity has led Schaeffer and Horvath to suggest an electrophilic attack by SeO_2 or $HSeO_2^+$ on the carbon–carbon double bond as the initial stage of the reaction[89]. The similar oxidation of 3-deuterio-1,3-diphenylpropene gave an allylic acetate which retained about three-quarters of the original deuterium and this corresponds to a kinetic isotope effect of $k_H/k_D = 3{\cdot}1$ at 115°, thus suggesting carbon–hydrogen bond breakage during the rate-determining stage[89]. In addition, the distribution of deuterium in the product indicated that positions 1 and 3 become equivalent. The results were rationalized by the following mechanism which involves a selenite ester(**28**):

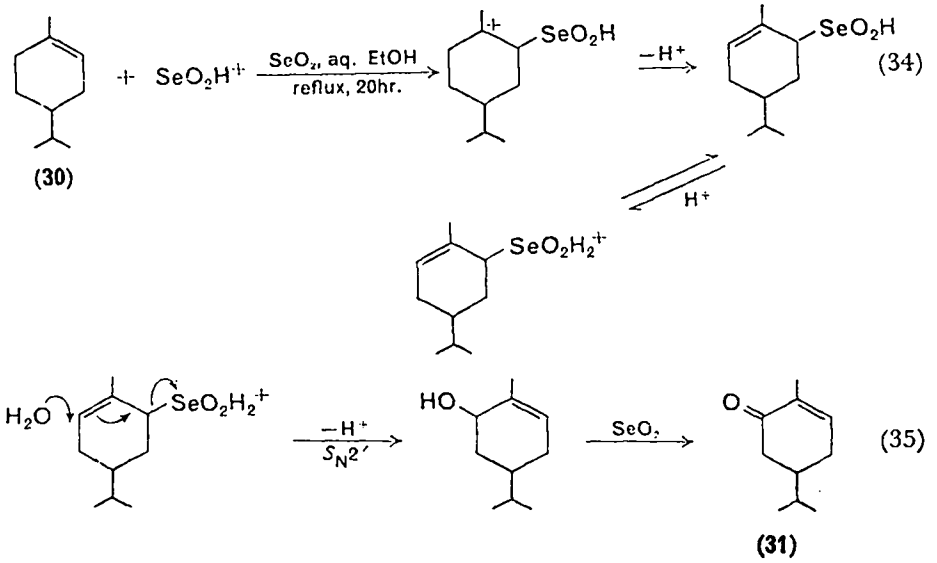
$$PhCH_2CH{=}CHPh + HSeO_2^+ \longrightarrow PhCH{=}CHCH(OSeOH)Ph + H^+ \quad (31)$$

$$(27) \quad \cdots\cdots \quad (28)$$
$$(28) \longrightarrow [PhCHCHCHPh]^+ + HSeO_2^- \quad (32)$$
$$(29)$$

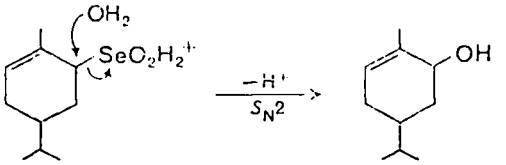
$$(29) + HOAc \longrightarrow PhCH(OAc)CH{=}CHPh + H^+ \quad (33)$$

Stages (32) and (33) are described here as an S_N1 solvolysis. An alternative path in solvents of lower ionizing power or higher nucleophilicity, or where the internal structure of the selenite ester is less favourable to ionization, would be that of S_N2 or S_N2' solvolysis. Reactions proceeding by these latter routes could provide the basis of an explanation of the observed formation of optically active products[66, 89]. For example, (+)-carvomenthene (**30**) is oxidized in aqueous ethanol by SeO_2 to (+)-*p*-menth-6-en-2-one (**31**) with ca 50% retention of configuration suggesting a mainly S_N2' solvolysis by water[66].

Whereas some authors describe the reaction path in terms of the formation and decomposition of a selenite ester by analogy with ketone oxidation, Wiberg and Nielsen suggest a selenic acid as intermediate, by analogy with oxymetallation[66]. According to this scheme, the oxidation of (+)-carvomenthene (**30**) is formulated as the following S_N2' process:



The alternative S_N2 path leads to stereochemical inversion:



(36)

The intermediacy of carbonium ions in these reactions involving cyclic olefins is not yet established and it may be significant that the bicyclic olefin α-pinene oxidizes without rearrangement or cleavage[66].

Unlike other olefins examined, cyclohexene reacts with SeO_2 in acetic acid to give mainly a selenium-containing adduct which yields 3-acetoxycyclohexene and selenium on pyrolysis. The reaction has been carried out using cyclohexene with ^{13}C-labelling of both carbon atoms of the double bond; analysis of the product showed that the acetoxy group was attached to one of the original olefinic carbon atoms to the extent of 90%[66]. This result requires either the S_N2 mechanism or an olefin-forming elimination of an oxyselenation adduct. It is confusing and perhaps indicative of the present state of this area to find that (+)-4-methylcyclohexene is reported to be oxidized to 5-methyl-2-cyclohexen-2-yl acetate with the same stereochemical features as (+)-carvomenthene and unlike cyclohexene[65].

III. THE INTRODUCTION OF OH GROUPS VIA CERTAIN REACTIONS WITH MOLECULAR OXYGEN

A. Oxidation via Singlet Oxygen

The normal or triplet ground state of molecular oxygen is that of a biradical $^{\bullet}O–O^{\bullet}$. It is through the agency of this form that autoxidations, either spontaneous or promoted by initiators, take place. The products and homolytic characteristics of these reactions are dissimilar to those described in this section. Direct comparisons have been made experimentally, e.g., in the autoxidation of (+)-limonene[90].

The heterolytic decomposition of hydrogen peroxide or peracids with, e.g., alkaline solutions of chlorine or bromine produces electronically excited singlet oxygen, O=O, which is structurally similar to ethylene[91]. Other methods of chemical generation in situ are known and include the decomposition of a triaryl phosphite–ozone adduct[92] and of *endo*-peroxides of 9,10-disubstituted anthracenes[93]. Singlet oxygen may also be generated externally by subjecting oxygen to radio-frequency, electrodeless discharge[94]. Oxygen resulting from all these processes has one or other of the excited singlet

states, $^1\Delta g$ or $^1\Sigma g^+$, whose energies are ca 22·5 and 37·5 kcal/mole respectively, above that of triplet ground state ($^3\Sigma g^-$) oxygen. Chemiluminescence occurs when the excited singlet states of oxygen emit radiation on returning to the ground state, this reversion may involve the bimolecular process:

$$2\,O_2(^1\Delta g) \longrightarrow 2\,O_2(^3\Sigma g^-) + h\nu$$

and other species [95–97]. In the case of the singlet oxygen formed by reaction between chlorine and hydrogen peroxide in alkaline solution, red light of wavelength 635 mμ is observed[96].

The singlet oxygen generated by these and other methods is of considerable theoretical and synthetic interest as an oxidant of olefins[98]. Alkenes yield allylic peroxides with double bond migration, and cyclic conjugated dienes yield *endo*-peroxides, from which alcohols may be obtained by a variety of reducing agents. A selection of illustrations from the literature is given in Table 1. The products of these oxidations are identical with those resulting from dye-photosensitized autoxidations, and high yields may be expected when high quantum yields in the photosensitized autoxidations are obtained. There is growing evidence that photosensitized autoxidation probably proceeds via singlet oxygen.

Two mechanisms have been suggested for the dye-photosensitized autoxidations of dienes and olefins which are consistent with the products, kinetics and energy considerations. These mechanisms differ in steps (39) and (40) of the following scheme, where superscripts refer to electronic spin states, Sens = sensitizer, and A is a substrate[91]:

$$\text{Sens} \xrightarrow{h\nu} {}^1\text{Sens} \qquad (37)$$

$$^1\text{Sens} \longrightarrow {}^3\text{Sens} \qquad (38)$$

$$^3\text{Sens} + {}^3O_2 \longrightarrow {}^{\cdot}\text{SensOO}^{\cdot} \qquad (39a)$$

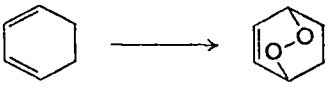
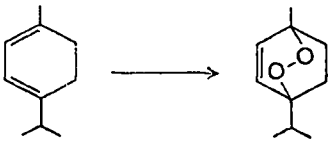
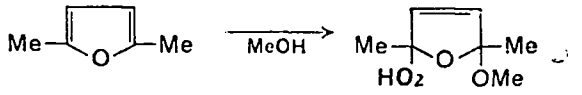
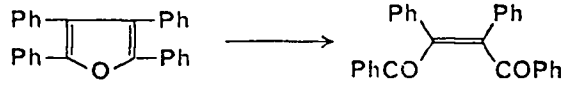
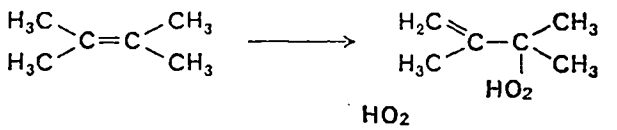
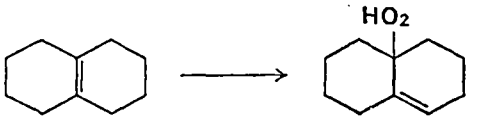
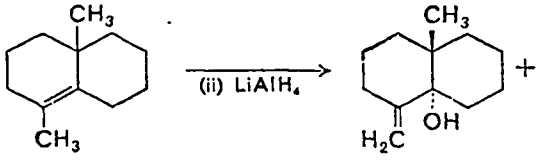
$${}^{\cdot}\text{SensOO}^{\cdot} + \text{A} \longrightarrow \text{AO}_2 + \text{Sens} \qquad (40a)$$

$$^3\text{Sens} + {}^3O_2 \longrightarrow \text{Sens} + {}^1O_2 \qquad (39b)$$

$$^1O_2 + \text{A} \longrightarrow \text{AO}_2 \qquad (40b)$$

Whereas path b was not previously favoured, the recent demonstrations of similarities in oxidations with independently generated singlet oxygen and dye-photosensitized autoxidation have now made path b more probable. Foote and co-workers[101] find that the product distributions are indistinguishable in the oxidation of three olefins both by the Rose Bengal-photosensitized reaction and with singlet oxygen from hydrogen peroxide–hypochlorite mixtures. Further evidence for the intermediacy of singlet oxygen was gained by Kopecky and

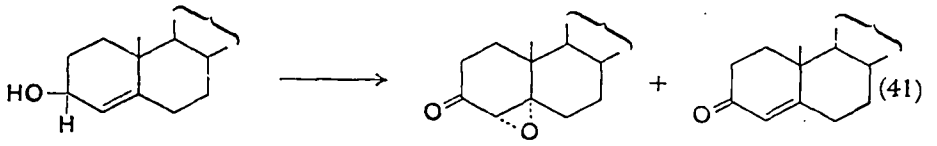
TABLE 1. Oxidations by singlet oxygen

Reaction	Method*	Reference
	a b	91, 98 92
	d	94
	a d e	99 94 99
	a	91, 98, 99
	a c	91, 98 93
	a b c	91, 98 92 93
	a	98
	a	100

* *Methods:* a, H_2O_2–NaOCl/NaOBr. b, Triphenyl phosphite–ozone adduct. c, 9,10-Diphenylanthracene *endo*-peroxide. d, Radio-frequency discharge on oxygen. e, Alkaline peracid.

Reich[102] who compared the reactivity sequences of a number of olefins towards established radical and electrophilic reagents with that for Methylene Blue-photosensitized oxidation. The results indicated that the reactive intermediate in the photosensitized oxidation is electrophilic, i.e., singlet oxygen. It was also shown, to the same end, that the relative rates of the photosensitized oxidation of pairs of olefins do not vary significantly with different sensitizers, indicating a common intermediate which could not include the sensitizer[102, 103]. Singlet oxygen is probably involved in, e.g., the dye-photosensitized oxidation of tetra-*O*-methylpurpurogallin[104], of caryophyllenes[105, 106], and of diacetylfilicinic acid[107].

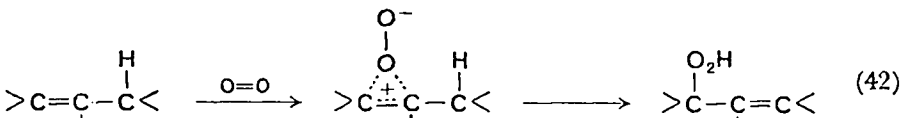
The dye-sensitized photoxygenation of cholest-4-en-3β-ol (**32**) is particularly interesting as two products, an epoxy ketone (**33**) and an enone (**34**) are formed in proportions varying from 30 : 1 to 1 : 5 depending upon the sensitizer present:



(**32**) (**33**) (**34**)

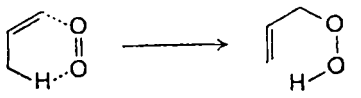
A correlation is reported between these product ratios and the energies of quenching the excited triplet state of the sensitizers by molecular oxygen[108, 109]. The product ratio **34**:**33** increases with increasing energy of the triplet state sensitizer, and this has been interpreted as due to the greater proportion of $^1\Sigma g^+$ oxygen formed in comparison with $^1\Delta g$ oxygen. The species $^1\Sigma g^+$ oxygen in effecting **32** → **34** has, therefore, a different chemical activity from $^1\Delta g$ oxygen which effects **32** → **33** [108, 109]. This suggestion may find an explanation in the observation that $^1\Sigma g^+$ has two antiparallel electrons in separate orbitals and possibly resembles the triplet ground state ($^3\Sigma g^-$) in its chemical properties[98]. The reaction **32** → **34** could proceed via homolytic removal of allylic hydrogen.

The mechanism of oxygenation of monoolefins by singlet oxygen from any source is not yet agreed. Sharp has suggested that an intermediate per-epoxide is formed which rearranges with a synchronized proton shift to yield an allylic peroxide[110]:



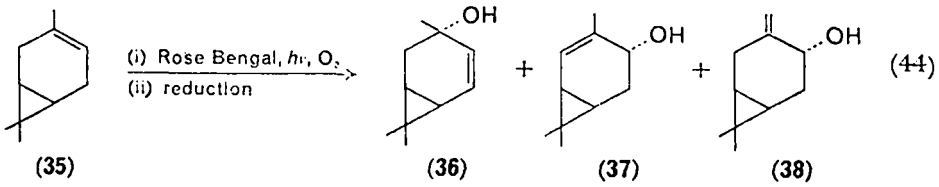
(42)

whereas Nickon and Bagli have suggested a cyclic process without commitment to timing of bond breaking and making[111]:



(43)

The formation of epoxy ketones from cyclohexenoid systems is stereospecifically *cis* in that the C–H bond cleaved and the C–O bond formed have a *cis* relationship (e.g. **32** → **33**). Hydroperoxides may be intermediates in the formation of these epoxy ketones[112]. Investigations with cyclic and semicyclic olefins have shown that the dye-photosensitized oxygenations are highly sterically controlled[113–116]. For example, the allylic peroxidation of (+)-3-carene (**35**) followed by reduction led to three optically active alcohols, namely, (−)-2-caren-*trans*-4-ol (**36**), (+)-4-caren-*trans*-3-ol, (**37**), and (−)-4(10)-caren-*trans*-3-ol (**38**) in the ratio ca 2:1:1 respectively; no *cis* allyl alcohols were found:



(35) (36) (37) (38) (44)

As had been previously observed with α-pinene, the oxygen molecule attacked that side of the olefin which was free from the steric screening effect of the isopropylidene group[113]. There is a marked dependence of rate of Methylene Blue-photosensitized oxygenation on the structure of the olefin, e.g., 2,3-dimethyl-2-butene is oxidized 5500 times faster than cyclohexene[102], suggesting considerable carbonium ion character in the transition state. This latter point is in greater accord with Sharp's proposal than a concerted form of Nickon and Bagli's. Stepwise making and breaking of bonds in the cyclic mechanism would differ essentially from Sharp's mechanism only in the molecularity of the proton transfer. Wagner–Meerwein rearrangements accompanying allylic oxidation by singlet oxygen have not been reported.

The 1,4-cycloaddition reactions of conjugated dienes with molecular oxygen to yield peroxides have been comprehensively re-

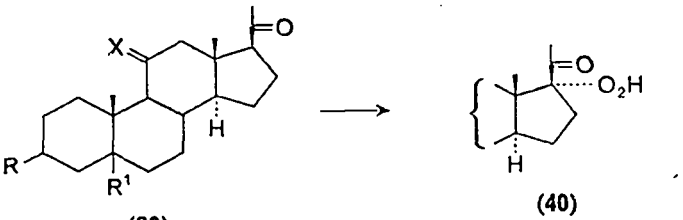
viewed[117]. These reactions, involving oxygen as dienophile, generally have to be performed photochemically. The dye-photosensitized peroxidation may now be interpreted in terms of singlet oxygen species thus becoming mechanistically equivalent to the thermal formation of Diels–Alder adducts in carbocycloaddition. Like the Diels–Alder reactions, the dye-photosensitized formation of *endo*-peroxides is reversible and mention has already been made of the use of 9,10-diphenylanthracene *endo*-peroxide to effect oxidation through the agency of singlet oxygen[93]. The reversion of *endo*-peroxide to hydrocarbon and oxygen is frequently accompanied by luminescence whose spectrum is often similar to that of the fluorescence of the hydrocarbon. It is possible that the origin of this radiation is the return of singlet oxygen to the triplet state[96].

The use of chemically generated singlet oxygen in organic synthesis is at present restricted because of the wastage of reagents due to unconsumed singlet oxygen, particularly with the less reactive oxygen acceptors. Likewise with dye-photosensitized oxidations, long reaction periods are often required. In connexion with the latter observation, Forbes and Griffiths report that the solvent system carbon disulphide, methanol (or ethanol) and ether (ca 14:1:1·5 v/v) produces comparable or better yields in a shorter time than the single solvents methanol or isopropanol, or a mixture of methylene chloride and benzene[118]. The role they ascribe to carbon disulphide is that of an efficient promoter of singlet-triplet intersystem crossing thus leading to a higher concentration of triplet sensitizer.

B. The Autoxidation of Carbanions

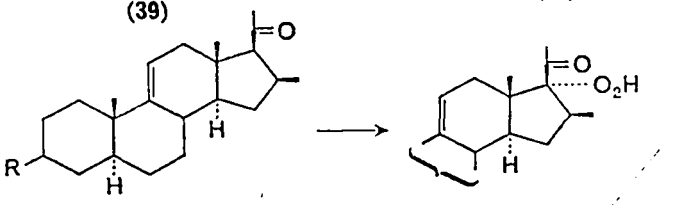
The enol forms of ketones react readily with oxygen in many solvents to give α-hydroperoxy ketones which may frequently be isolated. Keto forms are much less active and the conditions required to oxygenate these are usually sufficiently drastic to cleave the carbon skeleton of the products[119]. Although α-hydroperoxy ketones may be decomposed by base, the autoxidation of αβ-unsaturated ketones of the cyperone series to their γ-hydroxy derivatives and certain rotenone derivatives to the α-ketols in the presence of aqueous base have been accomplished[119]. Barton and co-workers[119, 120] have found that even in the presence of a strong base, namely reaction with oxygen in a *t*-butanol solution containing potassium *t*-butoxide, many steroidal 20-ketones (**39** and **41**) without a substituent at 17 or 21 are converted into reasonable yields of the 17α-hydroperoxides

(**40** and **42**) which may be reduced in good yield to 17α-alcohols. Some examples follow:



(45)

(**39**) (**40**)

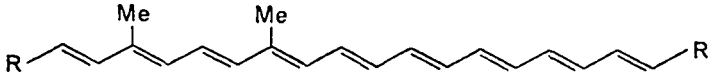


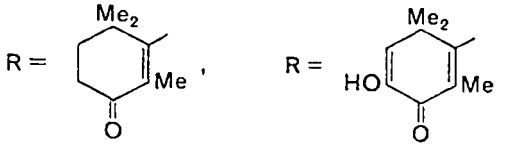
(46)

(**41**) (**42**)

R = α/β OAc, OH; R′ = α/β H; X = H_2, O.

This method has been used to convert canthaxanthin (**43**) into the corresponding bisdiosphenol, astacene (**44**) [121], and in the elucidation of the structure of limonin[122]. Both examples involve the conversion of a cyclic ketone into an enolized α-diketone probably via the hydroperoxide.





(**43**) (**44**)

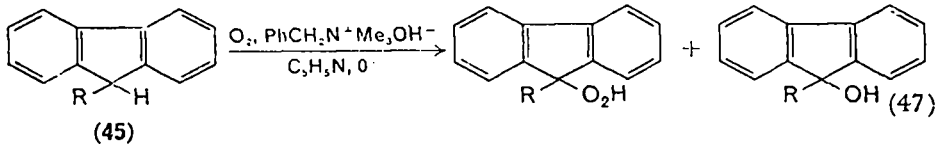
Alkoxides are stronger bases in aprotic solvents, and autoxidations in the presence of potassium *t*-butoxide in an ethylene glycol–dimethyl ether solution of structurally simpler ketones and esters rapidly give high yields of α-hydroperoxides at low temperatures without significant degradation of the products[123]. Similar results with esters of diaryl- and (arylalkyl)aryl-acetic acids have been achieved with benzyltrimethylammonium hydroxide in pyridine solution[124].

The function of the base in all these autoxidations has a ready explanation, since it is the carbanion derived from the substrate which is the active entity and attacked by molecular oxygen.

Certain solvents, e.g., dimethyl sulphoxide (DMSO), markedly increase the basicity of potassium *t*-butoxide[125, 126], and it has been possible to autoxidize normally unreactive hydrocarbons via their carbanions in these systems. DMSO has a pK_a of ca 31 [127, 128], and it is itself susceptible to autoxidation to form dimethyl sulphone or methanesulphonic acid[129], or it may appear in the product via a carbanion reaction, consequently the solvent is usually diluted with *t*-butanol. This mixed solvent does not effectively ionize the weaker hydrocarbon acids and has led to the introduction of the more effective and less oxidizable diphenyl sulphoxide[130] and hexamethylphosphoramide (HMPA)[131]. The latter solvent is particularly unreactive towards base, as shown by the absence of detectable base-catalysed proton exchange, and towards oxygen[131]. It has been possible to autoxidize the weakly acidic toluene and related compounds through their carbanions in this solvent to the corresponding carboxylic acids with moderate yields[131].

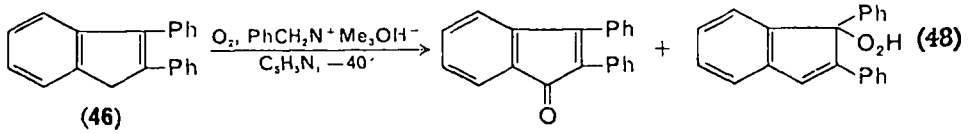
The synthetic utility of the autoxidation of hydrocarbon anions in these systems to hydroperoxides or alcohols has not yet been exploited even to the limited extent of that of carbonyl compounds. There are several reports of hydrocarbon autoxidations, e.g., of xanthene[129], diphenylmethane[130], alkylated benzenes, *p*-cymene, tetralin[131], fluorene[129, 132], picolines[133], 9,10-dihydroanthracene[129, 134] and 1- and 3-arylpropenes[134], but in these cases the products isolated are mainly carboxylic acids or ketones although the reactions presumably proceed via the hydroperoxides. Limitations to applications in the synthesis of alcohols include acidity of the hydrocarbon, further oxidation of initial carbinol products, and the known facile base-catalysed dehydration of primary and secondary hydroperoxides to carbonyl compounds[135]. Hydrocarbon anion autoxidations in which hydroperoxides and alcohols are among the products are few and include those of 9-alkylfluorenes (**45**), 2,3-diphenylindene (**46**) [132], triphenylmethane (**47**), diphenylmethane (**48**) [129, 136, 137] and fulvenes (**49** and **50**) [138].

The mechanisms of carbanion autoxidations have received considerable attention particularly by G. A. Russell and co-workers[136]. Kinetic measurements show that the formation of the carbanion is the rate-determining stage in the oxidation of certain triarylmethane types[139]. These oxidations are independent of oxygen pressure above



(45)

R = Me, Et, Bu, Ph, $PhCH_2$, $CH_3C_6H_4CH_2$, $CH_3OC_6H_4CH_2$



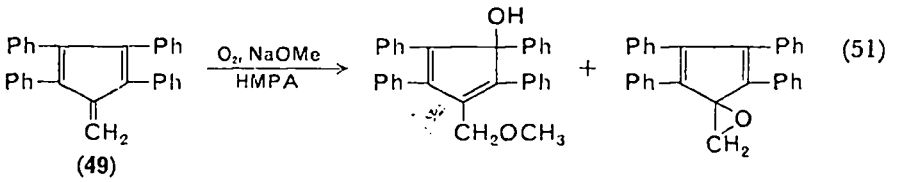
(46)

$$Ph_3CH \xrightarrow[DMSO,\ t\text{-BuOH},\ 25^\circ]{O_2,\ t\text{-BuOK}} Ph_3COH\ (+\ DMSO_2) \qquad (49)$$

(47)

$$Ph_2CH_2 \xrightarrow[DMSO,\ t\text{-BuOH},\ 25^\circ]{O_2,\ t\text{-BuOK}} Ph_2CHOH\ +\ \text{other products} \qquad (50)$$

(48)



(49)

(50)

a minimum value and have large kinetic isotope effects. In addition, agents capable of electron transfer such as aromatic nitro compounds which should catalyse radical chain oxidations are without effect[136]. On the other hand, the triarylmethane types which are stronger carbon acids[127, 128] e.g., tri-(*p*-nitrophenyl)methane or 9-phenylfluorene, show different behaviour. In these cases the rates of oxidation are much slower than ionization and the rate-determining stage is the reaction between carbanion and oxygen, although detailed kinetic analysis shows that the basicity of the reaction medium may also be a limiting feature[140]. Catalysis by aromatic nitro compounds has been observed. The comparative inactivity of these compounds is analogous to the inactivity of *β*-diketones, e.g., cyclohexane-1,3-dione, which form delocalized, stable carbanions which are not

autoxidized[136]. Two mechanisms are currently suggested as reaction paths for carbanion autoxidation:

$$Ar_3CH + (CH_3)_3CO^- \rightleftharpoons Ar_3C^- + (CH_3)_3COH \quad (53)$$

$$Ar_3C^- + O_2 \longrightarrow Ar_3COO^- \quad (54a)$$

$$Ar_3C^- + O_2 \longrightarrow Ar_3C^{\cdot} + O_2^{\cdot -} \quad (54b)$$

$$Ar_3C^{\cdot} + O_2 \longrightarrow Ar_3COO^{\cdot} \quad (55b)$$

$$Ar_3COO^{\cdot} + Ar_3C^- \longrightarrow Ar_3COO^- + Ar_3C^{\cdot} \quad (56b)$$

Aromatic nitro compounds would catalyse a radical chain process by reactions such as[136]:

$$R^- + ArNO_2 \longrightarrow R^{\cdot} + ArNO_2^{\cdot -} \quad (57)$$

$$ROO^{\cdot} + ArNO_2^{\cdot -} \longrightarrow ROO^- + ArNO_2 \quad (58)$$

Path b was formerly preferred for many autoxidations and appears definitely to operate in the oxidation of 2-nitropropane. Many autoxidations do not show features characteristic of radical chain reactions and so path a may operate, e.g., in the oxidation of triphenylmethane and diphenylmethane, in spite of the objection to stage (54a) that it violates the spin conservation rule[139, 141]. The mechanism of autoxidation of carbanions derived from aliphatic ketones and esters is not certain[136, 141]; the oxidation of acetophenone is catalysed by aromatic nitro compounds[136]. The stereochemistry of the hydroperoxide products of suitably chosen hydrocarbons or carbonyl compounds does not appear to have been directly investigated. The autoxidation of steroidal 20-ketones[119, 120] mentioned earlier gives mainly the 17α-hydroperoxides indicating strong steric control. Further investigations of stereochemical aspects might yield information concerning mechanisms.

Volger and Brackman[142] have studied the copper(II)–pyridine complex catalysed autoxidation of α,β- and β,γ-unsaturated aldehydes and ketones which are oxidized specifically at the γ-carbon atom to yield subsequently dicarbonyl compounds, via base-catalysed decomposition of a hydroperoxide. The role of the copper(II) complex is to oxidize the dienolate anion to a dienoxy radical susceptible to oxygenation, and the peroxy radical resulting from this is reduced to hydroperoxy anion by copper(I) complex formed in a previous step. Adaptation of this type of system to other carbanion autoxidations may lead to useful methods in organic synthesis.

C. *The Autoxidation of Metal Alkyls and Aryls*

Continuing industrial interest in the autoxidation of aluminium and boron alkyls for the production of aliphatic alcohols is considerable if the incidence of patent registrations is any guide[143].

The processes are particularly suitable for preparing higher alcohols from the long chain alkyls of these metals which are themselves readily synthesized from the addition of lower aluminium alkyls or diborane to olefins. The alkyls are autoxidized in the liquid phase (this term will be used synonymously for reactions in solution) and the resulting alkoxides hydrolysed to the corresponding alcohols. Studies of these autoxidations have revealed much information as to mechanisms but the picture is not yet completely clear. Earlier work on autoxidation has been reviewed[144] and there are several reviews on the properties of organometal and metalloid peroxides[145, 146]. The gas and liquid phase autoxidations of boron and aluminium alkyls in particular probably exemplify the range of product-types and mechanisms encountered in autoxidations of metal alkyls generally. At present the mechanisms of the autoxidations are considered to differ principally according to the physical phase of the reaction mixture[147]. However, the dichotomy may be more apparent than real and perhaps only a reflexion of the comparative lack of investigation this area has received. It is more probable that a number of factors apart from phase such as temperature, nature of metal and organic group, together determine reaction paths. It is still convenient to subdivide the material according to reaction phase for the purposes of presentation.

The gas phase autoxidations of the alkyls of boron, zinc[147], aluminium[147–149] and indium [150] in the first instance are essentially similar in that they are free radical chain reactions involving peroxidic compounds or peroxy radicals. Peroxides have been isolated in the cases of boron (Me_2BO_2Me) and indium (Et_2InO_2Et), and are suspected in the case of zinc[151] because of observed catalysis. A peroxide was not detected in the slow gas phase autoxidation of trimethylaluminium[147]. The methyl derivatives are much the least active in all cases examined and for zinc alkyls the sequence of reactivity is: *n*–Pr > Et > Me[151, 152]. The methyl compounds also consume less oxygen even when this is present in excess and the stoichiometry approximates to, e.g., with zinc:

$$ZnMe_2 + \tfrac{1}{2}O_2 \longrightarrow ZnMe_2O \qquad (59)$$

in comparison with homologues, e.g.,

$$ZnEt_2 + O_2 \longrightarrow ZnEt_2O_2{}^{151} \qquad (60)$$

The eventual solid products in all cases are the metal alkoxides. The autoxidation of triethylindium produces considerable amounts of the

hydrocarbons ethane and ethylene and the oxygenated products ethyl alcohol, diethyl ether and acetaldehyde[150]. In this latter respect it differs from other gas phase autoxidations reported in which only hydrogen and/or hydrocarbons are found, e.g., trimethylaluminium yields hydrogen (trace) and methane[147], dimethylzinc yields methane and ethane, and diethylzinc yields ethane and butane[151].

The complex kinetic features of gas phase metal alkyl autoxidation strongly suggest that the peroxy intermediates are formed by a free radical chain mechanism, and the dependence of the reaction rate on the nature and extent of the vessel surface also indicates the importance of heterogeneous steps[147, 150–152]. In addition, there is further support for homolytic mechanisms from two other sources. First, the autoxidation of metal alkyls induces the oxidation of hydrocarbons at low temperatures, and secondly, metal alkyl–oxygen mixtures induce the polymerization of olefins. In both cases, the reactions effected are considered to be initiated by radicals arising in the autoxidation of the metal alkyl[149, 153–155]. The polymerization reactions were carried out in the liquid phase. The mechanisms proposed to account for autoxidations differ in detail depending on the particular metal and organic group present. For example, the following scheme which has been suggested for the initiation and propagation stages of the slow autoxidation of trimethylaluminium involves a peroxy radical rather than a peroxidic compound[147]:

initiation: $Al_2Me_6 + O_2 \longrightarrow Me_2AlOO^{\bullet} + Me_2Al^{\bullet} + 2Me^{\bullet}$ (61)

propagation: $Me_2Al^{\bullet} + O_2 \longrightarrow Me_2AlOO^{\bullet}$ (62)

$Me_2AlOO^{\bullet} + Al_2Me_6 \longrightarrow 2Me_2AlOMe + Me_2Al^{\bullet}$ (63)

The production of methyl radicals in the initiation stage is able to account for the quantity (ca 18%) of methane accompanying autoxidation. By contrast, the autoxidation of the less electron deficient triethylindium and possibly boron alkyls may proceed according to the scheme[150]:

initiation: $Et_3In + O_2 \longrightarrow Et_2In^{\bullet} + EtOO^{\bullet}$ (64)

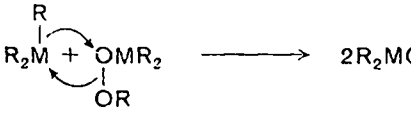
propagation: $Et_2In^{\bullet} + O_2 \longrightarrow Et_2InOO^{\bullet}$ (65)

$Et_2InOO^{\bullet} + Et_3In \longrightarrow Et_2InOOEt + Et_2In^{\bullet}$ (66)

An important feature here is the proposed formation of the intermediate peroxide, $Et_2InOOEt$. This may yield the predominant product of alkoxide by a nonsurface-catalysed, nucleophilic

migration of alkyl or alkoxyl group either intra- (equation 67) or intermolecularly (equation 68)[150]:

(67)



(68)

Some of the additional oxygenated products must arise from the homolytic decomposition of peroxides[150, 156, 157], thus diethyl ether from the process:

$$Et_2InOOEt \longrightarrow Et_2InO^{\cdot} + EtO^{\cdot} \quad (69)$$

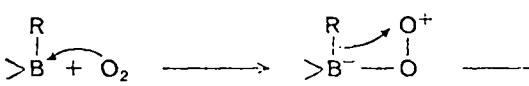
$$EtO^{\cdot} + Et_3In \longrightarrow Et_2O + Et_2In^{\cdot} \quad (70)$$

and ethanol from:

$$EtO^{\cdot} + Et_3In \longrightarrow EtOH + Et_2InCHCH_3 \quad (71)$$

The origin of the hydrocarbon products occurring in the gas phase autoxidation of other metal alkyls can also be rationalized as a consequence of the homolytic decomposition of peroxide or homolytic steps preceding this.

The chief apparent difference between the mechanisms of autoxidation of metal alkyls in the gas and liquid phases is in the universal formation of an intermediate peroxide in the case of the latter and in the manner of its formation. That this species is undoubtedly involved is attested by the numbers of different examples isolated and characterized (e.g., References 144, 157–160). The peroxides of organoboron compounds have been used in the synthesis of primary and secondary alkyl hydroperoxides. The procedure involves the autoxidation of trialkylboranes to the diperoxyboronates which are treated with a peracid to yield the alkyl hydroperoxide[161]. The formation of the peroxide is generally considered to involve coordination of the oxygen molecule with the metal followed or accompanied by a nucleophilic 1,3-migration of alkyl to electron-deficient oxygen, e.g., with boron[157]:



(72)

Recently, evidence has been reported in support of the reversible formation of a coordination-polymeric species of oxygen with boron trimethyl at 77°K [162]. In common with the heterolytic autoxidation of carbanions is the requirement for oxygen to change its spin state and preliminary coordination of oxygen to metal may achieve this. The effect of the nature of the organic radical upon the reactivity of the organometal compound towards autoxidation has been investigated most completely in the case of boron where the following sequence of reactivity is observed: alkyl > aryl, vinyl; tertiary alkyl > secondary alkyl > primary alkyl > methyl[157]. This is not the order known for nucleophilic 1,2-migrations to electron-deficient carbon termini but resembles that for the Baeyer–Villiger oxidation[13] and the oxidative dealkylation of trialkylboranes with hydroperoxides[157]. The latter reaction is part of the useful synthetic route which effects anti-Markownikoff hydration of olefins via hydroboration. These oxidations have features in common with the mechanism (equation 72) suggested for the formation of a peroxide in the liquid phase. Both have nucleophilic addition as the first stage followed by a nucleophilic migration of alkyl to electron-deficient oxygen, e.g., the oxidation of a tributylborane[163]:

$$i\text{-Bu}_2\text{BBu-}t + \text{HO}_2\text{H} \longrightarrow \left[i\text{-Bu}_2\text{B}(t\text{-Bu})\text{—O—OH} \right] \longrightarrow i\text{-Bu}_2\text{BOBu-}t + \text{OH}^- \quad (73)$$

At temperatures below about 80° the unimolecular homolysis of peroxides to alkoxy radicals is slow and under these conditions there is general agreement that alkoxides result from the intra- or intermolecular, nucleophilic rearrangements of alkyl and alkoxy groups in the manner of equations (67) and (68). The molecularity of this stage has been the object of some investigation and, e.g., in the case of trialkylboranes[164], is claimed to be intermolecular.

The overall picture, therefore, of the mechanism of autoxidation of metal alkyls in the liquid phase is that essentially heterolytic processes yield alkoxides. However there is evidence to suggest that this view is not representative of all liquid phase autoxidations under all conditions and is merely an extreme type or one of several reaction types occurring concurrently with homolytic routes. It has already been mentioned that metal alkyl–oxygen mixtures induce the liquid phase polymerization of olefins. The best known case is that of the polymerization of vinyl monomers with trialkylborane–oxygen mixtures[153–155, 165]. The presence of both oxygen and trialkylborane is essential and the derived peroxide initiates the polymerization at

low temperatures only if the trialkylborane is also present. It is clear that the peroxide does not initiate polymerization via unimolecular homolysis to alkoxy radicals. The origin of the free radicals in these systems is not yet known but the following suggestions have been made:

(i) decomposition of peroxide by excess of boron alkyl[155]:

$$R_3B + R_2BOOR \longrightarrow R_3B + R_2BO^{\cdot} + RO^{\cdot} \qquad (74)$$

(ii) decomposition of peroxide by a complex of monomer (M) and boron alkyl[165]:

$$R_3BM + R_2BOOR \longrightarrow R_3BMRO^{\cdot} + R_2BO^{\cdot} \qquad (75)$$

(iii) a cage reaction following coordination of peroxidic oxygen to boron alkyl[166]:

$$\rangle BR + EtOOB\langle \longrightarrow \rangle BOEt + R^{\cdot} + \rangle BO^{\cdot} \qquad (76)$$

It is also a possibility that radicals may arise from stages preceding and otherwise leading to the formation of the peroxide.

Other evidence for homolytic reactions comes from careful analysis of all reaction products formed in metal alkyl autoxidations. Tri-*n*-butylborane on autoxidation gives considerable quantities of the hydrocarbons butene, butane and *n*-octane, and lesser quantities of oxygenated products, e.g., *n*-butyraldehyde, di-*n*-butyl ether, and 4-octanone. These were all considered to be the consequence of radicals resulting from the homolytic decomposition of peroxide[156]:

$$\rangle BO_2R \longrightarrow \rangle BO_2^{\cdot} + R^{\cdot} \quad \text{and/or} \quad \rangle BO^{\cdot} + RO^{\cdot} \qquad (77)$$

The autoxidation of triethylaluminium in *n*-heptane gives as by-products hydrogen, ethylene and ethane[167, 168] and these are comparable with the by-products obtained from the gas phase autoxidation of trimethylaluminium[147]. The autoxidation of Grignard reagents appears to proceed along the lines of those of metal alkyls and it is of interest here that products formed from aromatic[160] and aliphatic[169] examples may be accounted for in terms of radical processes. An additional point of interest is that the autoxidation of aromatic Grignard reagents and of alkali metal aryls is accompanied by chemiluminescence but whether this originates in a mechanism of peroxide decomposition or electron transfer is not known[96, 170]. The latter compounds are autoxidized to several products including phenols and biphenyl but the yields are generally small[144, 171].

Other evidence suggesting the generation of free radicals derived from the organometal compound during liquid phase autoxidation comes from reactions carried out in solvents which are active towards

radicals. Triphenylaluminium on autoxidation (80°) in ^{14}C-labelled benzene yields after hydrolysis of the reaction product mainly biphenyl and phenol both of which are partially ^{14}C-labelled. Phenyl radicals do not exchange between benzene and triphenylaluminium in the absence of oxygen at 80°, and the results may be interpreted in terms of radical processes[172]. Similar results were obtained from the autoxidation (room temperature) of diphenylzinc and diphenylmagnesium except that the phenol was formed entirely from the organometal compound. The use of D- or ^{14}C-labelled benzene showed that the solvent partly participated in the formation of biphenyl and part of the phenyl groups of the organometal compound were converted into benzene[173].

The autoxidation of cadmium dialkyls in a variety of solvents proceeds readily to the peroxides which may be isolated[174]. The autoxidation of diphenylcadmium possibly follows a similar route but, in solvents capable of chain transfer, products are formed which are best regarded as resulting from attack of phenyl radicals on those solvents. For example, when diphenylcadmium is autoxidized in carbon tetrachloride (room temperature) the hydrolysed products contain chlorobenzene, phenol, biphenyl, benzotrichloride and hexachloroethane[175]. The results of autoxidation carried out in chloroform, deuterochloroform and ^{14}C-labelled benzene substantiate the occurrence of homolytic processes. The oxidation of several mercury alkyls in organic solvents (50—60°) gives reaction products which contain mercury, alkoxyalkylmercury, alkylmercury hydroxide, products of the oxidation of the alkyl group of the original organomercury compound (the corresponding aldehydes and ketones), unsaturated and saturated hydrocarbons formed from the alkyl group of the mercury compound, and products of the oxidation of the solvent. When halohydrocarbons were used as solvent, products of the interaction of the solvent with the mercury compound were also formed. It was also observed that the ease of oxidation of the mercury alkyls increased with increasing nucleophilicity of the organic group[176]. The overall results were interpreted in terms of intermediate peroxide and homolytic processes; these will be mentioned later.

The majority of reported investigations of the autoxidation of metal alkyls and aryls have been directed towards establishing stoichiometries, the identities of intermediates and products, the influence of solvents and organic group, etc. Kinetic studies in the liquid phase are comparatively few in number and thus the reported

investigation of the kinetics of the autoxidation of diisopropylmercury at 70° in *n*-nonane solution[177] is of interest. A variety of products are formed and these are mainly isopropylmercury isopropylate (greatest proportion), mercury, isopropylmercury hydroxide, acetone and isopropanol, and probably oxidation products of the solvent. The reaction is autocatalytic and displays the characteristics of a free radical chain process; e.g., it is almost completely suppressed by the addition of small quantities of the inhibitor *p*-hydroxydiphenylamine. The average chain length of the process is 160. The initiation of the oxidation in the early stages is probably due to reaction (78) and to a much lesser extent reaction (79):

$$R_2Hg + O_2 \longrightarrow [RHgOOR] \xrightarrow{R_2Hg} 2\,RHgOR \qquad (78)$$

$$[RHgOOR] \longrightarrow RHg^{\bullet} + RO_2^{\bullet}$$

$$R_2Hg \longrightarrow RHg^{\bullet} + R^{\bullet} \qquad (79)$$

Later on, as the quantity of isopropylmercury isopropylate accumulates then this compound becomes on thermal decomposition the major source of radicals (equation 80) which can account for both the autocatalytic rate curve and the nature of most of the products:

$$RHgOR \longrightarrow RHg^{\bullet} + RO^{\bullet} \qquad (80)$$

The mechanism of the autoxidation, therefore, involves a combination of concurrent and consecutive reactions of homolytic type with the formation and decomposition of isopropylmercury isopropylate playing a key role[177].

The picture which emerges with regard to the mechanisms operating in the thermal autoxidation of metal alkyls and aryls is unequivocal in only a few parts. Whereas the gas phase autoxidations generally on the one hand and the liquid phase oxidation of diisopropylmercury on the other appear to involve free radical chain reactions, evidence for homolytic processes in other liquid phase oxidations is absent, incomplete or circumstantial. For example, the series of investigations on the participation of the solvent during autoxidations of various metal aryls[168, 172, 173, 175] whilst strongly indicating homolytic processes is not able to identify the origin or mode of formation of the initiating species.

Of relevance to the subject of autoxidation of metal alkyls and aryls is the preliminary report of a homolytic mechanism in the autoxidation of optically active 1-phenylethaneboronic acid to the

racemic peroxide, in benzene solution at room temperature[178]. The stereochemistry of this reaction is in contrast to the similar reaction with the oxidants hydrogen peroxide and trimethylamine oxide where retention of configuration is observed[179]. The rate of the reaction was affected only slightly by weak inhibitors but copper(II) *NN*-dibutyldithiocarbamate and galvinoxyl caused induction periods of about one and four half-lives respectively. The following propagation steps were suggested for a free radical chain process[178]:

$$R^{\bullet} + O_2 \longrightarrow RO_2^{\bullet}$$

$$RO_2^{\bullet} + >BR \longrightarrow \left[RO_2^{\bullet}\overset{|}{B}R \longleftrightarrow RO_2\overset{|}{B}{}^{\bullet}R \text{ etc.} \right] \longrightarrow RO_2B< + R^{\bullet} \quad (81)$$

Inhibition of autoxidation in other organoboron derivatives was also observed with the efficient radical scavenger, galvinoxyl[180].

It is perhaps to be expected that the homolytic mechanisms for the thermal autoxidation of metal alkyls resemble those suggested for photoinitiated autoxidation. There have been very few studies reported of the latter reactions but, e.g., the photoinitiated oxidation of tetraethyl-lead and tin involves the formation of a peroxide which decomposes by routes (82) and (83)[181]:

$$Et_3PbOOEt \xrightarrow{Et_4Pb} 2\,Et_3PbOEt \quad (82)$$

$$Et_3PbOOEt \longrightarrow Et_3PbO^{\bullet} + EtO^{\bullet} \quad (83)$$

IV. INTRODUCTION: REDUCTION

Since certain of the processes and reagents which reduce oxygenated compounds to alcohols have been the subject of a previous volume in this series[182] and others have been reviewed elsewhere, these topics will be mentioned only briefly.

The photoreduction of ketones to alcohols involving inter- or intra-molecular transfer of hydrogen atom[183, 184] has not found much use in synthesis although the mechanistic aspects of the reactions have been well investigated. Many ketones are reduced to the corresponding pinacol in the presence of a hydrogen atom donor such as an alcohol, hydrocarbon[184] or amine[185, 186]. Even those ketones which have an excited state with the π,π^* configuration may reduce to pinacol in the presence of an efficient hydrogen atom

source such as organometal hydrides. Photoreductions under basic conditions pursue a different course and in many cases lead to high yields of monomeric alcohol. These reductions appear to have been little investigated recently. The mechanisms and other aspects of photoreduction have been summarized elsewhere[184]; the characterization of an intermediate in the photoreduction of benzophenone is claimed[187].

The electroreduction of ketones was reviewed in an earlier volume[182] and comparatively few reports have appeared since. Diimide generated from potassium azodicarboxylate has been used to reduce aromatic aldehydes to the corresponding alcohols in good yields[188]. Chromium(II) acetate is able to reduce α,β-epoxyketones to β-hydroxyketones under controlled conditions[189].

V. REAGENTS AND PROCESSES WHICH REDUCE OXYGENATED COMPOUNDS TO ALCOHOLS

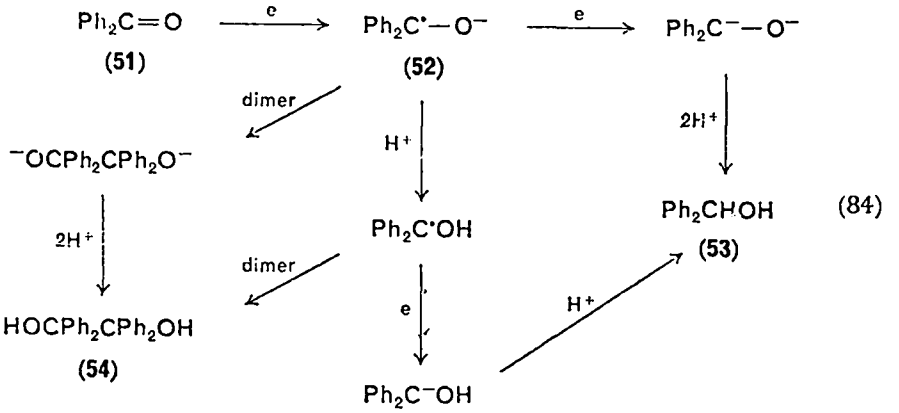
A. Metals

Metals effect the reduction or reductive fission of a wide variety of unsaturated and saturated, organic and organometallic compounds. The metals in common use for these purposes are lithium, sodium, potassium, calcium, magnesium, iron and tin. They are utilized in a variety of procedures including suspension in an inert solvent, or, particularly for the alkali metals and calcium, as a solution in liquid ammonia (the Birch reduction[182, 190–195]), or as a dissolving metal such as zinc amalgam in an aqueous solution of an acid (the Clemmensen reduction [182, 193, 196]) or sodium metal in an alcohol (the Bouveault–Blanc reduction). The first two methods require a proton source which may be incorporated into the reaction mixture or introduced during the recovery of products.

The Birch reduction is considered superior to the Bouveault–Blanc method and has found considerable synthetic use. Ketones, esters and epoxides are reduced to alcohols but the method has largely been superseded in these particular cases by reduction with metal hydrides. Aldehydes may undergo ammonolysis rather than reduction, aliphatic and alicyclic acetals and ketals are inert and this feature may be used to protect a particular carbonyl group from reduction[192]. Dialkyl ethers are also stable but aralkyl and diaryl ethers are cleaved to phenols[192].

The type of mechanism operating in the Birch reduction and associated reactions involving reduction by metals in various sol-

vents, was first stated in the currently accepted form by Michaelis and Schubert[197]. The structure of the blue solutions which alkali and alkaline earth metals form when dissolved in ammonia and other solvents is not yet clear but it is possible that the active reducing species is the solvated electron[198, 199]. A nonenolizable ketone such as benzophenone (**51**) forms first a radical anion or ketyl (**52**). This species has several alternative reaction paths open to it, many of which are reversible[192], but the overall result for practical purposes is the eventual formation of the monomeric product benzhydrol (**53**) or the dimeric product benzopinacol (**54**):



(84)

The choice of reaction conditions in the synthetic applications of the method is in part concerned with directing the reduction to one type of product or the other. The production of high concentrations of radical anions by using magnesium[200], zinc or aluminium in the absence of a proton source encourages dimerization as also do structural features in the ketyl which render it more stable by delocalization of the additional electron. A cosolvent is frequently used with reactions in liquid ammonia in order to dissolve more of the substrate. It now appears that the choice of cosolvent may partially control the yield of dimeric product[201]. The stereochemistry of the reduction of cyclanones is frequently but by no means exclusively such as to give the more stable equatorial alcohol[202]. The proportion of components in a product consisting of epimers depends both on the structure of the ketone and on the metal used for the reduction. α-Substituted ketones may suffer the loss of this substituent from the ketyl if it is a good leaving group and this is commonly observed with α-halo, α-acyloxy and α-hydroxy ketones. Enolizable ketones require

the presence of a proton source, such as an alcohol, in the reaction mixture to carry the reaction forward which may otherwise remain at the stage of a stable enolate anion. Other details concerning the reduction of carbonyl compounds may be found in References 182 and 190—194.

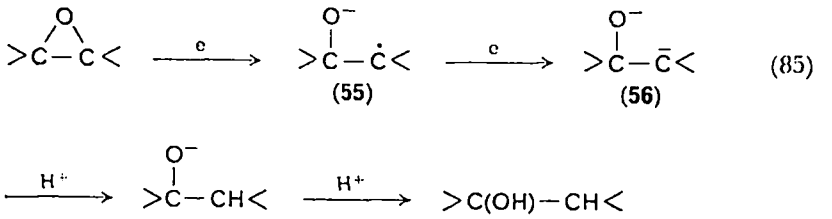
There are few examples of the reduction of carbonyl compounds with metal–alkali combinations. It is noteworthy that a nickel–aluminium alloy added to an aqueous or aqueous-ethanolic solution of sodium hydroxide reduces aliphatic and aromatic aldehydes and ketones to carbinols[203], and that aromatic aldehydes and ketones are reduced by zinc and alkali to hydrobenzoins and pinacols, respectively[204].

The synthetic applications of reductions by metals continue to be explored and the following illustrations have been selected from recent communications. The method has been adapted to the synthesis of diethylenic glycols by the reductive dimerization of α,β-unsaturated carbonyl compounds with zinc or magnesium and acetic acid[205, 206]. The reaction of magnesium in tetrahydrofuran with γ- and δ-halogenated ketones leads to cyclanols[207]. Depending on whether magnesium or lithium is used, ε-diketones are reduced to linear ε-glycols or 1,2-disubstituted *cis*-cyclohexane-1,2-diols and other products[208]. The reduction of α-furyl ketones with several metals gave pinacols and some rearranged products[209], and the sodium reduction of hexamethylacetone does not lead to the pinacol but to a mixture of 3-ethyl-2,2,4,4-tetramethylpentan-3-ol and a 1,4-glycol[210]. Pinacols and unstable epimers have been prepared from A-norcholestanones by reduction with alkali metals in liquid ammonia[211].

Hexamethylphosphorotriamide dissolves alkali metals to form blue solutions of radical anions whose paramagnetic electron resonance spectra have been recorded[199, 212]. Such solutions containing also tetrahydrofuran effect the condensative reduction of a number of non-enolizable ketones to epoxides, e.g., benzophenone is converted into tetraphenylethylene oxide, benzaldehyde into *trans*-stilbene oxide, and acetophenone into *cis*- and *trans*-2,3-diphenyl-2-butene epoxide[212–214]. The active reducing agent is considered to be the species $(Me_2N)_2P{-}O$ which attacks ketonic oxygen in a homolytic mechanism but the evidence gained so far is inconclusive. Similar results have been obtained in the reduction of benzophenone with the sodium derivative of the anion $(EtO)_2P{-}O$ in a solution of HMPA and tetrahydrofuran[214].

The aromatic ketone fluorenone and several phenylpyridyl ketones have been reductively alkylated to 1,1-diarylalkanols by alkyl halides and sodium in liquid ammonia solution[215].

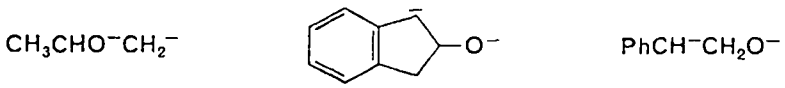
There are comparatively few reports of the reduction of epoxides to alcohols with metals. Under the Birch reduction conditions and in presence of a proton source the conversion of epoxide into alcohol might be expected to proceed:



(85)

In the cases examined no pinacol-type products have been observed, suggesting that intermediate **55** is formed in low concentration, or is short-lived, or non-existent. The latter alternative necessarily implies a synchronous two-electron transfer to the epoxide giving intermediate **56**. The reductive cleavage of optically active 2-methoxy-2-phenylbutane by potassium in alcohols as solvents has suggested a stepwise addition of two electrons and the importance of solvation on the stereochemical course of the reaction[216].

Propylene oxide is reduced under Birch conditions to propan-2-ol, and indene oxide to indan-2-ol[192, 217]; styrene oxide is reduced by sodium and water to β-phenylethyl alcohol[217]. The structures of the dianions leading to these products must be the following:

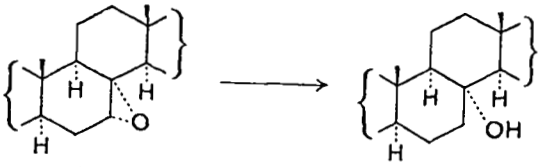


It has been noted that of the two possible dianions, that containing the more stable carbanion moiety is observed. This principle has also been used to rationalize the orientation of reductive fission of aralkyl and substituted diaryl ethers under similar conditions[190, 192].

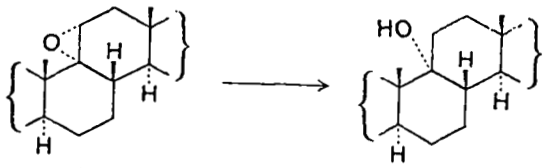
The reduction of epoxycyclohexanes of the steroid series is mainly similar to those effected by lithium aluminium hydride. The alcohols which result from the reduction of the following selection of epoxides[218–220] are shown: 5α,6α-epoxycholestane (**57**), 3β-acetoxy-7α,8α-epoxyergost-22-ene (**58**), 3β-acetoxy-9α,11α-epoxyergostane

(**59**), 3β-acetoxy-9α,11α-epoxyergosta-7,22-diene (**60**), and 3α,5α-epoxycholestane (**61**):

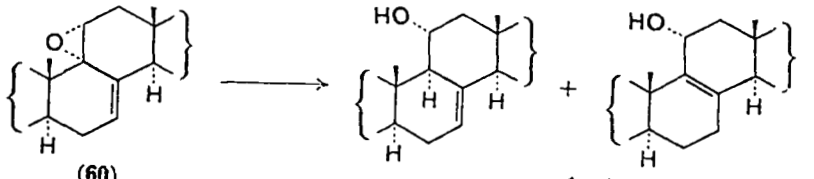
(**57**) (86)



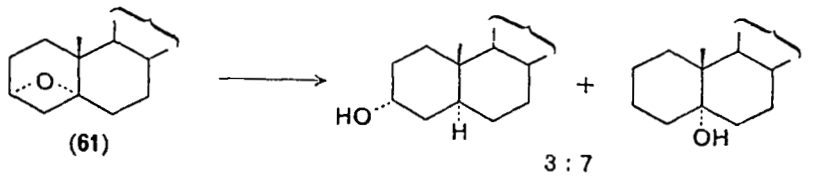
(**58**) (87)



(**59**) (88)



(**60**) ca. 1 : 1 (89)



(**61**) 3 : 7 (90)

In these illustrations the reductive fission can be interpreted as proceeding via the more stable carbanions, namely, a secondary rather than a tertiary carbanion, leading to tertiary alcohols. The secondary alcohols of equation (89) may be rationalized in terms of the intermediacy of an allylic carbanion[218]. Mainly axial alcohols result and this, like reductions with lithium aluminium hydride, is presumably a consequence of the preferred geometry for the transi-

tion state leading to nucleophilic, *trans*-diaxial opening of epoxide rings. The 7α,8α- and 9α,11α-epoxy steroids (**58** and **59** respectively) are not reduced by lithium aluminium hydride and this has led to the suggestion that solvated electrons of low steric requirement are responsible for Birch reductions[218]. Some other secondary–tertiary epoxides, e.g., 5β,6β-epoxycholestane[218], 2,3-epoxypinane[221] and α- and β-3,4-epoxycaranes[222], yield mainly or considerable proportions of secondary alcohols. This feature has also been noted with lithium aluminium hydride and ascribed to a conformational effect[223] which may also operate in the Birch reduction. The Birch reduction of α- and β-3,4-epoxycaranes gives different mixtures of alcohols from the reduction with lithium aluminium hydride[222].

B. Catalytic Hydrogenation

Catalytic hydrogenation and hydrogenolysis offer a general method for the reduction of oxygenated compounds to alcohols. Suitable combinations of metal and reaction conditions are described in several sources[224–226] for the conversion of aldehydes, ketones, epoxides, peroxides, acids and esters into alcohols, although the latter two are hydrogenated with some difficulty. Similar reagents are used to convert epoxides and peroxides into alcohols. The factors controlling the direction of ring opening accompanying hydrogenolysis of epoxides are numerous and have been noted elsewhere[227, 228]; there is little more recent work reported. Summaries of proposed mechanisms and stereochemical aspects of the hydrogenation of ketones may be found in recent publications[226, 229, 230]. The area continues to attract new investigations, e.g., the stereochemistry of the reduction of 2-acetoxy-1-tetralone and 3-acetoxy-4-chromanone by both catalytic hydrogenation and metal hydrides is reported[231]. In suitable cases the catalytic hydrogenation may be sterically controlled to effect asymmetric synthesis as, e.g., in the platinum and palladium catalysed hydrogenation of (−)-menthyl α-naphthylglyoxylate[232]. A relatively new development is the attempt to produce an asymmetric synthesis by the hydrogenation of ketones with modified Raney-nickel catalysts. The modification consists of treating the nickel with an aqueous solution of an optically active compound such as an amino acid[233], D-tartaric acid[234, 235], D-mandelic acid and (−)-ephedrine[235], which appear to be rapidly adsorbed on the nickel surface[233]. The reaction mainly studied has been the hydrogenation of ethyl acetoacetate to ethyl β-hydroxybutyrate.

The degree of conversion into optically active product depends

both on the modifying agent and reaction conditions such as acidity. For example, the hydrogenation of ethyl acetoacetate with Raney-nickel modified by an aqueous solution of (+)-1,2-dihydroxycyclohexane-1,2-dicarboxylic acid has its greatest asymmetric activity in the range pH 5—7, and falls off sharply at pH < 5. The greatest activity coincides with the region in which the acid is half ionized and it is suggested that the carboxylate ion moiety is not adsorbed by nickel and is important in sterically controlling the approach of substrate to catalyst[236]. The relationship between the chemical and stereochemical properties of the modifying reagent and the asymmetric activity of the catalyst is not yet clear but preliminary accounts have appeared[233, 237]. In the hydrogenation of ethyl acetoacetate the stereochemistry of the product resembles that of the modifying agent, e.g., D-tartaric acid produces ethyl β-hydroxybutyrate with the D-configuration. The asymmetric activity of Raney-nickel modified with D- and L-tartaric acid is similar but for the sign of optical rotation; *meso* and racemic forms are inactive. An effective asymmetric catalyst must have a modifying reagent containing at least two functional groups such as hydroxy and carboxy with a strong ability to be adsorbed or chelated to Raney-nickel, although too high a stability of the complex may impair asymmetric catalysis[233, 237]. In addition, the modifying reagent should not contain a bulky substituent on the asymmetric carbon atom, e.g., L-α-methylmalic acid is less effective than L-malic acid. Chemical modification of functional groups by, e.g., acylation or esterification, may destroy the asymmetrical activity of the modified nickel.

C. Grignard Reagents and Organometal Compounds

Where the normal addition of a Grignard reagent to a ketone is sterically hindered by structural features present in either component, then reduction to carbinol often occurs. Limited synthetic use of the method has been made despite the degree of steric control of the product offered. Reductions which lead to asymmetric synthesis have been discussed recently[238], some examples of other various types follow. Ethanol-1-*d* of partial optical purity and other alcohols with H–D asymmetry have been prepared by the reduction of appropriate carbonyl compounds with isobornyloxymagnesium-2-*d* bromide[239]. The reduction of camphor to borneol and isoborneol with isopropylmagnesium chloride, bromide and iodide produced equal proportions of the products but the chloride afforded the higher overall yield; the latter effect was also noted with cyclohexyl-

magnesium chloride. 2-Butylmagnesium chloride gave more isoborneol than did the bromide and it was also observed that the isomer ratio was not affected by higher temperatures but the total yield increased[240]. An interesting variation with possible synthetic utility is the bimolecular reduction of aromatic ketones to high yields of glycols of the type $[ArAr'C(OH)]_2$ with ethylmagnesium bromide in the presence of cobalt(II) chloride[241]. The structure of Grignard reagents has been reviewed[242] and it appears that RMgX, R_2Mg and associated species (dimers and trimers) may coexist, the degree of association depending on the type of reagent, its concentration and the solvent. The mechanism of the addition of a Grignard reagent to a ketone is not settled, the main contending suggestions all involve two portions of magnesium compound to one of carbonyl compound in the transition state[242]. This may have a bearing on the structure of the transition state for the reduction of ketones but this reaction has received little kinetic investigation. Possibly the only kinetic study is the reduction of di-*t*-butyl ketone with *t*-butylmagnesium chloride and with di-*t*-butylmagnesium in tetrahydrofuran[243]. There were some similarities in the kinetics of reduction by the two reagents but the mechanistic conclusions are not clear. Organometal compounds continue to be used for reductions in synthesis, e.g., the pyridine-*n*-butyllithium-adduct reduces 4-*t*-butylcyclohexanone and 3,3,5-trimethylcyclohexanone to mainly equatorial alcohols[244]. Epoxides are also converted into alcohols by metal alkyls and aryls and Grignard reagents[33, 245]. A recent example is the reduction of styrene oxide with several Grignard reagents and alkyls of magnesium and cadmium to alcohols of the general formulae $PhCHRCH_2OH$ and $PhCH_2CHOHR$[246].

D. Meerwein–Ponndorf–Verley and Related Reductions

Grignard reagents reduce carbonyl compounds by serving as a source of hydride ion[247] and in this respect resemble the reduction of aldehydes in the Cannizzaro and Tishchenko reactions and the reduction of aldehydes and ketones in the Meerwein–Ponndorf–Verley (MPV) reaction[182]. The kinetics of the Tishchenko reaction have received little investigation and two mechanisms are proposed. In one, the preliminary stage is the addition of the aldehydic oxygen of one molecule to the carbonyl carbon atom of a second portion of aldehyde which is coordinated with metal alkoxide, in the other, the shift of an alkoxide group within a complex of aldehyde coordinated with metal alkoxide from the metal to the carbonyl carbon; in both

suggestions this is followed by hydride transfer. A recent report concerning the kinetics of the Tishchenko conversion of acetaldehyde into ethyl acetate with aluminium isopropoxide in benzene lends support to the latter mechanism[248]. A substantial review in the Polish language of many aspects of the reaction is available[249].

The synthetic utility and other features of the MPV reduction continue to be explored and some illustrations of recent reports follow. The use of optically active MPV catalysts has not proved very successful hitherto in the synthesis of optically active alcohols[182]. However, it is now reported in preliminary form that optically active aluminium tri(2-methylbutoxide) in optically active amyl alcohol reduces methyl ethyl ketone, acetophenone and 3-methylcyclohexanone to good yields of alcohols with a high degree of optical purity[250]. Much less satisfactory results were obtained when an optically inactive reagent in an optically active solvent or an optically active reagent in an optically inactive solvent were used. Also reported are investigations into the asymmetric reductions of α-phthalimido-β-substituted propiophenones by aluminium isopropoxide in isopropanol[251] and of cyclohexanones, alkyl methyl and aralkyl ketones by isobornyloxyaluminium dichloride[252–254]. In the latter work, the optical purity of the aralkyl carbinols was much higher than that of the alkyl methyl carbinols. 1,2-Cyclohexanedione is reduced to the glycol by aluminium isopropoxide in toluene. The isomeric product is mainly *cis* but the proportion of this varies from 57 to 75% according to the relative concentrations of reactants and this is claimed to be an example of stoichiometric control of stereochemistry via several competing reaction paths[255, 256].

Formally similar reactions to the MPV reduction are effected by treating carbonyl compounds with an alcohol and an alkali[182, 257]. Potassium hydroxide in boiling ethylene glycol solution reduces benzophenone, norbornanone and certain of its derivatives to carbinols in moderate yields[258]. The reaction has received little investigation but probably involves a hydride transfer from alkoxide to the carbonyl carbon atom of the ketone. High yields of axial alcohols have been obtained by prolonged heating of an aqueous isopropanol solution of cyclohexanones containing chloroiridic acid and trimethyl phosphite. In this way, 3-*t*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone and cholestanone have been reduced to axial alcohols in 92—99% yield[259]. Acetone is formed from the isopropanol solvent; dimethyl sulphoxide may be used in place of trimethyl phosphite but the proportion of axial alcohol is reduced. The pre-

sence of a tervalent iridium species with one or more phosphorus-containing ligands is suspected to be present and compounds containing dimethyl sulphoxide coordinated to iridium were isolated.

E. Metal and Organometal Hydrides

The number of different types available and selectivity in action make the metal hydrides and related reagents the most important single group of compounds currently available for reducing oxygenated compounds. The reduction of carbonyl compounds and epoxides has received attention in previous volumes of this series[182, 245] and elsewhere[260–264]. The use of organotin hydrides for reduction[265] and the chemistry of complex aluminohydrides[266] has been described.

The essentially nucleophilic character of sodium borohydride has been demonstrated in a Hammett study of the reduction of 2-, 3- and 4-substituted fluorenones to the corresponding alcohols in isopropanol solution[267]. The reduction of a large number of organic compounds including aldehydes, ketones, acids, esters, lactones and epoxides with lithium aluminium hydride, lithium trimethoxy- and tri-*t*-butoxy-aluminohydride and aluminium hydride under nearly similar conditions has been reported[268, 269]. The alkoxyaluminohydrides are predictably less reactive and more selective than lithium aluminium hydride, e.g., the latter reagent converts norcamphor into 90% of *endo*-norborneol whereas the trimethoxyaluminohydride produces 98%; aluminium hydride produces 93% of *endo*-norborneol. In another study, aluminium hydride was considered to react via a six-centred transition state which is less product-like than in the case of lithium aluminium hydride as the former reagent gave a relative enrichment of axial alcohol in the reduction of several steroidal ketones[270]. Aluminium hydride is more selective than lithium aluminium hydride in reducing α,β-unsaturated aldehydes and esters to unsaturated alcohols[271]. Diborane is another electrophilic reagent, its reduction of hindered monocyclic ketones is similar to that of lithium aluminium hydride in producing mainly the equatorial alcohol although there is increased stereospecificity observed in the reduction of the bicyclic ketone norcamphor to *endo*-norborneol[272]. The more hindered dialkylboranes, e.g., dicyclohexylborane, produce considerably more axial alcohol than lithium aluminium hydride in the reduction of 2-methylcyclanones[272]. Similarly, 3-methylcyclohexanone and *cis*- and *trans*-dimethylcyclohexanone-3,4-dicarboxylate yield on reduction with diborane mostly the

equatorial alcohol, whereas dihydroisophorone gives mostly the axial isomer. Hindered alkoxyboranes give with dihydroisophorone more of the axial alcohol the bulkier the reducing agent[273]. The origin of the differing degrees of stereospecificity exhibited by nucleophilic and electrophilic reducing agents in their action on flexible monocyclic and rigid bicyclic ketones is not yet clear. The kinetics of the reduction of some substituted cyclohexanones by diborane have been measured and the rate is first-order in ketone and three-halves order in diborane; in the presence of high concentrations of boron trifluoride more axial isomer is produced and the rate tends to the first order in diborane[273].

Applications of hydride reagents to the synthesis of optically active alcohols is still limited but some progress is being made. The reagents (+)- and (−)-diisopinocampheylborane have been used in the asymmetric synthesis of (3*S*)(−)- and (3*R*)(+)-4-methylpentane-1-diols from carbonyl compounds[274]. Lithium aluminium hydride in the presence of (−)-quinine, (−)-menthol and others, effects some degree of asymmetric synthesis in the reduction of ketones[275, 276]. There is a correlation between the configuration of the optically active reducing agent and that of the product. Other reagents investigated are lithium aluminium hydride complexes with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[277], and 3-*O*-benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose[278, 279]. It was shown in the case of the latter reagent that the configuration of the secondary alcohol product changed from (*S*) to *R*) with increasing quantities of added ethanol[278] and the reduction of, e.g., acetophenone yields optically active alcohols of up to 70% optical purity. This reagent shows no more stereospecificity in reducing 3,3,5-trimethylcyclohexanone than do lithium aluminium hydride and sodium borohydride, and this was interpreted by postulating the participation of the flexible form of the ketone[279].

Apart from the reduction of carbon–oxygen double bonds, metal hydrides are also able to effect the hydrogenolysis of carbon–oxygen single bonds in many compounds. The reduction of epoxides to alcohols has been particularly useful. A comparison of the direction of ring opening of styrene oxide by lithium trimethoxy- and tri-*t*-butoxy-aluminohydride, lithium aluminium hydride, aluminium hydride and mixed hydride shows that the proportions of primary alcohol product are 0, 1, 4, 24 and 95—98% respectively[269]. Similar results for styrene oxide and other unsymmetrical epoxides including

those for reduction by hydridoaluminium halides have been reported[280–282]. The high proportion of primary alcohol produced by mixed hydride[283] may be explained in terms of the strong Lewis acidity of the hydridoaluminium halides present. The effect of substituents on the stereochemistry and direction of ring opening of cyclopentene[284] and cyclohexene[285] oxides by lithium aluminium hydride and mixed hydride has been reported. The mechanistic aspects of the anomalous reduction of cyclobutene oxides with lithium aluminium hydride to cyclobutanols and ring-cleaved primary alcohols have received attention[286]. The reduction of *cis*- and *trans*-2-alkoxy-3,4-epoxytetrahydropyrans by lithium aluminium hydride exclusively at the epoxide carbon atom remote from the alkoxy substituent is attributed to the polar influence of the two geminal oxygen atoms[287]. Skeletal rearrangements have been observed in the reductions with lithium aluminium hydride of terpene[288] and steroid[289] epoxides. Among other recent studies reported may be mentioned the reductive cleavage with hydrides of tetrahydropyranyl[290, 291] and furanyl[291] ethers, acetals and ketals[292], dioxolanes and dioxanes[293] and cyclic acylals[294].

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The Chemistry of The Hydroxyl Group: Part 1
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CHAPTER 5

Electrochemistry of the hydroxyl group

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I. INTRODUCTION

Electrolysis of an organic compound involves generally one or more steps in which electrons are transferred to or from the electrode—the electrochemical step(s)—and some chemical steps before and/or after the electrochemical steps. Electrode reactions may thus be divided into two main types (A and B) depending upon whether the electron transfer occurs directly between the electrode and the substrate (A) or the electron is transferred to (or from) another species which then reacts with the substrate (B).

A. Direct Electron Transfer Reactions

Reactions following the direct electron transfer mechanism may be classified according to whether the potential necessary for the electron transfer can be reached within the decomposition potentials of the medium or not. In the former case (A 1) a reaction at controlled electrode potential can occur with 100% current efficiency, in the latter (A 2) a certain part of the current is always consumed in the decomposition of the medium and the current yield depends on how well the substrate competes with the medium for the electrons.

1. The A 1 mechanism

Reactions of this type have been investigated in more detail than the others. On the basis of results obtained by some electroanalytical methods (e.g. polarography, cyclic voltammetry) meaningful predictions can be made about the optimum conditions for an electrolysis; e.g. the dependence of the electrode potential on experimental conditions and the number of electrons participating in the electrode reaction can be found. A short introduction to the use of polarography as a guide in controlled potential electrolysis together with a brief description of cells and apparatus used in such experiments was given in a previous volume of this series[1].

In the classical electrolytic reactions the current density, measured in A/dm^2, was the quantity which was controlled, possibly because it was the easiest factor to measure and keep constant. For a long time nearly all electrolytic reactions were performed with a control of the current density, although Haber[2, 3], as early as 1898, in his famous papers on the stepwise reduction of nitro compounds, realized that the potential of the working electrode was the proper quantity to control.

The differences in the two ways of controlling the electrolytic

reaction are illustrated in Figure 1. In this figure curve I depicts the connexion between the current through the cell and the potential

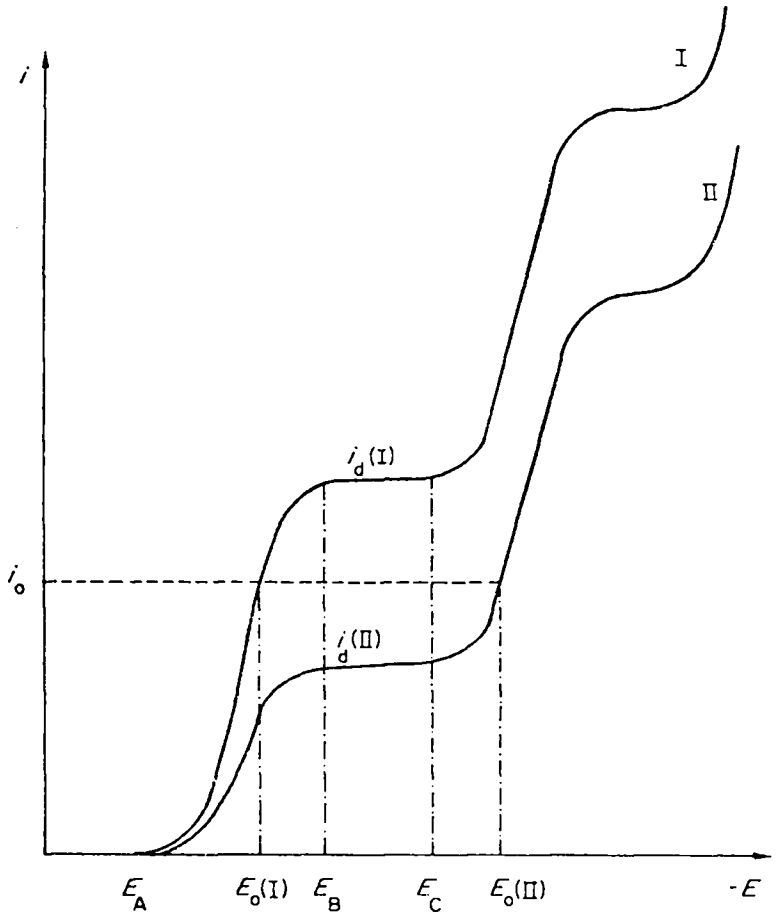


FIGURE 1. Schematic representation of the connexion between the current and the potential of the working electrode in a solution containing a compound with two groups reducible at different potentials. Curve I, before electrolysis; curve II, after the passage of some current; i_0 is an applied current, E_0(I) and E_0(II) the potentials corresponding to i_0; i_d is the limiting current, and E_A, E_B and E_C are applied potentials.

of the working electrode in the initial solution containing two reducible compounds or one compound with two groups reducible at different potentials. When the potential at the cathode is between 0 and E_A, no electron transfer across the electrical double layer can take place and thus no current runs through the cell. If the cathode

potential is made more negative, the electron transfer becomes possible, that is, the reduction of the most easily reducible compound or group starts. Between E_A and E_B the current rises in dependence on the potential, but when the value E_B has been reached, all the molecules that arrive to the electrode and which can undergo the first reduction are reduced as soon as they reach the electrode. In the potential interval E_B to E_C the current is limited by the transportation of the reducible compound to the cathode; this current is called the limiting current, i_d, and it is, under fixed conditions, proportional to the concentration of the electroactive compound.

A further lowering of the electrode potential results in the occurrence of the second electrode reaction and the current rises; a similar S-shaped curve results from this reduction. At more negative potentials a third reaction or a reduction of the medium takes place.

If a suitable current i_0 [$i_0 < i_d(I)$] is sent through the cell, the cathode potential assumes the value $E_0(I)$, and when $i_0 < i_d(I)$ this is well below the potential (E_C) where the second electrode reaction starts; a selective reduction thus occurs at the beginning of the electrolysis. During the electrolysis the concentration of the reducible compound, and thus its limiting current, diminishes and after a while (curve II) the limiting current becomes smaller than the applied current [$i_0 > i_d(II)$]. The cathode potential has then, by necessity, reached the value $E_0(II)$ and at this potential the second electrode reaction also takes place; the electrolysis is no longer selective.

On the other hand, when the electrode potential is the controlled factor and is kept at a suitable value, e.g. E_B, the second electrode process cannot take place, and the reduction remains selective to the end. The current through the cell is never higher than the limiting current corresponding to the first electrode reaction; this means that the current decreases during the reduction and becomes very small towards the end of the reaction, as the limiting current is proportional to the concentration of the electroactive material.

2. The A 2 mechanism

Many of the 'classical' electrolytic reactions occur at a potential which is either more negative (reductions) or more positive (oxidations) than the decomposition potentials of the medium. The mechanism of such reactions must be investigated in each case, but can usually be classified as one of the following three cases. (i) A direct electron transfer from electrode to substrate (A 2), (ii) A

formation of 'solvated electrons' which in turn reduce the substrate (B 1), or (iii). A formation of an active species in the electrochemical step (adsorbed hydrogen, active metals, hydrogen peroxide, hydroxyl radicals, etc.) which reacts chemically with the substrate (B 2).

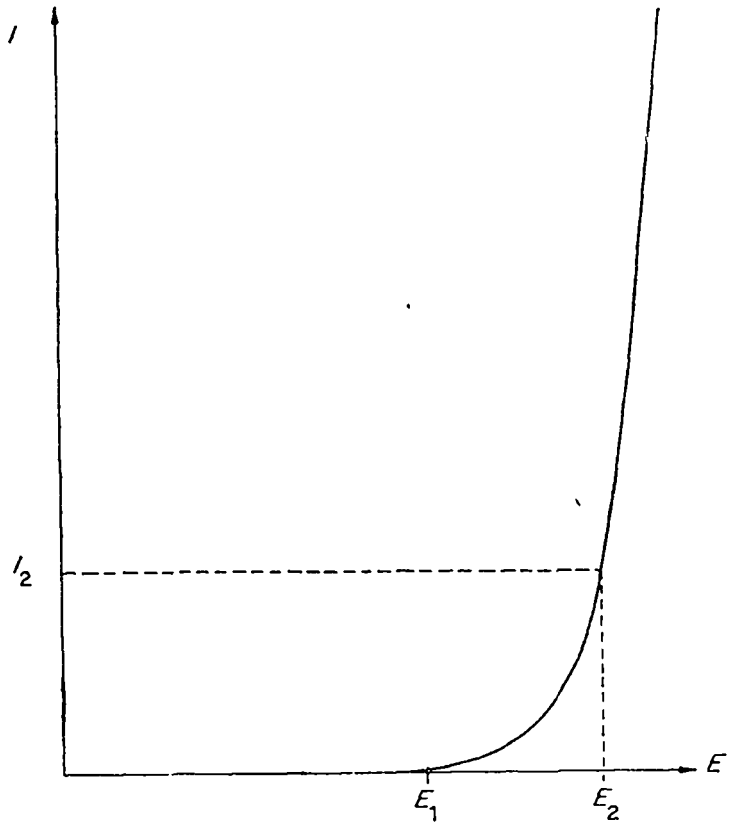


FIGURE 2. Schematic representation of the connexion between electrode potential E and the current density I in the decomposition reaction of the medium. Hydrogen (oxygen) evolution starts at E_1; if the substrate requires for the electrochemical step a potential (numerically) higher than E_2, transfer of electrons to the substrate only becomes appreciable at $I > I_2$.

In hydroxylic media the electrode reactions involve probably a direct electron transfer between electrode and substrate when the electrode material has a high overvoltage and a low catalytic effect; such reactions are not, in principle, different from those treated as A 1, only the potential necessary to bring about the electron transfer is (numerically) higher than that at which the medium is decomposed. This is illustrated in Figure 2.

In Figure 2 is shown the dependence of the current density I on the electrode potential E in an electrolysis involving the decomposition of the medium which may be evolution of hydrogen or oxygen, starting approximately at $E = E_1$. Curve I can be described by the well known Tafel equation $E = a + b \log I$ (1) where a and b are constants and I the current density; a is dependent on the electrode material and b is determined by the mechanism of the electrode reaction.

If the substrate requires a potential E_2 for the transfer of electrons it is only possible to obtain that potential when a certain current density I_2 is reached. At potentials numerically higher than E_2 (and thus current densities higher than I_2) the reduction (oxidation) of the medium and of the substrate compete. The outcome of this competition, the current efficiency, is determined by several factors as electrode material, specific adsorption of the substrate, concentration of the substrate, and composition of the medium. Generally, it can be said that an electrode material with high overvoltage, a high concentration of the substrate, and a high current density (but not higher than the effective limiting current of the substrate) will favour a high current efficiency.

The picture of the electrode reaction presented above and in Figure 2 is a very simplified one and is only meant to illustrate the basic idea; the presence of a high concentration of substrate changes the medium considerably, especially near the electrode surface if specific adsorption of the substrate, which often is of importance for the reaction, occurs.

The Kolbe electrochemical synthesis is an example of this mechanism; an excellent presentation of this reaction has been given previously in this series[4]. Many other of the more important 'classical' electrolytic reactions (e.g. the reduction of carboxylic acids to alcohols at lead cathodes) also follow this path, but many points in these processes are not clear; a rich field is here wide open for investigations by modern methods.

B. Indirect Electrochemical Reactions

1. Reduction by solvated electrons

Among the electrolytically produced reagents which have been considered to be operating is the solvated electron. It may be formed in reductions in nonaqueous media such as ammonia[5], ethylenediamine[6, 7], methylamine[8], polyethylene glycol dimethyl ether[9] and ethanol containing hexamethylphosphoramide[10], at electrodes with

high hydrogen overvoltage and with tetraalkylammonium or lithium ions as supporting electrolyte. The reaction is formally

$$e^- + \text{solv} \rightleftarrows e^-_{\text{solv}}$$
$$e^-_{\text{solv}} + S \rightleftarrows S^- + \text{solv}$$

where S is the substrate.

The standard potential of the solvated electron is about $-2{\cdot}6$*vs* Normal Hydrogen Electrode (NHE)[11] and solvated electrons can only be formed in the absence of more easily reducible substrates.

2. Other indirect electrochemical reactions

Whereas the reductions involving solvated electrons stand between the purely electrochemical and the indirect reductions, the reactions involving the formation of adsorbed hydrogen, amalgams, hydroxyl radicals, halogens, etc., are clearly indirect electrolytic reactions.

a. The electrocatalytic reduction may be important at electrodes with low hydrogen overvoltage and high catalytic activity, and its mechanism is closely related to the mechanism of the hydrogen evolution. The mechanism of this reaction at a platinum electrode in acid solution has been proposed[12] to be

$$H^+_{(\text{solv})} + e^- \rightleftarrows H_{(\text{ads})} \quad (2)$$
$$H^+_{(\text{solv})} + H_{(\text{ads})} + e^- \rightleftarrows H_{2(\text{ads})} \quad (3)$$
$$H_{2(\text{ads})} \rightleftarrows H_{2(\text{gas})} \quad (4)$$

In this reaction both equation (2) and equation (3) may be rate-controlling and the factor b in the Tafel equation (equation 1) acquires the value 0·116, or 0·038 when equation (2) or equation (3), respectively, is the rate-determining step.

An important point in the reaction mechanism for the electrocatalytic reactions may be illustrated by an investigation of the electrolytic reduction of acetone at a Raney-nickel cathode in alkaline solution[13]. It was found that the dependence of the electrode potential on log I had the form shown in Figure 3. In the absence of acetone the hydrogen evolution commenced at E_{II} and the slope of the straight line was 0·04 V cm^2/A. In the presence of acetone the current started to rise at a numerically lower potential (E_I), and between E_I and E_{II} the slope was 0·116; above E_{II} the slope again was 0·04. The current density, but not the potential at which the change in slope took place, was dependent on the concentration of acetone.

It has been suggested[14] that these results can be explained by

assuming that the reactions (equations 2—4) occur also at Raney-nickel electrodes in alkaline solution, and that reaction (equation 5) is a fast reaction. Between E_I and E_{II} the following reactions are assumed to occur with a measurable rate.

$$H^+_{(solv)} + e^- \rightleftarrows H_{(ads)} \qquad (2)$$

$$H_{(ads)} + \text{Substrate}_{(ads)} \longrightarrow \text{Product} \qquad (5)$$

The Tafel slope 0·04 is in accordance with the assumption that equation (3) is the slow step in the hydrogen evolution in the absence

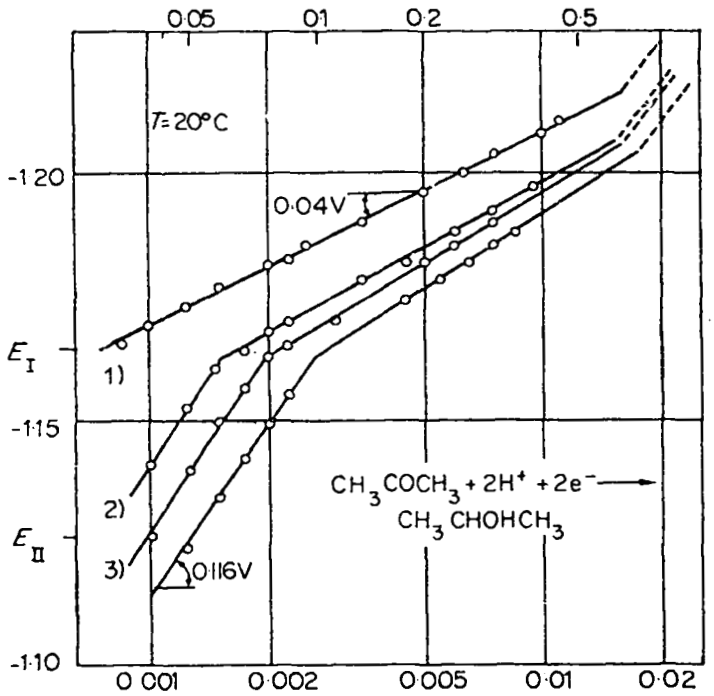


FIGURE 3. The dependence of the electrode potential E (vs SCE) on the current density I (on a semi-logarithmic scale) in the electrocatalytic reduction of acetone at a Raney-nickel electrode. Medium: aqueous solution of KOAc + KOH. Concentration of acetone: (1) 0; (2) 0·26; (3) 0·34; (4) 0·52 mole/l.

of acetone; reaction (5) is then able to compete successfully with equation (3) for the adsorbed hydrogen atoms; if reaction (5) also would be reasonably fast compared to reaction (2), the Tafel slope would change from 0·038 to 0·118, which compares well with that found experimentally (0·04, 0·116).

Recent investigations[15] have shown that two independent paths are accessible for the electrocatalytic reduction of acetone in 6N H_2SO_4 at a platinized platinum electrode; one leads to propane

and the other to isopropyl alcohol. The rate of formation of these two products depends on the voltage and on the history of the electrode.

Two types of adsorption for hydrogen are found, one of them being interstitial. The 'interstitial' hydrogen is important in the electrocatalytic reduction of acetone to isopropyl alcohol, but not in the reaction leading to propane. At an anodic treated electrode no interstitial hydrogen is found, but the concentration of it is gradually built up. Besides being of importance in the reduction of substrate the interstitial hydrogen modifies the adsorption properties of the electrode, and the importance of the adsorption of the substrate to the electrode prior to the reduction is evidenced by the kinetics of the reaction.

The nature of the reaction changes with time; at a freshly anodized electrode acetone is preferentially reduced to propane whereas later isopropyl alcohol is the main product; eventually both electrocatalytic reactions are suppressed and hydrogen evolution becomes the main reaction.

In many cases the formation of amalgams, active metals, hydrogen peroxide, halogens, or hydroxyl radicals has been postulated as the electrochemical step, which is then followed by a purely chemical reaction. One of the usual arguments for these intermediates is that the reaction follows a route which may be duplicated by the chemical reagent, but this does not prove the presence of these intermediates in the electrolytic reaction. In some, but rather few cases, the occurrence of an indirect electrolytic reaction has been proved conclusively.

II. ELECTROLYTIC PREPARATION OF ALCOHOLS AND PHENOLS

A. By Reduction

Hydroxyl compounds may be formed in the electrolytic reduction of carboxylic acids, esters, amides, thioamides, acid chlorides, ketones and aldehydes, in some cases as main product, in other cases in minor amounts.

1. From acid derivatives

a. Carboxylic acids. The carboxyl group is rather difficult to reduce electrolytically, and its reduction potential is less negative than the decomposition potential of the medium only in the cases where the

carboxyl group is activated by a suitable electron-attracting substituent. The substituent is also activated by the electron-attracting carboxyl group, and sometimes there is a competition between the reduction of the carboxyl group and of the substituent; in such cases the reduction of the carboxyl group will generally be favoured in acid solution and the reduction of the substituent in alkaline media.

Examples of this kind are found in the reduction of carboxy-derivatives of some π-electron deficient aromatic heterocyclic compounds. Thus, e.g., isonicotinic acid[16] (**1**), 2-carboxythiazole[17] and 2-carboxyimidazole[18] are reduced in acid solution, through the aldehyde, to the corresponding alcohols. The reduction of isonicotinic acid follows the scheme[16]:

$$\underset{(1)}{\overset{+}{\mathrm{HN}}\mathrm{C_5H_4COOH}} \xrightarrow{2e+2H^+} \underset{(2)}{\overset{+}{\mathrm{HN}}\mathrm{C_5H_4CHO}} \underset{\leftarrow}{\xrightarrow{H_2O}} \underset{(3)}{\overset{+}{\mathrm{HN}}\mathrm{C_5H_4CH(OH)_2}}$$

$$\underset{(2)}{\overset{+}{\mathrm{HN}}\mathrm{C_5H_4CHO}} \xrightarrow{2e+2H^+} \underset{(4)}{\overset{+}{\mathrm{HN}}\mathrm{C_5H_4CH_2OH}}$$

If the reduction of the acid is carried out at low temperature and at a suitable pH (1—4) and is stopped after the uptake of two electrons per molecule, the aldehyde **2** can be isolated in fair yield, as in this medium it is present predominantly in the non-reducible hydrated form, the *gem*-diol (**3**). When, however, the electrolysis is allowed to proceed to completion, the alcohol **4** is the isolated product, as the free aldehyde present in equilibrium with the hydrated form is reducible at a less negative potential (more easily reducible) than the acid. If the reduction is carried out at a slightly higher pH (e.g. 5—6), the aldehyde cannot be isolated as an intermediate and the carbinol is formed in a four-electron reduction. As only a few aldehydes are highly hydrated, the latter type of reduction is more typical for the reduction of carboxylic acids than the former in which the aldehyde is an isolable intermediate.

In alkaline solution the reduction of such heterocyclic acids takes place in the nucleus, and, using acids in which more than one nitrogen atom is present in a six-membered ring, reduction of the ring occurs even in acid solution.

Oxalic acid and its mono- and di-ester are polarographically reducible[19, 20] as the two carboxyl groups activate each other, and oxalic acid is reducible at a mercury or lead cathode through the aldehyde to glycolic acid. When the reduction is performed in dilute sulphuric acid at low temperatures, where the rate of the

dehydration of the hydrated aldehyde is low, glyoxylic acid may be isolated; the yield, determined as glyoxylic acid phenylhydrazone, is reported to be 87·5% [21].

A similar activation by a carboxyl group is found in phthalic acid which may be reduced to phthalide[22] in weakly acid solution; in strongly acid solution, however, dihydro compounds were formed at a lead cathode from phthalic and terephthalic acid, whereas isophthalic acid produced the dialcohol under such conditions[23].

Generally, however, the carboxyl group is not reducible at a potential between the decomposition potentials of the medium. This means that a polarographic or voltammetric reduction wave cannot be obtained in such cases, and the valuable guidance with respect to, e.g., reduction potential, number of electrons in the electrode reaction, pH-dependence of reduction potential normally acquired from such curves, is not available.

The rather high negative reduction potential of the carboxyl group also means that a reduction of this group is not possible without a simultaneous reduction of the cations of the supporting electrolyte which most often in this kind of reduction are hydrogen ions; this electrode reaction is therefore an example of the kind illustrated in Figure 2, and, accordingly, in the competition between the reduction of hydrogen ions and carboxylic acid, the reduction of the latter is favoured by a high concentration of the substrate, an electrode with high overvoltage, and a high current density. An adsorption of the substrate to the electrode might be necessary for the reaction, but the importance of adsorption in such reactions has not been sufficiently investigated.

Aromatic acids are generally reducible at a lead cathode to the corresponding benzyl alcohol in a medium containing sulphuric acid[23–26]. A typical catholyte could consist of a mixture of 70 g alcohol and 30 g sulphuric acid; in this medium 20—40 g benzoic acid is reduced with a current density of 0·1 A/cm^2 [24]; yield of benzyl alcohol, 85%. Table 1 gives the yields of alcohols from the reduction of some carboxylic acids.

The yields of benzyl alcohols are generally good, except when the benzene ring carries two substituents *ortho* to the carboxyl group; the substituents may interfere with the coplanarity of the benzene ring and the (possibly protonated) carboxyl group. Lack of coplanarity might influence both the reduction potential and the adsorbability of the carboxylic acid. The potential at the cathode was generally not measured in the 'classical' electrolytic reactions, but

it would be interesting to compare the electrode potential prevailing during the reduction of benzoic acid with that found in the reduction of phenylacetic acid. The latter is also reducible at a lead cathode in sulphuric acid, but the yield of alcohol is inferior to that obtained from benzoic acid[24]. If the interpretation of the reaction mechanism given above (and in section I.B.) is correct, the cathode potential found during the reduction of phenylacetic acid would be expected to be more negative than that prevailing during the reduction of benzoic acid. Conclusions drawn on the basis of structural considera-

TABLE 1. Yields of benzyl alcohols in the electrolytic reduction of substituted benzoic acids at a lead cathode in a medium containing sulphuric acid. Current density ca 0·1 A/cm^2.

Substituents	Yield (%) of subst. benzyl alcohol	Ref.
None	85	24
3-Bromo	75	24
3-Carboxy	60	23
3-Hydroxy	45	24
2-Amino	70	24
2-Amino-3-methyl	45	25
2-Amino-4-methyl	65	25
2-Amino-5-methyl	76	25
2-Amino-6-methyl	about 10	25
2-Amino-3,5-dimethyl	73	25
2-Amino-3,6-dimethyl	poor	25

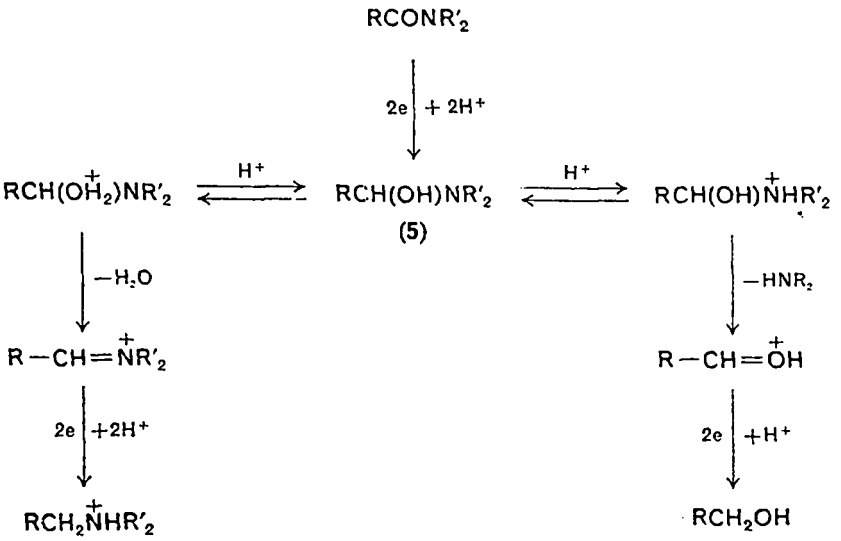
tions give the same result, as the electron-withdrawing phenyl ring is further removed from the carboxyl group in phenylacetic acid than in benzoic acid.

In basic medium the carboxyl group is not reduced; instead the benzene ring is attacked, and from a reduction of benzoic acid under these conditions 1,2,3,4-tetrahydrobenzoic acid was isolated[23].

b. Esters. The reduction of esters is similar to the reduction of the acids; thus the carbethoxy pyridines are reduced through the aldehydes to the alcohols[16], ethyl phthalate yields phthalide in weakly acid solution, and methyl benzoate is reduced to benzyl alcohol in sulphuric acid at a lead cathode. In the latter case some methyl benzyl ether was obtained, and it was the main product when the solvent was methanolic sulphuric acid[21].

c. Amides and thioamides. On electrolytic reduction amides generally yield a mixture of alcohol and amine, but sometimes one of the

products predominates. In acid solution the product distribution is determined by the relative rates of the loss of water or amine from the primarily formed reduction product, the *gem*-aminoalcohol (**5**), to either aldimine or aldehyde, according to the scheme.



An illustrative example is the reduction of different isonicotinic amides[27] at a mercury cathode; isonicotinic amide is in dilute hydrochloric acid reduced predominantly through the aldehyde, which it is possible to obtain in good yield, to the alcohol, whereas the anilide forms some 40% anilinomethylpyridine together with the alcohol; isonicotinic *N*-methylanilide yields predominantly the pyridylcarbinol. Similar results were obtained from other heterocyclic amides[17, 18].

Benzamide yields on reduction in sulphuric acid at a lead cathode a mixture of benzyl alcohol and benzylamine[28, 29], and other aromatic amides behave similarly. Table 2 gives the yields of amine and alcohol from the reduction of some ring substituted benzamides. From the reduction of *N*-substituted benzamides under these conditions no formation of alcohols has been reported.

Aliphatic amides[30] may be reduced electrolytically to alcohols in fair to excellent yield at a smooth platinum cathode in an amine-medium containing lithium chloride as supporting electrolyte. A typical catholyte would consist of 0·01 mole amide, 0·8 mole lithium chloride and 450 ml anhydrous methylamine; Table 3 lists the

yields of alcohols from some primary, secondary and tertiary aliphatic amides.

In the presence of a hydrogen donor stronger than the amine, e.g., alcohol, a high yield of aldehyde or its reaction product with

TABLE 2. Yields of amines and alcohols in the electrolytic reduction of some substituted benzamides at a lead cathode[29] in alcoholic sulphuric acid; current density 0·2 A/cm².

Substituents	Yield of amine	Yield of alcohol
None	74	23
2-Methyl	83	11
3-Methyl	53	35
4-Methyl	79	18
4-Methoxy	73	22
3-Bromo	64	19
4-Bromo	67	—
4-Chloro	65	—

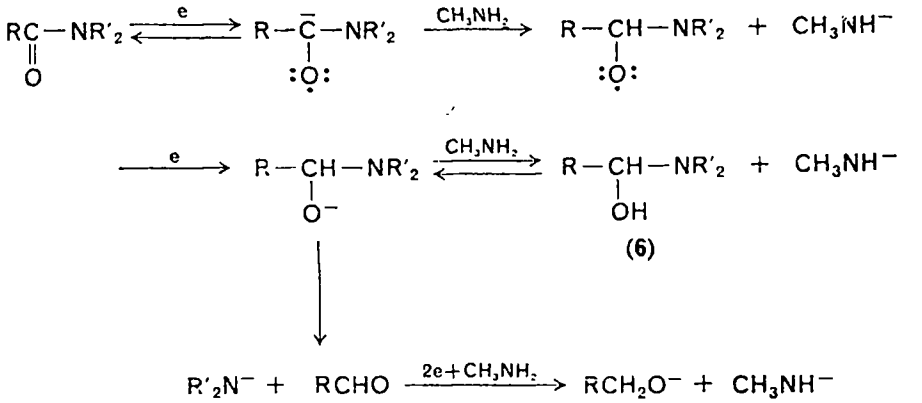
TABLE 3. Yields of alcohols in the electrolytic reduction of aliphatic amides at a smooth platinum cathode in methylamine containing lithium chloride[30].

Amide (moles)		Methylamine (ml)	Yield of alcohol (%)
$CH_3(CH_2)_4CONHMe$	(0·05)	600	51
$CH_3(CH_2)_4CONH_2$	(0·05)	700	58
$CH_3(CH_2)_8CONH_2$	(0·05)	600	59
$CH_3(CH_2)_{10}CONH_2$	(0·02)	450	79
$CH_3(CH_2)_{10}CONHMe$	(0·02)	450	84
$CH_3(CH_2)_{12}CONH_2$	(0·02)	450	92
$CH_3(CH_2)_{12}CONMe_2$	(0·02)	450	97
$CH_3(CH_2)_{14}CONH_2$	(0·01)	450	86
$CH_3(CH_2)_{16}CONH_2$	(0·01)	450	79
$CH_3(CH_2)_{16}CONHCH_3$	(0·01)	450	72

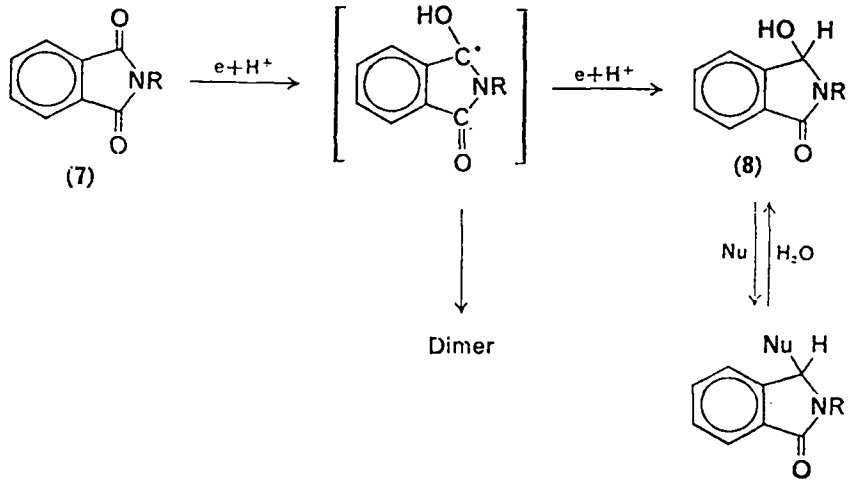
methylamine is obtained; no reduction product from an *N*-methylimine has been isolated. From these observations the first scheme on the following page was proposed[30].

In the presence of a stronger proton donor than methylamine the *gem*-aminoalcohol (**6**) survives until the reaction mixture is worked up.

In some cases the *gem*-aminoalcohol primarily formed in the re-



duction of an amide or imide is sufficiently stable for its isolation. Derivatives of phthalimide (**7**) are reduced to hydroxyphthalimidines (**8**) in slightly acid solution[31]; in a medium of high alcohol content the isolated product is predominantly ethoxyphthalimidine. In weakly alkaline solution (**7**) is reduced in two one-electron reductions, and the result of the first one-electron reduction is a radical, which dimerizes.

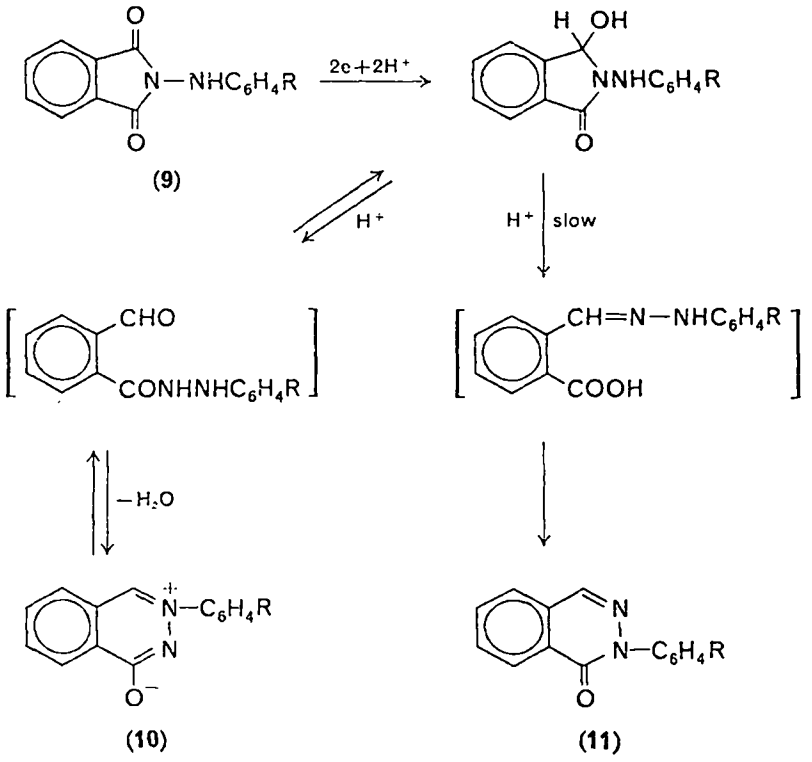


In the presence of a nucleophile (Nu) the hydroxyphthalimidine **8**, which is a derivative of phthalaldehydic acid, reacts with the nucleophile; in the presence of ethyl alcohol ethoxyphthalimidine is formed and in the presence of isoindoline, 1-*N*-isoindolino-3-oxoisoindoline[31]. When phenylhydrazine is added to an aqueous

solution of hydroxyphthalimidine, 2-phenylphthalazinone-1 precipitates; similar ring closure reactions may prove to be of synthetic value[32].

Other products, e.g., phthalimidines and isoindolines, have been obtained from electrolytic reduction of phthalimide[33, 34]. An acid-catalysed dehydration of **8** would produce an intermediate which is easily reduced to phthalimidine in a similar way as in the reduction of 2,3-dimethyldihydrophthalazinedione[35]. The further reduction of this compound is analogous to the reduction of benzamides[26]. An electrolytic preparation of **8** requires thus a medium in which the dehydration step is slow; Dunet and Willemart used 50% aqueous dioxane containing some hydrochloric acid; an alternative method is reduction in cold base at −1·6 V (SCE)[32].

In some derivatives of phthalimide, such as *N*-anilinophthalimide (**9**), another type of reaction may follow the initial reduction to a hydroxyphthalimidine, and from **9** is formed either 3-phenyl-ψ-phthalazinone (**10**) or 2-phenylphthalazinone (**11**). The following scheme has been suggested[36].



Thioamides are reduced more easily than the corresponding amides, and the primary reduction product, the *gem*-aminothiol, is generally more stable than the corresponding *gem*-aminoalcohol; the *gem*-aminothiol from the reduction of isonicotinic thioamide[27] is thus stable for hours in acid solution at 5—10°. The thioamides are generally not well suited for the preparation of alcohols.

d. Acid chlorides. The electrolytic reduction of an acid chloride must be performed in an indifferent medium as, e.g., acetonitrile; a polarogram of benzoyl chloride in this medium shows a reduction wave due to the hydrogenation of the carbon–chlorine bond followed by the reduction wave of the benzaldehyde thus formed[37].

When a preparative reduction is made in an aprotic medium such as acetonitrile the question of availability of protons arises. In a voltammetric experiment the amount of material reduced is so small that the residual water present in 'dry' acetonitrile can furnish the necessary protons, but when larger amounts are reduced, a suitable proton donor must be added if the reduction requires protons. The proton donor must be neither a very strong acid, as protons are then preferentially reduced, nor a very weak one. Phenol is in some cases an acceptable compromise.

Benzoyl chloride on reduction in dry acetonitrile yields benzil and its reduction products[37] whereas benzaldehyde and its reduction products are obtained in the presence of phenol as proton donor. The following reduction scheme may be proposed for the first step,

$$\mathrm{RCOCl} \xrightarrow{e} \mathrm{Cl^-} + \mathrm{R\dot{C}O} \xrightarrow{e+H^+} \mathrm{RCHO}$$

$$\mathrm{R\dot{C}O} \rightarrow \mathrm{R{-}\overset{|}{\underset{|}{C}}{=}O} \quad \text{(dimerization)}$$

The reductive cyclization of the dichlorides of dicarboxylic acids to the corresponding diketones may prove useful in the formation of rings as an alternative to the acyloin condensation.

2. From aldehydes and ketones

a. Reduction mechanism. Electrolytic reduction of aldehydes and ketones may produce pinacols, alcohols or hydrocarbons depending upon the experimental conditions, especially upon pH and electrode material. In the following the reduction to pinacols and alcohols is discussed.

Information concerning the reduction mechanism at a mercury electrode may be obtained from polarographic studies; references to such investigations may be found in a recent paper by Zuman[38]; the discussion below follows essentially the one given in that paper on the reduction of aromatic carbonyl compounds; aliphatic ketones are reduced at rather negative potentials which can only be reached in neutral and alkaline solution containing tetraalkylammonium ions as supporting electrolyte.

In acid solution a protonation of the carbonyl compound takes place prior to the electron transfer and the radical thus formed may either react chemically or be reduced further. Under these conditions the reduction may be described by the following steps:

$$H^+ + ArCOR \rightleftarrows Ar\overset{+}{C}(OH)R \tag{6}$$

$$Ar\overset{+}{C}(OH)R + e \overset{E_1}{\rightleftarrows} Ar\dot{C}(OH)R \tag{7}$$

$$2\,Ar\dot{C}(OH)R \longrightarrow \text{dimer} \tag{8}$$

$$Ar\dot{C}(OH)R + Hg \longrightarrow \text{organometallic compound} \tag{9}$$

$$Ar\dot{C}(OH)R + \text{solvent} \longrightarrow \text{products} \tag{10}$$

$$Ar\dot{C}(OH)R + e \xrightarrow{E_2} Ar\bar{C}(OH)R \tag{11}$$

$$Ar\bar{C}(OH)R + H^+ \rightleftarrows ArCHOHR \tag{12}$$

The pH-dependent reduction potential E_1 of the first electron transfer is generally less negative than the pH-independent potential E_2 of the second electron transfer, which often at low pH is more negative than the reduction potential of the hydrogen ions, and only one reduction wave is then seen on a polarogram. A reduction of an aromatic carbonyl compound in acid solution at a mercury cathode with a cathode potential controlled at E_1 would thus be expected to give a high yield of pinacol, and this is also found in a preparative reduction. The stereochemistry of the products is discussed below.

As E_1, but not E_2, is dependent on pH, E_1 approaches E_2 at higher pH and they may merge at a certain pH above which only one two-electron wave is seen.

In the medium pH-range the preprotonation becomes unimportant as the equilibrium (equation 6) is shifted too far to the left. The electron transfer occurs then to the unprotonated carbonyl compound and the radical ion acquires a proton; this radical may react chemically or be reduced further.

$$ArCOR + e \xrightarrow{E_3} Ar\dot{C}(O^-)R \quad (13)$$

$$Ar\dot{C}(O^-)R + H^+ \rightleftarrows Ar\dot{C}(OH)R \quad (14)$$

$$Ar\dot{C}(OH)R \longrightarrow \text{dimer} \quad (8)$$

$$Ar\dot{C}(O^-)R + Ar\dot{C}(OH)R \longrightarrow \text{dimer} \quad (15)$$

$$Ar\dot{C}(OH)R + e \xrightarrow{E_2} Ar\bar{C}(OH)R \quad (11)$$

$$Ar\bar{C}(OH)R + H^+ \rightleftarrows ArCHOHR \quad (12)$$

Polarographically a two-electron wave is observed which means that under these conditions the second-order reactions (equations 8 and 15) cannot compete successfully with the further reduction; at higher concentration and current density varying yields of pinacols are formed.

In alkaline solution the polarographic behaviour depends—besides on pH—on the nature and concentration of the supporting electrolyte. The reduction of the primarily formed radical ion (equation 16) occurs at a more negative potential (E_4) than that of the first reduction (E_3); E_4 is sometimes more negative than the decomposition potential of the medium. The reduction potential of the coordinated radical (E_5) is most often between E_3 and E_4. (M^+ is a cation.)

$$ArCOR + e \xrightarrow{E_3} Ar\dot{C}(O^-)R \quad (13)$$

$$Ar\dot{C}(O^-)R + e \xrightarrow{E_4} ArC^-(O^-)R \xrightleftharpoons{2H^+} ArCHOHR \quad (16)$$

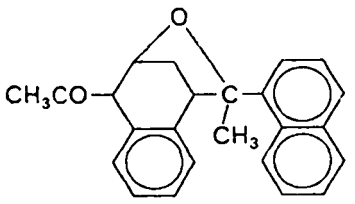
$$\uparrow\downarrow +M^+$$

$$Ar\dot{C}(OM)R + e \xrightarrow{E_5} ArC^-(OM)R \xrightleftharpoons{2H^+} ArCHOHR + M^+ \quad (17)$$

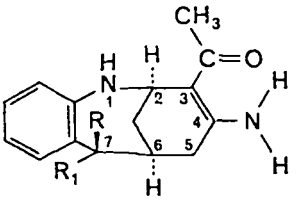
On electrostatic grounds the radical ion would not be expected to dimerize with another negatively charged radical ion; at least one of the partners must coordinate with a positively charged species, a proton or another cation, prior to the coupling as in equation (5); if the protonation took place near the electrode surface, the protonated species would be reduced immediately; this would indicate that if equation (5) were responsible for the formation of pinacols under basic conditions, the dimerization takes place at some distance from the electrode. A dimerization as equation (18) must also be taken into consideration.

$$2\ Ar\dot{C}(OM)R \longrightarrow \text{dimer} \quad (18)$$

The reaction mechanism must also take into account that other coupling products than pinacols may be formed, thus **12** and **13** are among the products obtained from reduction in alkaline solution of 1-acetonaphthone[39] and 2'-aminoacetophenone[40], respectively, at a mercury electrode.

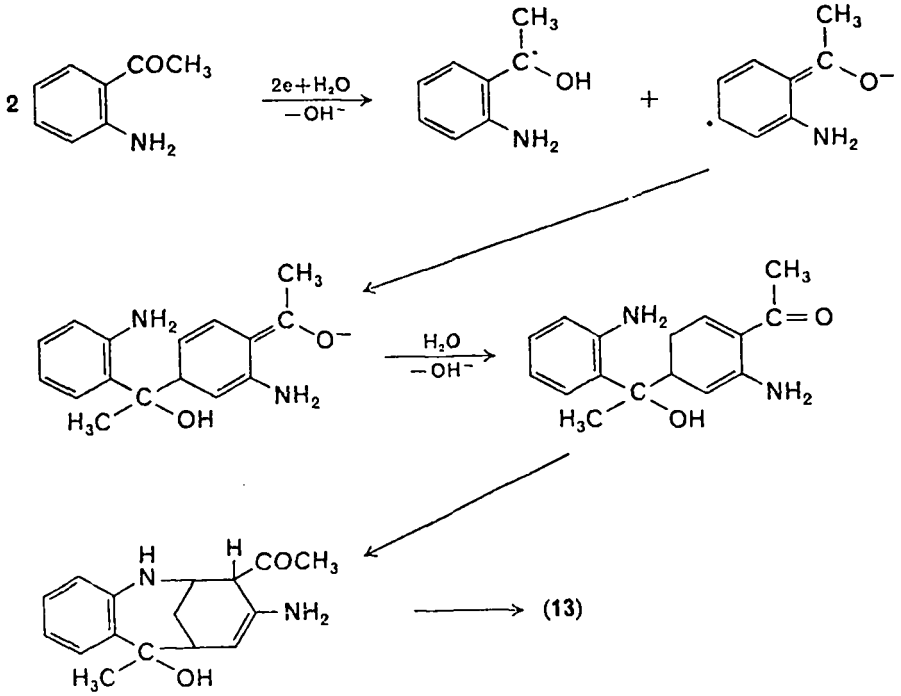


(12)



(13) R = OH, R_1 = CH_3
R = CH_3, R_1 = OH

13 is formed, as shown below, by coupling of a radical and a radical ion followed by a nucleophilic addition of the aromatic amino group to the α, β-unsaturated ketone:



The effect of the cations on the polarographic behaviour of carbonyl compounds usually increases with size and charge of the ions,

and the presence of a high concentration of tetraalkylammonium ions often results in the occurrence of a single rather than two polarographic waves. The effect of added metal cations on the stereochemistry of the product is not known.

The electrode reactions of ketones at other cathode materials have been much less thoroughly investigated, and the reductions have generally been performed without measurement and control of the electrode potential. At a platinum electrode acetophenone is reduced in alkaline solution to a pinacol[41]; unfortunately the stereochemistry (*d,l/meso*) was not reported; it would have been of interest to compare the results at an electrode with low hydrogen overvoltage and high catalytic activity with those obtained at a mercury cathode. The *d,l/meso* ratio of pinacols produced at a copper or tin electrode did not differ significantly from that found at a mercury cathode[42].

Acetone yields in acid solution at a lead cathode a mixture of pinacol, isopropyl alcohol and metalorganic compounds such as diisopropyllead and tetraisopropyllead[43]. The reduction of many other ketones follows the same pattern, and the results have been compiled in different monographs and reviews[44–46].

α,β-Unsaturated ketones, which are not conjugated to a phenyl ring, are usually reduced polarographically in a one-electron reduction. The primarily formed radical may form a mercury compound, dimerize at the β-carbon or at the carbonyl carbon, or form an unsymmetrical coupling product, so ε-diketones, pinacols, dihydrofurans, cyclopentenes and some other compounds may be formed[47, 48]. Often the hydrodimerization at the β-carbon to the saturated ε-diketone is the preferred reaction, but if a dimerization at this point is sterically unfavourable, α,β-unsaturated pinacols may be the major product; the latter reaction is important in the reduction of α,β-unsaturated steroid ketones[49]. In acid solution the reaction is:

$$RCH{=}CHCOR' \underset{}{\overset{H^+}{\rightleftharpoons}} RCH{=}CHC^+(OH)R'$$

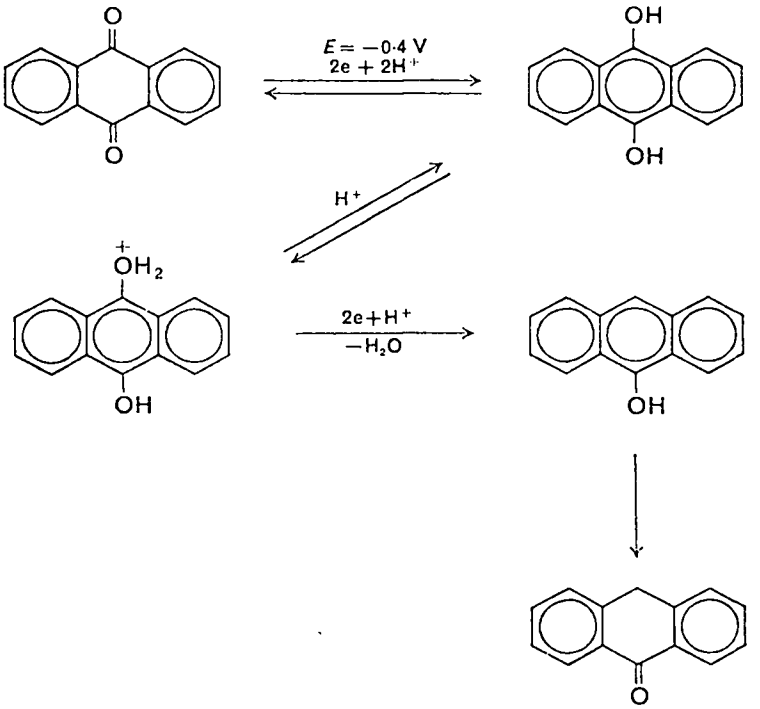
$$RCH{=}CHC^+(OH)R' \xrightarrow{e} \left\{ RCH{=}C\dot{C}(OH)R' \leftrightarrow \dot{R}CHCH{=}C(OH)R' \right\} \longrightarrow \text{dimers and organometallic compounds}$$

In acid solution protonation takes place prior to the electron transfer; in alkaline solution a radical ion is formed primarily; this

difference is reflected in the stereochemically different products found in acid and alkaline solution in the reduction of α,β-unsaturated steroid ketones.

The polarographic reduction of α,β-unsaturated aromatic carbonyl compounds is more complicated; often three waves are observed, and organomercury compounds, dimeric and saturated carbonyl compounds, pinacols and alcohols may be expected as products. A very thorough discussion of the polarographic behaviour of such compounds has recently been published[50].

Quinones are reduced to hydroquinones, and they form together a reversible redox system; sometimes semiquinones have considerable stability which can be judged from their polarographic behaviour. Of synthetic interest might be the fact that in a suitable medium a hydroquinone such as anthrahydroquinone may lose a hydroxyl group on reduction; in a medium consisting of 50 vol % ethanol and 50 vol % sulphuric acid anthraquinone is reduced at a suitable potential to anthrone[51] according to



The dehydration step (and the solubility) is favoured by higher temperatures and at 50—60° the reaction goes reasonably fast. By

controlling the potential at −0·4 V (SCE) further reduction of the anthrone is avoided.

b. Stereochemistry of the reduction of carbonyl compounds. Any reduction mechanism must take the stereochemistry of the products and its dependence on the medium into consideration. Several reports have appeared on the dependence on pH of the stereochemistry of the hydroxyl derivatives obtained by electrolytic reduction of carbonyl compounds. Thus different mixtures of pinacols were obtained in acid and alkaline solution from α,β-unsaturated steroid ketones[49], deoxybenzoin[42, 52], *p*-dimethylaminoacetophenone[53], and other acetophenones[42, 54, 55]. Also the stereochemistry of the reduction product, *erythro*-phenyl-α-phenylethyl-carbinol, from α-methyldeoxybenzoin has been reported[56]. The influence of added unsymmetrical constituents to the medium has recently received attention[57].

An important aspect of the pinacol formation is whether the dimerization occurs at the surface of the electrode or in the bulk of the solution. The electrical double layer is considered to consist of an inner layer of adsorbed molecules and a more diffuse outer layer; the electrical gradient is high (10^7 V/cm) in the inner layer, but falls rapidly to a negligible value. At a distance from the electrode of about 100 Å the influence of the electrode is no longer of importance.

Other questions are whether a radical, a radical anion, a radical anion coordinated with a cation, or a metalorganic compound is involved in the dimerization. A priori it cannot be excluded that a pinacol may be formed by reaction between a carbanion and an unreduced ketone.

One piece of evidence which may point to a fixation of the stereochemistry of the reaction product near the surface of the electrode is the reduction of benzil to stilbenediol[58]. The ratio of *cis*-stilbenediol to *trans*-stilbenediol was found to be dependent on the electrode potential in such a way that the *trans*-isomer predominates near the half-wave potential of benzil [~0·7 V (SCE) at pH 10] whereas *cis*-stilbenediol is the more abundant one about −1·0 V (SCE); at more negative potentials the *trans*-isomer predominates again. It is well known that in the absence of strongly adsorbed species the mercury cathode is positively charged with respect to the solution at potentials more positive than −0·7 V (SCE) and negatively charged at more negative values. The half-wave potential of benzil is thus near the point of zero charge; it has been suggested

that the control of the stereochemistry in the reduction of benzil operates by the influence of the electric field in the electric double layer on the conformational equilibrium of benzil, as the dipoles in the carbonyl groups may be influenced by the field.

The analysis of the *cis–trans* ratio at the different potentials was made by anodic voltammetry at a hanging mercury electrode, at which the electrode reaction had proceeded for about 30 sec; as both of the stilbenediols tautomerize to benzoin (at different rates), an exhaustive electrolysis would not be applicable. The *trans*-isomer was taken to be the more easily reducible isomer, and this was substantiated by later work[59].

Another result which has been taken as evidence for a fixation of the stereochemistry near the surface of the electrode is the reduction of acetophenone to the alcohol in methanol in the presence of an optically active supporting electrolyte[57]. With 0·1M (−)-ephedrine hydrochloride as supporting electrolyte *R*-(+)-methylphenylcarbinol was obtained in 44% yield with an optical purity of 4·2%, whereas *S*-(−)-methylphenylcarbinol with an optical purity of 4·6% was obtained in 38% yield when (+)-ephedrine hydrochloride was used as electrolyte. The optical purity of the product was not raised when a 0·2M solution of ephedrine was used, but lowered to 3·1% when a 0·05M solution was employed.

These findings have been interpreted as evidence for the theory that it is the ephedrine adsorbed at the interface which predominantly influences the stereochemistry of the product and to a much lesser degree the electrolyte present in the bulk of the solution.

Another conclusion was reached in a work on the pinacol isomer distribution in the reduction of some acetophenones, benzaldehydes and related compounds[42, 53]. The results are given in Table 4. In acid solution the coupling of two neutral radicals is considered, whereas a neutral radical and a radical ion rather than two radical ions are believed to couple in alkaline solution. In order to explain the higher yield, especially in alkaline solution, of *d,l*-pinacols compared to the *meso*-form, which would be favoured on steric grounds, a combination of steric factors and hydrogen bonding interactions is considered to determine the stereochemistry of the pinacols. The conclusion is reached that the stereochemistry of the product is determined so far from the electrode that it does not play any significant role here, and it seems substantiated by the lack of dependence of the stereochemistry on the nature of the electrode material; approximately the same stereochemical results were

TABLE 4. Stereochemistry (*d,l/meso* ratio) of the pinacols obtained on reduction of some acetophenones and related compounds in 80% ethanol[42, 54, 55].

Electrode	Potential [−V vs (SCE)]	Medium	% Pinacol	Ratio (*d,l/meso*)
		Acetophenone		
Hg	1·1—1·2	1M LiCl/1·5M AcOH	48—74	1·0—1·2
Sn	1·1	1M LiCl/1·5M AcOH	58	1·0
Cu	1·1	1M LiCl/1·5M AcOH	68	1·0
Hg	1·7	2M KOAc	74	2·5
Sn	1·6	2M KOAc	56—70	2·9—3·0
Cu	1·5—1·6	2M KOAc	77—78	2·8—2·9
Hg	1·6—1·8	M KOH	66	2·7
		Propiophenone		
Hg	1·2	1M LiCl/1·5M AcOH	55	1·4
Hg	1·6	2M KOAc	41	2·7
Hg	1·6	0·1M KOH	52	2·8
Cu	1·7	2M KOAc	24	3·2
		p-*Chloroacetophenone*		
Hg	1·1	1M LiCl/1·5M AcOH	88	1·2
Hg	1·5	2M KOAc	95	3·1
		p-*Methoxyacetophenone*		
Hg	1·2	1M LiCl/1·5M AcOH	94	1·2
Hg	1·7	2M KOAc	96	3·0
		p-*Trifluoromethylacetophenone*		
Hg	1·2	1M LiCl/1·5M AcOH	87	1·0
		Deoxybenzoin		
Hg	1·2	1M LiCl/1·5M AcOH	44	1·3
Hg	1·4	1M KOH	98	3·2
		o-*Chloroacetophenone*		
Hg	1·6	2M KOAc	28	2·1
		o-*Methoxyacetophenone*		
Hg	1·7	2M KOAc	51	1·2
		2-*Acetopyridine*		
Hg	0·78	1M LiCl/1·5M AcOH	11	0·73
Hg	1·2	2M KOAc	98	0·28
Hg	1·22	1M KOH	68	0·46
Cu	1·6	1M KOH	55	0·53
		Benzaldehyde		
Hg	1·2	1M LiCl/1·5M AcOH	69	1·1
Hg	1·6	2M KOAc	85	1·2
Cu	1·6	2M KOAc	73	1·2

obtained at mercury, copper, and tin cathodes. Furthermore, the *d,l/meso* ratio found in the electrochemical reductions was essentially the same as that obtained in photopinacolization studies[60].

Further experimental evidence must be accumulated before a unified picture of the reduction mechanism can be presented, and especially stereochemical evidence as described above will be of great value in elucidation of the reaction path.

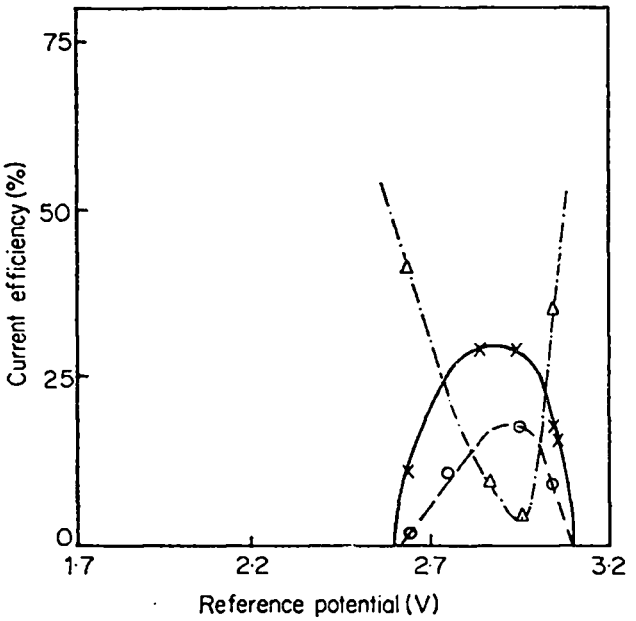


FIGURE 4. Plot of current efficiency against potential of the working electrode. Medium 1·0M sodium acetate, 0·4M sodium hydroxide. Products: ——— methanol; - - - - - - ethane; -·-·-·- oxygen; △ experimental points.

[Reproduced from *Trans. Faraday Soc.*, **63**, 1470 (1967), Fig. 2.[62]]

B. Preparation of Hydroxyl Compounds by Anodic Oxidation

1. Formation of alcohols

The well-known Kolbe electrochemical reaction which under 'normal' conditions produces predominantly hydrocarbons by anodic coupling of carboxylate ions may be directed by a suitable choice of reaction conditions towards a production of alcohols in the so-called Hofer–Moest reaction[61]. The reaction is schematically:

$$R{-}COO^- - 2e^- + OH^- \longrightarrow CO_2 + ROH$$

As illustrated in Figure 4, the anodic electrode reaction at a platinum electrode in an alkaline acetate solution is oxygen evolu-

tion below a certain potential; above that the Hofer–Moest reaction starts and, at a slightly higher potential, some of the Kolbe product is also obtained, while the oxygen evolution is suppressed to a high degree. At still higher potentials there is indication for oxygen evolution taking over again; this might be dependent on the acetate concentration.

The reaction mechanism is still under active discussion; the main question is whether the alcohol is formed by reaction between an adsorbed alkyl radical and an adsorbed hydroxyl radical or between an alkyl carbonium ion and a hydroxyl ion (or water molecule).

In the 'radical mechanism' the following steps are considered[62, 63],

$$CH_3COO^- \longrightarrow CH_3COO\cdot(M) + e \quad (19)$$

$$CH_3COO\cdot(M) \longrightarrow CH_3\cdot(M) + CO_2 \quad (20)$$

$$CH_3\cdot(M) + CH_3\cdot(M) \longrightarrow C_2H_6 \quad (21)$$

$$CH_3\cdot(M) + CH_3COO^- \longrightarrow C_2H_6 + CO_2 + e \quad (22)$$

$$OH^- \longrightarrow HO\cdot(M) + e \quad (23)$$

$$CH_3\cdot(M) + HO\cdot(M) \longrightarrow CH_3OH \quad (24)$$

$$CH_3\cdot(M) + \overline{O}H \longrightarrow CH_3OH + e \quad (25)$$

in which (M) indicates that the species is adsorbed to the electrode.

The first two steps are common for both the Kolbe and the Hofer–Moest reactions, and the branching occurs after the formation of methyl radicals which are considered to be stabilized by adsorption to the electrode. The methyl radicals may either form the Kolbe product (equations 21 and 22) or react with adsorbed hydroxyl radicals (equation 24) or hydroxyl ions in an electrochemical desorption step (equation 25) to the Hofer–Moest product. A loss of an electron from the alkyl radical thus forming a carbonium ion (equation 26) is considered for carboxylate ions having branched alkyl chains, but is thought less likely for methyl radicals.

$$R\cdot(M) \longrightarrow R^+ + e \quad (26)$$

$$R^+ + \overline{O}H \longrightarrow ROH \quad (27)$$

The formation of carbonium ions as general intermediates in the Hofer–Moest reaction has been assumed primarily from the carbonium ion-type rearrangements found in some products and from the stereochemical results. As a chapter in this series[4] covers this aspect of the Hofer–Moest reaction thoroughly, no further discussion of these points is necessary here.

Electrolysis of a sodium acetate solution at a smooth Pt-anode in a cell without diaphragm has been shown to give methanol in 93% yield (54% current yield)[64, 65], but in general the Hofer–Moest

reaction has been investigated not as a preparative method in its own right, but rather as a side reaction to the Kolbe synthesis[66–68]. Besides the expected alcohol other alcohols and alkenes are often found in the reaction mixture, as would be reasonable from a rearrangement of or elimination from a primarily formed carbonium ion. The yields of alcohols are generally reasonably fair, but may possibly be raised by suitable choice of conditions. It would be expected that the use of a carbon anode would favour the alcohol formation; also an alkaline medium, e.g., made alkaline by addition of pyridine, containing a high concentration of difficultly oxidizable anions such as perchlorates, sulphates, carbonates or bicarbonates, would probably be favourable for the Hofer–Moest reaction.

It remains, however, to be seen how good yields may be obtained under such conditions; the further oxidation of alcohols must, of course, be avoided.

Some hydroxyl compounds have been prepared by anodic oxidation of different hydrocarbons to carbonium ions which react with solvent to alcohols. Thus among other products from the anodic oxidation of α-pinene at a platinum anode in sulphuric acid is found α-terpineol[69] and *cis*-terpine; also, *p*-nitrotoluene yields some *p*-nitrobenzyl alcohol at a platinum anode in glacial acetic acid containing sulphuric acid[70, 71]. The latter reaction is analogous to the anodic acyloxylation described in another chapter in this series[4].

III. ELECTROLYTIC REACTIONS OF HYDROXYL COMPOUNDS

Only few hydroxyl compounds can be reduced electrolytically, whereas many of them can be oxidized anodically.

A. Reductions

Certain activated hydroxyl groups may be reduced electrolytically, generally in acid solution. Thus in α-hydroxyketones, e.g., α-hydroxy steroid ketones[72] or derivatives of 2-hydroxyacetophenone[52] (**14**), and certain heterocyclic carbinols[73], as derivatives of 4-pyridylcarbinol, the hydroxyl group is reductively removed.

$$\underset{\textbf{(14)}}{C_6H_5COC(CH_3)_2OH} \xrightarrow[2e+H^+]{H^+} CH_3COCH(CH_3)_2 + H_2O$$

In these reactions there appears no indication of a primary loss of water; in some cases, such as the reduction of triaryl carbinols (**15**),

in methanesulphonic acid[74] or of tropyl alcohol in aqueous buffer solution[75], an acid-catalysed dehydration precedes the reduction of the carbonium ion thus formed

$$Ar_3COH \xrightarrow{H^+} Ar_3C^+ + H_2O \xrightarrow{2e+H^+} Ar_3CH$$

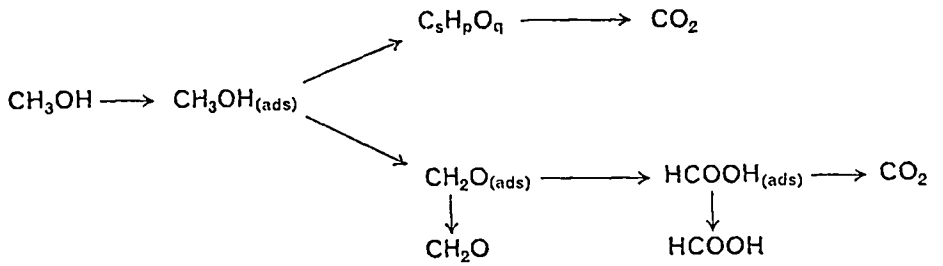
(15)

It might also be mentioned that phenol can be reduced electrolytically to cyclohexanol in 2N sulphuric acid at a platinized platinum electrode[76].

B. Oxidations

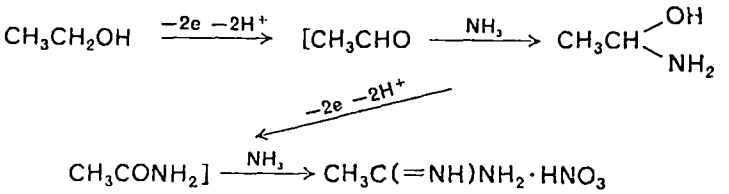
1. Aliphatic alcohols

Primary aliphatic alcohols are generally oxidized[44, 45, 77] anodically through the aldehyde to the acid and secondary alcohols to the ketones or further; in some cases the aldehyde may be trapped. The reaction mechanism is not fully agreed upon; the oxidation of alcohols[78–80] at platinum has been subject to many investigations, especially in connexion with the development of fuel cells[81], and the following tentative scheme for the oxidation of methanol seems plausible in the light of recent results[82].



The formation of a chemisorbed carbonaceous species, $C_sH_pO_q$, during the anodic oxidation of methanol on platinum is generally recognized, but the exact composition of this species is not known.

In an aqueous medium containing ammonium carbonate the anodic oxidation of ethanol at a platinum electrode yields acetamidine which was isolated as the nitrate. The following reaction path was suggested[83]:



but the formation of acetamidine from acetamide under these conditions seems not attractive; perhaps an oxidation involving a carbonium ion rather than a dehydrogenation of the aldehyde–ammonia takes place.

In alkaline medium the anodic reactions of alcohols are more complex; the aldehyde formed may condense to resins before it is oxidized further. Other reactions lead to the formation of hydrocarbons and molecular hydrogen[84]. Some explanations of the latter reaction have been put forward[85, 86], but a reliable reaction path must await the results of investigations performed with modern techniques.

Ene-diols such as ascorbic acid are easily oxidizable[87] in a two-electron oxidation to the α-diketone

$$R{-}CO{-}CHOH{-}R' \rightleftharpoons R{-}\underset{HO}{C}{=}\underset{OH}{C}{-}R \xrightleftharpoons{-2e\ -2H^+} RCOCOR$$

As mentioned in section II, the α-diketone is reducible through the ene-diol to the α-hydroxyketone.

2. Aromatic compounds

Electrolytic oxidation of aromatic compounds involves an abstraction of one or more electrons from the aromatic system. Reviews of the anodic reactions of aromatic compounds have recently been published[77, 88]. The primarily formed radical cation may react in different ways:

a. It may lose another electron and stabilize itself by (1) losing two protons, (2) reacting with a nucleophile and losing one proton, (3) reacting with two molecules of nucleophile. This reaction sequence may be represented by eecc (electron-transfer, electron-transfer, chemical step, chemical step).

b. It may lose a proton to a neutral radical which most likely will lose an electron and then react chemically, an ecec-sequence. Another ecec-reaction would be a reaction between the radical cation and a nucleophile followed by loss of an electron, followed by a chemical step.

c. The radical may couple either with another radical in a purely chemical step or with a substrate molecule in an electrochemical desorption step.

One of the difficulties in controlling the oxidation of organic aromatic compounds is that the product is often more easily oxidiz-

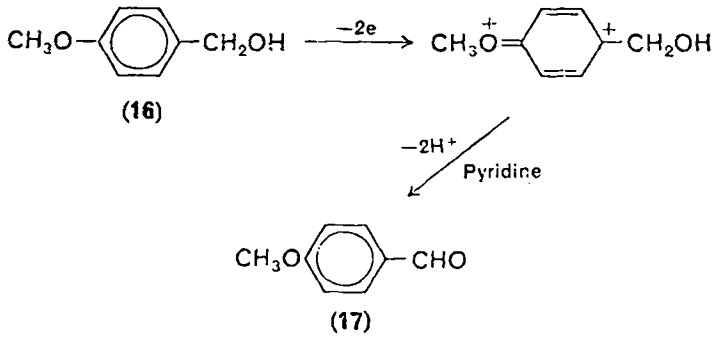
able than the substrate. If, for example, the nucleophile is water or hydroxyl ion, the resulting phenol is more easily oxidizable than the parent hydrocarbon.

Another is that the oxidation potential of many aromatic compounds is rather positive, which restricts the choice of medium and electrode material. Acetonitrile, which is rather resistant towards oxidation, is often used as solvent; other useful solvents are dimethylformamide, methylene chloride, acetic acid or acetone; as supporting electrolytes perchlorates or tetrafluoroborates may be used.

3. Oxidation of aromatic alcohols

An investigation of the oxidation potentials of aromatic alcohols in acetonitrile at a platinum electrode[89] showed that the potential was mainly determined by the aromatic nucleus; substituents may influence the oxidation potential of an aromatic nucleus by their electron-donating or -attracting properties. Methoxy groups lower the oxidation potential; the $-CH_2OH$ group acts mostly as a weakly electron donating substituent, but in some difficultly oxidizable aromatic compounds the nonbonding electrons on the oxygen atom may be the most easily removable.

Controlled potential oxidations of aromatic alcohols have been made in a few cases; thus anisyl alcohol (**16**) was oxidized to anisaldehyde (**17**) in good yield at a platinum anode in acetonitrile containing sodium perchlorate as supporting electrolyte and pyridine as proton acceptor[89]. The reaction was formulated as



without any attempt to determine whether or not a proton was lost before the second electron was removed from the system.

The product (**17**) is more difficult to oxidize under these conditions than **16** (anisyl alcohol: $E_{\frac{1}{2}} = 1{\cdot}22$ V (vs Ag^+/Ag), anisaldehyde: $E_{\frac{1}{2}} = 1{\cdot}63$); the reason is that the electron-attracting aldehyde

group will raise the oxidation potential compared to anisole, whereas the slightly electron-donating $-CH_2OH$ group will lower it somewhat. This supports the view that the potential-determining step is the loss of an electron from the aromatic system; towards most chemical oxidants the aldehyde is more reactive than the alcohol.

When an aprotic solvent such as acetonitrile is used as a medium, it is necessary to add a proton acceptor to facilitate the removal of protons. Pyridine has been found to be a suitable base as it is oxidized at a rather positive potential. Aliphatic or aromatic amines are much more easily oxidized[76] and can thus not be used.

Very often side reactions take place when an attempt is made to oxidize an aromatic alcohol under these conditions. The reason is that a radical or radical ion intermediate starts a polymerization reaction at the electrode surface which is then fairly rapidly covered with a layer of tarrish product; this insulates the electrode from the solution and prohibits further transfer of electrons. This type of side reaction not only lowers the yields but in most cases prevents the use of the method for the preparation of aromatic aldehydes.

Certain aromatic alcohols, such as benzophenone pinacol and fluorenone pinacol[90], are oxidizable at controlled potential even in aqueous solution; the reaction involves a carbon–carbon cleavage with the formation of the parent ketone

$$R_2C(OH)C(OH)R_2 \longrightarrow 2e + 2H^+ + 2\,R_2CO$$

C. Oxidation of Phenols

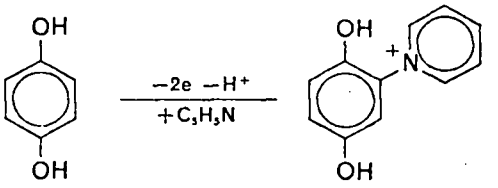
The presence of a hydroxyl group on an aromatic nucleus lowers the oxidation potential of the system considerably; thus in acetonitrile the halfwave potentials, at a platinum anode, of benzene, phenol and hydroquinone are 2·00, 1·21 and 0·71 (vs Ag^+/Ag), respectively.

Electrolytic oxidation of phenols generally yields a mixture of compounds, but often the amount of high-molecular weight coupling products can be kept lower than in most chemical oxidations. The electrode reactions of phenols can be described by the general scheme for the electrochemical oxidation of aromatic compounds given above. The two-electron oxidations (a and b) often involve an attack by a nucleophile, whereas the one-electron oxidations result in coupling.

1. Two-electron oxidations

A simple overall two-electron oxidation is the oxidation of hydro-

quinones to quinones which is the common reaction of *o*- and *p*-dihydroxy benzenes; it might be mentioned, however, that on anodic oxidation[14, 91] of hydroquinone (**18**) in acetonitrile containing pyridine and sodium perchlorate *N*-(2,5-dihydroxyphenyl)-pyridinium perchlorate (**19**) was formed. This oxidation is analogous to the oxidation of anthracene to 9,10-dihydroanthranyl dipyridinium diperchlorate[92].



(18) (19)

In this case the electron-attracting properties of the pyridinium substituent make the system more difficultly oxidizable than the parent hydroquinone, and the product is not oxidized further at the potential used.

When the attacking nucleophile is a hydroxyl ion (or water) the product is more easily oxidizable than the starting material, and the primary product is oxidized further in preference to the starting material. The existence of the hydroxylated compound is then only indicated by its oxidation products. Thus phenol is oxidized to benzoquinone and maleic acid; when hydroquinone has been reported as a product, the oxidation has been performed in a non-divided cell and the hydroquinone is formed by reduction at the cathode of some of the quinone.

Under voltammetric conditions the anodic hydroxylation may be demonstrated; this is illustrated in Figure 5 which shows (curve A) the result of a cyclic voltammetric[93] investigation of 1,5-dihydroxy-naphthalene (**20**) in 2M perchloric acid at a carbon paste electrode[94]. The initial anodic oxidation peak N [at +0·54 V vs (SCE)] is not followed by the expected cathodic reduction peak of the corresponding quinone. Instead, a rapid follow-up chemical reaction produces another product, and its reduction and subsequent reoxidation occurs at J and J′, respectively; as seen from Figure 5, they form a reversible redox system. This system was subsequently identified as 5-hydroxy-1,4-naphthoquinone (**21**) 1,4,5-trihydroxynaphthalene (**22**). Curve B depicts the cyclic voltammetric trace of this redox system, and it shows that the product obtained by anodic hydroxylation

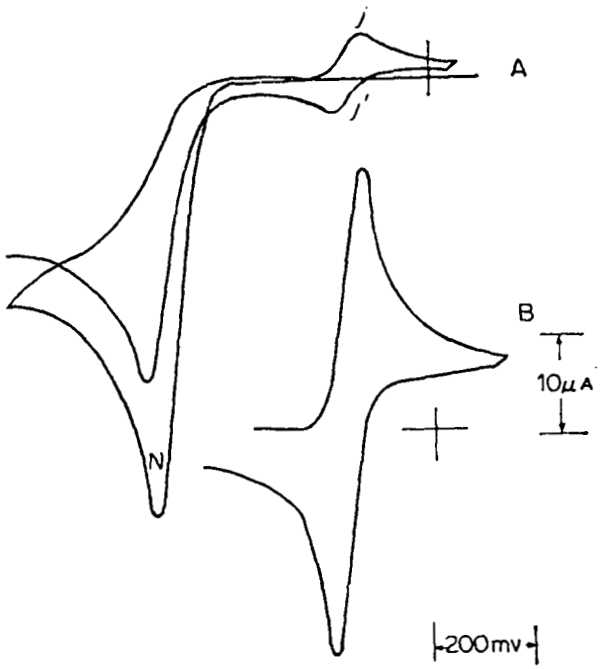
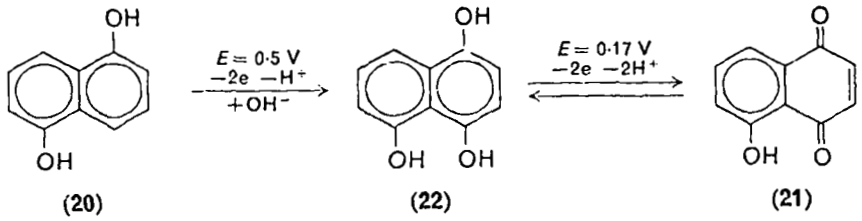


FIGURE 5. Cyclic voltammetry of anodic hydroxylation of 1,5-dihydroxynaphthalene: (A) cyclic polarogram of 1,5-dihydroxynaphthalene in 2M $HClO_4$; (B) cyclic polarogram for oxidation of 1,4,5-trihydroxynaphthalene in 2M $HClO_4$.

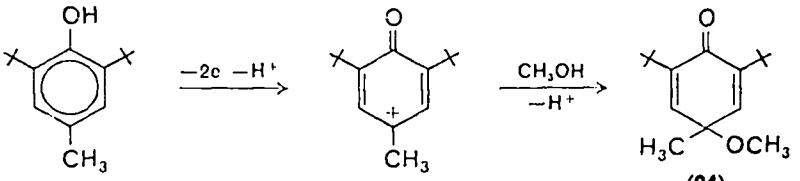
of 1,5-dihydroxynaphthalene is oxidized at a potential about 0·35 V less positive than that of the starting material,



(20) (22) (21)

Other nucleophiles such as halogens, thiocyanate ions, methoxide ions or methanol may attack during the anodic oxidation. In some cases it may be questionable whether an oxidation of the nucleophile rather than that of the phenol is the electrochemical step. An electrochemical oxidation of a phenol may be illustrated by the anodic

reaction of 2,6-di-*t*-butyl-4-methylphenol (**23**) in acetonitrile containing some methanol[95]:

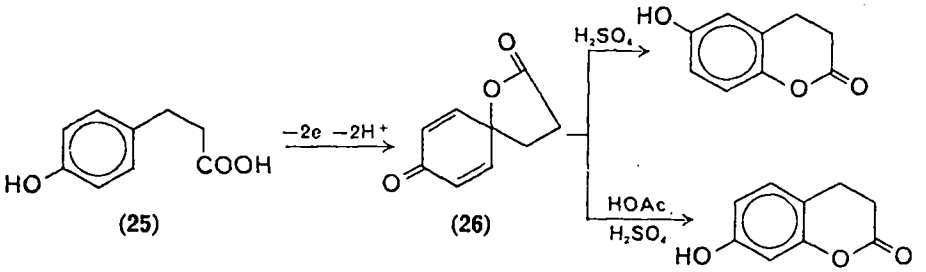


(23) (24)

Besides the dienone (**24**) 2,6-di-*t*-butylbenzoquinone was isolated, formed by further oxidation of **24**.

The primary oxidation product from a phenol may also be stabilized by an intramolecular nucleophilic attack which results in a ring closure. The two following examples may illustrate this.

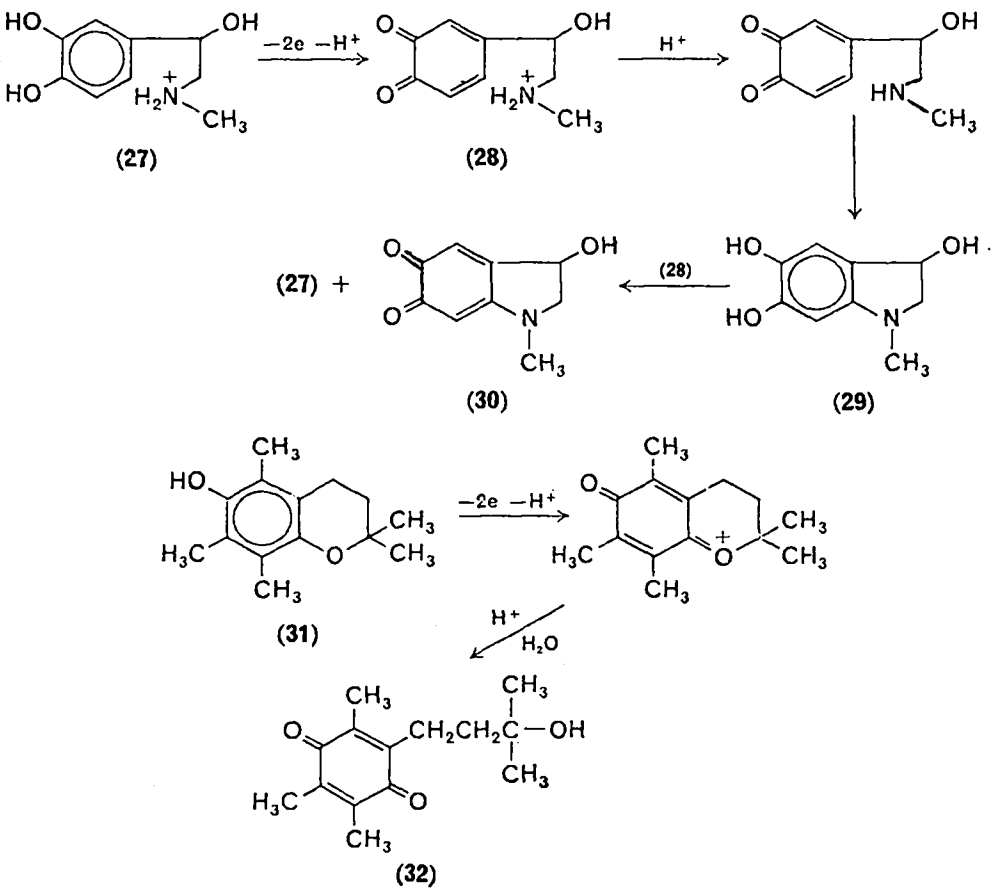
Electrolysis at a platinum anode of *p*-hydroxyphenylpropanoic acid (**25**) yielded the dienone lactone (**26**) in 20% yield. Using **25** labelled in the carboxyl group with ^{18}O it was demonstrated that the reaction proceeds intramolecularly[96].



(25) (26)

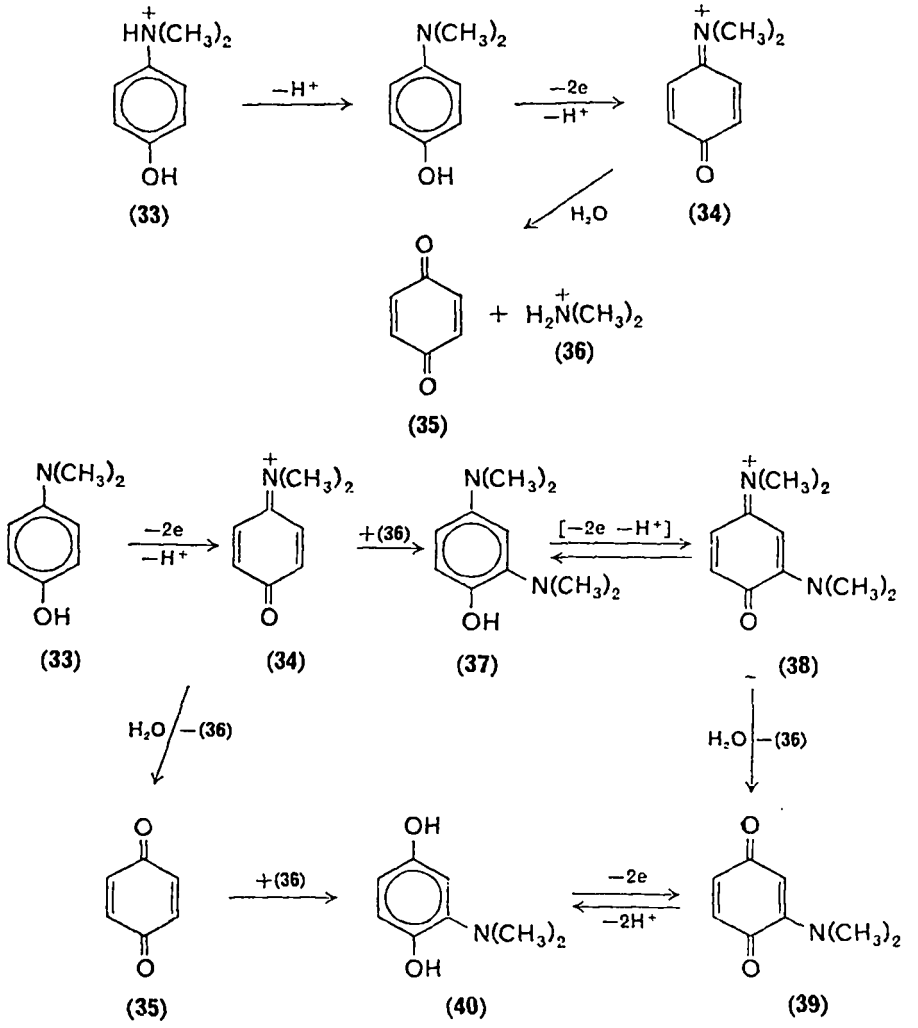
In a cyclic voltammetric investigation at the carbon paste electrode of various catecholamines such as adrenaline (**27**)[97], it was shown that in 1M H_2SO_4 the oxidation yielded the 1,2-benzoquinone (**28**). At pH 3, however, sufficient of the free amine of **28** was present to make an intramolecular nucleophilic addition to the *o*-quinone. As would be expected, the resulting catechol (**29**) is more easily oxidizable than adrenaline (**27**) and is converted into the quinone, adrenochrome (**30**) by chemical oxidation by adrenalinequinone (**28**).

A ring fission may also be induced anodically. Thus the chromane (**31**) is cleaved to the quinone (**32**)[98], as the initial oxidation product is attacked by water. A similar cleavage is often found when O-alkylated[99] or acylated[100] derivatives of hydroquinones are oxidized anodically to a quinone.



The oxidation of *p*-dimethylaminophenol (**33**)[101] shows some interesting features. In acid solution the oxidation is a two-electron reaction to yield *N,N*-dimethylquinoneimine (**34**) followed by hydrolysis to benzoquinone (**35**) with loss of dimethylamine (**36**). This reaction is similar to the anodic oxidation of *p*-aminophenol[102].

In alkaline solution, however, the reaction is complicated by an attack of **36**, formed by hydrolysis of the primarily obtained **34**, on unhydrolysed **34** to give 2,4-bis(dimethylamino)phenol (**37**), which then is oxidized by **34** to 3-dimethylamino-*p*-*N,N*-dimethylbenzoquinoneimine(**38**) (in the scheme below this is represented by an electrochemical oxidation in brackets). Hydrolysis of **38** yields dimethylamino-*p*-benzoquinone (**39**). **39** can also be obtained by electrochemical oxidation of 2-dimethylaminohydroquinone (**40**) which is formed by attack of **36** on **35**; this Michael addition is

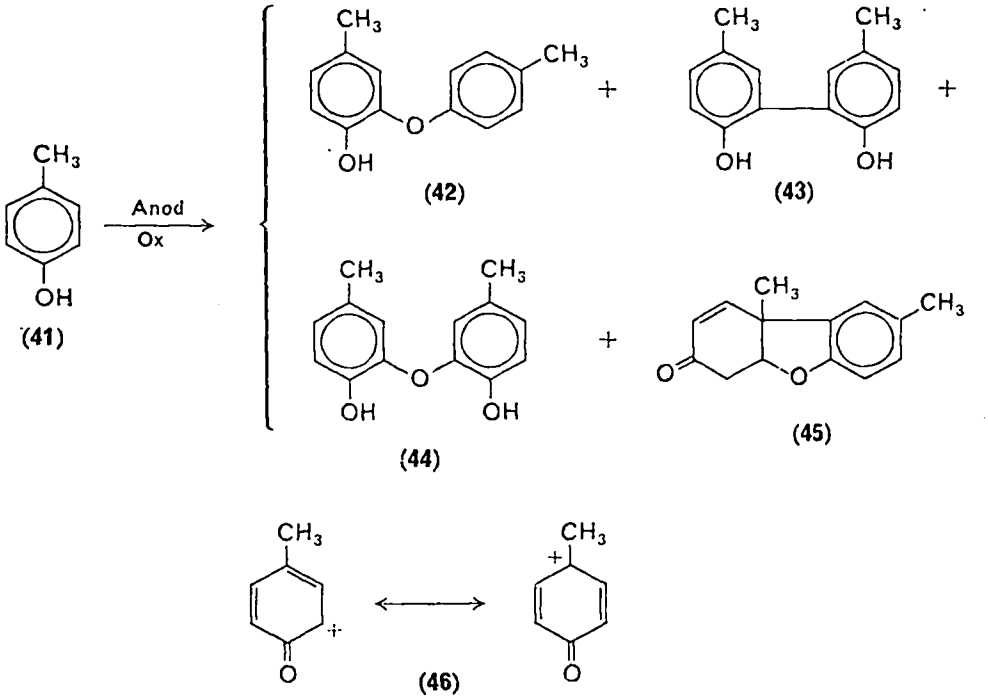


slower than the addition of **36** to **34**. The reactions are depicted above.

The overall reaction of **33** is thus a four-electron oxidation to **39**.

2. One-electron oxidations

When the primarily formed radical from the oxidation of a phenol reacts with another radical a C–C or a C–O coupling may occur[103–106]. The coupling products may then undergo further reactions. The oxidation of *p*-cresol (**41**) may be taken as a typical example[103, 104].



In some of these reactions in which **42**, **43**, **44** and **45** are formed it can be discussed whether the coupling occurs between two radicals or between a carbonium ion and a nucleophile. **42** can thus be formed by a reaction between the nucleophile **41** or its anion and a two-electron oxidation product (**46**) of *p*-cresol or from two cresoxy radicals in a similar way as **43**. Also the Pummerer ketone **45** may, in principle, be formed by an electrophilic attack by **46** on *p*-cresol, followed by intramolecular Michael addition of the hydroxyl group to the dienone. It is thus necessary to obtain unequivocal data in each case before any reaction mechanism is accepted.

Besides the simple coupling products described above further coupling may be induced anodically with the formation of polymerized material, but such tarrish material is often formed to a lesser degree than in many chemical oxidations.

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The Chemistry of The Hydroxyl Group: Part 1
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CHAPTER 6

Detection and determination of hydroxyl groups

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I. DETECTION AND DETERMINATION OF HYDROXYL GROUPS

The discussion below includes alcohols, glycols, polyhydric alcohols and enols (including phenols). The hydroxyl group has some characteristic chemical reactions; these form the basis of *chemical methods* of detection and determination. In addition, the group has certain *optical absorption* properties which can also be used. Since there is a proton in the hydroxyl group, *nuclear magnetic resonance* is an excellent method for detection and determination.

Mass spectrometry is not discussed in this chapter since the fragmentation which occurs is not definitive for the hydroxyl group. The same is to be said for X-ray diffraction though it should be realized that both these approaches are very valuable in characterizing and proving structure. Powder X-ray patterns, however, make an excellent method for comparing unknown and known samples of hydroxyl compounds or their derivatives.

II. CHEMICAL METHODS

A. Qualitative

1. Identification of hydroxyl compounds with derivatization

References 1 and 2 yield boiling point or melting point data for a wide variety of liquid and solid hydroxyl compounds. Reference 3 gives boiling point, melting point, refraction index and density for a very wide range of alcohols and phenols.

X-ray diffraction parameters on solid hydroxyl compounds provide an excellent method of identification. This is discussed on page 298. The X-ray measurements on some hydroxyl compounds are listed in the ASTM compilation of X-ray data. Even if the X-ray data on the specific hydroxyl material are not listed in the ASTM compilation, X-rays can serve to compare the unknown with suspected known materials.

2. Dinitrobenzoate derivatives

These are the most common derivatives of hydroxyl compounds. They are generally solids with convenient melting points and characteristic X-ray diffraction patterns.

Preparation[4]: For alcohol samples containing less than 5% water, 1·5–2 millimoles are heated in a small test tube with 1 millimole of 3,5-dinitrobenzoyl chloride*. The mixture is heated gently at the lowest temperature at which it remains liquid. The lower alcohols are heated for 3–5 minutes and the higher alcohols for 10–15 minutes. The melt is cooled and the solidified mass is then broken up with a spatula. The resultant solid is shaken with 2% sodium carbonate at 50–60°C for about 10–30 seconds and filtered. This removes the unreacted acid halide and any free acid from the derivative. Prolonged carbonate treatment should be avoided since it could cause hydrolysis of the ester. The product is crystallized from methanol or ethanol to which water is added to the first cloudiness before cooling. Usually only one crystallization is needed. However, a faulty carbonate wash could necessitate two or three crystallizations.

In cases of unreactive alcohols or polyhydric alcohols, the use of a solvent is recommended. Isopropyl or *n*-butyl ether are recommended (making sure that they are free of alcohol). The mixture of alcohol solution and reagent is refluxed for 0·5–1 hour. The mixture is then washed with sodium carbonate solution. The ether layer is separated and evaporated to dryness. The crude ester is recrystallized as above. With tertiary alcohols which are difficult to esterify, pyridine is used as a solvent. One millimole of reagent is mixed with 1·5 millimole of alcohol in a small test tube with 2 ml of pyridine. The mixture is refluxed for 0·4–1 hour, cooled and extracted with 4 ml of 1% sulphuric acid to remove the pyridine and precipitate the crude ester. Recrystallization is as described above.

Samples which contain more than 5% water might hydrolyse the acid chloride reagent. In this case, a sample containing 250–500 mg of alcohol is cooled to 0°C and is shaken with a solution of 500 mg of the acid chloride in a mixture of 2 ml of specially purified hexane (ligroin or petroleum ether) and 3 ml of benzene. The hexane is

* 3,5-Dinitrobenzoyl chloride is susceptible to hydrolysis by atmospheric water on standing. It is best to check the melting point of the available reagent. If the melting point is 1–2° lower than the literature value, the acid halide should be recrystallized from carbon tetrachloride. On purchasing the acid halide, it is best to buy several small bottles rather than one large one to avoid atmospheric contamination of unused material.

purified by washing, first with concentrated sulphuric acid, next with water, drying over calcium chloride or sulphate and then distilling. The reaction mixture is kept below 5°C with shaking for 15–30 minutes. Alcohol-free ether is then added, followed by vigorous shaking. The upper layer is separated, washed first with diluted sodium hydroxide, then with diluted hydrochloric acid, then with water. The solvent is evaporated and the crude ester is recrystallized as above.

Another reference to the above derivatization of hydroxyl compounds is given in Reference 5.

Tables of melting points of the 3,5-dinitrobenzoate esters of hydroxyl compounds are given in References 1–3. In addition, Garska, Doutkit and Yarborough[6] give the crystal data obtained by X-ray diffraction of 3,5-dinotrobenzoates. In addition, the identity of the components in mixtures of hydroxyl compounds can often be ascertained, and otherwise impure derivatives can be identified without complete purification being required. The authors of this chapter recommend the X-ray approach for comparing the derivative parameters of the unknown hydroxyl compound to those of the known.

3. Other ester derivatives

Less common ester derivatives for hydroxyl compounds include acetates, benzoates, *p*-nitrobenzoates, phthalates and nitrophthalates. Methods for preparation of these derivatives are given in References 7 and 8. The melting points of the derivatives are found in References 1–3.

4. Urethane derivatives

Among urethane derivatives of hydroxyl compounds the α-naphthyl urethanes are probably the most common since so many are solids. However, the phenyl urethanes are also used. Occasionally the β-naphthyl, *p*-bromophenyl, *o*-nitrophenyl, *m*-nitrophenyl and *p*-nitrophenyl urethanes are also used. The urethanes are prepared from the corresponding isocyanates:

$$R'OH + RNCO \longrightarrow RNHCOOR'$$

Preparation[9]: One millimole of hydroxyl compound is mixed with 1·25 millimoles of α-naphthyl isocyanate in a small test tube and heated in a water bath at 60–70°C for 10–15 minutes. The crude product solidifies on cooling and is pulverized with a microspatula.

This powder is then extracted with a minimum amount of petroleum ether to remove the soluble impurities. The first extract contains a large amount of the urethane derivative along with the impurities. A second extraction is made; this extract usually contains rather purer urethane. The insoluble residue is usually di-α-naphthyl urea formed by reaction with water in the sample or reagents used. It is well to note that this method cannot be applied to samples which contain more than a trace of water.

In the case of rather unreactive hydroxyl compounds such as phenols, the isocyanate and the sample are mixed in a test tube and heated for 2–5 minutes. If no reaction is observed, 1 ml of pyridine is added along with one drop of 10% trimethylamine in hexane, and the mixture is heated for 20–30 minutes. If the urethane does not separate on cooling, 1 ml of 5% sulphuric acid is added. The crude urethane is crystallized from petroleum ether.

Another description of the preparation of urethane derivatives can be found in Reference 10.

Tables of melting points of the urethane derivatives of a wide range of hydroxyl compounds can be found in References 1–3.

5. Other derivatives

Xanthates are formed by reaction of primary and secondary alcohols with carbon disulphide and base can be used[10].

$$ROH + CS_2 + KOH \longrightarrow ROCSK + H_2O$$

Tertiary alcohols are often difficult to derivatize by the above methods. However, these alcohols readily form the corresponding alkyl halides. The halide can then be derivatized further to the *S*-alkylthiuronium picrate[11].

Phenols react readily with bromine and these bromo derivatives can be used for identification[12]. However, the reaction is clear-cut only for a narrow range of phenols. Substituents on the phenol which are easily oxidized, such as –CHO, –SH, $-NH_2$ can cause problems. In alkyl phenols side-chain substitution may occur, giving a mixture of brominated products.

References 1–3 give melting points of some of these miscellaneous derivatives.

6. Handling of mixed derivatives

If the sample contains a mixture of alcohols, one usually obtains a mixture of derivatives. The mixed 3,5-dinitrobenzoates of alcohols

can often be resolved by column or paper chromatography[13–15]. Mixtures of the 3,5-dinitrobenzoates of phenols can often be similarly resolved[13,14] observing additional conditions[16–18]. Separation of mixed xanthate derivatives is possible[19]. The use of *p*-phenylazobenzoate derivatives is advantageous because they are coloured and the chromatography is more easily carried out[20].

B. Quantitative

1. Esterification methods

Esterifications for quantitative analytical purposes include the three general reactions illustrated in equations (1–3).

$$RCOOH + R'OH \rightleftarrows RCOOR' + H_2O \quad (1)$$

$$RCOCl + R'OH \longrightarrow RCOOR' + HCl \quad (2)$$

$$(RCO)_2O + R'OH \longrightarrow RCOOR' + RCOOH \quad (3)$$

Esterification with a carboxylic acid has the main disadvantage that it normally involves an unfavourable equilibrium. Bryant, Mitchell and Smith[21] succeeded in shifting the equilibrium almost completely to the right by using a large excess of acetic acid in the presence of boron trifluoride as catalyst and dioxane as solvent. After two hours at 67°C, pyridine was added to destroy the activity of the boron trifluoride. One mole of water is obtained per mole of alcoholic hydroxyl and is titrated with Karl Fischer reagent. This procedure is applicable to aliphatic, alicyclic and aralkyl alcohols and to hydroxy acids. Phenols react incompletely. Aldehydes and ketones interfere and amines decrease the activity of the catalyst. The accuracy reported was $\pm 0{\cdot}3\%$, but much care is required in the use of the sensitive Karl Fischer reagent.

Acid chlorides have not been widely used for hydroxyl group determinations. Although they react rapidly and completely their instability, due to great reactivity, discourages their use. However, procedures have been developed, based on the acid chloride reaction, and these have proved valuable, especially for some sterically hindered and tertiary hydroxyl groups which cannot be esterified by other methods.

Smith and Bryant[22] and Kaufmann and Funke[23] demonstrated quantitative esterifications with acetyl chloride in the presence of pyridine. One equivalent of titratable acid is produced for each mole of alcohol. Kappelmeier and Mostert[24] used a similar procedure to determine hydroxyl values of alkyd resins. Kepner and Webb[25] omitted the pyridine and used a toluene mixture and a semimicro

technique. Bring and Kadleck[26] employed stearoyl chloride as the reagent to determine the hydroxyl groups in epoxy resins.

Probably the most practical of the acid chloride procedures is that of Robinson, Cundiff and Markunas[27] involving 3,5-dinitrobenzoyl chloride. The reaction is illustrated in equation (4), with Ar = 3,5-

$$ROH + ArCOCl + C_6H_6N \longrightarrow ArCOOR + C_5H_5N.HCl \qquad (4)$$

$(NO_2)_2C_6H_3$–. The excess dinitrobenzoyl chloride is hydrolysed as indicated by equation (5). The pyridinium hydrochloride and the

$$ArCOCl + H_2O + C_5H_5N \longrightarrow ArCOOH + C_5H_5N.HCl \qquad (5)$$

dinitrobenzoic acid titrate simultaneously as strong acids and give the first inflexion in a potentiometric curve when titrated with tetrabutylammonium hydroxide solution. The dinitrobenzoate titrates as a weak acid, represented by a second inflexion. The amount of dinitrobenzoate formed is a measure of the organic hydroxyl content. Another end-point indication which can be used is a colour change from yellow to red by a reaction product at the first equivalence point. Polyols, sugars, phenols, primary and secondary amines, and some oximes may be determined. Aldehydes, if present in amounts less than 40% of the alcohol being determined and ketones do not interfere.

Procedure[27]: A fresh 0·2M solution of 3,5-dinitrobenzoyl chloride (1·15 g in 25 ml of pyridine) is prepared for each series of analyses. The solution should not be unnecessarily exposed to moist air.

To determine liquid samples, approximately 4 meq of the hydroxyl compound is pipetted into a tared 10-ml volumetric flask containing 3 ml of pyridine. The flask and contents are reweighed and the contents are brought to volume with pyridine. Four millilitres of the dinitrobenzoyl chloride and 1 ml of the sample solution are pipetted into a 125-ml glass-stoppered flask. The flask is stoppered tightly and allowed to stand 5–15 minutes at room temperature.

To determine solid samples, 0·4 meq of the hydroxyl compound is weighed directly into a 125-ml glass-stoppered flask and 4·0 ml of the dinitrobenzoyl chloride solution are added. The flask is stoppered, swirled to dissolve the sample and allowed to stand 5–15 minutes at room temperature.

In either case, at the end of the reaction period, the stopper is removed and 7–10 drops of water are added.

To prepare a blank solution, 4·0 ml of the dinitrobenzoyl chloride solution are pipetted into a flask and 7–10 drops of water are added immediately.

For the visual titration, 40 ml of pyridine are added to the reaction mixture, the mixture is heated nearly to boiling, cooled, and then titrated with 0·2N tetrabutylammonium hydroxide to the first definite and permanent red colour. The titration is best performed with the titrant and solution protected from moisture and air and the tip of the burette immersed in the titrating solution. For the potentiometric titration, 25 ml of pyridine are added to the reaction mixture and heated nearly to boiling. The mixture is cooled and transferred to a 250-ml beaker. The flask is rinsed with two 10-ml portions of pyridine and the washings added to the beaker. The mixture is titrated under nitrogen with 0·2N tetrabutylammonium hydroxide. If a blank is determined, the titration need proceed only through the first inflexion point. The differences in volume between the end-points of the blank and samples are used to calculate the hydroxyl content. If no blank is determined, the titration is carried through both inflexions and the volume between the first and second end-points is used to calculate the hydroxyl content.

Quantitative esterifications are usually accomplished by anhydrides, with acetic anhydride, phthalic anhydride and pyromellitic dianhydride being the reagents of choice. A primary or secondary alcohol is acetylated conveniently by reaction with acetic anhydride in the presence of a catalyst, equation (6). Catalysts include bases, Lewis acids, mineral acids and other strong acids. Sodium acetate is a weak basic catalyst. Pyridine is a more effective basic catalyst and is the one which has been most extensively used in quantitative acetylations. Boron trifluoride catalyses the reaction but strong acids such as sulphuric, hydrochloric, perchloric, 2,4-dinitrobenzenesulphonic and *p*-toluenesulphonic acids are more effective.

$$RCH_2OH + (CH_3CO)_2O \xrightarrow{\text{Catalyst}} CH_3COOCH_2R + CH_3COOH \qquad (6)$$

Among the acetylation methods the most practical approach involves the calculation of the hydroxyl content based on the difference between the acid formed by the alcohol reaction and the acid formed when a blank is treated with water, equation (7). Early methods for the determination of hydroxyl values of fats, oils and glycerol depended on the acetylation with acetic anhydride, neutralization of the acetylation mixture and determination of the saponification value of the ester. This method is now rarely used, but the technique may still be useful for the determination of alcohol groups in the

$$H_2O + (CH_3CO)_2O \longrightarrow 2\,CH_3COOH \qquad (7)$$

presence of compounds which react with the anhydride but do not form esters. For example, a method for the determination of hydroxyl groups in the presence of amine groups[28] involves the acetylation of both groups to form the corresponding esters and amides. Because esters in general hydrolyse much more rapidly than amides, a saponification reaction produces data for the calculation of the hydroxyl content of the original mixture.

Ogg, Porter and Willits[29] recommended a 1 : 3 mixture of acetic anhydride–pyridine and a 45 min reaction time on a steam bath followed by titration of the carboxylic acid formed. Primary and secondary amines and low molecular weight aldehydes interfere. Hydroxyl groups on tertiary carbon atoms and hydroxyls of 2,4,6-trisubstituted phenols react only very slightly[30]. Hydroxyl groups in less highly substituted phenols react readily with acetic anhydride.

Procedure[29]: A weighed sample containing from 0·010 to 0·016 equivalent of hydroxyl is placed in a 250-ml iodine flask and 10·00 ml of acetic anhydride–pyridine solution (1 : 3) are added. The flask stopper is moistened with pyridine and seated loosely. After the flask has been heated on a steam bath for 45 minutes, 5–6 ml of water are added to the cup of the flask and the stopper is loosened sufficiently to rinse it and the inside wall of the flask. The heating is continued for 2 minutes and the flask is then cooled under the tap with the stopper partly removed. The stopper and inside wall of the flask are rinsed with 10 ml of *n*-butanol. The contents are titrated with 0·5N alcoholic sodium hydroxide solution to a mixed indicator end-point (one part of 0·1% neutralized Cresol Red and three parts 0·1% neutralized Thymol Blue). A blank determination is made on 10 ml of the pyridine–acetic anhydride solution.

Triethylenediamine is claimed to be superior to pyridine for base-catalysed acetylations[31]. With this catalyst, the acetylation at reflux temperature of most primary and secondary alcohols is quantitative in 15–20 minutes. Salt catalysis with tetraethylammonium bromide was also found to produce quantitative results for the acetylation of cyclohexanol in 5 minutes and for tertiary alcohols in 45–65 minutes at reflux temperature[31].

Bring and Kadlecek[26] recommended acetic anhydride systems catalysed by sodium acetate, sulphuric acid, pyridinium chloride and pyridinium perchlorate. Fritz and Schenk[32] presented general methods based on the catalytic effect of perchlorate on the acetylation reaction. Ethyl acetate and pyridine were used as solvents. In most cases, the reaction was found to be complete in 5 minutes at

room temperature. Even highly hindered phenols can be determined.

Procedure[32]: 2M acetic anhydride in ethyl acetate is prepared by dissolving 4 g (2·35 ml) of 72% perchloric acid in 150 ml of ethyl acetate in a 250-ml glass-stoppered flask. Eight millilitres of acetic anhydride are pipetted into the flask and allowed to stand at least 30 minutes at room temperature. The contents are cooled to 5°C and 42 ml of cold acetic anhydride are added. The flask is kept at 5°C for an hour and then allowed to come to room temperature. The reagent is stable for at least 2 weeks at room temperature.

To prepare 2M acetic anhydride in pyridine, 0·8 g (0·47 ml) of 75% perchloric acid is added dropwise to 30 ml of pyridine in a 50-ml flask with magnetic stirring.

The 0·55M sodium hydroxide titrant is prepared by adding 430 ml of water and 5400 ml of methyl Cellosolve or absolute methanol to 185 ml of saturated aqueous sodium hydroxide.

One part of 0·1% neutralized aqueous Cresol Red is mixed with 3 parts of 0·1% neutralized Thymol Blue to prepare the mixed indicator.

A weighed sample containing from 3 to 4 millimoles of hydroxyl is placed in a 125-ml glass-stoppered flask. Five millilitres of 2M acetic anhydride in ethyl acetate or pyridine are added. The mixture is stirred until solution is complete and the reaction is allowed to proceed for at least 5 minutes at room temperature (some alcohols require a somewhat longer reaction period if pyridine is used as the solvent). One or 2 ml of water are added, mixed, and then 10 ml of 3 : 1 pyridine–water are added. The flask is allowed to stand 5 minutes. The mixture is then titrated with 0·55M sodium hydroxide using the mixed indicator and the end-point is taken as the change from yellow to violet. A reagent blank is run by pipetting exactly 5 ml of acetylating reagent into a 125-ml flask containing 1–2 ml of water. Ten millilitres of 3 : 1 pyridine–water solution are added and the mixture is allowed to stand 5 minutes. The titration is performed as for the sample.

Caution! Solutions acetylated with perchloric acid present should not be heated and the sample and blank solutions should be disposed of promptly after the determination is completed.

The same workers[32] used *p*-toluenesulphonic acid in pyridine to catalyse the acetylation of sugars. This reaction was completed in 5–10 minutes at 50°C. Magnuson and Cerri[33] claimed that 1,2-dichloroethane is superior to ethyl acetate as the solvent for the perchloric acid-catalysed acetylation. The perchloric acid-catalysed

system cannot be applied to polyethylene and polypropylene gycol ethers[30]. Erratic results are obtained, possibly due to oxidation of the chain by the perchloric acid. Pietrzyk and Belisle[34] suggested 2,4-dinitrobenzenesulphonic acid as a replacement for perchloric acid because it is highly acid and stable to heat and does not attack the polyglycol ethers.

A method has been reported for the analysis of mixtures of alcohols based on the difference in their esterification rates with acetic anhydride[35]. With this method the primary and secondary alcohol contents of mixtures can be determined, primary and secondary alcohol groups on the same molecule can be distinguished, and alcohols of a homologous series—even members different by only one carbon atom—can be distinguished. For the acetylation of mixtures of alcohols a conventional second-order rate plot shows a straight-line portion after the faster reacting hydroxyl has been consumed. The straight line is extrapolated to zero time and the amount of slower reacting component is calculated.

Procedure[35]: A sample containing 0·05 mole of hydroxyl is transferred to a 250-ml volumetric flask with pyridine and diluted almost to 240 ml with pyridine. Ten millilitres of acetic anhydride are pipetted into the flask. The mixture is rapidly diluted to volume with pyridine and the time noted. At intervals, 10 ml aliquots are pipetted into glass-stoppered flasks, 5 ml of water added and times again noted. Each is allowed to stand at least 10 minutes and is then titrated with 0·1N alcoholic potassium hydroxide to a mixed indicator end-point (a 2 : 1 mixture of 0·1% Nile Blue sulphate in 50% ethanol and 1% phenolphthalein in 95% ethanol). To determine the blank, 10 ml of acetic anhydride are pipetted into a 250-ml volumetric flask and diluted to volume with pyridine. A 10-ml aliquot of this is treated in the same manner as the sample.

Log $(b - x)/(a - x)$ is plotted against t, where x is the concentration of anhydride consumed in time t, a is the total initial hydroxyl group concentration and b is the initial concentration of anhydride. If the presence of two hydroxyl types is indicated by two slopes in the plot, a straight line is drawn representing the less reactive hydroxyl group (the second slope) and extrapolated to zero time. If the concentration of the more reactive hydroxyl group is designated a_1, then $x = a_1$ at the point (y) of intersection of the extrapolated line and the zero time coordinate. Substitution of a_1 for x gives the expression, $\log (b - a_1)/(a - a_1) = y$. The value of y can be obtained from the plot and the equation solved for a_1. Subtraction of the concentration

of the more reactive hydroxyl group from the initial total hydroxyl concentration gives the concentration of the less reactive hydroxyl.

The phthalation reaction is less rapid and is less widely applicable for hydroxyl analysis but does not suffer from interference by aldehydes. Phenols fail to react with phthalic anhydride; therefore, alcohols can be determined in their presence with this reagent. Elving and Warshowsky[36] carried out the reaction either under reflux or in pressure bottles in the presence of pyridine. The titrations of the phthalic acid formed were made with aqueous sodium hydroxide solution to a phenolphthalein end-point.

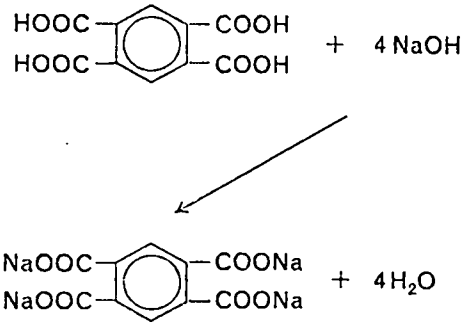
Procedure[36]: For samples containing a high percentage of ethanol, a sample weighing 1·0 to 1·5 g is pipetted into a weighed 50-ml volumetric flask containing 30–40 ml of pyridine. For higher alcohols and dilute solutions of ethanol, larger samples should be taken. After reweighing, the solution is made to volume with pyridine. Into a pressure bottle are pipetted 25 ml of a solution of 20 g of phthalic anhydride in 200 ml of pyridine, and 10 ml of the sample solution are added. The sealed bottle is placed in an air oven at 100°C and is heated for 1 hour. After cooling to room temperature, the pressure is carefully released and 50 ml of water are added. The mixture is cooled under a cold water tap and titrated with 0·35N sodium hydroxide, with phenolphthalein as the indicator. A blank determination is made in the same manner and the reagents employed.

Ethanol could be accurately determined in samples containing as much as 85% water. However, water adversely affects the phthalation of alcohols in general[30]. It appears that the observed esterification of ethanol was actually the reaction of the alcohol and phthalic acid.

Pyromellitic dianhydride combines the advantages of acetic anhydride and phthalic anhydride—it can be used in the presence of aldehydes, it is not volatile, it can be used to determine alcohols in the presence of phenols and its rate of reaction compares favourably with that of acetic anhydride[37]. The reaction is best carried out in dimethyl sulphoxide in the presence of pyridine[38]. All four acid groups are neutralized at the phenolphthalein end-point (equation 8). Pyromellitic dianhydride does not attack ether linkages of polyglycol ethers and is useful therefore for the determination of the hydroxyl contents of these compounds.

Procedure[38]: Fifty millilitres of 0·5M pyromellitic dianhydride (109 g dissolved in 525 ml of dimethyl sulphoxide and 425 ml of pyridine added) are pipetted into a glass-stoppered 250-ml flask.

The sample containing 0·010 to 0·015 equivalents of alcohol is weighed and added to the reagent. The flask is placed on a steam bath and the stopper is moistened with pyridine and loosely seated. The contents are heated for 15–20 minutes (30 minutes for polyglycols). 20 ml of water are added and the heating continued for 2 minutes. The mixture is then cooled to room temperature and titrated with 1N sodium hydroxide solution to the phenolphthalein end-point. A blank in which only the sample is omitted is treated in the same manner.



(8)

Other anhydrides have been recommended for hydroxyl determinations and may offer advantages in specific situations. These include stearic anhydride[39], *o*-sulphobenzoic anhydride[40], propionic anhydride[41], succinic anhydride[42] and 3-nitrophthalic anhydride with triethylamine as the basic catalyst[43]. The last three listed were specifically recommended for the determinations of polyglycol ethers.

2. Acid–base methods (enols, phenols and nitroalcohols)

Most alcohols are slightly acidic but not sufficiently to be titrated. However, enols, phenols and nitroalcohols are acidic enough to be titrated in nonaqueous media though not in water. Nitro- and polynitrophenols can also be titrated in aqueous media.

Various nonaqueous media and titrants are used. Moss, Elliot and Hall[44] used ethylenediamine as solvent and the sodium salt of ethanolamine as titrant. Fritz[45] extended the method to include dimethylformamide as solvent as well and used sodium ethoxide dissolved in benzene–methanol as titrant. Deal and Wyld[46] and Harlow, Noble and Wyld[47] summarize the earlier methods for titrating weak acids in various solvents. The currently most popular method is described on the following page.

Procedure[48]:

a. Reagents and apparatus

Beckman general purpose glass electrode, No. 4990–80.

Beckmann sleeve type calomel electrode, No. 1170–71, modified by replacing the saturated aqueous KCl solution in the outer jacket with a saturated solution of KCl in methanol (designated hereafter as methanol modified calomel electrode).

Tetrabutylammonium hydroxide, 0·1N in 10 : 1 benzene–methanol prepared as described below.

Technical grade. Acetonitrile, pyridine and dimethylformamide.

Benzene–isopropanol, 10 : 1.

Thymol Blue indicator solution: 0·3 gm in 100 ml isopropanol.

Azo Violet indicator, a saturated solution of *p*-nitrobenzeneazoresorcinol in benzene.

b. Preparation of titrant. Forty grammes of tetrabutylammonium iodide are dissolved in 90 ml of absolute methanol. Twenty grammes of finely powdered silver oxide are added, followed by vigorous agitation of the mixture for 1 hour. A few millilitres of the solution are centrifuged and the supernatant is tested for iodide with aqueous silver nitrate. If the test is positive, 2 grammes of additional silver oxide are added and agitation is continued for an additional 30 minutes. When the iodide test is negative, the mixture is filtered through a sintered glass filter funnel of fine porosity. The reaction flask and funnel are rinsed with three 50-ml portions of dry benzene which are added to the filtrate. The filtrate is diluted to one litre with dry benzene. This solution is flushed for 5 minutes with dry, prepurified nitrogen and then stored in a reservoir protected from carbon dioxide and moisture. The titrant remains stable on extended storage. It is standardized against pure benzoic acid using either the visual or potentiometric methods described below.

c. Potentiometric titrations. An accurately weighed sample, sufficient to consume 2–10 ml of titrant, is placed in a 250-ml beaker and dissolved in 50 ml of solvent (see discussion below for choice of solvent). Insert the glass and methanol-modified calomel electrodes. The burette is covered with an Ascarite tube. Best results are obtained if titrations are carried out under a nitrogen blanket when dimethylformamide or pyridine are used as solvents. Titrant can be added in 0·05 ml increments in the region of the end-point. A blank should be run on solvents to account for any acidic impurities. A curve is plotted of millivolts against millilitres of titrants, the inflexion point or points are then determined.

Pyridine is reported to be the best solvent and to give the best end-points. However, dimethylformamide is also usable. Acetonitrile is reported as the best of the neutral solvents.

Good titrations can be obtained with the glass and the normal saturated calomel electrode. However, the sharpness of the inflexion points was markedly increased when the methanol-modified calomel electrode was used.

Hydroxyl compounds titrated potentiometrically in the original work include phenol, resorcinol, hydroquinone, dimethyl dihydroresorcinol, thymol, pyrogallic acid, catechol, *o*-, *m*- and *p*-hydroxybenzoic acids, cresol.

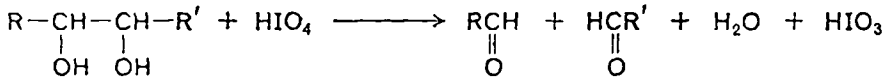
Tertiary butyl alcohol, isopropanol and acetone, as well as pyridine, were used as solvents, with a modified electrode system[49]. However, the general utility of the method remains as shown.

d. Visual titrations. An accurately weighed sample, sufficient to consume 5–10 ml of titrant is added to a 125-ml Erlenmeyer flask. Twenty-five ml of solvent is added with four drops of indicator (Thymol Blue for the weak acids or Azo Violet for the very weak acids). The titration should be as rapid as possible to the blue end-point in the case of Thymol Blue indicator to a violet (sometimes blue) end-point with the Azo Violet indicator. Blanks should be run on the solvents.

o- and *p*-nitrophenols were successfully titrated using Thymol Blue as an indicator and pyridine as sample solvent. Phenol, *p*-benzylphenol, *o*-phenylphenol, 1- and 2-naphthols, 2,5-dimethylphenol, *p*-bromophenol, catechol, pyrogallic acid and dimethyldihydroresorcinol were successfully titrated in pyridine as solvent with Azo Violet as indicator. Acetonitrile as solvent was used to titrate 1-naphthol. Phenolic compounds which were successfully titrated potentiometrically but which could not be visually titrated are thymol, hydroquinone, *p*-toluhydroquinone, *m*- and *p*-cresols.

3. Determination of 1,2 dihydroxy compounds (glycols)

The most general method for specifically measuring 1,2 dihydroxy compounds is the oxidation with periodic acid.



This reaction is specific and not generally influenced by the presence of monohydric alcohols or by polyhydric alcohols where

the hydroxyl groups are not on adjacent carbon atoms. Occasionally interference will be noted but this is rare; for example: 2-butyne-1,4-diol was found to be significantly oxidized by periodic acid under conditions of the analysis.

Procedure[50]: A sample containing 0·0005–0·001 moles of dihydroxy compound is weighed into a 50-ml glass-stoppered iodine flask. To this is added 100 ml of the reagent (5 g of HIO_4 dissolved in a mixture of 800 ml of acetic acid and 200 ml of distilled water). A blank is run on the reagent alone. The reaction mixture is allowed to stand for half an hour at room temperature; a few samples may require one hour but this can only be determined by trial. At the end of the reaction period 20 ml of 20% potassium iodide solution are added and the liberated iodine is titrated with 0·1N sodium thiosulphate. The titration on the sample should be more than 80% of the blank since the iodate formed in the reaction also liberates iodine, and, if all the periodic acid reacts, the back titration equals 75% of the blank.

$$\% \text{ glycol compound} = \frac{A \times N \times MW \times 100}{g \times 2000}$$

A = ml blank − ml sample
N = normality thiosulphate
MW = mole weight glycol compound
g = grammes sample

Long reaction periods should be avoided in cases where the reaction products include formaldehyde or formic acid, which are subject to slow oxidation.

1,2,3-Trihydroxy compounds consume two moles of periodic acid and generally liberate one mole of formic acid from the central carbinol moiety. The method of Bradford et al[51] enables the determination of these compounds (i.e. glycerol) in the presence of 1,2 dihydroxy compounds via the titration of the formic acid formed from the trihydroxy material.

4. Determination of trace quantities of hydroxyl compounds

a. Primary and secondary alcohols are determined through formation of benzoate esters, extraction of the ester and spectrometric determination of the ester in the extract. Johnson and Critchfield[52] esterified with 3,5-dinitrobenzoyl chloride. The ester was extracted with hexane. A colour was developed by addition of 2N sodium hydroxide and acetone to the extract, and measured at 575 mμ.

Scoggins[53] esterified with *p*-nitrobenzoyl chloride, extracted with

cyclohexane and measured the u.v. absorption of the ester in the extract at 253 mμ.

b. Secondary alcohols are oxidized to the ketone[54], the 2,4-dinitrophenylhydrazone of which is then prepared and measured colorimetrically. Primary alcohols do not interfere in this method since they are oxidized to carboxylic acids.

c. Tertiary alcohols can be determined by reaction with hydriodic acid to form the corresponding alkyl halide[55], which is extracted with cyclohexane and measured in the u.v. at the wavelength of maximum absorption (267–269 mμ).

Esterification[52] has been tried, but the reaction is very slow.

d. Phenols. The esterification methods[52, 53] may well be usable for measuring traces of phenols although apparently they had not been tried. However, an excellent method is the Azo dye formation when the phenol is coupled with a diazonium compound[56].

(9)

By using diazotized sulphanilic acid, the acid group lends water solubility to the resultant dyes. The method is fast, specific and sensitive to lower than 1 ppm of most phenols or naphthols.

III. PHYSICAL METHODS

A. *Infrared Spectroscopy*

1. Qualitative

In the infrared region the hydroxyl groups exhibit strong absorptions which are highly sensitive to structure. These absorptions provide an important means of characterizing compounds containing this function. Characteristic absorption positions are given in Table 1.

The hydroxyl group is highly polar and subject to strong association; therefore, the intensity of the hydroxyl stretching vibration is dependent on the degree of association in the system. Essentially, complete dissociation is observed only in the vapour state or, in some cases, when the hydroxyl-containing compound is diluted extensively with nonpolar solvents. In general, the presence of a band in the 2·7- to 3·0-μ region is a reliable indication of the presence of hydroxyl groups. Water, N–H groups and carbonyl groups cause interfering absorptions in this area.

TABLE 1. Infrared vibrations of hydroxyl compounds.

		Wavelength, μ	Ref.
	Free hydroxyl stretching vibrations		
Alcohols			
Fundamental vibration—	in alcohols in general	2·75–2·77	57
	in primary alcohols	2·746–2·753	58
	in secondary alcohols	2·754–2·762	58
	in tertiary alcohols	2·764–2·769	58
First overtone—	in alcohols in general	1·40–1·46	59
	in primary alcohols	1·405–1·410	60
	in secondary alcohols	1·413–1·415	60
	in tertiary alcohols	1·418–1·420	60
Second overtone—	in alcohols in general	0·877–0·980	59
Third overtone—	in alcohols in general	0·738–0·744	61, 62
Combination band—	in alcohols in general	1·95–2·15	58
Phenols			
Fundamental vibration		2·77–2·78	63
First overtone		1·404–1·418	64
Second overtone (doublet)		1·00 and 0·971	62,65
Third overtone (doublet)		0·7466 and 0·7698	66
	Bonded hydroxyl stretching vibrations		
Intermolecular hydrogen bonding—	dimeric	2·82–2·90	67
	polymeric	2·94–3·09	67
Intramolecular hydrogen bonding—	hydroxyl–organic group interaction	2·79–2·92	67
	hydroxyl–metal interaction (chelation)	3·12–4·00	68
	Hydroxyl bending vibration		
Hydroxyls in general		7·14–7·70	69
	Carbon–oxygen stretching vibrations		
Alcohols			
Primary—	straight chain	9·22–9·52	70
	α-branched and/or α-unsaturated	beyond 9·52	70
Secondary—	saturated aliphatic	8·90–9·20	70
	highly symmetrical	8·30–8·90	70
	branched at one α-carbon	9·10–9·20	70
	α-unsaturated	9·22–9·52	70
	alicyclic (5- or 6-membered ring)	9·22–9·52	70
	di-α-unsaturated	beyond 9·52	70
	α-branched and α-unsaturated	beyond 9·52	70
	alicyclic (7- and 8-membered ring)	beyond 9·52	70
Tertiary—	saturated aliphatic	8·30–8·90	70
	α-unsaturated	8·90–9·22	70
	cyclic	8·90–9·22	70
	highly unsaturated (e.g. triphenylcarbinol)	beyond 9·52	70
Phenols			
Phenols in general		about 8·3	70

Both intermolecular and intramolecular associations of the hydroxyl group are possible and displace the absorption to longer wavelengths. The type and degree of intermolecular bonding are dependent on temperature, molecular structure and environment. High temperature favours dissociation. Normally, most alcohols are found as polymeric species in the absence of steric effects. Indications are that cyclic dimers occur at relatively low concentrations as a result of nonlinear hydrogen bonding[71]. Solute–solvent hydrogen bonding can also influence the infrared spectra.

In contrast to intermolecular hydrogen bonding, which is highly concentration-dependent, intramolecular bonding is not affected by dilution with a nonpolar solvent such as carbon tetrachloride. Any electron-rich system, such as a double bond, a cyclopropyl ring, an aromatic ring, a halogen atom, and carbonyl, amino, nitro, ether and ester groups, will interact with the hydroxyl group if close enough in space and result in a shift and splitting of the free hydroxyl bond[72]. Diols show both intermolecular and intramolecular bonding[72–74].

The molar absorptivities of the hydroxyl groups of phenols are 3–4 times larger than those of alcohols which vary between 30–100 and remain within $\pm 10\%$ for alcohols of similar structure[58].

Hydrogen bonding also affects the hydroxyl bending vibrations, shifting the spectra to shorter wavelengths[75]. The C–O stretching vibrations are of great value in the differentiation of primary, secondary and tertiary alcohols for qualitative and structural work[70].

2. Quantitative

Many applications of infrared spectroscopy to the quantitative determination of hydroxyl-containing compounds have been made. However, because of the tendency of hydroxyl groups to form bonds with other polar groups, there are serious limitations of the technique for general use. With proper control of the conditions, infrared methods are successful in many specific situations. For example, samples have been diluted to the point where the concentration of the associated species is negligible and, in other cases, samples are run under conditions of complete association. Other methods depend on strict control of conditions so that the ratio of associated to unassociated species is constant and can be related to calibration curves prepared under the same conditions. Also, methods involving the preparation of derivatives and their examination at appropriate wavelengths have been used.

Ahlers and McTaggert[76] devised infrared methods for the determination of hydroxyl groups in autoxidized or copolymerized fatty esters and related compounds. Measurements were confined to dilute solutions in carbon tetrachloride where no absorption of the associated species was observed. The free hydroxyl determination was then based on the intensity of the absorption at 2·76 μ. Crisler and Burrill[64] determined aliphatic primary alcohols, using the hydroxyl stretching overtone band at 1·4 μ and in 0·04–0·06M solutions of the samples in carbon tetrachloride or tetrachloroethylene. It was found that a single calibration curve cannot be used for all hydroxyl-containing compounds because the band positions and intensities depend on the structures of the compounds. Hilton[77] used the 2·0–3·2-μ region to determine hydroxyl contents of polyesters and polyethers in 1 : 10 chloroform–carbon tetrachloride as the solvent. Temperature control of $\pm$0·1°C was found to be necessary and each new compound required calibration. Burns and Muraca[78] demonstrated that the hydroxyl absorptions at 2·84 μ of 14 different polypropylene glycols follow Beer's law with a standard deviation of 2·2%. The polypropylene glycols appear to exhibit intramolecular bonding through the hydroxyl group and an ether oxygen forming a five-membered ring. The hydroxyl band position was unaltered by dilution with benzene or carbon tetrachloride indicating the absence of intermolecular bonding. Murphy[79] determined the hydroxyl contents of alkyd resins in dichloromethane solutions at 2·85 μ. Corrections were required for the water and organic acid present in the resin. Adams[80] determined the hydroxyl content of epoxy resins at 3·08 μ. Pyridine was used as a solvent to produce associated hydroxyl bands exclusively. In the determination of the hydroxyl equivalents of steroids[81], the absorbance in pyridine was found to be linear with concentration for the associated band which appears near 3·05 μ and is essentially independent of the type of hydroxyl group, excepting those with phenolic hydroxyl groups. Dvoryantseva and Sheinker[82] used the molecular extinction coefficient of the band at approximately 3 μ to determine the number of hydroxyl groups in steroids that do not contain phenolic hydroxyl groups. It was demonstrated that the extinction coefficient does not depend on the position of the hydroxyl group in the molecule but is an additive value depending on the number of these groups.

Partridge and Kirby[83] used the absorption band at 2·80 μ to determine residual 2-ethylhexyl alcohol in di-2-ethylhexylphthalate. Interference due to water was eliminated by subtraction of the

absorption at 2·74 μ. Mitchell, Bockman and Lee[84] determined the acetyl content of cellulose acetate by measuring the absorbance due to residual hydroxyl groups at 1·445 μ. Shauenstein and Puchner[85] also used the 1·4-μ band to determine unbranched aliphatic primary alcohols in chloroform solution. The relative content of primary and secondary fatty alcohols (C_9 to C_{18}) in various industrial products of the oxidation of paraffins was based on the relation between the molar extinction coefficient and wave number in the region 960–1200 cm^{-1} [86]. Oba[87] used the 9·84-μ band to determine 0·2 to 5·0% methanol in ethanol by a differential technique. Gronau, Broadlick and Hamilton[88] determined the ethanol content of Thimerol Tincture NF at 11·37 μ after extraction of the alcohol from the sample with carbon tetrachloride.

Using a very thin absorption cell with barium fluoride windows, Potts and Wright[89] determined 5% solutions of ethylene glycol and diethylene glycol in water. The absorption at about 8·8 μ determines uniquely the amount of diethylene glycol present; ethylene glycol can be determined by the absorption at 9·2 μ after correcting for diethylene glycol present. It was also shown that 5% phenol and 10% ethanol in water could be determined.

Friedel[90] studied the absorbance at 2·89–3·01 μ of 22 phenols, mostly alkyl derivatives. Compounds containing methyl groups in both *ortho* positions showed no associated hydroxyl band or shoulder but ethyl or larger groups *ortho* to the hydroxyl showed weak associated hydroxyl bands at 2·89–2·93 μ. The use of these bands for quantitative analysis was suggested. Goddu[91] used the 2·7- –3·0-μ range for the qualitative and quantitative analysis of phenols. Samples containing as little as 25 ppm phenolic hydroxyl were analysed. The intramolecular bonding shifts in the hydroxyl band, which differ in degree depending on the type of phenol, were used to analyse mixtures which contain several phenolic species. Phenolic hydroxyl end groups were determined in solutions of aromatic polycarbonates using the band at 2·79 μ. Average molecular weights obtained by this method were in good agreement with data from osmometry, fractionation methods and ultracentrifugation.

Lippmaa[92] measured the absorption of solutions of phenols in anisole at 2·82 μ and 2·95 μ in lithium fluoride cells. Beer's law was found applicable for concentrations of 0·1 to 0·4 g equivalents of phenolic hydroxyl per litre. The ratio of the molar extinction coefficients for the two maxima was consistent for the phenols studied.

Kyriacou[93] determined hydroxyl groups in polypropylene glycol

by a procedure which basically involved a spectrophotometric titration with acetyl chloride. Different and definite amounts of acetyl chloride were added to equal weight portions of the sample. The amounts of acetylating reagent were chosen to obtain absorbances between 0·2 and 0·8. The absorbance was determined for each portion at 2·87 to 2·88 μ and plotted vs the respective acetyl chloride concentration. The amount of acetyl chloride required to react with the sample was taken as the point at which there was no further decrease in the hydroxyl absorption. Mamiya[94] determined hydroxyl groups in polyethylene and polypropylene glycols by titration of their toluene solutions containing zinc powder with toluene solutions of acetyl chloride. The absorption at 1·45 μ was used to determine the end-point.

Jaffe and Pinchas[95] determined dipentaerythritol in the presence of pentaerythritol by measuring the absorption of the corresponding acetates in carbon tetrachloride. The hydroxyl content of oxidized polyethylene was determined by infrared analysis after quantitative acetylation with acetic anhydride[96].

Hendrickson[97] determined primary hydroxyl groups in polyglycols by following the rate of disappearance of the hydroxyl band at 3·05 μ using triphenylchloromethane as the reactant. A rate plot was made and extrapolated to zero time. The rate of disappearance of the secondary hydroxyl band was measured and the quantity of primary alcohol determined by difference.

B. Nuclear Magnetic Resonance

Nuclear magnetic resonance is a powerful tool for functional group analysis. Each distinct type of atom is characterized by a specific chemical shift which does not change greatly from one molecule to another. In a manner analogous to vibrational frequencies, tables of chemical shifts have been compiled for the common functional groups containing hydrogen[98]. Utilizing these data together with the rules governing multiplet splitting, it is generally not difficult to assign the lines in an experimental spectrum. Consequently, n.m.r. has become one of the most commonly used instrumental methods in qualitative organic analysis.

Protons bound to an oxygen atom have two properties which complicate the interpretation of their spectra. First, the –OH groups have a variable chemical shift, depending on the extent of hydrogen bonding, if present. Secondly, although the O–H bond is thermodynamically stable, it is kinetically labile. The –OH proton

is capable of exchanging with labile protons on other sites. If this exchange is rapid enough, several distinct types of protons may be observed as a single n.m.r. signal, thus confusing the assignment of the spectrum. Furthermore, this exchange will also lead to the collapse of the multiplet structure of the –OH signal, causing the loss of valuable analytical information.

Hydroxyl groups in liquid organic samples are often involved in intermolecular hydrogen bonding with solvents containing basic groups. If the solvent is inert, dimers and higher polymers may be formed, or intramolecular hydrogen bonds can be formed if the steric factor is favourable. The complete absence of hydrogen bonding is observed only when no intramolecular hydrogen bonding is possible and the sample is a very dilute solution in an inert solvent. Then the chemical shift of the –OH proton of saturated aliphatic alcohols is approximately 0·5 ppm downfield from tetramethylsilane (δ scale). However, the experimental conditions most often encountered in n.m.r. work involve a moderately concentrated solution of the sample in an inert solvent. Under these conditions, a chemical shift between 3·0 and 5·2 is seen for hydroxyl protons of saturated alcohols. A higher degree of hydrogen bonding is reflected by a larger downfield shift.

A finite time is required for a collection of protons to come to equilibrium with the radio frequency field generated by the spectrometer. This depends on the relaxation times of the sample; it is usually several seconds for ordinary samples. Chemical processes taking place within this time span will affect the observed n.m.r. spectrum. Hydroxyl hydrogens may exchange with labile protons in mineral acids, carboxylic acids, water and other –OH containing compounds; in the absence of these the –OH protons on a given compound will exchange with each other. The n.m.r. spectrum reflects the exchange by an averaging process. When protons are exchanging rapidly between sites that ordinarily would have different chemical shifts, only one line is observed. The shift of this line is the average shift of the two sites occupied by labile protons weighted for the relative numbers of each site present. It is given by the relation[99]:

$$\sigma_{obs} = p_I\sigma_I + p_{II}\sigma_{II}$$

where σ_{obs} is the experimental chemical shift, σ_I is the chemical shift at site I, and p_I is the probability that a given proton be found at site I. The quantities p_{II} and σ_{II} refer to site II. In cases where

exchange takes place among equivalent sites, as in a pure liquid alcohol, the process has no effect on the chemical shift; but it does eliminate the spin–spin coupling between the –OH proton and neighbouring protons causing collapse of the multiplet structure of the line. Multiplet collapse also results in exchange between non-equivalent sites.

I. Direct analysis

Since –OH chemical shifts can vary over a large range, the presence of hydroxyl cannot be established unequivocally from a simple n.m.r. spectrum. If an –OH group is suspected, and a single line is observed in the proper region, it can be tentatively assigned as an –OH signal, but additional information will be required to confirm the assignment. The chemical shifts for several types of groups are given in Table 2.

TABLE 2. Chemical shift[a].

Group	Ordinary conditions	Infinite dilution
Saturated alcohol	3·0–5·2	0·5
Phenol	4·5–7·7	4·0–5·0
Enol	15·0–16·0	15·0–16·0

[a] Shifts are quoted in the δ scale, ppm downfield from tetramethylsilane.

a. Alcohols. If the sample contains no acidic impurities, the –OH signal usually falls in the predicted region. It is not uncommon for the line to be broadened slightly due to incipient spin coupling with neighbouring protons. This often shows up as a lack of ringing on the –OH peak. This effect cannot be used to make reliable assignments, however.

The common methods of identifying –OH signals are based on the lability of the hydroxyl proton. A small quantity of acid added to the sample will cause a pronounced downfield shift of the –OH signal. This is due to the rapid exchange of acid protons with –OH groups which causes an averaging of the signals from the two sites. Since the shift difference between an alcohol and an acid may be as large as 10 ppm, a relatively small amount of acid will cause a noticeable shift in the –OH resonance. Trifluoroacetic acid is a

favourite for this test since it is soluble in most n.m.r. solvents, and the molecule contains no protons other than the acid proton itself.

Another experiment that is diagnostic of hydroxyl protons (or labile protons in general) depends on hydrogen exchange with water. If the sample is shaken with a quantity of deuterium oxide, the labile hydrogens will be replaced by deuterium. Since the latter give no signal, a drastic reduction in the intensity of the labile proton signal results.

Recently a degree of success has been achieved in hydroxyl detection through the artifice of tying up the proton in a strong hydrogen bond, using a strongly basic solvent such as acetone or dimethyl sulphoxide (DMSO). In such solvents the lability of the –OH proton is reduced and spin–spin coupling can be observed. On the basis of the splitting pattern, the –OH can be classified as primary, secondary or tertiary. Furthermore, since all of the hydrogen bonding is between alcohol and solvent, there is no alcohol association–dissociation equilibrium. Hence the chemical shift of the –OH group will be concentration independent, and useful shift measurements can be made at convenient concentrations.

Such measurements were first made in acetone solution[100, 101] where it was noted that the proton exchange of benzyl alcohol is strongly inhibited. Later, Chapman and King[102] introduced the use of DMSO which is the favoured solvent today. In DMSO the –OH resonance is shifted downfield to $\delta = 4$ or lower, and the multiplet structure of the hydroxyl signal can be resolved. An early application of this technique was made by Casu et al[103] in their study of reducing sugars. DMSO is an excellent solvent for sugars, and it has the effect of slowing the mutarotation to the point where the spectrum of individual anomers can be seen, which is not the case in water. Since signals of individual –OH groups can be distinguished, this is a powerful tool for the investigation of such molecules. This solvent has also been used in the study of the conformation of cyclohexanols[104]. The coupling constant between the –OH and the carbinol protons has been used to estimate the HO–CH dihedral angle in a manner analogous to the work of Karplus[105] on HC–CH couplings.

Unfortunately, the DMSO technique is not applicable to all alcohols. Traynham and Knesel[106] discovered that the –OH splitting does not always appear in alcohols which contain an electron-withdrawing group close to the –OH. Groups such as alkoxide, vinyl and halide are effective in this respect. In some cases the

splitting can be developed by shaking the sample with solid K_2CO_3, but some alcohols are intractable even with this treatment. Later, Moniz et al[107] were able to observe –OH splitting in difficult cases by using dilute solutions in DMSO or in CCl_4 that had been rigorously dried. Replacement of CCl_4 by DMSO decreases the values of $J_{HC\text{-}OH}$ and has a levelling effect on their variation. Recently, Takino et al[108] were unable to observe splittings in certain alcohols. They suggested that acetone is more effective in producing splittings, although its effectiveness as a solvent is limited.

There have been several studies of chemical shifts of alcohols in DMSO solution. For example, Brook and Pannell[109] recorded hydroxyl shifts for a large number of substituted triphenylsilyl phenyl carbinols. They correlated the shifts with empirical parameters such as Hammett's σ function. In general, however, –OH analysis has been based on splitting patterns rather than chemical shifts. A typical example is shown in the work of Rothweiler and Tamm[110] on the structure of the antibiotic phomin. They showed that both –OH groups on the molecule were secondary since they appeared as doublets which disappeared on treatment with D_2O.

When recording spectra in DMSO, it is very advantageous to use the deuterated solvent to avoid interference from solvent protons. If common DMSO must be used, one can anticipate difficulties due to overlap of the sample spectrum with the DMSO signal. All factors considered, the higher expense of DMSO-d_6 is usually well justified.

b. Phenols and enols. These compounds have not been studied as extensively as alcohols. Since there are no protons neighbouring the phenolic group, the –OH shows no splitting and the chemical shift is the only parameter obtainable. In inert solvents the chemical shift is concentration dependent and ranges from $\delta = 4{\cdot}5$–8. Some *o*-substituted phenols are intramolecularly hydrogen bonded; their chemical shifts are nearly independent of concentration. The intermolecular association of phenols does not occur in strong hydrogen bonding solvents such as DMSO, and useful shift data can be obtained. Traynham and Knesel[111] studied a large number of phenols in DMSO, and observed values ranging from 8·5–11·0 ppm downfield from TMS. Dietrich et al[112] investigated a number of basic solvents and found that in hexamethylphosphoramide proton exchange is sufficiently slowed to allow observation of a distinct –OH signal from each individual phenol in a mixture. Hexamethylphosphoramide (HMPA) is potentially as useful as DMSO.

Stable enols owe their existence to strong intramolecular hydrogen bonds. The β-diketones are an especially favourable case and their enols have been studied in the greatest detail. The –OH chemical shift is far downfield (δ = 15–16) and shows little concentration dependence. Since the keto–enol conversion is slow in these cases, the equilibrium can be studied by observing the relative areas under the peaks from the –CH= and the $-CH_2-$ groups. Many studies of keto–enol equilibria have been made, utilizing this approach. For example, Reeves[113] studied the effect of the solvent on the acetylacetone equilibrium. An interesting, but not generally applicable, method was developed by Gorodetsky et al[114]. They observed the oxygen resonance in ^{17}O enriched β-diketones. The spectra showed separate peaks for keto and enol forms, and it was possible to derive equilibrium constants for the conversion.

2. Derivativization methods

A different approach depends on making derivatives of the alcohol function, and then studying the derivatives. An early suggestion of this method was made by Jackman[115] who noted that esterification of an alcohol resulted in a downfield shift of the α hydrogens. Useful structural information can be obtained from the multiplicity and the area of the shifted peaks. Mathias[116] has made a systematic study of this effect. One frequently finds that α proton signals from primary and secondary alcohols overlap. When the alcohols are acetylated, the resonances separate. In some cases this effect can be used to obtain primary/secondary ratios.

Manatt[117] proposed studying the resonance of the protons of the acetyl group. However, these protons are insensitive to their environment, so the trifluoroacetate esters were prepared, and the ^{19}F signal utilized as the analytical probe. Fluorine chemical shifts are more sensitive than proton shifts in most cases. In the fluorine-containing esters, separate signals from primary and secondary groups are often observed. This approach requires the use of a ^{19}F spectrometer, but sometimes this problem can be circumvented by using the α protons. For example, Ludwig[118] showed that the α proton signal could be used to determine primary/secondary ratios in alcohol mixtures.

Babiec et al[119] prepared dichloroacetate esters by addition of dichloroacetic anhydride. The shielding of the lone proton on the dichloroacetyl group is sensitive to its environment, the order being tertiary > secondary > primary. The chemical shift will readily

distinguish between tertiary and secondary, but there is sometimes overlap between secondary and primary. The latter shift can be enhanced by the use of DMSO-d_6 as a solvent. In common with other esterification techniques, the α hydrogens can also be used as the analytical probe, and they often serve as a useful check.

Goodlett[120] investigated the use of ketones and isocyanates as derivatizing agents. He concluded that trichloroacetyl isocyanate, TAI, (CCl_3--CO—N=C=O), was superior. This compound contains no protons, has a long shelf life and reacts smoothly in situ, even with hindered –OH groups. The α protons are the analytical probe. Primary protons are shifted downfield by 0·5 to 0·9 ppm while secondary protons are shifted by 1·0 to 1·5 ppm. The use of TAI is further discussed by Trehan et al[121] and by Butler and Mueller[122]. The latter group has extended its use to –SH groups.

Seikel et al[123] recently studied the structure of thomasic acid. Here the –OH spectrum is complicated by the fact that the carbinol carbon is an asymmetric centre. The TAI derivative was used to identify the peaks due to the carbinol hydrogens, while the splitting pattern of the –OH was obtained from a solution of the alcohol itself in DMSO. With the combined results of these experiments, the authors were able to locate the hydroxyl group within the molecule.

3. Hydrogen bonding

A voluminous literature has developed on the use of n.m.r. for the study of association equilibria in alcohols and phenols. This subject is too vast to be reviewed here, but several representative references will be cited. The work usually involves the determination of the –OH chemical shift as a function of concentration in some suitable solvent. The relative amounts of the various polymeric species can be calculated.

Saunders and Hyne[124] investigated the behaviour of *t*-butanol in CCl_4 solution. Their data indicate a simple equilibrium between the unassociated alcohol and a trimeric species. In reviewing the earlier literature, Littlewood and Willmott[125] were able to show that most alcohols associated into linear polymers of varying length. Phenols usually associate into trimers in solution[126].

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CHAPTER 7

Acidity and inter- and intra-molecular H-bonds

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I. INTRODUCTION

The percentage of chemical literature which is in some way concerned with hydrogen bonding has increased steadily over the years since the concept of the H-bond was first introduced in 1920[1, 2]. Furthermore, quantitative studies of the H-bonding of OH groups to a wide variety of acceptors (bases) have made a decisive contribution to our knowledge of the characteristic properties of H-bonds and their influence on chemical reactions and molecular structure. A comprehensive consideration of the appropriate data would be impossible here and is therefore not attempted. The authoritative text by Pimentel and McClellan[2] on H-bonding was published in 1960. We have therefore concentrated in this article on contributions which have appeared since that date with adequate reference to the older work where appropriate. In particular, results for phenols and alcohols are emphasized.

The theoretical interpretations of hydrogen bonding have been discussed by Coulson[371, 372] and Murrell[373]. The relative magnitudes of the contributions due to electrostatic, exchange, induction, dispersion and charge-transfer energies to the H-bond interaction are considered. A complete discussion would be inappropriate here. However, for weak hydrogen bonds the electrostatic energy is the dominant attractive contribution. Delocalization effects are only important for strong hydrogen bonds. The predominantly electrostatic nature of hydrogen bonds favours a linear bond. However, bent bonds are possible. The variation of interaction energy with angle will be of the form $E = E^{\circ} \cos \theta$ which reduces to zero when the bond angle is $\pi/2$. In general, molecular orbitals with low s-character are better H-bond acceptors than orbitals with high s-character.

The acidity and basicity of OH groups are considered in sections V and VI.

II. INTERMOLECULAR H-BONDING

A. Self Association

1. Alcohols

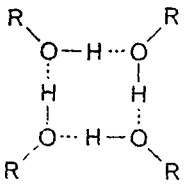
Studies of the association of alcohols in the vapour phase have the advantage that they are free from the effects of solute–solvent interactions. It is well established that alcohol vapours exist as monomer, dimer and tetramer units[3, 4]. Thermodynamic data for the forma-

tion of the dimers and tetramers of several alcohols are given in Table 1. The tetramers are believed to be cyclic[3–5] (structure **1**)

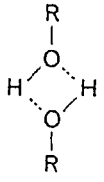
TABLE 1. Thermodynamic parameters for the formation of the dimers and tetramers of alcohols in the gas phase[4].

	$-\Delta H_2$ (kcal/mole)	$-\Delta S_2$ (e.u.)	$-\Delta H_4$ (kcal/mole)	$-\Delta S_4$ (e.u.)	Ref.
Methanol	3·22	16·5	24·2	81·3	3
	4·0	11·0	22·1	94	6
	4·1	17·5			374
	3·5		18·4		5, 7
Ethanol	4·0	11·0	20·1	88	8
	3·4	16·6	24·8	81·5	9
n-Propanol	3·4	15·4	25·2	75·4	10
2-Propanol	4·0	11	22·6	95	6
	5·3	22·4	22·3	74·2	10
	4·5	19·5	22·9	75·3	11
2-Butanol	5·3	21·4	23·1	74·7	12
2-Methyl-2-propanol	4·6	19·0	25·1	82·2	13
Methanol-*d* (CH_3OD)	5		14		7

whereas both linear (**2**) and cyclic (**3**) dimers probably exist. The results for methanol-*d* were deduced from infrared spectra (2400–2800 cm^{-1}) of deuterated methanol at 305 and 335°K[7]. It is



(1)



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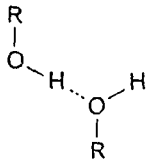


(3)

surprising that the enthalpy of dissociation of the CH_3OD tetramer is less than that for the CH_3OH tetramer. Further evidence for this result is however given by consideration of the Badger–Bauer relationship[14, 15]. This states that $\Delta\nu/\nu$ should be a linear function of ΔH where ν is the infrared OH stretch frequency of the free OH group and $\Delta\nu$ is the frequency change on forming a hydrogen-bonded complex with heat of formation ΔH. For the CH_3OD and CH_3OH tetramers $\Delta\nu/\nu$ was 0·070 and 0·082 respectively. Thus

$$\Delta H_4(CH_3OD) < \Delta H_4(CH_3OH).$$

The self association of alcohols in solution in nonpolar solvents has been widely studied in particular by measurement of infrared OH stretching frequencies[16–24]. The method is based on the principle that if an OH group undergoes H-bonding a shift to lower frequencies occurs. Furthermore in general ν(monomer) > ν(dimer) > ν(trimer) > ν(tetramer) for the association of a particular monomer[25, 26, 36]. This is exemplified by data for the OH stretch frequencies of methanol at 20°K[25]. Frequencies were assigned as follows: for the monomer 3660 cm^{-1}, cyclic dimer 3490 cm^{-1}, cyclic trimer 3445 cm^{-1}, tetramer 3290 cm^{-1}, and for higher (linear) polymers 3250 cm^{-1}. Explanations of why absorption bands in the region 2500–3400 cm^{-1} are obtained for H-bonded systems have recently been discussed and summarized[26–28]. Proton magnetic resonance studies of alcohol association similarly allow association constants (from chemical shifts as a function of concentration) and heats of association (from chemical shifts as a function of temperature and concentration) to be evaluated[24, 29–31]. Agreement between results from infrared and p.m.r. measurements is emphasized by the data in Table 2. Vapour pressures[17] and viscosities[32–34] have also

TABLE 2. Thermodynamic parameters for the dimerization of some alcohols in carbon tetrachloride[20, 24, 31].

Alcohol	$-\Delta H$ (kcal/mole)	$-\Delta S$ (e.u.)	Method of determination
Methanol	9·2	28	i.r.
	9·4		p.m.r.
Ethanol	7·2	20	i.r.
	7·6		p.m.r.
i-Propanol	7·3		p.m.r.
t-Butanol	4·8	11	i.r.
	4·4		p.m.r.
Di-*t*-butylcarbinol	4·12	13·1	i.r.
	4·21	13·9	p.m.r.

been used to study the intermolecular H-bonding of alcohols. Calorimetric measurements of heats of H-bonding of alcohols have been reported[35, 36]. The dimers of methanol and ethanol are probably cyclic[20, 24]. However, for higher alcohols in which steric factors hinder the formation of the cyclic dimer, the linear dimer becomes predominant[24]. The thermodynamic parameters for dimerization also reflect the effects of steric hindrance (Table 2)[16, 18, 19]. Cyclic

trimers of methanol are supposed to exist[17, 29] but cyclic tetramers appear more likely[3, 19, 30]. The association of 1-octanol is considered to give both linear and cyclic tetramers for which free energies, enthalpies and entropies of formation have been deduced[23]. The dimerization constant and heat of dimerization of cholesterol in CCl_4 at 23° are 4·5 l/mole and −1·8 kcal/mole respectively[66]. A trimer has been reported for cholesterol in CCl_4 [66].

It does not follow that information about the H-bonding of alcohols in inert solvents may necessarily be equally applicable for the pure liquid alcohols. The heats of vaporization[37, 38], dielectric constants[39], viscosities[33, 34] and n.m.r. spectra[40] of aliphatic liquid alcohols have all shown that the geometry of the alcohol molecules through steric factors greatly influences their H-bonding ability. Both linear and cyclic dimers may exist[4, 39]. However, whether higher polymers are cyclic[4, 17] or linear[39, 40] appears to be uncertain. Radial distribution functions[41] for liquid methanol have shown that the O · · · O distance (2·7 Å) for two H-bonded molecules is about the same as for the solid[42, 43]. The structure of liquid alcohols and alcohol–water mixtures has been reviewed by Franks and Ives[44]. The effect of pressures up to 25,000 atm on the H-bonds of polyvinyl alcohol has been investigated[45].

Structures of carbohydrate crystals show that in general all the hydroxyl groups are hydrogen-bonded[46]. X-ray studies of β-D-glucopyranose[47] and methyl β-D-xylopyranoside[48] suggest that some of the OH groups are not H-bonded. However, the infrared spectra for these compounds are not compatible with this conclusion[49].

2. Phenols

The OH stretching frequencies and intensities of phenols[50, 51] both follow a Hammett $\rho\sigma$ relationship[52]. For *ortho*-substituted phenols where intramolecular H-bonding can occur it is the frequency of the *trans*-hydroxyl group which correlates with the substituent constant[53]. On H-bonding the OH stretch vibrations move to lower frequencies[26]. Hall and Wood[26] have listed the following four specific frequencies for different types of interaction:

type α: monomer, 3611 cm^{-1},

type β: acceptor end group (Ph—O⟨H⟩), 3599 cm^{-1},

type γ: donor end group (Ph⟨O—H · · ·), 3481 cm^{-1},

type δ: OH acting as both acceptor and donor, 3393 cm^{-1}.

The frequencies quoted refer to phenol itself in carbon tetrachloride solution[21, 22]. The bands are shifted slightly for other sterically unhindered phenols.

The frequency shifts of phenols on dimerization are greater for the phenols with the greatest H-bonding ability[54, 55]. In particular a pronounced reduction in $\Delta\nu$ is produced by bulky substituents in the 2-position of phenols[59, 61]. A comparison of the frequency shifts with the dimerization constants K for some phenols is given in Table 3.

TABLE 3. Infrared frequency and p.m.r. signal shifts, association constants and heats of association for the dimerization of some phenols in carbon tetrachloride (room temperature).

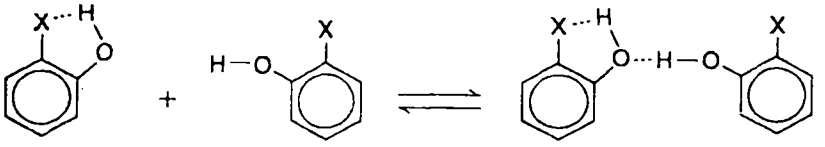
Phenol	K (l/mole)	$-\Delta H$ (kcal/mole)	$\Delta\nu$ (cm^{-1})	$\Delta\tau$ (ppm)
Phenol	13 ± 7^a	$5{\cdot}12^d$	262^e	$3{\cdot}05^g$
4-Chlorophenol	$7{\cdot}77^a$	$3{\cdot}78^d$		
4-Cresol	10^d	$6{\cdot}09^d$	276^e	
2-Cresol	8 ± 4^a		172^e	$2{\cdot}04^g$
2-*i*-Propylphenol	$1{\cdot}7^b$		172^e	$1{\cdot}78^g$
2-*t*-Butyl-4-methylphenol	$1{\cdot}37^c$		114^e	
2-*t*-Butylphenol	$1{\cdot}0^b$		70^f	$0{\cdot}22^g$
2,6-Di-*t*-butylphenol	$\leqslant{\cdot}05^b$		ca 3^e	$0{\cdot}0^g$

[a] Ref. 56; [b] ref. 57; [c] ref. 18; [d] ref. 58; [e] ref. 59; [f] ref. 60; [g] ref. 62.

Also tabulated are the shifts $\Delta\tau$ in the p.m.r. signals caused by hydrogen bonding. In general both $\Delta\tau$[57, 62] and $\Delta\nu$[54, 59, 61] decrease as K decreases. The p.m.r. chemical shift or the infrared frequency change on hydrogen bonding for a particular phenol gives an indirect measure of the ability of that phenol to form H-bonded dimers. Association constants may be deduced from $\Delta\tau$ or $\Delta\nu$ measurements as a function of phenol concentration[18, 56, 57]. Varying the temperature allows the enthalpy of dimerization to be calculated[58, 63]. The three enthalpies given in Table 3 show the same trend as the free energies of ionization of phenol ($\Delta G^\circ_{298} = 13{\cdot}57$ kcal/mole)[64], 4-chlorophenol (12·86 kcal/mole)[64] and 4-cresol (14·02 kcal/mole)[65]. When deducing ΔH from infrared frequency shifts it is unwise to assume that the temperature dependencies of the free and associated band absorptions are equal[63].

For *ortho*-substituted phenols in which intramolecular H-bonds are possible intermolecular H-bonding may be reduced[67–70]. For a

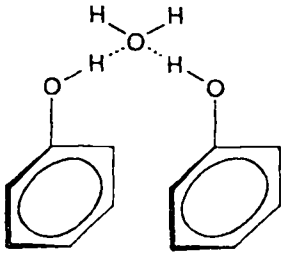
series of substituted 2-bromophenols as liquid films or nujol mulls a sharp infrared band at ca 3500 cm^{-1} was assigned to intramolecular H-bonds whereas a broad (3450–3250 cm^{-1}) less intense absorption was attributed to intermolecular H-bonding[68]. Many of the phenols showed both forms of bonding. Allan and Reeves[69] have pointed out that the *trans* form of 2-halophenols is available in CS_2 solution as a hydrogen bond donor whereas the *cis* form can only act as a H-bond acceptor. Dimerization is considered to occur via hydrogen bonding from a *trans* to a *cis*- isomer as follows.



(*cis*) (*trans*) (*cis–trans* dimer)

Equilibrium constants (mole fraction units, 300°K) are 23·48, 11·22 and 5·24 for 2-chlorophenol, 2-bromophenol and 2-iodophenol respectively. The self association of phenols is also profoundly influenced by solvent[21, 57, 61, 68, 70]. A solvent which is itself a strong H-bond acceptor such as dioxan[57], ether[68, 70] or pyridine[61] reduces the extent of phenol dimerization considerably.

Evidence for the formation of phenol trimers in CCl_4 solution has been discussed[71–74]. Trimerization constants of 4·1 $(mole/l)^{-2}$ at 25° [71] and 4·78 $(mole/l)^{-2}$ at 21° [74] have been evaluated for phenol in carbon tetrachloride. Trimerization is prevented for phenols such as 2-nitrophenol, 2-hydroxyacetophenone and 2-fluorophenol in which intramolecular H-bonding occurs[72]. Unlike the dimers which probably have an open-chain structure[21] the phenol trimers are cyclic[73]. A trimolecular species containing two phenol molecules and one water molecule has been assigned the structure **4** [75] with the benzene nuclei of the phenol rings parallel and facing



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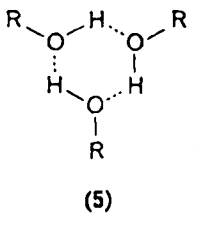


(5)

each other. However phenol (P) and water (W) in benzene, 1,2,2-1, tetrachloroethane and 1,2-dichloroethane form a series of aggregates of stoichiometry P_3, P_2W, PW_2 and W_3 [73]. These are considered to have the cyclic structure **5** with R = H or C_6H_5.

The –O–H · · · O– vibrations in the far infrared of H-bonded forms of several phenols have been determined[76]. The stretching vibrations are in the range 98–187 cm^{-1}. Phenols for which different H-bonded associates are known to exist showed more than one –OH out of plane deformation mode (γOH) in the range 280–690 cm^{-1}. Thus each H-bonded species probably gives rise to its own distinct γOH frequencies. In strongly intermolecularly H-bonded complexes γOH is around 600 cm^{-1}. However, for sterically hindered phenols the mode becomes an –OH torsional vibration at about 300 cm^{-1}. The H-bond stretching frequencies ν(O · · · O) for two solid phases of phenol are 175 cm^{-1} for a strongly H-bonded phase and 135 cm^{-1} for a weakly H-bonded phase[77]. The frequency ν(O · · · O) of the H-bond vibration is therefore, as expected, smaller for a weaker H-bond. However, this result does not appear to be general[27].

Phenols are strongly hydrogen bonded in the solid state. Phenol forms H-bonded chains in the form of a threefold spiral[78, 79, 82]. The 2,3-, 2,5- and 2,6-xylenols[80, 81] and resorcinol[83] are similar. Bois[84] has proposed that 4-cresol exists as H-bonded discrete tetramers and not as H-bonded chains. A second more weakly H-bonded phase of phenol appears at pressure greater than 5 kbar[77].

B. Alcohols as H-bonding Acids

Infrared spectra of the complexes formed between six alcohols and several H-bond acceptors in the gas phase have been studied by Reece and Werner[85]. The OH stretch frequency shifts on H-bonding were found to obey a product rule $\Delta\nu = A.D$ cm^{-1} where A and D are suitably defined acceptor and donor capacities. Similar results were obtained for the same complexes in CCl_4 solution. Equation (1) relates the frequency change on H-bonding in the vapour phase

$$\Delta\nu_{\text{vapour}} = -1{\cdot}7 + 0{\cdot}816\Delta\nu_{CCl_4} + 1{\cdot}2 \times 10^{-4}(\Delta\nu_{CCl_4})^2 \qquad (1)$$

with the corresponding change in CCl_4 solution. The equation was obeyed for six alcohols. Figure 1 demonstrates the relationship between $\Delta\nu$ and the half-intensity widths of the bands due to the complexes of some alcohols with four H-bond acceptors[85]. Each acceptor gives its own characteristic line. Similar correlations of $\Delta\nu$ and $\nu_{\frac{1}{2}}$ have been described[86, 87] and the temperature dependence

of $\Delta\nu$ and $\nu_{\frac{1}{2}}$ has been investigated[88]. Whereas $\Delta\nu$ varies significantly, $\nu_{\frac{1}{2}}$ is insensitive to temperature. The increase in intensity $\Delta B°$ of the OH stretching absorption on H-bonding at 25° is related to $\Delta\nu$ by equation (2) for the complexes of methanol, ethanol and *t*-butanol

$$\Delta B° = 225\Delta\nu \qquad (2)$$

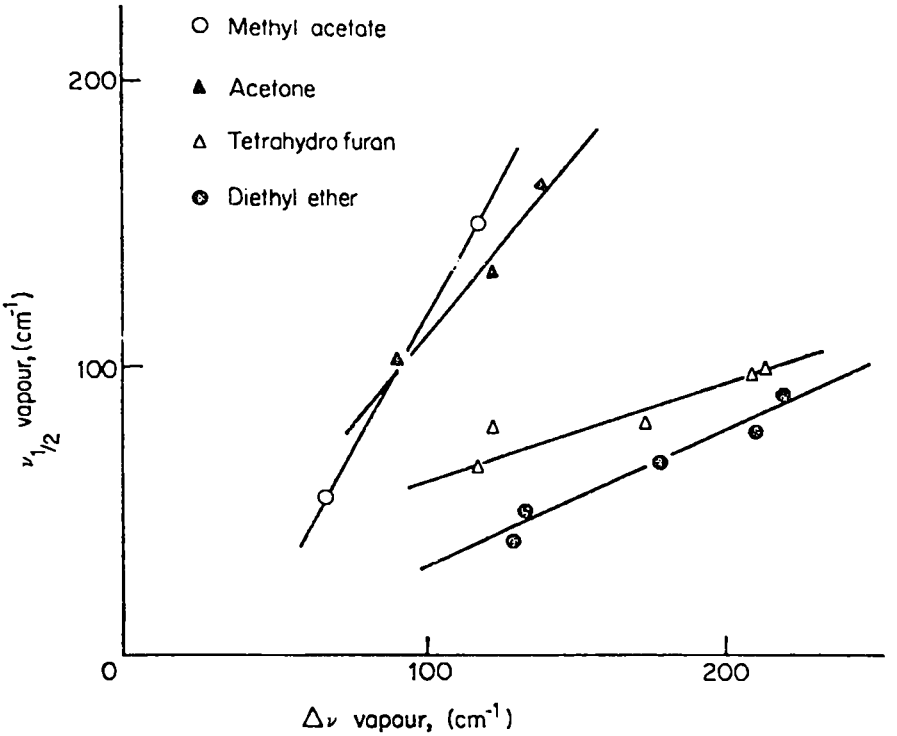


FIGURE 1. Correlation between $\nu_{\frac{1}{2}}$ for the H-bonded complex and $\Delta\nu$ on H-bonding for the complexes of some aliphatic alcohols with four H-bond acceptors[85]. Reproduced by permission from I. H. Reece and R. L. Werner, *Spectrochim. Acta*, **24A**, 1271 (1968).

with acetone, ethyl acetate, dioxan, benzophenone, dimethylformamide and pyridine[88]. The intensities of the OH bands of the complexes of methanol and *t*-butanol with three substituted benzene derivatives are linearly related to $\Sigma(\sigma_I + \sigma_R)$, the sum of the inductive and resonance σ parameters for the substituents in the benzene rings[89]. A linear relationship between band intensity and the nuclear quadrupole coupling constants of 5 acceptors has been demonstrated[89]. The coupling constants and $\Sigma(\sigma_I + \sigma_R)$ were also linear functions of $(\Delta\nu/\nu)$ the relative frequency shifts on hydrogen bonding.

Gordon has discussed correlations between the equilibrium constants K_{assoc} and the infrared frequency shifts $\Delta\nu$ for H-bond complex formation, pK_a for the H-bond donors and pK_b for the H-bond acceptors[90]. For example, the shift $\Delta\nu$ for methanol-*d* (CH_3OD) increases as the proton basicity of the acceptor molecules increases. This general trend has been tested for a range of 22 pK_a units over which $\Delta\nu$ varies from 30 cm^{-1} (for $pK_a \simeq -11$) to 270 cm^{-1} (for $pK_a \simeq +11$)[91]. The association constants for the complexes of CH_3OD H-bonded with the π-systems of substituted benzenes increase with increasing proton basicity of the benzenes[90]. P.m.r. OH proton shifts $\Delta\delta$ on H-bonding lead to similar correlations since $\Delta\delta$ is a linear function of $\Delta\nu$ for alcohols. Thus equation (3) relates $\Delta\nu$ (cm^{-1}) with $\Delta\delta$ (ppm) for 2,2,2-trifluoroethanol H-bonding to

$$\Delta\delta = 0{\cdot}0121\Delta\nu + 0{\cdot}43 \qquad (3)$$

a series of Lewis bases of widely differing structural types[92]. The ability of methanol to H-bond to organophosphorus compounds depends upon the electron density on the phosphoryl oxygen of the latter. Support for this point is gained from the observed linear plot of log K_{assoc} against the sum $\sum\sigma^*$ of the Taft constants σ^* for the substituents in the organophosphorus compounds[93]. Plots of $\Delta\nu$ against σ^* for complexes of methanol with nitriles or isonitriles were similarly linear[94].

The Badger and Bauer[14, 15] relationship suggests that the relative frequency shift ($\Delta\nu/\nu$) when a hydrogen bonded complex is formed should provide an indirect measure of the strength of the H-bond. This has been generally accepted[86]. The relationship between ΔH and $\Delta\nu$ is exemplified by Figure 2 for the interactions of 3 alcohols with 9 Lewis bases[95]. However, the linear relationship is not always obeyed[86, 88, 96, 97]. The H-bonding of alcohols to ketones shifts the C=O stretching frequency of the ketones to lower wavenumbers[98]. A linear relationship between ($\Delta\nu_{CO}/\nu_{CO}$) and the H-bond energy has been recorded for methanol–ketone complexes[99]. The antisymmetric and symmetric stretching frequencies of the NH_2 group are shifted to lower frequencies when alcohols (or phenols) H-bond to aniline. The magnitude of the shifts correlates both with the OH stretch shift $\Delta\nu_{OH}$ and with pK_a for the donor alcohol[101]. Thus for a more acidic alcohol a stronger H-bond is obtained as indicated by the larger changes in ν_{OH} and ν_{NH_2} on H-bonding. An approximate correlation exists between ΔH for H-bond formation and the intensity of the infrared OH stretching bands of the H-bonded complexes of

methanol, ethanol and *t*-butanol, each with the acceptors acetone, benzophenone, ethyl acetate, dioxan, dimethylformamide and pyridine[88].

Heats of H-bond formation give somewhat scattered but approximately linear graphs when plotted against the corresponding entropies or free energies of ionization[88, 96, 97, 100, 103]. Some selected

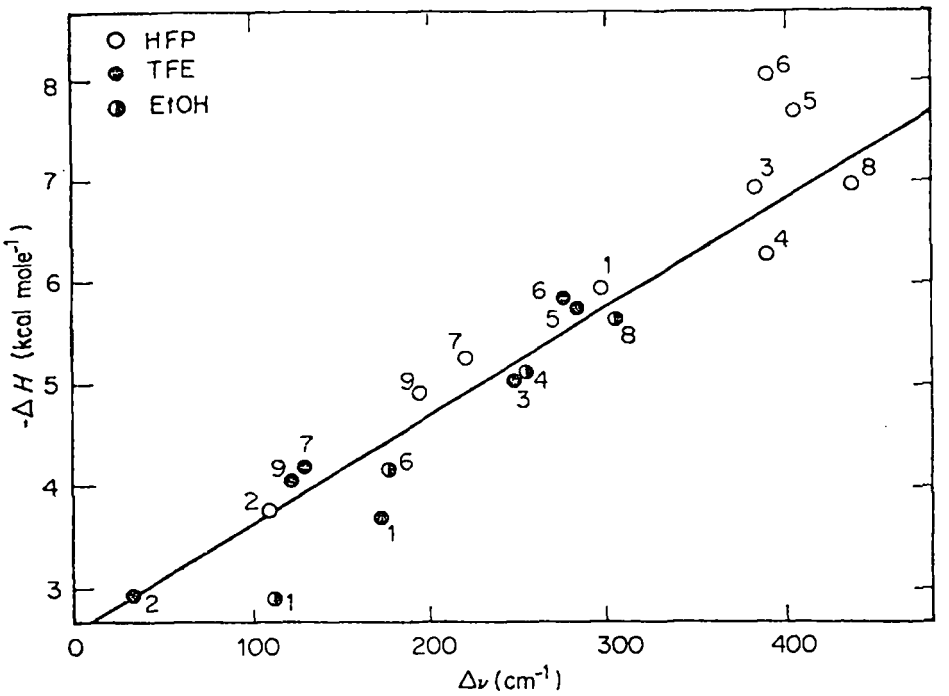


FIGURE 2. Relationship between ΔH and $\Delta\nu$ for 1,1,1,3,3,3-hexafluoro-2-propanol (HFP), ethanol, and 2,2,2-trifluoroethanol (TFE) as H-bond donors[95]. Acceptors were (1) acetone, (2) 1,1,1-trifluoroacetone, (3) di-*i*-propylether, (4) tetrahydrofuran, (5) *N*,*N*-dimethylacetamide, (6) tetramethylurea, (7) *N*,*N*-dimethyltrifluoroacetamide, (8) dimethyl sulphoxide, (9) sulpholane. Reproduced by permission from A. Kivinen, J. Murto and L. Kilpi, *Suomen Kemistilehti*, **40B**, 301 (1967).

values of ΔG, ΔH and ΔS are given in Table 4. In general, as ΔH becomes more negative ΔS becomes more negative. A more negative ΔH implies a stronger H-bond and therefore a more restricted configuration in the H-bond complex[96, 100]. Therefore ΔS should also be more negative. It follows that the differences between ΔH and ΔS for series of structurally related H-bond donors or acceptors contribute to ΔG in a compensating manner and therefore ΔG is comparatively insensitive to change. Increasing the acidity of the

donor[101] or the basicity of the acceptor[91, 102] produces a stronger H-bond. These correlations may be upset if there is any steric hindrance to the formation of the H-bonded complex[91]. Thus the

TABLE 4. Free energy, enthalpy and entropy changes on forming H-bonded complexes of alcohols and H-bond acceptors in carbon tetrachloride solvent.

Alcohol	Acceptor	$-\Delta G$ (kcal/mole)	$-\Delta H$ (kcal/mole)	$-\Delta S$ (e.u.)	Temp. (°C)	Ref.
Methanol	Acetone	0·35	2·52	7·3	25	88
Methanol	Benzophenone	0·24	2·16	6·5	25	88
Methanol	Ethylacetate	0·20	2·52	7·8	25	88
Methanol	Dioxan	0·24	2·80	8·6	25	88
Methanol	DMF	1·01	3·72	9·1	25	88
Methanol	Pyridine	0·65	3·88	10·8	25	88
Propan-1-ol	Pyridine	0·19	4·3	11·9	45	96
Propan-2-ol	Pyridine	0·2	6·1	18·9	45	96
Butan-1-ol	Pyridine	0·5	5·0	14·2	45	96
Butan-2-ol	Pyridine	0·02	4·1	12·6	45	96

logarithms of the association constants for a series of methanol-substituted pyridine complexes are a linear function of pK_a for the pyridines, providing the latter have no bulky substituents in the 2-positions[102]. However, for 2-*i*-propylpyridine, and 2,6-di-*i*-propylpyridine the H-bonding ability is reduced by steric factors to a much greater extent than the corresponding reduction in the Brønsted basicity of the pyridines. This behaviour parallels the effect of bulky 2-substituents on the Lewis basicity of pyridine[104]. It is relevant to note that although heats of H-bond formation have been usually deduced indirectly from infrared[63] or p.m.r.[105] measurements direct calorimetry gives results close to the spectroscopic values[103].

The infrared ν_{OH} stretching frequencies and the H-bond enthalpies of alcohol-acceptor complexes are sensitive to changes in solvent composition[22, 109, 110]. Typical frequency shifts are given in Table 5. Allerhand and Schleyer[109] found that an empirical relationship, equation (4), fitted the observed solvent shifts of the H-bond ν_{OH}

$$(\nu^0 - \nu^S)/\nu^S = aG \qquad (4)$$

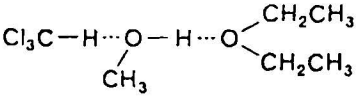
absorption bands. Here ν^0 is the infrared frequency for the H-bonded complex for which ν^S is the corresponding frequency in a particular solvent, a is a function of the particular vibration being studied and G is a function only of the solvent. Equation (4) represents an empirical form of the Kirkwood–Bauer–Magat relation-

TABLE 5[a]. Infrared OH stretching frequency of the methanol (0·05 mole/l)–ether complex in ether–chloroform mixtures[22].

% $CHCl_3$	0	10	20	30	35	40	45
ν (cm^{-1})	3508	3504	3498	3491	3482	3473	3465
% $CHCl_3$	50	60	70	80	90	98	
ν (cm^{-1})	3463	3459	3454	3452	3449	3444	

[a] Reproduced by permission from L. J. Bellamy, K. J. Morgan and R. J. Pace, *Spectrochim. Acta*, **22**, 535 (1966).
ν = 3558 cm^{-1} for MeOH–Et_2O complex in gas phase[111].

ship[112]. The latter only fits the H-bond frequency shift data for the phenol–acetonitrile complex in CCl_4 solutions; equation (4) appears much more generally applicable. However, this approach has been criticized by Bellamy and co-workers[22] who suggest that specific interactions between solvent molecules and H-bonded complexes are largely responsible for the observed results. Thus, for example, for the methanol–ether complex (Table 5) in chloroform the interaction between the proton donor solvent chloroform and the complex may be represented as



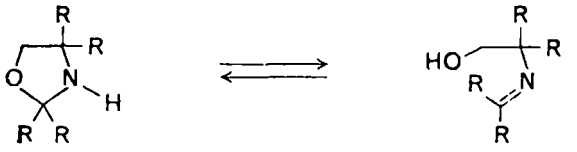
(6)

and would be expected to lead to a decrease in frequency as the chloroform concentration is increased. Proton acceptor solvents give a similar effect. The magnitude of the shifts is therefore dependent on the extent to which the solvent molecules can act as H-bond donors or acceptors.

Alcohols can hydrogen bond to the π-electron systems of olefins or aromatic hydrocarbons. H-bonding of this type is favoured by increasing the number of conjugated double bonds or the number of condensed rings in the π-system[107]. It has been suggested that this type of interaction is responsible for the affinity between many dyes and cellulosic substrates[108]. Calorimetric measurements of heats of mixing of benzyl alcohol, ethylbenzene and cyclohexane have provided evidence for an OH→π H-bond interaction with $\Delta H = -1{\cdot}48$ kcal/mole[106]. For the *m*-cresol–*m*-xylene–cyclohexane system $\Delta H = -3{\cdot}14$ kcal/mole: a stronger H-bond for a more acidic

proton donor. A weak H-bond interaction exists between alcohols and nitro groups[113, 114]. Thus, comparison of the OH stretching frequency of methanol in carbon tetrachloride, nitromethane, nitrobutane and nitrobenzene shows that ν_{OH} is displaced to lower frequencies in the latter three solvents[114]. Also the band intensity and half-width increase, both effects being characteristic of H-bond interactions[86]. When a nitro compound is added to methanol in CCl_4 a reduction in intensity (but no change in position) of the free OH absorption occurs and a new broad maximum at a lower frequency appears[113]. The nitro compounds must therefore be acting as H-bond proton acceptors. Phenol gives spectral shifts 2–3 times greater than those for methanol in accord with its greater strength as an acid.

A study of the effect of H-bonding on the ring–chain tautomerism **7** $\rightleftarrows$ **8** of oxazolidines demonstrates how H-bonding solvents can in-



(7) (8)

fluence tautomeric equilibria of solute species[115]. Structure **8** was favoured relative to **7** by using solvents which can H-bond strongly with the alcoholic group in **8**. For a series of 8 solvents the H-bonding ability was assessed by measuring $\Delta\nu_{OH}$ for di-*t*-butylcarbinol (DTBC) when mixed with each solvent in CCl_4 solution. The enthalpy changes $\Delta H°$ for equilibrium **7** $\rightleftarrows$ **8** in the 8 solvents were a linear function of $\Delta\nu_{OH}$(DTBC) in the sense that as $\Delta\nu_{OH}$ became greater so $\Delta H°$ became less positive or more negative. The effect of solvent on the equilibrium therefore primarily arises through the influence of H-bonding.

C. Phenols as H-bonding Acids

1. Phenol

General studies of H-bonding of phenol to a variety of H-bond acceptors of different structural types have been made by Gramstad[116] and by Drago and co-workers[117–119]. Acceptors included ethers, amines, aldehydes, ketones, esters, amides, sulphoxides, phosphoryl compounds, acid fluorides and alkyl halides. The p.m.r.[118] and infrared[116, 117] methods give results which are consistent with each other[120]. Thus the p.m.r. chemical shifts of the phenol proton

in the H-bonded complex and the infrared ν_{OH} frequency shift on forming the complex were both linear functions of the enthalpy of H-bond formation. Equations (5)[118] and (6) fit the experimental

$$\delta_{obs} = 0{\cdot}748\Delta H - 4{\cdot}68 \quad (5)$$

$$-\Delta H = 0{\cdot}016\Delta\nu_{OH} + 0{\cdot}63 \quad (6)$$

results with δ in ppm, $\Delta\nu_{OH}$ in cm^{-1} and ΔH in kcal/mole. A theoretical justification for equation (6) has been deduced and dis-

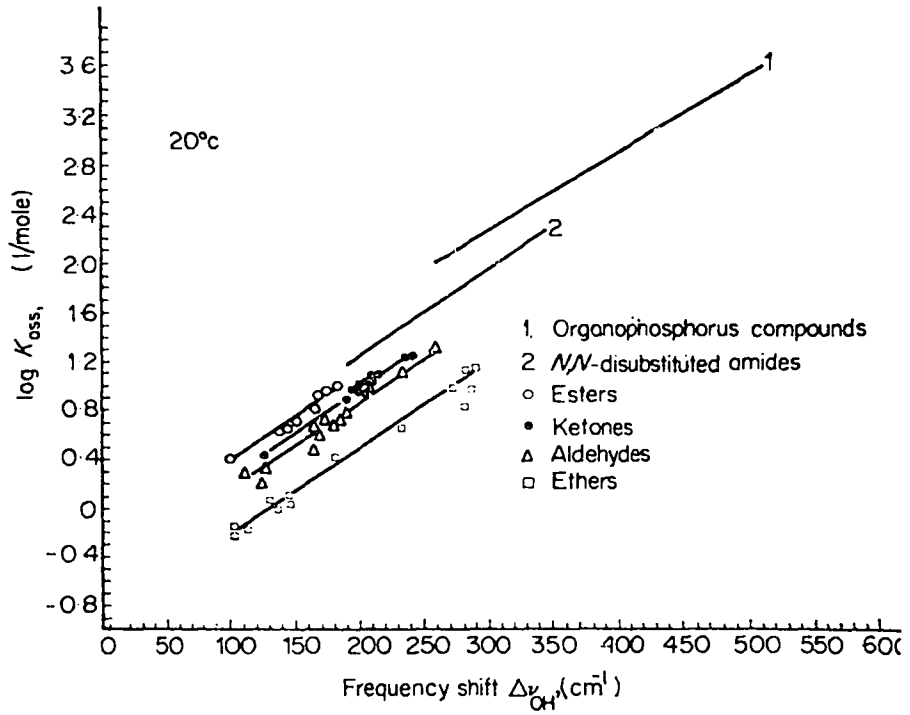


FIGURE 3. Correlation between log K_{assoc} and the ν_{OH} frequency shifts for the association of phenol with H-bond bases of different structural types[116]. Reproduced by permission from T. Gramstad, *Spectrochim. Acta*, **19**, 497 (1963).

cussed[119]. The correlation between the association constant and the infrared frequency shift for H-bond formation is not as general as the corresponding enthalpy correlations[117]. However, Gramstad[116] has shown that a plot of $\Delta\nu_{OH}$ against log K_{assoc} is linear for H-bond bases of similar structural class. Figure 3 demonstrates these results. The changes in ν_{OH} frequency or δ_{OH} chemical shift produced with phenolic H-bonds are greater the more strongly basic the acceptor molecule[120]. The magnitudes of the shifts also vary inversely as

the overall length (R_{xy} for X–H · · · Y) of the H-bond at equilibrium[27, 86, 120]. The shifts in carbonyl stretch frequency when phenol H-bonds to ketones is a linear function of the enthalpy of formation of the H-bonds[99].

H-bonding of phenol with ten sulphoxides and three nitroso compounds has been studied by Gramstad[121]. Plots of log K_{assoc} against $\Delta\nu_{OH}$, ΔH against $\Delta\nu_{OH}$, ΔG against $\Delta\nu_{OH}$, ΔS against $\Delta\nu_{OH}$ and $\nu_{\frac{1}{2}}$ against $\Delta\nu_{OH}$ were all linear. Sulphoxides are intermediate between amides and esters[116] in their ability to form an H-bond with phenol. Nitroso compounds are intermediate between aldehydes

TABLE 6. Thermodynamics of H-bond formation of complexes of phenol with several structural types of H-bond acceptor.

Acceptor	Solvent	K_{assoc} (l/mole)	$-\Delta H$ (kcal/mole)	$-\Delta S$ (e.u.)	Ref.
Acetone	CCl_4	13·5 (25°)	3·3	6·2	117
Ethyl acetate	CCl_4	9·3 (25°)	3·2	6·3	117
Diethyl ether	CCl_4	4·99 (37·5°)	5·63	14·9	128
Diethyl sulphide	CCl_4	0·84 (39°)	3·35	11·1	128
Diethyl selenide	CCl_4	0·63 (39·5°)	3·15	11·0	128
Acetonitrile	C_2Cl_4	5·69 (25°)	5·22	14·0	125
Benzonitrile	C_2Cl_4	4·70 (25°)	4·62	12·4	125
Dimethyl sulphoxide	C_2Cl_4	187·7 (25°)	6·93	12·8	125
Cyclohexyl fluoride	CCl_4	9·12 (25°)	3·13	6·1	127
Cyclohexyl chloride	CCl_4	4·34 (25°)	2·21	4·5	127
Cyclohexyl bromide	CCl_4	4·19 (25°)	2·05	4·0	127
Cyclohexyl iodide	CCl_4	3·99 (25°)	1·72	3·0	127
Pyridine	CCl_4	59 (20°)	6·5	14·9	129
4-Cyanopyridine	CCl_4	12 (20°)	3·2	6·0	129
4-*t*-Butylpyridine	CCl_4	84 (20°)	7·1	12·0	129

and ketones. Nitro compounds form weakly H-bonded complexes with phenol[113, 136]. Phenol can H-bond to sulphones and sulphonates[122]. The frequency shifts $\Delta\nu_{OH}$ correlate linearly with the symmetric and asymmetric stretching frequencies of the sulphuryl ($-SO_2-$) group. A higher basicity gives a lower stretching frequency ν_{SO_2}. $\text{Log}_{10} K_{assoc}$ and the Taft σ^* constants[52] for the substituents in a series of sulphones were both linear functions of the observed OH stretch frequency shift for phenol on H-bonding. Similar results to those for organosulphur compounds have also been obtained for organophosphorus compounds[116, 123, 124].

The association constants of phenol with eight pyridines show a smooth dependence on the σ-constants for the pyridine substi-

tuents[120]. Electron-withdrawing substituents give less negative enthalpies and entropies of H-bond formation in accord with the decrease in both the Lewis and Brønsted basicity of the pyridine nitrogen atom[104]. Linear correlations between $\Delta\nu_{OH}$ and σ^* were also observed for the H-bonding of phenol to nitriles and isonitriles[94]. For the latter, which probably exist as $R-N^+\equiv C^-$, phenol hydrogen bonds to the carbon and not to the nitrogen atom. The H-bond of phenol to isocyanides is stronger than that to cyanides. For cyanides typical values for the enthalpy of H-bond formation are $-3{\cdot}54 > \Delta H > -5{\cdot}72$ kcal/mole[125]. The more negative enthalpy changes are accompanied also by more negative entropies of H-bond formation. The generality of this ΔH–ΔS correlation is exemplified by the data in Table 6 and also by the plot in Figure 4 which compares results for several different H-bond donors as well as acceptors.

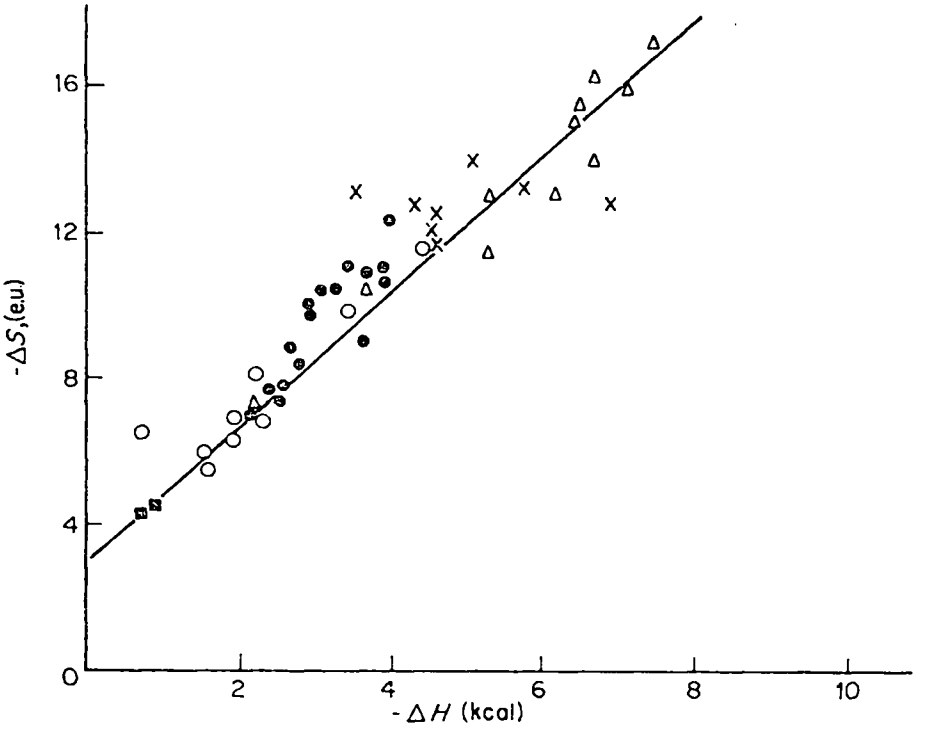


FIGURE 4. Relationship between ΔH and ΔS for the formation of H-bonded complexes (25°)[125]. X—phenol with nitriles; ○—*t*-butanol with nitriles; ▣—2,6-di-*t*-butylphenol with nitriles; ◎—alcohols with ethers, ketones etc.[86]; △—thiocyanic acid with ethers. Reproduced by permission from M. C. Sousa Lopes and H. W. Thompson, *Spectrochim. Acta*, **24A**, 1367 (1968).

Enthalpy changes of −2·13, −1·65, −1·57 and −1·25 kcal/mole have been observed when phenol in tetrachloroethylene H-bonds to *n*-heptyl fluoride, *n*-heptyl chloride, *n*-heptyl bromide and *n*-heptyl iodide respectively[126]. The corresponding ν_{OH} frequency shifts were 39·7, 58·7, 69·2 and 71 cm^{-1}. The enthalpy and frequency shift results therefore apparently lead to conflicting conclusions about the order of H-bond strength for the four interactions. The order of enthalpies is I < Br < Cl < F, that is, the correct order if the H-bond accepting ability of the halide is predominantly influenced by the electronegativity of the halogen atom. The Badger–Bauer relationship[14, 15] is not applicable in this case. Similar results were obtained for the association of phenol with the four cyclohexyl halides in CCl_4 (Table 6)[127]. The relative frequency shifts ν_{OH} for several acceptors are not a reliable measure of H-bond strength when different acceptor atoms are being compared. Phenol forms H-bonds with *n*-butyl[127] or ethyl[128] (Table 6) chalcogenides of strengths ($-\Delta H$) in the order: ether > sulphide > selenide. In contrast to the data for the alkyl halides the infrared ν_{OH} frequency[127, 128] and p.m.r. OH chemical shift[128] changes for the chalcogenides are both greater for the stronger H-bonds.

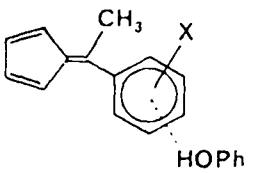
Phenol H-bonds to the π-electrons of substituted benzenes. The ν_{OH} frequency shift on H-bonding is given by equation (7)[130] where σ_m and σ_p are the appropriate *meta* and *para* substituent constants respectively[52]. Equation (8) is the corresponding result for

$$\Delta\nu_{OH} = [-62 \Sigma (\sigma_m + \sigma_p)/2] + (53 \pm 9)\ cm^{-1} \quad (7)$$

$$\Delta\nu_{OH} = [-44 \Sigma (\sigma_m + \sigma_p)/2] + (47 \pm 6)\ cm^{-1} \quad (8)$$

substituted naphthalenes. That the best correlations were obtained by plotting $\Delta\nu_{OH}$ against $(\sigma_m + \sigma_p)$ emphasizes the importance of the whole π-electron system as an H-bond acceptor[130]. For methyl substituted benzenes both $\Delta\nu_{OH}$ and ΔG on H-bond formation with phenol increase regularly with the number of methyl groups substituted in the benzene ring[131]. Similar results have been recorded for methyl-substituted furans and thiophens as H-bond acceptors[132]. Typical values of ΔG for phenol associating with condensed benzenoid systems in CCl_4 (20°) are −0·62 kcal/mole (benzene) < ΔG < 0·46 kcal/mole (fluoranthene)[131]. Frequency shifts $\Delta\nu_{OH}$ are generally below 100 cm^{-1}, although hexamethylbenzene ($\Delta\nu_{OH}$ = 127 cm^{-1}) is an exception. 6,6-Dialkylfulvenes are stronger proton acceptors than methylbenzenes[132]. With arylfulvenes and azulenes as acceptors two infrared absorption maxima both char-

acteristic of H-bonded complexes were observed[132]. These may be assigned to the H-bond complex of phenol to the benzene **9** and to the fulvene **10** ring for the arylfulvenes. It is logical tentatively to



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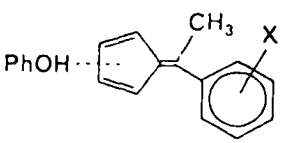
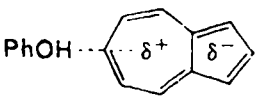


(10)

assign the two bands for the azulenes to phenol H-bonding to the seven **11** and to the five **12** membered ring. Alkyl groups increase



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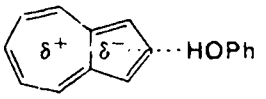


(12)

the H-bonding basicity of olefins as measured by K_{assoc} or $\Delta\nu_{OH}$ on complexing with phenol[133, 134]. 1,3-Butadienes give smaller frequency shifts but larger association constants than the monolefins.

The effect of deuteration on the H-bond strength of phenol to several structurally dissimilar bases has been investigated by Singh and Rao[135]. The enthalpy of formation of the H-bond was always greater than that for the deuterium bond. Also $\Delta\nu_{OH} > \Delta\nu_{OD}$. The ratio of association constants K_H/K_D was dependent on the structure of the acceptor molecule and varied from 0·2 for self-dimerization to 4·3 for association with tetra-*n*-heptylammonium iodide.

2. Comparison of phenols

a. Unhindered phenols. The ability of a phenol to form a strong H-bond increases with increasing Brønsted acidity of the phenol. The ν_{OH} frequency shift, $\log_{10} K_{assoc}$, and ΔH for H-bond formation of a series of phenols with a given acceptor are all linear functions of pK_a for the phenols. Acceptors for which one or other of these correlations have been established include methyl acetate[90], triethylamine[90], tri-*n*-butylamine[137], carbon disulphide[138], *n*-heptyl fluoride[126], several nitro compounds[136], and acetone[97]. The typical relationship between acidity and H-bond strength is exemplified by the results of Huyskens and co-workers[137] for tri-*n*-butylamine acceptor (Figure 5).

The usual linear correlations of ΔH with ΔG and $\Delta\nu_{OH}$ for H-bond formation were not observed when results for several phenols complexing with acetone were considered[97]. However, the enthalpy changes were linear functions of the length of the H-bonds[97]. Lengths ranged from 2·9 Å ($\Delta H = -5{\cdot}20$ kcal/mole) for 3-bromophenol to 3·2 Å ($\Delta H = -1{\cdot}91$ kcal/mole) for 2,6-di-*t*-butyl-4-methylphenol. The curvature of the ΔH against ΔG and $\Delta\nu_{OH}$

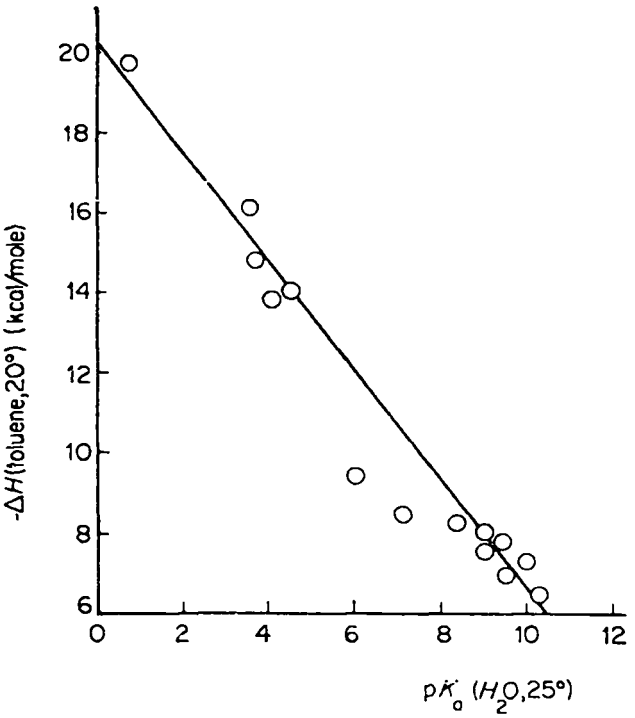


FIGURE 5. Correlation between acidity of phenols and ΔH for the formation of H-bonds between the phenols and tri-*n*-butylamine. ΔH data from reference 137.

graphs probably arises because some of the phenols studied had bulky *ortho* substituents which introduce a severe steric restriction to H-bonding. When *meta* and *para* substituted phenols only are considered good linear correlations are obtained[126, 139]. Thus equations (9) and (10) (ΔH kcal/mole; $\Delta\nu_{OH}$ cm^{-1}) describe the lines for a series of sterically unhindered phenols complexing with *n*-heptyl fluoride[126] and diphenyl sulphoxide[139] respectively, both in C_2Cl_4

$$-\Delta H = 0{\cdot}053\Delta\nu_{OH} \text{ (}n\text{-heptyl fluoride)} \quad (9)$$

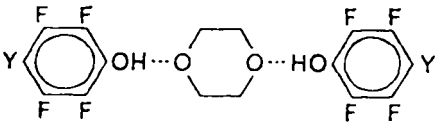
$$-\Delta H = 0{\cdot}0134\Delta\nu_{OH} + 3{\cdot}378 \text{ (diphenyl sulphoxide)} \quad (10)$$

solvent. From the significant difference between the two equations Ghersetti and Lusa[139] concluded that $\Delta\nu_{OH}$ can only be used to estimate H-bond strengths providing a given acceptor and a series of structurally related donors are being compared.

For a given phenol bonding to a series structurally related acceptors both $\Delta\nu_{OH}$ and $\log_{10} K_{assoc}$ are linear functions of the σ-constants for the substituents in the acceptors[116, 123, 136]. However, for a given acceptor both $\Delta\nu_{OH}$ and $\log_{10} K_{assoc}$ are larger for a more acidic phenol. The shifts in OH stretching frequencies for a series of *p*-substituted phenols on H-bonding to dioxan in cyclohexane increased linearly with the increment in OH bond moment calculated to explain the measured dipole moments of the phenols in dioxan[140]. Equation (11) is applicable and emphasizes the simple

$$y = 0{\cdot}00814\Delta\nu_{OH} - 1{\cdot}43 \qquad (11)$$

relationship between bond moment and H-bonding strength. Pentafluorophenol and 2,3,5,6-tetrafluorophenol form 2 : 1 crystalline complexes of type **13** (Y = H or F) with dioxan[141]. Pentafluoro-



(13)

phenol also forms complexes with triphenylphosphine oxide of 1 : 1, 1 : 2 and 2 : 1 stoichiometry[142]. Heats and enthalpies of formation of the complexes in CCl_4 are for $(C_6H_5)_3PO \cdots HOCF_{65}$ — 5·5 kcal/mole and —1·1 e.u., for $(C_6H_5)_3PO \cdots 2\,HOC_6F_5$ — 4·8 kcal/mole and —9·5 e.u., and for $C_6F_5OH \cdots 2\,OP(C_6H_5)_3$ —1·9 kcal/mole and —3·6 e.u.

The H-bonding of phenols to aniline has been studied by Zeegers-Huyskens[101]. The OH stretch frequencies in the H-bonded complexes showed a steady drift to lower frequencies as the acidity of the phenols became greater. Thus $\nu_{OH} = 3350\ cm^{-1}$ for 2,4,6-trimethylphenol ($pK_a = 10{\cdot}88$) and $\nu_{OH} = 3160\ cm^{-1}$ for 4-nitrophenol ($pK_a = 7{\cdot}15$) represent the extremes for the series. The asymmetric and symmetric stretching frequencies of the aniline NH_2 group showed corresponding shifts to lower frequency. 2,4-Dinitrophenol, 2,6-dinitrophenol, pentachlorophenol, 2,3,5-trichlorophenol, and 2,6-dichloro-4-nitrophenol form complexes with aniline in the solid phase which have a broad infrared absorption at 2100–2900 cm^{-1}. This arises because proton transfer has occurred and the

H-bond becomes $NH^+ \cdots O^-$. The fluorescence spectrum of the α-naphthol–triethylamine H-bonded complex is identical with the fluorescence spectrum of α-naphthol in alkaline solution. Thus proton transfer from α-naphthol to triethylamine occurs when the H-bonded complex absorbs radiation. The excited state of the complex is in the ion-pair form[143].

b. Steric effects. Bulky *ortho* substituents in phenols hinder the formation of H-bonds which involve the OH group[144]. The effect of *ortho* substituents on the relative frequency shifts ($\Delta\nu_{OH}/\nu_{OH}$) for several phenols H-bonding to many acceptors of different structural types has been investigated by Bellamy and Williams[61]. Plots (Figure 6) of

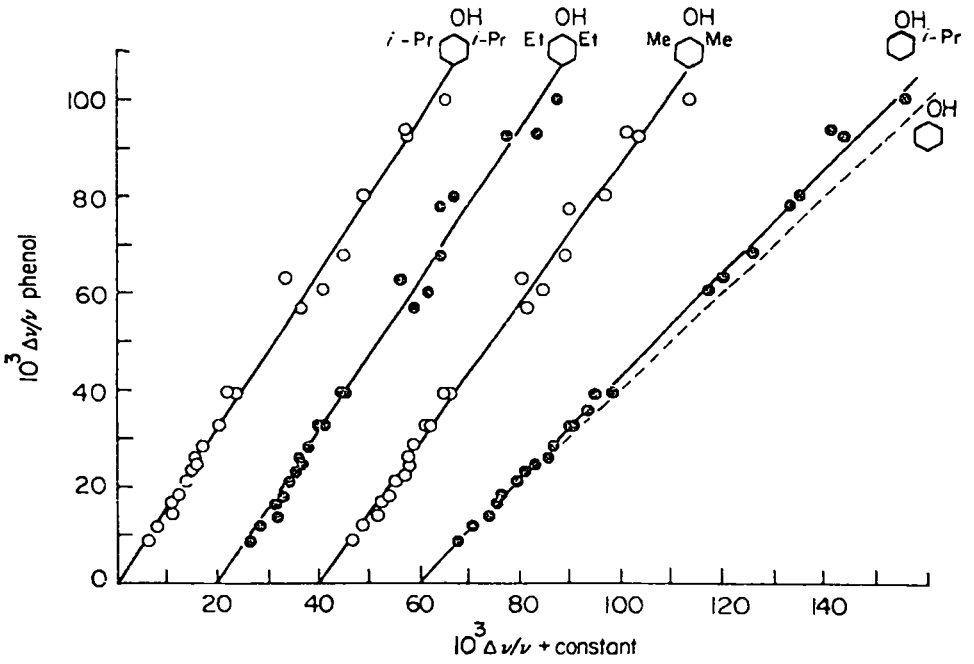


FIGURE 6. Relative frequency shifts for four phenols compared with those for phenol itself on H-bonding to 23 acceptor solvents[61]. The intercepts on the $10^3\Delta\nu/\nu$ axis are staggered by 20 units for clarity. Reproduced by permission from L. J. Bellamy and R. L. Williams, *Proc. Roy. Soc.*, **A254**, 119 (1960).

($\Delta\nu_{OH}/\nu_{OH}$) for 2-*i*-propyl, 2,6-dimethyl, 2,6-diethyl and 2,6-di-*i*-propyl phenols against ($\Delta\nu_{OH}/\nu_{OH}$) for phenol were linear, suggesting the absence of steric effects. For 2,6-di-*t*-butylphenol the geometry of the acceptor molecules has a decisive influence on whether H-bonding can occur. There is no association with pyridine, tri-

ethylamine, dimethylamine or ether except at high concentrations. However, 2,6-di-*t*-butylphenol does H-bond to dioxan. It appears uncertain whether H-bonding to π-electron systems can occur[61] or not[130].

Although the frequency shift data only give a clear indication of steric hindrance for 2,6-di-*t*-butylphenol, the association constants of several phenols with ethers show that smaller *ortho* substituents than *t*-butyl also have an effect[145]. This is exemplified by the figures in Table 7. One *ortho* alkyl group is not sufficient to cause an appreciable

TABLE 7. Equilibrium constants (l/mole) for the association of some substituted phenols with ethers in CCl_4 at 29° [145].

Ether	Et_2O	*i*-Pr_2O	*n*-Bu_2O	*t*-Bu_2O
Phenol substituents				
2-Methyl	3·4	3·2	2·6	1·7
2-*i*-Propyl	3·9	3·9	3·0	2·0
2-*t*-Butyl	3·7	4·1	2·9	2·3
2,6-Dimethyl	0·67	0·62	0·63	0·22
2,6-Di-*i*-propyl	0·51	0·48	0·23	0·19
2,6-Di-*t*-butyl	~0	~0	~0	~0

steric effect. However 2,6-dialkyl substitution produces a steric inhibition to H-bond formation which is more severe either for larger alkyl groups or for a more sterically hindered acceptor site. Association constants for H-bonding of *N*-methylacetamide or *N*,*N*-dimethylacetamide with three phenols were in the order 2,6-di-*t*-butylphenol < 2-methyl-6-*t*-butylphenol < 2-*t*-butylphenol, which is consistent with the expected relative steric requirements of the phenols[146]. The steric hindrance to H-bonding of 2,4,6-tri-*t*-butylphenol with acetone[147] is paralleled by a corresponding hindrance to the H-bonding of phenol with the oxygen atom attached to C_1 of 2,6-di-*t*-butyl-1,4-benzoquinone[148]. In general, steric factors have a greater influence on H-bonding association than on the proton acidity of phenols[97]. This difference parallels the relative effects of bulky 2,6-substituents on the Lewis and Brønsted basicity of pyridines[104].

The conclusion[61, 145] that the reduction in K_{assoc} caused by steric interference is an entropy rather than an enthalpy effect does not seem to be wholly justified[97, 125, 146]. Thus for 2,6-di-*t*-butylphenol H-bonding to acetonitrile (C_2Cl_4, 25°) $K_{assoc} = 0{\cdot}41$ l/mole,

$\Delta H = -0{\cdot}8$ kcal/mole and $\Delta S = -4{\cdot}4$ e.u., and H-bonding to benzonitrile $K_{assoc} = 0{\cdot}43$ l/mole, $\Delta H = -0{\cdot}9$ kcal/mole and $\Delta S = -4{\cdot}6$ e.u.[125]. Comparison with the corresponding results for phenol (Table 6) shows that both the enthalpy and entropy changes are affected. In general steric hindrance leads to a weaker ($-\Delta H$ smaller) and longer H-bond[97] than would be expected from electronic considerations alone.

3. Solvent effects

The frequency shifts observed for H-bonded complexes on changing the solvent may be approximately fitted to the Kirkwood–Bauer–Magat equation (12)[112] provided no specific interactions occur between the solvent molecules and the complex[149]. C is a constant

$$\nu = \nu_0 - C\frac{\varepsilon - 1}{2\varepsilon + 1} \tag{12}$$

for a particular complex, ε is the dielectric constant of the solvent and ν_0 is the OH stretching frequency for the complex in the vapour phase. Thus ν_{OH} is a linear function of $(\varepsilon - 1)/(2\varepsilon + 1)$ for the H-bonded complexes phenol–acetonitrile, phenol–propionitrile, phenol–methyl iodide and phenol–dimethyl sulphoxide in various solvents[100, 149]. The values of C for the complexes of five phenols with acetonitrile in acetonitrile–tetrachloroethene mixtures were a linear function of the σ-constants[52] for the substituents in the phenol rings[149]. Equation (12) is not consistent with the frequency shifts for the phenol–ether complex in ether–chloroform mixtures[109]. In this context the empirical equation (4) is found to have a wider generality than equation (12)[109]. However, a more rigorous theory of solvent effects should also take variations of refractive index n of the solvent into account[150]. Thus the Buckingham[150] equation (13) often gives an impressive agreement between experimental and calculated frequency shifts (Table 8)[149]. Extensions of the Buckingham equation have also been tested[89, 149].

$$\nu = \nu_0 - C_1\frac{\varepsilon - 1}{2\varepsilon + 1} - C_2\frac{n^2 - 1}{2n^2 + 1} \tag{13}$$

The effect of specific solute–solvent interactions on the behaviour of H-bonded complexes in different solvents must also be considered[22, 110, 151, 152]. Thus for the phenol–triphenylphosphine oxide complex in CBr_4/CCl_4 mixtures ΔH, ΔG and ΔS for H-bond formation all become less negative as the mole fraction of CBr_4 in the solvent is increased[152]. This probably arises because a specific inter-

action between triphenylphosphine oxide and CBr_4 occurs and is much stronger than the corresponding interaction with CCl_4. Specific solvent effects are most likely to influence the H-bond in a solute complex when the solvent molecules themselves can act as H-bond donors or acceptors[22]. An example has been given in structure **6** above. The OH stretch frequencies for the H-bonded complexes of phenol with di-*n*-butyl ether or mesitylene in *n*-hexane, carbon tetrachloride or chloroform are all dependent on temperature. It has been argued[151] that these results indicate that specific solvent–solute interactions are the predominant cause of solvent effects on H-bond equilibria. The 'inductive association' concept of solvation[109, 149] is considered unsatisfactory.

TABLE 8. Comparison of the experimental OH stretch frequencies for the phenol–tetrahydrofuran H-bonded complex in CCl_4 with the values calculated from equation (13)[149].

Volume % tetrahydrofuran	ν_{OH} (experimental) (cm^{-1})	ν_{OH} (calculated) (cm^{-1})
1	3323	3323·5
10	3319	3318·5
30	3313	3312·0
50	3307	3307·8
70	3305	3305·3
100	3304	3303·7

o-t-Alkylphenols exist as *cis* and *trans* isomers[153]. The *cis–trans* ratio at equilibrium is increased by solvents which can act as acceptors for an H-bond from the OH of the *cis* isomer[154]. H-bonding from the *trans* isomer is sterically hindered. The solvation by water of the conjugate acid of 2,4,6-trimethoxybenzene is increased by progressively substituting OH groups for OCH_3 groups[155]. In the tri-substituted compounds solvation by H-bonding decreases in the order $(OH)_3 > (OH)_2(OCH_3) > (OH)(OCH_3)_2 > (OCH_3)_3$. In a similar way, substituting hydroxyl groups in aromatic nuclei should increase their solvation through H-bonding and therefore their solubility in water. The reverse is often true, particularly for heterocyclic nuclei[156]. The hydroxypteridines are a good example: the solubilities are in general in the order tetrahydroxypteridine < trihydroxypteridines < dihydroxypteridines < hydroxypteridines < pteridine. The increase in H-bonding ability in the solid

state clearly outweighs the increased solvation of the molecules on adding an OH group.

4. Spectroscopy and H-bonding

H-bonding alters the p.m.r. chemical shifts and infrared stretching frequencies of the OH group. Shifts in the stretching frequencies associated with the acceptor site in molecules to which phenols are H-bonding have also been noted[98, 99, 101]. H-bonding by 2- or 4-substituted phenols produces appreciable shifts in p.m.r. spectra of the ring protons of the phenols[120]. The perturbation to the OH group caused by the formation of an H-bond is spread over the whole phenol molecule. The π–π^* transition in the electronic spectrum of phenols is generally shifted to lower frequencies (longer wavelength) when a phenol becomes an H-bond donor[138, 157–160, 162]. The stabilization of the appropriate ground ($^1A_1$) and excited ($^1B_2^-$) states on H-bonding is greater for the latter than for the former and therefore a smaller excitation energy is necessary to induce the electronic transition in the H-bonded molecule[160]. The conclusion[159] that 4-nitrophenol is a stronger H-bond donor in the excited state than in the ground state is analogous to the increase in acidity of some phenols in going from the ground to the excited states[161].

Far infrared[76, 77, 163–168] studies have given values for the vibrational frequencies of the H-bonds between phenols and various electron acceptors. For phenol the H-bond stretching frequency ν_σ is 175 cm^{-1} for the solid[76, 77, 163], 162 cm^{-1} for the liquid[76], and 130–150 cm^{-1} for solutions in CCl_4 [163, 165]. The frequencies for substituted phenols are shifted[76, 163, 167] but there is no direct correlation between the values of ν_σ and the corresponding changes in $\Delta\nu_{OH}$ for the OH stretching frequencies[76, 167]. If both the H-bond frequency ν_σ and the OH frequency shift $\Delta\nu_{OH}$ were a reliable measure of H-bond strength a smooth relationship between the two would be expected. For the phenol–triethylamine, phenol–trimethylamine and phenol–pyridine complexes the ν_σ frequencies are 123 cm^{-1}, 143 cm^{-1} and 134 cm^{-1} respectively[165]. The values are 120 cm^{-1}, 141 cm^{-1} and 130 cm^{-1} for the corresponding C_6H_5OD complexes. The ν_σ frequency for a particular complex varies with solvent composition. Thus, for the phenol–pyridine complex in pyridine–carbon tetrachloride mixtures ν_σ (cm^{-1}) varies linearly with the mole fraction X_{py} of pyridine according to equation (14)[166].

$$X_{py} = 0{\cdot}126\nu_\sigma - 16{\cdot}455 \qquad (14)$$

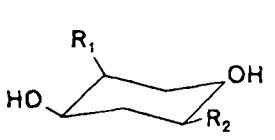
III. INTRAMOLECULAR H-BONDING*

A. Alcohols

The easiest test for intramolecular H-bonding is to measure the variation of infrared or Raman spectra at low concentrations or pressures[169]. The spectral characteristics of intermolecular H-bonding disappear at low concentrations when H-bonding intermolecular association becomes absent. Intramolecular H-bonding does not disappear. A general comparison of the properties of intra- and intermolecular H-bonds has been given by Pimentel and McClellan[169].

Intramolecular H-bonding in dihydroxy compounds was studied by Kuhn[170]. In general, only those compounds for which the calculated length of the H-bond was less than 3·3 Å formed intramolecular H-bonds. Thus, cyclohexane-1,4-diol does not H-bond intramolecularly. However, cyclohexane-1,3-diol forms an H-bond in its *cis* form but not in its *trans* form. The strongest intramolecular bond (measured as that giving the largest shift $\Delta\nu_{OH}$) was for 1,2-dimethylolcyclohexane in which the H-bond leads to the formation of a seven-membered ring. In the series $HO(CH_2)_nOH$ the $\Delta\nu_{OH}$ differences between the frequencies for the free and the intramolecularly H-bonded OH groups were (CCl_4 solvent) 32 cm^{-1} for $n = 2$, 78 cm^{-1} for $n = 3$, and 156 cm^{-1} for $n = 4$. The H-bond is apparently stronger when the geometry of the molecule allows a close approach of the two OH groups. For $n = 6$ however no intramolecular H-bond is formed. Such bonding is favoured when it leads to the formation of five-, six- or seven-membered ring structures[174].

Although cyclohexane-1,4-diol does not form an intramolecular H-bond[170] its *cis*, *cis*, *cis*-2,5-dialkyl derivatives (**14**) in CCl_4 (25°) can exist in intramolecularly H-bonded twist conformations (**15**)[171, 172]. The population of the twist form at equilibria depends upon the size of the alkyl groups R_1 and R_2. It is about 5% for



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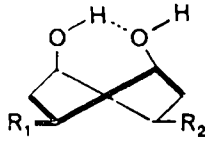
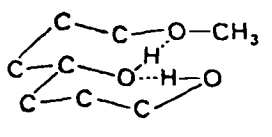


(15)

* Intramolecular H-bonding leads to cyclic structures. The number of atoms in an H-bonded ring is counted in this section to include the hydrogen atom involved in the H-bond.

$R_1 = R_2 = CH_3$, >98% for $R_1 = R_2 = t$-alkyl, 14% for $R_1 = CH_3$, $R_2 = CH(CH_3)_2$ or $R_1 = CH_3$, $R_2 = C(CH_3)_3$, and about 80% or $R_1 = R_2 = sec$-alkyl. Increasing the size of R_1 or R_2 increases the proportion of the H-bonded twist structure. Structure **16** which resembles the shape of *trans* decalin has been suggested for the H-bonded form of heptane-1,4,7-triol-1-methyl ether[173]. The H-bonded structures of the isomeric triols 1,1,1-trimethylolethane and pentane-1,3,5-triol are probably **17** and **18** respectively.



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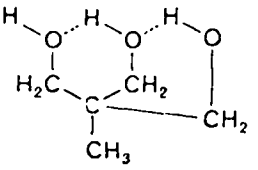

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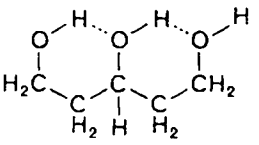
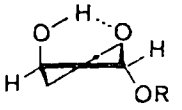


(18)

Intramolecular H-bonding from OH to the ether linkage in the series $MeO(CH_2)_nOH$ is favoured when a five-, six- or seven-membered ring results[174]. For $n = 2,3$ and 4 the ν_{OH} frequency shifts in going from the nonbonded to the H-bonded conformations were 30, 86 and 180 cm^{-1} respectively[175]. The corresponding heats of H-bond formation (CCl_4 solvent) were 2200, 2100 and 2700 cal/mole respectively. The Badger–Bauer relationship[14, 15] is not applicable for these intramolecular H-bonds.

Intramolecular H-bonding occurs in both the *cis* and *trans*-2-alkoxy-3-hydroxytetrahydrofurans[176]. For the latter, because the alkoxy and hydroxy groups are *trans*, H-bonding between OH and the heterocyclic oxygen must occur. A possible structure for the H-bonded form of the *trans* isomer is **19** in which $R = CH_3$,



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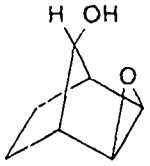

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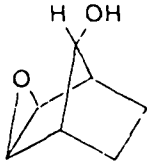
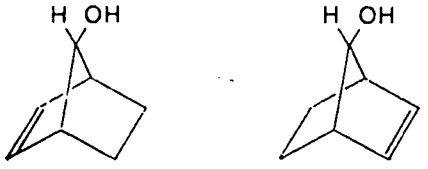


(21)

CH_3CH_2, $CH(CH_3)_2$, or $C(CH_3)_3$. The infrared frequency difference between ν_{OH} for non H-bonded and H-bonded forms is about 24 cm^{-1} for all four alkyl substituents. Proton magnetic resonance hydroxy proton chemical shifts and rates of change of chemical shift with concentration at infinite dilution sometimes enable intra- and inter-molecular H-bonding to be distinguished. Thus for fifteen

isomeric epoxyalcohols with the bicyclo[2,2,1] heptane skeleton the chemical shifts (relative to tetramethylsilane) were characteristically large and the limiting slopes of the chemical shift against concentration plots were small in cases where intramolecular H-bonding occurred[177]. Compounds **20** and **21** serve as examples. For **20** in which H-bonding to an epoxide linkage occurs, the limiting chemical shift (CCl_4 solvent) was 192·0 cps and the limiting slope 85 cps/mole fraction. The corresponding figures for **21** which can only H-bond intermolecularly were 44·0 cps and 3580 cps/mole fraction. The large concentration dependence of the chemical shift for intermolecular H-bonding compared to that for intramolecular H-bonding is a general result[169]. Infrared evidence has been recorded for the intramolecular H-bonding by OH groups to the oxirane rings of some epoxyalcohols[178]. Thus for glycidol (in CCl_4) three ν_{OH} absorptions exist at 3638, 3611·8 and 3590 cm^{-1}. The first is due to free OH and the last to OH H-bonded to the epoxide oxygen atom. The middle band has been ascribed to H-bonding of OH to the electrons of the CO bond of the oxirane ring. This interaction is favoured when the OH is orientated in the plane of the ring.

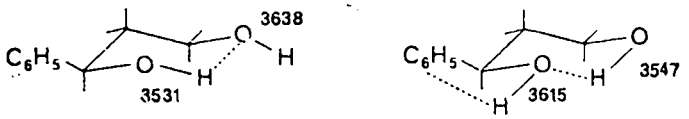
The strength of the intramolecular H-bond between the alcoholic OH and the ethylenic double bond π-electrons in ethylenic alcohols depends upon the relative positions of the OH group and the double bond in the molecules[179, 180]. Hydroxy stretching frequency shifts on H-bonding are 1–2 cm^{-1} for α,β ethylenic alcohols, 25–45 cm^{-1} for a β,γ double bond, and 60 cm^{-1} for a γ,δ bond. The corresponding enthalpies of H-bond formation ΔH are −0·8 kcal/mole (α,β), −1·0 kcal/mole (β,γ) and −2·3 kcal/mole (γ,δ). The heat of formation of an intramolecular H-bond between an alcohol group and a triple bond in β,γ acetylenic alcohols is about −1·1 kcal/mole[181]. Frequency shifts $\Delta\nu_{OH}$ on H-bonding for the intramolecular interactions between the hydroxyl groups and the π-electrons of unsaturated bonds in the methyl esters of unsaturated monohydroxy acids may be divided into three groups depending upon the geometry of the molecules[182]. It has been concluded that studies of the strength of H-bonds in novel compounds might prove a useful aid in the determination of molecular structure[182]. A further example involving OH→π H-bonding is analogous to the difference (discussed above) in H-bonding properties of structures **20** and **21**. Thus for **22** and **23** the limiting chemical shifts were 60·5 ppm and 121·0 ppm and the limiting chemical shift against concentration slopes were 2380 and 320 ppm/mole fraction respectively[177]. Clearly



(22) (23)

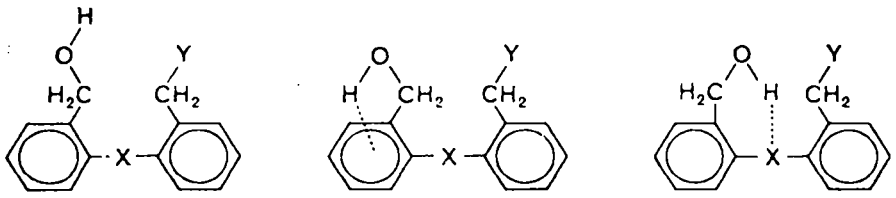
the geometry of **23** is such that OH→π intramolecular bonding can occur whereas in **22** it becomes impossible.

In many compounds competition between different types of intramolecular H-bonding can occur. Thus for the phenyl-α,ω-alkanediols $PhCHOH(CH_2)_nOH$ the H-bonding of the hydroxyl groups with each other and with the phenyl π-electron system has been studied[183]. The primary hydroxyl group H-bonds to both the secondary OH and the phenyl ring if $n = 1$. However for $n = 2$ or 3 only bonding to the secondary OH groups occurs. The primary OH is not intramolecularly H-bonded when $n = 4$. The secondary OH H-bonds to the primary OH and the phenyl ring when $1 \leqslant n \leqslant 3$ but only to the π-system when $n > 3$. For example, for 1-phenyl-propane-1,3-diol ($n = 2$) there are four infrared OH stretching absorptions which have been assigned in accord with structures **24**

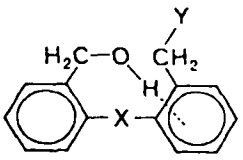


(24) (25)

and **25**. Competition between different intramolecular H-bonding possibilities is further exemplified by a study of substituted benzyl alcohols with structure **26** in which Y = H or OH and X is C≡C, CH=CH (*cis* or *trans*) or CH_2CH_2 [184]. Four H-bonded structures (**27–30**) are possible. The infrared ν_{OH} frequencies were around 3640 cm^{-1} for **26**, 3618 cm^{-1} for **27**, 3585 cm^{-1} for **28** and 3535 cm^{-1}



(26) (27) (28)



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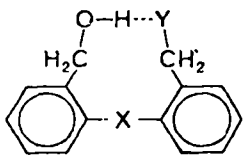


(30)

for **29**. Conformer **30** was only observed for two of the alcohols for which ν_{OH} (**30**) were 3507 and 3575 cm^{-1}. From the relative intensities of the absorptions the proportions of each conformer at equilibrium in CCl_4 were evaluated. The results are given in Table 9. For the dihydroxy compounds (Y = OH) the sum of the conformations for both OH groups contributes to the infrared intensities.

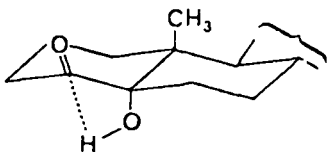
TABLE 9[a]. Approximate percentages of each conformer of the substituted benzyl alcohols (**26**) present in CCl_4 at about 30°C [184].

Substituents		Conformers				
X	Y	**26**	**27**	**28**	**29**	**30**
C≡C	H	35	40	25		
C≡C	OH	25	40	15		20
CH=CH (*cis*)	H	25	50	15	10	
CH=CH (*cis*)	OH	25	50	15	10	Not obsd.
CH=CH (*trans*)	H	20	55	15	10	
CH=CH (*trans*)	OH	20	55	15	10	Not obsd.
CH_2-CH_2	H	10	75		15	
CH_2-CH_2	OH	20	60		10	10

[a] Reproduced by permission from I. D. Campbell, G. Eglington and R. A. Raphael, *J. Chem. Soc.* (**B**), 338 (1968).

Intramolecular H-bonding in hydroxyketones and hydroxyesters leads to a reduction in the carbonyl stretching frequency. The p.m.r. chemical shifts of the OH protons for a series of such compounds were a linear function of the carbonyl stretching frequencies in the H-bonded molecules[185]. The stronger the H-bond the lower is $\nu_{C=O}$. Intramolecular H-bonding of OH to a carbonyl group also produces the usual shift to lower frequencies of the OH stretching vibration. For a series of ketoalcohols the shift $\Delta\nu_{OH}$ may be correlated with the relative geometrical orientation of the hydroxyl group and the lone pair electrons on the oxygen atom of the carbonyl group[186]. The frequency shift is biggest for shorter H-bonds and for bonds in

which the maximum overlap occurs between the orbitals of the hydroxyl hydrogen atom and the lone pair molecular orbitals of the carbonyl oxygen atoms. There is evidence that the latter are predominantly $2p$ in character. In some cases where this interaction is unlikely from steric considerations there is still a small $\Delta\nu_{OH}$ shift (8–34 cm^{-1}) indicative of a weak intramolecular H-bond. This has been attributed to an interaction between the hydroxyl groups and the π-electrons of the carbonyl group. An example is 5α-cholestan-5α-ol-4-one (**31**) for which $\Delta\nu_{OH} = 11$ cm^{-1}. For 5α-hydroxyergosta-7,22-dien-3-one (**32**) competition occurs between H-bonding to a carbonyl group and an ethylenic double bond. The relevant frequency shifts are 10 and 24 cm^{-1} respectively.



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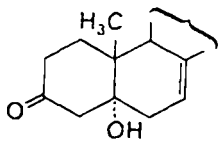

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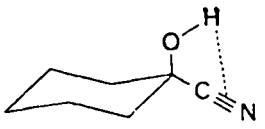
H-bonding intramolecular interactions between the alcoholic group and the π-electrons of the cyano group occur in α-cyanoalkanols[94, 187]. Thus, for example, the OH stretch absorption for cyclohexanone cyanohydrin is symmetric (ν_{max} 3591 cm^{-1}) indicating that the molecule exists predominantly in one of the interacting conformations **33** or **34** and not as the non-interacting forms



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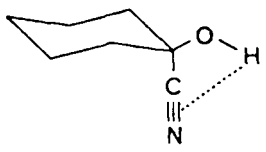

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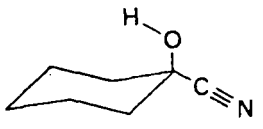

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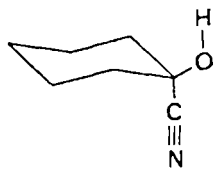
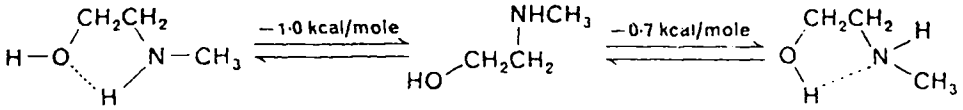


(36)

35 or **36**. For the cyanoalkanols $NC(CH_2)_nOH$ an H-bond interaction with the CN π-electrons occurs only if $n = 1$ or 2.

The frequency shifts $\Delta\nu_{OH}$ for intramolecular H-bonding in the 2-haloethanols were 12 cm^{-1} for F, 32 cm^{-1} for Cl, 38 cm^{-1} for Br and 46 cm^{-1} for I [188]. However, the strengths ($-\Delta H$) of the H-bonds are in the order $F > Cl \simeq Br > I$ [189]. The Badger–Bauer relationship[14, 15] is therefore not applicable. In general the H-bond strength increases with increasing electronegativity of the halogen atom. The frequency shifts $\Delta\nu_{OH}$ cannot be used to compare H-bond strengths when the interactions involve different acceptor atoms or groups. None of the 3-halopropanols can form an intramolecular H-bond[190]. The enthalpy of H-bond formation is too small compared with the entropy loss on forming a cyclic H-bonded structure when a ring of six or more atoms would result.

Aminoalkanols can form either NH · · · O or OH · · · N intramolecular H-bonds. For example, the enthalpies of interconversion of the three predominant conformers of *N*-methylethanolamine are as follows[191] (C_2Cl_4 solvent).



(37) (38) (39)

The OH · · · N interaction provides the most stable conformer. For the diethylaminoalkanols $(C_2H_5)_2N(CH_2)_nOH$ the $\Delta\nu_{OH}$ values are much larger than those for the corresponding halo, cyano or alkoxyalkanols[188, 192]. Furthermore, cyclic H-bonded conformers could be detected for $n \leqslant 5$ although the equilibrium constants for formation of the conformers from the non H-bonded forms decreased in the sequence 14, 4·7, 3·5, 0·11 for $n = 2$, 3, 4 and 5. For $n = 6$ intramolecular H-bonding could not be detected.

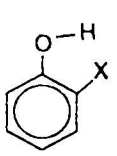
Evidence for intramolecular H-bonding between hydroxyl groups and nitro groups in 2-nitroalcohols includes the detection of ν_{OH} absorption bands for the alcohols which are at 10–28 cm^{-1} lower frequencies than the bands for the non H-bonded alcohols[113]. Spectra of two 2-alkyl-2-nitropropane-1,3-diols showed three absorptions: a free OH band at 3632 cm^{-1}, an OH · · · O_2N bonded band at 3604 cm^{-1} and an OH · · · OH absorption at 3550 cm^{-1}. The nitro group is a weaker acceptor than the second hydroxyl group but is suitably orientated for an interaction to occur.

A concentration-independent sideband at lower frequencies than hc main absorption appears on the hydroxyl stretch band contour

for aliphatic alcohols in carbon tetrachloride[193]. This has been attributed to an interaction between the CH group in the γ position and the lone pair electrons on the oxygen atom of the hydroxyl group. Interaction enthalpies of $-0{\cdot}44$ kcal/mole for *n*-heptanol and $-1{\cdot}06$ kcal/mole for 4-heptanol have been deduced.

B. Phenols

2-Substituted phenols exist as *cis* **40** or *trans* **41** isomers[51, 53, 61, 154, 155]. The hydroxyl group is in the plane of the benzene ring even for 2,6-di-*t*-butyl phenols[51, 61]. For bulky 2-substituents the *trans* isomer becomes preferred to the *cis* isomer with increasing size of the group[53, 154, 155]. However, if the group is capable of acting as an H-



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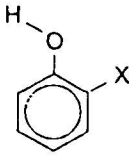

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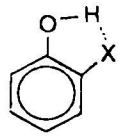


(42)

bond acceptor intramolecular H-bonding **42** occurs and leads to an increase in the thermodynamic stability of the *cis* isomer[53, 67, 69, 194]. The experimental differences (Table 10) in ν_{OH} frequencies for **40** and **42** are characteristic of an H-bonding interaction in the latter. The corresponding shifts of the hydroxyl proton magnetic resonance signal δ_{OH} are approximately a linear function of $\Delta\nu_{OH}$ [67, 194]. This is an analogous result to the one, exemplified by equation (3), for intermolecular H-bonds. Typical values of $\Delta\delta_{OH}$ and $\Delta\nu_{OH}$ for the intramolecular H-bonding of phenols are given in Table 10. The 1,2-diol catechol shows two ν_{OH} absorptions of about equal intensity, one at 3618 cm^{-1} due to an OH group acting as an H-bond acceptor and one at 3570 cm^{-1} due to the other OH group which is the H-bond donor[173]. The 1,2,3-triol pyrogallol exists as a conformer in which two of the OH groups act as H-bond donors.

The out of plane deformation vibration γ_{OH} of the OH group in intramolecularly H-bonded 2-substituted phenols occurs in the 300–860 cm^{-1} frequency region[202]. A curved plot of γ_{OH} against ν_{OH} has been obtained for about 50 phenols with γ_{OH} increasing as ν_{OH} decreases. Comparing H-bonds of quite different strengths, the strongest bonds give rise to the highest γ_{OH} frequencies. The far infrared ν_σ H-bond stretching frequency for 2-chlorophenol is at 84 cm^{-1} which is about 40 cm^{-1} lower than ν_σ for the cresols,

TABLE 10. Typical changes in the position of the OH p.m.r. signal $\Delta\delta_{OH}$ and infrared shifts $\Delta\nu_{OH}$ caused by intramolecular H-bonding of phenols in carbon tetrachloride[67, 194, 195, 203].

Phenol	Acceptor group	$\Delta\delta_{OH}$ (ppm)[a]	$\Delta\nu_{OH}$ (cm^{-1})
Salicylaldehyde	CHO	6·71	471
2-Nitrophenol	NO_2	6·34	364
Methyl salicylate	$COOCH_3$	6·32	395
2-Iodophenol	I	1·33	105
2-Methoxypheno	OCH_3	1·18	60
2-Chlorophenol	Cl	1·17	61
2-Bromophenol	Br	1·15	92
2-Allylphenol	$CH_2CH{=}CH_2$	1·07	66
2-Fluorophenol	F	0·80	18
2-Cresol	CH_3	0·32	−8

[a] Measured with respect to a cyclohexane internal standard and corrected for ring currents.

3-chlorophenol, and 4-chlorophenol which cannot form intramolecular H-bonds[167].

For 2-halophenols the *trans–cis* ratios and the infrared frequency shifts $\Delta\nu_{OH}$ (Table 10) both increase in the order F < Cl < Br < I [67, 194–197]. However, measurements of the enthalpies of formation of the H-bonds (Table 11) have shown that this is not the same

TABLE 11. Strengths of the intramolecular H-bond of 2-halophenols as a function of solvent.

Phenol	$-\Delta H$ (kcal/mole)[198] in vapour	$-\Delta H$ (kcal/mole)[67] in CS_2	$-\Delta H$ (kcal/mole)[197] in CCl_2CCl_2
2-Chlorophenol	3·41	2·36	1·28
2-Bromophenol	3·13	2·14	1·86
2-Iodophenol	2·75	1·65	0·99
2-Chlorophenol-*d*	2·81		
2-Bromophenol-*d*	2·65		
2-Iodophenol-*d*	2·65		

as the order of H-bond strengths[67, 197, 198]. In the vapour and in CCl_4 solution the order of strength is I < Br < Cl whereas in ethylene tetrachloride solvent the OH · · · Br H-bond becomes the

strongest. From a study of the infrared spectra of unsymmetrical 2,6-dihalophenols in CCl_4 it has been deduced that the OH · · · F intramolecular H-bond is intermediate in strength between the bonds to Br and to I [199]. The Badger–Bauer relationship[14, 15] is clearly not obeyed for these H-bonds. The infrared frequency shifts are anomalous because of an orbital–orbital repulsion between the donated lone pair orbital of the halogens and the O–H bonding orbital[199]. The greatly varying size of the halogen atoms also has an effect[197, 199]. Anomalies in the correlation between p.m.r. chemical shift and H-bond strength have been attributed to the varying diamagnetic anisotropies of the *ortho* C–X group for the four halogens[67]. Comparison of the enthalpies in Table 11 for phenol vapours and in CCl_2CCl_2 or CS_2 solutions emphasizes the effect of solvent on the strength of intramolecular H-bonds. The reduction in H-bond strength is due to the stabilization of the *trans* isomers **41** of the phenols through intermolecular interaction with the solvent[68, 200]. In the vapour phase the OD · · · X intramolecular bonds are weaker than the corresponding OH · · · X interactions (Table 11)[198]. However, in general a D-bond can be weaker or stronger than the corresponding H-bond depending on the shape of the potential function and the geometry of the particular interaction being considered. A quantum mechanical tunnel effect may also be significant[201].

The ν_{OH} frequency shifts and enthalpies of intramolecular H-bond formation for some interactions between OH groups and π-electrons are given in Table 12. The frequency shifts are the same order of

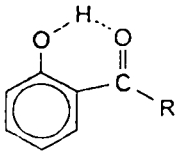
TABLE 12. Frequency shifts and enthalpies of intramolecular H-bonding of phenol OH group to π-electrons (CCl_4 solvent)[203, 204].

Phenol	$\Delta\nu_{OH}$ (a)[a] (cm^{-1})	$\Delta\nu_{OH}$ (b)[a] (cm^{-1})	$-\Delta H$ (kcal/mole)
6-Methyl-2-(β-methylallyl)phenol		99·2	0·98
2-(β-Methylallyl)phenol		91·8	1·04
2-Isopropenylphenol		82·0	0·76
2-Isobutenylphenol	37·0	70·5	
2-Allylphenol		65·6	0·46
2-(*cis*-Propenyl)phenol	24·2	63·6	
2-(*trans*-Propenyl)phenol		59·7	−0·60
2-Benzylphenol		50·8	0·33
2-Phenylphenol		42·0	1·45

[a] For explanation see text.

magnitude as those for the 2-halophenols (Table 10) although the enthalpies (Table 11) show that the OH · · · π interactions are somewhat weaker. That an interaction occurs for 2-phenylphenol implies that the two benzene rings are not coplanar[195, 202]. For 2-isobutenylphenol and 2-(*cis*-propenyl)phenol three distinct OH stretching absorptions have been observed[203]. Because of steric requirements in these compounds the coplanarity of the 2-substituents and the benzene ring is not possible. However, because a minimum resonance interaction occurs when the substituents are at 90° to the plane of the ring this orientation is also not energetically favoured. It follows that there are two stable conformers, one in which the angle of twist θ of the C=C bond is somewhere between 0° and 90° out of the plane of the benzene ring, and the other for which $90° < \theta < 180°$. The actual value of θ depends on the balance between the steric repulsions which increase as $\theta \rightarrow 0°$ or $\theta \rightarrow 180°$ and the stabilizing resonance interaction which decreases as $\theta \rightarrow 90°$. H-bonding interaction between OH and the π-electrons can occur in both conformers and gives rise to the two ν_{OH} frequencies (Table 12) due to H-bonded OH. For 2-(*trans*-propenyl)phenol the propenyl group can exist coplanar with the phenyl ring but orientated away from the OH group. A very weak OH · · · π interaction occurs, making the enthalpy of the H-bond appear to be smaller than the resonance energy involved.

Large shifts of the OH p.m.r. signal and infrared stretch frequency occur when an OH group intramolecularly H-bonds to the lone pair electrons on a carbonyl oxygen atom[67, 185, 194, 195, 202, 205]. The ν_{OH} absorption is moved about 350–500 cm^{-1} (Table 10) and becomes very broad because of the contributions of several resonance forms exemplified by **43**, **44** and **45** [98, 202]. A six-membered H-



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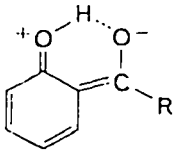

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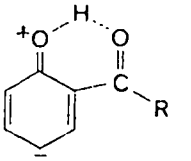
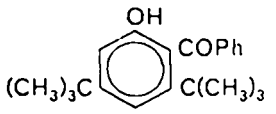


(45)

bonded ring is formed. The spectroscopic results suggest a strong H-bond and this is confirmed by the enthalpies of H-bond formation which were ($-\Delta H$ kcal/mole) 5·7, 6·9, 9·0 and 8·4 for the methyl esters of 3-hydroxy-2-naphthoic acid, salicylic acid, 2-hydroxy-1-naphthoic acid and 1-hydroxy-2-naphthoic acid respectively, and

6·8 for 2-hydroxy-1-naphthaldehyde[99]. The shifts in the carbonyl stretching frequency for these H-bonded phenols correlate both with the p.m.r. chemical shifts[185] and with the strengths ($-\Delta H$) of the H-bonds[99]. The strengths of the H-bonds are increased by substituents in the 3-position which force the carbonyl group nearer to the hydroxyl group thus increasing the interaction[206]. A different steric effect is observed for 2-hydroxy-4,6-di-*t*-butylbenzophenone (**46**) which shows two ν_{OH} bands at 3609 cm^{-1} and 3588 cm^{-1} [98]. The latter is attributed to a weak interaction **47** between OH and the



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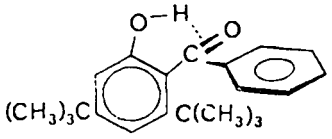
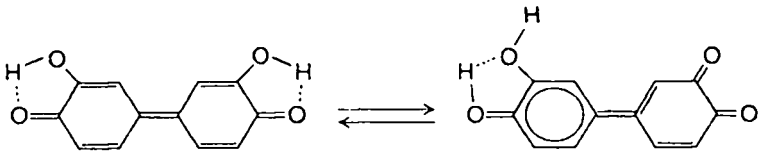


(47)

π-electrons of the carbonyl bond which is twisted out of the plane of the phenol ring. The twisting occurs because of the steric repulsion between a *t*-butyl group and the second benzene ring. A similar OH · · · π (C=O) interaction has been proposed for aliphatic systems[186].

The electronic spectra of 2-hydroxyacetophenone and of 2-hydroxybenzaldehyde are nearly identical in ether and in cyclohexane[157]. The intermolecular H-bond in these compounds is sufficiently strong to prevent intermolecular H-bonding to solvent ether. However, the tautomeric equilibria of some dihydroxydiphenoquinones is influenced by solvent. Thus 3,3′-dihydroxy-4,4′-diphenoquinone (**48**) (**49**) exists predominantly as its diphenoquinone form (**48**) in dioxan and as its 2-benzoquinone form (**49**) in



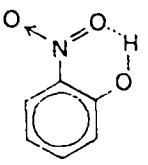
(48) (49)

methanol[207]. In the H-bond donor solvent intermolecular interactions become more significant than intramolecular H-bonding.

The high first ionization constant of salicylic and related acids may be attributed to the strong intramolecular H-bond between the *ortho* phenol and carboxylate groups in the acid anions[208-212]. The second ionization constant of substituted salicylic acids is unusually

small[213]. A kinetic study[214] has shown that the rate of abstraction of the salicylate OH proton by hydroxide ions is slow since the intramolecular H-bond must be broken if the reaction is to take place.

A strong intramolecular H-bond **50** from OH to a nitro group exists in 2-nitrophenols[216]. The canonical formulation **51** requires



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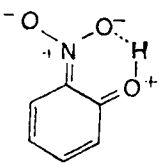
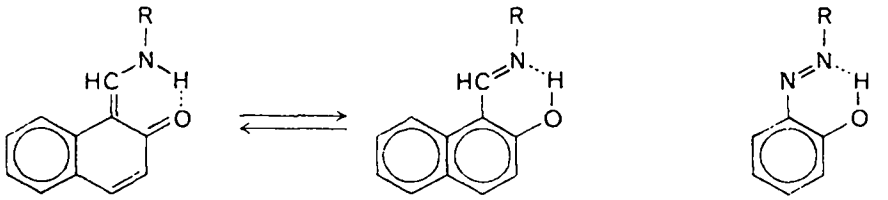


(51)

that the nitro group should be coplanar with the benzene ring; a requirement for the formation of a strong bond[113]. Small 3- or 6-substituents strengthen the H-bond interaction probably because the nitro or hydroxyl groups are pushed slightly closer together[202]. Thus 3- and 6-methyl-2-nitrophenol have stronger H-bond interaction than 2-nitrophenol[215]. For 3,6-dimethyl-2-nitrophenol the effect is further magnified. However, more bulky 3-substituents [e.g., Cl, $C(CH)_3$, CF_3] twist the nitro group out of the plane of the aromatic ring and weaken the H-bond[215, 217, 218]. Similar effects have been observed for the nitro coumarins[215]. Changes in solvent can also alter the extent and strength of intramolecular H-bonds. Thus 3-trifluoromethyl-2-nitrophenol has a weak intramolecular H-bond interaction in cyclohexane solvent but no such interaction in ether, methanol or water[218]. Intermolecular solute–solvent H-bonding becomes predominant in these three solvents. For 3-hydroxy-2-nitrophenol which has two intramolecular interactions even ethanol solvent fails to disrupt both H-bonds completely. The ability of a polar solvent to disrupt an intramolecular H-bond depends not only on the overall strength of the H-bond but also on the individual acidity of the donor and the basicity of the acceptor in the H-bond interaction[219]. Thus, comparing the effect of an H-bond accepting solvent (dioxan, acetone) on two intramolecular H-bonds of equal strength the H-bond which owes its strength to the high acidity of the H-bond donor rather than to the basicity of the acceptor will be ruptured more easily.

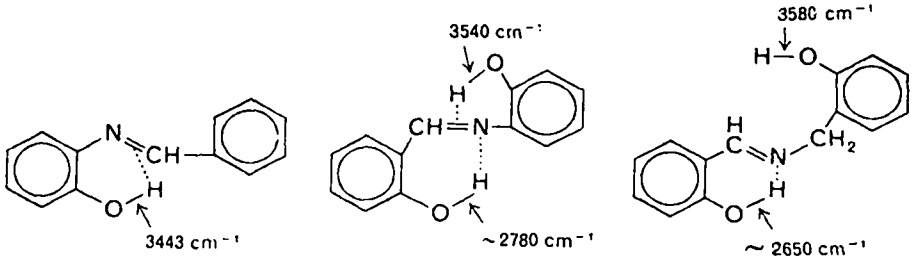
Intramolecular H-bonding in Schiff bases has been investigated by p.m.r.[220–223], infrared[224] and electronic[225, 226] spectroscopy. Schiff bases undergo a keto (**52**)–enol (**53**) equilibrium the position

of which is influenced by solvent[220–222]. Specific H-bonding interactions of the solvent are more important than variations in dielectric constant. Thus in chloroform (dielectric constant $\varepsilon = 4{\cdot}81\ \mu$) there is a greater proportion of **52** (R = C_6H_5) at equilibrium than there is in acetonitrile ($\varepsilon = 37{\cdot}5\mu$). This is unexpected but explicable in terms of a specific solute–solvent interaction between $CHCl_3$ and the carbonyl group of the keto form **52** [222]. Other specific solute–solvent interactions for H-bond donor and acceptor solvents have been discussed by Charette and co-workers[225]. Intermolecular H-bonding (dimerization) of Schiff bases also occurs in solution to a small extent[225]. At equilibrium there is therefore competition between intramolecular, solute–solute intermolecular, and solute–solvent intermolecular H-bonding. H-bonding in aromatic azo compounds



(52) **(53)** **(54)**

54 is analogous to that in Schiff bases. The intramolecular H-bond in substituted α-benzeneazo-β-naphthol compounds is stronger than that in the corresponding 2-benzeneazophenol compounds[227]. Intramolecular H-bonding from OH to the π-electrons of a –CH=N– double bond occurs in benzylidine-2-aminophenol (**55**) and salicylidene-2-aminophenol (**56**) [228]. The infrared ν_{OH} stretching frequency for the latter may be compared with those for salycilidene-2-



(55) **(56)** **(57)**

hydroxybenzylamine (**57**). The presence of an OH · · · π (CH=N) interaction in **56** results in the OH · · · N (lone pair) interaction being weaker in **56** than in **57**. In general for intramolecular H-bond

interactions OH · · · N bonds are stronger than OH · · · O bonds[228, 229].

IV. H-BONDING AND KINETICS

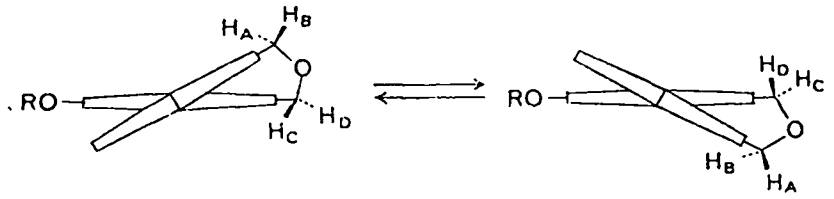
The influence of solvent on the kinetics of reactions in solution embraces many different effects. Specific H-bonding solute–solvent interactions play an important role in determining the reaction rates. Thus there are significant differences between the variations with increasing acid concentration of the rates of aromatic hydrogen exchange for 1,3,5-trihydroxybenzene and 1,3,5-trimethoxybenzene. For the HCl catalysed reactions plots of $\log_{10} k_{exp}$ against the Hammett acidity function[230–232] had slopes of 0·80 for 1,3,5-trihydroxybenzene, and 1·14 for 1,3,5-trimethoxybenzene[233]. These results are in part due to specific H-bonding interactions between solvent water and the phenolic OH groups in the reactant 1,3,5-trihydroxybenzene and 1-methoxy-3,5-dihydroxybenzene[234]. The correlation between acidity function dependencies and the solvation of reacting molecules and of transition states has been discussed for both acid-catalysed[232, 235] and base-catalysed reactions[232, 236].

The second-order rate constants for the alcoholysis of acetic anhydride in carbon tetrachloride or cyclohexane decrease as the concentration of the alcohol is increased[237]. Similar decreases occur if typical H-bond acceptors such as dioxan or acetone are added. Hydrogen bonding of the reacting alcohols either with themselves or with other molecules results in the need to break the H-bonds before the transition state in the reaction can be formed. The activation energy for the reaction is increased by an amount corresponding to the energy required to break the H-bonds. The relative rates of ethanolysis in benzene and cyclohexane are 0·264 : 1 which is consistent with an estimate that a fraction 0·24 of ethanol in benzene is monomeric whereas the other 76% is H-bonded in an ROH · · · $\pi(C_6H_6)$ interaction[237].

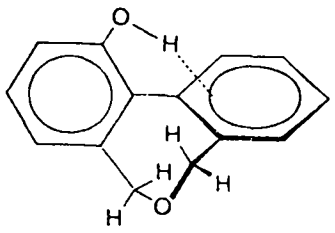
The activation parameters for the inversion of the methyl ether of 1-hydroxy-5,7-dihydrodibenz[*c*,*e*]oxepin are insensitive to change of solvent from $CDCl_3$ to dimethyl sulphoxide[238].

The inversion may be represented, looking end on along the two benzene rings, as shown at the top of the next page.

For the parent phenol the activation energy is about 1 kcal/mole less in $(CH_3)_2SO$ than in $CDCl_3$. In the latter solvent the phenol is stabilized with respect to the transition state by an intramolecular



OH · · · π interaction **58** which leads to a non-planar configuration for the molecule. In dimethyl sulphoxide a strong intermolecular H-bond is formed which stabilizes, through canonical structures such as **59**, the planar configuration which is required for the



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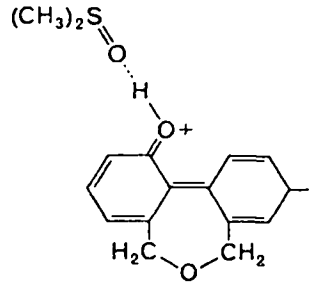


(59)

activated complex in the inversion. The OH · · · π intramolecular H-bond does not exist in $(CH_3)_2SO$. The stabilization of the transition state in $(CH_3)_2SO$ through intermolecular H-bonding and the ground state in $CDCl_3$ through intramolecular H-bonding may both contribute to the observed difference between the activation energies in the two solvents.

The influence of solute–solvent interactions on the rates of acid–base reactions of some phenols and their anions in methanol has been studied[239]. The rate constants and deuterium isotope effects for the ionization of some phenolic azobenzene derivatives are influenced by the intramolecular OH · · · NH-bonds in the reacting molecules[229]. The removal of the second phenolic proton from the salicylate anion is retarded by intramolecular H-bonding with the neighbouring carboxylate group[214]. The relative rates of removal of tritium from OH-labelled 2- and 4-nitrophenol by methyl radicals show that for this reaction tritium participating in an intramolecular H-bond is more reactive than tritium in an intermolecular H-bond[240]. The rates of intermolecular proton transfer reactions are in accord with the order of H-bond strengths[241]. For example, in

the absence of charge or steric effects, proton transfers from OH to O are faster than those from OH to N.

V. THE ACIDITY OF HYDROXYL GROUPS

A. Alcohols

The most reliable measurements of the acidity of alcohols in water were made by Long and Ballinger[242–244] using a conductivity method (Table 13). Data for several carbinols[259] and fluorinated alcohols[246, 247, 258] are also available. The high acidity of perfluoropinacol has been attributed to OH · · · O⁻ intramolecular H-bonding in the anion formed when an OH proton is removed from the

TABLE 13. The acidity of some alcohols in water at 25°C[a].

Alcohol	pK_a	Reference
Water	15·74	245
Methanol	15·5	243
Ethanol	15·9	243
2,2,2-Trichloroethano	12·24	243
2,2,2-Trifluoroethanol	12·3; 12·37; 12·42	246, 242, 247
2,2,3,3-Tetrafluoropropan-1-ol	12·74	243
2,2-Dichloroethanol	12·89	243
Allyl alcohol	15·5	243
Prop-2-yn-1-ol	13·55	243
2-Methoxyethanol	14·8	243
2-Chloroethanol	14·31	252
1,1,1-Trifluoro-3-aminopropan-2-ol	12·29	247
1,1,1-Trifluoro-3-diethylaminopropan-2-ol	12·56	247
Ethylene glycol	15·4[b]	243
Glycerol	14·4[b]	243
Pentaerythritol	14·1[b]	243
2,2,3,3-Tetrafluoro-1,4-butanediol	12·1[b]	246
	13·7[c]	246
2,2,3,3,4,4,5,5-Octafluoro-1,6-hexanediol	12·1[b]	246
	12·8[c]	246
Perfluoro-*t*-butanol	9·52	258
Perfluoropinacol	5·95[b]	258
Hexafluoro-2-propanol	9·30	258
1-Phenyl-2,2,2-trifluoromethylethanol	11·90	259
1-(4-Methoxyphenyl)-2,2,2-trifluoroethanol	12·24	259
1-(4-Methylphenyl)-2,2,2-trifluoroethanol	12·04	259
1-(3-Bromophenyl)-2,2,2-trifluoroethanol	11·50	259
1-(3-Nitrophenyl)-2,2,2-trifluoroethanol	11·23	259

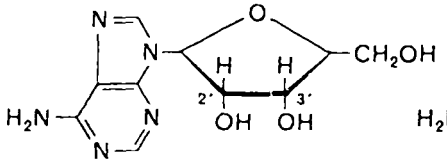
[a] See also J. Murto, this volume, Chap. 20, Table 3.
[b] First dissociation; [c] second dissociation.

diol[258]. The pK_a values for the substituted methanols (RCH_2OH) [243] are a linear function of the Taft σ^* constants for the R substituents[248, 249]. Equation (15) is applicable, the observed pK_a values

$$pK_a = 15{\cdot}9 - 1{\cdot}42\sigma^* \qquad (15)$$

being within $\pm 0{\cdot}2$ unit of the predicted values[244, 250]. The figure of 1·42 for ρ^* is close to that of 1·36 deduced[249] from measurement of the relative acidities of some alcohols in *i*-propanol solution[251]. Ionization constants of 2-chloroethanol[252] and 2,2,2-trifluoroethanol[242] in D_2O are given by $pK_a = 14{\cdot}99$ and $pK_a = 13{\cdot}02$ respectively. The magnitudes of the isotope effects are consistent with the corresponding magnitudes for certain phenols and carboxylic acids[243, 244]. The pK_a of several fluorinated alcohols in 50% aqueous ethanol have been reported[253]. However, potentiometric measurement[246, 247, 253] of such high pK_a values is probably not very accurate[244]. The acidity of some hydroxyalkylpyridines (and their conjugate acids) in water and in *i*-propanol are influenced by the electronic and steric effects of the substituent groups[254]. The intramolecular OH · · · π and OH · · · NH-bonds which exist in these compounds in CCl_4 are absent in polar hydroxylic solvents where solute–solvent intermolecular H-bonding becomes predominant.

The thermodynamics of ionization of several carbohydrates and their derivatives have been studied by thermometric titrimetry (Table 14)[255, 256, 257]. The ionization occurs from the 1-position in the monosaccharides. Changing from a pentose to a hexose or altering the stereochemistry of the hydroxyl groups only has a small effect on the observed thermodynamic quantities. Replacement of a hydroxyl group by a hydrogen atom (cf. ribose and 2-deoxyribose; glucose and 2-deoxyglucose) produces only small changes in pK_a, ΔH and ΔS. Both 2′ and 3′ hydroxy groups are necessary if adenosine (**60**) and its derivatives are to show their acidity. Thus, the substitution of CH_3 for H on the 2′ hydroxyl or the substitution of H for either the 2′ or the 3′ hydroxyl in adenosine leads to a considerable reduction in acidity for the molecule as a whole[255]. The enhanced



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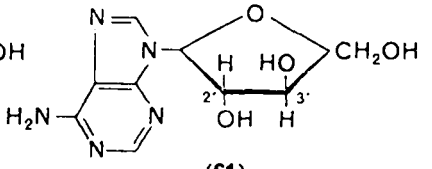


(61)

TABLE 14. Thermodynamics of ionization of some carbohydrates and their derivatives in water (25°)[255, 256, 257].

Compound	pK_a	$\Delta H°$ (kcal/mole)	$-\Delta S°$ (e.u.)
Fructose	12·27	8·2	28·6
Glucose	12·46	7·7	31·3
2-Deoxyglucose	12·52	8·2	29·7
Mannose	12·08	7·9	28·9
Galactose	12·48	9·0	26·9
Arabinose	12·54	8·3	29·6
Xylose	12·29	8·2	28·7
Ribose	12·22	8·1	28·7
2-Deoxyribose	12·67	7·7	32·1
Lyxose	12·11	8·0	28·6
Adenosine[a]	12·35	9·7	24·0
9-β-D-Xylofuranosyladenine[a]	12·34	8·4	28·3
Ribose 5-phosphate[a]	13·05	6·1	39·4
Glucose 6-phosphate[a]	11·71	8·4	25·0
Adenosine 5′-monophosphate[a]	13·06	10·9	23·3

[a] Ionization $HA^{2-} + H_2O \rightleftharpoons A^{3-} + H_3O^+$.

acidity given by vicinal OH-groups is independent of whether the OH groups are *cis* or *trans* because the thermodynamic quantities for adenosine and 9-β-D-xylofuranosyladenine (**61**) are very similar[257]. The small differences in ΔS for the two compounds probably arise because of different interactions with solvent caused by the change in stereochemistry.

Several measurements of the acidity of *gem* diols have been reported and are summarized in Table 15. The *gem* diols are carbonyl

TABLE 15. First ionization constants of some *gem* diols in water (25°).

gem Diol	pK_a	Ref.	*gem* Diol	pK_a	Ref.
$C_6H_5C(OH)_2CF_3$	10·00	259	$CF_3C(OH)_2CF_3$	6·58	258
$4\text{-}CH_3OC_6H_4C(OH)_2CF_3$	10·18	259	$CF_2ClC(OH)_2CF_2Cl$	6·67	258
$4\text{-}CH_3C_6H_4C(OH)_2CF_3$	10·15	259	$CF_2ClC(OH)_2CFCl_2$	6·48	258
$3\text{-}BrC_6H_4C(OH)_2CF_3$	9·51	259	$CFCl_2C(OH)_2CFCl_2$	6·42	258
$3\text{-}NO_2C_6H_4C(OH)_2CF_3$	9·18	259	$CF_2HC(OH)_2CF_2Cl$	7·90	258
$CH_2(OH)_2$	13·27	260	$CF_2HC(OH)_2CF_2H$	8·79	258
$CH_3CH(OH)_2$	13·57	260	$CF_3C(OH)_2CHBr_2$	7·69	258
$CCl_3CH(OH)_2$	10·04	260	$(CH_3)_2CHCH(OH)_2$	13·77	261

hydrates which are formed by the addition of water to an aldehyde or ketone according to the equilibrium

$$R_1R_2CO + H_2O \rightleftharpoons R_1R_2C(OH)_2$$

Equilibrium constants for the hydration equilibria have been summarized by Bell[262]. The anion of the *gem* diol can be assumed to be formed either by the loss of a proton from the diol or by the addition of an hydroxide ion to the unhydrated carbonyl compound. Aldehydes and ketones can also ionize to enolate anions in solution. However, for those *gem* diols for which pK_a has been determined the amount of enolate anion formed at equilibrium is negligibly small. Correlations between the pK_a values and Hammett (σ) or Taft (σ^*) constants have been noted[250, 259, 260, 262]. Evaluation of pK_a values from studies of the ionization of the enolic tautomers of ketones requires knowledge of the equilibrium constants for the keto–enol tautomerism of the neutral molecules in solution[263]. Thus for acetylacetone the ratio of enolate anion to neutral keto + enol species is in accord with $pK_a = 8{\cdot}9$. However, the equilibrium constant for the tautomerism is [C(enol)/C(diketo)] = 0·25 and therefore 8·2 is the true pK_a of the enol form of the diketone. Several combined studies of keto–enol equilibria and acidity have been made[263-268]. The enols of some substituted cyclohexane-1,3-diones (e.g., dimedone $pK_a = 5{\cdot}23$ for the enol form)[264] have $pK_a \sim 5$ in water[263]. The strongest acid of this type appears to be 2,4-dimethylcyclobutane-1,3-dione with $pK_a = 2{\cdot}8$. In general in 1,3-diketones or β-ketoesters enolization leads to a conjugated system and ionization leads to resonance stability and delocalization of charge in the ion. These compounds are more acidic than monoketones (e.g., acetone[269]) in which these effects cannot occur. The enols of ring 1,3-diketones or 2-acetyl or 2-formyl cycloalkan-1-ones are more acidic than analogous non-cyclic compounds[264]. The effect of substituent R on the acidity of the enols $CH_3COCR{=}C(OH)CH_3$ of acetylacetones correlates with the Taft σ^* constants for R[250].

The ability to undergo self-ionization is an important property of hydroxylic solvents. The ionic products (Table 16) of four alcohols have been determined by e.m.f. measurements[270, 271]. Values for methanol from 0° to 45° have also been determined and give $\Delta H = 11{\cdot}0$ kcal/mole for the self-ionization at 25°C [272]. Conductivity results are probably less reliable[273].

TABLE 16. The ionic product of alcohols at 25°C.

$K_s = \frac{a_{RO^-} \cdot a_{ROH_2^+}}{a^2_{ROH}}$ ($a_{ROH} = 1$ in pure liquid)

Alcohol	pK_s^a	pK_s^b	Ref.
Methanol	16·707	16·916	270
Ethanol	18·67	18·88	271
n-Propanol	19·24	19·43	271
i-Propanol	20·58	20·80	271

[a] K_s in units of (molality)^2.
[b] K in units of (molarity)^2.
($pK_s^a = pK_s^b + 2 \log_{10} d$, where d is the density of the particular alcohol at 25°.)

B. Phenols

1. Ionization of phenols in water

a. General correlations. There have been many studies of the acidity of phenols in aqueous solution[64, 65, 274–322]. These include not only measurement of pK_a (compilations[250, 301, 321, 322]) but also of enthalpies, entropies, heat capacities (Table 17) and volumes[320] of ionization. Results for many substituted naphthols are also available[250, 321–323]. Biggs and Robinson[293] showed that equation (16)

$$pK_a = 9{\cdot}919 - 2{\cdot}229\sigma \qquad (16)$$

was applicable for the ionization of fourteen 3- and 4-substituted phenols. The substituent σ-constants in the Hammett equation[52] were deduced by taking $\rho = 1$ for the corresponding benzoic acids. 4-Substituents which can undergo mesomeric interaction with the aromatic ring may not fit the correlation[324]. For 3-substituted phenols the correlation between pK_a and σ is excellent at any temperature in the range 10°C $\leqslant$ to $\leqslant$ 55°C [277]. Substituted 2-nitrophenols[302, 303] and 2,4-dinitrophenols[301] and 2,4,6-trinitrophenols[301] also exhibit linear relationships between pK_a and σ-constants although substituents which twist nitro groups out of coplanarity with the ring[325] give anomalous results. In general equation (17) is applicable and has been tested for a large number of sterically unhindered phenols[301]. Here $\sum \sigma$ is the sum of the σ-constants for the

$$pK_a = 9{\cdot}94 - 2{\cdot}26 \sum \sigma \qquad (17)$$

TABLE 17. Thermodynamic quantities for the ionization of some phenols in water at 25°.

Phenol	pK_a	$\Delta G°$ (kcal/mole)	ΔH (kcal/mole)	$-\Delta S°$ (e.u.)	$-\Delta C_p$ (cal/deg)	References
Phenol	9·99	13·63	5·55	27·1	53 (32)	64, 65, 274–6, 285
2-Cresol	10·33	14·10	5·73	28·1	36·0	64, 65
3-Cresol	10·10	13·78	5·52	27·7	38·6	64, 65, 274
4-Cresol	10·28	14·02	5·50	28·6	52·9	64, 65
2,3-Xylenol	10·54	14·39	5·70	29·1	38·0	64, 65
2,4-Xylenol	10·60	14·46	5·76	29·2	28·0	64, 65
2,5-Xylenol	10·40	14·19	5·58	28·9	24·2	64, 65
2,6-Xylenol	10·62	14·49	5·46	30·3	36·7	64, 65
3,4-Xylenol	10·36	14·13	5·37	29·4	31·8	64, 65
3,5-Xylenol	10·20	13·92	5·34	28·8	27·2	64, 65, 274
2-Fluorophenol	8·73	11·91	4·66	24·3		286
3-Fluorophenol	9·29	12·67	5·52	24·0		286
4-Fluorophenol	9·89	13·49	5·93	25·4		286
2-Chlorophenol	8·555	11·67	4·26	24·9	89 (52)	64, 65, 276, 283
3-Chlorophenol	9·119	12·44	5·35	23·8	23·5	278, 279
4-Chlorophenol	9·42	12·86	5·73	23·9	34·7	64, 276
2-Bromophenol	8·452	11·53	4·40	23·9	39	283
3-Bromophenol	9·031	12·32	5·35	23·4	35·7	278
4-Bromophenol	9·34	12·74	5·74	23·5	25·5	64
2-Iodophenol	8·513	11·61	4·27	24·6	49	283
3-Iodophenol	9·033	12·31	5·53	22·7	40·6	278
4-Iodophenol	9·33	12·72	5·38	24·6	43·8	64
3-Cyanophenol	8·56	11·69	5·20	21·8		282
4-Cyanophenol	7·95	10·87	4·92	20·0		282
2-Methoxyphenol	9·99	13·63	5·74	26·5		280

3-Methoxyphenol	9·652	13·17	5·02	27·3	35·1	277, 280
4-Methoxyphenol	10·20	13·92	5·70	27·6		280
2-Ethoxyphenol	10·109	13·79	6·18	25·5	23	283
3-Ethoxyphenol	9·655	13·17	5·08	27·1	56·5	274
3-Ethylphenol	10·069	13·74	5·29	28·3	47·5	277
2-Propylphenol	10·50	14·33	6·00	28·0		288
2-Allylphenol	10·28	14·02	6·01	26·9		288
2-Formylphenol	8·38	11·42	5·15	21·0		281
3-Formylphenol	8·983	12·26	4·99	24·4	33·3 (11·4)	277, 281, 287
4-Formylphenol	7·62	10·39	4·26	20·6	55·6	281, 287
2-Nitrophenol	7·230	9·88	4·60	17·7	38·1	64, 276, 290
3-Nitrophenol	8·360	11·41	4·79	22·2	20·9	276, 277, 291
4-Nitrophenol	7·156	9·78	4·72	16·8	34·6	64, 276, 284, 290
3,5-Dichlorophenol	8·179	11·16	4·88	21·1	24·5	274
3,5-Dibromophenol	8·056	10·99	5·25	19·3	79·5	274
3,5-Diiodophenol	8·103	11·06	5·45	18·8	79·4	274
3,5-Dinitrophenol	6·732	9·19	3·76	18·2	16·8	274
3,5-Diethoxyphenol	9·370	12·79	4·65	27·3	46·7	274
2,4,6-Trimethylphenol	10·89	14·85	5·44	31·6		282
3,4,5-Trimethylphenol	10·24	13·98	5·68	27·9		282
2,4,5-Trimethylphenol	10·57	14·41	6·40	26·9		282
2,3,5-Trimethylphenol	10·59	14·45	6·60	28·7		282
2-Hydroxymethylphenol	9·84	13·6	5·4	27·4		292
4-Hydroxymethylphenol	9·73	13·4	4·5	30·0		292
2,4-Dihydroxymethylphenol	9·69	13·4	4·9	28·4		292
2,4,6-Trihydroxymethylphenol	9·45	13·1	4·5	28·6		292
3-Methyl-4-nitrophenol	7·409	10·12	4·58	18·7	34·3	64, 290
2-Methoxy-4-formylphenol	7·396	10·09	3·75	21·3		281, 289
2-Methoxy-5-formylphenol	8·889	12·13	4·62	25·2		281, 289
2-Methoxy-6-formylphenol	7·912	10·79	4·13	22·3		281, 289

phenol substituents. These correlations have been recently reviewed[250]. The effect of substituents on the acidity of 1-naphthol and 2-naphthol has been correlated with σ-constants[250].

Intramolecular H-bonding accounts for the high first ionization constant[208–212] and the low second ionization constant[213, 214] of salicylic acid. The intramolecular OH $\cdots$ π interaction in 2-allylphenol has been invoked to explain the observed entropy of ionization of this phenol in water[288]. Comparison of entropies of ionization of nitrophenols suggests there is negligible intramolecular H-bonding for 2-nitrophenol in aqueous solution[299, 330].

Linear correlations between free energies, enthalpies, and entropies of ionization (Table 17) have been analysed in detail for several classes of phenols[275, 277]. In general 2- and 4-substituted phenols show excellent linear correlations but the plots for 3-substituted phenols are not so good. The entropies of ionization of 4-substituted phenols are a linear function of the σ^n substituent constants[275, 324]. Providing there are no appreciable steric effects the free energies of ionization (or pK_a) of phenols are additive, a particular substituent in a particular ring position always producing a similar increment to $\Delta G°$ or pK_a [65, 274]. For 3,5-disubstituted phenols the entropies of ionization are also additive[274]. Equation (18) is applicable. This

$$\Delta S_{3,5} = 1{\cdot}91\ (\pm 0{\cdot}08)\ \Delta S_3 - 24{\cdot}5\ (\pm 0{\cdot}4) \qquad (18)$$

result is demonstrated in Figure 7 (data are in Table 17).

The volume of ionization of phenol in water is $-17{\cdot}0$ cm^3/mole[320].

The acidity of many phenols in D_2O has been measured[330–333]. Deuteration results in increases in pK_a in the range $0{\cdot}44 \leqslant \Delta pK_a \leqslant 0{\cdot}62$. ΔpK_a is a linear function of $pK_a(H_2O)$ with positive slope 0·018[332, 333]. The following equation is applicable[333]. A few results

$$pK_a(D_2O) - pK_a(H_2O) = \Delta pK_a = 0{\cdot}41 + 0{\cdot}018pK_a(H_2O) \qquad (19)$$

are included in Table 18.

b. Hepler's theory. Hepler and co-workers[279, 280, 282, 326, 327] have considered the effect of a substituent on the acidity of phenol in terms of equilibrium (20) in which HA_s is a substituted phenol and

$$HA_s(aq) + A_u^-(aq) \rightleftharpoons A_s^-(aq) + HA_u(aq) \qquad (20)$$

HA_u is phenol itself. The increment $\delta\Delta G°$ in the free energy of ionization in going from HA_u to HA_S ($\delta\Delta G° = \Delta G_s° - \Delta G_u°$) is equal to the free energy change for reaction (20). The corresponding

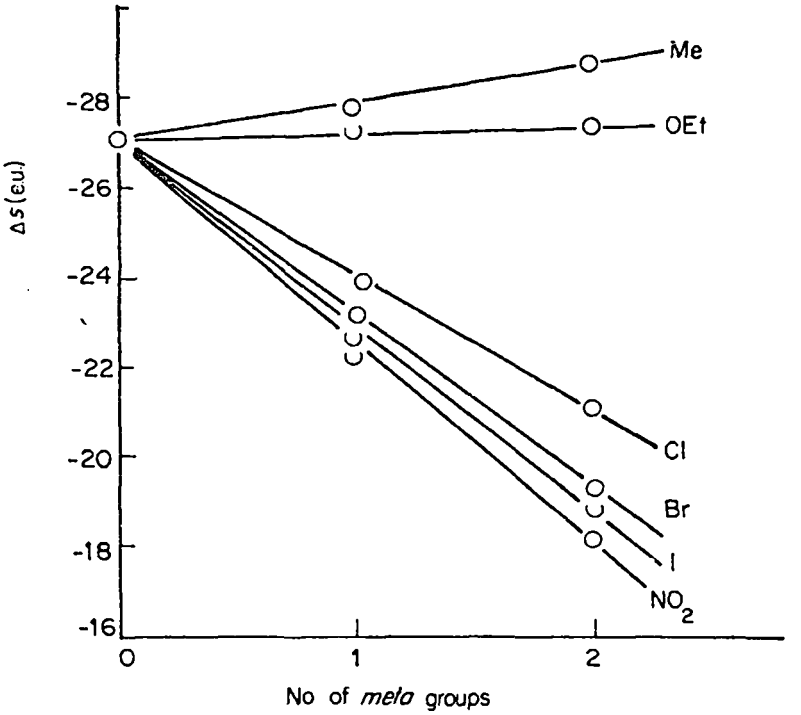


FIGURE 7. Effect of 3-substituents on the entropy of ionization of phenol in water[274]. Reproduced by permission from P. D. Bolton, F. M. Hall and J. Kudrynski, *Australian J. Chem.*, **21**, 1541 (1968).

increments in enthalpy and entropy change may each be written in terms of internal and external contributions as follows

$$\delta\Delta H^\circ = \Delta H_{int} + \Delta H_{ext} \quad \text{and} \quad \delta\Delta S^\circ = \Delta S_{int} + \Delta S_{ext} \qquad (21)$$

Taking $\Delta S_{int} \sim 0$ [326, 327] gives $\delta\Delta S^\circ = \Delta S_{ext}$. Also equation (22) is

$$\delta\Delta H^\circ = \Delta H_{int} + \beta\Delta S_{ext} \qquad (22)$$

applicable providing equation (23) is assumed valid[326, 327]. Com-

$$\Delta H_{ext} = \beta\Delta S_{ext} = \beta\delta\Delta S^\circ \qquad (23)$$

bination of these equations leads to equation (24) for the increment in ΔG° produced by a substituent.

$$\delta\Delta G^\circ = \Delta H_{int} + (\beta - T)\delta\Delta S^\circ \qquad (24)$$

Estimation of β is difficult. A method dependent on the assumption in equation (25) was originally suggested[327].

$$\Delta H_{int} = a(\nu_s^2 - \nu_u^2) \qquad (25)$$

Here ν_u and ν_s are the OH stretching frequencies of the unsubstituted

and substituted phenols and a is a proportionality constant. Two other methods have also been described[274, 326]. Hepler[326] concluded that $270° < \beta < 320°$K. A more recent value of 311° has been deduced[274]. The closeness of β to the absolute temperature 298° leads to

$$(\beta - T)\delta\Delta S° \ll \Delta H_{int} \tag{26}$$

which, combined with equation (24), gives[282, 286]

$$\delta\Delta G° \approx \Delta H_{int} \tag{27}$$

The increment to the pK_a of phenol produced by a substituent is therefore largely an internal enthalpy effect. Changes in solute–solvent interactions play a smaller role because the associated enthalpy and entropy changes approximately (or exactly?[328]) cancel. The effect of substituents on the entropies reflect changes in solute–solvent interactions[276, 287]. Thus, for example, $\Delta S°$ for 3-nitrophenol is more negative than $\Delta S°$ for 4-nitrophenol (Table 17). In the anion of 4-nitrophenol charge is delocalized from the phenoxide oxygen atom by the mesomeric effect of the nitro group. This does not occur in the 3-nitrophenoxide anion. The solvation of the phenoxide group is greater in the 3-nitrophenol anion because of the greater localized charge density on the oxygen atom. A more negative entropy of ionization is therefore expected[276].

c. Steric effects. Bulky substituents in the 2-position of phenols lead to decreases in acidity because of steric effects[311]. Thus, for example, $pK_a = 10{\cdot}23$ for 4-*t*-butylphenol[300, 312] and $pK_a = 11{\cdot}34$ for 2-*t*-butylphenol[300]. Equation (17) is not obeyed[283]. Linear Hammett plots[52] are obtained for series of substituted phenols all with the same 2- or 2,6-substituent groups. However, the slopes ρ differ from that (2·26) for the unhindered phenols. Thus $\rho = 2{\cdot}610$ for 4-substituted 2,6-dichlorophenols[315], $\rho = 2{\cdot}700$ for 4-substituted 2,6-dimethylphenols[314] and $\rho = 3{\cdot}50$ for 4-substituted 2,6-di-*t*-butylphenols[312]. The increment in pK_a produced by a given 4-substituent is increased when bulky substituents are present in the 2,6-positions. This has been attributed to steric inhibition of solvation of the phenol anions[104, 312, 314, 315]. The anomalous acidities of 4-nitroso-2,6-dimethylphenol[314] and 4-nitroso-2,6-di-*t*-butylphenol[312] have been ascribed to the predominant existence of the quinone monoxime tautomers of these molecules in solution.

The additive nature of pK_a [65, 274] is often absent when steric factors are operating[300, 313, 329]. For the cresols and xylenols the pK_a increments are additive and so steric effects are not obvious

from consideration of $\Delta G°$ alone[65]. However, comparison of the pK_a values for these phenols with the corresponding values for the picolines and lutidines suggests that one 2-methyl substituent in a phenol introduces an increment to pK_a of +0·14 units through steric hindrance to solvation of the phenol anions[319].

A further steric effect arises when substituents which can undergo mesomeric interaction with the benzene nucleus are twisted out of the plane of the ring[325]. Thus the increment in pK_a on introducing 3,5-dimethyl groups into 4-nitrophenol is 1·06 units[309] compared with +0·21 units[65] for the same substitution in phenol itself.

TABLE 18. Effect of deuterium substitution and electronic excitation on the acidity of phenols[161, 333]. Values for the excited states were deduced via the Förster cycle.

Phenol	$pK_a(H_2O)$	$pK_a^*(H_2O)$	$pK_a(D_2O)$	$pK_a^*(D_2O)$
4-Methoxyphenol	10·20	5·7	10·85	6·2
Phenol	9·99	4·1	10·62	4·6
3-Methoxyphenol	9·65	4·6	10·20	5·1
2-Naphthol	9·46	2·5, 3·0	10·06	
4-Bromophenol	9·34	2·9	9·94	3·4
1-Naphthol	9·23	2·0		
2-Naphthol-5-sulphonate	9·18	0·53		
2-Naphthol-6-sulphonate	9·10	1·65		
4-Phenolsulphonate	9·03	2·3	9·52	2·7
4-Hydroxyphenyl trimethylammonium chloride	8·34	1·6	8·90	2·0
3-Hydroxypyrene-5,8,10-trisulphonate	7·30	1·0		

d. Acidity of phenols in excited electronic states. Phenols in their electronically excited states are more acidic than the ground state molecules. The pK_a of an excited state may be deduced from the absorption spectrum of the ground state and the fluorescence spectrum of the excited state using equation (28) in which pK_a refers to the ground state and $\Delta\bar{\nu}_h$ (cm^{-1}) is the arithmetic mean of the spectral shifts in absorption and fluorescence in going from the neutral acid to its anion.

$$pK_a^* = pK_a - \frac{0{\cdot}625}{T}\Delta\bar{\nu}_h \qquad (28)$$

The determination of pK_a of excited states has been discussed in detail by Weller[161].

Results for the first excited singlet state of some phenols in water and in D_2O are given in Table 18. The deuterium isotope effect

ΔpK_a^* for the excited molecules is consistent with equation (19) and therefore the isotope effects for the ground and excited states conform to the same equation[333]. The values of pK_a^* deduced from the Forster cycle are in reasonable agreement with values evaluated from kinetic measurements[161]. For a series of 4-substituted phenols ($pK_a - pK_a^*$) correlates with the substituent σ-constants and is greater for more electron-withdrawing groups[334]. A value $pK_a(293°) = 8{\cdot}1$ has been reported for the triplet state of β-naphthol in water[335]. pK_a^* values for thirteen phenols in their lowest singlet excited states have been measured by Avigal, Feitelson and Ottolenghi[375].

2. Non-aqueous and mixed aqueous solvents

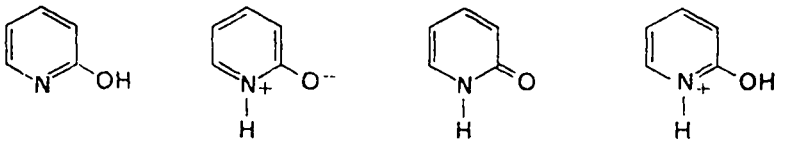
The effect of solvent on acid–base equilibria has been discussed in detail by Bell[336]. He concluded that 'the relative strengths of acids of the same charge and chemical type are independent of the solvent'. This conclusion is justified for the ionization of phenols[337–340]. For phenol itself at 25°C $pK_a = 14{\cdot}46$ in methanol[340] and 15·58 in ethanol[341, 271] (both with K_a in molarity units). Ionization constants for the cresols and xylenols in methanol have been measured[339]. An increment of +0·33 units due to steric effects has been estimated to contribute to the pK_a of 2-methyl phenols[342]. For pentamethylphenol $pK_a(25°) = 16{\cdot}35$ in methanol[343]. The acidity of several nitrophenols in methanol[337, 338, 344], ethanol[345], acetone[346], acetonitrile[347] and alcohol–water mixtures[351–354] has been determined. Among the factors affecting relative acidities of a given phenol in different solvents[336] must be included comparison of solvent–solute interactions and particularly solvation effects around the phenol anions[337]. Hammett $\rho\sigma$ correlations have been tested for 4-substituted phenols, 2,6-dimethylphenols and 2,6-dichlorophenols in hydroxylic and aprotic solvents[316]. For each solvent ρ is higher for 2,6-dimethyl or 2,6-dichloro phenols than for unhindered phenols. This is attributed to steric inhibition to solvation in all solvents.

The effect of steric hindrance on acidity is particularly marked when 2,6-di-*t*-butyl groups are introduced into phenol, 4-cresol or 4-*t*-butylphenol[310, 312, 329]. For methanol solvent the change in pK_a is about +2·7 units[329]. However, 2,6-*t*-butyl-4-nitrophenol is a *stronger* acid than 4-nitrophenol[312, 340, 348]. In general, for a series of 4-substituted 2,6-di-*t*-butylphenols in methanol a plot of pK_a against σ gave $\rho = 4{\cdot}76$ compared with $\rho = 2{\cdot}24$ for the corresponding 4-substituted phenols[349]. Similar results are obtained for

aqueous and 50–50 volume % ethanol–water solutions[312]. Rochester and Rossall have measured the free energies[340], enthalpies, entropies[349] and volumes[350] of ionization of 4-*t*-butylphenol, phenol, 4-bromophenol, 4-formylphenol, 4-nitrophenol and their 2,6-di-*t*-butyl analogues in methanol. The effects of 2,6-di-*t*-butyl groups on the acidity of phenols are largely caused by the influence of steric factors on solute–solvent interactions particularly for the phenol anions.

C. Heteroaromatic Hydroxyl Compounds

The study of the ionization of hydroxy substituted heteroaromatic molecules is often complicated by the possibility of several tautomeric structures for the parent molecule. In fact, measurement of the acidity of these compounds provides information about the extent of the tautomeric equilibria[356, 357]. The method is exemplified by the work of Mason[355]. Thus for 2-hydroxypyridine (**62**) a tautomer with either zwitterionic (**63**) or amide (**64**) character exists in equilibrium with **62**. Mason deduced that $pK_a(20°) = 8{\cdot}66$ for the ionization of the OH proton in **62** and $pK_a = 0{\cdot}75$ for the corresponding OH dissociation of the conjugate acid **65** of **62**. Care must

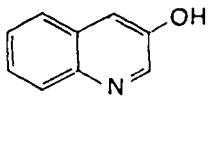


(62) (63) (64) (65)

be taken to distinguish between the loss of NH and OH protons in these molecules. This can only be done if a complete knowledge of the equilibrium concentrations of all the possible tautomers of each acid and base species is obtained. Infrared, ultraviolet and p.m.r. spectroscopy are often useful in this respect[370].

The ionization constants of the hydroxyl groups in eighteen heterocyclic hydroxyl compounds have been correlated with the π-electron energies of the species present in the equilibria[355]. The effect of substituents on the acidity of heterocyclic hydroxyl compounds is consistent with the Hammett $\rho\sigma$ relationship[250].

The true OH dissociation constants of the ground states of 3-hydroxyquinoline (**66**) and its conjugate acid **67** are given by $pK_a(20°) = 8{\cdot}03$ and 5·52 respectively[355]. In their lowest electronically excited states these acidities are increased to $pK_a(18°) = 3{\cdot}6$



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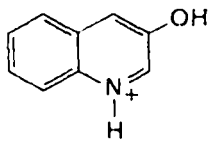
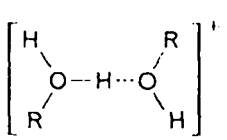


(67)

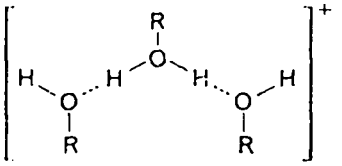
and −0·3 respectively[358]. This effect is similar to that observed for phenols[161, 333, 334].

VI. THE PROTONATION OF HYDROXYL GROUPS

Aliphatic alcohols are protonated in concentrated acid solutions[359, 360]. The basicities of eight alcohols have been tabulated by Arnett[91]. They range from $pK_a(CH_3OH_2^+) = -2{\cdot}2$ to $pK_a = -7{\cdot}0$ for the conjugate acid of β-phenyl-β-hydroxypropionic acid. For the conjugate acids of a series of glycols $4{\cdot}4 \leqslant pK_a \leqslant 1{\cdot}5$ [361] and for phenol $pK_a = -6{\cdot}74$ at 0°C [362]. The protonation of three alcohols in acetonitrile has been studied by Kolthoff and Chantooni[363]. Methyl alcohol and *n*-butyl alcohol form the species $\overset{+}{R}OH_2$, $(ROH)_2H^+$ and $(ROH)_3H^+$ whereas *t*-butyl alcohol only forms the first two of these. The structures **68** and **69** may be written for the



(68)



(69)

protonated alcohol dimer and trimer respectively. An appreciable concentration of **69** is only present at alcohol concentrations about or >1M.

In 100% sulphuric acid triarylcarbinols give a cryoscopic van't Hoff factor $i = 4$ [364–366]. The relevant ionization equilibrium is given by equation (29). Equilibrium constants K for equilibrium

$$Ar_3COH + 2\,H_2SO_4 \rightleftharpoons Ar_3C^+ + H_3O^+ + 2\,HSO_4^- \quad (29)$$

$$Ar_3COH + H^+ \rightleftharpoons Ar_3C^+ + H_2O \quad (30)$$

(30) have been deduced from measurements using concentrated sulphuric[367], hydrochloric[368], perchloric[369], nitric[369] and phosphoric acids[368]. Thus pK ranges from −0·82 for 4,4′,4″-trimethoxytri-

phenylcarbinol to 16·27 for 4,4',4''-trinitrotriphenylcarbinol in water at 25°C [367].

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CHAPTER 8

Directing and activating effects

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I. INTRODUCTION

In this chapter we are concerned only with the hydroxyl group as a substituent and with its effects on chemical reactions occurring at some other site in the molecule. No consideration is given to reactions which lead to chemical modification of the hydroxyl group, unless this is temporary and leads to a product with the hydroxyl group apparently unchanged.

The hydroxyl group is highly polar; it displays strong directing and activating effects and it is often a convenient scapegoat when reaction rates or products are unexpected. There has had to be much selection from the large body of information; we have chosen the

data which appeared to be most generally useful and we have preferred the quantitative study to the qualitative observation.

In discussing polar effects, our use of symbols is similar to that of Chuchani[1]. For example, electron attraction by an inductive mechanism is a $-I$ effect, and electron release by the conjugative (resonance) mechanism is a $+R$ effect. Work on linear free-energy relationships has given rise to several scales for substituent constants. Of the symbols to which reference is made in the following sections, σ is the Jaffé–Hammett substituent constant[2]; $\bar{\sigma}_m$ (or $\bar{\sigma}_p$) is the constant derived for the *meta-* (or *para-*) position from a particular reaction series; σ^o and σ^n are, respectively, Taft's[3] and Wepster's[4] versions of substituent constants free from resonance interaction; σ_I and σ_R are the polar and resonance contributions of a given substituent as resolved by Taft[5] ($\sigma = \sigma_I + \sigma_R$); σ^+ is the constant applicable to a $+R$ substituent when conjugated to an electron-deficient reaction site[6], and assumed to apply to normal electrophilic substitution at the benzene ring; σ^- is the constant for a $-R$ substituent when conjugated to a negatively charged site.

II. REACTIONS OF ALIPHATIC SYSTEMS

A. Electronic Effects

Attempts to apply Hammett-type structure–reactivity relationships to aliphatic systems have been limited in number and in scope by difficulties in the assessment and control of steric effects.

The first attempt to eliminate steric influences was that of Roberts and Moreland[7] who measured the relative reactivities of a number of 4-substituted bicyclo[2,2,2]octane-1-carboxylic acids, in which the carbon cage has a rigidity comparable with that of the benzene ring. They demonstrated the existence of a linear free-energy relationship between the acidity and the rates of both the reaction with diphenyldiazomethane and ester hydrolysis.

The derived substituent constants (σ' values) were indicative of polar (inductive) effects and may be considered as equivalent to σ_I values. The results showed that, in the absence of steric and resonance effects, the hydroxyl group behaves as a moderately strong electron-withdrawing substituent roughly comparable in strength with the carbethoxy substituent.

$$H < OH \sim CO_2Et < Br < CN$$

Later work by other groups[8, 9, 10] extended this series. Other relevant studies involving relatively rigid systems are those by Siegel

and Komarmy[11] on the 1,4-disubstituted cyclohexane series and by Stetter and Mayer[12] on 1,3-derivatives of adamantane.

A more extensive treatment of aliphatic systems became possible when Taft derived substituent constants (σ^* values) from the measurement of base-catalysed ester hydrolysis rates[13]. He did this through a comparison with corresponding rates of acid hydrolysis, in which similar steric effects are expected, but in which polar effects are unimportant. Most of Taft's polar substituent constants referred to CH_2X groups and he used these constants to correlate other aliphatic reaction data. The results showed that the experimental approaches of Taft and of Roberts were compatible and reinforced one another.

Taft's substituent constant for the hydroxymethyl group (0·555) was based on eleven reaction series. It was found that the mean deviation for this substituent was considerably greater than for most others. However, the deviation was not large enough to be unacceptable and, since a wide variety of solvents and reaction conditions were used, the variation could possibly be attributed to changes in solvation of the hydroxyl group. For this group, the differences between individual $\bar{\sigma}$ values (both for Taft's reactions and for other, more recent studies) cannot be systematically linked to changes in either solvent or reaction type but there are in fact no spectacular departures from the mean. In all of the reactions the hydroxyl group appears to act as a moderately consistent and quite strongly electron-withdrawing substituent.

Several groups of workers[14–21] have been able to correlate aliphatic reactivities by means of Hammett aromatic substituent constants in unsaturated structures which allow conjugation between substituent and reaction site. In these cases the system would be expected to bear some resemblance to that of a *para*-substituted benzene derivative. These reactions cannot be satisfactorily correlated by means of inductive substituent constants.

It is therefore assumed that the resonance component of a normal aromatic substituent constant (σ_R) is making an effective contribution. In later work[5], Taft changed from σ values to the more convenient σ_I scale by using the relationship $\sigma_I^X = 0{\cdot}45\ \sigma^{CH_2X}$. This σ_I scale, derived from aliphatic reactivities, is but one of three available scales which differ from each other in their experimental origins but which should give, within experimental limits, identical values for a given substituent. A second scale is based on the separation of normal aromatic σ values into inductive and resonance compon-

ents[22], and the third is based on ^{19}F shielding parameters of *m*-substituted fluorobenzenes[23]. Table 1, compiled from figures in the review by Ritchie and Sager[24], shows the differences between the scales that exist for representative substituents. As an example of

TABLE 1. Aliphatic substituent constants.

X	σ_I (aliphatic)	σ_I (aromatic)	σ_I (n.m.r.)
$-N(CH_3)_3^+$	0·92	0·90	0·93
$-NO_2$	0·63	0·68	0·60
$-CN$	0·56	0·52	0·53
$-F$	0·52	0·45	0·52
$-Cl$	0·47	0·42	—
$-Br$	0·45	0·45	0·44
$-I$	0·38	0·42	—
$-CO_2R$	0·30	0·34	0·21
$-COCH_3$	0·28	0·32	0·23
$-OCH_3$	0·25	0·28	0·29
$-OH$	0·25	0·32	0·16
$-NH_2$	0·10	0·04	0·05
$-H$	0·00	0·00	0·00
$-CH_3$	0·00	−0·03	−0·08
$-O^-$	—	−0·12	−0·16

the general success of the treatment, Figure 1 shows the good correlation obtained between the pK_a's for aliphatic acids of the type XCH_2CO_2H in water and σ_I (n.m.r.), the scale for which the greatest number of σ_I values have been measured.

B. Proximity Effects

1. Nucleophilic substitution

Compounds of the type R–CH(OH)(R)–X, where X is a good leaving group (as X^-), are often unstable, breaking down to give carbonyl compounds and HX.

With the hydroxyl substituent on a β-carbon or on a more distant atom, the compounds are stable, and several mechanistic studies of nucleophilic displacement are available. In most cases the leaving group X has been Cl, Br or I but the same principles should apply to other cases in which X is any good leaving group. A general prediction based on electronic factors is that the presence of the electron-withdrawing hydroxyl group should result in a decrease in the rate

of halide displacement, because the positive nature of the attached carbon atom is increased in the transition state. This is particularly the case for tertiary halides which solvolyse by a S_N1 mechanism. The effect of the corresponding ionized substituent, (O^-) which should be inductively electron-releasing, is more difficult to assess. Through its $+I$ effect, it should stabilize the transition state but, because of its negative charge, approach of the attacking nucleophile may be hindered. However, under the basic conditions producing the alkoxide ion, the normal reaction of $HO-(CH_2)_n-X$ is intra-

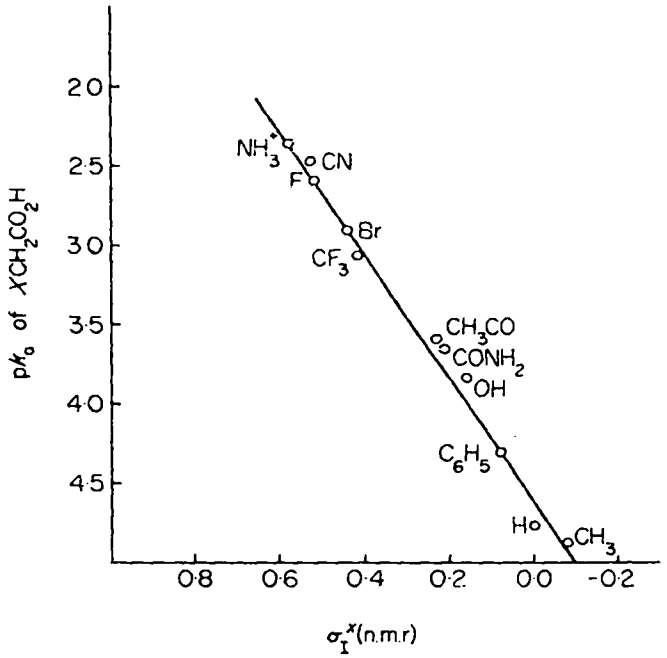
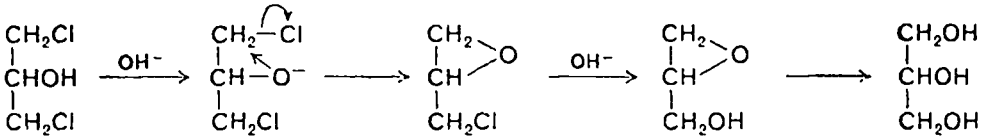


FIGURE 1. Correlation of the acid dissociation constants of XCH_2CO_2H in water at 25° [25] with σ_I (n.m.r.).

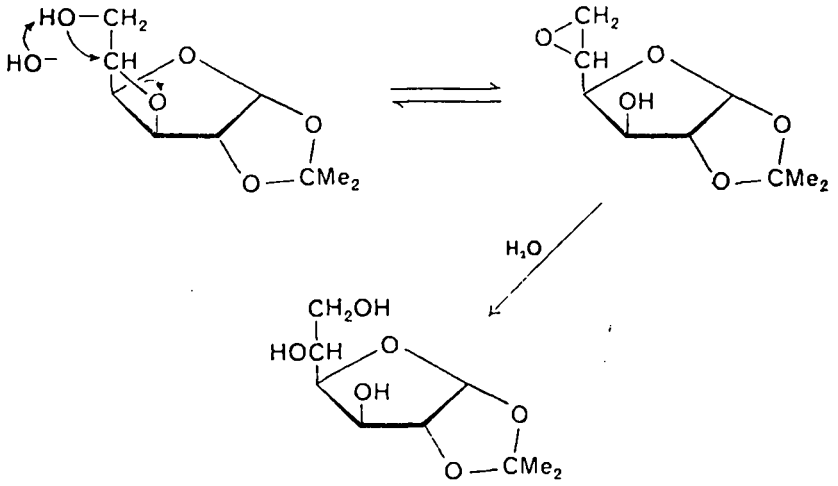
molecular and results in the formation of cyclic ethers[26], even in the case where $n = 2$. Such reactions, leading to the conversion of OH into some other functional group, do not come within the scope of this review, unless the cyclic ether is a transient intermediate in a reaction regenerating the hydroxyl substituent. Of the cyclic ethers formed, only the ethylene oxides (oxiranes) show any tendency to cleave in the presence of alkoxide or hydroxide ions, and the conditions are frequently more vigorous than those required for oxirane formation from the halohydrin.

There are at least two cases in which such breakdown is unavoid-

able and in which the cyclic intermediate is not isolated. Myszkowski and co-workers[27] examined the kinetics of alkaline hydrolysis of 1,3-dichloro-2-propanol and observed that the rate of liberation of chloride ion was greater than the rate of formation of glycerol. They suggested that glycidol was an intermediate in the reaction and proposed the following mechanism.



Buchanan and Oakes[28] reported examples of intramolecular nucleophilic catalysis of the opening of an oxetane ring. They found, for instance, that the 3,5-oxide ring of 3,5-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose is opened more rapidly than that of the corresponding xylose derivative. The ring-opening reaction is believed to involve the reversible formation of a 5,6-epoxide intermediate:

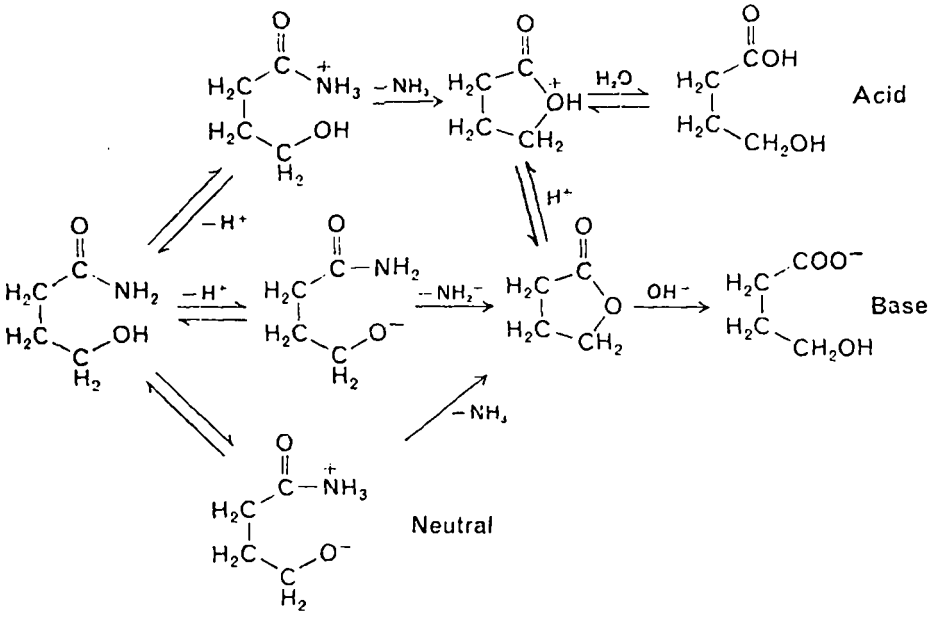


Under neutral or acidic conditions, oxirane and oxetane intermediates are not formed[29]. Normal solvolysis products are obtained and the reaction rates are compatible with those predicted from simple electronic effects.

2. Hydrolysis of carboxyl derivatives

Bruice and Benkovic[30] have given an authoritative account of hydroxyl group participation in some ester and amide reactions;

sections of Capon's comprehensive review[31] are also relevant. In the hydrolysis of simple hydroxy-amides, the combined work of Bruice[32] and of Zürn[33] has established neighbouring group participation for the γ- and δ-hydroxyl substituents, which leads to much faster hydrolysis than that shown by the corresponding unsubstituted amides. For γ-hydroxybutyramide hydrolysis over different pH ranges, Bruice has suggested mechanisms involving lactone or protonated lactone intermediates:

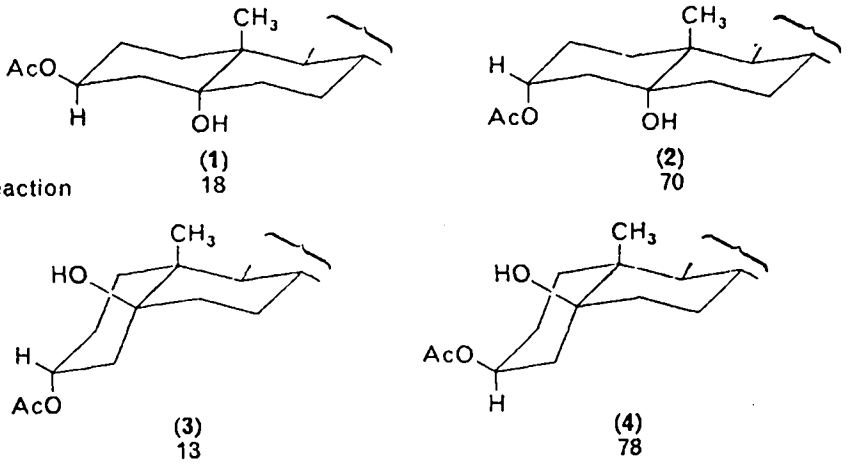


Lactone intermediates have also been suggested for other cases in which hydrolysis of an amide group is accelerated by the presence of a δ-substituted hydroxyl group[34, 35].

The participation by hydroxyl groups in the alkaline ester hydrolysis of 1,2- and 1,3-diol monoesters has been established by a number of workers. Henbest and Lovell[36] measured the extent of hydrolysis under standard conditions for cholestane-3,5-diol monoacetates. The results shown on p. 401 indicate that *cis*-1,3-diaxial compounds (**2**) and (**4**) are hydrolysed more rapidly than *trans*-1,3-compounds, (**1**) and (**3**)*.

Other significant increases in the rates of alkaline methanolysis

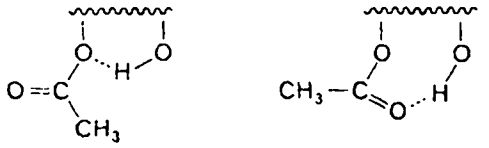
* This is in spite of the general observation for alicyclic compounds that equatorial acetates are more susceptible to alkaline hydrolysis than axial ones[40].



of *cis*-1,3-diaxial diol monoesters have been noted for derivatives of the steroidal alkaloids, germine and cervine[37–39]. Similar accelerations have been observed in the alkaline hydrolysis of 1,2-diol monoesters in cholestane-3β,4β-diol and its derivatives[41].

For 1,2-diol monoesters in five-membered rings, in both substituted cyclopentanes[42] and tetrahydrofurans[43], there are marked rate accelerations, the effect of a *cis*-hydroxyl group being greater than a *trans*-group.

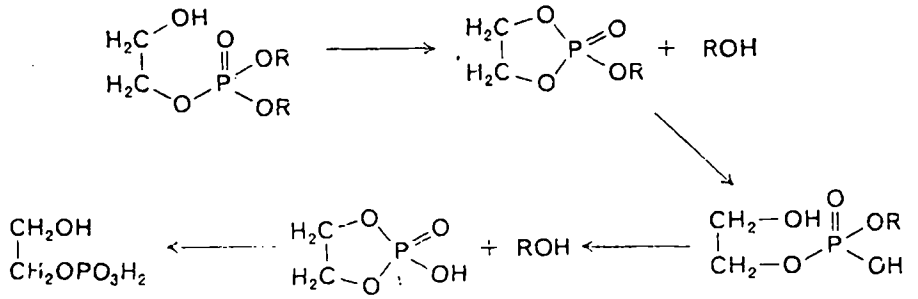
For all these observations a hydrogen-bonding explanation is generally accepted, but there is difficulty in deciding whether the effective hydrogen bond is to the ether oxygen or to the carbonyl oxygen atom:



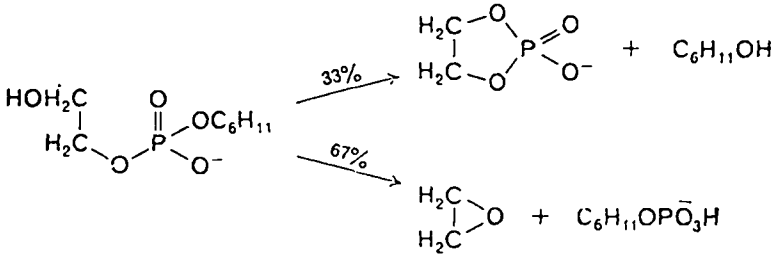
Henbest and Kupchan have both favoured ether–oxygen participation in the cyclohexane derivatives examined by them. Bruice and Fife[42], after kinetic and infrared studies, firmly concluded that, for the hydrolysis of 1,2- and 1,3-cyclopentanediol monoacetates, the transition state is one in which the activating hydrogen bond is to the carbonyl oxygen atom. However, generalizations are not readily made and, as has been emphasized in more than one report, the geometry may be all-important. Capon[31] has also pointed out that the rate enhancement is not usually very great and that this also makes it difficult to generalize.

3. Hydrolysis of Phosphorus (v) esters

The stability of phosphorus esters to basic hydrolysis can be severely reduced by a neighbouring hydroxyl group[44]. Cyclic intermediates are believed to be formed and subsequently hydrolysed:



In the case of the alkaline hydrolysis of *O*-cyclohexyl *O*-2-hydroxy ethyl phosphate, an alternative hydrolysis path, involving an epoxide as the cyclic intermediate, has also been observed:

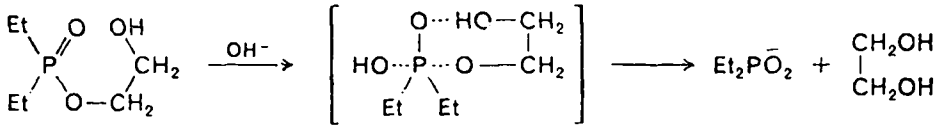


When there are alkyl substituents on C-1 and C-2 of the 2-hydroxy ethyl group, there is an even greater predominance of the epoxide route. In these cases the products are mainly cyclohexyl phosphate and the glycol.

The accelerating effect of similarly placed, β-hydroxyl, substituents has also been observed by Larsson and Wallerberg[45] for the alkaline hydrolysis of alkoxy-diethyl-phosphine oxides, $ROP(O)(Et)_2$. Rate constants are as follows:

R	$k \times 10^4$ (l/mole sec)
CH_3CH_2-	0·573
$CH_3OCH_2CH_2-$	2·55
$HOCH_2CH_2-$	4·42

The authors attribute the rate enhancement to acid catalysis via hydrogen-bonding:



They believe that ester hydrolysis in compounds of this type is S_N2 (on phosphorus) and, if so, this would seem to be the only reported case in which an un-ionized hydroxyl group acts as an acid catalyst for a nucleophilic displacement.

4. Aliphatic acid–base equilibria

In the series glycollic acid ($K_a = 1{\cdot}5 \times 10^{-4}$), hydracrylic acid ($HOCH_2CH_2CO_2H$; $0{\cdot}311 \times 10^{-4}$) and γ-hydroxybutyric acid ($0{\cdot}193 \times 10^{-4}$)[46], the changes in acidity constant are close to those predicted from application of the Taft fall-off factor[13] of 1/2·8. There is therefore no participation by the hydroxyl substituent.

For 1,2-disubstituted-4-*t*-butylcyclohexane and *trans*-decalin derivatives, Sicher and co-workers[47] examined the influence of a neighbouring hydroxyl group on the pK_a values of equatorial and axial carboxylic acids and ammonium ions. Their results indicated that the introduction of an axial hydroxyl group adjacent to an axial carboxyl or ammonium group lowers the pK_a by about 0·45 unit (for acids) or 0·90 unit (for amines). The arrangement of the two groups is *trans* and the effect can be regarded as a simple polar one. The assumption was made that any marked variation from these figures for other orientations is caused by interaction between the hydroxyl group and the functional group. Hydrogen-bonding was proposed but no detailed mechanism was offered. Sicher's results are summarized below; ΔpK is the difference between the *trans* diaxial value and the pK actually found:

Conformation			ΔpK
–OH	$-CO_2H$	$-NH_3^+$	
e	e		+0·12
a	e		+0·36
e	a		+0·94
e		e	−0·23
a		e	−0·49
e		a	−0·24
trans[a]		boat	−0·16
cis[a]		boat	−0·72

[a] From bicyclo[2,2,2]octane derivatives.

No allowance was made for any steric effect caused by the presence of the hydroxyl group but, if this is accepted as minor, the results indicate that hydroxyl group participation increases acid strength for carboxylic acids and decreases base strength for amines. These effects are predictable on the basis of stabilizing hydrogen bonds in the carboxylate ion and the free amine:

Kilpatrick and Morse[48] have measured the dissociation constants of the various hydroxycyclohexanecarboxylic acids in water, glycol, methanol and ethanol. The results are given in Table 2.

TABLE 2. pK's of *cis*- and *trans*-hydroxycyclohexanecarboxylic acids.

Position of OH group	Conformation relationship	$K_{a(H_2O)} \times 10^5$	$K_{c(glycol)} \times 10^9$	$K_{a(MeOH)} \times 10^{10}$	$K_{a(EtOH)} \times 10^{11}$
cis 2-OH	ea or ae	1·60	30·6	4·42	17·0
trans 2-OH	ee or aa	2·08	21·0	2·33	7·79
cis 3-OH	ee or aa	2·50	18·2	1·70	3·09
trans 3-OH	ea or ae	1·53	9·06	0·817	1·56
cis 4-OH	ea or ae	1·46	8·62	0·761	1·48
trans 4-OH	ee or aa	2·10	14·8	1·50	2·45
Cyclohexanecarboxylic acid		1·25	9·50	0·923	1·70

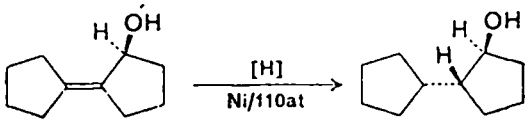
The situation is much more complex than that in Sicher's system; for each case there are two possible conformations for the molecule in the ionized and in the un-ionized states and the pK_a's of axial and equatorial carboxyl groups differ considerably. In spite of this, it is apparent from the Table that as the solvent becomes less polar, and consequently less capable of effectively solvating carboxylate anions, the strength of each 2-hydroxy acid relative to that of cyclohexanecarboxylic acid in the same solvent is increased markedly. For example, although the *cis*-2-hydroxy acid and the unsubstituted acid have roughly comparable strengths in water, the former is ten times stronger in ethanol. The acid-strengthening effect is presumably due to hydrogen-bonding between the hydroxyl group and the carboxylate ion and seems to be greater for ea conformational relationships than ee (the most probable conformation for the *trans*-2-hydroxy compound). This is supported by Sicher's observations.

Since the acid-strengthening effect (relative to cyclohexane-

carboxylic acid) associated with solvent change is only significant for the *cis*-2-hydroxyl derivatives, participation by the hydroxyl group in the 3- and 4-positions may be presumed to be relatively unimportant.

C. Miscellaneous Aliphatic Reactions

Howard[49] has reported that 2-cyclopentylidene-cyclopentanol (**5**), on hydrogenation over Raney-nickel gives at least 96% *trans*-2-cyclopentylcyclopentanol (**6**) and only 1–2% of the *cis*-isomer. The



(5) (6)

overwhelming preference for the *trans*-isomer in spite of the essentially planar nature of **5** is attributed to some form of bonding between the hydroxyl group and the catalyst surface, resulting in *cis*-addition of hydrogen from the 'hydroxyl' side of the molecule. A similar effect has been reported by Henbest[50] and by Nishimura[51] in cholestene derivatives.

However, in the course of other work on steroid derivatives in which the hydroxyl group is more remote from the double bond, it was noted that *cis*-hydrogenation appeared to be the result of a main attack from the side of the ring remote from the hydroxyl group[52], which is simply exerting a steric effect. The difference in findings may arise from differences in catalyst and in reaction conditions.

III. REACTIONS OF AROMATIC SIDE-CHAINS

A. Electronic Effects

In this section we consider the effects of *meta*- and *para*-hydroxyl substituents on side-chain reactivities. The proximity effects normally associated with *ortho*-substituents are particularly prominent with hydroxyl substituents; because of their high polarity and their tendency to form hydrogen-bonds, these substituents often complicate the transition state through direct interaction with groups at the reaction site*.

* In spite of this, Tribble and Traynham[53] have recently determined σ^- values for a large number of *ortho*-substituents from n.m.r. measurements. The measured value for *o*-hydroxyl (−0·40) proved to be within the range of reported *p*-hydroxyl values.

A large amount of general information is available on the effect of *m*- and *p*-hydroxyl groups on side-chain reactivity. Much of this is qualitative, and a useful picture of the electronic effects of the hydroxyl substituent is only obtained by restricting discussion to those cases in which there are quantitative data on reactivity effects relative to other substituents. This restriction results in a marked reduction in the number of reactions to be considered.

Most of these reaction series were looked at by Jaffé[2], who correlated each set of data by means of the Hammett equation and calculated σ values for the *meta*- and *para*-hydroxyl substituent. He found that, compared with most other substituents, the derived σ values showed a much greater variation from reaction to reaction and that it was not possible to estimate a reliable value for either σ_m or σ_p.

There seem to be about sixty reactions (see Tables 3–8) from which we can derive, with varying reliability, about forty σ_m values and about fifty σ_p values for the hydroxyl group. The observed variations in these substituent constants may be caused by insufficient or inaccurate data (1), or they may reflect the variation of substituent constants with solvent (2), or with the nature of the side-chain (3).

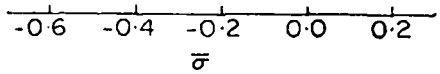
The first of these causes is the most serious and can hinder attempts to systematize variations of types (2) and (3). Some early, imprecise work is readily recognized and may be ignored. In other studies, inaccurate experimental information on known 'well-behaved' substituents (e.g., H, *m*-CH_3, *m*-Cl, *m*-NO_2) can lead to quite serious errors in σ_p for the hydroxyl substituent because this adds to the uncertainties in extrapolation. For $\sigma_{m\text{-OH}}$ the problem is not serious because the value of this constant is normally within the range covered by the reliable substituents. In fact, for the *meta*-hydroxyl substituent, one can clearly see the variation of σ with solvent. With $\sigma_{p\text{-OH}}$ random scatter is often increased by the inclusion of results derived from studies which cover too few 'well-behaved' substituents; this is especially true of some earlier investigations. In addition, in compiling tables for this section, we have excluded reaction series which have to be built up from the studies of separate working groups; any exceptions are specified.

1. Solvent effects

In Table 3 are listed the data on acidity constants of *meta*- and *para*-substituted benzoic acids in various solvents. It will be seen

TABLE 3. Ionization of $ArCO_2H$ in various solvents.

Reaction	System	Probable range of $\bar{\sigma}_m$ and $\bar{\sigma}_p$[a]	Ref.
(1)	H_2O, 25°		54
(2)	H_2O, 25°		54
(3)	H_2O, 25°		55
(4)	H_2O, 25°		56
(5)	26·5% Dioxan–H_2O, 25°		57
(6)	43·5% Dioxan–H_2O, 25°		57
(7)	73·5% Dioxan–H_2O, 25°		57
(8)	20% EtOH–H_2O[b], 25°		58
(9)	40% EtOH–H_2O, 25°		58
(10)	50% EtOH–H_2O, 25°		58
(11)	50% EtOH–H_2O, 25°		59
(12)	70% EtOH–H_2O, 25°		58
(13)	80% EtOH–H_2O, 25°		58
(14)	90% EtOH–H_2O, 25°		58
(15)	95% EtOH–H_2O, 25°		58
(16)	EtOH, 25°		60
(17)	MeOH, 25°		61
(18)	*n*-PrOH, 25°		62
(19)	*n*-BuOH, 25°		63
(20)	Glycol, 25°		64
(21)	Benzene[c], 25°		65



[a] The range of σ values indicated in the table was determined by basing Hammett plots on only a small number of 'well-behaved substituents' (*m*-NO_2, *m*-CN, *m*-Cl, *m*-Br, *m*-I, H, *m*-CH_3). We would consider any sigma value within the ranges tabulated to be acceptable. The spread is not intended as an indication of the experimental error in any of the individual points.

[b] Insufficient points for a reliable rho value. An estimate of $\rho = 1{\cdot}2$ was used.

[c] Based on the equilibrium constant for the reaction between the benzoic acid and diphenylguanidine.

that in only two cases has the benzoic acid series been systematically studied by more than one group of investigators—in water, and in 50% ethanol. Of the four sets of data on aqueous solution, those from studies (3) and (4) must be considered the most reliable by a considerable margin.

Much of Table 3 is based on the work of two groups. Most results support a generalization that, in moving from water to solutions containing substantial proportions of low molecular-weight alcohols, the value of $\bar{\sigma}_m$ shifts from a value of about $+0{\cdot}1$ to a figure of approximately $-0{\cdot}1$. This is an appreciable change. In the move from water to dioxan-rich solvents, the shift in sigma values is very much smaller. There is one report on benzene as solvent, and the sigma value is intermediate between those in water and alcohols; on the whole, this conclusion is supported by other isolated studies on non-polar solvents.

The $\bar{\sigma}_p$ values from Bright's data[58] on ethanol–water mixtures perhaps imply changes similar to those observed for σ_m—a shift to more negative values as the proportion of alcohol is increased. But the work of Kilpatrick[60–64] does not indicate that the values in pure alcoholic solvents are substantially different from the figure in water.

2. Dependence on side-chain

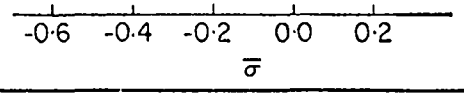
Two key reviews of σ values are relevant: that by Taft and Lewis[3] in which they compiled a list of σ^o values, and that by Wepster[4], who derived σ^n values. Taft and Lewis do not quote a value for $\sigma^o{}_m$ or $\sigma^o{}_p$ for the hydroxyl group in hydroxylic solvents, but merely state that the value is strongly dependent on the nature of the solvent. They give figures for $\sigma_m{}^o$ and $\sigma_r{}^o$, relating to nonaqueous solvents, of $+0{\cdot}04$ and $-0{\cdot}13$ respectively, and these may be based on Reaction 21 in Table 3. In his paper, Wepster reports $\sigma^n{}_{m\text{-OH}}$ as $+0{\cdot}095 \pm 0{\cdot}025$ and concludes that $\sigma_{p\text{-OH}}$ is variable.

There are no Hammett data covering the effect of either a *meta*- or *para*-hydroxyl substituent on the reactivity of a functional group which is insulated from the benzene ring (e.g., by a methylene group) and there is therefore no standard of reference for any discussion of variations in interaction between such a substituent and the side-chain. In Tables 4–7 data on a selection of different reactions are given. If a reaction has been investigated by more than one group under similar conditions, we have made the choice of what appears to be the most reliable figure. The reactions are classified on the basis of the electronic nature of the side-chain.

There are only four reactions in the Tables in which the values for σ_m differ significantly from those expected from the nature of the reaction solvent. These are reactions (33), (34), (38) and (43). For reactions (33) and (34) the differences may be caused by hydrogen-bonding between solvent and phenolic oxygen; in each

TABLE 4. Reactions of weak $-R$ side-chains.

	Reaction	Probable range of $\bar{\sigma}_m$ and $\bar{\sigma}_p$[a]	Ref.
(1–21)	Ionization of $ArCO_2H$	see Table 3	
(22)	Rate, $ArCO_2H + HN_3$, trichloroethylene, 40°		66
(23)	Rate, $ArCO_2H + Ph_2CN_2$, EtOH, 30°		59
(24)	pK_a, $ArP(O)(OH)_2$, H_2O, 25°		67
(25)	pK_a, $ArP(O)(OH)_2$, 50% EtOH–H_2O, 25°		67
(26)	pK_a, $ArPO_2H^-$, H_2O, 25°		67
(27)	pK_a, $ArPO_2H^-$, EtOH–H_2O, 25°		67
(28)	pK_a, $ArAs(O)(OH)_2$, H_2O [b], 22°		68
(29)	pK_a, $ArAsO_2H^-$, H_2O [c], 22°		68
(30)	pK_a, $ArCH{=}CHCO_2H$, H_2O, 25°		69
(31)	pK_a, $ArC_6H_4CO_2H$, 50% Butyl cellosolve–H_2O, 25°		70
(32)	Rate, $ArCOOCH_3 + PhNH_2$, $PhNO_2$, 100° [d,e]		71



[a] See footnote to Table 3.
[b] Other data have also been reported for this reaction at 18°[72,73].
[c] The authors assign pK_2 to the OH group and pK_3 to the AsO_2H^-. This would lead to a very high value for the substituent constant for the AsO_2H^- group. We have assigned pK_3 to the OH ionization which leads to a $\sigma_p^{AsO_2H^-}$ of approximately zero.
[d] The conditions for this reaction are rather vigorous and the stability of phenols in this system is unknown.
[e] The authors also report data at other temperatures that lead to similar $\bar{\sigma}$ values.

TABLE 5. Reactions of strong $-R$ side-chains.

	Reaction	Probable range of $\bar{\sigma}_m$ and $\bar{\sigma}_p$[a]	Ref.
(33)	pK_a, $ArCO_2H_2^+$, H_2SO_4–H_2O, 25°	*p* *m*	74
(34)	pK_a, ArC^+OHCH_3, H_2SO_4–H_2O, 25°	*p* *m*	75
(35)	pK_a, Ar_3C^+, H_2O, 25°	*p*	76
(36)	pK_a, $Ar—C_7H_6^+$, 50% CH_3CN–H_2O, 25°	*p*	77
(37)	pK_a, $Ar{=}NNHPh^+$, 20% EtOH–H_2SO_4[b], 25°	*p*	78
(38)	pK_a, $ArC(=NH_2^+)Ph$[c, d], H_2O	*m* *p*	79
(39)	pK_a, $ArCH{=}NH_2^+Ph$, MeCN[e], 25°	*p* *m*	80
(40)	Rate, $ArC(=NH_2^+)Ph$ + H_2O[c], H_2O[f], 25°	*p* *m*	79
(41)	Rate, $ArNO_2$ + $SnCl_2$, H_2O, 90°	*p*	81

-0·8 -0·6 -0·4 -0·2 0·0 0·2

$\bar{\sigma}$

[a] See Table 3.

[b] The author assumes proton sharing by the two nitrogens to account for the single Hammett plot for both $+T$ and $-T$ substituents.

[c] The 3,5-dimethyl substituent was used in constructing the Hammett plot for this reaction.

[d] The measured dissociation constant for the *p*-OH product may be that of phenolic group.

[e] The same series was also studied using compounds with substituents in the other aromatic ring. Differences in $\bar{\sigma}$ values were not considered significant and correlation was poorer than in the series listed here.

[f] An additional value for $\bar{\sigma}_m$ based on the rate at 0° was available from the same source but this was not significantly different from the one here.

instance similar positive deviations in $\bar{\sigma}$ have been noted for the *meta*-alkoxy group[74, 75].

The $\bar{\sigma}_p$ values cover a wide range but, as a rough guide, they can be placed in one of two groups—the values between −0·2 and −0·4, which may arbitrarily be called 'normal' substituent constants, and the 'exalted' values lying between −0·5 and −0·9. The first range is generally linked with the reactions of weak $-R$ and with $+R$ side-chains; the second range is applicable to strong $-R$ side-chains. Clear exceptions to the generalization are reactions (31), (42), (43) and (50). The high value for $\bar{\sigma}_p$ in reaction (31) is matched by the correspondingly high negative σ value required for the *para*-amino group in this reaction (but not for the *p*-methoxyl group). However, the rho value for the reaction is rather low (about 0·45) and the experimental error may be greater than usual.

The high sigma value in reaction (50) is interesting. Although the reaction is tabulated as that of a $+R$ (amino) side-chain, the suggested mechanism[85] involves an electron-deficient nitrogen intermediate:

$$\mathrm{Ar-\overset{+}{N}-\underset{\displaystyle \underset{\displaystyle NH_2}{|}}{C}=N-N=\overset{-}{N}}$$

We should therefore treat the reaction as that of a strong $-R$ side-chain, and it yields a $\bar{\sigma}_p$ value within the expected range for such a reaction.

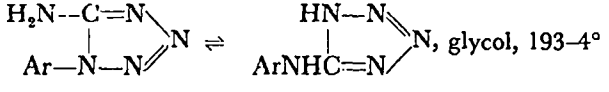
The value for $\bar{\sigma}_p$ for phenol dissociation appears to be out of line, but this trend towards less negative $\bar{\sigma}_p$ values for phenolic ionizations is also discernible for the *p*-NH_2 group—and is possibly true for other $+R$ substituents.

The exalted sigma values obtained for reactions either involving 'strong' $-R$ side-chains and/or attack at aromatic centres can, of course, be attributed to large changes in resonance interaction in the system in going from the ground state to the transition state. Within the given range, the values appear to either be around −0·6 ($-R$ side-chains) or around −0·8 (aromatic centres), but once again the data are not numerous.

3. Comparison of substituent constants for methoxyl and hydroxyl groups

The substituent constants for the methoxyl group, like those for the hydroxyl group, appear to vary from reaction to reaction. The

TABLE 6. Reactions of $+R$ side-chains.

	Reaction	Probable range of $\tilde{\sigma}_m$ and $\tilde{\sigma}_p$[a]	Ref.
(42)	pK_a, ArOH, H_2O, 25°[b]		b
(43)	pK_a, ArOH, 8% Dioxan, 38°		82
(44)	pK_a, ArOH 48·9% EtOH–H_2O, 20–2°		83
(45)	pK_a, ArOH 95% EtOH–H_2O, 20–2°		83
(46)	pK_a, ArSH 48·9% EtOH–H_2O, 20–2°		83
(47)	pK_a, ArSH 95% EtOH–H_2O, 20–2°		83
(48)	pK_a, $ArNH_3^+$, H_2O[c], 25°		54
(49)	pK_a, Pyridine N-oxides, H_2O[d], 23–5°		84
(50)	K_{eq},  glycol, 193–4°		85
(51)	pK_a, ArN=CHPh MeCN[e], 25°		86
(52)	pK_a, $ArNH_3^+$, MeCN, 25°		86

[a] See Table 3.

[b] A composite graph based on pK_a, H_2O, 25° taken from Kortum[25]; pK_a for *m*-OH is an estimate based on the value at 18°, pK_a *p*-OH is that of Bishop and co-workers[87].

[c] Additional data on this reaction at 25° and at 20° are available[54, 88]. The range given is consistent with all three.

[d] Additional data (also unreliable) are available[89].

[e] The same series was also studied using compounds with substituents in the other aromatic ring. Differences in $\tilde{\sigma}$ values were not considered significant, and correlation was poorer than in the series listed here.

TABLE 7. Reactions of aromatic nuclei.

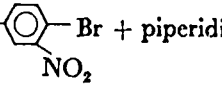
	Reaction	Probable range of $\bar{\sigma}_m$ and $\bar{\sigma}_p$ [a]	Ref.
(52)	pK_a, Pyridines, H_2O, 23–5°	*m*	84
(53)	Rate, $ArGe(Et)_3 + H_3O^+$, 71·4% MeOH–H_2O, 50°	*p*	90
(54)	Rate, $ArSi(Me)_3 + H_3O^+$, 71·4% MeOH–H_2O, 51·2°	*p*	91
(55)	Rate, $ArH + Br_2$, CH_3COOH, 25°	*p*	92

-1·0 -0·8 -0·6 -0·4 -0·2 0·0

$\bar{\sigma}$

[a] See Table 3.

TABLE 8. Reactions involving the O^- substituent.

	Reaction	Probable range of $\bar{\sigma}_m$ and $\bar{\sigma}_p$ [a]	Ref.
(56)	pK_a, $ArC(=N^+H)NBu_2^n.HCl$, 50% MeOH–H_2O, 25°	*p*	94
(57)	Rate, $ArCO_2Et + OH^-$, H_2O [b], 25°	*p* *m*	95
(58)	Rate, $ArCO_2Et + OH^-$, 56% Me_2CO–H_2O, 25°	*p* *m*	96
(59)	Rate, $ArCONH_2 + OH^-$, H_2O, 100°	*p*	97
(60)	pK_a, ArOH, H_2O [c], 25°	*m* and *p*	c
(61)	Rate,  + piperidine, piperidine[d], 25°	*p*	98

-1·2 -1·0 -0·8 -0·6 -0·4

$\bar{\sigma}$

[a] See Table 3.
[b] The data for substituents other than *m*-OH and *p*-OH are obtained from reactions in mixed aqueous organic solvents by extrapolation.
[c] See Footnote [b], Table 6. Data on *p*-O^- are from Bishop[87], data on *m*-O^- are unreliable.

para-methoxyl group appears to parallel the *para*-hydroxyl group in reactivity but to be slightly less reactive.

For the *meta*-methoxyl substituent Taft[3] suggests a value of +0·13 for pure aqueous solutions and +0·06 for nonhydroxylic media and most mixed aqueous organic solvents. Only a minority of the listed reaction studies (Tables 3–7) yield data on both the *m*-OH and *m*-OMe substituents and most of these refer to aqueous solution. In his review, Wepster[4] has tabulated $\bar{\sigma}$ values for *m*-OMe for forty reactions and although there is a tendency for $\bar{\sigma}_{OMe}$ to fall to about +0·05 in alcoholic solvents it rarely becomes negative, and never as negative as *m*-OH in similar solvents. This implies that negative shifts of *m*-OH in alcoholic solvents may be caused by hydrogen-bonding of the phenolic hydroxyl group, perhaps in the manner proposed by de la Mare[93].

4. The oxide ion substituent as an activating group

In contrast to the –OH group which is inductively electron-withdrawing (−*I*) and conjugatively electron-releasing (+*R*), the negatively charged oxygen of a phenoxide ion is strongly electron-releasing by both mechanisms (+*I*, +*R*). There are few data available, however, to give a quantitative estimate of its reactivity. For only six reaction series can the effect of an O^- substituent in the *meta*- (or *para*-) position be estimated as a $\bar{\sigma}$ value. These are given in Table 8. It is clear from the Table that few useful conclusions can be drawn, and practically all that can be said about $\bar{\sigma}_m$ is that, as would be predicted, it is negative.

Reactions (58), (59) and (60) involve attack by the negatively charged hydroxide ion on a species already bearing a negative charge. Such attack would be comparatively slow and would lead, in these cases, to $\bar{\sigma}_m$ and $\bar{\sigma}_p$ values more negative than otherwise expected. It is noteworthy that $\bar{\sigma}_p$ for reaction (56) is less negative than for other reactions.

The one apparently abnormal value in Table 8 is the value for $\bar{\sigma}_m$ in reaction (61). There is only one reported measurement of pK_2 for resorcinol[99] and until this figure receives further support, it should be treated with caution.

5. The substituent constant for the hydroxyl group

The generally accepted substituent constants for the *meta*- and *para*-hydroxyl substituents are given in Table 9.

TABLE 9. Substituent constants for the hydroxyl group.

Author	Symbol	σ_m	σ_p
Jaffé[2]	σ	-0.002 ± 0.106	-0.357 ± 0.104
McDaniel and Brown[100]	σ	$+0.121 \pm 0.02$	-0.357 ± 0.04
Wepster[4]	σ^n	$+0.095 \pm 0.025$	-0.178 ± 0.036
Taft[3]	σ^o	$(+0.04)^a$	(-0.13)
Brown and Okamoto[6]	σ^+	—	-0.92
Deno[76]	σ^+	—	-0.82
Hine[101]	σ	$+0.165$	-0.21
Yukawa–Tsuno[102]	σ^o	—	-0.16

[a]Nonhydroxylic solvent only. The value in hydroxylic solvents is variable.
In addition, for the $-O^-$ substituent, Jaffé gives σ_m as -0.708 and σ_p as -0.52; Hine suggests -0.47 and -0.81 respectively.

The available data lead us to suggest that the following hydroxyl sigma values can be expected under the given conditions:

$\sigma_{m\text{-OH}}$ $+0.10 \pm 0.05$ for aqueous and water-rich aqueous mixtures.
-0.10 ± 0.03 for alcohols and alcohol-rich solvents.
0.0 ± 0.05 for nonhydroxylic solvents.
$+0.20 \pm 0.05$ for very strongly acidic solutions (e.g., H_2SO_4)

These values are considered to be independent of the nature of the side-chain.

$\sigma_{p\text{-OH}}$ -0.20 to -0.40 for reactions of weak $-R$ and $+R$ side-chains, e.g., CO_2H, NH_2
-0.50 to -0.80 for reactions of strong $-R$ side-chains, e.g., $CO_2H_2^+$, $-C(R)=NH_2^+$
-0.70 to -0.90 for electrophilic aromatic substitution.

For $\sigma_{p\text{-OH}}$ solvent dependence is considered unlikely to shift the values outside the given ranges.

6. The substituent constant for the oxide ion

There are two influential features of this substituent: the electronic effect of the group, and the overall charge on the molecule in the transition state. With only three reactions as a guide, the rough estimate of σ_m is -0.35 ± 0.1. For σ_p, the best that can be said is that the value is expected to lie between -0.5 and -1.0, higher values being associated with nucleophilic attacks on negatively charged substrates.

B. Proximity Effects

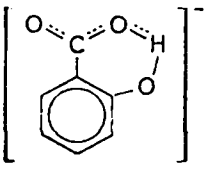
1. Aromatic acid–base equilibria

The best known and most widely quoted example of the proximity effect of a hydroxyl group on an acid–base reaction is the abnormally high acidity of salicylic acid[103]. This can be seen most readily by comparison with the other monohydroxybenzoic acids and methoxybenzoic acids:

$10^5 K_a$ in H_2O, 25°

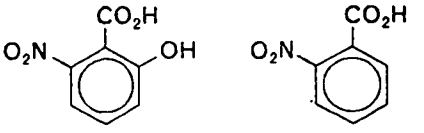
	o	*m*	*p*
hydroxy (K_1)	105	8·3	2·9
methoxy	8·06	8·17	3·38

This high acidity is attributed to abnormal stabilization of the salicylic acid mono-anion by internal hydrogen-bonding:



The negative charge is shared by all three oxygen atoms. The importance of the proton in stabilizing the system is illustrated by the fact that K_2 for salicylic acid is more than 2500 times smaller than that for either the *meta*- or the *para*-isomer. However, the issue is complicated by the effect of high charge repulsion in the *ortho*-dianion.

Dippy and co-workers[104] have reported that 6-nitrosalicylic acid (**7**) is a weaker acid than *o*-nitrobenzoic acid (**8**) indicating that the acid-strengthening factor in salicylic acid is no longer present in **7**.



(7) $K_a = 5{\cdot}81 \times 10^{-3}$

(8) $K_a = 6{\cdot}71 \times 10^{-3}$

Dippy considers that the carboxyl group is forced out of plane. In these circumstances hydrogen-bonding is less effective and stabilization of the mono-anion accordingly lower.

In the case of 2,6-dihydroxybenzoic acid ($pK_a = 1{\cdot}3$) the prox-

imity effect in the primary dissociation is even greater[105]; the pK_a of 2,6-dimethoxybenzoic acid is 3·44[106]. A similar but much smaller exaltation of pK_a is found for catechol.

pK_a of phenols[25], H_2O, 25°

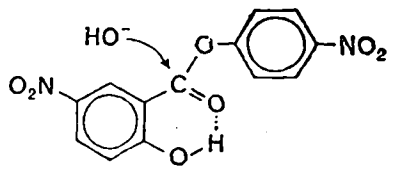
	o	*m*	*p*
hydroxy	9·48	9·44	9·96
methoxy	9·98	9·65	10·21
hydroxymethyl	9·92	9·83	9·82

It will be seen that for the hydroxymethyl phenols, differences are too small to be significant.

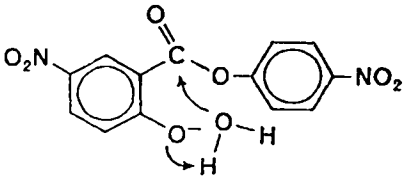
For *o*-aminophenols, there is no evidence for hydroxyl participation. Furthermore, no pK_a value is available for the *o*-hydroxybenzylammonium ion, and no conclusion can be drawn from the closely similar figures for 2-hydroxy-3-methoxybenzylamine (8·70) and 3-hydroxy-2-methoxybenzylamine (8·89)[107].

2. Hydrolysis of carboxyl derivatives

Bender, Kezdy and Zerner[108] found that the alkaline hydrolysis of *p*-nitrophenyl-5-nitrosalicylate was unexpectedly fast. The data were consistent with either **9**, reaction of hydroxide ion with the un-ionized ester (intramolecular general acid-nucleophilic catalysis) or **10**, reaction of the ionized ester with water (intramolecular general-base catalysis). The accelerations observed for the reaction



(9)



(10)

were much greater than those for corresponding reactions involving nucleophiles in which acidic hydrogens are absent (e.g. azide ion) and mechanism **10** was considered to be the more likely.

Other studies of esterification and ester hydrolysis have led to the suggestion of lactone intermediates. Kupchan and Saettone[109] have proposed that the esterification of *o*-hydroxyphenoxyacetic acid proceeds through the lactone since the rate is at least ten times greater than that of the *o*-OCH_3, *o*-Cl or *p*-OH compounds. The considerable accelerating effect of a 2-hydroxy substituent on the

rate of hydrolysis of methyl triptoate has also been accounted for in terms of the intermediacy of a lactone[110].

The occurrence of intramolecular general-base catalysis in amide hydrolysis has been established by Bruice and Tanner[111], who investigated the mechanism of hydrolysis of salicylamides. If general-base catalysis were operative, the introduction of a nitro group in the 5-position should increase the reactivity of the amide side-chain and decrease the ability of the oxide ion substituent to act as a general base. If intramolecular general-acid catalysis occurred, on both grounds the introduction of the nitro group should increase the reaction rate. The rate of hydrolysis for salicylamide proved to be lower than for the 5-nitro compound, a result that supported the general-base mechanism.

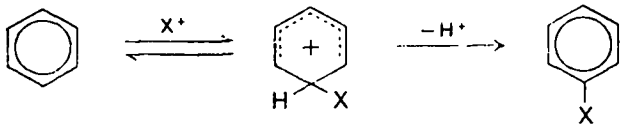
IV. AROMATIC SUBSTITUTION REACTIONS

A. *Electrophilic Substitutions—General Considerations*

The very large amount of information available in this field enforced selection. Most of the subsequent sections deal with this type of aromatic substitution. We have decided that the more profitable results are those related to phenol itself. The extremely powerful directing and activating effect of the hydroxyl group gives it a strong tendency to swamp the effects of most other substituents in phenol derivatives*, and it is often true that trends observed for phenol can be carried over to its substitution products.

1. The mechanism for electrophilic aromatic substitution in phenol

The generally accepted mechanism for electrophilic aromatic substitution involves the rate-determining formation of an intermediate σ complex (Wheland intermediate) followed by rapid loss of proton[112], e.g., for benzene,



There is no evidence against a Wheland intermediate in the case of substitution in phenols, but there is considerable support for the opinion that the actual scheme is much more complex than that

* A notable exception is that 2,4-dimethoxyphenol undergoes bromination in the 5-position; Fries rearrangement of the acetate also leads to the 5-ketone[113].

pictured here. For instance, it has been established that, in certain halogenations of phenol, dienone intermediates may be formed and that weakening or breaking of the O–H bond may be involved in the rate-determining step[93]. Whether this is caused by hydroxyl 'hyperconjugation' or solvent interactions is still a matter for argument. However, the observations that phenol is more activated than anisole in the *para*-position and that phenol is brominated in acetic acid nearly twice as rapidly as in *O*-deuteroacetic acid demonstrate the inadequacy of the simple mechanism, at least for halogenations*.

Electrophilic attack at the *ortho*-position of phenol may be complicated by interaction with the hydroxyl group. In some cases the electrophile attacks oxygen first and later migrates; in others some form of weak bonding between the attacking electrophile and the phenolic oxygen results in abnormally high *ortho–para* ratios. In the case of phenoxides, participation in *ortho* attack may be even more pronounced. One case has been reported where the phenoxide ion oxygen acts as a general base in removing the proton from the Wheland intermediate. In other cases, *ortho* attack may be preceded by the formation of some sort of preliminary complex involving the O^- substituent, the associated metal ion and the electrophile. It is probable, indeed, that electrophilic substitution at the *ortho*-position of phenols and phenoxides is rarely a 'normal' reaction.

2. The ortho–para ratio

The usual site for electrophilic attack on the aromatic ring of phenol is *ortho* or *para* to the hydroxyl group. There is some activation of the *meta*-position. Illuminati[114] estimates a value for σ_m^+ of $-0{\cdot}133$ for bromination in acetic acid but in view of the very high rho value (>10) for this system and the relatively high negative value expected for σ_o and σ_p ($\sigma_p \approx -0{\cdot}8$), one would not predict appreciable amounts of *meta*-substitution products. The occurrence of *meta*-substitution products is most common in cases such as sulphonation or Friedel–Crafts reactions, where substitution is reversible and the *meta*-isomer is thermodynamically the most stable.

In a monosubstituted benzene derivative, the steric effect of the substituent normally decreases the accessibility of the *ortho*-positions. In addition, the $-I$ and $+R$ electronic characteristics of the hydroxyl group combine to favour *para*- substitution. Overall then, an *ortho–para* ratio of less than the statistical 2 : 1 should be found. Some

* The mechanism of bromination of phenols is discussed thoroughly by de la Mare[93].

experimental observations support this prediction but in the majority of cases the *ortho–para* ratio is high, sometimes greater than 2 : 1. An accounting in terms of participation by the OH or O^- group has been referred to in the previous section.

3. Replacement of substituents other than hydrogen

Substitutions of this type have been observed quite frequently in aromatic systems[115]. They can be divided conveniently into two groups: those in which the replacement group is hydrogen, and those in which the electrophile is some other group or atom. The replacement of substituents by hydrogen is the most widespread, probably because the hydrogen ion is an extremely powerful electrophile and can readily be generated in high concentrations. The ease of reaction varies considerably. Some groups such as MgX are displaced extremely readily while others require strong acids and/or activation by other substituents in the ring, e.g., protodehalogenation. One or two of the reactions are mentioned elsewhere in this review—dealkylation, desulphonation, desilylation and degermylation for instance. The pronounced activating effect of the hydroxyl substituent *ortho* or *para* to the leaving electrophile is most apparent in the more difficult displacements, e.g., dehalogenation and decarboxylation[115].

The replacement of substituents by groups other than hydrogen are not as common, because these reactions are reversible and restricted to powerful attacking electrophiles. A number of such displacements have been observed in nitration and halogenation. For example, *para*-substituents are often replaced during nitration or halogenation of phenols[116]. However, in these cases the mechanism may not be simple. Addition products of phenols have been isolated during the course of halogenations[93], and the normal product of bromination of phenol in aqueous solution is the ketone, 2,4,4,6-tetrabromocyclohexadienone[117].

B. ortho–para *Ratios in Electrophilic Substitution*

1. Nitration and nitrosation

The nitration of aromatic compounds has been extensively studied, and some impressive and comprehensive reviews are available[118–120].

a. Nitration in organic solvents. On the nitration of phenol, perhaps the most surprising feature of the data is the constancy of the

ortho–para ratio for nitration in organic solvents. Table 10 is from the work of Arnall[121].

TABLE 10. Nitration of phenol with nitric acid in various solvents.

Solvent	Nitrophenol (%)		
	ortho	*para*	*meta*
Acetic anhydride	59·6	37·8	2·6
Acetic acid	59·2	38·1	2·7
Acetone	57·4	39·6	3·0
Ether	57·8	39·2	3·0
Ethanol–acetic acid (2 : 1)	57·6	39·3	3·1
Ethanol	57·7	39·2	3·1

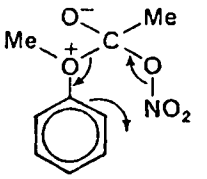
The change in orientation with temperature is not great at room temperatures and above. Presumably this is because nitration, unlike sulphonation and Friedel–Crafts alkylation and acylation, is not reversible under the reaction conditions. However, at low temperatures a change in the *ortho–para* ratio has been observed by Spryskov[122] for nitration with nitric acid–acetic anhydride mixtures.

TABLE 11. Nitration of phenol with 99·6% HNO_3 in acetic anhydride.

T(°C)	Nitrophenol (%)		
	ortho	*para*	*meta*
+20	54·9	45	
0	62·5	32·3	5·2
−15	68·8	31·2	
−30	72·0	28·0	
−50	79·5	16·2	4·3
−56	80·0	16·3	3·7
−70	79·0	16·0	5·0

A limiting $o : p : m$ ratio of 80 : 16 : 4 appears to be obtained for temperatures below −50°. The increased amount of *ortho*-product may be attributable to increased participation by the hydroxyl group at low temperatures. Participation by the lone pairs on the oxygen has been proposed[123] to explain the anomalously large

amount of *ortho*-product formed during the nitration of anisole by acetyl nitrate, e.g.,



An alternative explanation based on a change in the nitrating agent is also possible. Bordwell and Garbisch[124] have shown that whereas acetyl nitrate is rapidly formed by the reaction of nitric acid and acetic anhydride at room temperature, at $-10°$ most of the nitric acid does not react, and nitration is a much slower process. Spryskov's nitration technique involved the addition of the nitric acid last; accordingly the nitrating agent under his conditions is more likely to be nitric acid or $H_2NO_3^+$ than acetyl nitrate except for his runs at 0° and above. It may be significant that the runs with the highest *ortho–para* ratios are also those which would be expected to involve reaction of nitric acid rather than the larger acetyl nitrate species. However, since the *ortho–para* ratio has in many cases proved to be almost independent of the nitrating agent, this explanation is not as attractive as the first.

b. Nitration in aqueous solution. Ingold and co-workers[125] have investigated the nitration of phenol in aqueous solution and found that the reaction is catalysed by nitrous acid which, if not initially present, is formed as a by-product. In addition to the effect of the catalyst on reaction rates, the *ortho–para* ratio is drastically changed. The same workers found that in acetic acid solvent similar trends were observed, the *ortho–para* ratio changing from about 45: 55 (cf. Arnall's figures) to about 74: 26 when considerable quantities

TABLE 12. The effect of nitrous acid on the *ortho–para* ratio for nitration by nitric acid in strongly acid aqueous solutions[125].

$T = 20°$ [PhOH] = 0·45M, $[HNO_3]$ = 0·50M, $[H_2SO_4]$ = 1·75M	
$[HNO_2]$	*ortho* : *para*
0·00	73 : 27
0·25	55 : 45
1·00	9 : 91

of N_2O_4 were added. These changes are probably caused by changes in the nature of the nitrating species, but at present it is uncertain which species are involved.

c. meta-*Nitration.* Arnall suggested a figure of 2–3% for *meta*-nitration under all conditions[121]. Spryskov[122] gave a somewhat higher value of 4·5% but it is unlikely that the difference is significant.

d. Nitrosation. Phenol reacts with acidified solutions of sodium nitrite to form the *o*- and *p*-nitroso derivatives. The reaction has been studied in detail by Veibel[126]. He found that the main point of attack was *para* to the hydroxyl group. The proportion of *ortho*-compound in the product was about 6% at 0°, and rose to 10% at 40°. The kinetics of nitrosation have been studied by Suzawa and co-workers[127] but they were unable to identify the nitrosating agent.

2. Halogenation

In the halogenation of phenol, the tendency to high *ortho–para*-substitution ratios is much less marked than in nitration. Data on these particular ratios are not easily found in spite of the existence of a considerable body of published work on phenol halogenations[118]. Most mechanistic studies on phenol have been concerned with reaction rates determined by following the rate of disappearance of halogen. Isomer ratios have seldom been determined. However, from preparative halogenations, the following information can be drawn.

TABLE 13. Halogenation of phenol.

Halogen	*ortho*	*para*
Cl_2, CCl_4 [128]	74	26
Br_2, CCl_4 [129]	11·4	88·6
I_2, benzene[a] [130]	23	77

[a] In the iodine case, the reaction may be with the phenoxide ion[131], and the $+I$ effect of the O^- group should to some extent offset the depressing effect of the large halogen on *ortho*-substitution.

It would appear that some participation by the hydroxyl group is likely because the corresponding data for anisole ($o:p = 21:79$ for chlorination and 2:98 for bromination)[132] show a much stronger tendency for anisole to be attacked in the *para*-position. In addition, chlorination of phenol in methanol at 0–5° has been stated to give

o-chlorophenol[133]. Both the higher overall reactivity of phenol as compared with anisole, and the greater proportion of *ortho*-isomer formed, would be consistent with a greater concentration of negative charge on the phenolic oxygen. Norman and Harvey[128] have reported on the chlorination of phenol using Bu^{t}OCl. They conclude that in acidic or neutral solutions the halogenating agent is Cl^+ and that in base the reactive species is HOCl. Comparative figures are given in Table 14.

TABLE 14. Chlorination of phenol in different systems[128].

	System	*ortho*	*para*
(1)	*t*-BuOCl, CCl_4	51	49
(2)	Cl_2, CCl_4	74	26
(3)	*t*-BuOCl, H_2SO_4	50·8	49·2
(4)	Cl_2, PhOH (molten)[a], 60°	39·5	60·5
(5)	Cl^+, H_2O	51·4	48·6

[a] Bing and co-workers[134] report an *ortho–para* ratio of 37 : 63 for this system.

Systems (1) and (3) are those that appear to involve attack on the phenol by Cl^+. Presumably in the case of (1) the phenol is sufficiently acidic to generate this species. To account for the difference in *ortho–para* ratio between (2) and (4), Norman and Harvey assumed that in (2) hydrogen-bonding involved molecular chlorine, while in (4) the hydrogen bonds were between phenol molecules.

The same authors have also measured *ortho–para* ratios for the chlorination of phenoxide ion under various conditions[128]. The attacking reagent is probably HOCl in every case, and the experimental results are as follows.

TABLE 15. Chlorination of phenoxide ion in different systems[128].

	System	*ortho*	*para*
(6)	*t*-BuOCl, 4N NaOH, 25°	78·9	21·1
(7)	HOCl, H_2O, 25°	80·7	19·3
(8)	*t*-BuOCl, 15N NaOH, 50°	78·9	21·1
(9)	*t*-BuOCl, 15N KOH, 50°	81·3	18·7
(10)	*t*-BuOCl, 3·5N $HNMe_3^+OH^-$, 25°	63	37

There are three possible causes of the high percentage of *ortho* attack: (a) the high electron density in the vicinity of the O^- group,

(b) interaction between HOCl and the O^- group, (c) coordination involving the HOCl, O^- and M^+ functions (cf Lederer–Manasse reaction). Suggestion (c) would seem to be the most probable.

Chlorination of phenol using sulphuryl chloride has been studied[135]. In nitrobenzene, nitromethane, ether, and in the absence of solvent the reaction has been found to lead to *ortho–para* ratios of around 70 : 30.

3. Sulphonation[136]

Phenol is sulphonated in the *ortho-* and *para*-positions. In all investigations there have been analytical difficulties but it is clear that the site of attack is temperature-dependent, the *ortho*-product being favoured at low temperatures, and the *para*-product at high temperatures. Obermiller[137] noted that the proportion of *ortho*-product was less than 40% even at low temperatures (0–5°), while Muramoto[138] estimated that the amount of *ortho*-product changed from 39% at 20° to 4% at 100°. Olsen and Goldstein[139] have also studied the reaction. Table 16 is based on the work of Chase and McKeown[140].

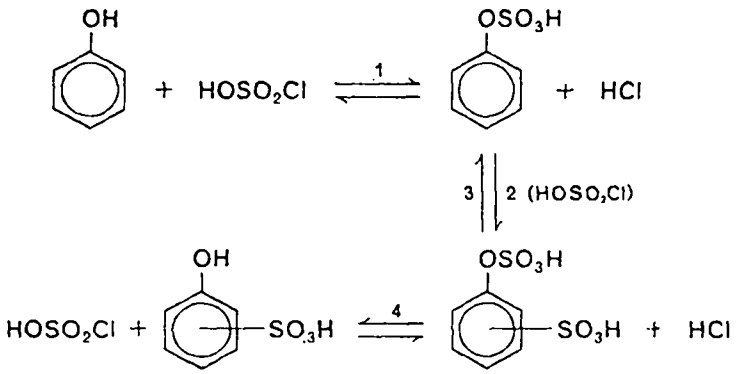
TABLE 16. Temperature dependence in the sulphonation of phenol.

T (°C)	*ortho* : *para* (20% oleum)	*ortho* : *para* (98% H_2SO_4)
20	42 : 58	49 : 51
30	—	41 : 59
40	37·5 : 62·5	35 : 65
50	35·5 : 64·5	—
60	34 : 66	33 : 67
70	27 : 73	25 : 75
80	18 : 82	14·5 : 85·5
100	12 : 88	9·5 : 90·5
120	9 : 91	11 : 89
140	—	10·5 : 89·5

Changes in the *ortho–para* ratio with temperature for aromatic sulphonation have been attributed to (i) desulphonation of the sulphonic acid products, the rate of this process being dependent on the position of substitution, (ii) direct isomerization of the products—this has been demonstrated in some cases, (iii) variation in selectivity due to variations in the reactivity of the attacking species. In the case

of phenol (iii) can be excluded because it should result in a limiting *ortho* figure of 40% at high temperatures.

Spryskov has investigated the sulphonation of phenol, in dichloroethane between 0° and −40°, using chlorosulphonic acid[141]. He found that the variation in product composition was not large, and that *ortho*- and *para*-isomers were formed in approximately equal quantities, accompanied by about 2% of the 2,4-disulphonic acid. Typical *ortho–para* product ratios were 14·2 : 9·9 at −40° and 42·4 : 48·5 at 0°, the amount of unchanged phenol being very much larger at the lower temperature. When the solvent was changed to carbon disulphide, the product composition at −15° was 45·5% *ortho*, 48% *para* and 6·5% 2,4-disulphonic acid. By the use of labelled phenol he established the mechanism below for the reaction in dichloroethane:



The sulphate ester of the *ortho*-sulphonic acid cleaves much faster in the presence of hydrogen chloride (via path 3) and there is a tendency for the *ortho–para* ratio to decrease as the temperature is raised. In view of the present belief that it is the phenylsulphuric acid that is being sulphonated this reaction is not strictly comparable with the normal sulphonation of phenol. The reaction should be considered more akin to neighbouring group participation rather than illustrative of electronic effect of the hydroxyl group.

Since sulphonation is a reversible reaction and *m*-hydroxybenzenesulphonic acid is the most resistant to hydrolysis, equilibrium control of sulphonation should lead to the formation of the *meta*-product. This had never been isolated from low-temperature sulphonations but Spryskov was able to obtain, after prolonged sulphonation at higher temperatures, yields of the *meta*-isomer approaching 40%[142].

TABLE 17. Sulphonation of phenol with sulphuric acid.

T (°C)	Time (hours)	*ortho* (%)	*meta* (%)	*para* (%)
120	30	low	3·7	96
160	150	low	20·8	79
180	50	low	23·2	76
209	20	low	38·1	61

4. Diazonium coupling[143]

Arene diazonium salts will attack the aromatic nucleus of highly activated aromatic compounds such as phenols and amines, but only in basic solution. A kinetic investigation of the reaction with phenols showed that the reaction is second-order and that the rate-determining step involves either the diazonium cation and a phenoxide ion or a diazotate ion and a neutral phenol molecule[144]:

$$\frac{\mathrm{d(product)}}{\mathrm{d}t} = k(\mathrm{ArN_2^+})(\mathrm{ArO^-}) \text{ or } k(\mathrm{ArN_2O^-})(\mathrm{ArOH})$$

For aqueous solutions, the two expressions are kinetically indistinguishable. However, Pütter[145] made a careful study of the pH dependence of the rate of coupling in naphtholsulphonic acids. Using substrates which differed greatly from each other in the pK_a of the naphtholic hydroxyl group, he was able to show that for this case at least, the two reacting species are the diazonium cation and the naphthoxide ion. He excluded not only attack of the diazotate on the naphthol, but also attack of the diazonium cation on the naphthol. The result is not too surprising since diazonium cations, unless highly activated, do not attack aromatic ethers. Subsequently, semiquantitative experiments in 60–80% sulphuric acid have shown that under these conditions phenols are attacked but that such attack on the neutral molecule is slower (by a factor of 10^{10}) than reaction with the phenoxide ion[146].

Bamberger[147] determined the *ortho–para* product distribution for the reaction with phenol itself. He found that the product contained about 98% *para*-compound, with 1% of *ortho* and 1% of 2,4-disubstituted product. Most studies of *ortho–para* ratios have involved 1-naphthol derivatives, for which the *ortho–para* ratio is much nearer unity. In these cases the ratio has been shown to depend on the nature of the diazo component[148] and the reaction conditions.

Stamm and Zollinger's[149] results on the coupling reaction between the *o*-nitrobenzene diazonium ion and 1-hydroxynaphthalene-3-sulphonic acid are:

Buffer system	pH	$k_o \times 10^5$	$k_p \times 10^5$
0·05M NaOAc/0·05M AcOH	4·59	2·9	0·21
0·17M NaOAc/0·17M AcOH	4·61	3·6	0·37
0·50M NaOAc/0·50M AcOH	4·64	4·4	1·04
0·50M NaOAc/0·05M AcOH	5·60	4·2	0·88

k values are in l/mole sec.

The reaction was general base-catalysed at both *ortho-* and *para-*positions by external bases but extrapolation to zero buffer concentration revealed that the water-catalysed reaction at the *ortho-*position was much faster. This was attributed to the naphthoxide ion acting as a general base in removing a proton from the sigma-complex for *ortho* attack.

5. Friedel–Crafts alkylation*

In Friedel–Crafts alkylation an alkyl group is introduced into an aromatic substrate by means of a combination of an alkylating agent and a Lewis acid catalyst. The most commonly encountered alkylating agents are alkyl halides, alkenes and alcohols, although various other reagents (aldehydes, ketones, alkynes, inorganic esters, ethers, alkanes, mercaptans, sulphides, thiocyanates) have been used. Lewis acid catalysts used include $AlCl_3$, $FeCl_3$, BF_3, $SbCl_5$, $ZnCl_2$, $TiCl_4$. In addition, Brønsted–Lowry acids have been used—HF, H_2SO_4, H_3PO_4, etc. Acidic-oxide catalysts of the silica-oxide type, and cation exchange resins have also been used. Except for the case of alkylation with alcohols, only catalytic quantities of acids are needed. The order of catalytic activity for metal halides in the acetylation of toluene is[151]:

$$AlCl_3 > SbCl_5 > FeCl_3 > TeCl_2 > SnCl_4 > TiCl_4 > BiCl_3 > ZnCl_2$$

and a similar order would be expected for alkylation. For proton acids, the order appears to be[152]:

$$HF > H_2SO_4 > H_3PO_4$$

The order may change with the conditions. The choice of a catalyst

* Exhaustive reviews of this and other reactions of the Friedel–Crafts type are given in the treatise edited by G. A. Olah[150].

for a particular Friedel–Crafts alkylation is governed by the activities of substrate and alkylating agent, the solvent, reaction temperature, etc.

In the alkylation of phenols, the substrates are strongly nucleophilic. They can be alkylated under mild conditions but then ethers are often formed, i.e., *O*-alkylation occurs rather than *C*-alkylation. The major complication is reaction with the catalyst. With some catalysts, e.g., H_2SO_4, the nucleus is attacked but in most cases initial reaction is with the hydroxyl group. Consequently it is not surprising that *ortho–para* ratios vary widely with catalyst type and reaction conditions.

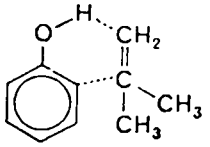
The measurement of *ortho–para* ratios for alkylation of phenols is often easy but the meaning of the results obtained is seldom clear. The major complicating factors are:

(1) Alkylation is reversible under normal reaction conditions and the kinetic and thermodynamic *ortho–para* ratios are invariably different.
(2) The introduction of an alkyl group activates the ring towards further substitution. Polyalkylation is difficult to prevent and, when it occurs, the *ortho–para* ratio loses its significance.
(3) A combination of (1) and (2) can lead to disproportionation of monoalkylated products.
(4) Ring alkylation can occur through intramolecular rearrangement of an intermediate ether. (Intermolecular rearrangement leading to the *para*-product is a dealkylation–realkylation reaction.)
(5) Ether formation can lead to abnormal results if substitution takes place in the ether and the product is subsequently *O*-dealkylated.

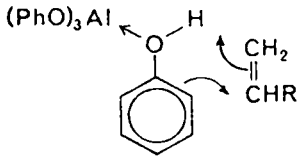
To all these factors must be added the modification of the electronic nature of the hydroxyl substituents by reaction with the catalyst (particularly Lewis acids). Interpretation of particular findings is, therefore, often difficult and unwise. Some practical generalizations can be made, of which the widest and the most obvious is that alkylation of phenol almost invariably occurs *ortho* or *para* to the hydroxyl group. There have been instances involving apparent *meta*-alkylation but they are very rare[153, 154].

a. Thermal alkylation using alkenes (no catalyst). Phenol can be alkylated by heating with alkenes to 320° under pressure[155]. Under these conditions the principal product is *ortho*. Direct alkylation of

the phenol via a cyclic transition state rather than a thermal Fries rearrangement has been suggested:



b. Catalytic alkylation using alkenes[156]. Although systematic investigations are rare the amount of available information is quite large. Conditions and catalysts may be altered to favour either *ortho-* or *para*-products. Briefly, results show that the *ortho*-isomer is the kinetically favoured product, with the *para*-isomer being thermodynamically the more stable[157]. Low concentrations of catalyst lead to the *ortho*-product, as do certain catalysts, particularly aluminium phenoxide[158]. With this catalyst, alkylation appears to involve the species $HAl(OPh)_4$ and a six-membered transition state:



Aluminium chloride reacts with phenol, and most reactions involving the use of $AlCl_3$ probably involve $Al(OPh)_3$ as the true catalyst. An interesting example of the effect of time on product composition has been reported by Buls and Miller[159] (Table 18).

TABLE 18. Reaction of isobutylene (4 moles) with phenol (1 mole) in the presence of aluminium chloride.

Time (hours)	Phenol (moles) recovered	Substituted phenols (moles)				
		2-	4-	2,4-	2,6-	2,4,6-
0	1·0	0·00	0·00	0·00	0·00	0·00
0·16	0·35	0·4	0·02	0·03	0·05	0·06
0·23	0·24	0·61	—	0·05	0·03	0·03
0·36	0·18	0·54	0·02	0·03	0·19	0·02
0·50	0·05	0·32	0·01	0·03	0·45	0·11
1·14	—	0·05	0·03	0·16	0·38	0·37
7·10	—	0·02	0·01	0·25	0·04	0·66

c. Catalytic alkylation using alkyl halides and alcohols. Apart from $AlCl_3$, the most commonly used catalyst for the alkylation of phenols

is $ZnCl_2$ [160]. This has the advantage of being strong enough to catalyse *C*-alkylation but weak enough to complex only loosely with the hydroxyl group. Strong Lewis acids such as $AlCl_3$ decrease the reactivity of the phenol by complexing with the hydroxyl group. In all cases substitution occurs mainly in the *para*-position.

6. Alkylation of phenoxides (no catalyst)

The phenoxide ion behaves as an ambident nucleophile towards reactive alkyl halides of the benzylic or allylic type and it undergoes both *O*- and *C*-alkylation. Kornblum[161] found that the relative importance of the two pathways depended mainly on the solvent, and, in protic solvents at least, selective solvation of the phenoxide ion appeared to favour *C*-alkylation. In homogeneous solution, the *C*-alkylation occurs at both the *ortho*- and *para*-positions. Kornblum obtained the results in Table 19. The attacking electrophile in these

TABLE 19. Alkylation of sodium phenoxide with allylic and benzylic halides[161].

Reaction conditions	*ortho* : *para* ratio
Allyl bromide/NaOPh/H_2O, 27°	35 : 65
Benzyl chloride/NaOPh/H_2O, 27°	38 : 62
Allyl bromide/NaOPh/PhOH, 43°	48 : 52
Benzyl chloride/NaOPh/PhOH, 43°	49 : 51
Benzyl chloride/NaOPh/CF_3CH_2OH, 27°	52 : 48

cases was considered to be the alkyl halide, and the possibility of a main reaction between the phenoxide ion and the derived carbonium ion was ruled out.

Under heterogeneous conditions, where reaction is believed to occur at the crystal surface, the *ortho*-isomer is the only *C*-alkylation product isolated[162].

7. Hydroxyalkylation: reaction with aldehydes and ketones

a. Baeyer reaction[163]. This refers to the reaction between phenol and ketones or aldehydes other than formaldehyde. Hydroxyalkyl derivatives are initially formed and sometimes react with other phenol molecules to form bis-arylalkanes under the reaction conditions. The general reaction requires the use of Friedel–Crafts catalysts, usually either $AlCl_3$ or anhydrous HCl/HOAc. Aldehydes other than formaldehyde usually react with phenol to form polymeric products

which decompose on heating to give alkylphenols[164, 165]. Ketones usually give bis-hydroxyarylalkanes directly[166]. In all the reported cases attack on phenol is at the *para*-position; if this is blocked, then *ortho* attack will occur. Yields are usually less than 50%.

b. Lederer–Manasse reaction[167]. This is the reaction of phenols with formaldehyde to form hydroxymethyl derivatives. The reaction takes place under acidic or alkaline conditions. Further reaction of the hydroxymethyl derivative often occurs to form dihydroxydiarylalkanes. The reaction goes with great ease even in the absence of catalysts. Resin formation, through polysubstitution and cross-condensation, is common. Under controlled conditions it is possible to examine the monohydroxyalkylation reaction. As expected, the *ortho*- and *para*-positions are the most susceptible to attack. The *ortho–para* ratio depends upon the reaction conditions and experimental findings indicate that attack on the *para*-position is favoured by polar solvents and acidic conditions, while attack on the *ortho*-position is favoured by nonpolar solvents, alkaline conditions and Group II metal oxide, hydroxide or acetate catalysts[167]. These conclusions may be rationalized by assuming that acid catalysis involves reaction of the hydroxymethylcarbonium ion ($^{+}CH_2OH$) with phenol and that nonpolar solvents encourage participation of the phenolic hydroxyl group in stabilizing the transition state for *ortho* attack.

Alkaline reaction involves attack by formaldehyde on the phenolate anion which is more *ortho*-directing than phenol. Highest yields of *ortho*-product occur in those cases where the greatest amount of ion-pairing between the metal ion and the phenoxide is to be expected. A mechanism involving some form of chelate is therefore likely (cf. aluminium phenoxide-catalysed alkylation). The solvent has a major effect (Table 20).

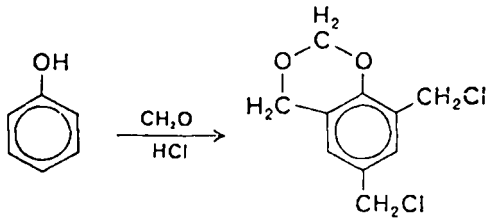
TABLE 20. Alkaline phenol–formaldehyde condensation[167].

Catalyst	Solvent	*ortho* : *para* ratio
NaOH	H_2O	65 : 35
$Mg(OH)_2$	H_2O	69 : 31
Et_3N	H_2O	55 : 45
Et_3N	C_2Cl_4	77 : 23
Et_3N	toluene	87 : 13

8. Haloalkylation[168]

Haloalkyl groups can be introduced directly into aromatic nuclei using methods similar to those for alkylation. By far the most common haloalkylation reaction is chloromethylation[168, 169]. This reaction is usually carried out with a mixture of formaldehyde (or one of its polymers) and hydrogen chloride in the presence of a Friedel–Crafts catalyst such as zinc chloride. Other haloalkylating agents include chloromethyl ether[170] or chloromethyl sulphide[171].

Phenols normally react so readily with HCHO/HCl that a catalyst is unnecessary, and even then monomeric products are difficult to obtain unless deactivating groups are present[172]. The usual product with phenol is a bicyclic methylene ether[173].



The mechanism of chloromethylation is not known with certainty, but in the case of the HCHO/HCl/phenol system there is evidence that the reaction involves initial hydroxymethylation (see Lederer–Manasse reaction) followed by replacement of hydroxyl by halogen[174].

9. Friedel–Crafts acylation[175]

Most of the general remarks on Friedel–Crafts alkylation also apply to acylation. The major difference is that acylation requires at least 1 mole of catalyst per mole of reagent because Lewis acids form complexes by coordination with the carbonyl oxygen of the acyl derivative. The most common acylating agents are acid halides and anhydrides, but ketones and carboxylic acids have also been used. The same problems of reversibility and kinetic versus thermodynamic control are encountered, and with phenols competing *O*-acylation also occurs. Acylation, like alkylation, occurs mainly *ortho* and *para* to the hydroxyl group. Since an acyl group is deactivating, acylation differs from alkylation in leading to far less polysubstitution and disproportionation. The *ortho–para* ratio is usually less than unity and depends mainly on the catalyst employed. The largest amount of *ortho*-product is obtained using aluminium chloride or polyphosphoric acid as catalyst. The *para–ortho* ratios for acetylation of phenol are PPA 3·2, $ZnCl_2$ 3·5, $AlCl_3$

4·6, $TiCl_4$ 6·3, BF_3 30 [176]. The ratio can also be influenced by solvent. For example, the octanoylation of phenol with $AlCl_3$ catalyst gives a *para–ortho* ratio of 0·24 in tetrachlorethane and 2·7 in nitrobenzene[176]. The use of phenoxyaluminium chloride as a reagent cum catalyst leads to approximately equal amounts of *ortho-* and *para-*product[177] (cf. aluminium phenoxide alkylation). An extensive series of tables covering acylation of phenols has been drawn up by Gore[178].

a. The Fries rearrangement[179]. Phenolic esters rearrange on heating with Friedel–Crafts catalysts to give *o-* and *p*-acylphenols. The mechanism has not been elucidated. The *para*-product is formed by an intermolecular deacylation–reacylation[180], but in the cases so far investigated, the *ortho*-product appears to form by an intramolecular reaction[180]. These are therefore independent reactions and competitive processes. This should be reflected in a changing *ortho–para* ratio with change in reaction conditions. In general, yields of *ortho*-product are greater at higher temperatures. *Para*-substitution is facilitated by the use of polar solvents and by the presence of hydrochloric acid[181]. It is possible that the *para*-Fries rearrangement is a simple Friedel–Crafts acylation process, while the *ortho*-Fries is a true rearrangement.

10. Formylation

a. Gattermann–Koch reaction[182]. Many aromatic compounds can be successfully formylated by a mixture of carbon monoxide and hydrogen chloride in the presence of aluminium chloride. Normally high pressures are required but with added cuprous chloride, which appears to act as a carrier, the reaction proceeds at atmospheric pressure. Generally, phenols and phenol ethers cannot be formylated by this latter and more common method. This was attributed by Gattermann to insolubility of cuprous chloride in the system, but this explanation has since been challenged[183]. The only hydroxyl compound successfully formylated under Gattermann–Koch conditions is 3-hydroxyretene, which is said to give a mixture of aldehydes in good yield[184]. Formyl derivatives of phenols are usually prepared by a closely related reaction, the Gattermann aldehyde synthesis.

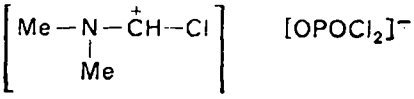
b. Gattermann aldehyde synthesis[185, 186]. The Gattermann aldehyde synthesis in its original form was the reaction of a mixture of HCN and HCl with an aromatic substrate in the presence of $AlCl_3$ or $ZnCl_2$. A later modification[187] removed the necessity for working with large amounts of HCN by passing HCl into $Zn(CN)_2$ to gener-

ate the required mixture. The reaction is most satisfactory for strongly activated aromatic compounds such as phenols and ethers.

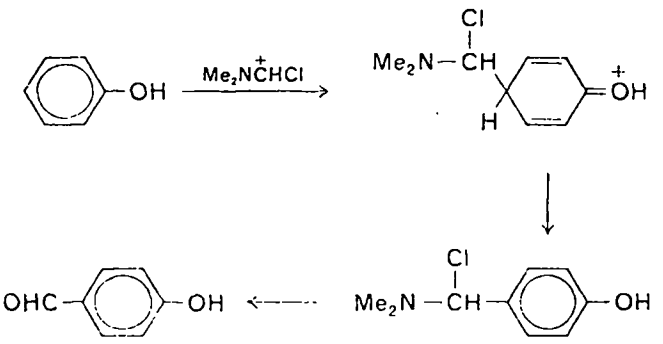
Monohydric phenols usually require $AlCl_3$ as the catalyst. The yields vary with the structure of the phenol. Phenol itself is formylated in 30% yield, entirely in the *para*-position[188]. In general, only one formyl group is introduced and it always enters *para* to the phenolic hydroxyl group if that position is unoccupied. If the *para*-position is blocked, the reaction may not proceed at all or it may give a poor yield of the *ortho*-product. An exception is 2-naphthol, which gives good yield of 2-hydroxyl-1-naphthaldehyde[189], but there are cases in which even replacement of a *para*-substituent is preferred to *ortho* attack[190].

The nature of the attacking electrophile is not known, but an isolable nitrogen-containing intermediate is formed and may be hydrolysed to the aldehyde. Possibly this is the imino-hydrochloride $ArCH{=}NH_2{}^+Cl^-$. The Gattermann reaction may be regarded as a special case of the Houben–Hoesch reaction (see later).

c. Vilsmeier reaction[191, 192]. This is currently the most common method for the formylation of aromatic rings. The formylating agent is a mixture of a substituted amide (usually dimethylformamide or *N*-methylformanilide) and phosphorus oxychloride. It is only applicable to substrates such as amines, phenols and certain aromatic hydrocarbons and heterocycles that are highly activated. It is closely related to both the Gattermann synthesis and Friedel–Crafts acylations. The attacking species (for the case of *N,N*-dimethylformamide) is believed to be[193]



and the assumed mechanism (in the case of phenol) is



Like the Gattermann synthesis, reaction with phenols occurs at the *para*-position if this is free. If it is blocked, then *ortho* attack will occur[194]. Phenol reacts with $DMF/POCl_3$ to give an 85% yield of the *p*-hydroxybenzaldehyde[195]. No *ortho*-product has been reported but, as was the case with the Gattermann synthesis, no serious attempt has apparently been made to obtain it.

d. Reaction with dichloromethyl ether. Dichloromethyl ethers, e.g., CH_3OCHCl_2, in the presence of Lewis acids, react with aromatic compounds to form α-alkoxybenzyl chlorides which decompose, either on heating or on the addition of water, to form aldehydes[196].

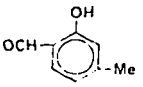
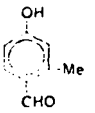
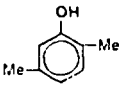
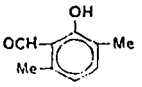
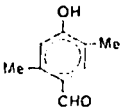
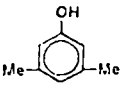
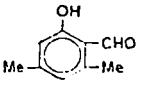
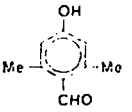
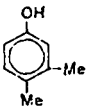
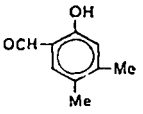
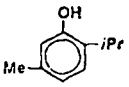
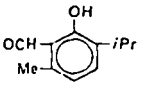
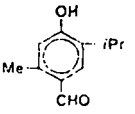
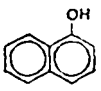
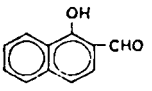
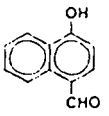
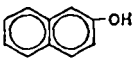
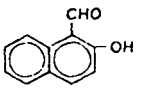
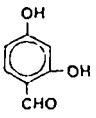
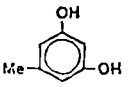
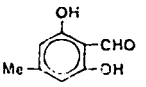
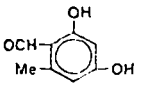
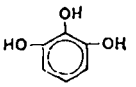
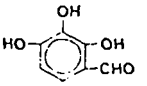
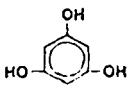
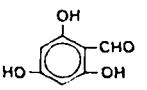
$$ArH \xrightarrow[\text{F.C. catalyst}]{HCCl_2OR} Ar-\underset{\displaystyle OR}{\overset{\displaystyle Cl}{\underset{|}{\overset{|}{CH}}}} \xrightarrow[\text{or } H_2O]{\text{heat}} Ar-CHO$$

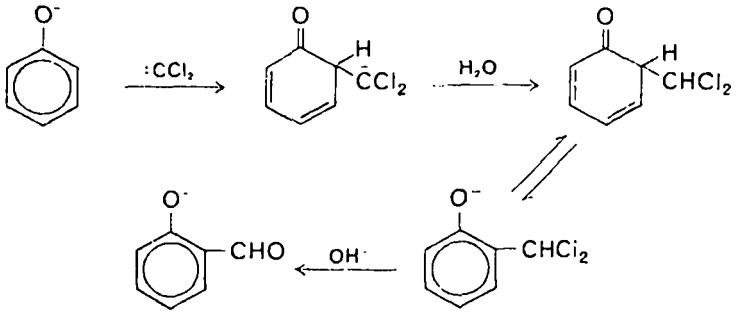
The catalysts most frequently used are $TiCl_4$, $SnCl_4$, $SnBr_4$ and $AlCl_3$. The reaction is closely related to Friedel–Crafts alkylation and acylation and also to formylation by trialkyl orthoformates (see below). No data are reported for formylation of phenol, but a number of substituted phenols have been formylated, often in good yields[197] (Table 21). The tabulated figures indicate that *ortho*-substitution is more important than in most other formylation reactions involving electrophilic substitution (see, however, the Reimer–Tiemann reaction).

e. Reaction with trialkyl orthoformates. Gross and co-workers have reported a direct aldehyde synthesis using trialkyl orthoformates in the presence of aluminium chloride[197]. Using this method, phenol aldehydes were obtained in good yield. This reaction, although similar in many ways to formylation using dichloromethyl methyl ether, gives far less *ortho*-product, which is in keeping with a much greater steric requirement for the attacking group.

f. The Reimer–Tiemann reaction. Phenols (as phenoxide ion) and certain highly reactive heterocyclic compounds may be formylated by reaction with chloroform in the presence of alkali[198]. The reactive electrophile is believed to be dichlorocarbene. Although this species is neutral its carbon is highly electron-deficient. The proposed mechanism is as shown on p. 438. Both *ortho*- and *para*-products are formed. Yields of the mixed aldehydes are usually less than 50%. The main product is usually the *ortho*-isomer but the *ortho–para* ratio varies quite considerably with the reaction conditions. Experimental results all indicate, however, that *ortho* attack is favoured over *para* (this is usual for electrophilic attack on the phenoxide ion) but that

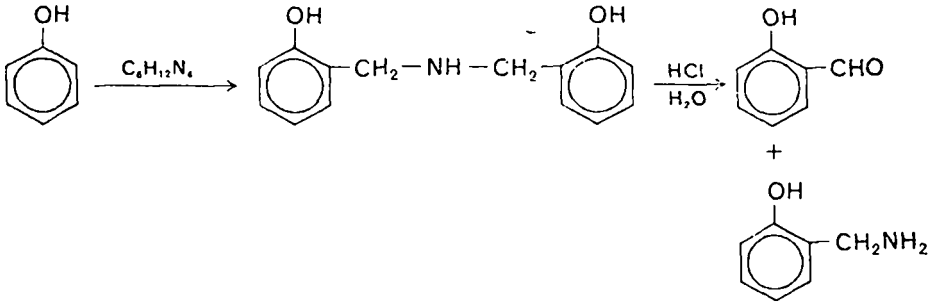
TABLE 21. Alkylation with dichloromethyl ether : $TiCl_4$.

Phenol	Yield (total %)	Products		*ortho* : *para* ratio
	52%			77 : 23
	60%			33 : 67
	84%			82 : 18
	61%			—
	77%			53 : 47
	78%			13 : 87
	82%			—
	68%			—
	48%			40 : 60
	52%			—
	36%			—



para attack can be made more favourable by hindering the *ortho*-position by introducing large cations which complex with the O^- group[199].

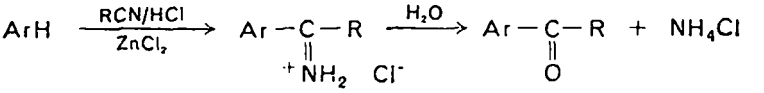
g. The Duff reaction. Hexamethylenetetramine will condense with phenols to form intermediate products which, on acid hydrolysis, give hydroxy aldehydes[200]:



Attack on phenol occurs at the *ortho*-position, but the yields are even lower than those of the Reimer–Tiemann reaction.

11. Houben–Hoesch ketone synthesis[201]

This ketone synthesis is a variation of the Gattermann synthesis of aldehydes. The reaction is one between a phenol and a nitrile in the presence of hydrogen chloride (and sometimes a Lewis acid such as $ZnCl_2$) to form a ketimine hydrochloride, which readily hydrolyses to give a ketone.



The precise nature of the attacking electrophile is not known but it is believed to be a complex of $R{-}C^+{=}NH$ with HCl. Phenol itself does not undergo nuclear acylation with most nitriles; it forms instead the hydrochloride of an iminophenyl ester[202]. An exception is

the reaction of phenol with trichloroacetonitrile in the presence of aluminium chloride to give a 95% yield of ω-trichloro-4-hydroxyacetophenone[203]. The formation of the *para*-product is consistent with the *para*-directing effect of the hydroxyl substituent in the Gattermann aldehyde synthesis. It is possible that this product is formed by a Fries rearrangement of the imino ester but independent rearrangement of such esters has not been achieved.

12. Carboxylation

a. Kolbe–Schmitt reaction[204]. From the middle of the nineteenth century this reaction has been used for the preparation of aromatic hydroxy acids. The reaction is between the dry metal phenoxide and carbon dioxide and normally is carried out at 120–130° under pressure.

It is usually assumed that reaction occurs through attack on the electron-rich ring of the phenoxide ion by the electrophilic carbon of the CO_2 molecule. In general, substitution occurs *ortho* to the hydroxyl group but cases of *para*-substitution are known. The *ortho–para* ratio for phenol is strongly dependent on the nature of the metal ion in the phenoxide as well as on reaction conditions such as temperature, reaction time, etc. With different alkali metal phenoxides, the proportion of *ortho*-product diminishes in the order Na > K > Cs[205]. The substitution is apparently reversible and *ortho–para* migration occurs at higher temperatures[206]. It would seem therefore that there is probably association between the phenoxide oxygen and the metal ion and that *ortho*-substitution may go through a cyclic transition state involving CO_2, the phenoxide oxygen and (perhaps) the metal ion (cf. aluminium phenoxide alkylations).

13. Other electrophilic substitutions

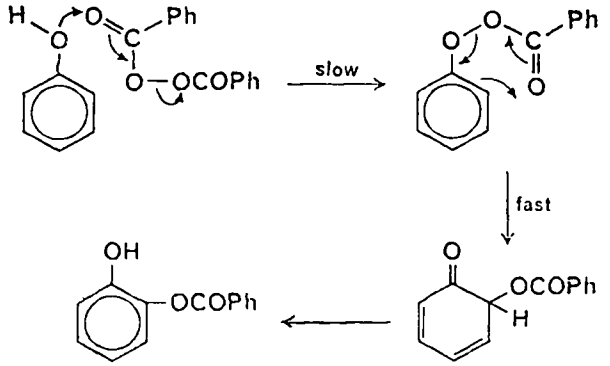
a. Hydrogen exchange in aromatic systems under acidic conditions is an electrophilic substitution. It has been established that three nuclear hydrogens are readily exchanged in phenol under these conditions and that these are at the *ortho*- and *para*-positions[207]. The *ortho*- and *para*-hydrogens in phenol are also rapidly exchanged in alkaline solution; in these circumstances the attacking species is thought to be a Brønsted acid, and the substrate the highly activated phenoxide ion[208]. The relative reactivities of the *ortho*- and *para*-positions have not been measured but for anisole an *ortho–para* ratio of 29·5 : 70·5 is indicated[209]. It is unlikely that the figure for phenol would be lower than this.

b. Mercuration of aromatic compounds has been shown to occur through

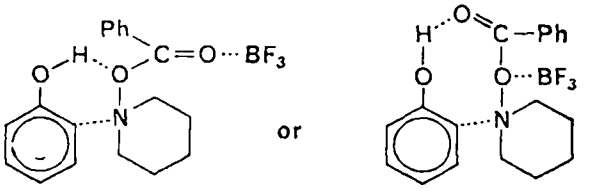
either a radical or electrophilic mechanism. The electrophilic mechanism is favoured by the presence of acids, while in nonpolar solvents the homolytic path is often followed[210]. For highly reactive aromatics such as phenol, however, the electrophilic path is likely to be the more important under all conditions.

An accurate *ortho–para* ratio for the mercuration of phenol is not available. A preparative procedure for *o*-chloromercuri-phenol via the acetate[211] leads to an isolated yield of the *ortho*-isomer of up to 44% with an amount of the *para*-product which is substantially lower. In contrast, mercuration of anisole at 25° in acetic acid leads to an *o–p* ratio of only 14:86 [212]. The considerable difference between phenol and anisole can be attributed to participation of the hydroxyl group and/or preferential reaction of the mercurating species with phenoxide ion—the system would not be strongly acidic under the reaction conditions.

c. Hydroxylation of aromatic systems may be either a homolytic or electrophilic substitution, but, even in homolytic substitution, the attacking species is likely to be sufficiently electrophilic to prefer the normal substitution pattern, i.e. for phenol, *ortho* and *para* to the hydroxyl group. The most common hydroxylating agents are acidified hydrogen peroxide or solutions of peracids. Hydroxylation of phenols is usually accompanied by oxidation of the product to *ortho*- and *para*-quinones[213]. Phenol on treatment with peracetic acid gives a mixture of benzoquinone (40%) and a muconic acid (35%), indicating an *ortho–para* ratio around unity for initial attack[213]. Diacyl peroxides are also effective hydroxylating (or acyloxylating) agents and have been reported to attack phenols mainly in an *ortho*-position if this is free[214]. There is a large negative entropy of activation and a cyclic mechanism rather similar to that proposed for the Claisen rearrangement has been proposed:



In a similar reaction, *N*-benzoyloxypiperidine was found to react with phenol in the presence of boron trifluoride to give *N*-(*o*-hydroxyphenyl)piperidine. A cyclic mechanism was also proposed[215], the key intermediate structure being one of the following:



C. Comparative Directing Power of the Hydroxyl Group

If the σ^+ values of Brown and Okamoto[6] apply reasonably well to electrophilic substitution reactions then the order of relative *ortho–para* directing powers are:

NMe_2, −1·7; NH_2, −1·3; OH, −0·92;
OMe, −0·78; CH_3, −0·31.

In view of the high rho values (>5) normally encountered in electrophilic aromatic substitutions the expected rate differences found between the hydroxyl group and amino groups should be at least 100-fold and the hydroxyl substituent should in turn be at least five times as activating as methoxyl. It is to be expected, then, that in systems containing the hydroxyl group and any of the other substituents, electrophilic substitution would be dominated by the more reactive of them. This is the usual observation. As examples, the bromination of *p*-aminophenol ($Br_2/CHCl_3$) gives 3,5-dibromo-4-aminophenol[216], and the nitration of *p*-hydroxyacetanilide gives 4-hydroxy-3-nitroacetanilide[216]. However, electrophilic substitutions are often carried out under strongly acidic conditions, with accompanying protonation of amino groups, which then become deactivating. Thus, sulphonation of *o*-aminophenol results in attack *para* to the hydroxyl group[217] and sulphonation of *p*-aminophenol occurs *ortho* to the hydroxyl group[218].

Chuchani and co-workers have observed an interesting case where the directing power of the phenolic hydroxyl group is, at first sight, more influential than its activating power[219]. They examined the kinetics of tritylation of a series of *ortho*-substituted phenols and obtained the results below (Table 22). Although the *o*-isopropoxyphenol (and in some cases the *o*-ethoxy compound also) can react more rapidly than catechol the only product of the reaction is that resulting from attack of the trityl cation *para* to the hydroxyl group.

TABLE 22. Relative rates of tritylation of o-$C_6H_4(OH)$ (X) with $Ph_3C^+ClO_4^-$ in nitromethane.

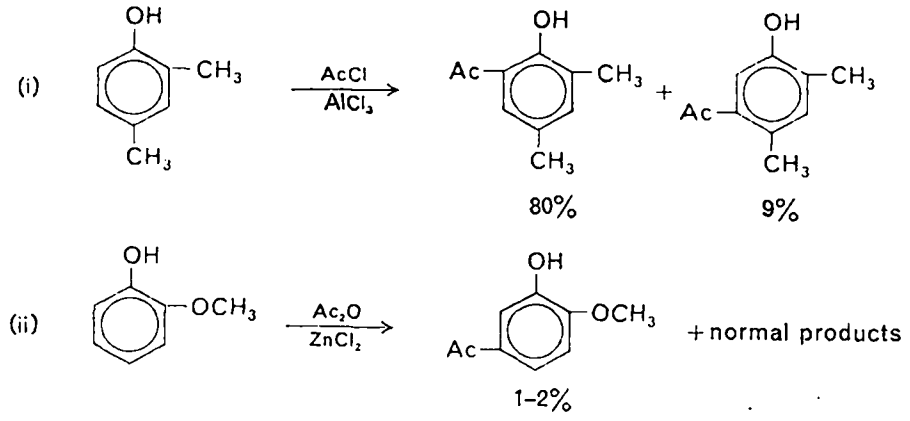
X	T =	30°	40°	50°	60°
H		46	41	45	49
OH		148	144	130	125
OMe		100	100	100	100
OEt		129	116	141	134
OPr-i		166	134	140	—

Chuchani attributed this to hydrogen-bonding between the hydroxyl group and the alkoxyl-oxygen. The activating power of the hydroxyl group would thereby be increased, and the strength of the hydrogen bond would presumably increase with the electron-donating power of the alkyl group. In monosubstituted benzene derivatives, such internal hydrogen-bonding is not possible, but the observed reactivity order is still not simple.

$$\text{OPr-}i > \text{OH} > \text{OEt} > \text{OMe}$$

Here, it was assumed, the hydroxyl group is hydrogen-bonded to the solvent. There is support for this explanation in the work of Campbell and co-workers[135] who noted that chlorination of o-cresol in carbon tetrachloride gives 50% of the 6-isomer, while in ether only 15% is formed. However, de la Mare has offered much evidence for hyperconjugation of the hydroxyl group in phenol and enhanced reactivity can be accounted for on this basis[93].

In spite of the demonstrated, very high o,p-directing power of the phenolic hydroxyl group, there are cases in which *meta* reaction products are isolable[220, 221], e.g.,



Each of these reactions was being carried out under conditions which could lead to *O*-acetylation, and it is possible that some *C*-acylation of the *O*-acetyl derivatives is followed by hydrolysis of the acetate side-chain.

D. Rates of Electrophilic Aromatic Substitution

The rate of an electrophilic aromatic substitution reaction can be expressed either as the rate of introduction of the attacking electrophile into the aromatic nucleus, regardless of the position taken, or else as the rate of attack at a specific site in the molecule. Most recorded rate measurements for electrophilic substitution in phenol are overall rates, and the most commonly studied reactions are nitration and halogenation. Direct experimental comparison of phenol and benzene rates, to give the relative activating power of the phenolic hydroxyl group, is impracticable because the difference in reactivity is always great and may be as high as 10^{10}–10^{12}.

Comparisons with other activating groups have, however, been made[222, 223]. Most of these have been based on competition experiments, involving either two aromatic substrates or else one aromatic substrate with two functional groups[219, 224] (see preceding section). All of these studies are in agreement and suggest that the order of activating power of the common strongly activating groups is

$$NMe_2 > NHMe > NH_2 > OH > OMe > Me$$

Alkyl-substituted amino groups, it will be noted, are more activating than the amino group itself, whereas the methoxyl group is less activating than the hydroxyl group. This finding may well be related to de la Mare's observation[93] that in the halogenation of phenol O–H bond breaking is involved in the rate-determining step. If so, the N–H bond is presumably too strong in amines for a similar reaction path to be involved.

Direct comparisons of phenoxide ion with other substrates have not been made but it is generally assumed that the oxide ion group is a very strongly activating substituent, stronger even than NR_2. Bell and Ramsden have estimated that *N,N*-dimethylaniline are about 10^{16}–10^{17} times as reactive as benzene in aqueous solution[225]. For the dimethyl compound at 25° they found a second-order rate constant of almost 10^9 l/mole sec. In a subsequent paper Bell and Rawlinson[226] reported that bromination of both the *p*-bromophenoxide and *m*-nitrophenoxide ions gave second-order rate constants around 10^9 l/mole sec, and that for the more active, unsubstituted

phenoxide ion, the rate could not be measured. Halogenation of aryloxides has, in fact, been stated as often occurring 'at about the encounter rate' in aqueous solution[227].

The most comprehensive description of reaction rate for aromatic substitution is in terms of partial rate factors. These represent the rate of substitution at a given position in the ring relative to that at one of the six positions in benzene. That is, for phenol.

$$f_{ortho} = \frac{k_{ortho}}{2} \Big/ \frac{k_{benzene}}{6}$$

$$f_{meta} = \frac{k_{meta}}{2} \Big/ \frac{k_{benzene}}{6}$$

$$f_{para} = k_{para} \Big/ \frac{k_{benzene}}{6}$$

A very large number of partial rate factors covering a wide variety of reactions have been calculated[228]. However, for phenol only three reactions have been examined in this way and even then, partial rate factors were obtained only for the *para*-position. The three reactions are (54), (55) and (56) in Table 7 (section III.A.2). Only one of these reactions (56), bromination in acetic acid at 25°, is a 'normal' electrophilic substitution; the other two involve replacement of groups other than hydrogen. The calculated partial rate factors are given below.

Reaction	f_{para}
Protodetriethylgermylation, $HClO_4$, CH_3OH–H_2O, 50°	$2{\cdot}73 \times 10^3$
Protodetrimethylsilylation, $HClO_4$, CH_3OH–H_2O, 51°	$1{\cdot}07 \times 10^4$
Bromination, CH_3CO_2H, 25°	$3{\cdot}7 \times 10^{12}$

The value of f_p for the bromination reaction was based on an assumed 100% attack at the *para*-position. On the basis of the measured *ortho–para* ratio for this system[93] the value of f_o should be about 2·5–3% of this figure. Illuminati[114] has estimated σ_m^+ for the hydroxyl group to be −0·133 for bromination in acetic acid and on this basis, f_m should be about 50. However, Illuminati's figure comes from work on mesitylene derivatives, in which a steric factor could well operate.

E. Nucleophilic Aromatic Substitution

Nucleophilic aromatic substitution does not take place very readily unless the substrate is activated by strong $-R$ or $-I$ groups in the aromatic nucleus. Most substitutions of this type actually occur

under basic conditions (cf. nucleophilic aliphatic substitution) and if an aromatic hydroxyl is present it is normally there as the O^- group. This group is strongly $+I$, $+R$, and therefore has a marked tendency to deactivate the system. This is apparent from the study of Berliner[98] on the reaction of 4-*X*-2-nitrobromobenzenes (section III.A.4) where the O^- group was found to have a $\bar{\sigma}_p$ value of about $-0{\cdot}8$. In this study the O^- group proved to be less deactivating than $-NH_2$. A similar order has been found for the reaction of *m*-substituted chlorobenzenes with sodium methoxide at 150° [229]. Here the activation order for substituents was $NO_2 > H > O^- > NH_2$. However, for the reaction of *p*-substituted chlorobenzenes under the same conditions, differences between the deactivating groups were less significant[229]. In this study, the activation order proved to be $NO_2 > Cl > H > NH_2 > CH_3 > m\text{-}O^-$. Other work on related dichloro compounds[230] confirms the CH_3 group as less deactivating than the O^- group. Clark and co-workers[231] give the following figures (Table 23) for the extent of halide ion liberated from

TABLE 23. Extent of reaction of ArCl with sodium methoxide after 50–60 hours at 155°.

X	[OMe⁻]	[Cl⁻] (% yield)
H	2·0	4
H	2·5	7
2-O⁻	2·0	0·0
3-O⁻	2·0	12
4-O⁻	2·0	0·0

chlorobenzene and the three monochlorophenols on heating with NaOMe. From these results, the *m*-O^- substituent would appear to act as an activating substituent and this surprising result requires corroborative evidence.

Miller and co-workers[232] have measured rates for the reaction of a number of 5-substituted 1-chloro-2,4-dinitrobenzenes, and have derived from this a $\bar{\sigma}_m$ for the O^- group of $-1{\cdot}358$. The very high value obtained here, compared with that of Berliner for $\bar{\sigma}_p$ value in reaction (61) ($\sim -0{\cdot}8$)[98], may result from the combination of a rather low $+I$ effect on the reaction site, and a very high $+R$ effect operating on the two nitro groups and thereby reducing their activating effect.

Polyfluoro compounds of the type C_6F_5X are attacked to varying degrees (depending on the nature of X) by strong nucleophiles, with the displacement of fluoride ion[233]. If X has no powerful electronic effect, the fluorine *para* to the substituent is displaced. Strongly electron-releasing substituents react much more slowly and there is an increasing tendency for a fluorine *meta* to the substituent to be displaced. Reaction with potassium hydroxide in *t*-butyl alcohol at 170° converts pentafluorophenol into tetrafluororesorcinol. Pentafluorophenol, in which the activating group is the oxide ion, is the least reactive of all compounds investigated.

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The Chemistry of The Hydroxyl Group: Part 1
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CHAPTER 9

Electrophilic attacks on the hydroxyl group

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I. INTRODUCTION

The problems involved in electrophilic attacks on the hydroxyl group are, in the last analysis, one aspect of the more fundamental problem about the underlying pattern of structural factors which determine the mutual reactivities of different electron-donor and electron-acceptor molecules. It is, therefore, quite natural that the reactions like, e.g., acylations, in which the hydroxyl group in an organic molecule becomes the primary site of the attack, have several counterparts in the chemistry of other functional groups.

Some characteristics of the hydroxyl group, made evident from its reactions with electrophiles, require especial attention to be drawn to them. In the first place, the hydroxyl group possesses only relatively moderate nucleophilic properties, that is, as a functional group of a Lewis base it is of an intermediate strength (section II.A). In terms of the concept of hard and soft acids and bases, this implies that the hydroxyl group is moderately reactive with Lewis acids of widely varying strengths. In fact, the spectrum of reactions involving the hydroxyl group as the electron donor seems to be extraordinarily wide in respect of the nature of the electrophile. In the second place, the influence of the structure of the alcohol upon the facility of the attack is normally very material. Apart from the steric factors involved, this can be attributed to the fact that the transmission of electronic effects from the remnant of the molecule through the C–O bond is facilitated by the similar sizes of the valence orbitals in the carbon and oxygen atoms, both being second-row elements.

The experimental material on various kinds of electrophilic attacks on the hydroxyl group is both diffuse and rich, and many extensive review articles and monographs on special topics have been published. Therefore, a rather drastic limitation in the scope of the present chapter seemed unavoidable. While some representative older results were included, the main part of the material dealt with elsewhere was simply omitted, making, wherever possible, citations to the pertinent literature. Primary attention was focused on relatively recent work covering mechanistically and practically impor-

tant aspects of the function of the hydroxyl group as the nucleophilic partner in various reactions.

II. ALKYLATION. CARBON ATOM AS THE ELECTROPHILIC CENTRE

A. Nucleophilic Reactivity of the Hydroxyl Group

The nucleophilic reactivity of the hydroxyl group towards carbon can be illustrated by comparing the formation of ethers from alkyl halides and alcohols (equation 1) with the reactions of alkyl halides

$$ROH + RX \longrightarrow ROR + HX \qquad (1)$$

with other nucleophiles. The relative rates of methyl iodide with methanol and some other nucleophiles are shown in Table 1. The data confirm conclusively that the proton basicity of the nucleophile is not the sole factor influencing its attacking capability; all the nucleophiles listed in Table 1 react more rapidly than methanol, notwithstanding the fact that many of them are less basic than methanol.

TABLE 1. Relative rates for the electrophilic attack of methyl iodide on the hydroxyl group and on various other nucleophiles[1, 2]. Temperature 25°C, methanol solution.

Nucleophile N	$\log (k_N/k_{MeOH})$	pK_a (in water)
MeOH	0·0	−1·7[a]
Cl^-	4·4	−7
Me_2S	5·3	−5·3
PhO^-	5·8	9·9
Br^-	5·8	−9
MeO^-	6·3	16
CN^-	6·7	9·1
Et_3As	7·1	2
I^-	7·4	−9·5
Et_3P	8·7	8·9
PhS^-	9·9	6·5

[a] Deno and Turner[3] have obtained a pK_a value of −2·5.

Another important factor affecting the reactivity of an alcohol towards electrophiles is the polarizability of the hydroxyl group. Normally, the oxygen atoms in hydroxyl groups are of moderately low polarizability. In terms of the concept of hard and soft acids and

bases, advocated by Pearson[1, 4, 5], this implies that alcohols are Lewis bases of an intermediate hardness. In the reactions between Lewis acids and bases hard bases have the strongest tendency to react with hard acids, and, correspondingly, soft acids with soft bases.

An existence of 'symbiotic effects' in nucleophilic displacement reactions has been suggested[2, 6]; a grouping of either several hard bases or soft bases around the central carbon atom will stabilize the transition state and thus increase the reaction rate. The relative rate coefficients shown in Table 2 illustrate this point. In these reactions the tosylate ion is a hard Lewis base and the iodide ion a soft base.

TABLE 2. Attack of MeOTs and MeI on the hydroxyl group and on various other nucleophiles[2, 6]. Relative rate coefficients are in methanol solution at 25°C.

Nucleophile and its classification		k_{OTs}/k_I
MeOH	hard	210
MeO^-	hard	4·6
Cl^-	hard	2·8
PhS^-	soft	0·13
$SeCN^-$	soft	0·23
I^-	soft	0·13
Ph_3P	soft	0·18

The decrease of the ratio k_{OTs}/k_I with increasing softness of the attacking nucleophile can be rationalized in this way.

The factors influencing the reactivity of alcohols have also been represented by equation (2), proposed by Edwards[7, 8]. Here a and b are constants, E is the susceptibility of the alcohol to an electrophilic attack, P is the polarizability factor of the alcohol in question and H is a factor depending on the basicity of the oxygen atom. In short, according to equation (2), the sole factors determining the

$$E = a\,P + b\,H \qquad (2)$$

reactivities of alcohols would be their proton basicities and polarizabilities. This, of course, must be a very crude simplification.

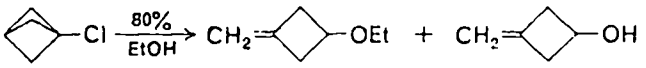
One obvious reason for the inadequacy of simplifications like equation (2) is that, in a series of formally similar compounds, the reaction mechanism may change when going from one compound to another. The data in Table 3 illustrate this point. The ratio of the alcoholysis rates of ROTs and RBr increase greatly in the sequence Me < Et < *i*-Pr < *t*-Bu. It has been assumed that this indicates

TABLE 3. Attacks of ROTs and RBr on the hydroxyl group. Relative rate coefficients are in ethanol at 25°C.

Nucleophile	R	k_{OTs}/k_{Br}	Mechanism	Reference
EtOH	Me	16	S_N2	9, 10
EtOH	Et	15	S_N2	9, 10
EtOH	*i*-Pr	73		9, 10
EtOH	*t*-Bu	>4000	S_N1	11, 12

an increasing charge separation between the alkyl group and the leaving group in the transition state[11]. The deuterium isotope effect on the solvolysis of *t*-butyl-d_9 chloride has been studied in various solvents[13–15]; the independence of the isotope effect of the solvent shows that there is only a weak covalent interaction between the solvent and the *t*-butyl group at the transition state. So the study of the deuterium isotope effect confirms the accepted view that the alcoholysis of *t*-butyl chloride occurs by the S_N1 mechanism; thus, differing from primary halides, the attacking electrophile is in this case a carbonium ion. The data in Table 3 point out that the alcoholyses of isopropyl tosylate and isopropyl bromide may also have some S_N1 character.

It is interesting to note in this context that bicyclic bridgehead halides are solvolysed slower than the corresponding *t*-butyl halides by several powers of ten, owing to the steric strain associated with the carbonium ion geometry. In contrast, Wiberg and Williams[16] have recently found that 1-chlorobicyclo(1,1,1)pentane (see equation 3) is about three times more reactive than *t*-butyl chloride and



(3)

10^{14} times more reactive than 1-chloronorbornane. This exceptional reactivity is probably due to the fact that much more energy will be gained when releasing the strain of the bicyclic system than will be lost when approaching the carbonium ion geometry.

Detailed information on reactions of various alcohols with a saturated carbon atom as the reaction centre is available in articles on nucleophilic substitution reactions[17–23].

B. Alkylation with α-Halo Ethers, Vinyl Ethers, Acetals and Carbonyl Compounds

I. Kinetics and mechanism

Experimental evidence derived from different independent sources indicates that oxonium–carbonium ions play an important role as intermediates in the reactions of α-halo ethers, vinyl ethers and acetals. The oxonium–carbonium ions are strong electrophiles and they are very fast to react with alcohols (equation 4). In a relatively

$$RO\overset{+}{=}CR^1_2 + ROH \longrightarrow ROCR^1_2OR + H^+ \qquad (4)$$

recent article Schmitz and Eichhorn[24] have discussed the formation of acetals. Most of the reactions involve an electrophilic attack on the hydroxyl group. Some additional observations, in particular those concerning the mechanistic and thermodynamic aspects of the reaction, may be mentioned in this context.

In their reactions in alcohol solution, α-halo ethers, vinyl ethers and acetals form unstable monoalkoxy carbonium ions as intermediates (equation 5). Although the intermediate is the same, the mechanism of its formation differs in three cases: the reaction (A) is

$$\begin{array}{l} ROCH(CH_3)Cl \xrightarrow{(A)} \\ ROCH{=}CH_2 \xrightarrow{(B)} RO\overset{+}{=}CHCH_3 \\ ROCH(CH_3)OR \xrightarrow{(C)} \end{array} \qquad (5)$$

solvolytic[23], reaction (B) exhibits general acid catalysis[25, 26], and reaction (C) is specifically hydronium ion-catalysed[27].

The alcoholysis reaction of α-halo ethers proceeds by the S_N1 mechanism[23]. The enhanced electrophilic reactivity of halo ethers as compared with that of alkyl halides (section II.A) has been explained in terms of the resonance stabilization present in oxonium–carbonium ions.

The reactions of α-halo esters with alcohols have also been used for the preparation of acetals[28–29]. Baldwin and Walker[29] synthesized in this way a number of acetals of α-bromophenyl acetaldehyde. These acetals were subsequently used for the preparation of ketene acetals by dehydrobromination. It is very likely that the attacking electrophile is the oxonium–carbonium ion (equation 6).

$$\begin{array}{l} RCHBrCHBrOCOCH_3 \longrightarrow RCHBrCH\overset{+}{=}OCOCH_3 \xrightarrow{MeOH} \\ RCHBrCH(OCH_3)OCOCH_3 \longrightarrow RCHBrCH\overset{+}{=}OCH_3 \xrightarrow{MeOH} \\ RCHBrCH(OCH_3)_2 \end{array} \qquad (6)$$

The thermodynamics and kinetics of reactions (5) have been recently studied[30]. Although ethyl vinyl ether is initially on a higher free energy level than diethyl acetal (about 3·3 kcal/mole), the two compounds produce oxonium–carbonium ions at rates which are virtually the same, because the transition state of the vinyl ether hydrolysis is on a higher energy level than that of the acetal hydrolysis.

On the basis of the above results it is possible to estimate the rate of an electrophilic attack on the hydroxyl group by the oxonium-carbonium ion. In the acetal solvolysis, the transition state is only by about 4 kcal/mole less stable than the intermediate ion. The smallness of this free energy difference shows that the energy well relating to the intermediate is not deep because the intermediate must further react at a rate which corresponds to a free energy of activation that is less than this difference. In this way the rate coefficient for the attack of the intermediate ion on water was estimated to be about 10^{10} s^{-1}. It is very probable that the rate of the attack in an alcohol solution is smaller by only one or two powers of ten.

Great variations in the stabilities of alkoxy carbonium ions become evident when the substituents are varied. The rate of an attack on alcohol depends largely on the stability of this ion. The following observations made on the hydrolysis of acetals provide further information on this point, which is of interest in the synthesis of structurally different acetals (see section II.B.3).

The overall hydrolysis rate of acetals can be dissected to partial rate factors relating to the leaving group and to the remnant of the

$$ROCH_2OR^1 \longrightarrow RO\overset{+}{=}CH_2 \longrightarrow ROCH_2OH \qquad (7)$$

molecule[31]. For reaction (7), in which R is varied and R^1 is held unchanged, the following partial rate factors have been calculated:

R	FCH_2CH_2	$ClCH_2CH_2$	$CH_3OCH_2CH_2$	CH_3	CH_3CH_2	$(CH_3)_2CH$
k_{rel}	0·0801	0·0480	0·201	1	4·48	22·1

The corresponding partial rate factors for various leaving groups (R^1 is varied) differ only slightly and exhibit a minimum:

R^1	FCH_2CH_2	$ClCH_2CH_2$	$CH_3OCH_2CH_2$	CH_3	CH_3CH_2	$(CH_3)_2CH$
k_{rel}	2·02	1·96	1·53	1	1·21	2·27

The minimum is caused by the circumstance that the structural effects on the pre-equilibrium protonation and on the rate-determining heterolysis act in opposite directions. Further information on the leaving group effects is available from a study of the basicities of symmetrical and unsymmetrical acetals[32].

2. Equilibrium studies

Kubler and co-workers[33, 34] have measured equilibrium constants for the reactions of methanol with various aldehydes and ketones (equations 8 and 9). The equilibrium constant for the hemiacetal

$$R^1COR^2 + CH_3OH \rightleftharpoons R^1R^2C(OH)OCH_3 \quad (8)$$

$$R^1R^2C(OH)OCH_3 + CH_3OH \rightleftharpoons R^1R^2C(OCH_3)_2 + H_2O \quad (9)$$

$$K = K_8K_9 = \frac{a_{\text{acetal}}\, a_{H_2O}}{a_{\text{ald.}}\, a^2_{CH_3OH}} \quad (10)$$

formation, K_8, was measured spectrophotometrically in neutral or basic solutions, in which no acetal was formed. Only a few of the aldehydes or ketones studied formed significant amounts of hemiacetals. If the carbonyl compound contained strongly electronegative substituents the extent of hemiacetal formation was substantial. For instance, *p*-nitrobenzaldehyde was predominantly in the form of a hemiacetal in neutral or basic methanol, but in acidic media the corresponding acetal was formed.

In acidic solutions the acetalization of saturated aliphatic aldehydes with primary alcohols is almost complete; in cases of aromatic aldehydes and α,β-unsaturated aldehydes the equilibria are less favourable. The conversion of ketones to acetals (ketals) is ordinarily so unfavourable that the latter cannot be isolated from the equilibrium mixture; however, the preparation of acetal can be successfully accomplished if one of the reaction products is removed from the mixture.

Kinetic studies of acetal hydrolysis provide additional information about the equilibria between carbonyl compounds and alcohols. The hydrolysis of 1,3-dioxan and its alkyl derivatives differs from the hydrolysis reactions of acyclic acetals[35] and alkyl-1,3-dioxolanes[36] in that the equilibrium is not completely on the side of the hydrolysis products[37] (see Table 4). Similar results have been reported by Aftalion and co-workers[38–40].

TABLE 4. Hydrolysis equilibria for six-membered cyclic acetals in dilute solutions (<0·1M) in water at 25°C [37].

Acetal	% Unhydrolysed at equil.
1,3-Dioxan	24
2-Methyl-1,3-dioxan	33
4-Methyl-1,3-dioxan	47
4,4,6-Trimethyl-1,3-dioxan	65
2,4,4,5,6-Pentamethyl-1,3-dioxan	71

3. Applications to synthesis

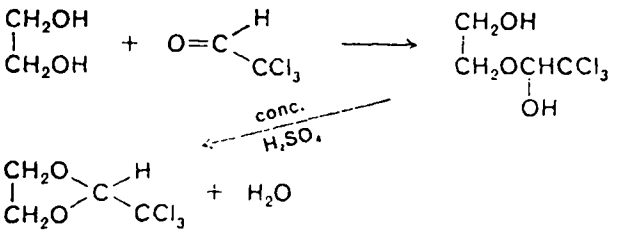
The facts discussed above make it possible to rationalize a number of observations made in connection with the synthesis of acetals. Thus, e.g., attempts to prepare the trichloroethyl acetal of formaldehyde from other formaldehyde acetals via *trans*acetalization (equation 11) were unsuccessful[41], the unsymmetrical acetal being the sole

$$(EtO)_2CH_2 \longrightarrow EtO\overset{+}{\cdots}CH_2 \xrightarrow{Cl_3CCH_2OH} EtO(Cl_3CCH_2O)CH_2 \longrightarrow Cl_3CCH_2O\overset{+}{\cdots}CH_2 \xrightarrow{Cl_3CCH_2OH} (Cl_3CCH_2O)_2CH_2 \quad (11)$$

product that could be isolated after the ethanol liberated had been distilled off. This is easily understood by the low stability of the chlorinated oxonium–carbonium ion; its energy level has been estimated from the partial rate factors of the corresponding acetals[42].

From the above it follows that the acetalization of alcohols having strongly electron-attracting substituents can be effected only under drastic conditions. Shipp and Hill[43] have used concentrated sulphuric acid for a number of negatively substituted alcohols. The yields were reportedly at least 70%.

The reaction of chloral with ethylene glycol (equation 12) provides a further illustration. The hemiacetal formed is exceptionally



(12)

stable in this case, drastic conditions (e.g., concentrated sulphuric acid) are therefore required to produce the corresponding acetal[44, 45]. This is quite understandable because here also the intermediate oxonium–carbonium ion is unstabilized by strongly electronegative substituents.

As discussed above (section II.B.2) the acetalization of aromatic aldehydes is usually facile. It is to be noted that here the oxonium–carbonium ion is stabilized by the resonance effect of the aromatic ring, the latter becoming conjugated with the partial double bond of the oxonium–carbonium ion.

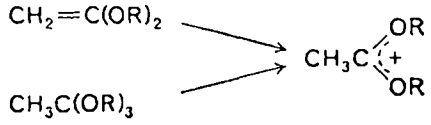
C. Alkylation with Ketene Acetals and Orthoesters

The stabilities of oxonium–carbonium ions are greatly increased when additional alkoxy groups are attached to the central carbon atom. The following stabilization energies, relative to the methyl cation, have been reported[46]:

Ion	$CH_3OCH_2^+$	$(CH_3O)_2CH^+$	$(CH_3O)_3C^+$
Stabilization energy (kcal/mole)	66	85	90

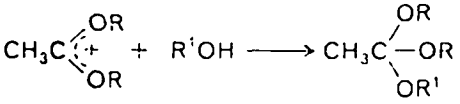
Although the above values refer to the gascous state and are not directly applicable to liquid solutions, it may be expected that reactions of alcohols with such substrates, which are capable of generating dialkoxy carbonium ions, take place much more readily than the reactions which involve monoalkoxy carbonium ions (section II.B).

In the presence of an acid catalyst, ketene acetals and orthoesters are readily transformed to dialkoxy carbonium ions (equation 13), which subsequently react rapidly with the nucleophiles present, e.g.,



(13)

with an alcohol. Some data on the kinetics of ketene acetals in water solution are available[47, 48]. The reaction of orthoesters has been the subject of a number of studies[35, 47c]. The electrophilic attack of the intermediate ion on a hydroxyl group of an alcohol yields orthoesters (equation 14). When alcohol R^1OH is present in great excess all of



(14)

the original alkoxy groups will be replaced. However, the preparation of the symmetrical orthoester from methyl orthoformate and 2,2,2-trichloroethanol was not possible except under relatively drastic reaction conditions[47b]. In this case, the stability of the intermediary alkoxy methyl cation was strongly reduced by the electronegative substituents.

Kinetic data on the hydrolysis of unsubstituted ketene acetals[47] suggest that the dialkoxy carbonium ion involved is only about 2 kcal/mole less stable than the reactant in the initial state. Because

of the stability of the intermediate ion, the electrophilic attack with this ion may be slower than that with the corresponding monoalkoxy carbonium ion. However, it is evident from the kinetic data that this attack is anyway much faster than the formation of the ion.

Kuryla and co-workers[49, 50] have recently described a new route to ketene acetals and orthoesters from dichloro olefins (equation 15).

$$2\ ROCH_2CH_2ONa + CH_2{=}CCl_2 \longrightarrow (ROCH_2CH_2O)_2C{=}CH_2 \qquad (15)$$

This reaction is characteristic of β-alkoxy alcoholates; unsubstituted alcohols do not give ketene acetals. When alcohol is used as the solvent the ketene acetal formed is then rapidly transformed to the corresponding orthoester. The proposed scheme for reaction (15) involved an electrophilic attack on alcohol by an acetylenic intermediate (equation 16)[49, 50].

$$RONa + CH_2{=}CCl_2 \longrightarrow CH{\equiv}CCl + ROH + NaCl \longrightarrow CH_2{=}\underset{\displaystyle Cl}{\underset{|}{C}}OR \longrightarrow CH{\equiv}COR + ROH + NaCl \longrightarrow CH_2{=}C(OR)_2 \qquad (16)$$

D. Alkylation with Ethylene and Acetylene Derivatives

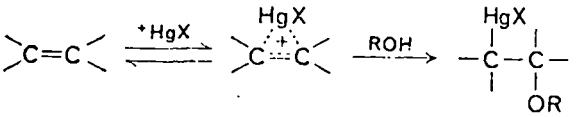
The general features of alkylation reactions with alkenes have been extensively discussed quite recently[51]. Only a few additional observations will be mentioned here.

It is evident from a great number of reactions that electron-withdrawing substituents attached directly to a sp^2-hybridized carbon atom enhance the electrophilic character of the double bond. Addition of alcohols to activated vinyl compounds like $R_2C{=}CRX$, where X is an electronegative substituent, has been extensively studied recently[52]. The activating effect of X was found to increase in the sequence: $CONHR < CONH_2 < CONR_2 < COOR < SO_2NR_2 < COR < {}^+PR_3$. The rate-enhancing effect of the $CONR_2$ group was rather surprising. No satisfactory explanation for this could be offered. In all cases the alkoxy group of the alcohol became attached to the neighbouring carbon atom having no electronegative substituents (equation 17).

$$R_2C{=}CRX + R^1OH \longrightarrow R_2(R^1O)C{-}CRXH \qquad (17)$$

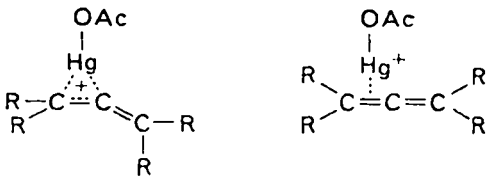
In contrast to its electrophilic properties, the nucleophilic strength of the carbon–carbon double bond is increased by electron-releasing substituents attached to the trigonally hybridized carbon atoms. Thus it is possible to prepare ethers from alkyl-substituted olefins, for instance, from $Me_2C{=}CH_2$, in alcohol solution containing added acid. In these reactions it is a carbonium ion that attacks the alcohols.

The addition of mercuric salt to a simple olefin involves a formation of a bridged or π-complexed mercurinium ion, followed by a product-determining *trans* attack on the solvent, e.g., on an alcohol (equation 18)[53, 54]. The structure of the intermediate, which subse-



(18)

quently attacks on the hydroxyl group, has been studied in the case of allene and its methyl derivatives[54]. These compounds reacted with methanol faster than simple olefins by factors of several powers of ten. The results were best interpreted in terms of a stable σ-bonded cyclic mercurinium ion **1**. The π-complex **2** was less probable as the reaction intermediate.



(1) (2)

Several technical methods for the alkylation of alcohols with acetylenes are available[55].

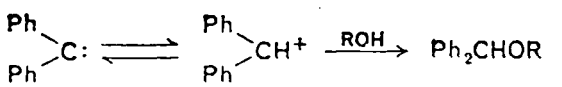
An intramolecular reaction of a hydroxyl group with the acetylenic linkage has been shown to occur in the transformation of acetylenic epoxides to the derivatives of furan[56].

E. Alkylation with Divalent Carbon

Carbenes may react as electrophiles with alcohols, leading to ethers (equation 19). Alternatively, the conjugate acid of the carbene

$$R^1OH + R{:}\ddot{C}{:}R \longrightarrow R^1OCR_2H \qquad (19)$$

may function as the attacking reagent. Kirmse[57, 58] has drawn the conclusion that in the case of phenyl-substituted carbenes there exists an acid–base equilibrium with the carbene and the corresponding carbonium ion as the conjugate acid–base pair. The carbonium ion then attacks on the hydroxyl group (equation 20).



(20)

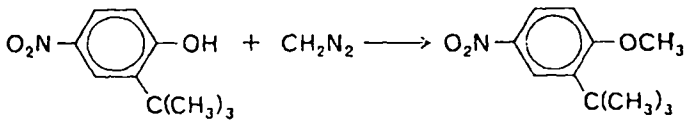
Carbenes are easily produced, for instance, from diazo compounds (e.g., equation 21). Methods of preparation of ethers with carbenes

$$\begin{aligned} CH_2N_2 &\longrightarrow :CH_2 + N_2 \\ N_2CHCOOC_2H_5 &\longrightarrow :CHCOOC_2H_5 + N_2 \end{aligned} \qquad (21)$$

as the intermediates have been reviewed recently[22].

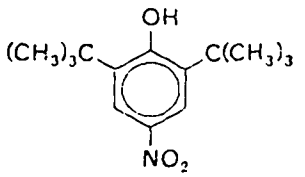
The cupric chloride-catalysed reactions of diazo acetates with butyl, benzyl and allyl alcohols are not selective[59]. In addition to the desired ether many other compounds have been found in the reaction product. The same is the case with the carbene produced from α-diazo-*p*-methoxyacetophenone in a light-induced reaction[60].

The carbene reactions of hindered phenols have been studied[61]. A normal diazo reaction was found in the case of 2-*t*-butyl-4-nitro



(22)

phenol (equation 22). In the case of the di-*t*-butyl derivative **3** the above reaction was sterically hindered and the nitronic ester **4** was the sole product. In the case of the 2,6-diisopropyl analogue of **3**



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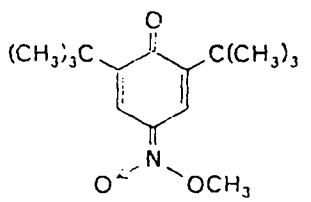


(4)

the steric hindrance can be assumed to be smaller. In fact, Meek and co-workers[61] have found that with this compound both the anisole derivative and the nitronic ester were formed. On the basis of these results it is surprising that the corresponding 2,6-diiodo analogue of **3** produces only anisoles, notwithstanding the bulkiness of the iodine atoms. It is very likely that, although *t*-butyl groups and iodine atoms are approximately of the same sizes, the alkylation of the hydroxyl group is much more hindered sterically by the *t*-butyl groups than by the iodine atoms. This is because the attacking reagent approaches the hydroxyl group from a direction which is almost perpendicular to the plane of the ring, and the hydroxyl group is much better shielded from these attacks by the *t*-butyl groups than by the iodine atoms. In addition, inductive effects of

electronegative substituents like iodine atoms at 2- and 6-positions will reduce the tendency of the *p*-nitro group to react as a nucleophile, which makes the formation of the nitronic ester less favourable.

Schönberg, Junghans and Singer[62] have reported that attacks of diphenyldiazomethane on alcohols (methanol, benzyl alcohol) in the presence of ninhydrin give acetals (equation 23) instead of ethers.

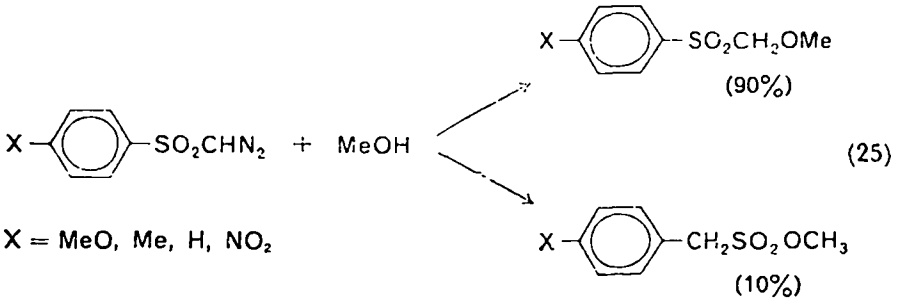
$$Ph_2CN_2 + 2\,ROH \xrightarrow{\text{ninhydrin}} Ph_2C(OR)_2 \qquad (23)$$

Saegusa and co-workers[63] have reported that isocyanides react with allyl alcohol producing allyl formimidate (equation 24). In the

$$CH_2{=}CHCH_2OH + RN{\equiv}C \xrightarrow{CuCl} CH_2{=}CHCH_2OCH\!\!\parallel\!\!NR \qquad (24)$$

absence of the cuprous chloride catalyst only the initial reactants could be recovered. In a more extensive study Saegusa[64] has investigated the effect of other catalysts.

The light-induced reaction of α-diazo sulphone with methanol gives aryl methoxymethyl sulphone and benzyl sulphonate (equation 25)[65]. The formation of benzyl sulphonate can be accounted for



(25)

by a rearrangement in which a minor part of the sulphonyl carbene is isomerized to sulphene (equation 26).

$$Ar{-}SO_2\ddot{C}H \longrightarrow Ar{-}CH{=}SO_2 \qquad (26)$$

III. ACYLATION. CARBON ATOM AS THE ELECTROPHILIC CENTRE

A. Introductory Remarks

The kinetics and mechanisms of the esterification of carboxylic acids and the reverse hydrolysis reaction (equation 27) have been

$$R^1COOH + R^2OH \rightleftharpoons R^1COOR^2 + H_2O \qquad (27)$$

the subject of considerable literature[66–70]. Other related reactions, the reactions of carbo diimides with alcohols, tioalcohols and phenols[71], and the synthesis and reactions of carbamate esters[72] have been reviewed recently.

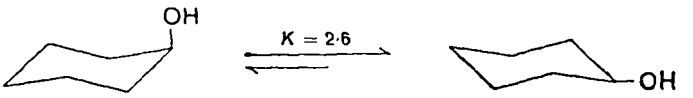
The above-mentioned publications cover the main area of the subject; the following discussion is limited to studies published during the last few years and, in particular, to those dealing with stereochemical and mechanistic aspects.

B. Structure and Mechanism

1. Conformational aspects

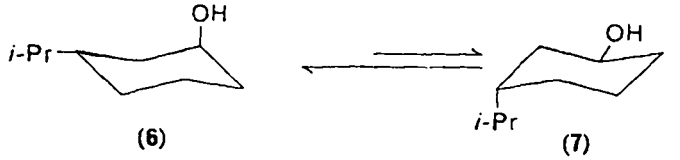
The acetylation rates of cyclohexanol and its derivatives have been used for the evaluation of the conformational energy of the hydroxyl group. It has been generally accepted[73] that the rate constant of a pure axial conformation (k_a) and that of the pure equatorial conformation (k_e) may be represented by the rate constants of the respective *cis*- and *trans*-4-*t*-butyl-substituted compounds. Then, generally, the observed rate coefficient is given by $k = N_e k_e + N_a k_a$, in which N_e and N_a are the respective mole fractions of the two conformational isomers at equilibrium. The latter mole fractions can be readily calculated from the measured values of the rate coefficients, and a value derived for the conformational equilibrium constant $K = N_e/N_a$.

Thus Eliel and Biros[73] have derived the value $-\Delta G_{OH}^0 = 0{\cdot}56$ kcal/mole for the interaction free energy of an axial hydroxyl group in cyclohexanol (**5**), from the acetylation rates of cyclohexanol (k) and *cis* (k_e) and *trans* (k_a) forms of 4-*t*-butylcyclohexanol. This estimation agrees closely with other estimates[74] (equation 28).



(5) $K = (k_a - k)/(k - k_e)$. (28)

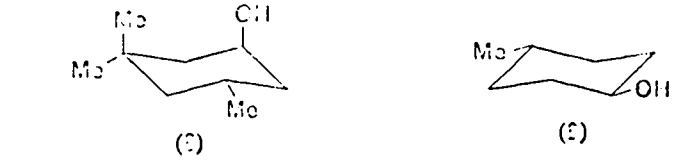
The *trans* form of 3-isopropylcyclohexanol is acetylated at a rate which corresponds to a conformational equilibrium (equation 29) with 93% of **6** and 7% of **7**. The value of the equilibrium constant

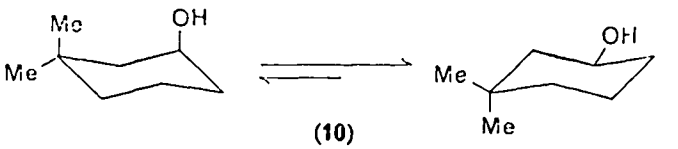


(6) (7) (29)

gives a free energy difference of 1·6 kcal/mole, in agreement with the difference $\Delta G_{OH}^{0} - \Delta G_{i\text{-}Pr}^{0} = -0{\cdot}7 + 2{\cdot}3 = 1{\cdot}6$ kcal/mole[74, 75].

An estimation of a *syn*-axial Me–OH interaction energy from the acetylation rates of **8**, **9** and **10** led to the value 1·8 kcal/mole (the *syn*-axial Me–H interaction energy and the *syn*-axial OH–H interaction energy are 0·85 and 0·3 kcal/mole, respectively), which is in poor agreement with the thermodynamic value, 2·4 kcal/mole[74, 76].





(10)

Eliel and Biros[73] have also given additional examples of instances in which estimations of conformational energies from the acetylation rates give erroneous values, proposing that only *cis* and *trans* *t*-butyl compounds[77] lead to reliable results.

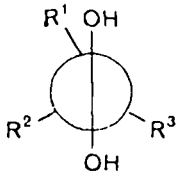
2. Steric effects and esterification rates

Steric effects in the acid-catalysed esterification of 3-substituted acrylic acids[78] and several other acids[79] in methanol have been investigated recently.

Bowden[78] has measured the rate coefficients for the acid-catalysed esterification of fourteen 3-substituted acrylic acids. The unsubstituted acid seems to be much more reactive than the substituted acids, and the esterification rates of the *trans* acids are always higher than those of the *cis* acids. The latter effect indicates that the steric effects in the *trans* acids are not material.

Bowden, Chapman and Shorter[79] have studied the kinetics of the acid-catalysed esterification of several aryl-substituted carboxylic acids in methanol. *p*-Toluenesulphonic acid was used as the catalyst instead of hydrogen chloride[80, 81]. The effect of substitution was discussed in terms of the Taft steric substituent constant, $E_s = \log (k/k_0)$, where k_0 is the esterification rate of acetic acid[82].

The initial and transition states in the esterification of the acid



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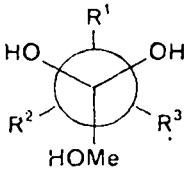


(12)

$R^1R^2R^3CCOOH$ were considered as **11** and **12**, respectively, both bearing a positive charge. The observed steric retardation was suggested to be a combination of a steric strain effect and of internal repulsive interactions. The increase in E_s caused by further substitution was found to depend on the bulk of all substituents R^1, R^2 and R^3. The following are examples of the results obtained by Bowden, Chapman and Shorter[79]:

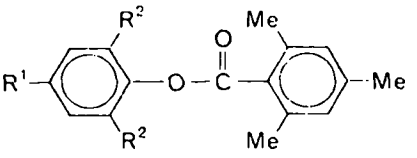
R^1	R^2	R^3	E_s
Me	H	H	—
Ph	H	H	−0·37
Ph	Ph	H	−1·43
Ph	Ph	Ph	−4·68

Most of the observed effects could be interpreted in terms of conformational factors. As an alternative line of argumentation the build-up of the total steric effects was discussed[78, 82].

C. *Applications to Synthesis*

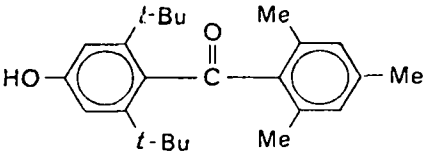
1. Esterification of hindered acids

The conventional methods of esterification of sterically hindered acids have been discussed by Newman[83]. A recent report of Parish and Stock[84] deals with the limitations involved in the reaction of methanol or other alcohols with the unsymmetrical anhydride of a hindered acid and trifluoroacetic acid[85, 86, 87]. The hindered acid was dissolved in trifluoroacetic anhydride and the alcohol was added, or, alternatively, a mixture of the acid and alcohol was treated with trifluoroacetic anhydride. It was found that **13** is easily formed from mesitoic acid and 2,6-dimethylphenol, whereas **15** is obtained from the same acid and 2,6-di-*t*-butylphenol in 83% yield. This alternative path, *C*-acylation, is facile in the latter case and therefore the esterification reaction may assume the minor role[87–89]. With a



(13) $R^1 = H$, $R^2 = Me$
(14) $R^1 = Me$, $R^2 = t\text{-Bu}$

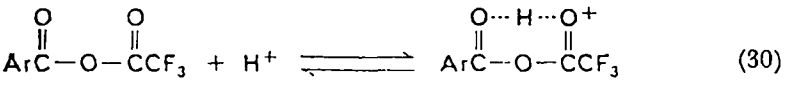
(13) (14)



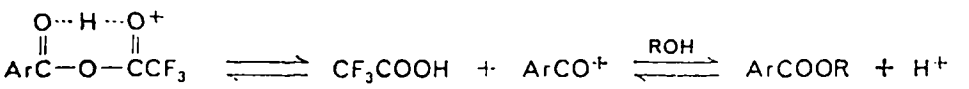
(15)

blocked 4-position, like 2,6-di-*t*-butyl-4-methylphenol, the reaction with mesitoic acid takes place very slowly (23% conversion to **14** took 3 days, whereas the complete conversion of 2,6-dimethylphenol to **13** took 5 minutes). The fast solvolytic reactions of tertiary alcohols with trifluoroacetic acid also influenced the yields[86]. Thus *t*-butyl trifluoroacetate was formed competitively with *t*-butyl mesitoate. The purest products and most complete conversions were achieved when *t*-butyl alcohol was used in large excess[86].

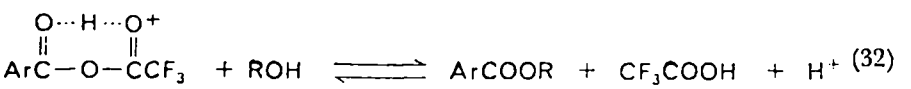
The major component in the solution of a hindered acid in trifluoroacetic anhydride is the unsymmetrical anhydride **16**[90, 91]. Acylation is generally assumed to occur via an oxocarbonium ion **17** which is formed from the acid-catalysed ionization of the anhydride (equations 30 and 31)[86, 92]. Parish and Stock[84] listed a number of observations which supported the protonated anhydride **18** as the reactive intermediate (equation 32). Experiments with mesitoic acid and benzoic acid showed, however, that both the carbon and oxygen acylations were much more rapid with the former acid. The



(16) (30)



(17) (31)

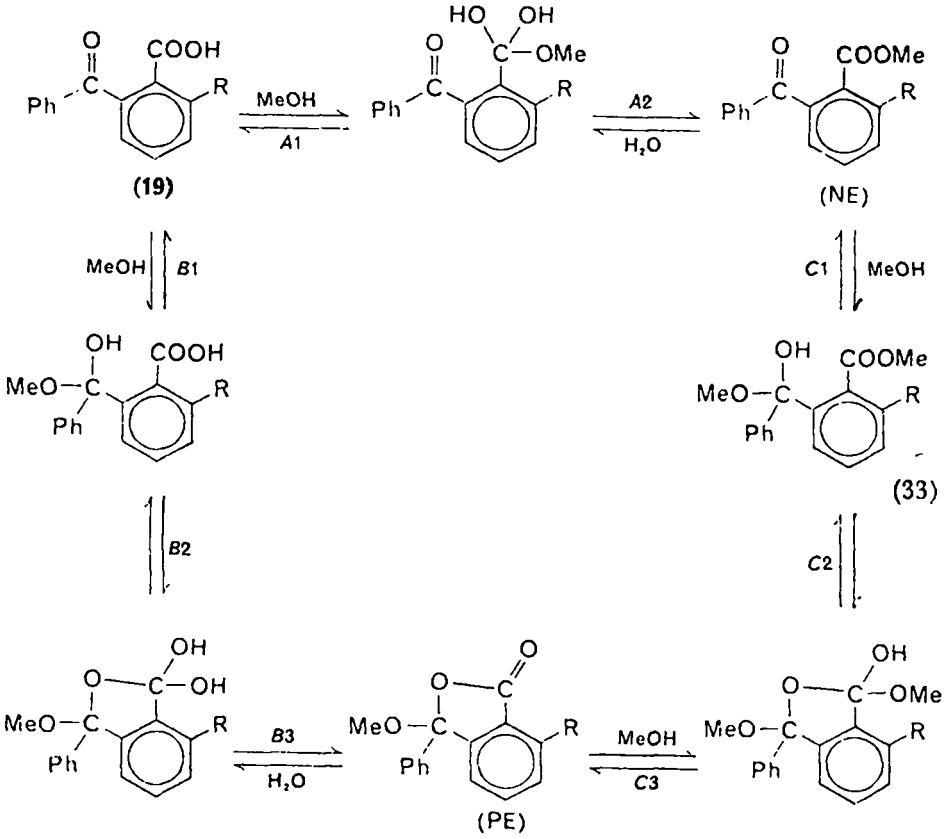


(18) (32)

great reactivity of mesitoic acid is also good evidence for the acylonium ion intermediate (equations 30 and 31). The relative esterification rates of *p*-toluic, benzoic and *m*-chlorobenzoic acids with phenol in trifluoroacetic anhydride at 25° were: *p*-Me 12, H 1·0 and *m*-Cl 0·062, respectively. These large substituent effects also indicate a relatively high electron deficiency in the transition state, and are consistent with the importance of the acylonium ion path.

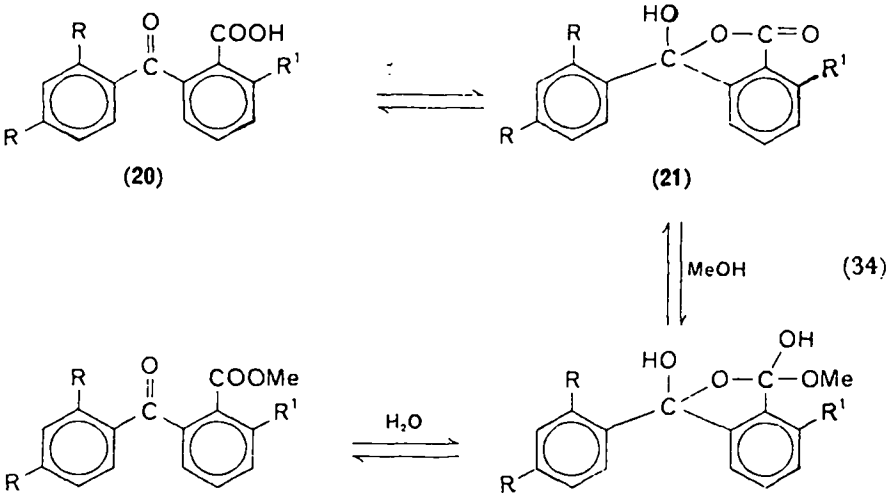
2. Thermodynamic and kinetic control in esterification

In addition to some kinetic studies on acid-catalysed esterification in methanol[78, 79] (section III.B.2) Newman and Courduvelis[93] have investigated the esterification of several *o*-benzoylbenzoic acids in the same solvent. A result of the most general interest was the observation that the composition of the reaction product could be



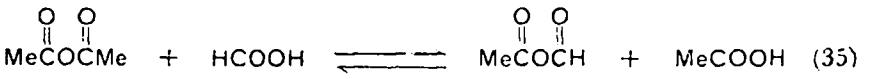
altered, depending on whether thermodynamic or kinetic control predominated under different conditions.

The reaction scheme (33) shows the possible routes to a normal (NE) or a pseudo ester (PE) in the acylation of *o*-benzoylbenzoic acids. The amounts of NE and PE were determined after 15 minutes (mainly kinetic control) and after 5 hours (thermodynamic control) in each experiment. For instance, *o*-benzoylbenzoic acid (**19**, R = H) forms at first mainly PE by route *B*, which is then rapidly converted into NE by route *C*. The conclusion that the first attack of methanol is on the carbonyl group has been confirmed experimentally[94, 95]. An additional, parallel route (equation 34) was proposed for the esterification of 2-benzoylbenzoic acid (**20**, R = H, R^1 = Me) and 2-(2,4-dimethylbenzoyl)benzoic acid (**20**, R = Me, R^1 = H) because of their enhanced esterification rates. The contribution of this route will depend on the equilibrium between the keto acid (**20**) and hydroxy lactone (**21**) forms.



3. Esterification with mixed anhydrides

Besides the esterification of hindered acids using mixed anhydrides[84] (section III.C.1) the preparation of formate and acetate esters in formic acid–acetic anhydride mixtures has been recently reinvestigated[96]. The method was originally introduced by Béhal[97], who did not report his experimental details. According to early reports[97–99] the esterification of alcohols with a 1:1 mixture of formic acid and acetic anhydride (equation 35) yielded only formates. Stevens and Van Es[96] utilized gas–liquid chromatography



and n.m.r. measurements for the determination of the product composition and found appreciable amounts of acetates from simple primary alcohols. Benzyl alcohol was an exception. Generally, the amount of acetate and the rate of esterification decreased in the sequence: primary > secondary > tertiary. In all cases detectable amounts of acetates were formed. It was concluded that the earlier reports[97, 100, 101] were erroneous because of the inadequacy of the available analytical methods.

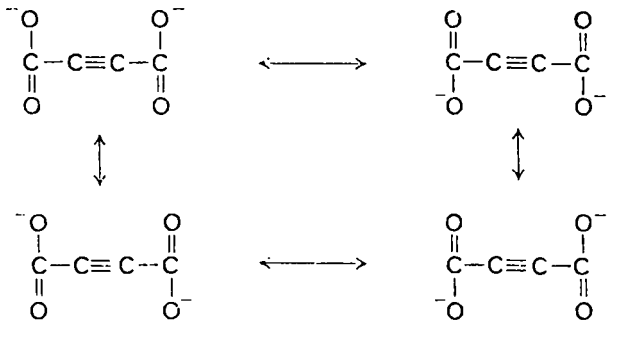
Similar experiments with phenols[102] gave formates with less than 10 mole-% of acetates as the by-products. This is in contrast to the report of Béhal[97], but in substantial agreement with the preliminary experiments of Ducasse[103]. The yield of separated formates exceeded 80% in each case[96, 102].

4. Autocatalytic esterification

In general, esterification without added catalyst is a very slow process. Sometimes the acid itself is acidic enough to catalyse its own esterification. Perfluoro acids have been frequently found to be esterified by autocatalytic reactions with nonfluorinated alcohols[104–106]. In a study of the autocatalytic esterification of acetylenic acids and fluoro acids with alcohols[107], only acetylene dicarboxylic acid and perfluoro acids showed autocatalytic activity. The diester was the sole product formed from acetylene dicarboxylic acid, which was understood in view of the similar pK-values of both carboxyls. The triple bond enhances the acidity of the two carboxyl groups in a similar manner, and the lack of steric effects due to the linearity of the molecule also suggests that the two pK values will not grossly differ. Moreover, the resonance structures stabilize the dianion (**22**) more than the monoanion (**24**) or the free acid (**23**). From the experiments carried out in benzene[107] it was concluded that acids with p$K \leq 2{\cdot}6$ will be autocatalytic, whereas with p$K \geq 3{\cdot}4$ they will not exhibit autocatalysis.

D. Miscellaneous Acid Derivatives

Prajecus and co-workers have studied the kinetics and mechanism of esterification via an amine-catalysed addition of alcohols to substituted ketenes[108–110]. At 20°C the reactions were formally of the first-order with respect to the alcohol, whereas the rate became



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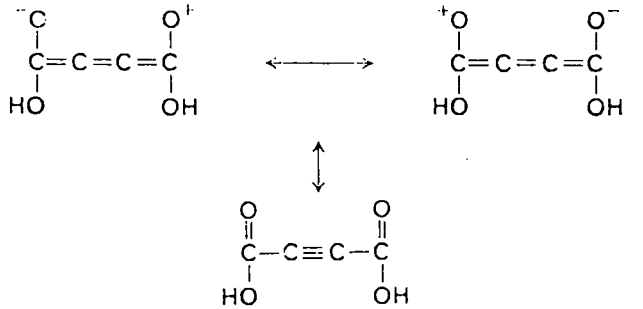

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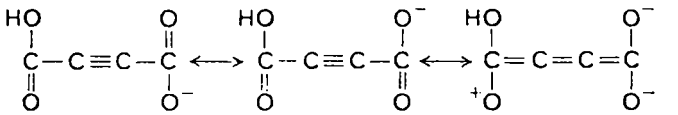
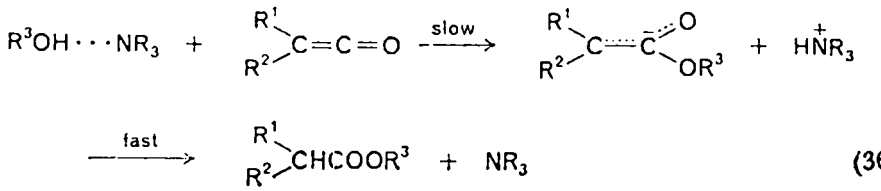


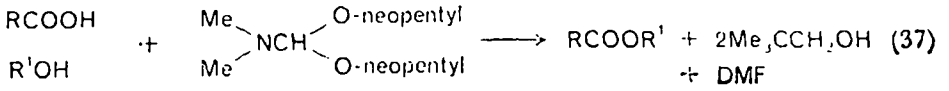
(24)

virtually independent of the alcohol concentration when the temperature was lowered to −95°C. Although no unequivocal distinction between the different possibilities could be made, it was shown that, with certain additional assumptions, the observed formal kinetics was in accordance with a rate-determining reaction between the ketene and an alcohol-amine adduct (equation 36).



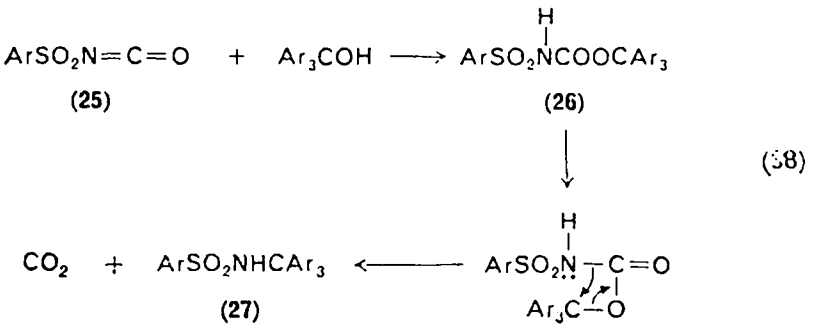
(36)

Brechbühler and co-workers[111] have prepared esters of several amino acids in methylene chloride solution in the presence of dimethylformamide dineopentylacetal (equation 37), the yields varying from 70 to 90%.



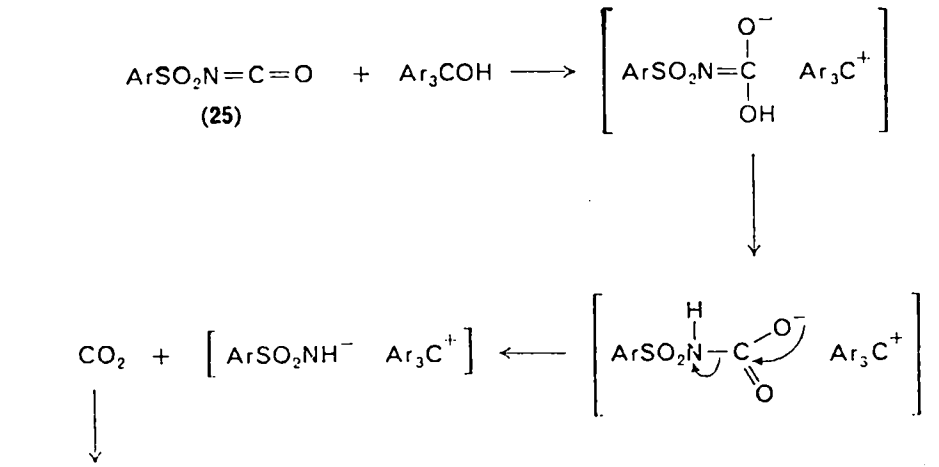
Satchell and co-workers[112–114] have investigated the kinetics and mechanism of some Schotten–Baumann type acylations. These include the acylation of β-naphthol by acetyl halides in the solvents nitromethane, acetic acid and acetonitrile, and the acylation of several phenols by acetyl, propionyl, butyryl, β-chloropropionyl and chloroacetyl chlorides in acetonitrile. The mechanism of the acylation was presumably similar for all these systems, the ionization (acylium ion) routes predominating[67, 112–114]. With chloroacetyl chloride and to a minor extent with β-chloropropionyl chloride, a concerted displacement of chlorine by the phenol predominates and the process is greatly facilitated by the presence of added salts[113].

McFarland and Howard[115] have investigated the reaction of sulphonyl isocyanates with hindered phenols and alcohols obtaining normal urethan products in high yields. In contrast to tertiary alkyl carbinols, tertiary aryl carbinols gave in most cases products other than urethans. When arylsulphonyl isocyanate (**25**) reacted with triphenylmethanol or with triaryl carbinols containing electron-releasing groups, *N*-(triarylmethyl) sulphonamides (**27**) and carbon dioxide were formed (equation 38).



Reaction (38) yielded no urethan (**26**) even at 0°C, whereas diphenylmethanol and **25** gave urethan in good yield[115, 116]. Two possible interpretations were proposed. Either the mechanism (38)

was not applicable, or, alternatively, the intermediate **26** was extremely unstable. An alternative mechanism without the urethan intermediate was also presented (equation 39). In view of the stability of triarylmethyl carbonium ions the mechanism (39) seems very plausible.



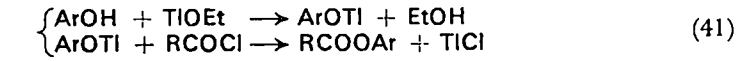
(39)

Ulrich and co-workers[117] have reported on the preparation of carbamates and 2,4-dialkyl allophanates from methyl isocyanate and phenols in the presence of potassium *t*-butoxide (equation 40).

(40)

The structure of the products was demonstrated by pyrolysis and by an independent synthesis starting from the appropriate phenol and 2,4-dialkyl allophanoyl chloride. However, similar reactions with aliphatic alcohols gave a mixture of carbamate, allophanate and trimethyl isocyanate[117].

Taylor and McLay[118] have recently reported that thallium(I) ethoxide is an excellent reagent for the acylation of phenols and carboxylic acids (equations 41 and 42).



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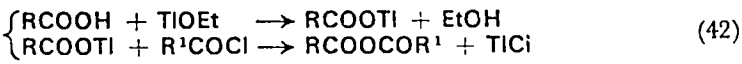


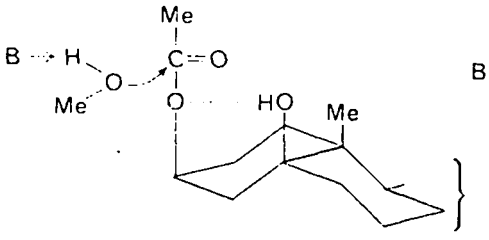
(42)

Because the thallium(I) salts of phenols and carboxylic acids are crystalline, sharp-melting compounds, they can be prepared and isolated relatively free from any impurities. Furthermore, the authors report that the yields of aryl esters and carboxylic acid anhydrides are virtually quantitative.

E. Intramolecular Catalysis by the Hydroxyl Group

A neighbouring hydroxyl group has been found to catalyse the hydrolysis and solvolysis of carboxylic esters (for earlier literature see Reference 66), the acylation of polyols, the hydrolysis of amines and amides, and the amination of esters.

Kupchan and co-workers[119–121] have shown that the alkaline hydrolysis of an alicyclic axial acetate is facilitated by a hydroxyl group bearing a 1,3-diaxial juxtaposition to the acetate. The solvolysis of 1,3-diaxial hydroxy acetates exhibits general base catalysis with simultaneous general acid catalysis by the neighbouring hydroxyl group[66, 122]. An introduction of a hydroxyl group to C-5 of coprostanol acetate, leading to the 1,3-diaxial hydroxy acetate, resulted in a 300-fold increase in the rate of solvolysis, the possible mechanism being shown in **28**. Correspondingly, an examination of the molecular models of strophanthidin 3-acetate 19-aldehyde and neogermitrine (**29** and **30**, respectively) showed that the hydrogen



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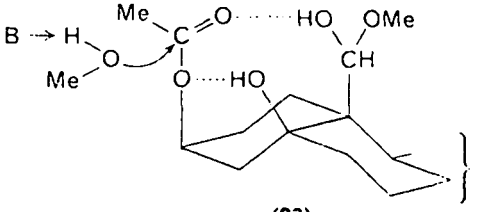

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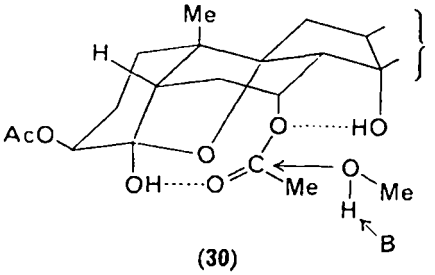
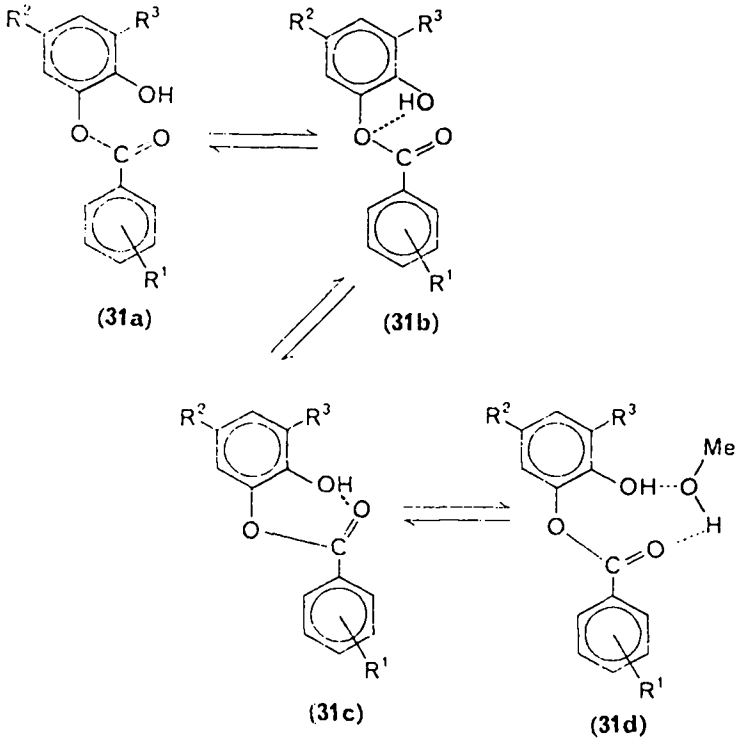


(30)

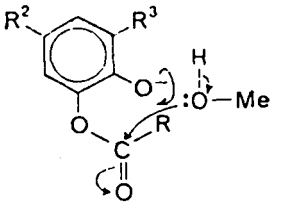
bonding via the acidic hemiacetal hydroxyl groups would polarize the carbonyl group and facilitate attack of the nucleophile.

Bruice and Fife[123] have suggested that a neighbouring hydroxyl group may assist ester solvolysis by changing the microscopic medium surrounding the ester group, for instance, by effecting a specific binding or orientation of water molecules in the critical complex. To investigate this possibility in the methanolysis of gallotannins, Biggins and Haslam[124] studied the effect of methanol on the i.r. spectra of compound **31** in carbon tetrachloride. When the concentration of methanol was increased the proportion of **31d** was greatly favoured over **32c**, which was probably due to the intramolecular hydrogen bond present in **31c**. In addition, the results showed that electron-attracting groups in the benzoyl residue favoured the formation of **31b** and electron-releasing groups the formation of **31d**; the ratio of the two species had a linear correlation to the



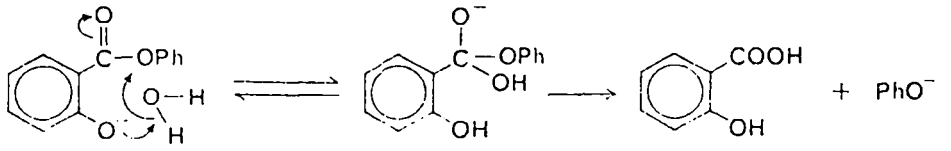
Hammett σ values. Because the methanolysis of **31** was found to be of the first-order with respect to methanol, and no general base catalysis was observed, it was concluded that the reaction was best rational-

ized in terms of the mechanism presented by Bender[66, 125], which involves an attack of a neutral methanol molecule on the ionized ester (**32**).



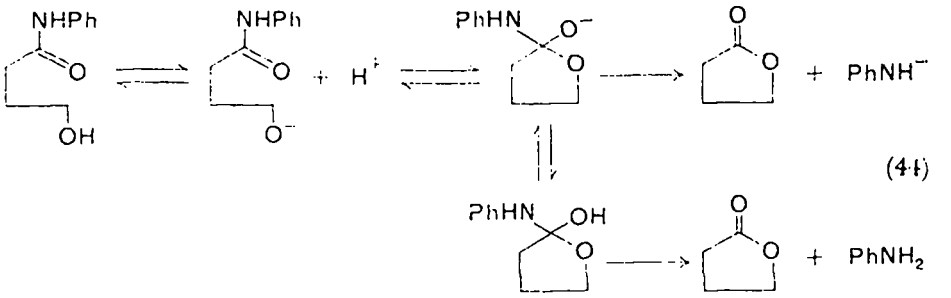
(32)

Capon and Ghosh[126] have proposed the mechanism (43) for the hydrolysis of phenyl salicylate, involving intramolecular general base catalysis by the ionized phenolic group. The solvent deuterium isotope effect ($k_H/k_D = 1{\cdot}7$) is also consistent with this mechanism[127]. Similarly, in contrast to the report of Hansen[128] for catechol monoacetate, Capon and Ghosh[126] suggested catechol monobenzoate to be hydrolysed by a mechanism with intramolecular general base catalysis ($k_H/k_D = 1{\cdot}8$).



(43)

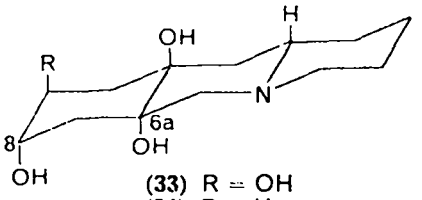
An interesting report has recently been made[129] about the hydroxyl group participation in amide hydrolysis. The mechanism (44) was presented for the hydrolysis of 4-hydroxybutyranilide in neutral and alkaline medium. The rate was found to be about ten-fold



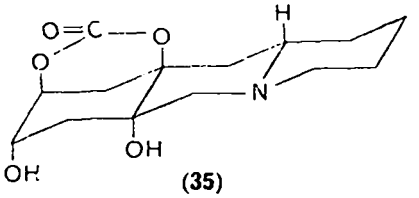
(44)

as compared with the hydrolysis rate of butyranilide. Similarly, the rate ratio of 4-hydroxybutryamide to butyramide was about twenty.

According to Kupchan and co-workers[130] the acylation of tertiary hydroxyl groups in alicyclic 1,3-diaxial diols may also be facilitated by hydroxyl group participation. They ascribed the ease of direct



(33) R = OH
(34) R = H



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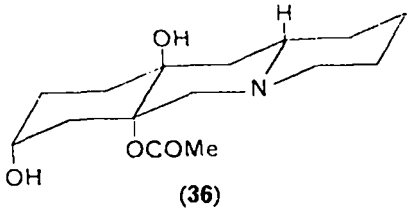


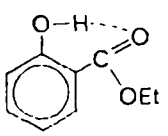
(36)

acylation of the tertiary hydroxyl groups in **33**, **34** and **35** to the intramolecular catalysis by the C-8 secondary hydroxyl group and the nearby tertiary nitrogen atom.

In addition to the acylation reaction, the solvolysis of the triol monoacetate **36** featured intramolecular base catalysis[130], the rate enhancement being 10,000-fold over that expected.

Openshaw and Whittaker[131] have reported that ethyl salicylate shows *o*-hydroxy catalysis in the aminolysis reaction. This catalysis can be attributed to the formation of the hydrogen-bonded intermediate **37**, or to a concerted displacement reaction with the amine (**38**).

Roberts and Traynham have studied the neighbouring hydroxyl group effect in the solvolysis reactions of *p*-toluenesulphonate esters of various cyclanols[132].



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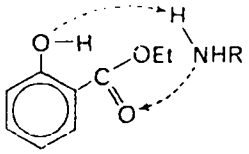


(38)

IV. HETEROATOMS AS THE ELECTROPHILIC CENTRES

A. Esterification with Inorganic Oxyacids

1. General

The reactions discussed below are formally represented as

$$ROH + HO\text{–}Y\text{–} = RO\text{–}Y\text{–} + H_2O \qquad (45)$$

where Y stands for a heteroatom, like sulphur, nitrogen or boron. Strictly, only in cases in which the reaction involves a cleavage of the O–Y bond is the alcoholic hydroxyl group actually attacked by the heteroatom; otherwise, when the R–O bond of the alcohol is cleaved, the reaction should be considered rather as a nucleophilic attack on the α-carbon atom of the alcohol.

Esterification of alcohols with inorganic oxyacids has been the subject of considerable study, and many exhaustive reviews on practical synthetic methods, both for laboratory and industry, may be found in the literature. The discussion below is therefore limited to a number of particularly chosen examples which serve to illustrate some of the general features of reaction (45).

In many instances the reversal of reaction (45), the hydrolysis of the ester, has been studied in more detail than the esterification itself. Examples of such cases are also given, bearing in mind that the principle of microscopic reversibility requires the forward and reverse reactions to pass through the same transition state, which makes the mechanistic information derived from both sources of study equally valuable.

2. Sulphuric acid

a. Primary and secondary alcohols. The reaction of ethanol with sulphuric acid leading to the formation of diethyl ether has probably been known for several centuries, although the intermediary formation of alkyl hydrogen sulphates (equation 46) remained unnoticed for a long time. Recent interest in these esters has been enhanced by, in addition to their importance as intermediates in alcohol–ether

and in alcohol–olefin transformations, a variety of practical applications, e.g., as wetting agents and detergents. The physiological significance of sulphuric esters has drawn attention to their enzymatic formation and hydrolysis reactions[133, 134].

$$ROH + SO_2(OH)_2 = SO_2(OH)(OR) + H_2O \qquad (46)$$

Several studies on primary and secondary alcohols[135–139], dealing with both the sulphation reaction (46) and its reverse hydrolysis under acidic conditions, indicate that the R–O bond of the alcohol remains intact during the reaction. The evidence includes structural rate effects, retention of configuration in the case of optically active alcohols, and oxygen-18 tracer experiments. A formation of a carbonium ion R^+ as a reaction intermediate seems thus to have been excluded, at least for primary and secondary alkanols, and the reaction can be considered, in the strict sense, as one involving an electrophilic attack on the hydroxyl group of the alcohol.

The effect of the structure of the alcohol on the rate and equilibrium of esterification has been studied in detail by Deno and Newman[136]. Some of their results are shown in Table 5. Most of

TABLE 5. Equilibrium constants and relative rates[136] for the sulphation of alcohols (equation 46) at 25°C. The values are calculated to correspond to 70·4% aqueous sulphuric acid.

Alcohol	$K_{equil.}$	Relative rate
Methyl	2·3	1
Ethyl	1·7	0·43
2-Propyl	0·54	0·12
1-Butyl	1·9	0·29
2-Butyl	0·50	0·12
Isobutyl	2·2	0·25
2-Pentyl	0·64	0·11
3-Pentyl	—	0·10
Neopentyl	1·7	0·23
Pinacolyl	—	0·05
Cyclohexyl	0·70	0·16

the differences in the relative rates can be accounted for by steric hindrance at the site of the attack. Secondary alcohols react slower than primary alcohols, whereas the various primary alcohols show but minor differences. Deno and Newman considered various mechanistic possibilities, of which a bimolecular mechanism (47, 48

$$ROH_2^+ + H_2SO_4 = ROSO_3H + H_3O^+ \quad (47)$$

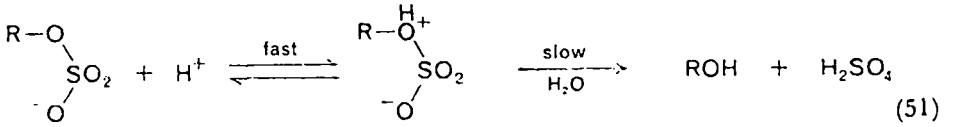
$$ROH + H_3SO_4^+ = ROSO_3H + H_3O^+ \quad (48)$$

$$ROH + H_2SO_4 = ROSO_3H + H_2O \quad (49)$$

or 49) seemed the most acceptable. Similar studies of the sulphation of 2,4-dinitrobenzyl alcohol, made by Williams and Clark[140], gave results which suggested an alternative, unimolecular rate-determining step (equation 50). The nature of the hypothetical reaction intermediate XH, the alcohol–sulphuric acid complex, was left open.

$$ROH + HSO_4^- \overset{\text{fast}}{\rightleftharpoons} X^-; \quad X^- + H^+ \overset{\text{fast}}{\rightleftharpoons} XH \xrightarrow{\text{slow}} ROSO_3H + H_2O \quad (50)$$

The existence of intermediary alcohol–sulphuric acid complexes in reaction (46) has found some support from a number of recent studies of the hydrolysis of hydrogen sulphate esters[138, 139, 141]. Thus, Batts[139] observed that the hydrolysis rates of methyl and ethyl hydrogen sulphates were increased by factors of about 10^7 when going from water to moist dioxan. Similar accelerations by solvents of low polarity had been previously noticed in the case of steroid hydrogen sulphates[142, 143]. These results can be rationalized only if the reactions involve charged species as the reactants and relatively nonpolar transition states. Accordingly, Batts[139] proposed the mechanism (51) with a rate-limiting decomposition of a zwitterion. A unimolecular decomposition of the zwitterion, with a sulphur



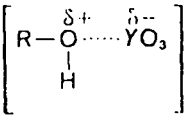
(51)

trioxide-like transition state, was preferred to covalent involvement of a water molecule. This hypothesis, which is discussed in some detail below, is essentially that made by Williams and Clark[140] for the reverse sulphation reaction (50), if one considers the complex XH as the zwitterion and does not account in detail for the individual reaction steps. It can be also argued that the apparent contradiction to the sulphation mechanism of Deno and Newman[136] with a bimolecular reaction between ROH and H_2SO_4 as the rate-limiting step (equation 49) is only in the degree to which the sulphur trioxide present in the transition state resembles the acid itself or the anhydride.

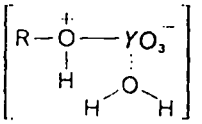
The main arguments given by Batts[139] for essentially unimolecular rate-determining steps in reaction (51) were, first, the variation of

the hydrolysis rate with the Hammett acidity function, and, second, the values of the activation entropies which were more positive than those generally associated with bimolecular *A*-2 reactions. One may further ask, whether the structural effects of the leaving groups on the hydrolysis rates, not discussed in detail by Batts, could be of value when making mechanistic conclusions. The relative hydrolysis rates in perchloric acid solutions were about 1, 1 and 3 for methyl, ethyl and *i*-propyl hydrogen sulphates, respectively. As these values are made up of the equilibrium constants of the protonation and of the rate coefficients for heterolysis of the alcohol molecules from the complex (equation 51), they may be compared directly with the effect of the leaving group on the rates of *A*-1 reactions involving the same alcohols. Thus, in the case of hydrolysis of formaldehyde acetals[31], the relative leaving rates (including the equilibrium protonation and the rate-determining heterolysis) are 1, 1·2 and 2·3, for methyl, ethyl and *i*-propyl alcohols, respectively. The effects of the leaving groups thus seem to follow the same structural pattern in both the reactions.

Some other recent studies also favour the unimolecular decomposition step with a sulphur trioxide-like transition state. In one of these investigations, the acid hydrolyses of phenyl and *p*-nitrophenyl sulphates were compared with that of methyl selenate[144]. Bunton and Hendy[145] had earlier presented strong evidence according to which the hydrolysis of the latter compound involved an *A*-2 type mechanism. The anhydride-like transition state **39** is relatively



(39) Y = S, Se



(40) Y = S, Se

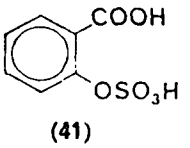
nonpolar, whereas the acid-like transition state **40** (*A*-2 mechanism), in which the $^{+}O-Y$ bond is cleaved to a smaller extent, still maintains much of its zwitterion character. One might therefore expect that in the former case the rate should increase much more markedly in solvents of low polarity than in the latter. This is actually the case as illustrated by the relative rates given in Table 6*.

* Alternatively, in terms of the theory advocated by Robertson[146], these solvent effects can be accounted for by the breakdown of the initial state solvation shells when the transition states **30** and **40** are approached, this breakdown being more complete in **39** than in **40**.

TABLE 6. Relative solvent effects on the acid hydrolyses of aryl sulphates and methyl selenate[141]. For both reactions, 40% dioxan–water is chosen as the reference solvent.

Solvent	Relative rate	
	Aryl sulphates	Methyl selenate
40% dioxan–water	1	1
60% dioxan–water	5·0	1·6
80% dioxan–water	67	6·3

Benkovic[147] has investigated carboxyl-substituted aryl sulphates **41** and **42**. The particular aim was to study the expected intra-



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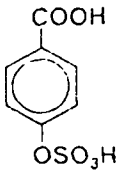


(42)

molecular carboxyl group catalysis in the case of salicyl sulphate (**41**). In fact, the pH–rate profile for **41** exhibited a plateau, as implied by involvement of the neighbouring carboxyl group, whereas in the case of **42**, with no possibility of such a neighbouring group participation, the rate decreased steadily with increasing pH. For the acid-catalysed reactions of both compounds the *A*-1 mechanism was suggested, first, because the activation entropies had positive values, and second, because the rate coefficients, along with earlier values, showed a marked increase with electron-attracting substituents. The relative rates in heavy and light water, k_D/k_H, were 1·30 and 2·34 for **41** and **42**, respectively. It was recognized that the former value, 1·30, is definitely within the range generally associated with an *A*-2 reaction. To overcome this controversy, the explanation was offered that the low value was due to the circumstance that the p*K* value of the protonation equilibrium (see equation 51) was lowered by intramolecular hydrogen bonding in the salicyl sulphate anion. Although this may be one of the factors involved, the magnitude of the isotope effect still seems to be surprisingly low, because in a series of similar acids the solvent deuterium isotope effect changes only slightly with the acid strength[148]. It is more likely that, if the

mechanism really is A-1 for both compounds, **41** and **42**, the main factors responsible for the different isotope effects are the free energies of transfer of the reaction participants from light to heavy water; energies which are incorporated in the experimental values of k_D/k_H[148]. This pertains particularly to the anions of **41** and **42**, the activity coefficients of which are expected to vary quite differently when going from H_2O to D_2O because of the intramolecular hydrogen bond present in the former anion. Additional studies of the solvent deuterium isotope effects on this and similar systems would seem desirable.

In a recent study, Benkovic and Benkovic[149] have further advocated sulphur trioxide-like transition states in the case of aryl sulphates. Table 7 shows some results of experiments in which the

TABLE 7. Amounts of methyl sulphate formed from aryl sulphates and sulphur trioxide in aqueous methanol[149]. The mole fraction of methanol in the solvent was 0·303.

Substrate	Reaction	Mole fraction l $MeOSO_3H$ in the product
Salicyl sulphate	Intramolecular catalysis	0·58
Salicyl sulphate	Hydronium ion catalysis	0·36
p-Carboxyphenyl sulphate	Hydronium ion catalysis	0·54
Monomeric sulphur trioxide	Solvolysis	0·58

relative amounts of methyl hydrogen sulphate and sulphuric acid formed from aryl sulphates in aqueous methanol were compared with those formed from sulphur trioxide in the same solvent. Except the acid-catalysed reaction of **41**, which also behaves abnormally here, the similar product compositions suggest that the product-forming stages of the reactions are similar.

b. Tertiary alcohols. In comparison with the conjugate acids of primary and secondary alcohols, those of tertiary alcohols have an enhanced tendency to dissociate to carbonium ions, which, even under relatively mild conditions, lead to products other than sulphate esters (e.g., olefins). In fact, tertiary alkyl sulphates have never been isolated from the reaction product, although their presence as reaction intermediates has sometimes been postulated.

An idea about the rate of formation of carbonium ions from tertiary alcohols in aqueous sulphuric acid, compared to that of

esterification of primary and secondary alcohols in the same medium, may be gained in the following way. Using the oxygen-18 technique, Taft and co-workers[150] measured the rate of reaction (52) in aqueous

$$(Me)_3COH + H^+ \overset{\text{fast}}{\rightleftharpoons} (Me)_3COH_2^+ \xrightarrow{\text{slow}} (Me)_3C^+ + H_2O \qquad (52)$$

sulphuric acid solutions at various acidities. When the rate coefficients are extrapolated to correspond to 70% sulphuric acid (see Table 5) it can be estimated that, in this solvent, *t*-butyl alcohol produces carbonium ions at a rate which is roughly 200,000 times that of the reaction of primary alcohols (forming alkyl hydrogen sulphates). Although the subsequent formation of isobutene is slower than the primary formation of the carbonium ion (by a factor of about thirty[151]), its rate still greatly exceeds that of the esterification.

c. Diesters of sulphuric acid. The second stage of the esterification of sulphuric acid (equation 53) has not been studied in detail, al-

$$ROSO_3H + ROH = (RO)_2SO_2 + H_2O \qquad (53)$$

though the presence of these esters in minor quantities has been recognized when treating primary alcohols with sulphuric acid. They are best obtained from alcohols with other sulphating agents[152, 153]. The mechanistic aspects of hydrolysis of the diesters, both open-chain and cyclic, have been dealt with in numerous studies (for literature, see References 138, 154–157). In general, the hydrolyses of the diesters are much more facile than those of the corresponding monoesters and involve both C–O and S–O cleavages, depending on the structure of the ester and external conditions.

From the experimental values given by Breslow, Hough and Fairlough[158] one can calculate a value of about 0·4 for the equilibrium constant of the disproportionation reaction (54) at temperatures of 25–50°C. As the equilibrium constant of reaction (55) is

$$2\ EtOSO_3H = (EtO)_2SO_2 + H_2SO_4 \qquad (54)$$

$$EtOH + H_2SO_4 = EtOSO_3H + H_2O \qquad (55)$$

about 2 (Table 5), one gets an estimate for the relative amounts of the mono- and di-esters at equilibrium. Thus, for example, if one starts from one mole of ethanol and one mole of sulphuric acid, the equilibrium mixture is calculated to contain 0·40 mole of ethyl hydrogen sulphate and 0·14 mole of diethyl sulphate, respectively.

3. Phosphoric acid

Although other phosphorylating agents (section IV.B.2), rather than phosphoric acid itself or its mixtures with anhydrides, are most

commonly used for the preparation of phosphate esters from alcohols, some structural effects involved in the formation and hydrolysis of these esters are discussed here because of their general interest. More extensive accounts have been published relatively recently[159-162].

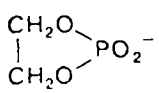
Noting that esterifications with phosphoric acid and their reverse hydrolysis reactions are formally similar (equation 56), some rationalizations can be made. First, the nature of the phosphate species

$$O{=}P(OR^1)_3 + R^2OH \rightleftharpoons O{=}P(OR^1)_2(OR^2) + R^1OH \qquad (56)$$
$$R^1, R^2 = H, \text{alkyl, aryl}$$

under attack, whether uncharged, deprotonated (anion) or protonated (cation), will depend on the acidity of the medium as well as on the relative rates of attack on the various species present simultaneously, even in minor quantities. This circumstance becomes evident from the complicated nature of the pH–rate profiles frequently observed in reaction (56).

Second, many, though not all, of the structural effects observed can be fairly well explained in terms of the electronic and steric factors involved in (56). Electron-releasing substituents in the phosphate species, like alkyl groups, render the attack on the hydroxyl group of the alcohol (or water) more difficult, and vice versa. Thus, the replacement of the second and third hydroxyl groups of phosphoric acid is extremely difficult as compared to that of the first. Similarly, trialkyl phosphates are much more stable toward hydrolysis than di- or mono-alkyl phosphates.

One peculiar aspect of nucleophilic attacks on phosphorus, which cannot be rationalized in terms of classical structure–rate relations, is illustrated by the fact that the cyclic ethylene phosphate anion (**43**) is hydrolysed faster than its acyclic analogue **44** by a factor which is about eight powers of ten[163, 164]. In view of the observation



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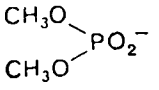


(44)

that the hydrolysis of **44**, unlike that of **43**, also contains a contribution from simultaneous C–O fission, the actual rate enhancement in the nucleophilic attack on phosphorus is even greater than the above-mentioned ratio. As the six-membered analogue of **43**, trimethylene phosphate anion, reacts at a rate comparable to that of **44** [165], it was assumed earlier that the acceleration was due to

release of the strain present in the five-membered ring. However, calorimetric measurement of the heats of hydrolysis of **43** and **44** showed that this strain is only about 5·5 kcal/mole[154], which would account for only 10^4-fold acceleration even in the extreme situation in which the strain would be wholly released at the transition state. It is more likely that open-chain phosphates like **44** are stabilized by π-type bonding involving the 3*d* orbitals on the central phosphorus atom[154, 166], whereas such a stabilization, on stereochemical grounds, is not possible for **43**. Similar argumentations may, of course, apply to esters derived from the oxyacids of sulphur, but not to esters with a second-row element as the central atom, like carbon, nitrogen or boron.

Molecular orbital calculations on the oxygen-2*p*–phosphorus-3*d* interactions in phosphate esters[167] are in fair agreement with the observations discussed above. One of the most striking results of these calculations is that the electrophilic reactivity of the central phosphorus, as measured by its calculated charge density, is greatly dependent on the conformation of the groups about this atom. This factor may have an important role, e.g., in bioorganic systems involving formation and decomposition of phosphate esters.

Whereas extensive data exist on the hydrolytic cleavage of phosphates and related esters[154, 159–173], very few and fragmentary studies have been made on the phosphorylation of alcohols and phenols with phosphoric acid. Mesnard and Bertucat[174] phosphorylated primary, secondary and tertiary alcohols with phosphoric acid using pyridine as the solvent. Very low yields were obtained in the case of tertiary alcohols.

If stronger phosphorylating agents are used, such as phosphoric acid or polyphosphoric acid, tertiary alcohols are mainly dehydrated[175] without noticeable ester formation. However, tertiary alcohols in which one of the alkyl groups has been replaced by a –COOR, –CN or $-CONH_2$ group, are reportedly acetylated to an extent of about 15%[175].

Clarke and Lyons[176] have studied the various products formed when phosphorylating alkanols with polyphosphoric acids of different average chain lengths. Acid–base titrations and phosphorus-31 n.m.r. were used in the analyses. No dialkyl esters of orthophosphoric acid could be detected among the reaction products, which was explained in terms of the steric and inductive effects, rendering an alkoxy-substituted phosphorus less susceptible to a nucleophilic attack in comparison to that of phosphoric acid (see above).

TABLE 8. Sites of cleavage and relative rates for the hydrolytic decomposition of monoalkyl phosphates $ROPO_3H_2$ in 4M perchloric acid at 100°C [169, 171].

R	Relative rate	% P–O cleavage	Mechanism
Methyl	1	27	*A*-2
Ethyl	0·66	48	*A*-2
i-Propyl	70	1	*A*-1
t-Butyl	1400 [a]	0	*A*-1

[a] Extrapolated from data at lower temperatures.

Table 8 illustrates some of the structural effects observed in the hydrolytic cleavage of alkyl phosphates. Differing from the acid hydrolysis of the esters of carboxylic acids, the change to an *A*-1 type mechanism occurs here when going from ethyl to *i*-propyl ester.

The hydrolyses of monoaryl phosphates are subject to acid catalysis only if the aryl group possesses a strongly electron-withdrawing substituent, such as a nitro or an acetyl group in the *para* position[172].

Intramolecular catalysis in a number of *o*-carboxyaryl phosphates has been studied in detail[168].

An observation of considerable interest for the study of acid-catalysed ester hydrolysis and esterification has been made by Bunton and co-workers[173, 177]. They investigated the hydrolyses of triphenyl and *p*-nitrophenyl diphenyl phosphates in moderately concentrated mineral acids and found the rates to exhibit maxima at 1·5–6M acid. Similar maxima had been observed earlier in such acid-catalysed reactions in which the substrate was basic enough to become wholly protonated, but the point here was that the maxima were not caused by the protonation, as shown by basicity measurements conducted independently. The results, which were rationalized in terms of the activity coefficient behaviour of the reactants and transition states in solutions of strong acids, expose the Achilles heel in mechanistic conclusions drawn from the rate-acidity relations.

4. Nitric acid

Esterification of alcohols with nitric acid is most familiar from the preparation of common explosives, the nitrate esters of glycerol ('nitroglycerine') and cellulose ('nitrocellulose'). The usual pro-

cedure is to add the alcohol slowly to cold acid (100% acid, its solution in an inert solvent, or, most commonly, its mixture with sulphuric acid), and to separate the ester by pouring the mixture into cold water[178]. Small amounts of urea are added to the mixture to destroy the nitrous acid present, since otherwise violent explosions might occur.

Klein and Mentser[179], using the oxygen-18 tracer technique, were the first to prove that the oxygen atom of the alcohol remains intact through the process; the reaction thus involves an electrophilic attack on this oxygen atom. The reaction mechanism, shown in equations (57) to (59), has been subsequently clarified by Ingold and co-workers[180].

$$HNO_3 + HNO_3 = H_2NO_3^+ + NO_3^- \text{ (fast)} \quad (57)$$

$$H_2NO_3^+ = NO_2^+ + H_2O \quad (58)$$

$$ROH + NO_2^+ = R\overset{+}{O}(H)NO_2 \quad (59)$$

Under conditions in which the medium does not contain substantial amounts of water, the reaction rate is of the zeroth order with respect to the alcohol and, moreover, different alcohols are esterified at equal rates which are the same as those for the *N*-nitration of amines and *C*-nitration of benzenoid hydrocarbons in the same media. When sufficient amounts of water are added to the solution the reaction becomes first-order with respect to the alcohol and exhibits individual differences which depend on the alcohol. An addition of sulphuric acid preserves the zeroth-order kinetics, but enhances the rate of esterification.

The facts enumerated above are readily understood in terms of reactions (57) to (59). In solutions of low water content, the reversal of the nitronium ion formation will be slow and it does not effectively compete with the nitronium ion–alcohol reaction (59). Put another way, the nitronium ions are captured by the alcohol molecules (or by other reactants, such as benzenoid hydrocarbons) as fast as they become available from the dehydration of the nitric acidium ion. In contrast, in solvents with appreciable amounts of water, the rate of the reaction between the nitronium ion and water becomes significant and, consequently, the electrophilic attack on the alcoholic hydroxyl by the nitronium ion (reaction 59) becomes rate-determining. The relative rates of attack by this ion on different nucleophiles were estimated as: water ~0·03; benzene 1; *N*-methyl-2,4,6-trinitroaniline 1·4; toluene 24; methanol 30.

Depending on the structure and external conditions the hydrolytic decomposition of nitrate esters may lead to three different products (equations 60–62). The experiments conducted by Baker

$$RONO_2 + H_2O = ROH + HNO_3 \quad (60)$$

$$RCH_2CH_2ONO_2 + H_2O = RCH{=}CH_2 + H_2O + HNO_3 \quad (61)$$

$$RCH_2ONO_2 + H_2O = RCHO + H_2O + HNO_3 \quad (62)$$

and co-workers[181–183] showed that for primary and secondary alkyl nitrates (and for aryl nitrates, having no available sites for elimination), the substitution reaction (60) predominated whereas concurrent elimination normally took place with tertiary alkyl nitrates. The structural and solvent effects observed followed the general pattern of substitution–elimination reactions.

Cryoscopic and spectrophotometric measurements on solutions of alkyl nitrates in 100% sulphuric acid[184] indicate the occurrence of reactions (63) to (65), which produce four ionic species from one molecule of nitrate ester. Because the alcohol formed in reaction (64) (reversal of reaction 59) is subsequently esterified by sulphuric acid (reaction 65), the nitrate ester is not regenerated when the reaction solution is poured into water.

$$RONO_2 + H_2SO_4 \longrightarrow RO^{+}(H)\text{—}NO_2 + HSO_4^- \quad (63)$$

$$RO^{+}(H)\text{—}NO_2 \longrightarrow ROH + NO_2^+ \quad (64)$$

$$ROH + 2\,H_2SO_4 \longrightarrow ROSO_3H + H_3O^+ + HSO_4^- \quad (65)$$

5. Boric acid

The esterification of boric acid with alcohols, in particular with polyhydroxylic compounds, is the subject of a considerable literature[185, 186]. Although many practically and mechanistically important features of the reaction are becoming understood, yet definite, quantitative equilibrium and kinetics data on relatively simple model systems are still virtually nonexistent.

The preparation of simple, symmetric alkyl or aryl triesters of boric acid usually takes place according to equation (66). The ester

$$B(OH)_3 + 3\,ROH = B(OR)_3 + 3\,H_2O \quad (66)$$

formation is monitored by removing the triester or water from the reaction zone, usually by means of azeotropic distillation. No mono- or di-esters have been isolated from the reaction mixture, other methods having been used for their preparation in particular cases[185]. For simple alkanols the equilibrium constants given in Table 9 have been reported[187]. It is seen that a lengthening of the alkyl chain

TABLE 9. Equilibrium constants for reaction (66) in acetone solution at 0°C [187].

Alcohol	Ester percentage at equil.	$K_{equil.}$
Methanol	33	0·062
n-Propanol	44	0·37
n-Butanol	45·5	0·48
n-Pentanol	46·5	0·55

increases the amount of ester at equilibrium; a comparable effect also becomes evident from the kinetic stability of these esters towards hydrolysis[188]. The general observation that the hydrolytic displacement of the first alkoxy group in boric triesters is much slower than those of the second and the third is in harmony with the polar and steric factors influencing the Lewis acidity of the central boron atom.

An interesting kinetic study, which clarifies many features of the formation and hydrolysis of aryl borates, has been recently published by Tanner and Bruice[189].

B. Miscellaneous Heteroatomic Electrophiles

1. Sulphur trioxide, halogen compounds of sulphur, etc.

The reaction of an alcohol with sulphur trioxide, oleum or a pyrosulphate differs from esterification with the acid itself in that the reaction is virtually irreversible. Ordinarily, these reagents bring about side reactions (oxidation, dehydration) and are therefore rarely used as such. A great number of sulphur trioxide complexes with various electron donors have been devised to prevent the side reactions, e.g., complexes with dimethylformamide[190, 191], dioxan[192] and tertiary amines[193]. In all cases the function of these electron donors is to moderate the reactivity of the anhydride, leading to more specific sulphating properties. They thus act in the same way as various bases in the Schotten–Baumann acylation of alcohols.

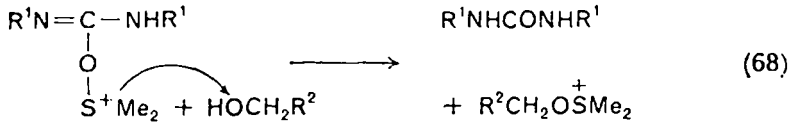
Preparation of sulphate esters with other sulphating agents, like chlorosulphonic acid, has been discussed elsewhere[152, 153].

A novel route to symmetric and unsymmetric tertiary amines from alcohols and sulphamoyl chlorides (equation 67) has been

$$R^1OH + ClSO_2NR^2_2 \longrightarrow R^1OSO_2NR^2_2 \xrightarrow{\Delta} R^1R^2_2N^+\text{–}SO_3^- \xrightarrow{H_2O} R^1R^2_2N \qquad (67)$$

reported by White and Ellinger[194]. The reaction was studied with R^2 = methyl, though it was considered probable that the reaction could also be applied to the preparation of primary and secondary amines (with two or one of the groups R^2, respectively, replaced by hydrogen atoms). The rearrangement step following the attack with sulphamoyl chloride was proposed to take place by the S_Ni mechanism, in accordance with the observed retention of configuration at R^1 and with the influence of the polar character of R^1.

Moffatt and co-workers[195–197] have recently studied the reaction with sulphoxide-carbodiimide adducts (equation 68). The reaction involves an electrophilic attack on the hydroxyl group, as shown by

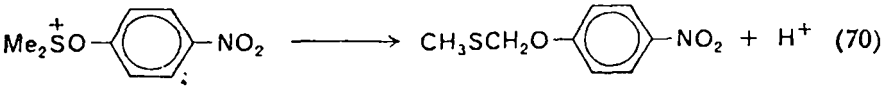


(68)

experiments with oxygen-18 [196]. As the alkoxy sulphonium ion is readily transformed (probably via an intramolecular rearrangement) to dimethyl sulphide and an aldehyde or a ketone (equation 69), the

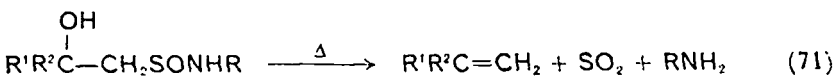
$$R^2CH_2\overset{+}{O}SMe_2 \longrightarrow RCHO + Me_2S + H^+ \qquad (69)$$

reaction is useful for a facile oxidation of alcohols to the corresponding carbonyl compounds under extremely mild conditions. In the case of phenols substituted at the *ortho* position, a number of different products were obtained. Strongly acidic phenols gave phenol ethers (equation 70).

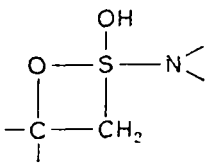


(70)

Several new, useful syntheses have been described which probably involve intramolecular electrophilic attacks on the hydroxyl group



(71)



(45)

by a sulphur atom. As an example, the thermal decomposition of β-hydroxysylphinamides (themselves obtained from sulphinamides, BuLi and R^1R^2CO) to alkenes[198] may be mentioned (equation 71). The reaction proceeds most probably through a cyclic intermediate, **45**, which subsequently, via 1,2-cycloelimination, leads to the olefin. This mechanism found strong support from experiments which showed that the reaction took place by the *cis* elimination.

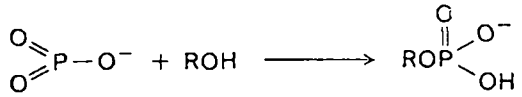
2. Electrophiles containing phosphorus

Various phosphorylation methods have been reviewed by Brown[159]. Whereas several convenient procedures are available for the preparation of di- and tri-substituted phosphate esters, relatively few methods have been designed for the synthesis of monoalkyl dihydrogen phosphates. One of the latter is that of Kirby[199], in which the solution of phosphorous acid in a large excess of alcohol is oxidized with iodine. The major disadvantage is that the method is not economic in case of alcohols which are available in only small amounts.

A novel synthesis of monoalkyl phosphates has been described by Obata and Mukaiyama[200]. A variety of monoalkyl phosphates could be obtained in good yields from reaction of alcohols with phosphorous acid and mercuric salts in the presence of tertiary amines (equation 72). When acetonitrile was used as the solvent

$$HPO(OH)_2 + ROH + HgX_2 \longrightarrow ROPO_3H_2 + Hg + 2\,HX \qquad (72)$$

only small excesses of alcohol were required. The investigators proposed an electrophilic attack of an intermediate metaphosphate anion (equation 73) on the hydroxyl group as the key step of the



(73)

reaction, the anion being first formed by oxidation with mercuric salt. It can be seen that reaction (73) has its counterpart in the formation and hydrolysis of sulphate esters (section IV.A.2).

In addition to the halides and oxyhalides of phosphorus, some substituted halides of phosphorus and their reactions with alcohols have drawn the attention of several investigators. Thus, e.g., methyl chloromethyl phosphinate (**46**), which is easily obtained by reaction (74), is shown to have many synthetic uses[201].

Ramirez and co-workers[202, 203] have made extensive studies on the formation and reactions of pentaoxy phosphoranes, $P(OR)_5$.

$$ClCH_2PCl_2 + 2\ CH_3OH \longrightarrow \underset{\underset{H}{|}}{ClCH_2P(=O)-OCH_3} + CH_3Cl + HCl \quad (74)$$

(46)

They showed that the earlier reports on the formation of pentaphenoxy phosphorane in reactions (75) and (76) were inconsistent.

$$PCl_5 + 3\ PhOH \xrightarrow{140°C} (PhO)_3PCl_2 + 3\ HCl \quad (75)$$

$$(PhO)_3PCl_2 + 2\ PhOH \xrightarrow{25°C} (PhO)_5P + 2\ HCl \quad (76)$$

However, when the reactions were carried out at low temperatures in hexane–benzene solution and in the presence of a tertiary amine, the pentaoxy phosphorane could be synthesized. The structure of the reaction product was ascertained by phosphorus-31 n.m.r. spectroscopy. A number of other cyclic pentaoxy phosphoranes with alkoxy groups attached to the central phosphorus atom were also described.

3. Electrophiles containing nitrogen, boron, etc.

In addition to the reaction with nitric acid (section IV.A.4), the *O*-nitration of alcohols can be effected by the use of other *O*-nitro or *N*-nitro compounds. The most commonly used reagents are benzoyl and acetyl nitrates[204, 205] (equation 77). The kinetics of the reaction have been recently studied by n.m.r. spectroscopy[205].

$$CH_3COONO_2 + ROH \longrightarrow RONO_2 + CH_3COOH \quad (77)$$

Transesterification (e.g., equation 78) is in several instances a convenient means for the preparation of esters of inorganic acids. Ordinarily, an ester of lower molecular weight is converted to one of higher molecular weight. The transesterification is easily effected if the liberated alcohol is of lower boiling point than the other components of the reaction mixture and can be removed by distillation. Alternatively, the required ester may be the most volatile constituent. The practical and mechanistic aspects of these transesterification reactions are usually similar to those of the hydrolysis reactions of the esters in question.

$$B(OR^1)_3 + 3\ R^2OH \longrightarrow B(OR^2)_3 + 3\ R^1OH \quad (78)$$

Electrophilic attacks on the hydroxyl group by halogens, yielding 'positive' halogen compounds, have several uses in organic synthesis. A familiar example is the formation of *t*-butyl hypochlorite from *t*-butanol and chlorine[206] in alkaline solution (equation 79). A

$$Me_3COH + Cl_2 + NaOH \longrightarrow Me_3COCl + NaCl + H_2O \quad (79)$$

recent application of *t*-butyl hypochlorite is the radical chain halogenation of alkenes and alkynes[207]. Ring cleavage of cyclopropanols with various 'positive' halogen compounds, including *t*-butyl hypochlorite, has been recently studied by DePuy, Arney and Gibson[208].

Several oxidation reactions of alcohols, including the reaction with lead tetraacetate[209-214], are initiated by electrophilic attacks on the hydroxyl group. As the subsequent stages of these reactions, leading to a variety of products, are those of primary interest in their applications, a detailed discussion is beyond the scope of this chapter.

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CHAPTER 10

Oxidation and reduction of phenols

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I. INTRODUCTION

One of the characteristic chemical properties of phenols is their facile oxidative conversion to compounds of different structural types. The diversity of phenol oxidation products offers interesting synthetic possibilities for the preparation of simple and polymeric molecules containing phenolic and/or quinonoid structural elements, particularly of those resulting from oxidative coupling of both like and unlike intermediate radical species[1-8]. In this way various natural products have been successfully synthesized from phenols[1, 4-6, 8]. In addition, mechanistic studies of oxidation reactions of phenols[1-8] have lent strong support to the interpretation that a number of biosynthetic processes actually proceed by biogenetic pathways involving the oxidative utilization of phenolic substrates[1, 4-6, 8].

The long-known fact that substituted phenols and the corresponding phenoxy radicals are efficient inhibitors in autoxidation processes of organic substances[9-11] has stimulated in recent years the development of chemical and physical methods, particularly of electron spin resonance (e.s.r.) spectroscopy, for the study of the detailed structure of phenoxy (and other) radicals and of their role as intermediates in free radical reactions[12, 13].

In this chapter the principles and the scope of oxidation and reduction of monohydric and polyhydric phenols are reviewed.

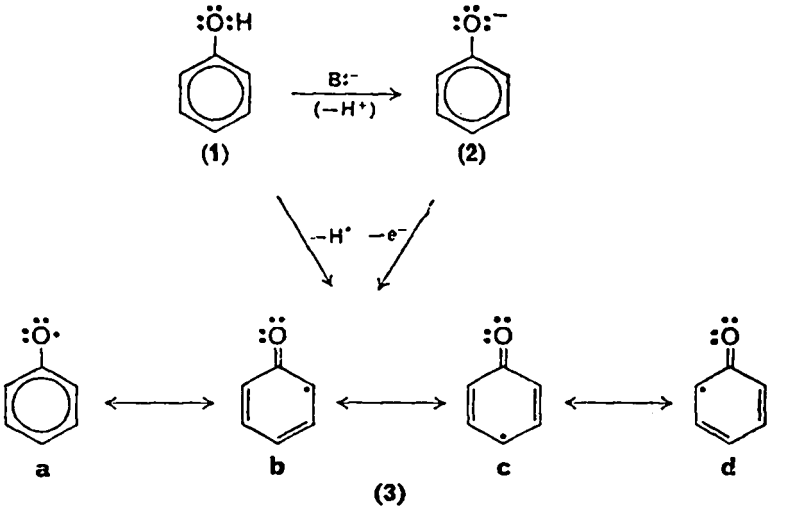
II. OXIDATION OF PHENOLS

A. Mechanism of One-Electron Oxidations

1. Phenoxy radicals and quinone methides

The first step in the oxidation of monohydric phenols, by oxidizing agents capable of one-electron abstraction[6, 8, 12, 14], such as lead

dioxide, silver oxide, manganese dioxide, ferric and ceric ions, electrochemical methods[15], alkaline potassium ferricyanide[2] and others, consists in the generation of free phenoxy radicals (**3**) (equation 1), either by homolytic cleavage of the O–H bond in the phenol (**1**) with loss of the hydrogen atom or by loss of one electron from the corresponding phenoxide anion (**2**). These phenoxy (or aryloxy)



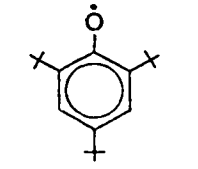
(3) (1)

radicals (**3**), which may be formally defined as monovalent oxygen radical species, are resonance-stabilized by delocalization of the unpaired electron over the aromatic ring, as shown by structures **3a–d**[1–8, 12, 13].

Although phenoxy radicals with *ortho* and/or *para* unsubstituted positions usually undergo further reactions very rapidly[1–8, 12, 13], because of resonance stabilization they have a longer lifetime than alkyl or aryl radicals and they do not attack the solvent or initiate polymerization (e.g., by removal of hydrogen from C–H bonds) as readily[6, 7]. Their transient existence, which was postulated mainly on the basis of chemical reactivity, has recently been confirmed by e.s.r. spectroscopy using a flow system technique[7, 16, 17]. The mean lifetime of the simplest phenoxy radical (**3**), derived from phenol itself, has been estimated to be about 10^{-3} second[7, 16].

For the production of 'stable' phenoxy radicals, which may survive for a sufficient time to be used as substrates for other experiments or which may exist in solution (and in certain cases in the solid state) over periods of hours or even days (in the presence of limited amounts of air), it is necessary that the reactive *ortho*- and *para*-positions be

blocked by suitable groups which give increased resonance stabilization or steric protection, since 2,4,6-trisubstitution usually retards or prevents further reaction (i.e. addition or substitution)[1-8] and the absence of α-CH groups in the substituents prohibits formation of quinone methides[18-21]. Some of these free aryloxy mono- and diradicals, e.g., **4** [22-25], **5** [26-32] and **6** [33], are highly coloured and stable both in solution and as solids[6, 12, 13], whereas others exist in the crystalline state as colourless dimeric quinol ethers, such as **7** [34-38], which in solution dissociate to varying degrees into coloured radicals[6, 12, 13], e.g. **8** [34-38]. It is interesting to note that when a benzene solution containing the red 2,4,6-triphenylphenoxy radicals (**8**) in equilibrium with the corresponding quinol ether **7** is treated with strong mineral acid (equation 2), a salt of the resonance-



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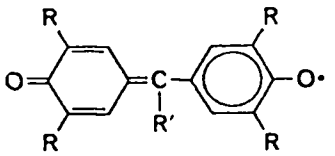
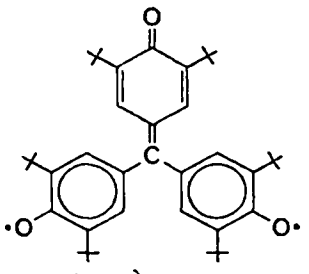


solid and solution, coloured
(a) R = *t*-Bu, R' = H
(b) R = *t*-Bu, R' = Ph
(c) R = OMe, R' = H

(5)



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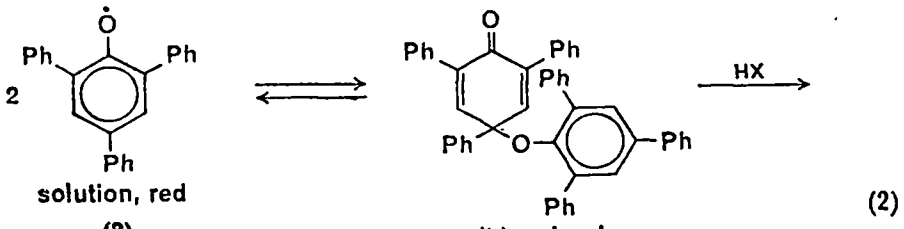
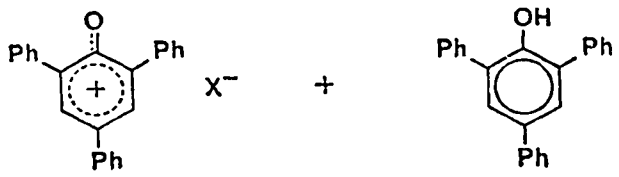


solution, red
(8)

solid, colourless
(7)

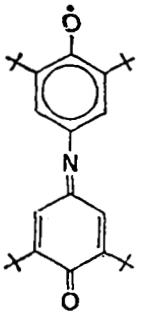
(2)



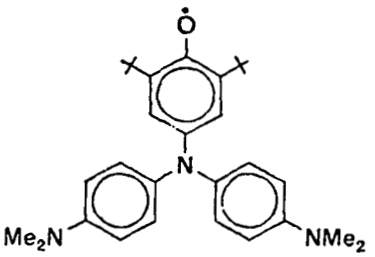
solution, blue
(9)

stabilized phenoxonium ion (**9**) is formed and the reaction mixture turns deep blue[39].

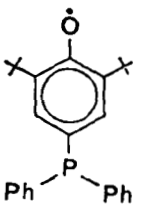
Aryloxy radicals with heteroatoms can also be prepared, as illustrated by examples of the nitrogen-containing radicals **10** [40] and **11** [41], which are very stable to oxygen and exist as such in the solid state, and of the moderately stable to unstable radicals **12** [42] and **13** [43] containing phosphorus and sulphur, which have been generated only in solution.



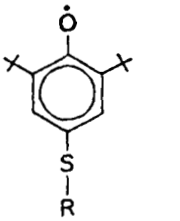
(**10**)



(**11**)



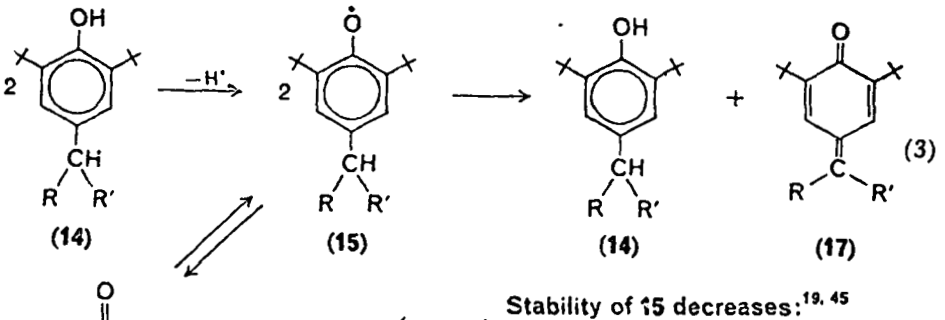
(**12**)



R = Me, *t*-Bu, Ph

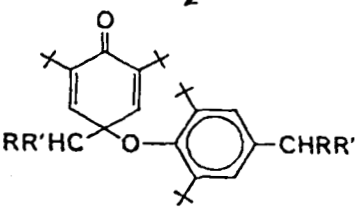
(**13**)

Stable free aryloxy radicals, such as galvinoxyl (**5a**) and 2,6,3′,5′-tetra-*t*-butylindo-phenoxyl [BIP] (**10**), which remain unchanged in



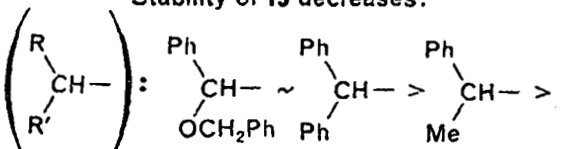
(**14**) (**15**) (**14**) (**17**)

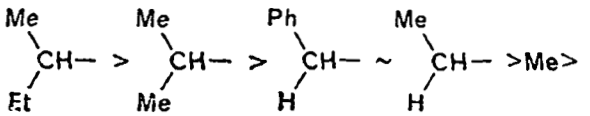
(3)



(**16**)

Stability of **15** decreases:[19, 45]





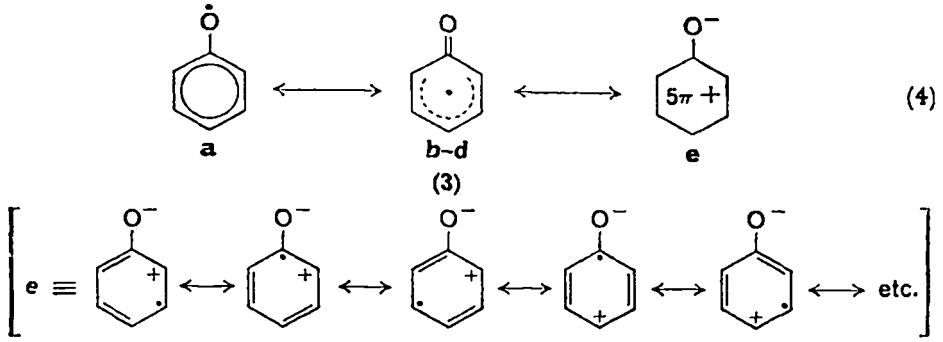
the solid state for months or years, have been used as efficient scavengers of alkyl and alkoxy or phenoxy radicals[28, 44, 45].

Hindered phenols (e.g., phenols with 2,6-di-*t*-butyl groups) containing an α-CH in the *para*-substituent can also be oxidized by one-electron abstracting agents (alkaline potassium ferricyanide, lead dioxide, silver oxide, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, etc.) to the corresponding phenoxy radicals (**15**) [12, 13]. These are only of moderate stability (a few hours) or of transient existence and undergo spontaneous irreversible disproportionation (equation 3), usually according to second-order kinetics[46, 47], to the parent phenols (**14**) and quinone methides (**17**) [18–21, 46, 47], which, depending on their stability, react further on (see section II. C.1) or can be isolated from the reaction mixture[18–21, 46–50].

2. Characterization and structure of phenoxy radicals

The existence and nature of aryloxy radical species, particularly of the more stable phenoxy radicals, has been investigated and established by various methods, such as chemical reactivity studies, magnetic susceptibility measurements and analysis of infrared, ultraviolet-visible, n.m.r. and e.s.r. spectral data.

Phenoxy radicals are paramagnetic[24, 30, 51–53], and usually show in their infrared spectra a broad strong band in the 1560–1600 cm^{-1} region [which probably arises from the contribution of the quinonoid resonance structures (**3b–3d**) (equations 1 and 4)] and a weak to medium band in the 1500 cm^{-1} region [which might correspond to resonance structures involving charge separation (**3e** in equation 4)][1, 12, 24]; they differ markedly from the diamagnetic colourless dimeric quinol ethers (e.g., **7** and **16**) which have a doublet at 1660

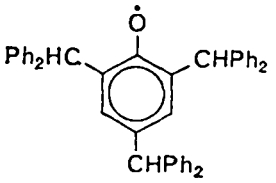


(4)

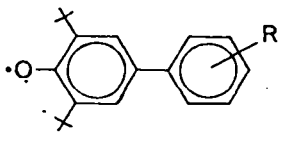
and 1640 cm^{-1} in the infrared spectrum[35, 52]. The electronic spectra of phenoxy radicals are quite different from those of the parent

phenols and show several maxima in the ultraviolet and visible regions[12]. These bands and the characteristic brilliant colours of most phenoxy radicals represent further evidence for the contribution of quinonoid and dipolar resonance structures **3b–3d** and **3e** (equations 1 and 4), respectively.

Particularly useful information regarding the detailed structures of phenoxy radicals, the mechanisms of phenol oxidation which involve radical species as intermediates and the characterization of new radicals has been obtained by the application of electron spin resonance spectroscopy. The determination of the *g*-values shows that stable aryloxy radicals, such as 2,4,6-tri-*t*-butylphenoxy radicals (**4**), have a very high radical content, which is close to the value ($g = 2{\cdot}0023$) for the completely free electron[24, 53, 54]. Analysis of the hyperfine splitting constants of the e.s.r. spectra of phenoxy radicals, particularly of the stable 2,4,6-tri-*t*-butylphenoxy (**4**) [53, 55, 56], 2,4,6-tris(diphenylmethyl)phenoxy (**18**) [55, 56], various 2,6-di-*t*-butyl-4-(substituted phenyl)phenoxy (**19**)[57], and 2,4,6-triphenylphenoxy radicals (**8**)[58], including the corresponding ^{17}O- and in the ring ^{2}H- and ^{13}C-labelled radicals[55–62], indicates[12, 13, 16, 17, 19, 31, 42, 52, 53, 55–60] (a) that all six carbon atoms in the central ring as well as the oxygen show a spin density for the unpaired electron; (b) that



(18)



(19)

a relatively high spin density resides on the oxygen; (c) that of the central ring carbon atoms the *para*-carbon (C-4) shows a considerable spin density which is higher than that on the *ortho*-carbons (C-2 and C-6), and that the densities at C-1 and the *meta*-carbons (C-3 and C-5) are low but not zero; (d) that the unpaired electron can also distribute itself over alkyl substituents and heteroatoms; (e) that in phenoxy radicals carrying phenyl groups in the *para*- and/or *ortho*-positions (such as **8**), the spin density of the odd electron is distributed over all phenyl substituents present in the radical, but that it is higher in the *p*-phenyl group than in the *o*-phenyl residue, probably because the latter is forced out of the molecular plane by the phenolic oxygen. Spin densities of the unpaired electron in some

short-lived and stable phenoxy radicals, found experimentally or calculated from available spectral data, are given in Table 1.

TABLE 1. Spin density distribution for some aryloxy radicals.

Radical	Spin density ρ					Refs.
	O	C-1	C-2, C-6	C-3, C-5	C-4	
Phenoxy[a]	[c]	—	0·28	−0·075	0·42	7, 16, 17, 63
4-Methylphenoxy	[c]	—	0·25	−0·06	0·44	16, 17
2,4-Dimethylphenoxy	[c]	—	0·24	−0·07	0·40	
2,4,6-Trimethylphenoxy	[c]	—	0·22	−0·06	0·44	
2,4,6-Tris(diphenylmethyl)phenoxy[b]	0·5	−0·06	0·176	−0·071	0·352	55, 56
2,4,6-Triphenylphenoxy	0·26	0·03	0·211	0·055 (0·065)	0·219	58

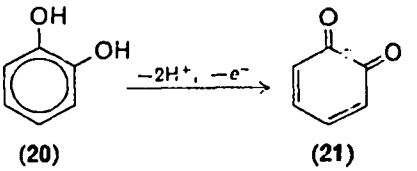
[a] The recalculated values are as follows[58]: C-2 and C-6, 0·255 (0·246); C-3 and C-5, 0·070 (0·066); C-4, 0·374 (0·374).
[b] It was stated[55, 56] that a similar distribution should be generally valid for 4-R-2,6-di-*t*-butylphenoxy radicals[57, 60].
[c] Not calculated.

These and other data on the distribution of the odd electron spin density substantiate the resonance-hybrid structure of aryloxy radicals (equations 1 and 4), inferred previously from chemical reactivity, and are in agreement with some experimentally observed chemical properties, e.g., with the finding that phenoxy radicals undergo coupling reactions only at the *o*- and *p*-positions, whereby *para*-coupling usually predominates (see section II.C.1).

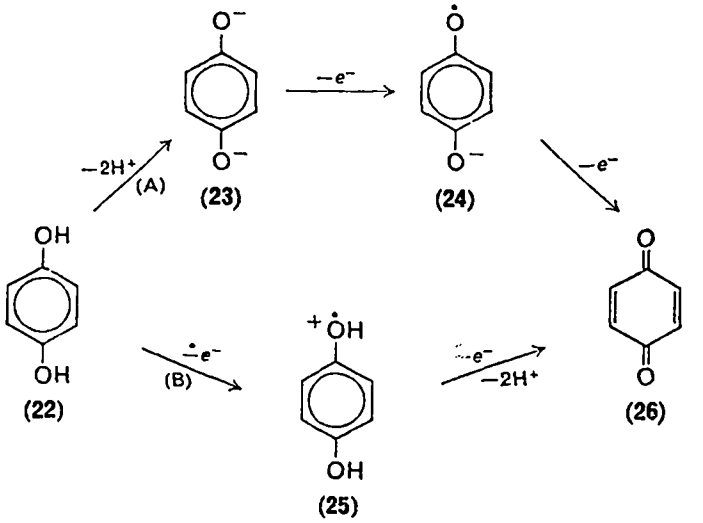
Although e.s.r. spectroscopy has already given valuable information about the ground state structures of phenoxy radicals and therefore offers the best approach to relative radical stabilities, further and more detailed studies are necessary in order to obtain additional and reliable knowledge on the influence of electronic and steric effects of substituents on the stability (as measured by intensity and duration of e.s.r. signals) and reactivity (as measured, for example, by rate of reaction with oxygen or of coupling dimerization) of aryloxy radicals[12].

Catechol (**20**) and hydroquinone (**22**), and their derivatives, are converted by most oxidizing agents to the corresponding *o*- (**21**) and *p*-quinones (**26**), respectively (equations 5 and 6) which, depending on reaction conditions, can either be isolated or react further, particularly with nucleophilic reactants[4, 6]. Complex polymers of the

humic acid-type are often the main products. Here too, the initial step (equation 6) consists of a one-electron transfer with formation

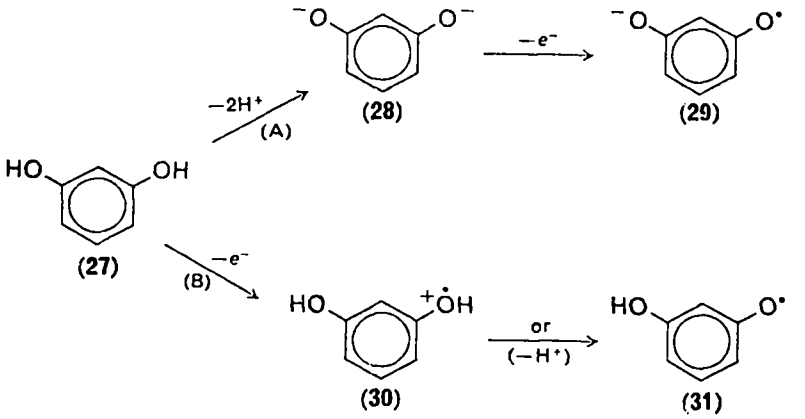


(5)



(6)

of a semiquinone radical which has usually a sufficiently long lifetime—in alkaline solution (pathway A) in the form of the symmetrically resonance-stabilized anion **24** (which arises from the intermediate dianion **23**) and in acidic solution as the cation **25**—that it can be detected and characterized by titration[64], spectroscopically[65, 66] or by e.s.r. measurements[67–70]. In the case of 2,4-di-*t*-butylcatechol, the alkali-metal salts of the semiquinone radical anion have been isolated in the form of their crystalline etherates[71]. The oxidation of resorcinol (**27**) and its derivatives[5, 6], which proceeds at a slower rate than that of catechols and hydroquinones[72], cannot give rise to products of the quinone type on removal of two electrons. Hence resorcinols (**27**) behave as monophenols, whose oxidation potentials are lowered by the second hydroxyl group, and afford as primary product, upon one-electron oxidation (equation 7), an unstable *m*-benzosemiquinone, either in the anion form **29** (e.g., when the oxidation of **27** is performed with an alkaline solution of potassium ferricyanide; pathway A)[5, 6, 73] or in the cationic (**30**)



(7)

or neutral form (**31**) (e.g., when the oxidation is carried out with an acid solution of ceric sulphate; pathway B)[74]. These short-lived radicals have been detected and analysed by e.s.r. spectroscopy[73], using a rapid-flow technique[16, 17].

B. Oxidation Potentials

The relative ease of oxidation of phenols to phenoxy radicals can be estimated from relative oxidation potentials corresponding to the half-wave potentials determined by polarographic methods[6, 15, 72, 74, 75]. Actually, thermodynamic redox potentials should be used for comparing oxidation rates, but these can only be measured for reversible systems, such as catechol/*o*-quinone (equation 5)[6, 72], hydroquinone/*p*-quinone* (equation 6)[6, 72] and phenol/stable phenoxy radical (equation 1) equilibria[76]. Most of the monohydric phenol (and resorcinol) oxidations are practically irreversible on account of further fast reactions of the initially formed aryloxy radicals[6, 12, 72], and therefore thermodynamic redox potentials for such systems cannot be determined experimentally†. However, since it was shown[72, 76, 81] that polarographic half-wave potentials for reversible systems are comparable, at least in their sequence, with the actual redox potentials, it is possible to use relative oxidation (e.g., half-wave) potentials of irreversible phenol oxidations, obtained by polarographic analysis, as a measure of phenol oxidizability.

* The equilibrium (reaction 6A) quinone (**26**) + hydroquinone (**22**) ⇌ semiquinone (**24**) is established very rapidly, with $k_1 = 2{\cdot}6 \times 10^8$ mole^{-1} sec^{-1} [65].

† The ease of phenol oxidation can be approximately gauged in terms of Fieser's 'critical' or 'apparent redox' potentials[77], which refer essentially to the oxidizing powers of suitable inorganic oxidants[6, 78, 79]. A rough but significant correlation exists between Hammett's σ-values and Fieser's critical potentials[80].

The values given in Table 2 [12, 15, 74] show on general lines that

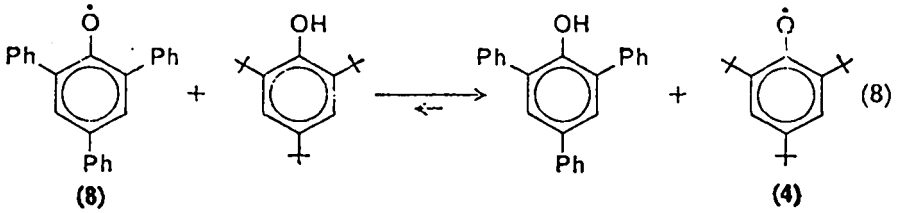
TABLE 2. Relative oxidation potentials of phenols (E in millivolts).

Phenol	$E_{\frac{1}{2}}$	Ref.	Phenol	$E_{\frac{1}{2}}$	Ref.
Phenol	+1004	82[a]	4-Phenyl-2,6-dicyano	> +800	
4-Methyl	543		4,6-Diphenyl-2-cyano	593	
3-Methyl	607		2,6-Diphenyl-4-cyano	549	
2-Methyl	556		Pentaphenyl	366	
4-Methoxy	406		2,4,6-Triphenyl-3-cyano	433	
3-Methoxy	619		3-Chloro-2,4,6-triphenyl	347	
2-Methoxy	456		2,3,4,6-Tetraphenyl	238	
4-Nitro	924		2,4,6-Triphenyl	211	
3-Nitro	855	83[b]	4-Fluoro-2,6-diphenyl	164	75[d]
2-Nitro	846		2,4,6-Tri-*p*-phenoxyphenyl	179	
4-Chloro	653		2,4,6-Tri-*p*-methoxyphenyl	124	
3-Chloro	734		4-*t*-Butyl-2,6-diphenyl	120	
2-Chloro	625		6-*t*-Butyl-2,4-diphenyl	112	
4-*t*-Butyl	578		4,6-Di-*t*-butyl-2-phenyl	76	
2-*t*-Butyl	552		2,6-Di-*t*-butyl-4-phenyl	−14	
4-Phenyl	534		2,4,6-Tri-*t*-butyl	−59	
4-Phenyl-2-chloro	560		1-Naphthol	+740	
2,4-Dichloro	660	84[c]	2-Naphthol	820	82[a]
4-Carboxy-2-chloro	920		2-Hydroxybiphenyl	970	
			4-Hydroxybiphenyl	890	

Dihydroxybenzene	E_0[e] (redox)[72]	$E_{\frac{1}{2}}$[f] (pH 5·6)[85]	$E_{\frac{1}{2}}$[g] (pH 0)[72]
Hydroquinone	699	234	560
Methylhydroquinone	644	—	505
2,6-Dimethylhydroquinone	593	—	454
Tetramethylhydroquinone	463	—	324
2,5-Di-*t*-butylhydroquinone	522	—	383
Catechol	792	349	600
Hydroxyhydroquinone	600	—	460
Resorcinol	—[h]	613	800
5-Methylresorcinol (Orcinol)	—[h]	—	750
2,5-Dimethylresorcinol	—[h]	—	700

[a] Pt anode, Ag/0·1N Ag^+ ref. electrode, solvent system: acetonitrile + perchlorate salt.
[b] Graphite anode, saturated calomel ref. electrode, aqueous buffered solution, pH 5·6.
[c] Pt anode, saturated calomel ref. electrode, solvent system: 0·14M aqueous LiCl.
[d] Graphite anode, Ag/AgCl ref. electrode, solvent system: acetonitrile–H_2O + $(CH_3)_4NOH$.
[e] Hydrogen ref. electrode.
[f] Graphite anode, Ag/AgCl ref. electrode, aqueous buffered solution.
[g] Saturated calomel ref. electrode.
[h] Irreversible system.

the oxidation potential of phenols, i.e., the oxidizing power of phenoxy radicals, decreases and therefore the ease of oxidation of phenols to the corresponding radicals increases with increasing steric crowding in the 2- and 6-positions, and with decreasing electron-withdrawing, i.e., with increasing electron-releasing properties of substituents in these and the 4-position. For example, in the case of the 2,4,6-triphenylphenoxy radical (**8**) and the 2,4,6-tri-*t*-butylphenoxy radical (**4**), the equilibrium (equation 8) is shifted to the right, since **8** is a stronger oxidizing agent than **4** (Table 2). The influence of steric and polar effects of 3- and 5-substituents on the relative



oxidation potentials of phenols is usually less pronounced. Since oxidation potentials refer to the oxidizing power of phenoxy radicals, they do reflect to a certain extent the relative stabilities and reactivities of aryloxy radicals, particularly of those which carry substituent groups in the positions 2, 4 and/or 6 [12]. Therefore, attempts have been made to correlate redox potentials (for reversible systems) and relative oxidation potentials (for irreversible systems) with the effectiveness of phenols (i.e., phenoxy radicals) as autoxidation inhibitors[9, 74, 86].

Phenoxy radicals, formed in the first step of the oxidation of phenols by one-electron transfer oxidants, may undergo a variety of reactions, depending on the reactivity and substitution pattern of the radicals, on experimental conditions, on the amount of oxidizing agent and on the presence of other compounds in the reaction mixture[12, 13]. The most important reactions of aryloxy radicals, which are related to the oxidation of the parent phenols, will be discussed in the following sections.

C. Oxidation by Ferric Salts

1. Potassium ferricyanide

One of the most widely used oxidizing agents for the generation of phenoxy radicals from phenols is potassium ferricyanide (KFC), $K_3[Fe(CN)_6]$, in alkaline solution[2, 6, 8]. Phenol oxidation with this reagent appears to be a process of considerable complexity, the

mechanistic details of which have not yet been fully elucidated. Kinetic studies and the requirement of a large excess of oxidizing agent to approach quantitative yields of aryloxy radicals are in agreement with a reversible one-electron transfer reaction (9) involving phenoxide anions as oxidizable substrate, the rate of oxidation being dependent on the basicity of the solution and on the ferricyanide/ferrocyanide ratio[78].

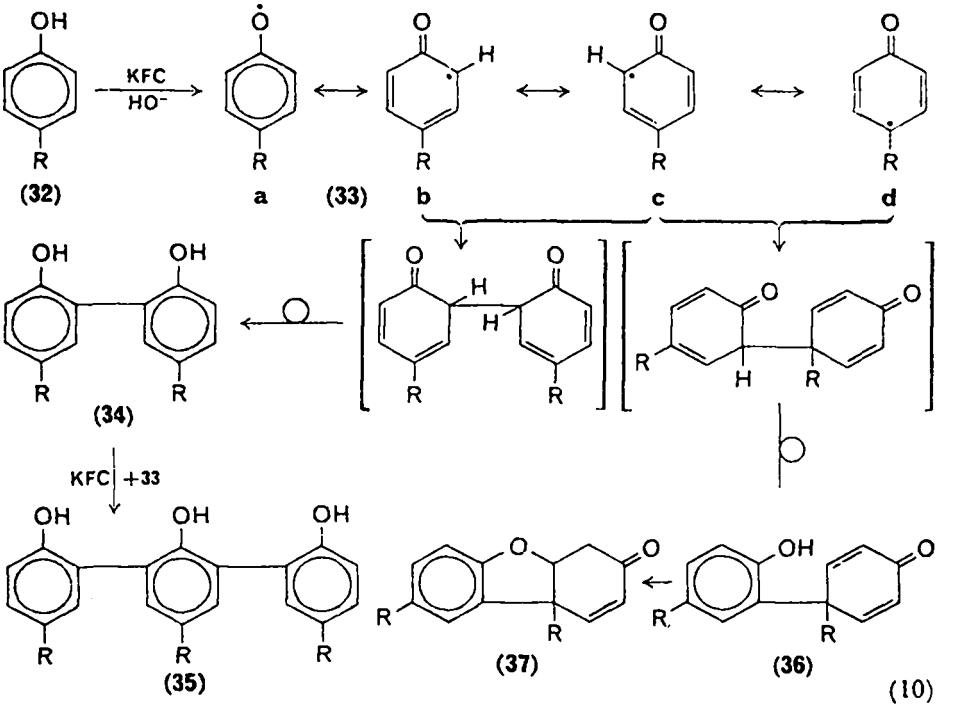
$$ArO^- + [Fe(CN)_6]^{3-} \rightleftharpoons ArO^{\cdot} + [Fe(CN)_6]^{4-} \quad (9)$$

Most of the stable aryloxy radicals mentioned in the preceding section were obtained by the ferricyanide oxidation of the corresponding phenols, e.g., **4** [22–25, 55], **5** [27, 29, 30], **6** [33], **7** [34–39], **18** [55], **19** [57] and others [18, 51, 52, 59–62, 87]. Unstable and moderately stable phenoxy radicals, i.e., radicals with free *ortho*- and/or *para*-positions and 2,4,6-trisubstituted phenoxy radicals containing α-hydrogens in the 4-substituent, can also be generated by the same method, but once formed, and in the absence of other reactive molecules, they usually undergo radical dimerization (and further polymerization) by way of self-coupling to furnish dimeric and trimeric products, and often ill-defined polymeric materials as well.

Phenoxy radical dimerizations, some of which are reversible, can be divided into six classes.

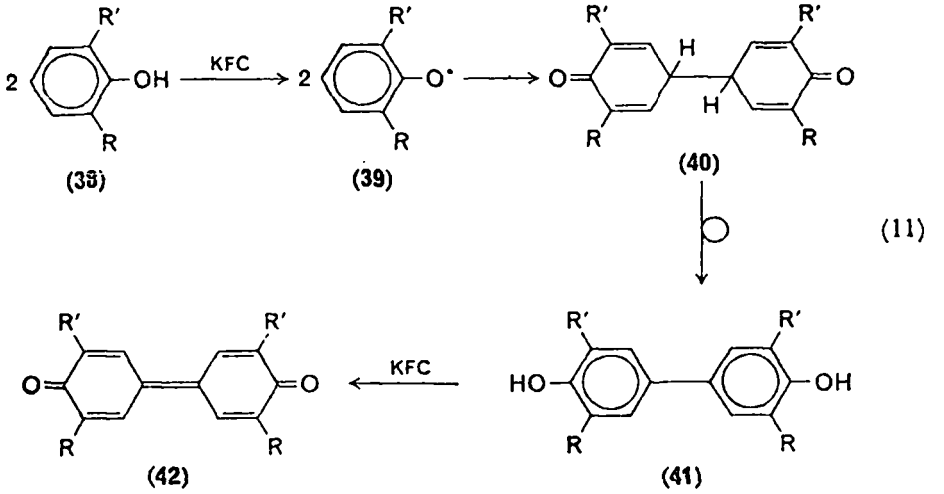
a. Carbon–carbon dimerization involving nuclear C–C coupling can take place at *ortho–ortho*, *ortho–para* or *para–para* positions, and it has been reported for a large number of phenols[2]. Thus, when *p*-cresol and other 4-alkylphenols (**32**) are oxidized with potassium ferricyanide in aqueous alkaline solution (equation 10), in addition to polymeric products, the *ortho*-linked dimer **34** and trimer **35**, and Pummerer's ketone (**37**) are obtained[78, 88–91]. The correct structure of Pummerer's ketone (**37**) (R = CH_3) was established by Barton[89], who also explained its formation (reaction 10), on the basis of initial *o,p'*-coupling of two 4-methylphenoxy radicals (**33**), followed by intramolecular β-addition of the *o*-hydroxyl group on to the enone system of the resulting cyclohexadienone(**36**). This reaction scheme was confirmed by the elegant synthesis of usnic acid, involving potassium ferricyanide oxidation of methylphloroacetophenone[89]. The dual course of the oxidation (equation 10) of *p*-cresol (**32**) lends further support to the resonance-hybrid structure of phenoxy radicals (**33**).

If in the starting phenol (**38**) the *p*-position or two of the three *o*- and *p*-positions are occupied by substituents, *ortho–ortho* and *para–para* C–C bonded dimeric phenols, e.g. **41**, are usually produced



(10)

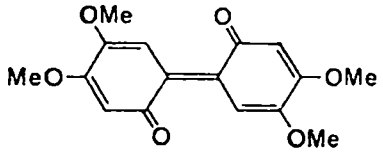
(equation 11) in high yields[2, 78, 91–102], although in the case of 2,6-di-*t*-butylphenol (**38**, R = R′ = Me_3C) the major product isolated was the keto-tautomer **40** (R = R′ = Me_3C)[92, 93]. Depending on the nature and basicity of the reaction medium, on the



(11)

amount of the oxidizing agent and on its oxidation potential (relative to that of the bisphenol **41**), oxidation can proceed further to furnish the corresponding diphenoquinones, such as **42** [2, 78, 92, 93, 97, 102–105]. The 4,4′-diphenoquinones (**42**) are stable compounds and, according to n.m.r. measurements, may show *cis–trans* isomerism (when substituents R and R′ are different)[97], whereas the formation of 2,2′-diphenoquinones (such as **43** and **44**) by further oxidation of the *o–o′* coupled bisphenols has been rarely observed[101, 106], probably because most of these products are relatively unstable (e.g., **44**), and more favourable routes are offered for the stabilization of their radical precursors (equation 11).

3,5-Di-*t*-butyl-4-hydroxybenzoic acid (**45**) undergoes oxidative decarboxylation when treated with alkaline ferricyanide in the absence of oxygen (equation 12) and affords 3,3′,5,5′-tetra-*t*-butyl-4,4′-diphenoquinone (**46**) in nearly quantitative yield[103]. The same



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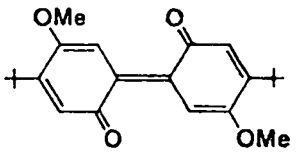
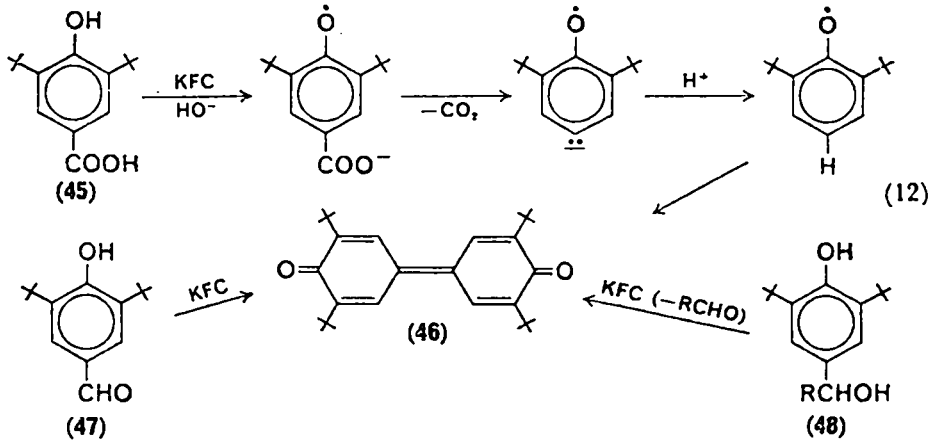
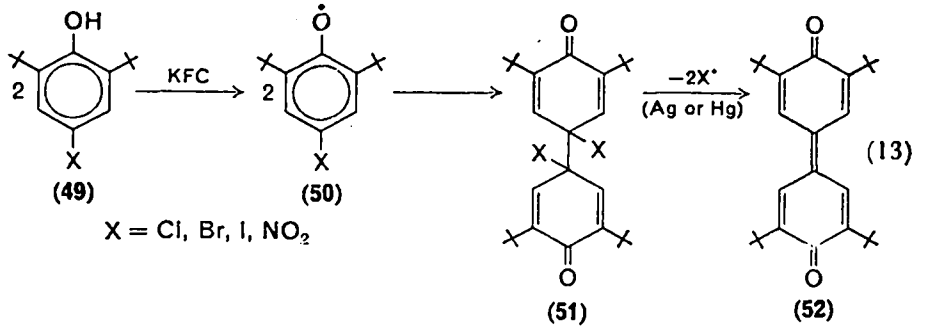


(44)

product is obtained in high yield by oxidation of the benzaldehyde **47** [103], and the benzyl alcohols **48** (R = H or C_6H_5)[19]; reaction schemes have been suggested involving intermediate anions and radicals[12, 103] or only radicals[19].



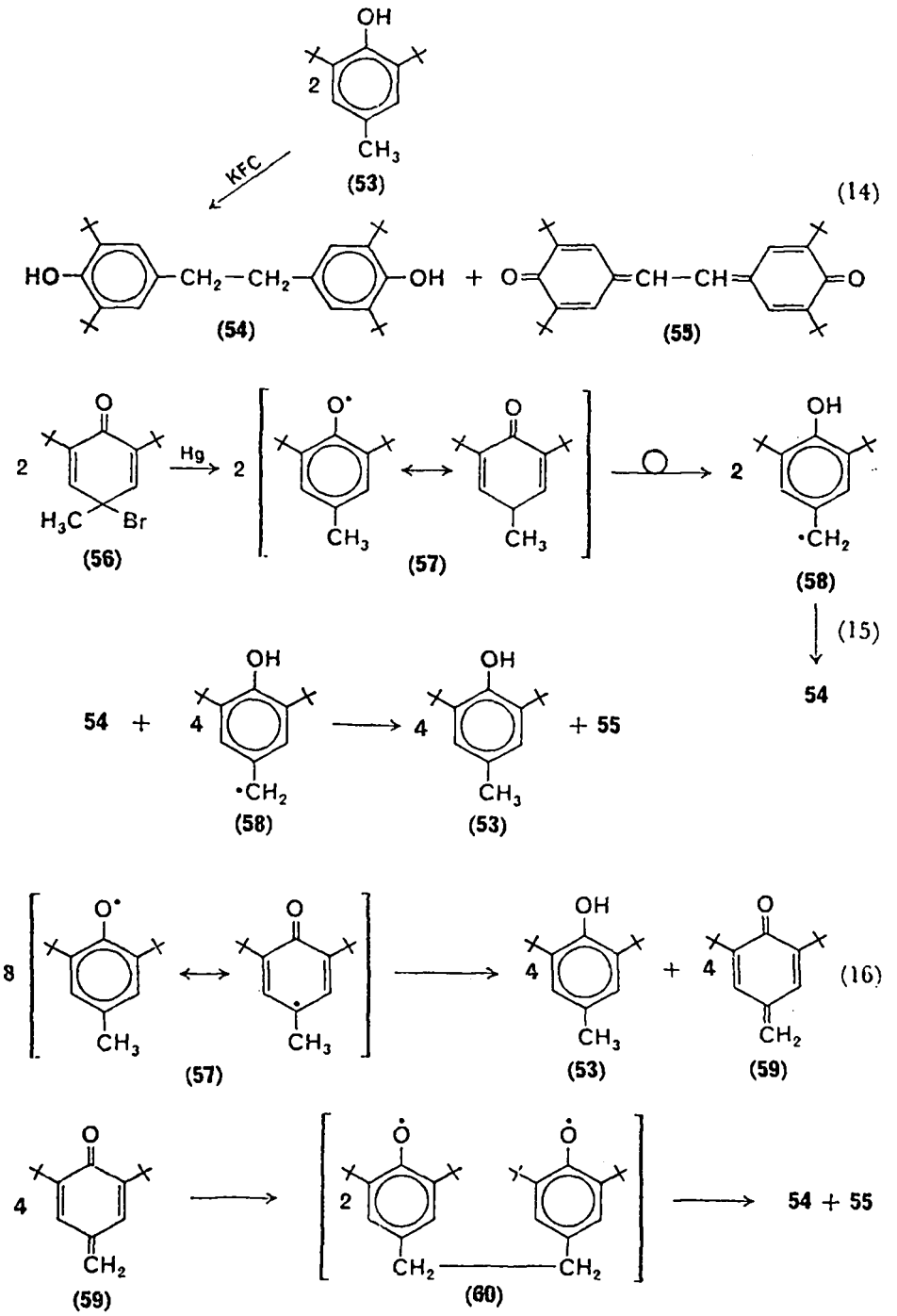
When oxidized with alkaline ferricyanide, the 2,6-di-*t*-butylphenols(**49**) carrying in position 4 a chlorine (X = Cl) or bromine atom (X = Br) are rapidly converted (equation 13), through their phenoxy radicals **50**, to the *p–p'* C–C coupled dimers **51**, which readily oxidize further to the corresponding diphenoquinones **52** [107, 108]. For the chloro compound (**51**, X = Cl) this conversion (to **52**) requires silver or mercury, whereas for the bromo compound (**51**, X = Br) bromine is already slowly lost at room temperature.



The dimer (**51**) resulting from the 4-iodo (**50**, X = I) and 4-nitro radical (**50**, X = NO_2) cannot be isolated since it loses the X-substituent rapidly and spontaneously to form the diphenoquinone **52** [107, 108].

b. Carbon-carbon dimerization involving coupling of substituent α-carbon atoms has been particularly studied in the case of 2,6-di-*t*-butyl-4-methylphenol (**53**). Upon oxidation with alkaline ferricyanide[109] and other oxidizing agents[110–116], **53** affords (equation 14) two major products, the dimeric bisphenol **54** and the stilbenequinone **55**. Since the phenoxy radical **57**, when generated by the treatment of the 4-bromocyclohexadienone **56** [109], afforded in addition to **54** and **55**, the phenol **53** (equation 15), it was suggested that the benzyl radical **58**, resulting from rearrangement of the initially formed aryloxy radical **57**, was the precursor of the diphenyl derivative **54** [109–111], and that **58** and **54** in a redox type reaction could eventually furnish the phenol **53** and the stilbenequinone **55** [109].

However, evidence has been later presented[20] which showed that the formation of the parent phenol **53** and the dimeric products **54** and **55** from the phenoxy radical **57** is in accordance with the general path of second-order disproportionation of 2,6-hindered aryloxy radicals containing an α–CH group on the 4-substituent


OH
2
CH3
(53)
KFC
(14)
HO
CH2—CH2
OH
+
O
CH—CH
O
(54)
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2
O
Hg
2
O·
O
CH3
CH3
(56)
(57)
OH
2
·CH2
(58)
(15)
54
54 +
4
OH
·CH2
(58)
4
OH
CH3
(53)
+ 55
8
O·
O
CH3
CH3
(57)
4
OH
CH3
(53)
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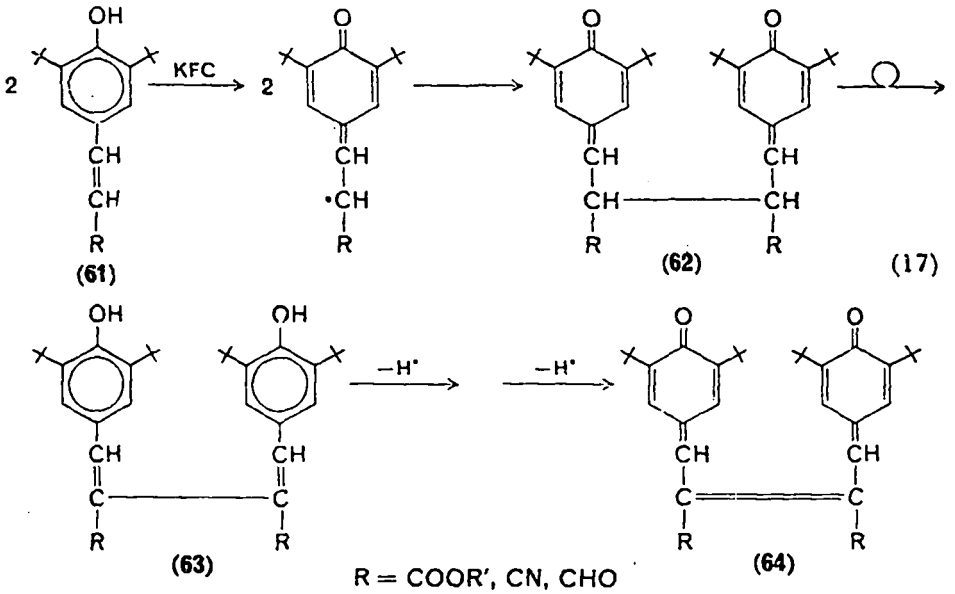
O
CH2
(59)
(16)
4
O
CH2
(59)
2
O·
O·
CH2
CH2
(60)
54 + 55

(**15**→**14** + **17**, equation 3)[18-21, 46-50, 108, 117] and that therefore the unstable quinone methide **59** (reaction 16), rather than the benzyl radical **58**, is an intermediate in the oxidative coupling through 4-methyl groups of 2,6-di-*t*-butyl-4-methylphenol (**53**) (reaction 14)[20]*. The formation of **54** and **55** from the intermediate quinone methide **59** (equation 16) involves free radical species of uncertain structure[20, 48, 49], one of which might well be the biradical **60** [49].

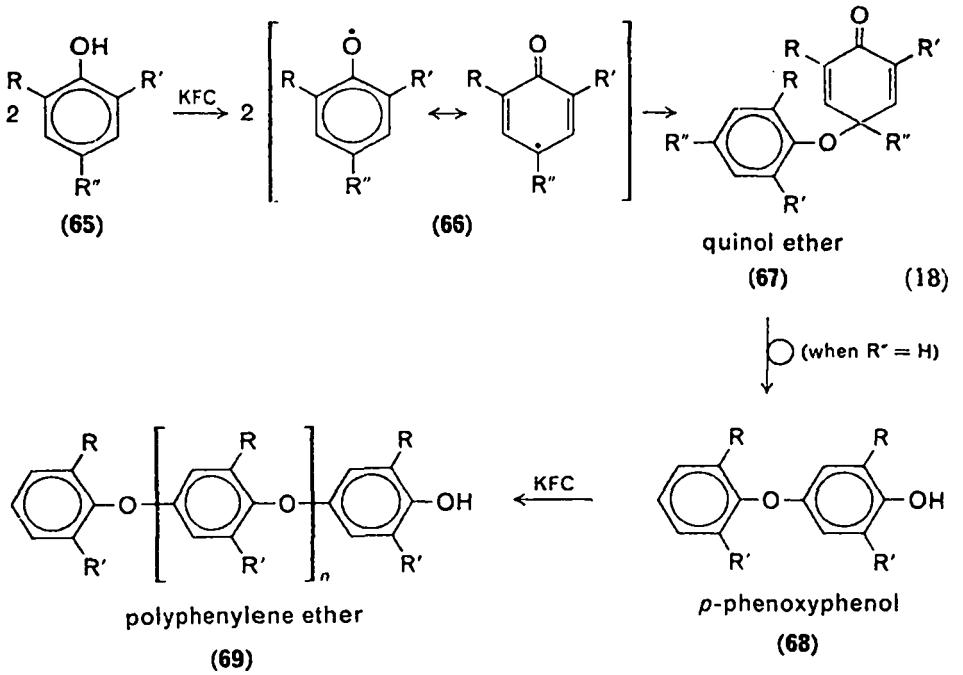
c. Carbon–carbon dimerization involving coupling of substituent β-carbon atoms has been observed upon alkaline ferricyanide oxidation (equation 17) of 4-hydroxyphenylethylene derivatives (**61**) related to coniferyl alcohol[118]. Depending on the nature of the R group, the dimeric products were either the bisquinone methides **62** (for R = COOR') or the tetra-*t*-butyl homologues of isoxanthocillin (**63**) (for R = CN and CHO), which could be further oxidized to the ethylenic bisquinone methides **64**.



d. Carbon–oxygen dimerization involving nuclear o- *or* p-*carbon–phenoxyl oxygen coupling* (equation 18) is often observed when 2,4,6-trisubstituted and other hindered phenols (**65**) are oxidized by potassium ferricyanide to the corresponding phenoxy radicals **66**, and these radicals then form by intermolecular reaction simple dimeric quinol

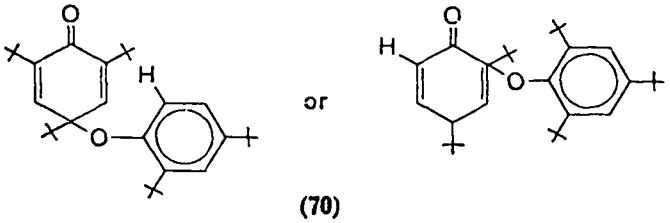
* Spectral and other data reported in connection with the mechanism of reaction (14) have been discussed in a previous review[12].

ethers, such as **67**, which are in equilibrium with the aryloxy radicals **66** (e.g., **7**⇌**8** in reaction (2), and **16**⇌**15** in reaction (3); section II.A.1)[6, 8, 12, 13, 21, 34–38, 102, 105, 119–121]. When the 4-position is free ($R'' = H$), the quinol ethers **67** of certain 2-mono- and 2,6-disubstituted phenols rearrange rapidly by 4-hydrogen shift to the corresponding hydroxy-ethers **68**, which undergo further coupling reactions to polyphenylene ethers **69** (for the mechanism of this polymerization see section II.G). Thus, upon alkaline ferricyanide oxidation of guaiacol (**65**, R = OCH_3, R′ = R″ = H) and 4-(2′,6′-dimethylphenoxy)-2,6-dimethylphenol (**68**, R = R′ = CH_3, R″ = H) the major products obtained were polymeric ethers of type **69** [122, 122a, 123].



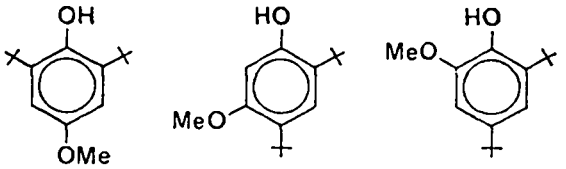
Hindered phenoxy radicals, such as the 2,4,6-tri-*t*-butylphenoxy radical (**4**), are quite stable in solutions of hydrocarbon solvents, but upon longer standing a slow decrease of radical content is observed, even when air and moisture are rigorously excluded[25]. This fact and the variation in yield of phenoxy radicals when prepared by oxidation of phenols in different solvents suggest that radical decomposition due to disproportionation may involve the solvent. A study of the rates of reaction of 2,4,6-tri-*t*-butylphenoxy

radicals (4) with various hydrocarbons (*n*-decane, isodecane, toluene, ethylbenzene and cumene) over a temperature range of 70–150° has shown that the reaction was first-order in phenoxy radical, and that the rate was fastest in ethylbenzene and slowest in isodecane[124]. Moreover, it was found that 2,4,6-tri-*t*-butylphenoxy radicals (4) decompose upon heating to give the parent phenol, isobutylene and two higher molecular weight products[87, 125]; the C–O coupled dimeric structure **70**, corresponding to a quinol ether which has lost an *ortho*-*t*-butyl group, was tentatively assigned to one of these products[87, 125].

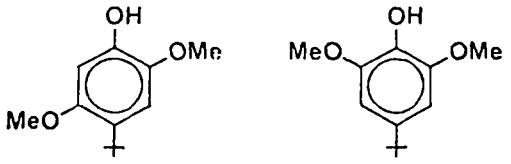


(70)

Depending on the position and number of substituents, *t*-butyl-methoxyphenols are oxidized by alkaline ferricyanide to a variety of products, resulting from C–C and/or C–O coupling reactions. Thus, di-*t*-butyl-monomethoxyphenols **71–73** and mono-*t*-butyl-dimethoxyphenols **74** and **75** afford as major products the corresponding



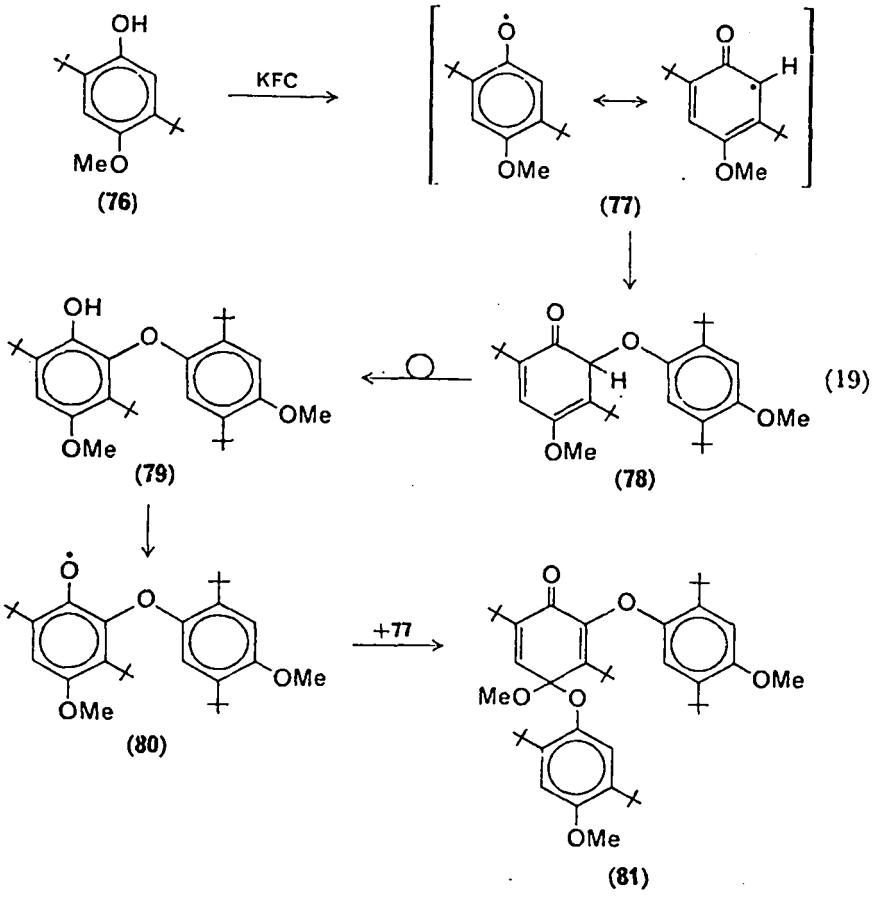
(71) **(72)** **(73)**



(74) **(75)**

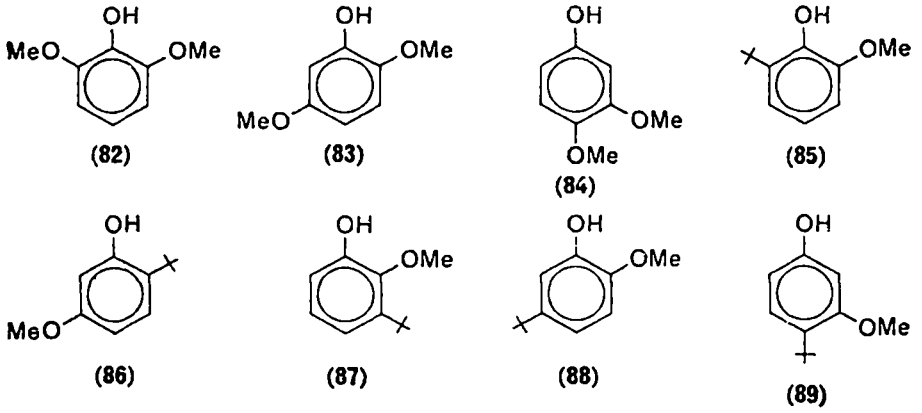
dimeric simple quinol ethers (of type **67**, equation 18) and, when an *o*-position is free (as in **72**), 2,2′-dihydroxy-diphenyl derivatives[102, 105, 126, 127]. On the other hand, oxidation of 2,5-di-*t*-butyl-

4-methoxyphenol (**76**) in methanol or light petroleum with alkaline potassium ferricyanide yields a C–O coupled trimer **81**, according to reaction scheme (19)[127, 128]. The same oxidation of **76** in benzene

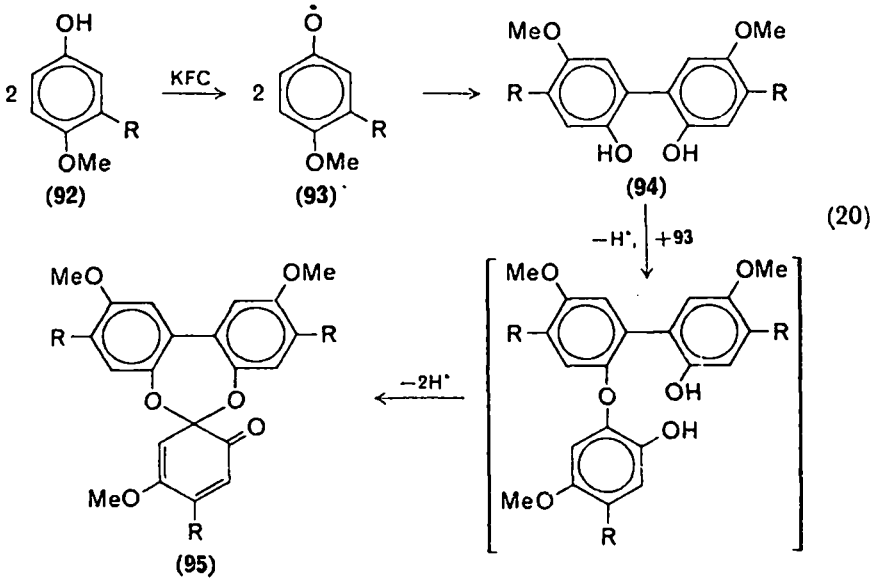


occurs with demethylation and affords only 2,5-di-*t*-butyl-1,4-benzoquinone[127].

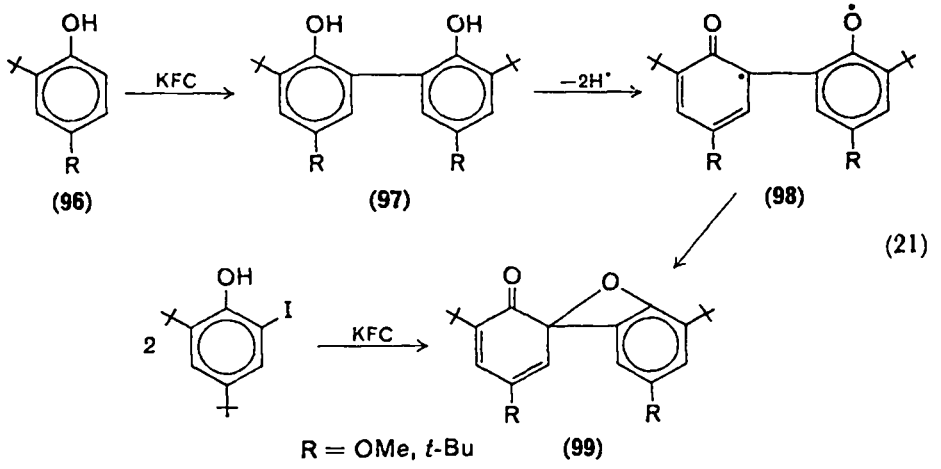
Less hindered dimethoxyphenols **82–84** and mono-*t*-butyl-monomethoxyphenols **85** and **86** are oxidized to the corresponding dimeric dihydroxydiphenyls or diphenoquinones[78, 97, 101, 102], whereas the mono-*t*-butyl-monomethoxyphenols **87–89** furnish only polymeric materials[97, 102, 105]. The ferricyanide oxidation of 3-alkyl-4-methoxyphenols (**90**) and 4-*t*-butyl-2-methoxyphenol (**91**) proceeds, via the corresponding 2,2′-dihydroxydiphenyls (of type **94**), to trimeric spiroketals (of type **95**) as one of the reaction products (equation



20)[91, 96–99, 129]. Whereas 4-methoxyphenols with relatively small alkyl substituents in position 2 (**92**) may be also oxidized to spiroketals (of type **95**)[99], 2-*t*-butyl-4-methoxyphenol and 2,4-di-*t*-butyl-

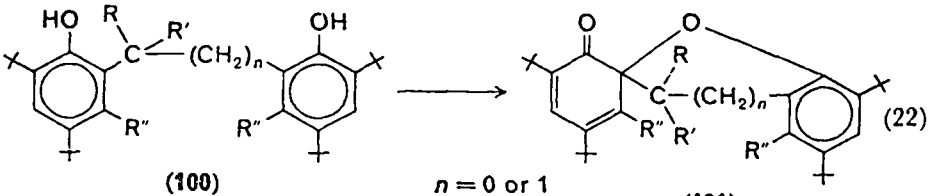


phenol (**96**) are converted (equation 21), via the corresponding 2,2′-bisphenols **97** (which have been isolated), to dimeric internal quinol ethers containing a four-membered oxetane ring



(21)

(**99**)[94, 95, 100, 130]. Similar intramolecular quinol ethers (**101**), but with larger heterocyclic rings, are formed (equation 22) upon oxidation of substituted bisphenolmethanes (**100**, $n = 0$) and 1,2-bisphenolethanes (**100**, $n = 1$)[94, 131], as well as of analogous β-naphthol derivatives[119, 132, 133].

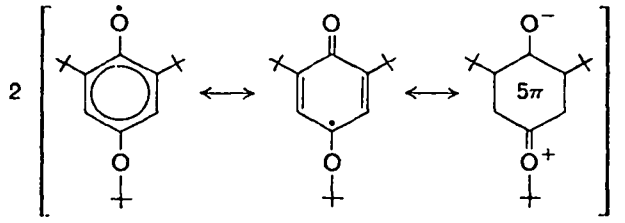


(22)

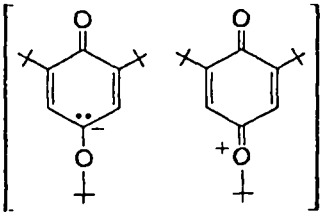
e. Oxygen–oxygen dimerization of phenoxy radicals leading to peroxides, ArO-OAr, although repeatedly postulated[12, 134], has actually never been observed, and all alleged compounds of this class probably belong to dimers resulting from C–C or C–O coupling. The instability of such diaryl peroxides is apparently due to the high resonance energy of phenoxy radicals, which makes the O–O bond dissociation energy very low[135].

f. Charge-transfer complexes have been proposed for certain phenoxy radical dimers, on the basis of chemical, steric or spectral evidence[31, 60, 126, 136, 137]. For example, for the diamagnetic, colourless solid dimer of 2,6-di-*t*-butyl-4-*t*-butoxyphenoxy radicals (**102**),

which even in nonpolar solvents dissociates nearly quantitatively to the highly coloured paramagnetic monomeric radical species, structure **103**, involving complete electron transfer, was suggested.



(102)



(103)

All the above described oxidative dimerizations have been discussed in terms of radical coupling mechanisms, which have been confirmed in many cases on grounds of chemical, spectral and other data[6, 8, 12, 13, 136, 139]. Although other reaction paths leading to dimeric products[6, 8, 78, 139], e.g., radical insertion (equation 23) and heterolytic coupling (equation 24), seem to be unlikely for the

$$\mathrm{ArO^{\bullet} + ArO^{-} \longrightarrow [(ArO)_2^{-\bullet}] \xrightarrow{-e^-} (ArO)_2}$$

$$\text{or} \qquad (23)$$

$$\mathrm{ArO^{\bullet} + ArOH \longrightarrow [(ArOArOH)^{\bullet}] \xrightarrow{-H^{\bullet}} (ArO)_2}$$

$$\mathrm{ArO^{\bullet} \xrightarrow{-e^-} ArO^{+}}$$

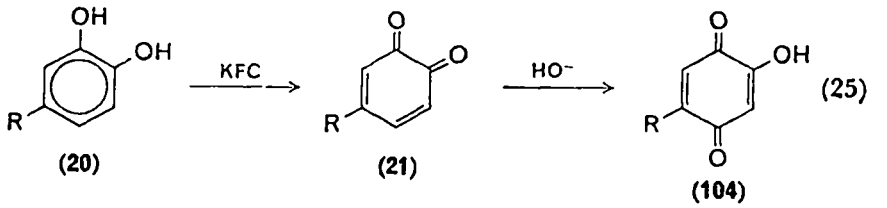
$$\mathrm{ArO^{+} + ArO^{-} \longrightarrow (ArO)_2} \qquad (24)$$

$$\text{or}$$

$$\mathrm{ArO^{+} + ArOH \longrightarrow [(ArOArOH)^{+}] \xrightarrow{-H^{+}} (ArO)_2}$$

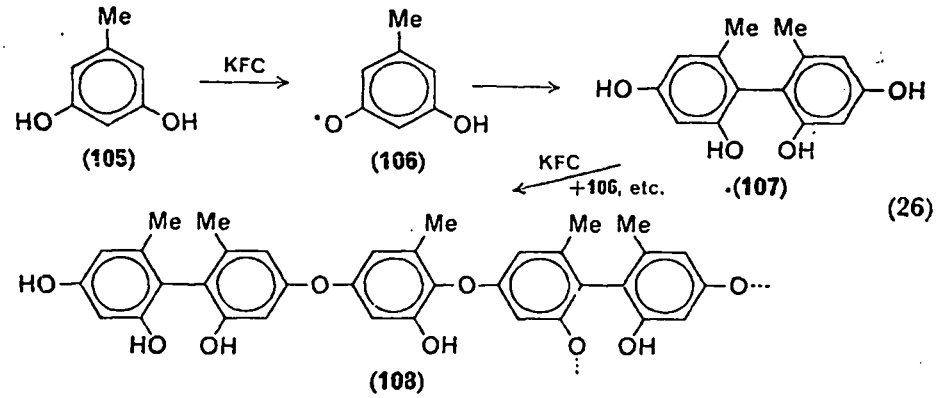
majority of phenol oxidations performed under usual conditions[6, 8, 138, 139], it is not impossible that these and similar mechanisms may operate in special circumstances and in different structural conditions[7, 21, 139–141].

Controlled oxidation of catechols (**20**, equation 5) and hydroquinones (**22**, equation 6) with alkaline ferricyanide affords the corresponding benzoquinones (**21** and **26**, respectively)[6], which can then be converted, by nucleophilic attack of hydroxide ions, to hydroxybenzoquinones, e.g., **104** (equation 25)[69].



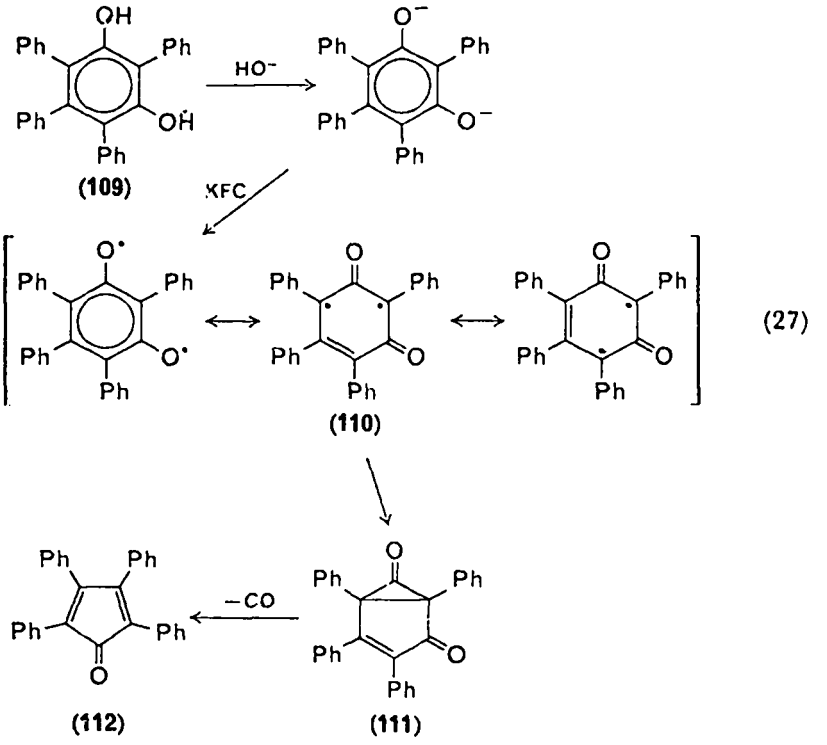
(20) (21) (104) (25)

The oxidation of orcinol (**105**) with alkaline ferricyanide proceeds as with monophenols (equation 26) and produces, via the intermediate radicals **106**, a mixture of C–C and C–O coupled dimeric (**107**) and polymeric products (**108**)[5, 6, 142].



(105) (106) (107) (108) (26)

When treated with alkaline ferricyanide, 2,6-di-, 2,4,6-tri- and tetraphenylresorcinol, e.g., **109**, undergo ring contraction with evolution of carbon monoxide (equation 27) and afford phenyl substituted cyclopentadienones, such as **112**[143]. The intermediate formation of resonance-stabilized biradicals **110** and bicyclic diketones **111** has been proposed to explain the course of this reaction[143].



(27)

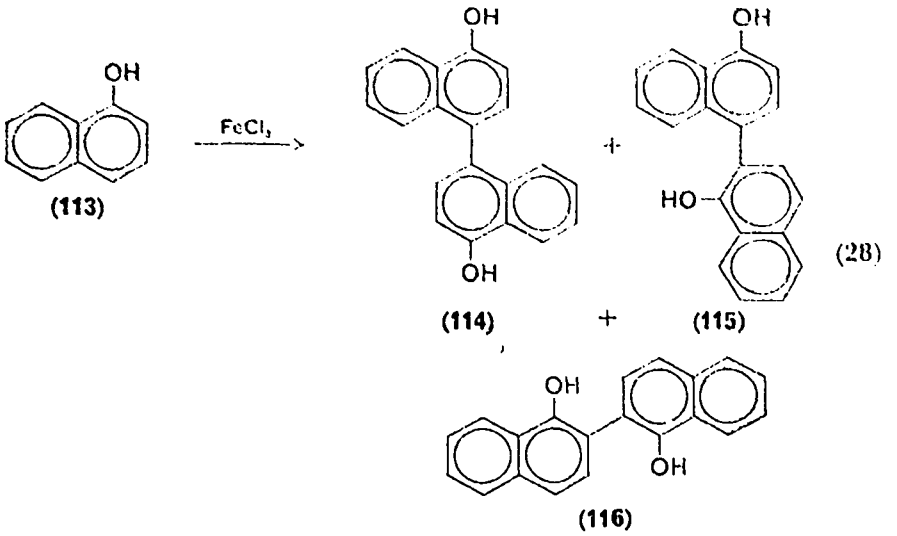
2. Ferric chloride

Ferric chloride, $FeCl_3$, is also a one-electron transfer oxidant, which has been used extensively for the oxidative coupling of various monohydric and particularly polyhydric phenols[1, 6, 8, 144, 145]. Compared with alkaline potassium ferricyanide, ferric chloride in aqueous or alcoholic solution has the disadvantage that it may form undesirable complexes with either starting material or product; on the other hand, it is to be preferred in cases when alkaline conditions may cause ring cleavage of sensitive polyhydric phenols[8].

Ferric chloride oxidizes phenol to the *o–o'* coupled dimeric 2,2'-dihydroxydiphenyl[8], whereas *p*-cresol (**32**, R = CH_3) is converted to the same products (**34**, **35** and **37**; R = CH_3) obtained when alkaline ferricyanide is used as oxidant (equation 10)[146].

1-Naphthol (**113**) is oxidized by ferric chloride (equation 28) to all three possible *ortho* and *para* C–C coupled dimers **114**, **115** and **116** [147]. 2-Naphthol (**117**, R = H) and 3-methoxy-2-naphthol (**117**, R = OCH_3) when treated with ferric chloride in acidic or neutral

solution afford (equation 29) the corresponding 1,1'-bisnaphthols (**119**) in good yield[105, 133, 148]. Oxidation with alkaline potassium ferricyanide, on the other hand, produces mostly polymeric products[105, 148, 150], from which, in the case of 2-naphthol itself (**117**,

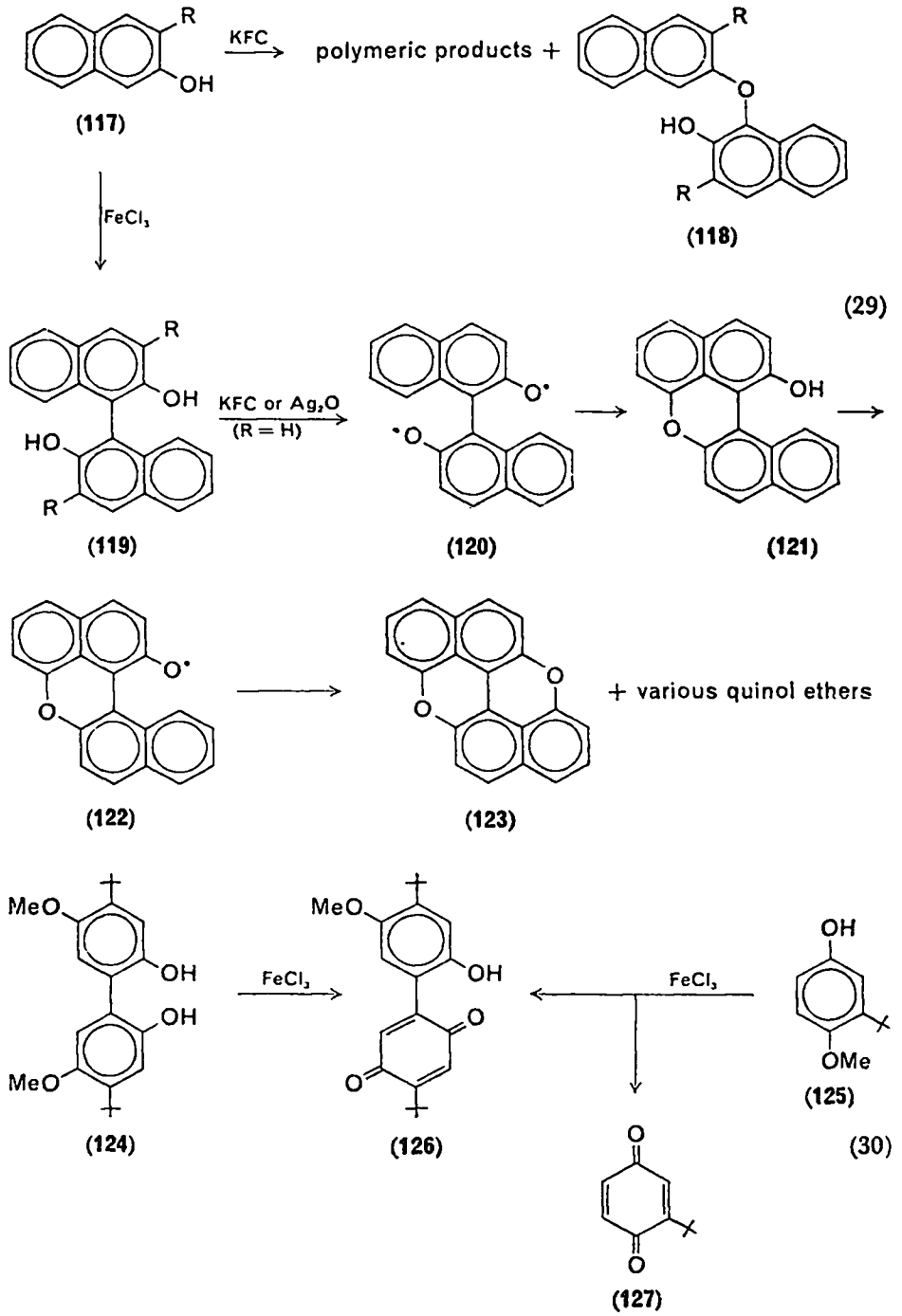


(28)

R = H), a small amount of the hydroxynaphthyl ether **118** could be isolated[149, 150]. The dimeric dixydroxy compound **119** can be oxidized further by potassium ferricyanide[151], silver oxide[152] or aryloxy radicals[133] to furnish **121, 123** and other intermolecularly coupled products derived from radicals **120** and **122** [133]. The existence of these highly coloured aryloxy radicals (**120** and **122**) has been verified by e.s.r. measurements[133, 153].

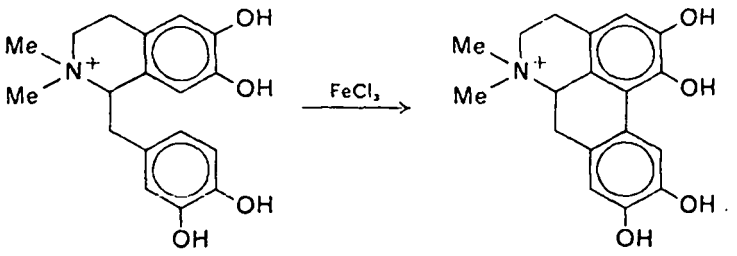
Ferric chloride oxidation of 4-methoxyphenols usually proceeds with demethylation and formation of *p*-quinones[100, 106, 127, 154], as illustrated by equation (30)[106]. Except in some special cases[127], the oxidation of methoxyphenols with alkaline ferricyanide does not involve the loss of a methyl group from methoxy substituents (e.g., see reactions 19–21).

The property of ferric compounds (potassium ferricyanide and ferric chloride) to effect oxidative coupling of phenols has been successfully applied for the syntheses of various natural products[1, 6, 8, 139, 144]. For example, oxidation of quaternary laudanosoline methiodide (**128**) with ferric chloride gives a 62% yield (equation 31) of the glaucine **129** from the aporphine series[144, 155].



(117) (118) (119) (120) (121) (122) (123) (124) (125) (126) (127)

(29) (30)

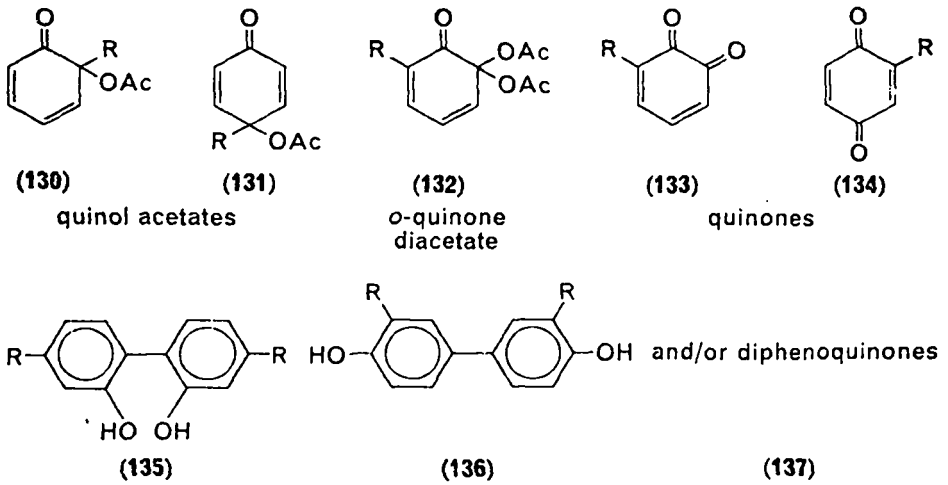


(128) (129) (31)

D. Oxidation by Tetravalent Lead

1. Lead tetraacetate

The extensive work on phenol and naphthol oxidations with lead tetraacetate $Pb(OAc)_4$, has been recently reviewed[156]. Depending on the nature, number and position of the substituents in the phenol, on the properties of the solvent, and on the ratio of oxidizing agent to substrate and dilution, different types of products may be obtained, e.g., **130–137** [38, 100, 105, 156–182]. Table 3 summarizes some of the results.



ortho- and *para*-coupled dimeric products

The effect of the solvent on the distribution of products is considerable, acetic acid favouring the formation of quinol acetates (**130–132**) and nonpolar solvents such as benzene enhancing C–C coupling reactions which lead to the dimeric products **135–137**, particularly when no excess of lead tetraacetate is used[158, 182]. In

TABLE 3. Oxidation of phenols by lead tetraacetate.

Phenol	Solvent	Yields of products (in % of theoretical)					Refs.
		o-Quinol acetate	*o*-Quinone diacetate	*p*-Quinol acetate	Quinone	*o*- and *p*-coupled dimers	
Phenol	AcOH	—	4	—	—	—	157
	Benzene	—	—	—	—	1	158
2-Methyl	Ether	22	3	—	4	1	159
	Benzene	—	—	—	—	1	158
4-Methyl	AcOH	—	57	14	—	—	159, 160
	Benzene	—	—	—	—	8	158
3-Methyl	AcOH	—	0, 5	—	4	—	157, 159
2-Ethyl	AcOH	36	4	—	—	—	161
2-*n*-Propyl	AcOH	42	4	—	—	—	161
2-*t*-Butyl	AcOH	2	44	—	—	—	161
4-*t*-Butyl	AcOH	—	14	5	—	—	162
2,4-Dimethyl	AcOH	34	—	—	—	—	159
	Benzene	—	—	8	—	7	158
2,3-Dimethyl	AcOH	33	5	—	1	—	163
2,6-Dimethyl	AcOH	95	—	—	—	1	158
	Benzene	—	—	—	—	20	158
2,4,6-Trimethyl	AcOH	65	—	—	—	—	158, 164
	Benzene	71	—	—	—	—	158, 164
	Chloroform	92	—	—	—	+	166
2,4,6-Tri-*t*-butyl	AcOH	60	—	30	—	—	161, 164
2-Methoxy	AcOEt	—	—	+	57	—	167
2,6-Dimethoxy	AcOEt	—	—	—	78	—	167
2-Methyl-6-formyl	AcOH	5	—	—	—	20	168
2-Methyl-6-cyano	AcOH	—	—	—	—	100	168
2,4-Dimethyl-6-cyano	AcOH	23	—	—	—	—	169
2,4-Dimethyl-6-acetyl	Chloroform	65	—	—	—	—	169
2,4-Dimethyl-6-nitro	AcOEt	18	—	—	—	—	170
2-Methyl-5-bromo	Acetone	38	—	—	—	—	171
2,4-Dimethyl-5-bromo	AcOH	32	—	6	—	—	171
2,6-Dimethoxy-4-carboxy	AcOEt	—	—	—	57	—	167
2,4-Dimethyl-6-carbethoxy	AcOH	50	—	—	—	—	169

acetic acid as solvent *ortho*-substituted phenols usually give *o*-quinol acetates (**130**) as main products, whereas *p*-quinol acetates (**131**) rom phenols containing a 4-alkyl group are formed in lower yield. When one *ortho*-position is free *o*-quinol diacetates (**132**) may be obt_ ned; these compounds are unstable but have been isolated in several cases[159–162]. If an electron-withdrawing group is present in one of the *o*-positions, acetoxylation takes place at the *o*-side with higher electron density, i.e. carrying an alkyl group or a hydrogen atom. *o*- and *p*-Quinones (**133** and **134**) are probably secondary products, arising from decomposition or hydrolysis of the initially formed unstable quinol diacetates (e.g., **132**)[105, 156, 180].

If one assumes that the first step of the lead tetraacetate oxidation of phenols involves the reversible formation of aryloxy-lead(IV)-acetates **138** (equation 32)[156, 183, 184], then two possibilities can be envisaged for the decomposition of these unstable intermediates:

$$ArOH + Pb(OAc)_4 \rightleftharpoons ArOPb(OAc)_3 + AcOH \quad (32)$$

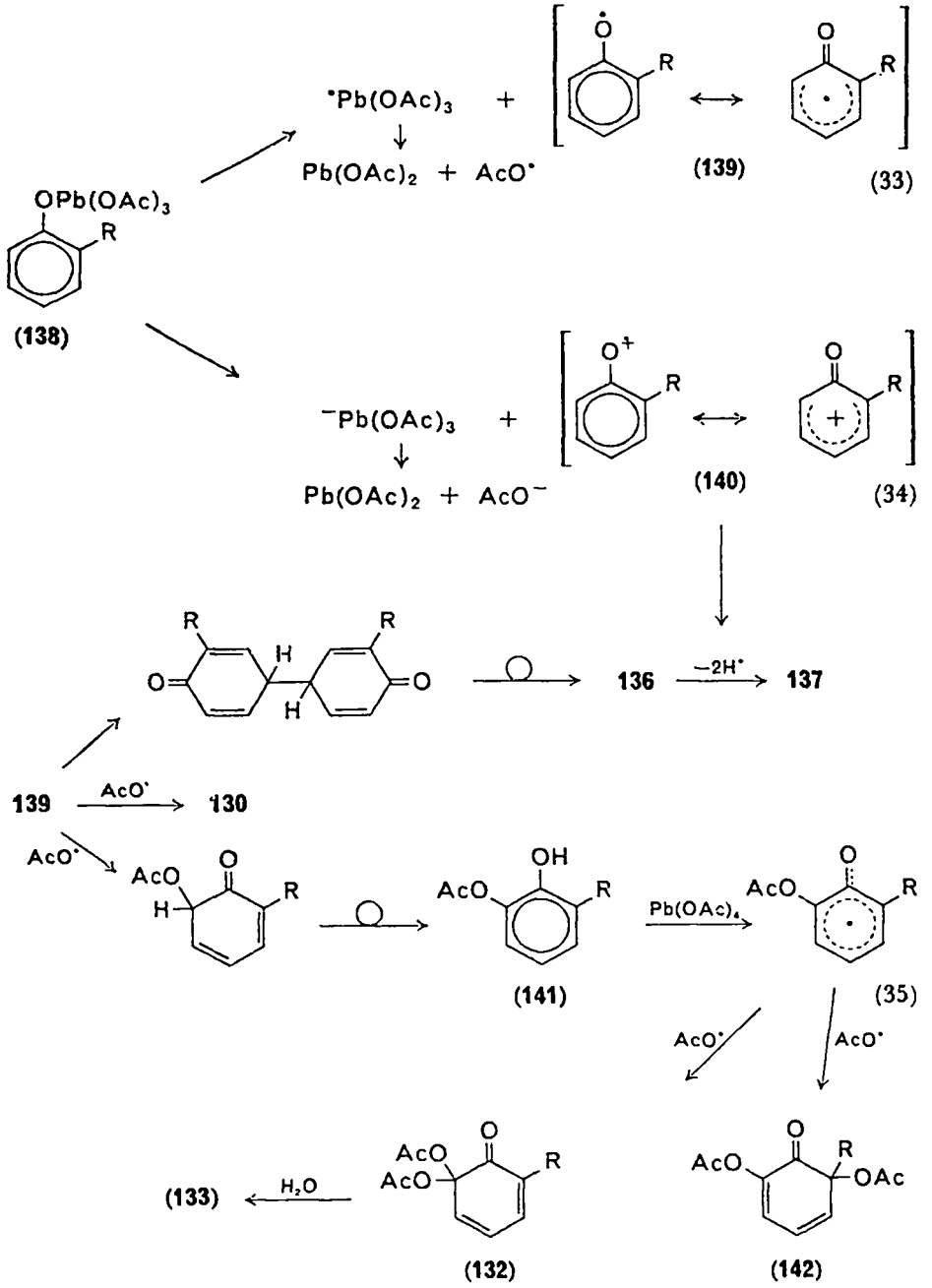
(138)

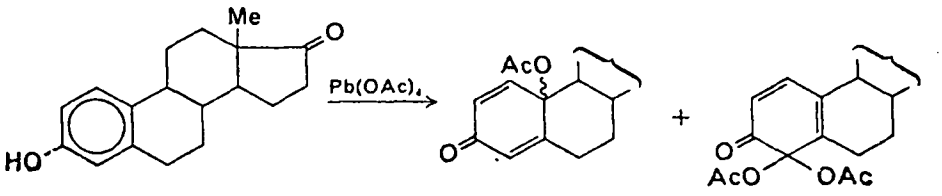
homolytic cleavage of the O–Pb bond (or one-electron transfer from O to Pb if this bond is ionic[184, 185]) leading to radical species **139** (equation 33)[156–158, 164, 165], or heterolytic cleavage of the O–Pb bond (or double-electron transfer if the bond is ionic[184, 185]) with formation of resonance-stabilized cationic aryloxy species **140** (equation 34)[156, 178, 179, 183]. Evidence, including e.s.r. spectroscopy, has been cited for both mechanisms[165, 179] and even the formation of coupling products (e.g., **135** and **136**) has been explained in terms of the ionic mechanism (34), as electrophilic substitution involving the intermediate phenoxonium ion (**140**) and the starting phenol (see also equation 24)[156]. On the basis of results obtained in the lead tetraacetate oxidation of alcohols, it appears that the radical mechanism (33) is more probable[184, 186]. Homolytic formation of various oxidation products is shown in scheme (35).

The lead tetraacetate acetoxylation of oestrone (**143**) affords (equation 36) about 20% of 10-acetoxy-1,4-oestradiene-3,7-dione (**144**), accompanied by a small amount of the *o*-quinone diacetate **145** [176–179].

Oxidative demethylation has been observed in the lead tetra-acetate oxidation of 4-methoxyphenols[100, 180, 181], as illustrated by reactions (37)[180] and (38)[181], particularly when an excess of oxidant is employed or acetic acid is used as solvent.

The dihydric phenols catechol, hydroquinone and their derivatives

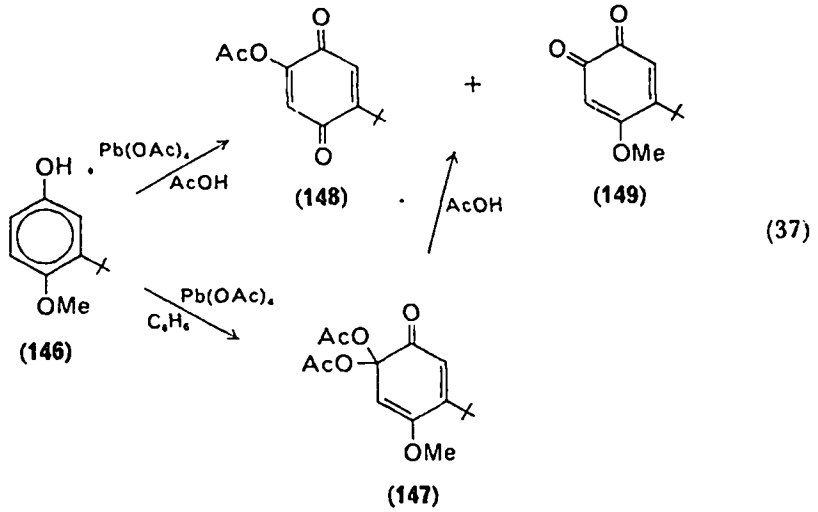

•Pb(OAc)3 +
Pb(OAc)2 + AcO•
(139)
(33)
OPb(OAc)3
R
(138)
−Pb(OAc)3 +
Pb(OAc)2 + AcO−
(140)
(34)
R
H
O
136
−2H•
137
139
AcO•
130
AcO
OH
Pb(OAc)4
(141)
(35)
(133)
H2O
(132)
OAc
(142)



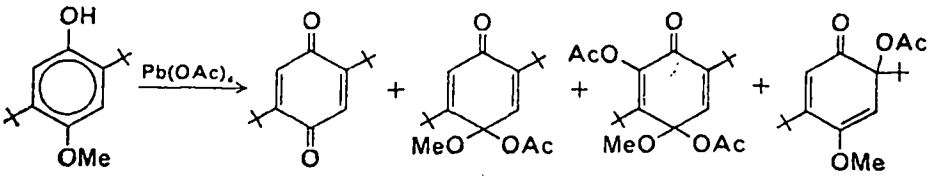
(143) (144) (145)

(36)

are rapidly and quantitatively oxidized by lead tetraacetate to the corresponding quinones[156], and even quinones with very high oxidation potentials can be conveniently prepared in this way[156, 187, 188].



(37)



(150) (151) (152) (153) (154)

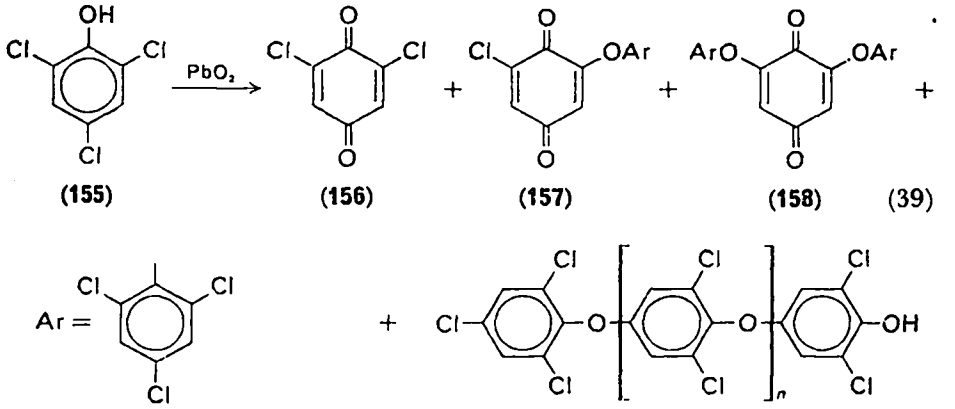
(38)

2. Lead dioxide

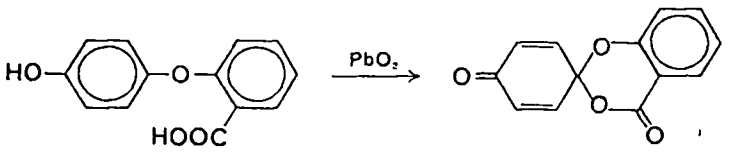
Lead dioxide, PbO_2, has similar oxidizing properties to alkaline potassium ferricyanide. It is used as suspension in organic solvents, preferably benzene, and its efficiency as oxidant frequently depends on the content of active oxygen and on the dilution[25, 189].

Lead dioxide oxidations have been applied for the conversion of phenols to hindered phenoxy radicals, such as **4** [22, 24, 25, 55, 60, 87], **5** [26, 28, 29, 32], **10** [40], **11** [41], **13** [43], **18** [55], **19** [57] and others[51, 87, 190]; to equilibrium mixtures between phenoxy radicals (e.g., **8**) and the corresponding dimeric quinol ethers (e.g., **7**)[34, 121]; to quinone methides (**17**)[18]; to C–C and C–O coupled dimeric and polymeric products **42** (equation 11)[97, 103], **46** (equation 12)[103], **68** (equation 18)[123], **69** (equation 18)[123], **81** (equation 19)[127], **95** (equation 20)[96, 97], **99** (equation 21)[94, 95], **107** and **108** (equation 26)[5, 6, 142]; to the C(methyl)–C(methyl) coupled dihydroxy compound **54** and the corresponding quinone **55**, arising from dimerization of the initially formed unstable quinone methide **59** (equations 14, 16)[22]; and to rearrangement products of type **112** (equation 27)[143].

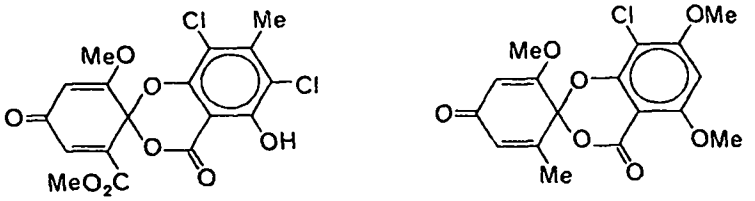
When treated with lead dioxide, 2,4,6-trichlorophenol (**155**) undergoes oxidative dehalogenation (equation 39) and affords products **156**, **157**, **158** and **159**, their ratio depending upon experimental conditions[191, 192]. 2,4,6-Tribromophenol is oxidized by lead dioxide (or alkaline ferricyanide) mainly to a polymeric ether corresponding in structure to **159** [140]. For this reaction a mechanism involving attack of a phenoxy radical on a phenoxide anion (see equation 23) has been tentatively suggested[7, 140].



Oxidative lactonization involving carboxyl–phenol coupling (reaction 40) and leading to the formation of the spirolactone **161** was observed upon oxidation of 2-carboxy-4′-hydroxydiphenylether (**160**) with active lead dioxide[193]. This reaction has been successfully applied in the last step of the synthesis of geodoxin (**162**)[193] and the geodoxin analogue of griseofulvin (**163**)[194].

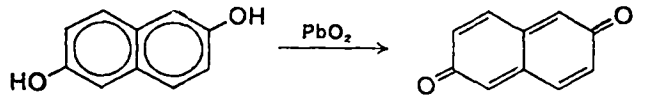


(160) (161) (40)



(162) (163)

Active lead dioxide, obtained from lead tetraacetate and water, oxidizes dihydric phenols to quinones; for example, it has been used for the preparation (equation 41) of amphi-naphthoquinone (**165**) from 2,6-dihydroxynaphthalene (**164**)[189, 195].



(164) (165) (41)

E. Oxidation by Peroxy Compounds

1. Hydrogen peroxide

Species resulting either from homolytic or heterolytic decomposition of hydrogen peroxide can attack and oxidize phenolic and other organic compounds.

Several different ways are possible for the generation of hydroxyl radicals (HO•) and hydroperoxy radicals (HOO•) derived from hydrogen peroxide[196, 197]. (a) Reduction of hydrogen peroxide by ferrous salts (Fenton's reagent) in aqueous solution produces hydroxyl radicals, according to the Heber–Weiss reaction (42)[197]; (b) molyb-

$$M^{n+} + H_2O_2 \longrightarrow M^{n+1} + HO^{\bullet} + HO^{-} \qquad (42)$$

dates as well as oxides and salts of other so called 'peracid formers', such as titanium, vanadium, tungsten, etc., in the presence of hydrogen peroxide, afford hydroxyl radicals[63a, 198–200]; (c) rupture of water molecules by ionizing radiations such as X-rays, γ-rays or neutrons furnishes hydroxyl radicals and hydrogen atoms (reaction

43)[201], whereby hydrogen atoms react immediately with oxygen

$$H_2O \xrightarrow{\sim\sim} H^{\bullet} + HO^{\bullet} \qquad (43)$$

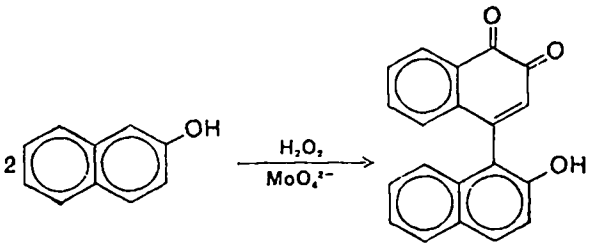
present in solution producing hydroperoxy radicals, $HOO^{\bullet}$; (d) hydroxyl radicals are also formed by photodecomposition of hydrogen peroxide in aqueous media[202].

Fenton's reagent (H_2O_2 + ferrous salts), which was regarded by Wieland[203] as a prototype model for oxidation by heavy-metal enzyme systems, is an efficient source of free hydroxyl radicals and has been extensively studied as oxidant of phenolic and related compounds[196, 201, 203–212]. Attack of 'electrophilic' hydroxyl radicals[199, 207, 210–212] by Fenton's reagent effects *ortho*- and *para*-hydroxylation of phenols affording catechols and hydroquinones. Secondary processes, including quinone formation, are also observed[201, 208], because the Fe^{3+} ions produced in reaction (42) form complexes with the phenols and the ferrous–ferric system enters into oxidation–reduction processes with the products[201]. However, the formation of quinones can be inhibited by the addition of ionic fluoride or pyrophosphate, which remove ferric salts as complexes. Under these conditions the ratio of hydroquinone to catechol formed from phenol is approximately 3 : 1[201], whereas in the usual Fenton's reaction, i.e., in the presence of ferric ions produced, the formation of catechol generally exceeds that of hydroquinone [196, 201, 204–208].

When the oxidation of phenols by Fenton's reagent is performed in an acidic medium, a change of product ratio is often observed and the reaction can even take a different course. Thus, the oxidation of *p*-cresol with ferrous ion–hydrogen peroxide in dilute sulphuric acid solution[209] does not yield the expected *o*-hydroxylation product but only dimeric compounds resulting from oxidative coupling and identical to those obtained by alkaline ferricyanide oxidation (equation 10)[78, 88–91], namely 2,2′-dihydroxy-5,5′-dimethylbiphenyl (**34**) and Pummerer's ketone (**37**).

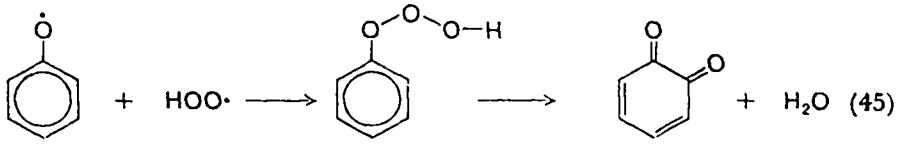
The use of Ti^{3+} ions[63a, 199] and molybdate salts[198, 200] in the hydrogen peroxide oxidation of phenols has been reported. With hydrogen peroxide and ammonium molybdate the oxidation of 2-naphthol does not stop at the *o*-hydroxylation stage, but proceeds further (equation 44) to 4-(2′-hydroxy-1′-naphthyl)-1,2-naphthoquinone (**166**)[200]. This product was shown to arise from initial oxidation of a 2-naphthol molecule to the corresponding 1,2-quinone followed by combination with a 2-naphthyloxy radical.

Secondary reactions which often complicate the *o*,*p*-hydroxylation



(166) (44)

of phenols can mostly be avoided if instead of Fenton's reagent hydroxyl radicals are generated by the action of ionizing radiations on water (reaction 43), since in this case metal ions are absent and a much wider range of pH can be used. Moreover, Fenton's reagent can lead to a chain reaction which is often difficult to reproduce exactly, whereas when penetrating rays are used the amount of radicals is known and easily controlled[201]. As with Fenton's reagent, hydroxylation of phenol by X-ray irradiation of its aqueous solutions takes place exclusively in the *ortho-* and *para*-position, the hydroquinone–catechol ratio in the products being between 1·5 and 2 in neutral solution, and rising to higher values (4·0–4·7) in acidic or alkaline media[201]. Towards both extremes of the pH range quinones are formed, apparently not from, but in place of, the dihydroxybenzenes. In acidic solution a possible mode of formation of *o*-benzoquinone has been envisaged as involving an intermediate resulting from coupling of phenoxy and hydroperoxy radicals (equation 45)[201].



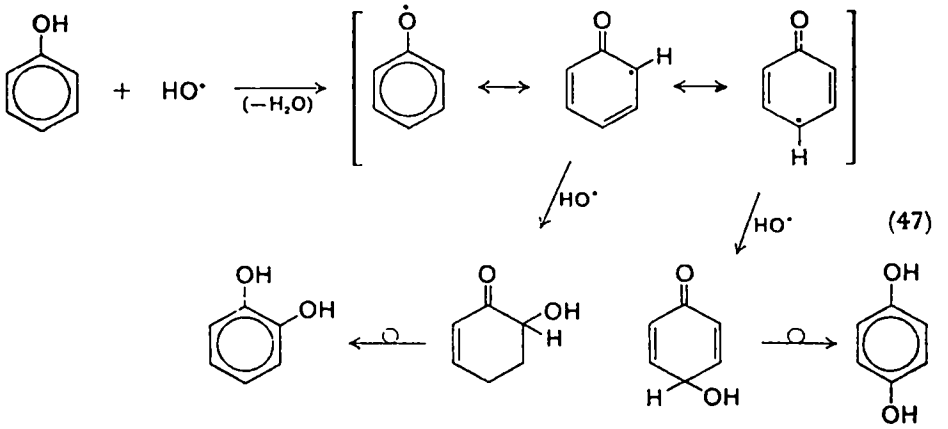
(45)

The photolysis of hydrogen peroxide in the presence of phenols in aqueous solution can be conveniently applied for the preparative *o*- and *p*-hydroxylation of various phenols[202]. Irradiation with light at 2537 Å results in the formation of catechols and hydroquinones as the main products, *ortho*-hydroxylation being predominant. With *p*-carboxy- and *p*-methoxyphenols, hydroquinone was obtained (as a result of displacement of the *p*-substituent by a hydroxyl group), in addition to the usual catechol derivative. Using light over 2800 Å at pH 1 *p*-cresol did not undergo *o*-hydroxylation but was converted

to a mixture of dimers **34** and **37** (equation 10). The primary reaction of the photodecomposition of hydrogen peroxide is considered as a fission of the O–O bond of the excited molecule to form two HO• radicals (equation 46) which initiate chain decomposition.

$$H{-}O{-}O{-}H \xrightarrow[(<4000\ \text{Å})]{h\nu} 2\ H{-}O^{\bullet} \qquad (46)$$

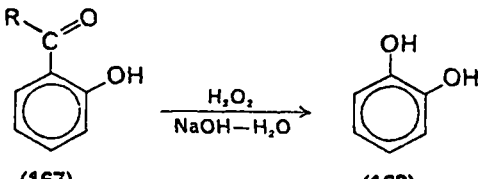
Hydroxylation of phenols by hydroxyl radicals then proceeds, most probably, through the intermediate formation of a phenoxy radical which combines with a second HO• radical to give an *o*- or *p*-dihydroxy compound (equation 47)[202]. This mechanism would also



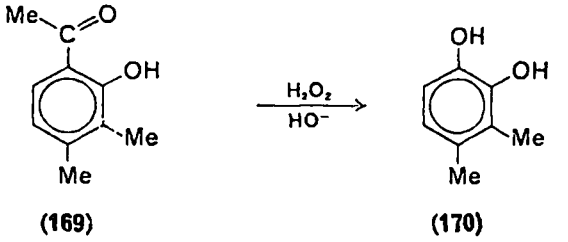
(47)

explain the formation of dimeric coupling products (from the phenoxy radicals). Furthermore, it is substantiated by e.s.r. studies, which have shown that phenol and *p*-cresol are converted by hydroxy radicals to the corresponding phenoxy radicals[63a].

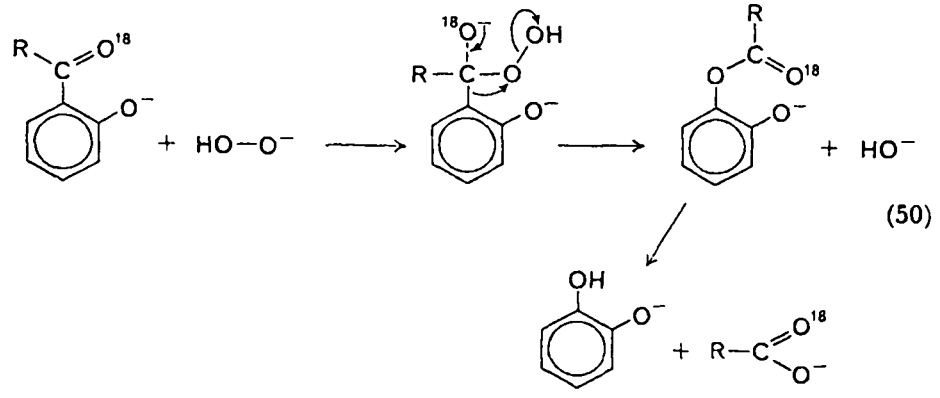
Under heterolytic conditions, i.e., in alkaline solution, hydrogen peroxide oxidizes *o*- and *p*-hydroxybenzaldehydes (e.g., **167**, R = H) or *o*- and *p*-hydroxyacetophenones (e.g., **167**, R = CH_3) (but not the *m*-isomers) to catechols (**168**) and hydroquinones, respectively (reaction 48)[213–217]. This reaction, discovered by Dakin[213], which is formally, (equation 48), the substitution of an *ortho*- or *para*-formyl or acyl group by a hydroxyl group, was first regarded as being applicable mainly to hydroxybenzaldehydes, but was later successfully extended[214–216] to the generally more accessible *o*- and *p*-hydroxyacetophenones and other higher alkyl hydroxyaryl ketones. Difficulties resulting from the tendency of *o*-acylated phenols to form sparingly soluble chelated alkali salts when the Dakin reaction is performed in aqueous sodium or potassium hydroxide, may be



overcome by using as the base tetramethylammonium hydroxide (or somewhat less satisfactorily benzyltrimethylammonium hydroxide), whose salt with the starting material is ionized and therefore readily soluble[216]. Thus, the yield of 3,4-dimethylcatechol (**170**) obtained in the Dakin reaction (equation 49) of 2-hydroxy-3,4-dimethylacetophenone (**169**) is only 2·5% when the base is potassium hydroxide, and over 25% when tetramethylammonium hydroxide is used instead[216].



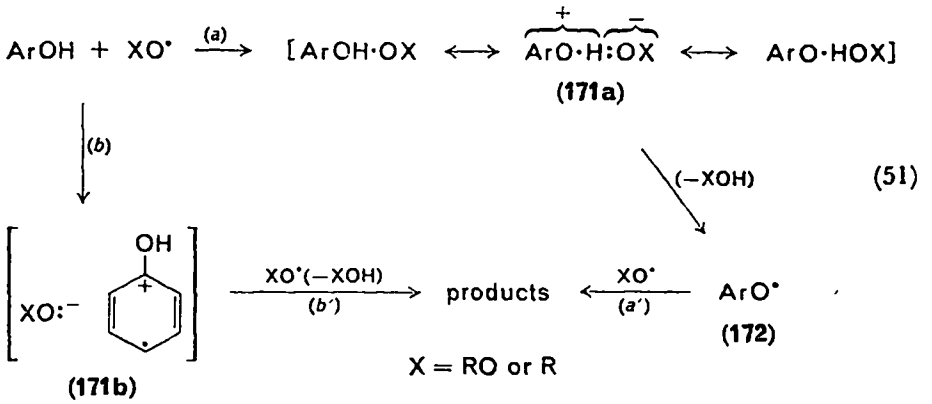
The Dakin reaction has been interpreted by a mechanism similar to that proposed for the Baeyer–Villiger oxidation and is formulated in scheme(**50**)[218].



2. Alkyl peroxides

The reactions of peroxy radicals, ROO•, and alkoxy radicals, RO•, with phenols are of particular interest in relation to autoxidation phenomena, since phenols act as inhibitors and destroy these radical species, which are active intermediates in autoxidation free radical chain processes[3, 7, 9].

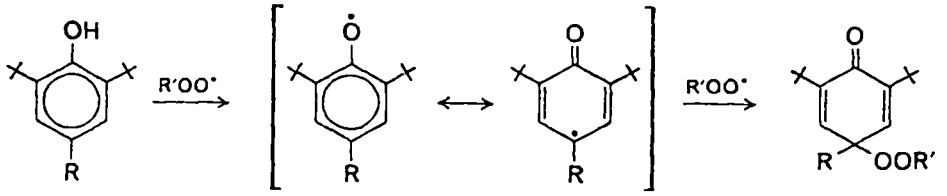
A large kinetic isotope effect (k_H/k_D = 6·5–10·5 at room temperature) is observed when the hydroxyl hydrogen in phenol is replaced by deuterium. On the basis of the retardation of the reaction rate and the decrease of phenol inhibiting efficiency[219–222], Ingold[219–221] and Shelton[222] have suggested that the rate-determining step (*a*), in the reaction (51) of a phenol with peroxy radicals (X = RO) consists in the abstraction of a hydrogen atom from the hydroxyl group by a peroxy radical, possibly through a transition state of type **171a** [12], with formation of a phenoxy free radical (**172**), which subsequently reacts (*a'*) with a second peroxy radical. A similar scheme was proposed for the rate-determining step in the reaction between phenols and alkoxy radicals[115, 223].



On the other hand, from kinetic measurements it appears that the transition state of the rate-determining step involves one molecule of phenol and two peroxy radicals[224], and Coppinger[48], following the proposal of Hammond and Boozer[224], has therefore suggested that as the rate-determining step (*b*) a charge-transfer complex (**171b**) was initially formed between a peroxy radical and the phenol which reacts directly (*b'*) with a second peroxy radical to give products, without passing through a phenoxy free radical (**172**). Hyperconjugation in this complex (**171b**) presumably could account for the observed kinetic isotope effect[48].

The relative rates of hydrogen abstraction from mononuclear phenols by peroxy and alkoxy radicals, and therefore the relative inhibiting properties of phenols in autoxidation processes, have been found to give a remarkably good correlation with Hammett's σ values[219, 224–226] and particularly with Brown's electrophilic σ^+ constants[220, 223, 227]. The maximum rate, i.e., inhibiting efficiency, is achieved when the substituents of the phenol have the largest possible negative $\sum \sigma^+$ consistent with a minimum of steric protection afforded to the hydroxyl group. Thus mononuclear phenols which contain a *t*-butyl group in the 2-position, substituents with large negative σ^+ constants (electron-releasing groups) in 3-, 4- and 5-positions, and a vacant 6-position should be and are in fact autoxidation inhibitors with optimum efficiency.

The oxidation of 2,4,6-trialkyl phenols (**173**) with peroxy radicals (equation 52) generated by the cobalt-catalysed decomposition of hydroperoxides[114, 228] or by the thermal decomposition (at 40–60°) of compounds producing alkyl radicals such as α,α'-azobisisobutyronitrile, in the presence of oxygen (and oxidation initiators)[114, 224, 229], generally affords mainly 4-peroxycyclohexadienones **174**. The yields of the latter depend on the phenol, on the peroxy radical and on the experimental conditions, and are nearly quantitative when 2,6-di-*t*-butylphenols containing a 4-methyl or 4-*t*-butyl substituent and *t*-butyl peroxy radicals or a mixture of α-tetralyl peroxy and isobutyronitrile peroxy radicals are used[114, 228, 229].



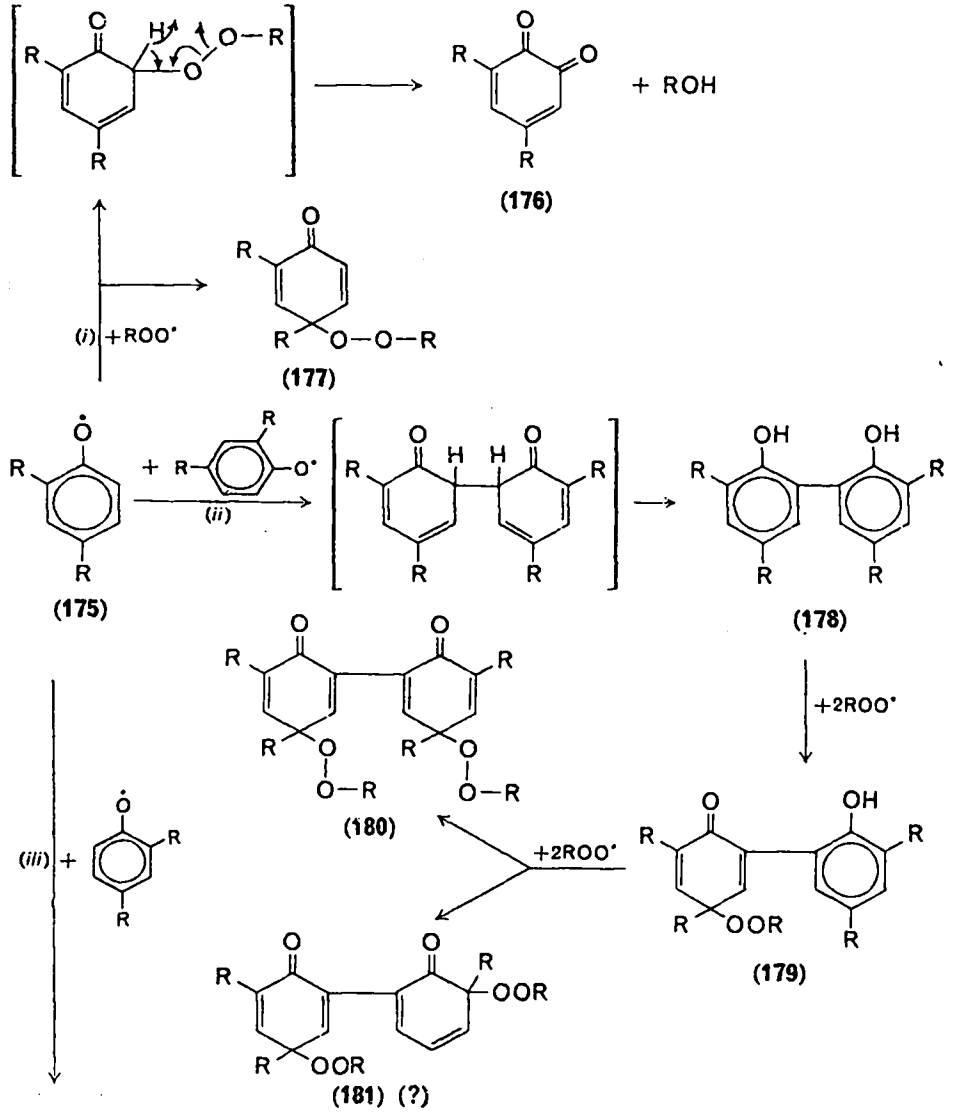
(173) R = Me, *t*-Bu **(174)**

(52)

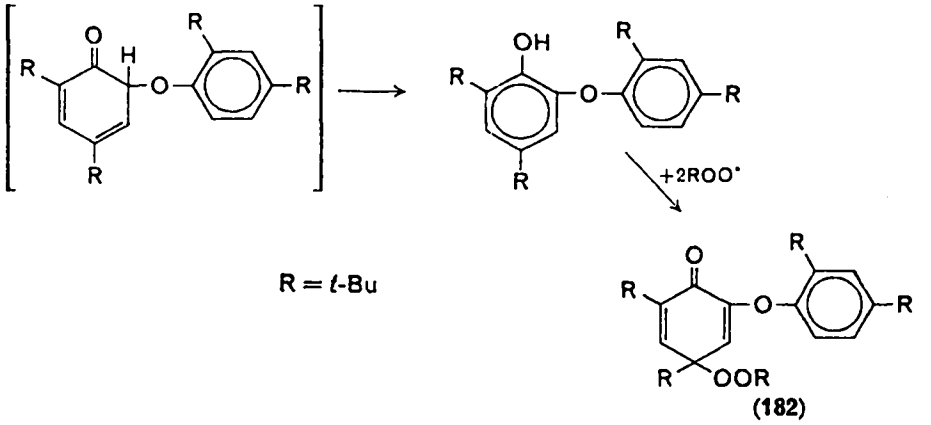
Under certain conditions 2,6-di-*t*-butyl-4-methylphenol (**173**, R = CH_3) undergoes oxidative C(methyl)–C(methyl) dimerization to products **54** and/or **55** (reaction 14), via the unstable *p*-quinone methide **59** (reaction 16), e.g., with triphenylmethylperoxy radicals[111, 114], or in the high-temperature air oxidation of cumene retarded by **173** (R = CH_3)[111, 230].

When mono- and di-alkyl phenols with an unsubstituted *ortho*- or *para*-position are oxidized by peroxy radicals a variety of products

can be formed[111, 230, 231]. Thus, from the reaction of 2,4-di-*t*-butylphenol (**175**) with *t*-butoxy radicals (generated by the cobalt toluate catalysed decomposition of *t*-butyl hydroperoxide below 30°) products **176–182** shown in scheme (53) have been isolated[231]. These can be divided into three groups, depending on the type of radical coupling reaction by which they are produced or in which theirprecursors are formed: (*i*) phenoxy–peroxy 4C–O and 6C–O



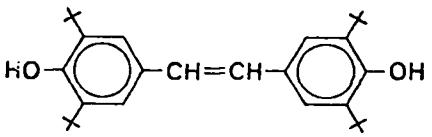
Scheme 53 (*cont. on next page*)

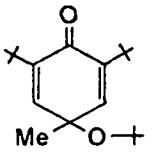


Scheme 53 (*cont.*)

coupling; (*ii*) phenoxy–phenoxy 6C–6C coupling; and (*iii*) phenoxy–phenoxy 6C–O coupling.

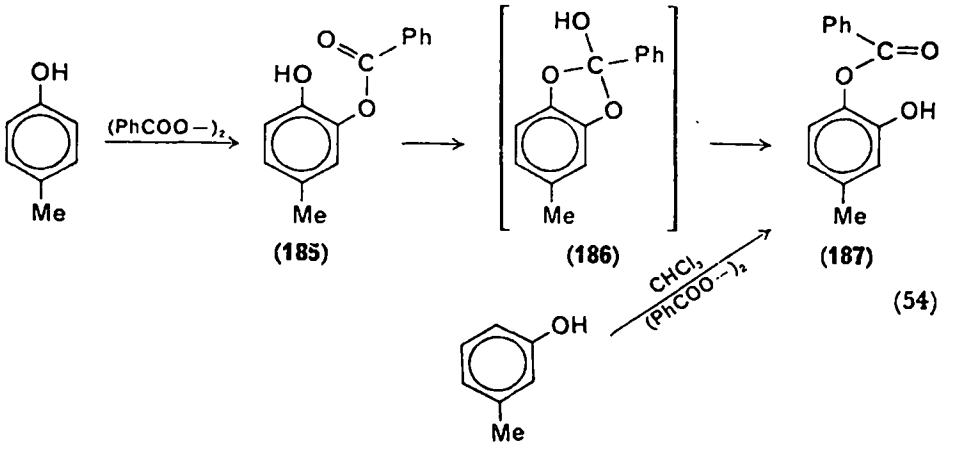
The reaction of *t*-butoxy radicals, $(CH_3)_3CO^{\bullet}$, generated by thermal decomposition at 122° of di-*t*-butyl peroxide, with 2,6-di-*t*-butylphenol [**38**, R = R′ = $C(CH_3)_3$] affords the expected 4C–4C coupled dimers **41** and **42** (equation 11)[115], whereas *t*-butoxy radical oxidation of 2,6-di-*t*-butyl-4-methylphenol (**53**) proceeds with the initial formation of the *p*-quinone methide **59** (equation 16), followed by C(methyl)–C(methyl) dimerization to **54**, **55** (equation 14) and **183** [115]. The absence of the 4-*t*-butoxycyclohexadienone **184** in this reaction is probably due to increased steric effects [compared to those present during the formation (equation 52) of the 4-peroxycyclohexadienone (**174**)] and to the instability of product **184** at 122°.


(183)


(184)

3. Acyl peroxides and peracids

When treated with benzoyl peroxide in refluxing chloroform, *p*-cresol is converted in 35% yield to 4-benzoyloxy-3-hydroxytoluene (**187**), and the same product is obtained, though in poorer yield (20%), from *m*-cresol (reaction 54)[232]. Other phenols with a free *ortho*-position behave similarly, i.e., the benzoyloxy group is introduced preferentially into a position adjacent to the hydroxyl

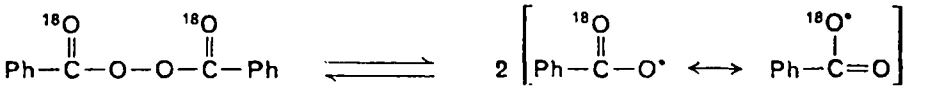


(54)

group[232]. However, with *p*-substituted phenols (such as *p*-cresol, 2,4-dimethylphenol and hydroquinone monomethyl ether), the benzoyl group of the initially formed product (**185**) usually undergoes rapid migration (**185**→**187**); this migration probably occurs by transesterification through an intermediate of type **186** [232]. When one of the *o*-positions in the phenol is occupied by a bulky substituent, as in 2-*t*-butyl-4-methoxyphenol, *ortho*-substitution by the benzoyloxy group is not followed by benzoyl migration[180].

Kinetic studies of this reaction by Walling and Hodgdon[233] have shown that radical traps (oxygen and iodine) have no effect upon rate or products, and that if the hydrogen of the phenolic OH group is replaced by deuterium the reaction velocity decreases (k_H/k_D = 1·32); moreover, no carbon dioxide is evolved during the reaction. These and other results indicate that the phenol–benzoyl peroxide reaction is not a free radical, but a simple bimolecular, probably 'four centre', process, involving the OH group of the phenol. Comparable results were obtained with both acetyl peroxide and *t*-butylperbenzoate[233].

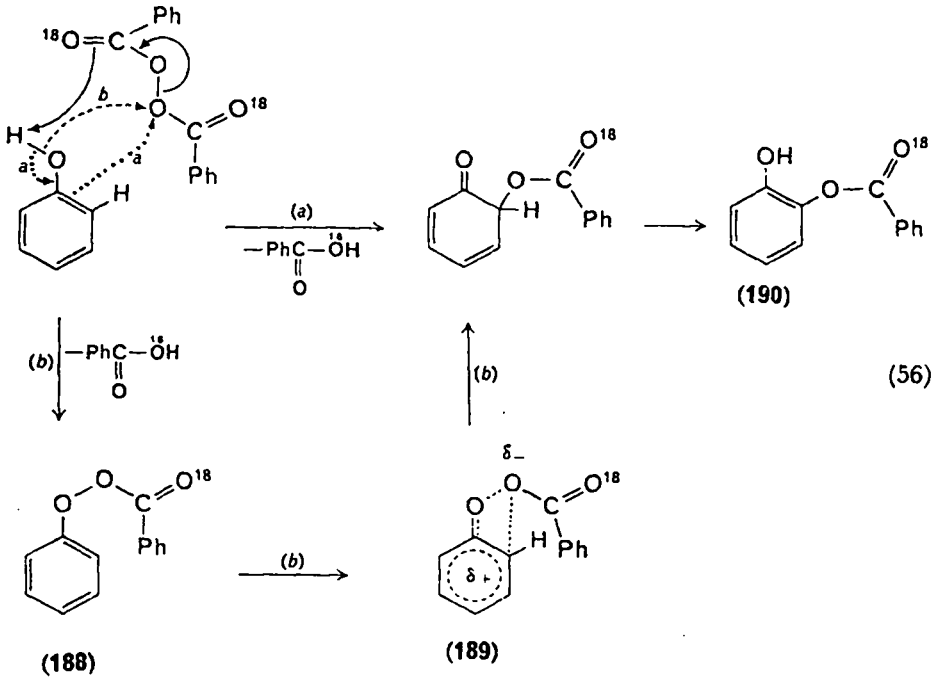
Further evidence was obtained by using benzoyl peroxide labelled with ^{18}O in the carbonyl groups[234]. Analysis of the product **190** (scheme 56) showed that about 87% of the excess ^{18}O was present in the carbonyl group of the benzoate substituent which had been introduced into the phenol. Therefore, benzoyloxy radicals could



(55)

not have been generated since the formation (equation 55) of such radicals would have led to product **190** in which half of ^{18}O was in the ester carbonyl and the other half in the phenolic hydroxyl group.

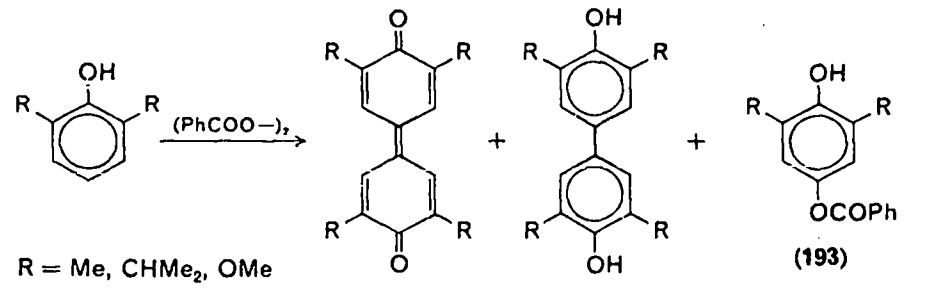
All these facts suggest that the reaction (scheme 56) involves a 'four centre' mechanism either concerted (path *a*)[7], or proceeding (path *b*) via an unstable perester (**188**) and ion-pair (**189**)[233, 234].

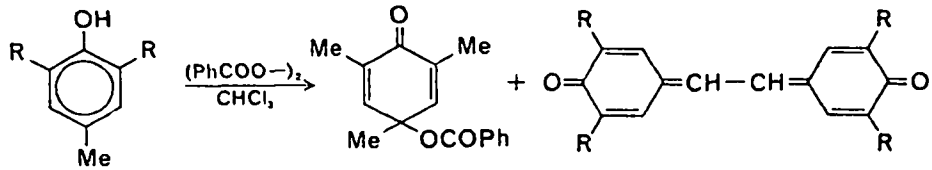


(56)

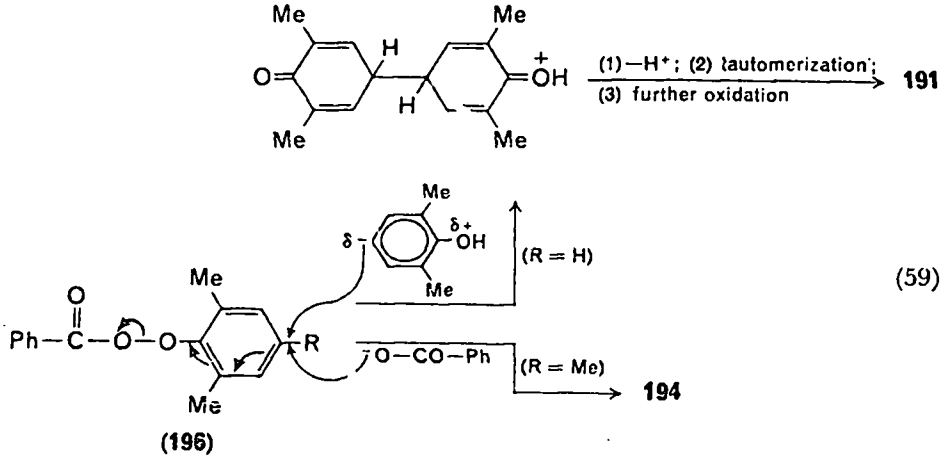
When both *ortho*-positions, but not the *para*-position, of a phenol are occupied, oxidation by peroxides in refluxing chloroform or benzene (reaction 57) affords as major product (50–70%) the 3,3′,5,5′-tetrasubstituted diphenoquinone (**191**), accompanied by small amounts (up to 10%) of the corresponding 4,4′-dihydroxydiphenyl (**192**) and the *p*-benzoyloxy derivative of the starting phenol (**193**)[110, 233].

On the other hand, when mesitol, in which both *o*-positions and the *p*-position are blocked by methyl groups, is treated with benzoyl peroxide in refluxing chloroform, the reaction (58, R = CH_3) affords over 90% of 4-benzoyloxy-2,4,6-trimethylcyclohexa-2,5-dienone (**194**) and only traces of 3,3′,5,5′-tetramethylstilbenequinone (**195**, R = CH_3)[110].



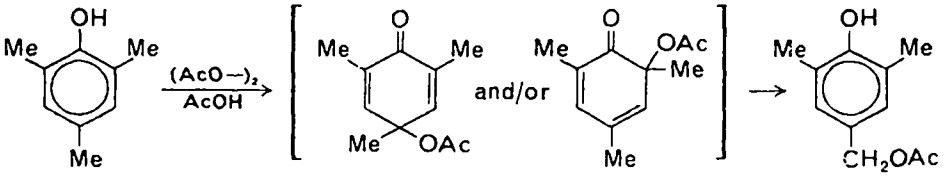


Both reactions (57) and (58) can be explained by scheme (59), postulating the intermediate existence of a perester **196**, which would be prone to electrophilic attack at the *para*-position[184].



Bulky *t*-butyl groups in the *o*-positions retard considerably the reaction (58) of 2,6-di-*t*-butyl-4-methylphenol (R = *t*-butyl) with benzoyl peroxide; no dienone of type **194** is obtained (probably because of steric hindrance to formation of **196**), and the only products isolated in moderate yield are the stilbenequinone **195** (R = *t*-butyl) and the corresponding 4,4′-dihydroxydibenzyl[110, 112].

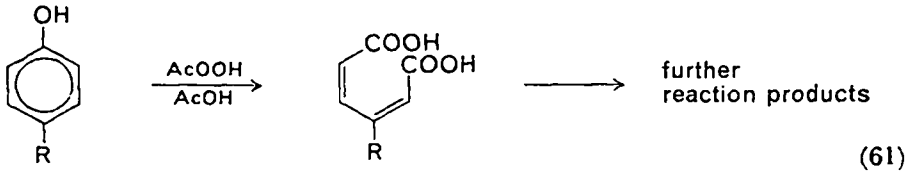
Treatment of the isomeric cresols and 2,4-dimethylphenol with acetyl peroxide in acetic acid at 62–77°, followed by acid hydrolysis of the phenol fraction, affords dihydric phenols corresponding to the introduction of the acetoxy group into the free *ortho*- and *para*-positions; moreover, derivatives of *o*- and *p*-hydroxyphenylacetic acid were found in the acid fraction, indicating that probably the radical $^{\bullet}CH_2COOH$ participates in the reaction[165, 235]. Acetyl peroxide in benzene reacts with 2,6-disubstituted phenols in the same way as benzoyl peroxide (reaction 57)[233]. When 2,4,6-trimethylphenol is treated with acetyl peroxide in acetic acid at 65° (reaction 60) it is converted in 80–90% yield to 3,5-dimethyl-4-hydroxybenzyl acetate (**199**), possibly by rearrangement of the initially formed, but not isolated, 4- and/or 2-acetoxy-2,4,6-trimethylcyclohexadienones **197** and **198** [166, 235].



(197) (198) (199)

(60)

Peracetic acid in acetic acid attacks preferentially the *ortho*-positions of phenol and *p*-substituted phenols, which are converted (reaction 61), probably through *o*-quinones, to the corresponding *cis-cis*-muconic acids (**200**) (phenol gives, in addition, some *p*-benzoquinone)[236, 237]. Since these acids easily undergo further reaction



R = H, Me, Cl, Br (200)

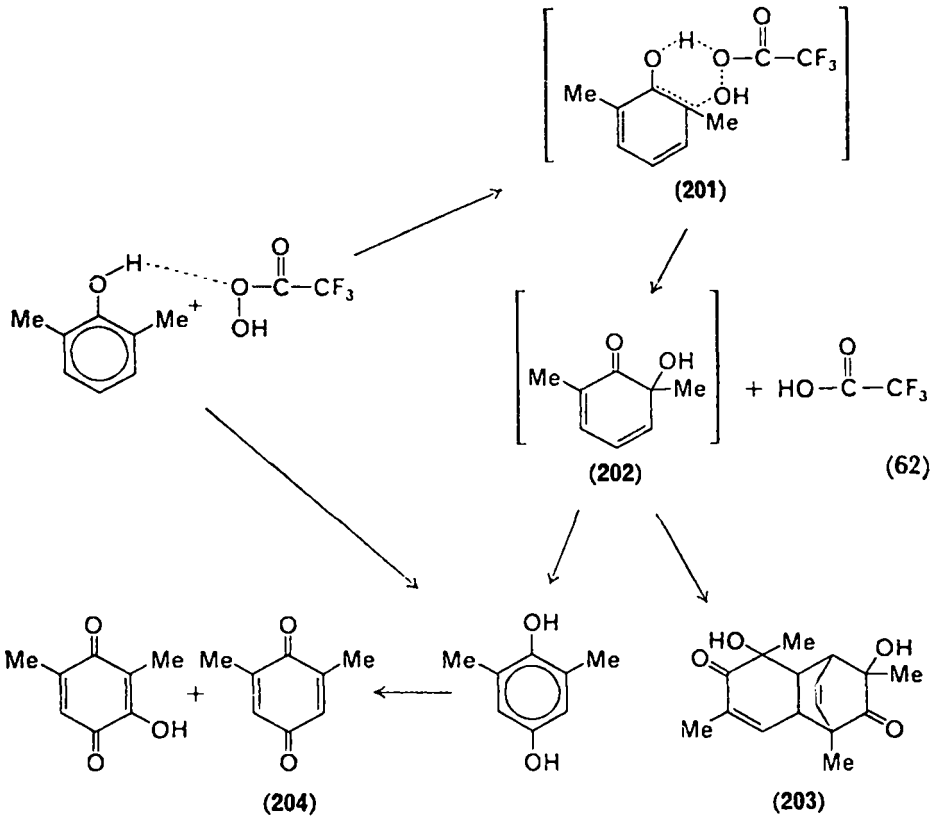
(61)

(cyclization to lactones, hydroxylation, etc.) and the resulting products are difficult to separate, this oxidation is not of great preparative value.

However, when peracetic acid is used in a mixture of sulphuric acid and acetic acid[238], or when oxidations are performed with

trifluoroperacetic acid in methylene chloride[239], 4-unsubstituted di- and tri-methylphenols, even when they contain a free *ortho*-position, are converted in yields up to 80% to the corresponding *p*-benzoquinones.

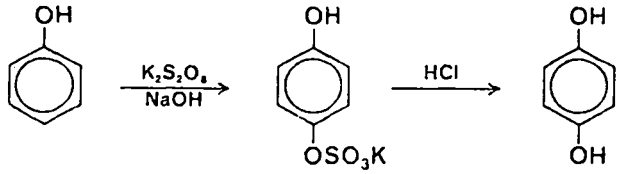
When trifluoroperacetic acid is generated slowly in situ, i.e., by slow addition of hydrogen peroxide to a solution of 2,6-dimethylphenol and trifluoroacetic acid in methylene chloride, the reaction (62)[240] affords as major product (42%) the Diels–Alder dimer **203** of 2,6-dimethyl-*o*-quinol (**202**), while 2,6-dimethyl-*p*-benzoquinone (**204**), which predominates under usual conditions (i.e., when hydrogen peroxide is added all at once)[239, 240], is obtained in only 27% yield. A cyclic hydrogen-bonded transition state **201** has been suggested to account for *o*-hydroxylation leading to the *o*-quinol **202** [240].



4. Persulphate oxidation

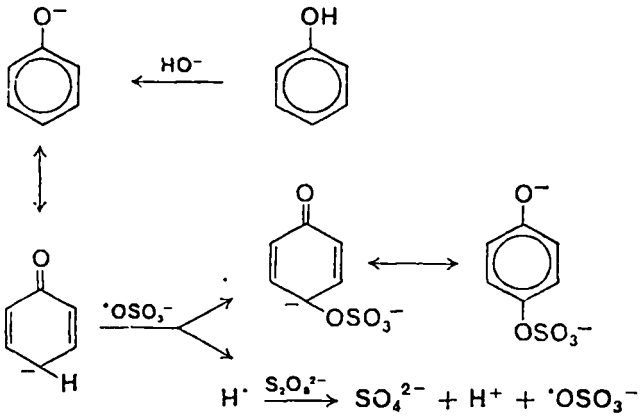
The oxidation of monohydric phenols to dihydric phenols by potassium or ammonium persulphate in cold aqueous alkali was discovered by Elbs[241]. When the *para*-position is free, *p*-hydroxylation (equation 63) gives hydroquinone derivatives (**206**); with *p*-substituted phenols reaction takes place at the *ortho*-position and derivatives of catechol are obtained, though usually in much lower yield[242, 243].

It was shown that a hydroxyphenyl alkali sulphate **205** is formed as an intermediate and is subsequently hydrolysed in acid solution to hydroquinone[242, 243].



(205) (206) (63)

Baker and Brown[243] have pointed out that the direct introduction of the sulphate group *para* or *ortho* (but never *meta*) to the phenolic oxygen atom, suggests that in the Elbs persulphate oxidation is the resonance hybrid of the phenoxide ion undergoing attack (scheme 64), and that the substituting agent is a reactive sulphate ion-radical, $^{\cdot}OSO_3^-$, which although an anion is yet electrophilic in character. This ion-radical might be initially generated by interaction of a trace of a metal cation present as impurity in the persulphate salt



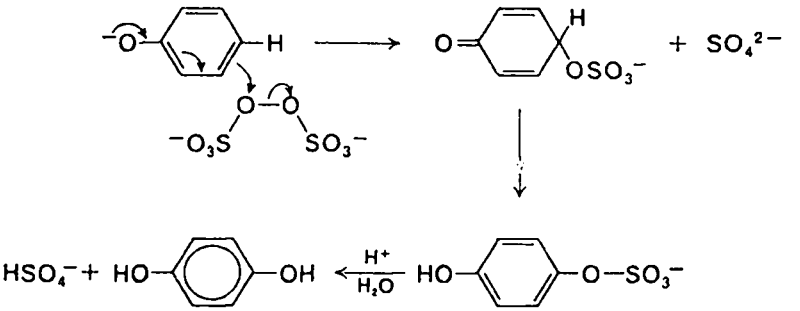
(64)

(such as a ferrous or silver ion) with a persulphate anion (equation 65).

$$Fe^{2+} + S_2O_8^{2-} \longrightarrow Fe^{3+} + SO_4^{2-} + {}^{\cdot}OSO_3^- \qquad (65)$$

The slow rate of the reaction can be correlated with the requirement in the above mechanism (64) that the sulphate anion-radical has to attack an anion. A further point in agreement with such a mechanism (64) is the fact that in general the yield of *para*-hydroxylation is increased by the presence of electron-attracting groups, by increasing substitution and by the effect of substituents on the activity of the position *para* to the hydroxyl group[242, 243].

Waters[7], however, considers the alkaline persulphate oxidation of phenols to be a completely heterolytic reaction (66), proceeding without the intervention of radical or ion-radical species.



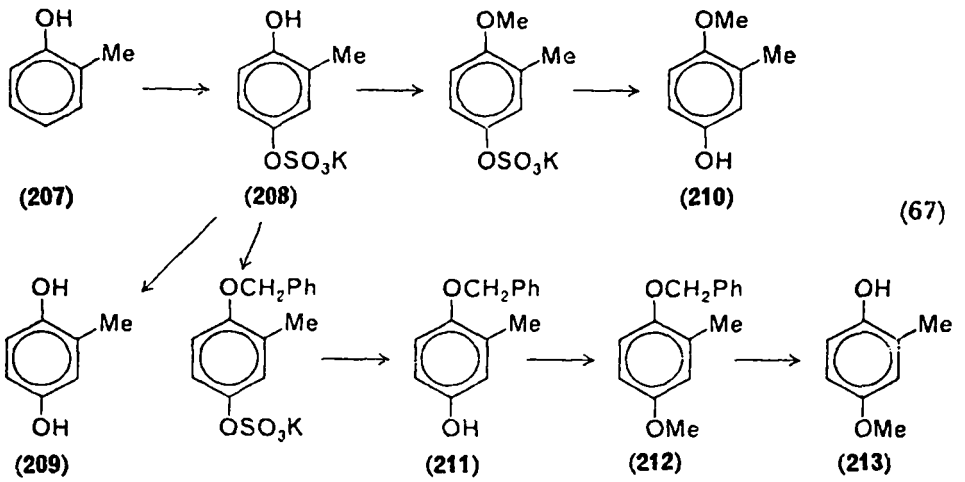
(66)

(205)

A variety of mono- and poly-substituted monohydric phenols (in which the position *para* to the hydroxyl group is free) have been successfully used as substrates in the persulphate reaction, the yield of the corresponding *para*-hydroxylation products ranging from 18 to 50% [241–243]. A substantial amount of unreacted starting material can usually be recovered, whereas the yields of products resulting from *ortho*-hydroxylation and/or oxidative coupling of the phenol nuclei, are generally very low[242].

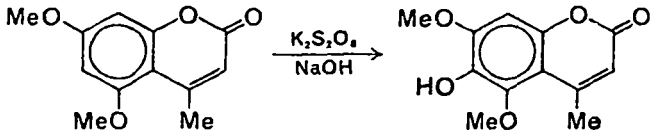
Because of its relative stability under alkaline conditions, the intermediate *p*-hydroxyphenyl potassium sulphate (**205**) (equation 63) can be alkylated and hydrolysed to an alkoxyphenol[243]. This modification offers useful synthetic possibilities, as illustrated (equation 67) by the preparation of products **209**–**213** from the same starting material **207** [243].

In the persulphate oxidation of polyhydric phenols, usually all except one hydroxyl group must be methylated prior to reaction, in

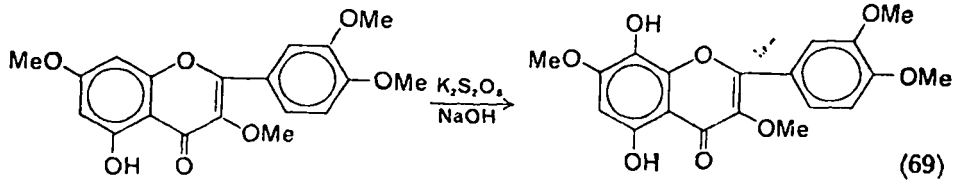


(67)

order to protect the molecule against general oxidation. A number of such partially alkylated phenols have been successfully oxidized to *para*-hydroxy derivatives[242]. 1-Naphthol and its derivatives are converted in good yields to the corresponding 4-hydroxy compounds, whereas 2-naphthols give poor yields of 1,2-dihydroxy products[244]. This is in agreement with the above mentioned observation that *ortho*-hydroxylation of *p*-substituted phenols proceeds in low yield. The persulphate oxidation converts coumarins to 6-hydroxycoumarins (equation 68)[242, 244], and 5-hydroxyflavones to the corresponding 5,8-dihydroxy compounds (equation 69)[242, 245].



(68)



(69)

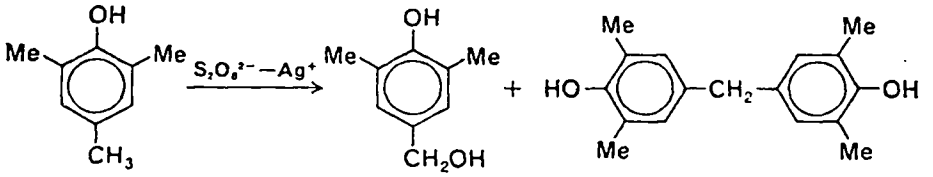
In neutral aqueous solution and in the presence of catalytic amounts of ferrous, ferric or silver ions, the reaction leads predominantly to oxidative coupling products[246, 247], similar to those described for oxidations with ferricyanide, ferric chloride or aqueous ferrous salts and hydrogen peroxide.

By analogy to the generation of $^{\bullet}OSO_3^-$ ion-radicals from persulphate ions and ferrous ions (equation 65), the primary step in the silver ion catalysed persulphate oxidation may be represented by equation (70)[246–249]. Oxidation would then involve removal of

$$Ag^+ + S_2O_8^{2-} \longrightarrow Ag^{2+} + SO_4^{2-} + {}^{\bullet}OSO_3^- \qquad (70)$$

hydrogen from a phenol by a radical, $^{\bullet}OSO_3^-$ or HO$^{\bullet}$ (produced by attack of $^{\bullet}OSO_3^-$ or Ag^{2+} on water[248, 249]), or Ag^{2+} ion[246–248], followed by coupling of the resulting aryloxy or hydroxyaryl radicals. The same radicals may be consumed, usually in a minor reaction, by oxygenation processes, of uncertain mechanism but presumably involving HO$^{\bullet}$ radicals or oxygen generated from these radicals[248, 249].

Thus, the $S_2O_8^{2-}$–Ag^+ oxidation of *p*-cresol affords the three known products **34**, **35** and **37** (equation 10), in 7, 7 and 15% yield, respectively[246]. When treated with the same reagent 2,6-dimethylphenol (**38**, R = R′ = CH_3) is converted in major part (about 60%) to the nuclear C–C coupling products **41** and **42** (equation 11), whereas nuclear *p*-oxygenation (either direct or involving *p*-hydroxylation followed by oxidation; see above) to 2,6-dimethyl-*p*-benzoquinone proceeds only in about 10% yield[247]. Under similar conditions, 2,4,6-trimethylphenol is attacked at the *para*-methyl group (equation 71), which, presumably via the corresponding benzyl radical, undergoes 22% of hydroxylation resulting in the formation of 4-hydroxy-3,5-dimethylbenzyl alcohol (**214**), and 13% of oxidative coupling and elimination to give 4,4′-dihydroxy-3,3′,5,5′-tetramethyldiphenylmethane (**215**)[247].



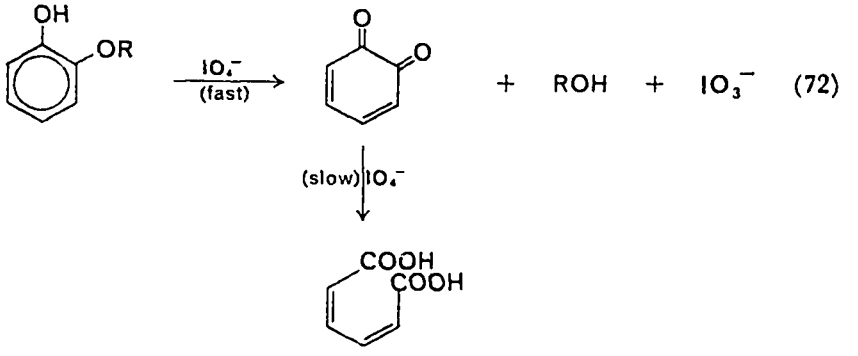
(214) (215) (71)

F. Periodate Oxidation

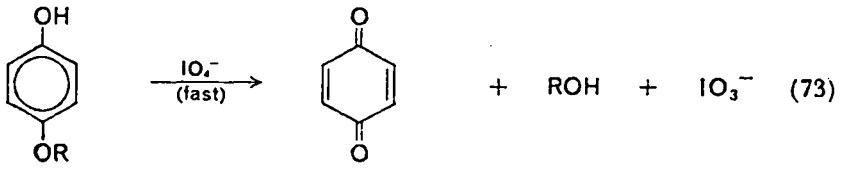
Treatment of monoethers of catechol and hydroquinone with sodium periodate ($NaIO_4$) in aqueous solution or in 80% acetic acid leads mainly to oxidative removal of the ether substituent with formation of *ortho*- and *para*-benzoquinone, respectively, and the corresponding alcohol (reactions 72 and 73)[250–252]. Thus, guaiacol (equation 72, R = CH_3) is rapidly converted to *o*-benzoquinone, which can be isolated in about 65% yield, but with excess periodate

is itself slowly oxidized to *cis-cis*-muconic acid (**216**)[252]. Catechol and hydroquinone (72 and 73, R = H) are also rapidly oxidized with periodate to the corresponding quinones[251, 252]. Sodium bismuthate, $NaBiO_3$, behaves in these reactions like sodium periodate[180, 252].

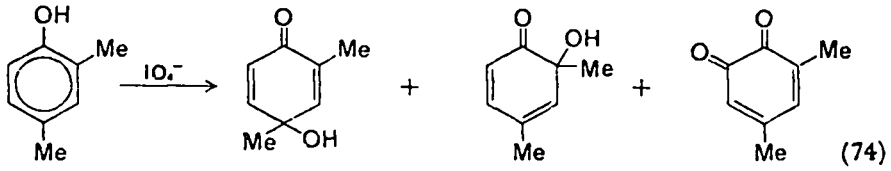
Resorcinol and its monomethyl ether are only slowly attacked by periodate, and so also is phenol itself[252, 253]. However, alkyl-substituted phenols are readily oxidized by sodium periodate to give mainly dimeric products[254, 255]. For example, 2,4-dimethylphenol is first converted (reaction 74) to 2,4-dimethyl-*p*-quinol (**217**), 2,4-dimethyl-*o*-quinol (**218**) and 3,5-dimethyl-*o*-quinone (**219**)[254]; of these products only the *p*-quinol **217** can be isolated, whereas the



(**216**)



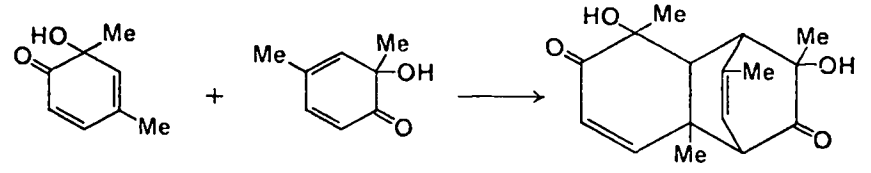
R = Me, Ph, $PhCH_2$, H



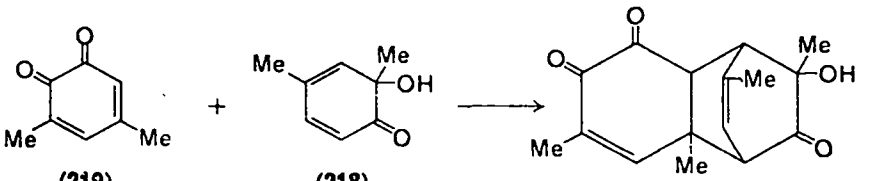
(**217**) (**218**) (**219**)

o-quinol **218** rapidly undergoes two further reactions: dimerization by a Diels–Alder addition (equation 75) to give a 1,4-ethenonaphthalene derivative **220**, and a similar type of addition (equation 76) to the *o*-quinone **219** resulting in the formation of the adduct **221**.

Similar dimeric products have been reported for the periodate oxidation of 2,6-dimethyl- and 2,4,6-trimethyl-phenol[255].

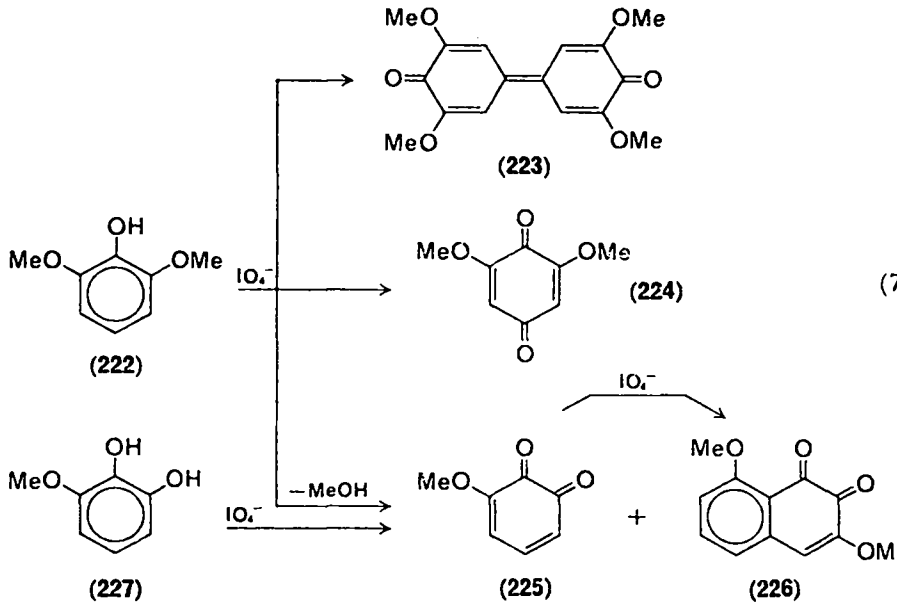


(218) (218) (220) (75)



(219) (218) (221) (76)

When treated with sodium periodate, mono- and di-ethers of pyrogallol are converted to various quinonoid products, depending upon experimental conditions. Thus, 2,6-dimethoxyphenol (**222**) is oxidized (reaction 77) to coerulignone (**223**), 2,6-dimethoxy-*p*-quinone (**224**), 3-methoxy-*o*-quinone (**225**), 3,8-dimethoxy-1,2-naphthoquinone (**226**) and a product of unknown structure[256]. Compounds **225** and **226** are also obtained by the periodate oxid-



(223)

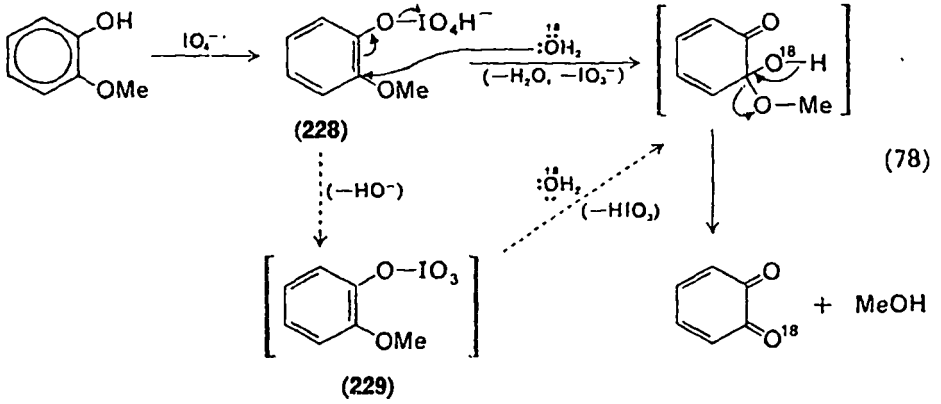
(222) (224) (77)

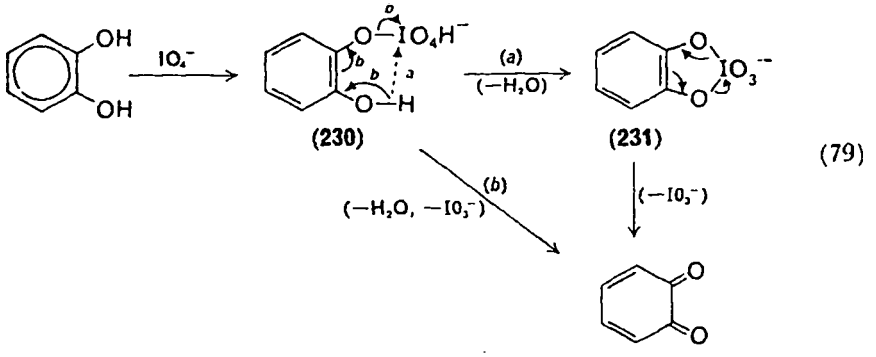
(227) (225) (226)

ation of 3-methoxycatechol (**227**)[256]. The formation of the naphthoquinone **226**, which can be obtained by treating the quinone **225** with periodate[256], has been formulated as involving a Diels–Alder type addition of the *o*-quinone **225** to its hydrated form followed by periodate oxidation[257, 258].

The oxidative demethylation of the monomethyl ethers of catechol (reaction 72, R = CH_3) and hydroquinone (reaction 73, R = CH_3) by sodium periodate in ^{18}O–water affords labelled *o*- and *p*-benzoquinone, respectively (and methanol without ^{18}O), whereas unlabelled quinones are obtained from catechol or hydroquinone (R = H) under the same conditions[259]. On the basis of these results, Adler has suggested the schemes (78) and (79), which both involve as intermediates aryl esters of periodic acid (**228–231**)[259]. Cyclic diester (**231**) formation (pathway *a* in 79) would be possible only with catechol, whereas hydroquinone oxidation would have to proceed via ester **230** according to path *b*.

Recent kinetic work on the periodate oxidation at pH 1–4 of





hydroquinone, its monomethyl ether and catechol monomethyl ether (guaiacol) to form the corresponding benzoquinones (reactions 78 and 79), has shown that the reaction is second-order but that there was no evidence for a detectable intermediate[260]; this suggests that if substrate–periodate complexes (possibly of type **228** and **230**) are intermediates, their formation rather than their decomposition to products is the rate-determining step. For the periodate oxidation of catechol, over a pH range 0–10, however, it was found that an intermediate is formed in a second-order reaction and that this intermediate (not isolated but discussed in terms of the cyclic diester **231** (equation 79) or a dissociable *o*-benzoquinone–iodate charge-transfer complex) then decomposes in a slower first-order reaction to products[250].

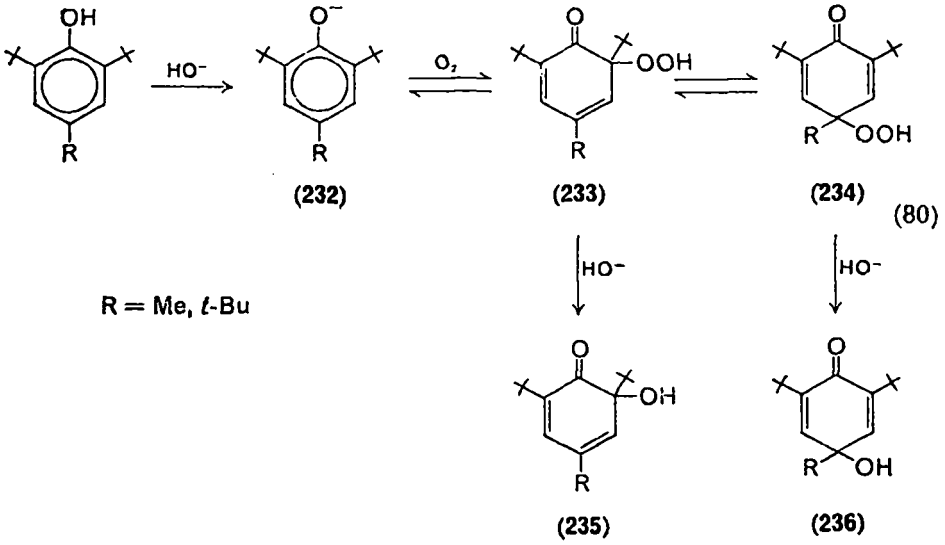
G. Oxidation by Molecular Oxygen

The reactions between atmospheric oxygen and phenols or their corresponding radicals are of special interest in relation to autoxidation processes and enzymic processes. In the presence of dissolved oxygen, reactions of this type might compete with other phenol oxidations, and should be taken into account when discussing products obtained by the use of various oxidizing agents.

When not controlled, the reaction of oxygen with mono- and polyhydric phenols, especially in alkaline media, gives rise to dark-coloured, very complex mixtures of poorly defined products. For example, black, intractable resins are formed from pyrogallol, which has been used in alkaline solution for many years to remove oxygen from gaseous systems. However, under mild alkaline conditions, pyrogallol is oxidized by oxygen to dimers and trimers of type **41** and **42** (equation 11)[261], whereas 4,6-di-*t*-butylpyrogallol undergoes oxidative opening of the benzene ring followed by recyclization to various products[262, 263].

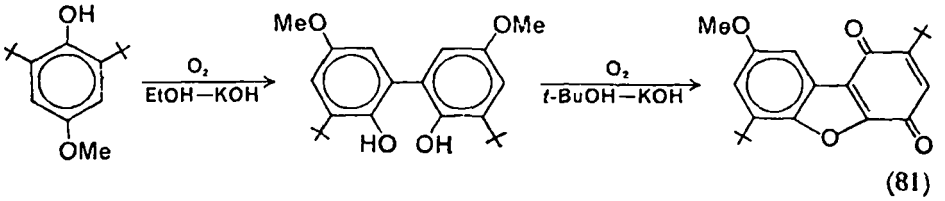
2,4,6-Trisubstituted phenols, such as 2,4,6-tri-*t*-butyl- and 2,6-di-*t*-butyl-4-methylphenol, are oxidized by oxygen in alkaline solution at room temperature (reaction 80), through the ions **232**, to an equilibrium mixture of 2- and 4-hydroperoxycyclohexadienones **233** and **234** (in yields up to 85%), which are decomposed by alkali to the corresponding quinols **235** and **236** [92, 264].

Under more vigorous conditions (prolonged action of oxygen at elevated temperatures, presence of metal catalysts), oxidation of 2,6-di-*t*-butyl-4-methylphenol affords a variety of compounds in low yield[112, 113, 265–267].

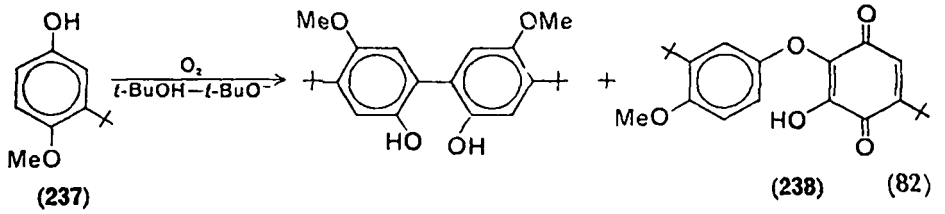


If the *p*-position is unsubstituted, as in 2,6-di-*t*-butylphenol, the intermediate phenoxy radical reacts faster with itself than with oxygen[92, 93, 107, 268], and the diphenoquinone **42** [reaction 11, R = R′ = $C(CH_3)_3$] is produced in very good yield[92, 264].

When one or both *o*-positions in the starting 4-methoxyphenol are free, the course of the reaction with oxygen depends mainly on the number and position of the *t*-butyl substituents, as illustrated by reactions (81–83)[269]. It has been suggested[269] that the C–O coupling

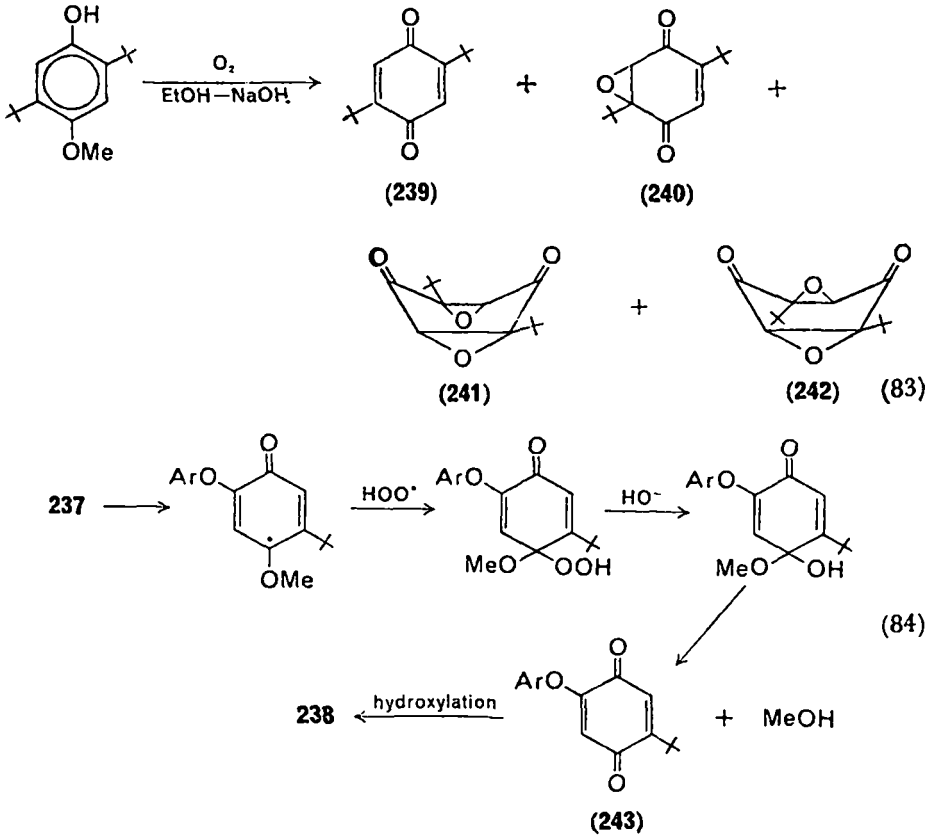


(81)



(237) (238) (82)

reaction in the formation (equation 82) of the phenoxy-quinone **238** precedes oxidative demethylation, which takes place as shown

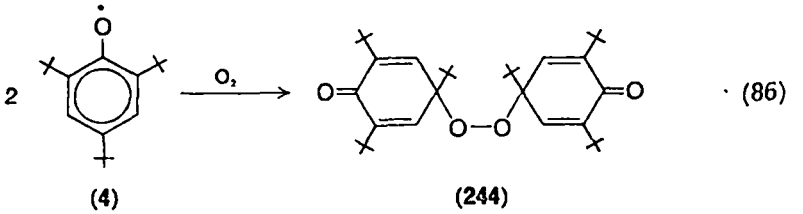


(equation 84). In reaction (83) the quinone **239** is probably first formed, with initial demethylation as in (reaction 84), and is then converted to the epoxides **240–242** by HOO^- ions produced in the course of the oxidation (reaction 85), since **239** is epoxidized when

$$\begin{aligned} ArO^- + O_2 &\longrightarrow ArO^{\cdot} + (O_2)^{\cdot -} \\ ArO^- + (O_2)^{\cdot -} + H^+ &\longrightarrow ArO^{\cdot} + HOO^- \end{aligned} \qquad (85)$$

treated with alkaline hydrogen peroxide (or *t*-butyl hydroperoxide) but is not affected by oxygen[269].

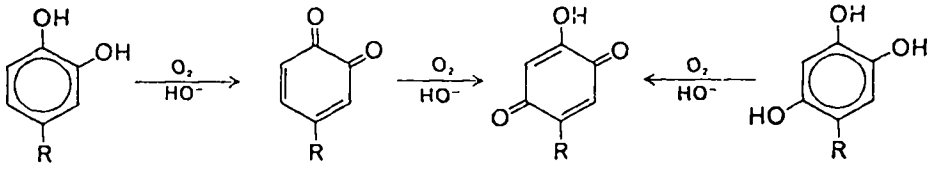
Stable, sterically hindered phenoxy radicals, such as **4**, react



(86)

with oxygen (equation 86) to produce quinol peroxides, e.g., **244** [18, 22–24, 87, 130]. The reactivity of phenoxy radicals towards oxygen is particularly decreased by phenyl substitution, 2,4,6-triphenylphenoxy radical being remarkably stable to attack by oxygen[34–36, 52].

Air-oxidation (reactions 87 and 88) of 4-alkylcatechols (**245**) and 2-alkylhydroquinones (**248**) in alkaline media affords up to 75% of hydroxy-*p*-benzoquinones (**247** and **253**, respectively), which differ



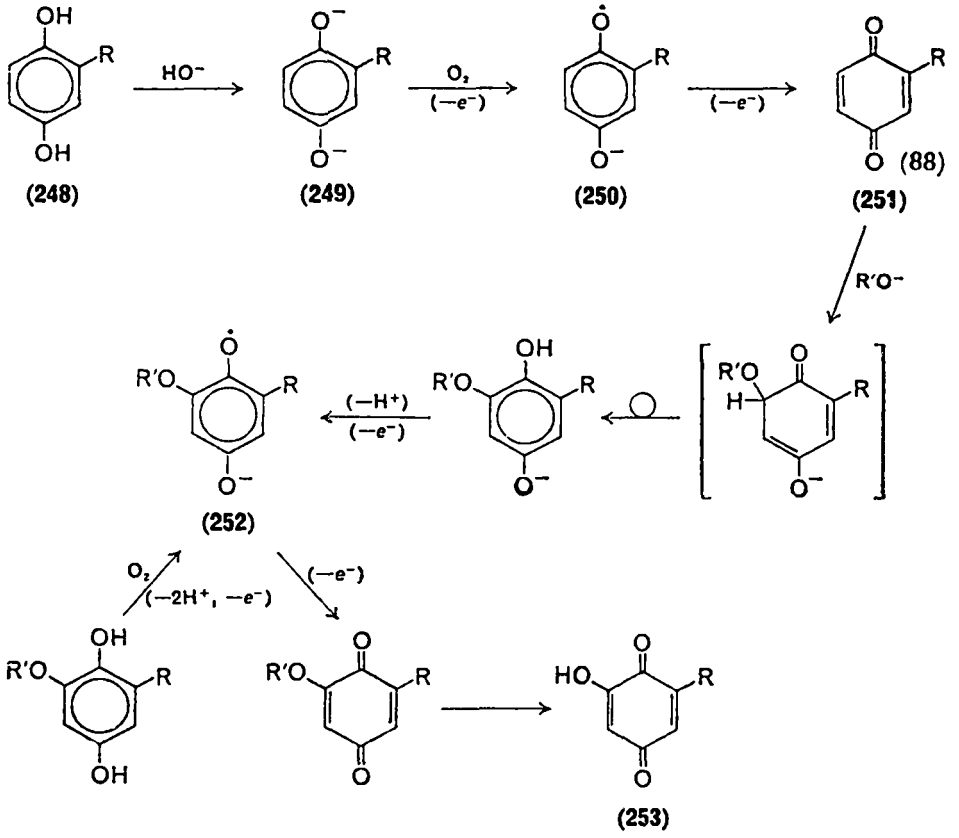
(245) (246) (247) (87)

R = H, Me, *t*-alkyl

in the position of the alkyl substituent[69, 70, 270, 271]. According to available evidence the mechanism of both reactions (87) and (88) is very probably the same[69, 70] and, as shown for the oxidation (equation 88) of hydroquinones **248**, proceeds successively through dianions **249** [72] and benzosemiquinone radicals of type **250** and **252**. These radicals have been detected by the e.s.r. technique[68–70]. Catechol itself (**245**, R = H) is oxidized by atmospheric oxygen to 2,5-dihydroxy-1,4-benzoquinone (**247**, R = OH)[272], but in the presence of dimethylformamide, dibenzo[1,4]dioxin-2,3-quinone (**254**) is also obtained[68].

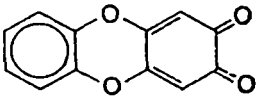
Oxidation of alkyl-derivatives of resorcinol with oxygen in alkaline solution affords a variety of monomeric and dimeric products, depending on the number, position and bulk of the alkyl substituents[5, 6, 72, 142, 273]. For example, orcinol (**255**) is converted in about 50% yield (equation 89) to a mixture of the dimeric mono- and bis-(hydroxy-*p*-quinones) **256** and **257**, respectively[5, 6, 142]. Free resorcinol monoradicals are not formed as intermediates in this reaction (compare reaction 26), and the rate-determining step appears to be electrophilic attack of oxygen on the resorcinol monoanion.

Air-oxidation of catechols and resorcinols in the presence of ammonia also involves the substitution of a hydroxyl group by an amino group, which can itself then undergo oxidation[5, 6, 274, 275]. In this way resorcinol derivatives have been converted to orceine and litmus dyes[5, 6, 274].



(248) (249) (250) (251) (252) (253)

R = *t*-alkyl; R' = H, Me (from MeOH) or Et (from EtOH)



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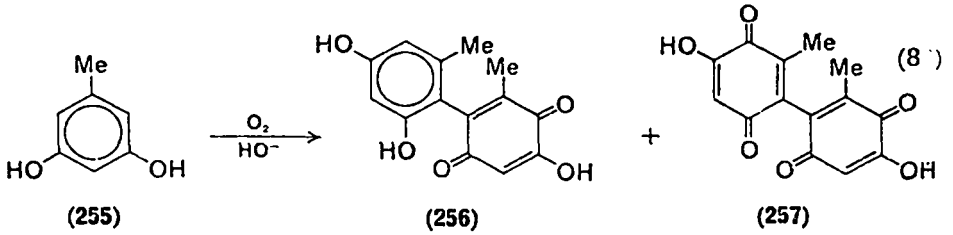
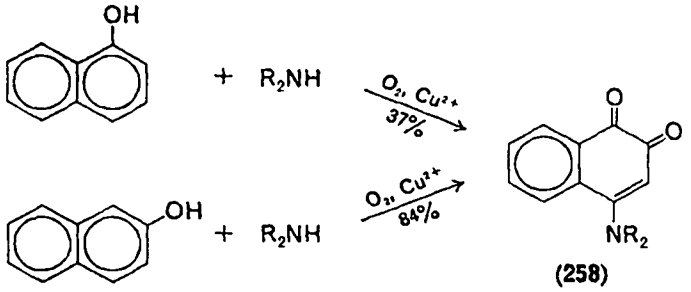


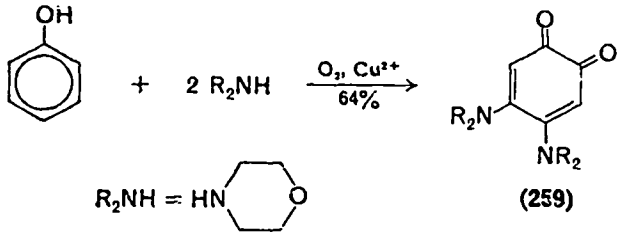
(255) (256) (257)

When the oxidation of monohydric phenols by molecular oxygen is accomplished in the presence of cupric ions and a secondary amine such as morpholine, a rapid reaction takes place at room temperature affording amino-substituted *o*-quinones[276]. Thus, with morpholine as the amine ligand in the cupric salt–amine complex catalyst, 1- and 2-naphthol are converted (reaction 90) to 4-morpholino-1,2-naphthoquinone (**258**), whereas phenol affords (reaction 91) 4,5-dimorpholino-1,2-benzoquinone (**259**). In scheme (92)[276],



(90)

(258)



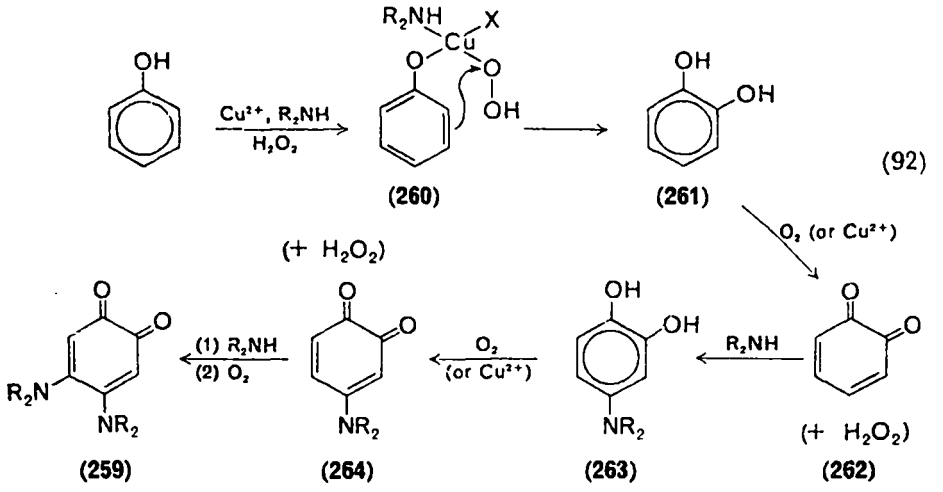
(91)

(259)

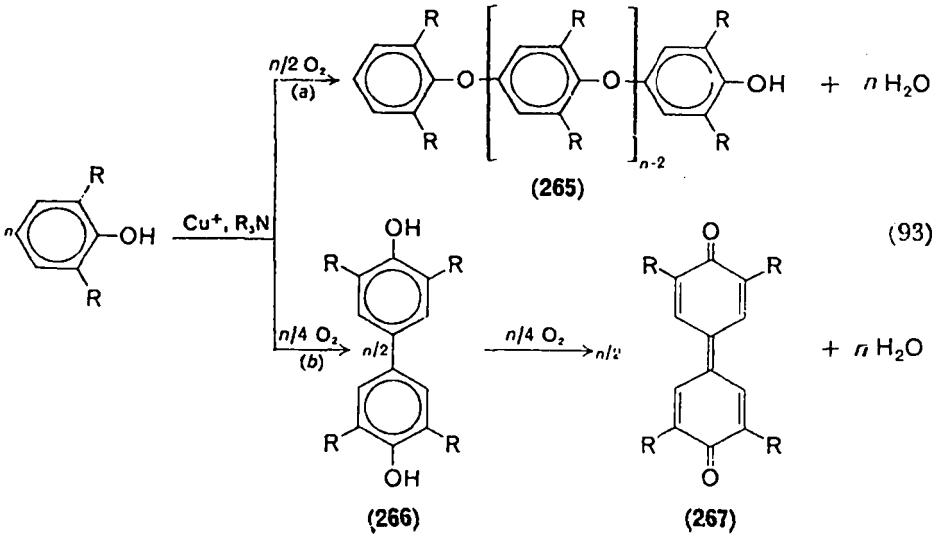
the initially formed copper complex **260** would explain the exclusive *o*-hydroxylation of phenols. In the case of phenol itself, product **264** is further converted into the dimorpholino-derivative **259**. These reactions have been particularly studied in search of a homogenous catalytic system which would represent a model simulating the action of tyrosinase, since it is known that this group of copper containing enzymes catalyses the oxidation of phenols and catechols to *o*-quinone derivatives.

2,6-Dimethylphenol reacts with oxygen in the presence of a cuprous chloride–amine (usually pyridine) catalyst to yield (reaction 93*a*) a high molecular weight linear polyphenylene ether **265** (see also equation 18, **65**→**69**)[123, 277, 278]. *p*-Cresols behave similarly[279].

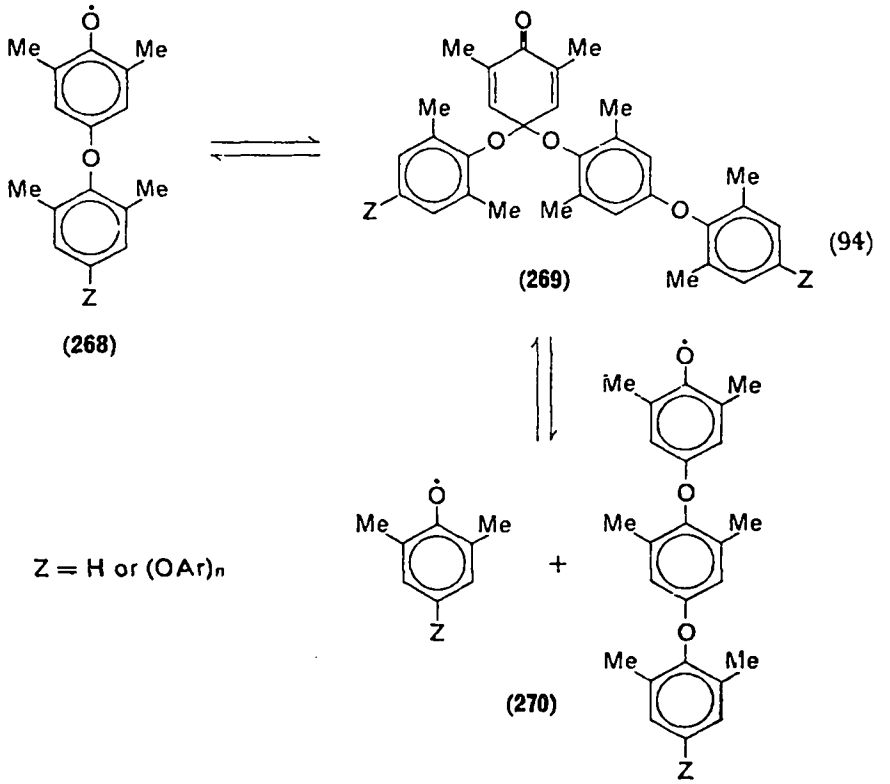
It was shown that in a series of 2,6-dialkyl substituted phenols, two different types of products tend to form, depending on the bulk of the substituents (equation 93). With larger groups, such as *t*-butyl,



C–C coupling (93*b*) predominates and tetrasubstituted diphenoquinones **267** [e.g., R = $(CH_3)_3C$] are produced, via intermediate dihydroxybiphenyl derivatives **266** [277, 278, 280]. On the other hand, with smaller substituents, such as methyl, a facile C–O coupling (93*a*) can occur, resulting in poly(2,6-dialkyl-1,4-phenylene ethers) (**265**) (e.g., R = CH_3) of high molecular weight[277–279]. However, C–O and C–C coupling can be competitive reactions even in the oxidation of 2,6-dimethylphenol, their relative rates being very sensitive to catalyst concentration, ligand ratio in the cuprous chloride–amine catalyst, temperature and steric hindrance in the amine ligand



of the complex[281]. It is highly probable that both reactions (93*a* and 93*b*) proceed through radical intermediates, with initial C–O or C–C coupling of monomeric phenoxy radicals to dimeric products such as **268** (X = H, reaction 94)[123, 279, 282, 283]. However, since the increase in the degree of polymerization towards the end of the reaction is inconsistent with the addition of monomeric phenoxy radicals to the growing polymer chain, in the formation of **265** polymeric quinone ketals **269** have been postulated as intermediates (equation 94), which arise from combination of two aryloxy radicals **268** and which decompose to give redistributed polymeric molecules (**270**), in such a way that one phenol unit at a time is transferred from polymer chain to polymer chain[123, 283–285].

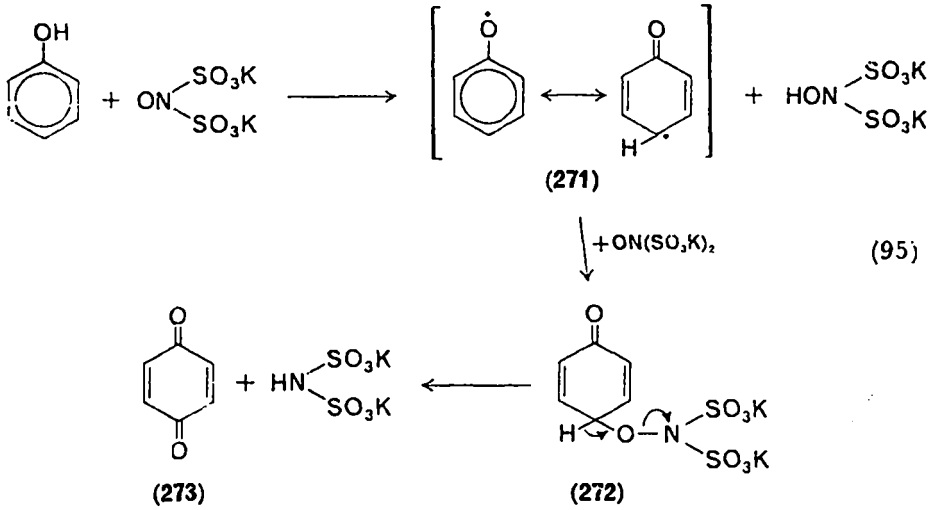


H. Miscellaneous Oxidations

1. Potassium nitrosodisulphonate (Fremy's salt)

Potassium nitrosodisulphonate, $ON(SO_3K)_2$, known as Fremy's salt, is one of the most efficient agents for the preparative oxidation of monohydric phenols to *o*- and *p*-quinones[286, 287]. This salt—a

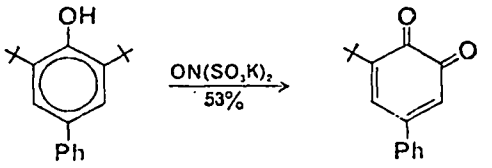
relatively unstable, deep yellow, solid dimer—is completely dissociated in water, forming a deep purple solution which is reasonably stable in the pH range 8–11, and contains the anion-radical $^{\bullet}ON(SO_3^-)_2$ [288]. Two moles of Fremy's salt are consumed per mole of phenol (reaction 95) and produce one mole each of potassium hydroxylamine-*N*,*N*-disulphonate and potassium imidodisulphonate, whereby the first mole generates from phenol a phenoxy radical (**271**) which then combines with the second mole to give an intermediate of the quinol type **272** ('quinitrol')[287]. The formation of such quinols has been demonstrated in particular cases[289], but they usually decompose rapidly into the quinone **273** and the potassium salt of imidodisulphonic acid.



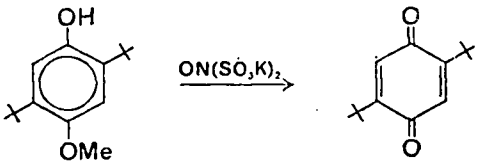
With *para*-unsubstituted phenols this process ('Teuber's oxidation') affords preferentially *p*-quinones even when the *ortho*-positions are free, in yields ranging generally from 50 to 99% [97, 102, 104, 176, 286, 287, 290]. If the *para*-position is occupied by alkyl (or alkoxy) groups, simpler phenols are converted to *o*-quinones in 70–90% yield[97, 102, 287, 291, 292]. By the use of this method quinones have been prepared from various naphthol derivatives[290], including equilenin[293]. This oxidation can also be applied for the synthesis of more complicated, labile *o*-quinones[291] and hydroxy-*p*-quinones[294], provided that the redox potential of the quinone to be formed is not too high.

Oxidative dealkylation and dealkoxylation with formation of quinones has been observed in the reaction of Fremy's salt with

2,4,6-trisubstituted phenols (reaction 96)[105, 116, 292], and with 2,4,5-trisubstituted phenols (reaction 97)[127, 292] in which attack by the reagent at the free *o*-position is sterically hindered by a *meta*-substituent. When in 2,4,6-trialkyl phenols the *para*-blocking group is methyl;

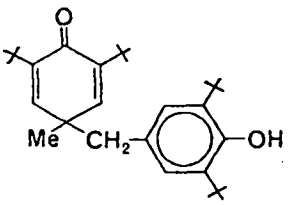


(96)



(97)

coupling products, e.g., **54**, **55** (equation 14) and **274**, arising from the intermediate *p*-quinone methide **59** (equation 16), are also formed[116].



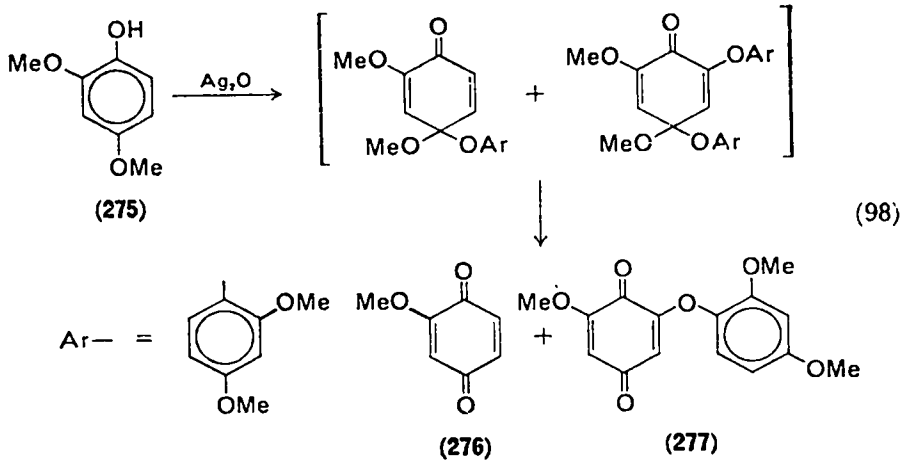
(274)

The use of other stable nitroxides instead of Fremy's salt in the oxidation of phenols does not show any particular advantage[295].

2. Silver oxide

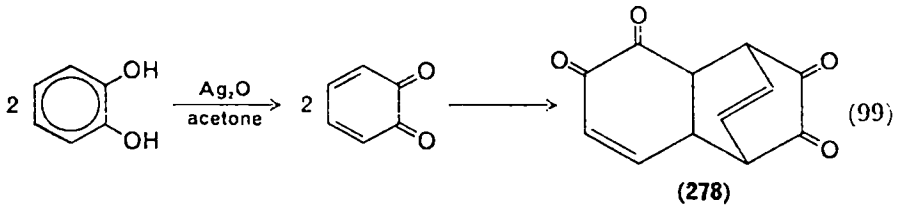
A one-electron oxidant, silver oxide (usually in benzene or diethyl ether), converts phenols to phenoxy radicals[1, 6, 12, 24, 41]. These, depending on their stability, may undergo the characteristic C–C and/or C–O coupling reactions such as in equations (11)[93, 101, 102], (14)[110], (18)[102, 122, 123], (20)[91, 96–99, 129], (22)[111], (29)[152] and oxidation (equation 98)[191], involving both coupling and oxidative demethylation.

Since silver oxide undergoes a rather facile thermal, photolytic or metal-catalysed decomposition to silver metal and oxygen, it may happen that some of the oxygen from silver oxide is incorporated



into the phenolic compound in the course of the reaction. Thus, Blanchard[93] has shown that the oxidation (equation 86) of 2,4,6-tri-*t*-butylphenol to bis(1,3,5-tri-*t*-butyl-2,5-cyclohexadien-4-on-1-yl) peroxide (**244**), via the corresponding phenoxy radical (**4**), with silver oxide in the presence of oxygen, requires the partial utilization of the oxygen from silver oxide, since 90–100% yields of peroxide (**244**) were obtained while only 60–70% of the theoretical amount of free oxygen was absorbed.

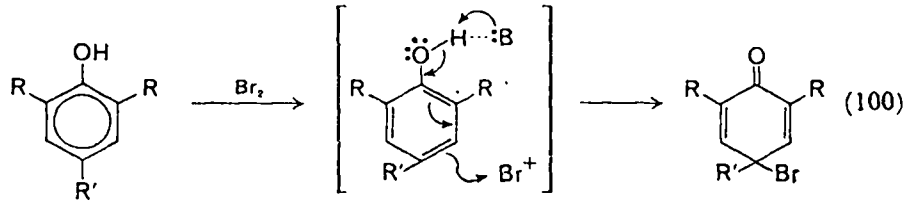
Hydroquinones and catechols are oxidized by silver oxide (in benzene or ether) to the corresponding benzoquinones[1, 6]. However, on running the reaction with catechol in acetone solution, two molecules of the initially formed *o*-benzoquinone undergo a Diels–Alder type addition (equation 99) to produce the yellow crystalline dimer **278** [296].



(99)

3. Halogens

When 2,4-dialkyl- and 2,4,6-trialkyl-phenols are treated with bromine in the cold in solvent systems containing a proton acceptor (e.g., AcOH–H_2O, Et_2O–H_2O–pyridine, CCl_4–pyridine, hexane–dioxan, etc.), 4-bromo-2,5-cyclohexadienones (*p*-quinobromides) (**279**) are obtained (reaction 100), in yields up to 98% [23, 25, 109, 297–302]. This

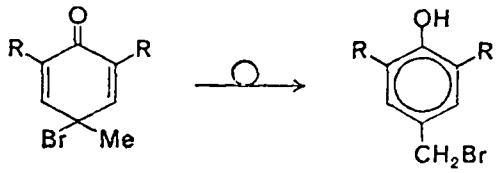


(100)

R' = H, Me, *t*-Bu

(279)

oxidation is considered to involve electrophilic attack of a bromonium ion (Br^+) at the 4-position of the phenol with elimination of the phenolic proton (reaction 100) [297, 299–301, 303]. 4-Bromo-4-methylcyclohexadienones (**280**) undergo a facile rearrangement (often on standing at room temperature) to 3,5-dialkyl-4-hydroxybenzyl bromides (**281**) (reaction 101)[109, 299, 301, 304]. According to e.s.r.



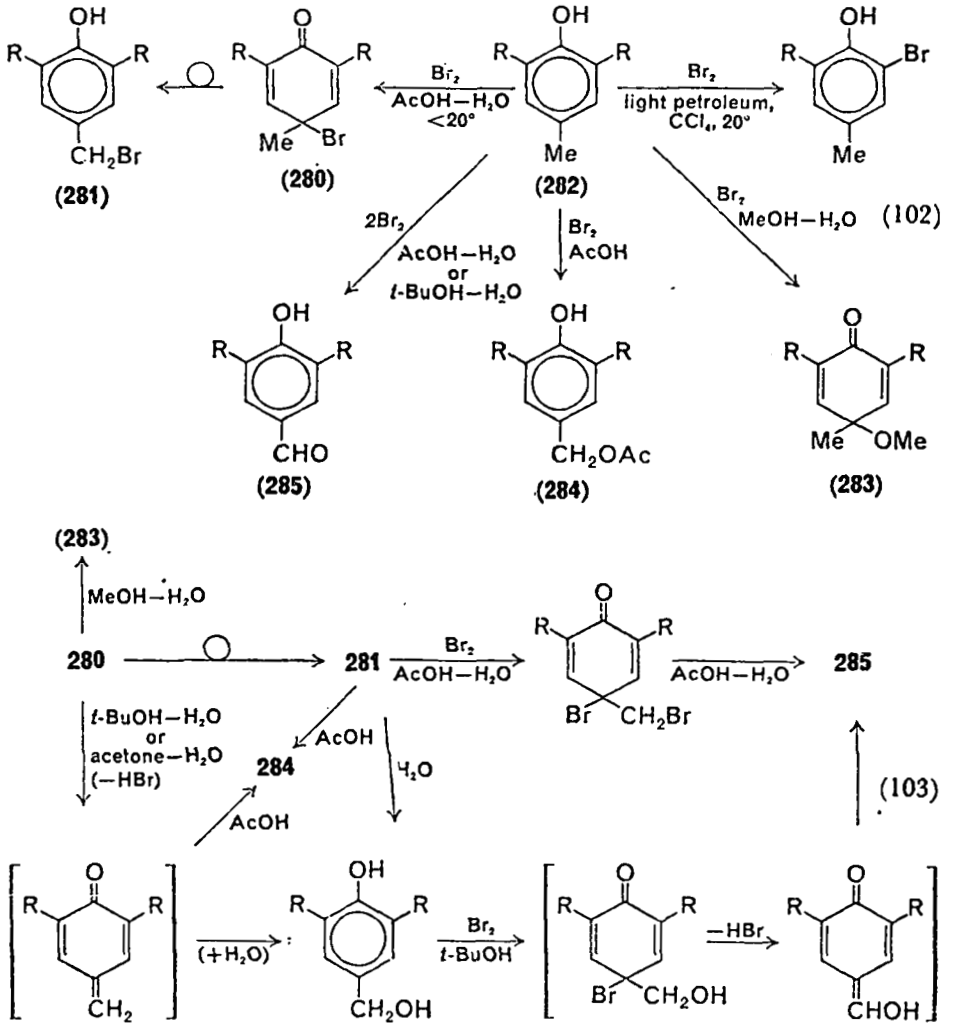
(101)

(280) (281)

measurements such a rearrangement in inert solvents, which is accelerated by u.v. light, proceeds homolytically through phenoxy radicals[109, 301, 302], but in the presence of traces of acids or bases and in polar solvents a heterolytic mechanism might be operative[109, 297, 299, 301, 305]. 2,4,6-Trialkyl-4-bromo-2,5-cyclohexadienones (**279**) when shaken with a metal (Hg, Ag, Cu, Zn, etc.) in an inert solvent under nitrogen can be converted, frequently in nearly quantitative yield, to the corresponding phenoxy radicals[12, 23, 25, 109].

By varying experimental conditions (solvent and temperature) the bromination of 2,6-dialkyl-4-methylphenols (**282**) can afford a variety of products in very good yields (reaction 102), most of which are derived from the initially formed 4-bromo-4-methylcyclohexadienones (**280**)[25, 297, 299, 301, 306]. Scheme (103) represents the possible reaction paths leading to products, most of which have been confirmed experimentally[297, 301, 306].

When 2,6-dialkylphenols containing a *para*-electron-withdrawing group (e.g., NO_2, CN, etc.) are oxidized by bromine in ether–water–pyridine, 2-bromo-3,5,cyclohexadienones (*o*-quinobromides) can be obtained in good yield[307].

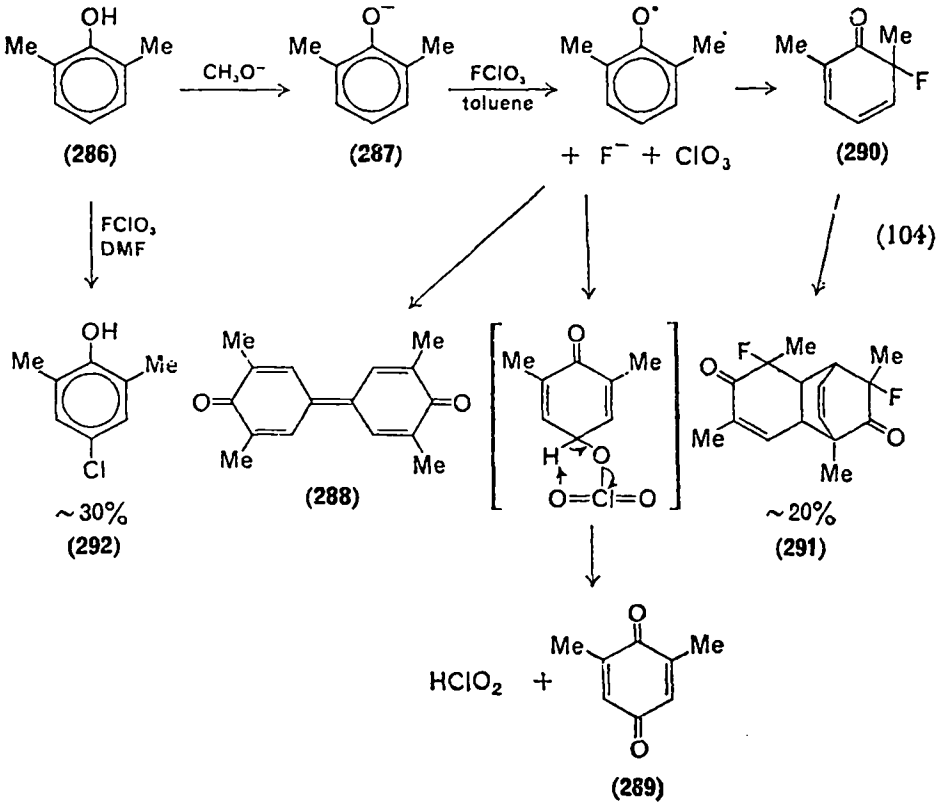


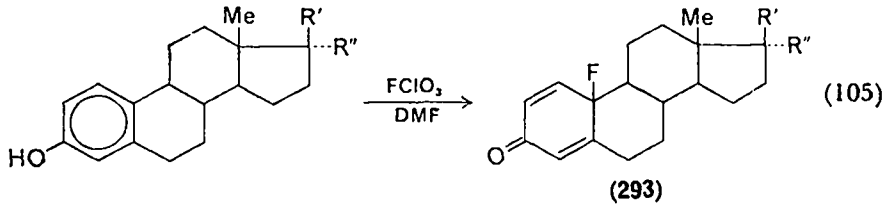
Oxidation of 2,4,6-trialkylphenols with chlorine or nitric acid in polar solvents at or below room temperature affords the corresponding 4-chloro- and 4-nitro-2,5-cyclohexadienones, respectively[23, 25, 190, 301, 303, 308, 309].

4. Perchloryl fluoride

Perchloryl fluoride, $FClO_3$, has not found much use in oxidations of phenolic compounds, since it offers no preparative advantages over other one-electron oxidizing agents. With 2,6-dimethylphenoxide anion (**287**) in toluene or dioxan at 0° it reacts exothermically

(a) by a one-electron oxidation–reduction process to give 3,3′,5,5′-tetramethyl-4,4′-diphenoquinone (**288**) and 2,6-dimethyl-*p*-benzoquinone (**289**), and (b) by nucleophilic displacement on fluorine leading to the Diels–Alder type fluoro-dimer **291** of the 2,4-cyclohexadienone intermediate **290** [310]. The neutral phenol **286** in dimethylformamide reacts slowly with perchloryl fluoride to give as additional and major product 2,6-dimethyl-4-chlorophenol (**292**), which probably arises from chlorination by intermediate species such as ClO_2 and HOCl [310] (scheme 104).





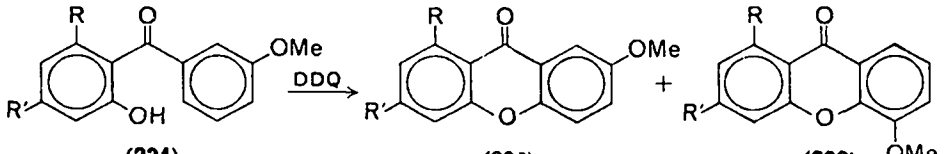
Treatment of steroidal ring A phenols with perchloryl fluoride in dimethylformamide solution results in the *para*-introduction of fluorine with formation of 10β-fluoro-dienones **293** (reaction 105)[311].

5. Chromyl chloride

Chromyl chloride (CrO_2Cl_2) has been used for the oxidation of different types of organic compounds[312, 313], but its action on phenols has only recently been reported. *p*-Benzoquinones are the major reaction products, their yields depending on the ratio of reactants and on the nature, number and positions of the substituents. The highest yields (about 80%) were obtained in the oxidation of pentachlorophenol[314] (which affords chloranil) and 2,5-di-*t*-butylphenol[315]. A mechanism similar to that proposed for the reaction of phenols with Fremy's salt (equation 95) has been suggested, the presence of polymeric material (probably polyphenols) and diphenoquinones indicating the initial formation of phenoxy radicals[315].

6. Organic oxidizing agents

Quinones of high oxidation potential have been used as oxidizing agents for phenols[41]. For example, with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) the reaction proceeds smoothly at room temperature in methanol solution and, depending on the structure of the phenol, leads to oxidative dimerization by either C–C or C–O coupling, oxidative debromination, or oxidative cleavage of hydroquinone monoethers and *p*-hydroxybenzyl ethers, as well as to benzylic oxidation[21]. It is believed that most of these products arise from intermediate phenoxy radicals[21], although in some cases involving a hydroxyl and a methoxy group (e.g., **294**), which are oxidized (equation 106) to C–O coupling products (e.g., **295** and **296**) only by DDQ and not by potassium ferricyanide, the intermediate formation of phenoxonium ions has been postulated[141]. Tetrachloro-1,2-benzoquinone (*o*-chloranil) has been applied for

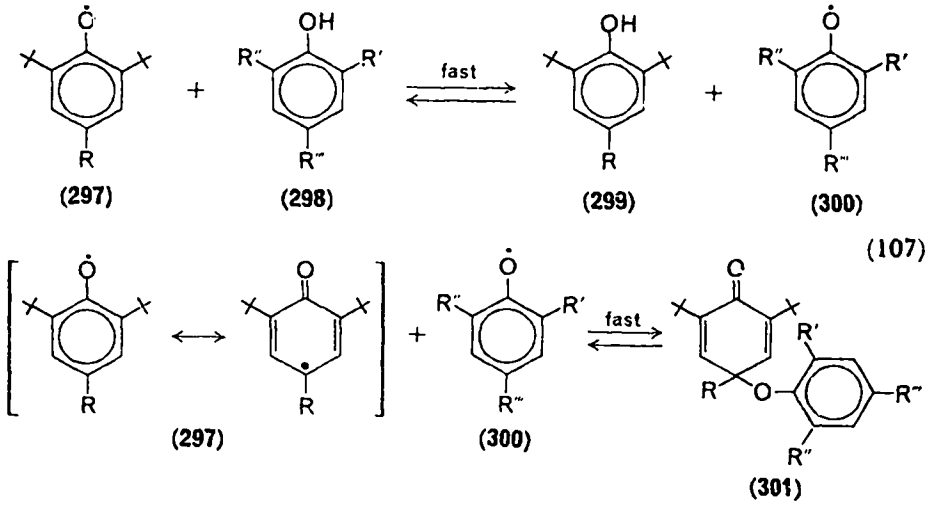


(294) (295) (296)

R = R' = H or OH (106)

the preparation of labile *o*-quinones from catechols and pyrogallols[6, 8, 316], and for the generation of aryloxy radicals from resorcinols[142].

Phenoxy radicals can also abstract the hydroxylic hydrogen from phenols to produce new aryloxy radicals[19, 38, 94, 121]. If the new radicals are stable, the position of the equilibrium will depend upon structural features (particularly upon oxidation potentials), concentration and solvent[34, 36, 51, 80, 87, 136, 190, 317]. By using two moles of a starting hindered phenoxy radical, e.g., **297**, per mole of phenol (**298**), mixed quinol ethers (**301**) are formed (equation 107), the less hindered phenol (**298**) reacting in the oxygen radical form (**300**)[12, 35, 37, 38, 55, 318–321].



(297) (298) (299) (300)

(107)

(297) (300) (301)

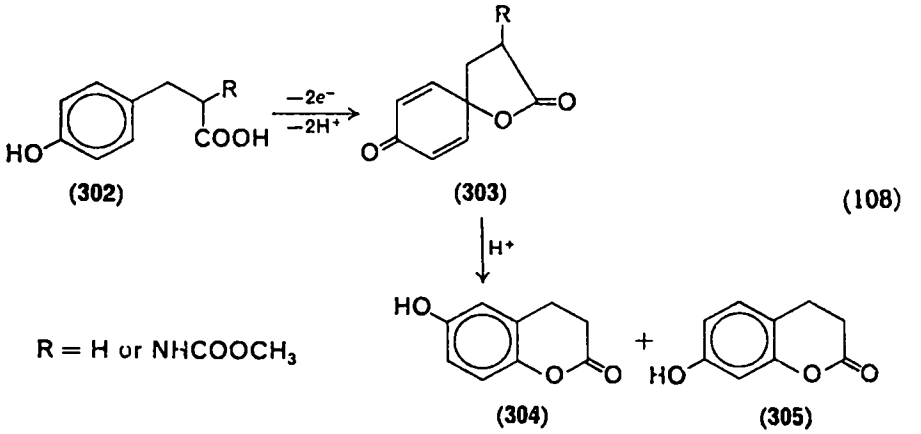
Several enzymatic systems and cell-free extracts of higher plants have been found to catalyse the oxidative coupling reactions of phenolic compounds[6, 8, 12].

7. Electrolytic oxidation

Electrochemical methods for the preparative scale oxidation of phenolic compounds have received far less attention than chemical procedures.

The phenoxy radicals produced by electrolytic oxidation of phenols in neutral or basic media may undergo, in addition to the usual C–C and C–O coupling processes, other reactions as well, such as hydroxylation and further oxidation to quinones[15]. An interesting case, related to coumarin biosynthesis, is the electrooxidation

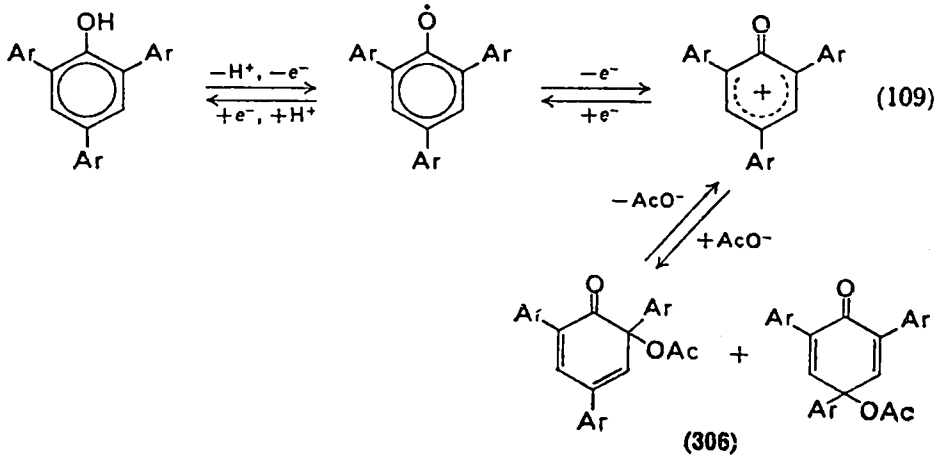
at a platinum anode of *p*-hydroxyphenylpropionic acids **302** (phloretic acids) (reaction 108), which leads, probably by way of radical coupling, to the dienone lactones **303** [322, 323]. When treated with



(108)

mineral acid the latter undergo rearrangement to a mixture of 6- and 7-hydroxydihydrocoumarins (**304**, **305**)[323]. *p*-Hydroxy-*cis*- cinnamic acid behaves similarly[323].

In acid solution the anodic oxidation of polyarylsubstituted phenols consists, according to the slopes of the curves corresponding to the half-wave potentials, of two single electron transfers, the initially formed phenoxy radicals being further oxidized to cations (equation 109)[75]. When aqueous acetic acid containing sodium acetate was used as solvent, quinol acetates (**306**) were obtained in nearly quantitative yields[75].

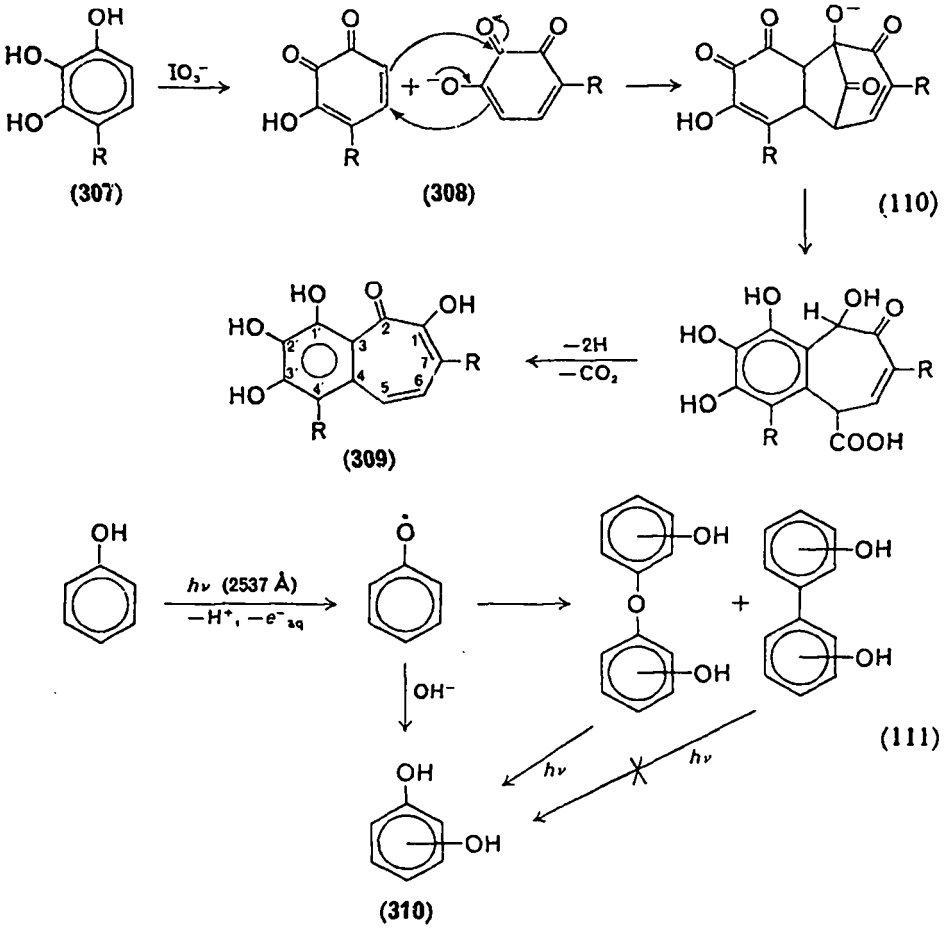


(109)

(306)

8. Other oxidants

The conversion of phenols to phenoxy radicals and further products can be effected by means of manganic ions (Mn^{3+})[324], ceric ions (Ce^{4+})[16, 17, 73, 100, 102, 106, 180, 325], activated manganese dioxide (MnO_2)[104, 123, 321], mercuric oxide (HgO)[49], cupric salts of carboxylic acids[326] and sodium bismuthate ($NaBiO_3$)[100, 101, 180, 252]. It is reported[327] that phenols are easily oxidized by vanadium (v) and cobalt (iii) salts. Permanganate readily attacks phenols and, given sufficient oxidant, converts them mainly to carbon dioxide and water[328]. Halate ions (XO_3^-) can also oxidize phenolic compounds[104, 130]. For example, pyrogallol and 4-substituted pyrogallols (**307**) are converted (equation 110) by means of aqueous

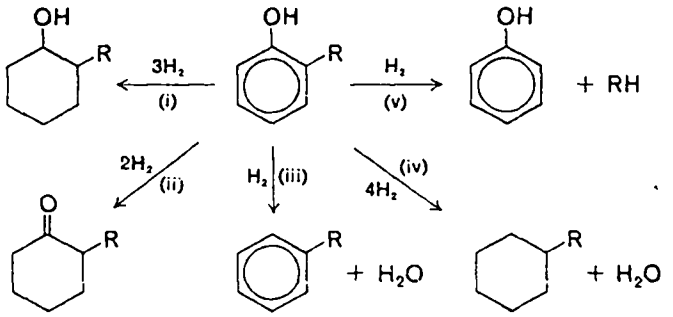


potassium or sodium iodate to purpurogallin and its 4′,7-disubstituted derivatives (**309**), probably through the initially formed *o*-quinone **308** [329–332].

Flash photolysis of phenols affords phenoxy radicals, which have been analysed by electron (u.v. and visible) and e.s.r. spectroscopy[12]. Various C–O and C–C coupled dimers and hydroxylated products were obtained (equation 111), the latter (**310**) being formed even when photolysis was performed under nitrogen[333].

III. REDUCTION OF PHENOLS

In general, the conversion of phenols to compounds of lower oxidation levels involves either hydrogenolysis of the phenolic hydroxyl group and/or hydrogenation of the aromatic ring[334]. Depending on the reaction conditions (nature and amount of catalyst, hydrogen pressure, temperature, solvent), the following reduction processes (equation 112) are possible: (i) hydrogenation of the benzene ring with retention of the hydroxyl group[334–336]; (ii) hydrogenation to alicyclic ketones[334, 337]; (iii) hydrogenolysis to aromatic hydrocarbons[334, 338, 339]; (iv) hydrogenolysis and hydrogenation to alicyclic hydrocarbons[334, 338–341]; (v) hydrodealkylation of alkyl-substituted phenols to lower homologues[334, 342].

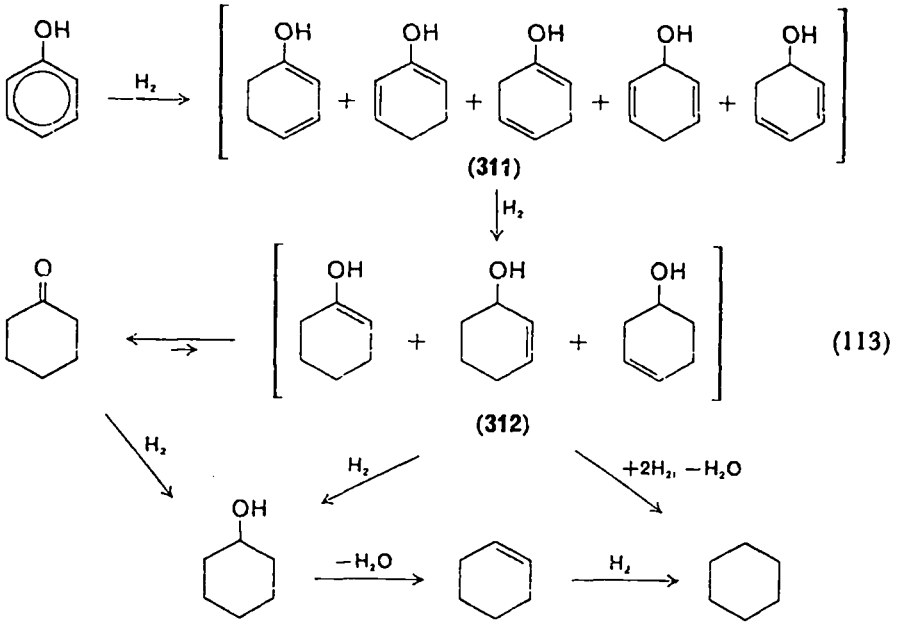


(112)

A. *Hydrogenation and Hydrogenolysis of Phenols*

When phenol undergoes hydrogenation, the predominant product may be cyclohexanol, benzene or cyclohexane, depending on the catalyst employed and the reaction. Under certain conditions and with specific catalysts, cyclohexanone may be isolated during the course of the reaction[334, 343–345]. According to kinetic evidence and product distribution in various reductions, it appears that the conversion of phenols to cyclohexanols and cyclohexanes proceeds

according to a complex mechanism (scheme 113)[334, 341, 344–346], involving successive hydrogenations of the substrate adsorbed on the catalyst surface to give short-lived intermediate cyclohexadienols **311** and cyclohexenols **312**. Tautomerization of 1-cyclohexenol to



(113)

cyclohexanone would be expected to take place since the keto form is more stable than the enol form by about 18 kcal/mole, and this would account for the presence of ketones in the reaction mixture without requiring that cyclohexanones are intermediates directly involved in the formation of cyclohexanols[344, 345]. Since reduction of cyclohexanol to cyclohexane proceeds by loss of water, i.e., by C–O bond cleavage, the hydrogenative conversion of phenols to alicyclic hydrocarbons (cyclohexanes and isomerization products, such as methylcyclopentanes) usually must be performed at higher temperatures (over 200°) and in the presence of catalysts with dehydrating properties[334, 340, 341, 345].

Catalysts used for the hydrogenation of phenols to cyclohexanols and further hydrogenolysis to cyclohexanes (and isomeric alicyclic hydrocarbons) are platinum, palladium, rhodium[344, 345, 347, 348], and nickel on alumina[348, 349], oxides of nickel, molybdenum and wolfram[350], and mixtures of metal oxides and sulphides, such as $WS_2 + NiS + Al_2O_3$ [351, 352], $MoS_2 + WS_2$ or $MoO_3 + S$ [353].

The effect of the hydroxyl group on the rate of catalytic hydrogenation of the benzene ring was investigated by comparing reaction rates of phenol and dihydric and trihydric phenols with those of benzene and its alkyl derivatives[345, 354]. It was found that in general the kinetic picture is similar, i.e., that the rate constants for the hydrogenation of hydroxybenzenes reveal the same effect of symmetry, number of substituents, etc., as for the methylbenzenes, and that in the platinum-catalysed hydrogenations the values of relative rates in both series are in fair agreement[345].

B. Hydrogenolysis of Phenols

Hydrogenolysis of phenols to aromatic hydrocarbons can be considered as displacement of the phenolic hydroxyl group by hydrogen (iii, equation 112).

Because of partial delocalization of the oxygen lone electron-pairs over the aromatic ring, the energy of the phenolic C–O bond is higher than that of an alcoholic C–O bond. Hence, the removal of the hydroxyl group from phenols without hydrogenation of the ring is a rather difficult operation and requires special experimental conditions or prior conversion of phenols to intermediates which can easily undergo hydrogenolysis[334].

With catalysts such as charcoal[339, 355] or oxides of aluminium, thorium and chromium[356], complex mixtures containing relatively low yields of corresponding aromatic hydrocarbons are usually obtained. More effective catalysts for the hydrogenolysis of mixtures of phenols are molybdenum oxides (MoO_2 and MoO_3)[357], their activity being increased by the addition of small amounts of copper or chromium oxides[358], or sulphur compounds[359]. Freshly prepared molybdenum disulphide, MoS_2 (obtained by reduction of molybdenum trisulphide), is an efficient catalyst for the hydrogenolysis of phenol and *o*-cresol, the yield of aromatic hydrocarbon obtained at 25 atm being about 90% [360]. However, as the pressure increases more products hydrogenated in the ring are formed[360, 361]. In general, the amount of aromatic hydrocarbon (iii, equation 112) increases and that of saturated hydrocarbons (iv, equation 112) decreases by decreasing the hydrogen pressure and reaction temperature and by increasing the number of alkyl substituents in the starting phenol[334, 351, 360–362].

Hydrogenolysis of the hydroxyl group can be achieved by treating phenolic compounds with phosphorus trisulphide at high temperature (equation 114)[338], but only one fourth of phenol present is

$$8\ ArOH + P_2S_3 \longrightarrow 2\ ArH + 2\ (ArO)_3PO + 3\ H_2S \qquad (114)$$

reduced. Therefore, by adding phenol itself, as coreactant, to the phenolic compound which is to be reduced, this reaction can be successfully applied for the synthesis of various polycyclic aromatic hydrocarbons[363].

Hydrogenolysis of the phenolic hydroxyl group can be achieved under milder conditions and in better yield if the starting phenol is first converted (by treatment with *p*-tosyl chloride) to its toluene-*p*-sulphonate ester followed by reduction in the presence of Raney-nickel as catalyst (equation 115)[364] or (by treatment with diethyl

$$2\ Ar{-}O{-}SO_2C_6H_4CH_3\text{-}p \xrightarrow[Ra\text{-}Ni]{H_2} 2\ ArH + Ni(O{-}SO_2C_6H_4CH_3\text{-}p)_2 \qquad (115)$$

phosphite in carbon tetrachloride containing triethylamine) to the corresponding diethyl phosphate, which is then easily reduced by

$$ArOH + HOP(OEt)_2 + CCl_4 + NEt_3 \longrightarrow ArO{-}\overset{\overset{O}{\|}}{P}(OEt)_2 + CHCl_3 + NHEt_3Cl \qquad (116)$$

$$ArO{-}\overset{\overset{O}{\|}}{P}(OEt)_2 + Na + NH_3 \longrightarrow ArH + NaNH_2 + NaO{-}\overset{\overset{O}{\|}}{P}(OEt)_2$$

lithium or sodium in liquid ammonia (equation 116)[365]. In reaction (116) the yields of aromatic hydrocarbons from simple phenols vary from 60 to 90%, but the reaction is much less successful with dihydric phenols[365]. Because of mild experimental conditions in both steps, the reaction sequence (116) has been applied for the hydrogenative conversion of sensitive polycyclic phenolic compounds to the corresponding aromatic hydrocarbons[366].

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The Chemistry of The Hydroxyl Group: Part 1
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CHAPTER 11

Displacement of hydroxyl groups

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I. INTRODUCTION

Alcohols are among the most easily obtained reagents of organic chemistry. For this reason the overall conversion

$$ROH \longrightarrow RX$$

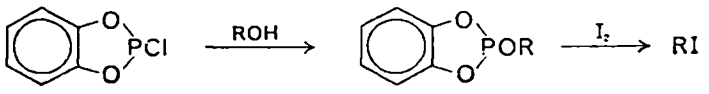
where R is any alkyl, aryl, allyl, benzyl, propargyl, vinyl or acyl group, where X is (typically) halide, hydride, azide, alkyl or amine, and where the reaction proceeds with rupture of the carbon–oxygen bond, is of great importance. Through it, a wide range of organic derivatives is available from readily accessible (including naturally occurring) starting materials, and furthermore, many of the fundamental mechanisms of organic reactions have been elucidated using similar displacements.

This chapter seeks to provide a survey of both the synthetic and mechanistic importance of replacing hydroxyl groups by other functional groups, although lack of space precludes an exhaustive coverage of these topics.

Displacement reactions involving the initial formation of an ester, ROY, even if the material is isolable, are included where the ester is usually prepared as an intermediate in the synthesis of RX (equation 1). Thus, reagents such as **1**, prepared from alcohols as inter-

$$ROH \longrightarrow [ROY] \longrightarrow RX \qquad (1)$$

mediates in their conversion to iodides[1], are included, whereas displacements of *p*-toluenesulphonate (tosylate), acetate, and similar derivatives of alcohols will not be covered in detail.



(1)

Displacement of hydroxyl groups by different groups will be dealt with in sequence, and different types of hydroxyl function will be discussed separately where applicable under each heading. The hydroxyl group in carboxylic and sulphonic acids will not be considered in detail.

The commonly available literature has been searched through the greater part of 1968. Many of the references quoted, particularly for reactions of classical importance, are of recent applications of the technique, and are not necessarily included for any other reason. Undoubtedly some contributions to our understanding of the problem have been overlooked.

II. DISPLACEMENT BY HALOGEN

A. Displacement by Iodine

1. Direct halogenation

(a) The classical method for converting alcohols to alkyl iodides[2] involves heating the alcohol with iodine in the presence of red phosphorus (equation 2). Like other iodinations using phosphorus-

$$6\,ROH + 2\,P + 3\,I_2 \longrightarrow 6\,RI + 2\,H_3PO_3 \qquad (2)$$

containing reagents, the reaction proceeds through an intermediate ester which is decomposed by hydriodic acid liberated in the formation of the ester (equation 3). The analogous mechanism of reactions

$$PI_3 \xrightarrow[ROH]{} P(OR)_3 \xrightarrow[HI]{} RI \qquad (3)$$

leading to alkyl chlorides[3] and bromides[3] is discussed in detail later: products of greater optical purity are formed from phosphorus trichloride and tribromide than from phosphorus triiodide. The intermediate phosphite esters are isolable in the absence of free acids.

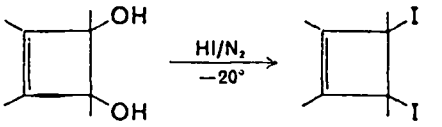
(b) Methanol is converted rapidly and quantitatively to methyl iodide using iodine in the presence of diborane[4] (equation 4),

$$MeOH \xrightarrow[LiBH_4]{I_2} MeI \qquad (4)$$

whereas the same alcohol requires an excess of red phosphorus mixed with the yellow allotrope[5] when the classical method is used for the preparation of methyl iodide.

2. The use of hydriodic acid

α-Glycols have been converted to vicinal diiodides[6] in high yield (equation 5) under very mild conditions, although a more typical



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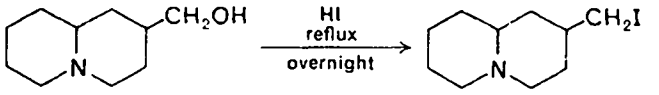
(avoiding pinacol–pinacolone rearrangements[7])

example of the displacement uses refluxing concentrated acid[8]



(6)

(equation 6) or the in situ generation of the acid[9] (equation 7). The

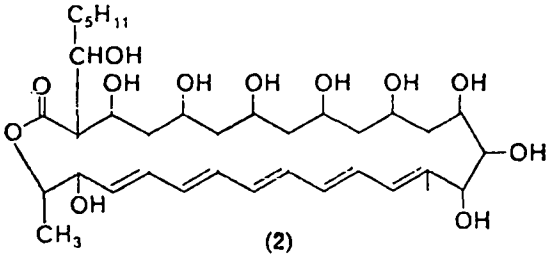
$$HO(CH_2)_6OH \xrightarrow[95\%\ H_3PO_4]{KI} I(CH_2)_6I \qquad (7)$$

generally accepted mechanism of the reaction involves displacement of water from the protonated alcohol (equation 8) by either an S_N1

$$ROH \xrightarrow{H^+} [\overset{+}{R}OH_2] \xrightarrow{I^-} RI + H_2O \qquad (8)$$

or S_N2 process, depending on the stability of the carbonium ion which is generated in an S_N1 ionization, but a recent suggestion[10], that all substitutions at saturated carbon proceed by a single mechanism accommodating these extremes, must be considered too. Hydriodic acid is more acidic than the other halogen acids, and iodide ion is a better nucleophile than the other halide ions, so that alkyl iodides are formed more readily than the other halides under corresponding conditions.

In common with all acid-catalysed reactions of alcohols, the production of alkyl iodides by this method is accompanied by rearrangements in unsaturated alcohols, although dehydration reactions are not troublesome. But hydriodic acid is a reducing agent, and can convert alkyl iodides to alkanes. This reduction was used by Cope in the structure-determination of the macrolide antifungal antibiotic fungichromin (**2**)[11], and in determining the carbon skeleton (**3**) of the aglycone of the related rimocidin[12].



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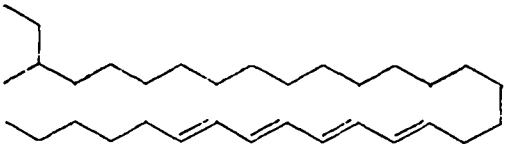

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3. Phosphonium salts and derivatives

(a) Work by Arbusov developed the reaction which now bears his name: phosphonium salts derived from alkyl halides and various organic phosphites (equation 9) disproportionate, on heating, to give (equation 10) a phosphonate, and a different alkyl halide, de-

$$RBr + P(OR')_3 \longrightarrow (R'O)_3\overset{+}{P}R\ Br^- \tag{9}$$

$$(R'O)_3\overset{+}{P}R\ Br^- \longrightarrow R'Br + RPO(OR')_2 \tag{10}$$

rived from the phosphite[13].

The reaction has recently regained prominence because of controversy over the reaction of phosphines with halo-ketones[14] and because the phosphonate by-products from the Arbusov reaction are used in a modification[15] of the Wittig olefin-forming reaction.

Triisopropyl phosphite gives a high yield of isopropyl iodide when heated with methyl iodide[16] (equation 11). In general the conversion of an alcohol to the iodide is effected in two stages (equation 12); an

$$[(CH_3)_2CHO]_3P \xrightarrow[\Delta]{MeI} (CH_3)_2CHI \tag{11}$$

$$ROH \xrightarrow[base]{PCl_3} P(OR)_3 \xrightarrow[\Delta]{R'I} RI \tag{12}$$

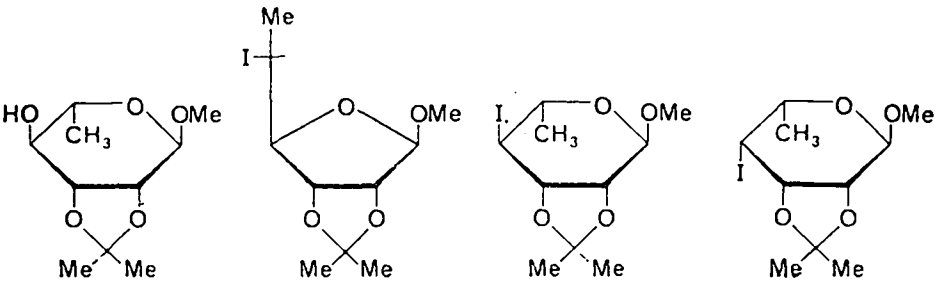
acidic reaction medium is avoided during the complete sequence, and rearrangements do not occur.

(b) The method was modified by Rydon and Landor[17], and developed by their co-workers. Phosphite methiodides give good yields of iodides when treated with alcohols (equation 13) and the only

$$(PhO)_3\overset{+}{P}Me\ I^- + ROH \longrightarrow RI + PhOH + (PhO)_2POMe \tag{13}$$

serious disadvantage in the method is in separating involatile, base-sensitive iodides from the phenol by-product. Where this separation is easy the method works well, and it has been used on a wide variety of alcohols, including primary[17], secondary[17], tertiary[17], propargylic[18] and other unsaturated systems[17], glycols[17], hydroxy acids[17], sugars (both as free carbohydrate[19, 20] and in nucleosides[21, 22]) and cholesterol[17].

In general, very little rearrangement occurs during the displacement, although a little is observed when neopentyl alcohol is converted to the iodide[23], and the reagent converts **4** to a mixture of **5** and **6** [24]. This corrects the earlier report[25], that the products obtained were **6** and **7**, and adds another example to the list of S_N2 reactions



(4) (5) (6) (7)

which involve rearrangements at C-4 [26, 27].

Propargyl alcohols give iodoallenes[18] in dimethylformamide solution, but unrearranged products in methylene chloride. The gross mechanism (equation 14) for displacements using phosphite methiodides involves either expulsion of phenol by the alcohol, followed by nucleophilic attack by iodide ion, or, more probably (with highly electrophilic triphenoxy alkyl salts) attack by iodide ion on an intermediate pentavalent phosphorus derivative.

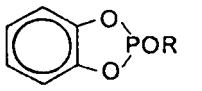
$$(PhO)_3\overset{+}{P}R\ I^- \xrightarrow{R'OH} \left\{ \begin{array}{l} PhOH + (PhO)_2\overset{R}{\overset{|}{\overset{+}{P}}}(OR')\ I^- \\ HI + (PhO)_3P\begin{array}{l}R\\ \diagup\\ \diagdown\\ OR'\end{array} \end{array} \right\} \longrightarrow R'I + (PhO)_2POR \qquad (14)$$

(c) The very similar phosphite diiodides $(RO)_3PI_2$ have also been used in this conversion, as have the corresponding dibromides and dichlorides for the preparation of alkyl (and aryl) bromides and chlorides. The diiodide has been used much less often than the other dihalides, and it has been shown in one case[18] that it gives poorer yields than the methiodide.

An early example of the interaction of iodine with phosphites was given by Forsman and Lipkin[28] (equation 15) and was developed by Corey[1] (equation 16) to give what seems to be the method of choice for the preparation of iodides without side-reactions.

The advantages of phosphine dihalide reagents are discussed in the

$$(PhO)_2P\,OC_6H_{11} \xrightarrow{I_2} C_6H_{11}I \qquad (15)$$



$$\xrightarrow{I_2} RI \qquad (16)$$

sections on bromination and chlorination. The stereochemical consequences of using the diiodo-,* dibromo- and dichloro-reagents are similar, and these also will be discussed later.

Modifications of the methiodide reaction have been reported, using halogen acids or metal halides instead of methyl iodide[17]. In general the yields are much less satisfactory, although *n*-butyl chloride can be formed in 63% yield using ammonium chloride as halogen source. The halogen acid-catalysed decomposition of phosphite esters is dealt with in section II. B.3.b.

4. Indirect displacements

The *p*-toluenesulphonate esters of alcohols readily undergo displacement by iodide ions in polar anhydrous solvents (equation 17). Dimethylformamide is rarely used, but acetic anhydride[29], acetone[30], dimethyl sulphoxide[31] and methyl ethyl ketone[32] have often been used.

$$ROTs \xrightarrow{I^-} RI \qquad (17)$$

Again, the displacement proceeds by S_N1 or S_N2 mechanisms and this is reflected in the observed optical purity of the products. The most polar solvents favour S_N1 reactions.

1-Apocamphanol has been converted to the corresponding iodide by irradiating the oxalic acid ester in the presence of iodine and mercuric oxide[33].

5. The use of inorganic iodides

Aluminium iodide, generated in situ, has been used to convert cholesterol into cholesteryl iodide[34].

B. Displacement by Bromine and Chlorine

The general methods for preparing bromo- and chloro-compounds from hydroxyl groups are so similar that they will be discussed together. Nearly a hundred categories of the conversion of alcohols to chloro-compounds are discussed in Houben–Weyl[35].

* Unpublished work using Ph_3PI_2 is referred to by Wiley and co-workers, *J. Am. Chem. Soc.*, **86**, 964 (1964).

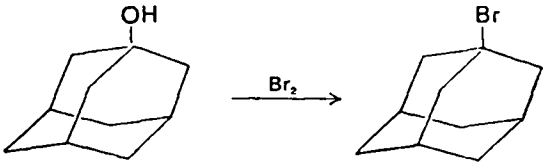
1. Direct halogenation

(a) Chlorination of alcohols, both photochemically and under ordinary conditions, often causes oxidation[36] (equation 18) and

$$HO(CH_2)_4SH \xrightarrow{Cl_2} Cl(CH_2)_4SO_2Cl \qquad (18)$$

affords no worthwhile preparative route to chloro-compounds[37].

(b) 1-Hydroxyadamantane gives a high yield of 1-bromoadamantane (**8**) when heated in refluxing anhydrous bromine[38] (equation 19). Since the adamantyl cation is known[39] to be formed much more



(19)

(8)

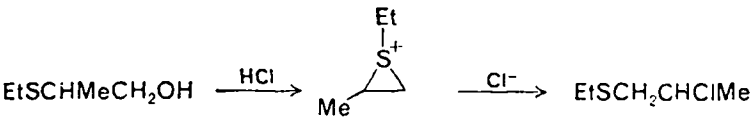
easily than other bridgehead ions, and bromine is a Lewis acid, the mechanism of the displacement probably involves the cation as an intermediate.

2. The use of halogen acids

The use of hydrochloric and hydrobromic acids in the preparation of halo-compounds from alcohols has long been a commonplace, and examples of these reactions are legion[40].

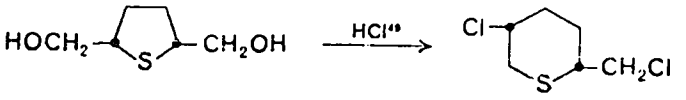
The observed reactivity gradations HI > HBr > HCl > HF for the acids, and tertiary > secondary > primary for the alcohols (the former the result both of acidity and anion nucleophilicity), and the use of hydrochloric acid in the presence of zinc chloride for distinguishing primary, secondary and tertiary alcohols (Lucas' test[41]) complete the classical scope of the methods. Phenols are not attacked by the halogen acids HBr and HCl.

The acids cannot be used on acid-sensitive alcohols. Dehydration to alkenes, and rearrangement of cyclopropyl-[42], allyl-[43, 44], propargyl-[45, 46] and, indeed, alkylcarbonium[47] ions in general, occur frequently. One of the earliest reported examples[48] of neighbouring group participation occurs during such a displacement (equation 20)



(20)

and other examples of rearrangements observed are given in equations (21–23).



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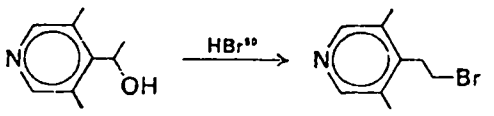

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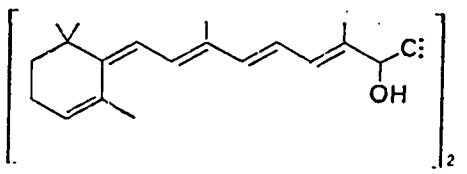

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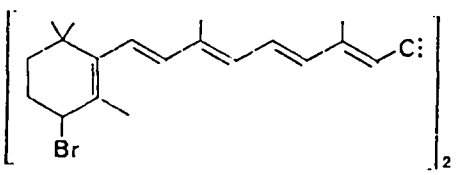
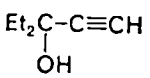


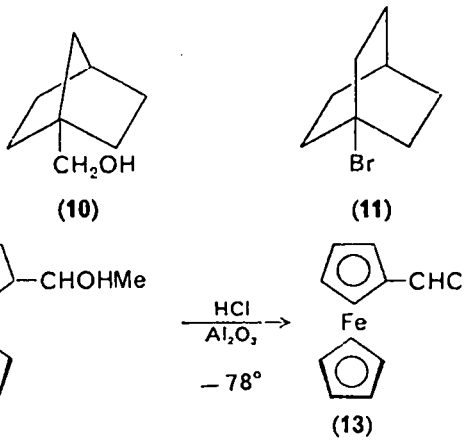
In the presence of cuprous chloride and calcium chloride, hydrochloric acid converted the propargyl alcohol (**9**) into the unrearranged chloro-compound in high yield[51] at 0°.



(**9**)

The rearrangement of alkylcarbonium ions in the course of reactions of alcohols with hydrochloric acid is catalysed by zinc chloride and by sulphuric acid[47, 52], but the results cast no doubt on the validity of Lucas' test since they were obtained at 100°. Zinc bromide and hydrobromic acid convert 1-(bicyclo[2,2,1]heptyl)-methanol (**10**) to 1-bromobicyclo[2,2,2]octane (**11**) [53].

Other catalysts used in conjunction with hydrochloric acid for the conversion of alcohols to chloro-compounds include alumina[54] (equation 24)—the reaction on **12** is carried out at low temperatures to render the highly reactive product **13** isolable—and methyl cyanide[55] and trichloromethyl cyanide[56, 57] as solvents (section II.



(10) (11) (12) (13) (24)

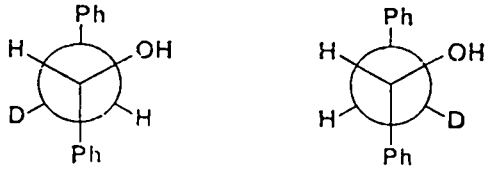
B.5.c). The latter reagent, in activating hydroxyl groups towards displacement, resembles the carbodiimides' action on carboxylic acids in the synthesis of peptides[58].

A general study of the reactions of halogen acids with alcohols[47, 52] has produced results in accord with the mechanism (equation 25).

$$ROH \xrightarrow{H^+} R\overset{+}{O}H_2 \xrightarrow{X^-} RX + H_2O \qquad (25)$$

No rearrangement is observed when primary alcohols derived from *n*-alkanes are converted to the halides below 120°, whereas some secondary alcohols readily rearrange at room temperature. These rearrangements occur not by a dehydration–addition mechanism, but through a carbonium ion mechanism catalysed by zinc chloride and by concentrated sulphuric acid.

Another report is germane to the problem of the mechanism of these and similar reactions: it is possible to distinguish between the diastereoisomeric alcohols **14** and **15** by n.m.r. spectroscopy, using



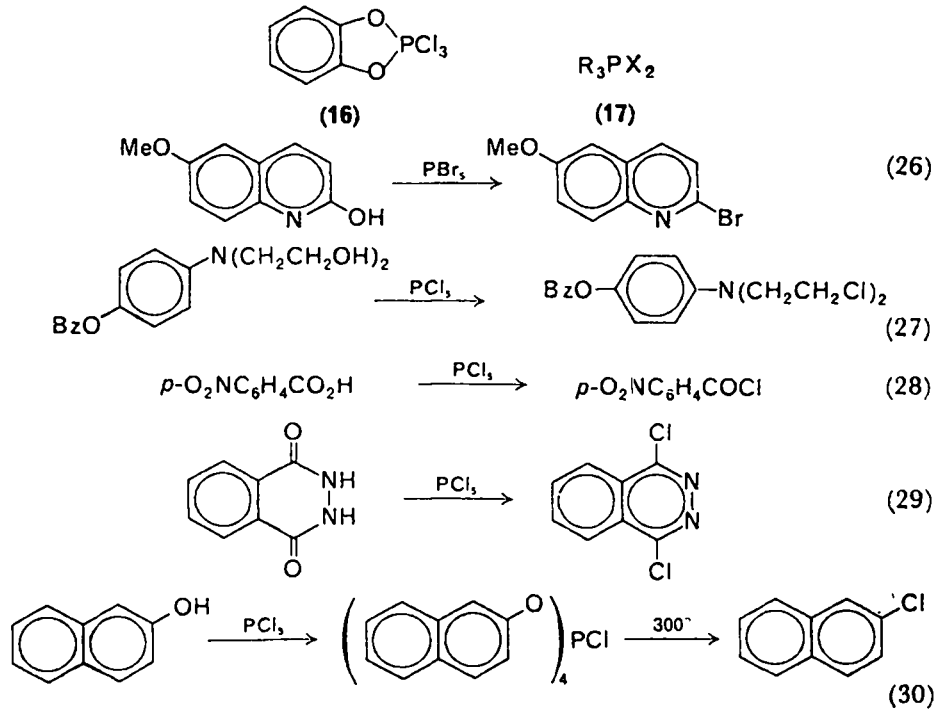
(14) (15)

the magnitude of the proton–proton coupling in the two forms. Conversion of the alcohols to their chloro-derivatives was then shown[59] to involve almost complete racemization using lithium chloride in hydrochloric acid, but retention of configuration with thionyl chloride (S_Ni mechanism[60]).

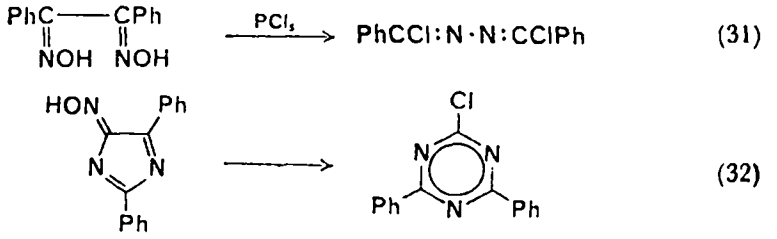
3. Phosphorus-containing reagents

a. Derivatives of P^V. The use of pentavalent phosphorus derivatives for halogenations, at first confined to the pentahalides and to the oxychloride, has been extended widely, and now includes reagents such as Ph_2PCl_3 [61], $PhPOCl_2$ [62], **16** [63], and the phosphine or phosphite adducts with halogens, **17**.

(i) Phosphorus pentabromide converts certain alcohols to bromides more cleanly than does the tribromide[64]. Phosphorus pentahalides react with certain phenols[65] (but not with phenol esters and ethers[66]) and with alcohols[66] to give halo-derivatives, with carboxylic acids to give acyl halides[67], and with amides to give haloimines[68] (equations 26–29). A phosphate ester has been isolated from the reaction of phosphorus pentachloride with a large excess of β-naphthol (equation 30). The ester decomposed to 2-chloronaphthalene only when



heated to 300° [69]. Tetraphenoxyphosphonium chloride has been reported to give no chlorobenzene[70]. The reagent can bring about Beckmann rearrangements in oximes, giving chloroazines[71] (equation 31) or analogous products (equation 32)[72] and converts secondary alcohols to vicinal dihalides in dry chloroform[73].

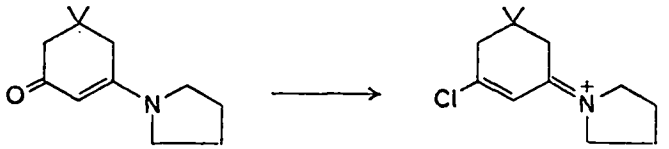


(31)

(32)

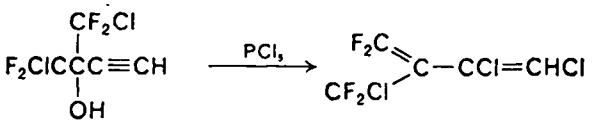
A comparison of the action of phosphorus pentachloride, phosphine dihalides (section II.B.3a.v) and thionyl chloride is made in section II.B.4: particularly significant differences occur with homoallylic alcohols[74], and these have been exploited in the steroid field[75].

Like oxalyl chloride (section II.B.6), phosphorus pentachloride converts keto-enamines to chlorovinyl immonium salts[76] (equation 33, cf equation 29) and, in the presence of phosphorus oxy-



(33)

chloride, benzoyl chloride or pentachloroethane, is used in the synthesis of chloropteridines[77], chloropyridines[78] and (with calcium chloride) chloroallenes[79]. It was found to be the only reagent capable of converting the fluoroalcohol **18** (presumably via an allene) into the diene **19** [80]. The proposed mechanism[80] has been criticized by

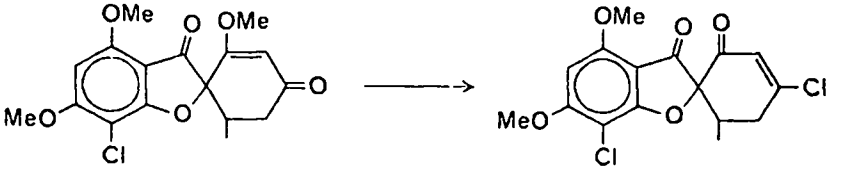


(18) **(19)**

others studying the same alcohol in its reaction with sulphur tetrafluoride[81] (section II.C.4).

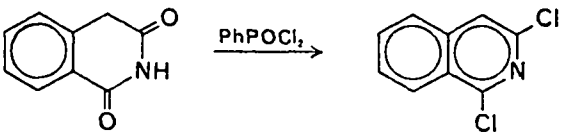
(ii) Phosphoryl chloride. Like the pentahalides, phosphorus oxychloride reacts with phenols[82, 83], alcohols[84], amides[85] and enols[86], to give chloro-derivatives. The reactions proceed through phosphate esters which are decomposed by halide ion, and give hydrochloric acid and phosphoric acid as by-products. (The reagent is a vigorous dehydrating agent[87], particularly in the presence of pyridine, though perhaps less so than thionyl chloride under the same conditions[88]. Both reagents catalyse the esterification of carboxylic

acids[89], through intermediate mixed anhydrides.) Phosphorus oxychloride was used in the presence of lithium chloride in the conversion of **20** to **21** [86].



(20) **(21)**

(iii) The imide **22** was converted to **23** in high yield using a large excess of $PhPOCl_2$ [62] at 160°: because of the involatility of the reagent no sealed tube was necessary, and the method was shown to be preferable to that using phosphorus oxychloride.



(22) **(23)**

(iv) The cyclic phosphorotrihalidates **16**, developed by Gross[63] have been used to prepare vinyl chlorides from ketones, and other uses of the bromo-reagents have been reviewed[90].

(v) As with the conversion of alcohols to iodides, the reagents most suited to the mild displacement of hydroxyl by chloride or bromide are the dihalophosphoranes and analogous compounds prepared by the interaction of phosphines with other halogen sources, notably carbon tetrahalides.

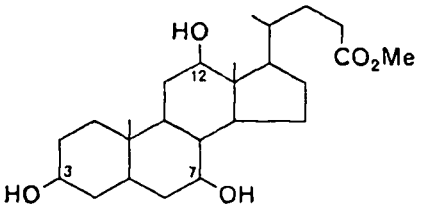
(α) Triphenylphosphine dibromide is readily prepared from bromine and the phosphine, and is available commercially. Its reaction with alcohols[91] and with phenols[61, 92] is outlined in equation (34): the

$$Ph_3PBr_2 + ROH \longrightarrow RBr + Ph_3PO + HBr \qquad (34)$$

conversion occurs at low temperatures, no addition occurs with unsaturated alcohols, and the major by-product, triphenylphosphine oxide, is neutral and unable to cause subsequent side-reactions.

Carboxylic acids yield acid chlorides with Ph_3PCl_2 [75]. However, amides[75] and oximes[75] may be dehydrated, the latter may undergo Beckmann rearrangement[93], and ethers[94] cleaved with the reagent, so that some thought must be given to whether a particular hydroxyl group can be displaced without changing the rest of the molecule.

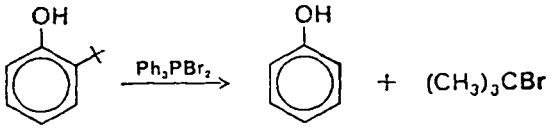
Hydroxy ketones in the steroid field can probably not be converted to pure bromoketones, as dehydrogenation occurs[75] adjacent to carbonyl groups, but the ester **24** can be brominated selectively[75]



(24)

with a relative reactivity 3 > 7 > 12, the same as that found for acetylation.

A limitation of the method has been found with phenols substituted in the *ortho* position with *tert*-butyl groups[95]. No halogenation of the nucleus occurs, and the bulky substituent is eliminated (equation 35)



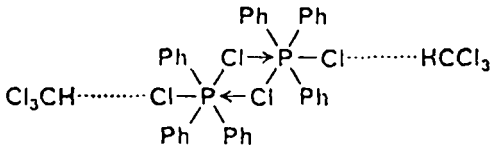
(35)

by a mechanism thought to involve a betaine intermediate. Smaller substituents are unaffected, and indeed the reaction of phenols, naphthols and heterocyclic hydroxy-compounds with triphenylphosphine dibromide provides a very useful and efficient route to aryl halides. When 1-bromo-2-naphthol is heated to 200° with triphenylphosphine[61] it is converted into 2-bromonaphthalene, an overall displacement of hydroxyl by bromine. Similarly, *p*-bromophenol gives bromobenzene: in view of the result with the naphthol derivative this must be also displacement of hydroxyl by bromine (with rearrangement) and not by hydrogen.

Direct bimolecular displacements from an aromatic nucleus only occur when the reaction is aided by an electron-poor nucleus (as in the displacement of halide ion from 2,4-dinitrohalobenzenes) or when the displaced group is very stable. Displacements are possible using the phosphine dibromide because triphenylphosphine oxide is a good leaving group. Enol-phosphonium salts behave similarly in some reactions[96].

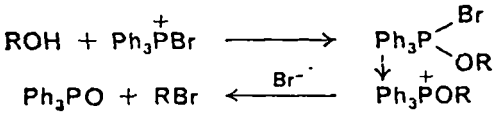
In solution the structure of the chlorine reagent has been shown[97] to involve an equilibrium (equation 36) and haloform-solvated

$$Ph_3PCl_2 \rightleftharpoons Ph_3\overset{+}{P}Cl\ Cl^- \rightleftharpoons Ph_3\overset{+}{P}Cl\ Ph_3\overset{-}{P}Cl_3 \qquad (36)$$



(25)

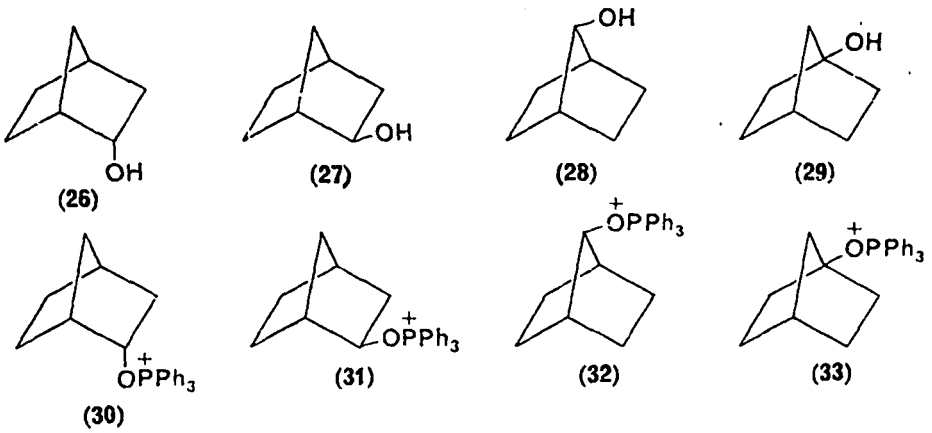
dimers, for which structure **25** [98] has been suggested, are isolable solids, stable in the absence of moisture. The structures of many other pentacoordinate chlorinated phosphorus compounds are similar in showing equilibria between covalent and ionic species[99], and nucleophilic attack by the alcohol seems the most reasonable first step in the conversion to halo-compounds using triphenylphosphine dihalides (equation 37).



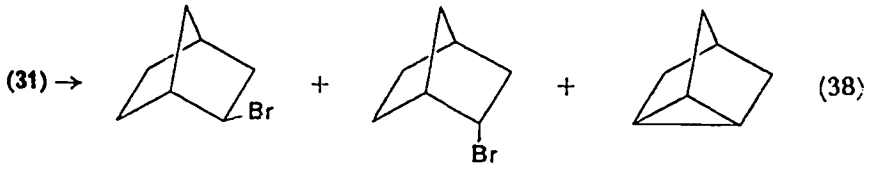
(37)

Preference for decomposition of the alkoxy-phosphonium salt by an S_N2 mechanism is shown in many cases.

The isomeric norbornanols **26–29** were treated with triphenylphosphine dibromide, with the formation of the phosphonium salts **30–33** [100].



The *endo*-alcohol **26** was converted smoothly to the *exo*-bromide with no loss of optical activity, classical evidence for an S_N2 mechanism. The phosphonium salt **30** is isolable, and only decomposes when heated above 115°. No analogous displacement is possible on **31** however, which decomposes at room temperature to give a

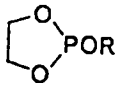


complex mixture of products (equation 38) the composition of which is very solvent dependent.

In triglyme the relative ratio of ion-pair-derived products (racemic *exo*-bromide and nortricyclene) to S_N2-derived product (optically active *endo*-bromide) is about 7:1; in dimethylformamide it is nearly 100:1. An *E*1 mechanism for the decomposition is made more likely by the isolation of nortricyclene, since Kwart[101] has shown that this product, rather than norbornene, is to be expected from the norbornyl cation.

The phosphonium salts **32** and **33** only decompose when heated to 170° and 200° respectively[100].

Analogous adducts between phosphites and halogen are also effective in converting alcohols to halo-compounds[102]. Many dihalotrialkyl phosphites decompose spontaneously to phosphorohalidates $(RO)_2POCl$ and alkyl halide[103], but stable adducts are also known[104]. An early report claimed that allyl alcohol was best substituted using butyl phosphite and bromine, whereas benzyl alcohols react in high yield with halogen and any phosphine or phosphite, including cyclic phosphites such as **34**. However, triphenyl



(34)

phosphite dichloride reacts with phenol to give no chlorobenzene[105]. The product is $(PhO)_5P$ from an intermediate $(PhO)_4\overset{+}{P}\,\overset{-}{Cl}$ [70] (section II.B.3a(i)). General considerations of the Arbusov-type mechanisms involved have been reviewed[106]: alcoholysis of triphenyl phosphite dibromide gives phenol[107], and not triphenyl phosphate (compare equation 37) as by-product in the formation of alkyl bromides.

(β) Intermediates similar to those of equation (36) are involved in the oxidation of phosphites to phosphates in the presence of alcohols and carbon tetrachloride[108, 109], a process which serves to convert alcohols to alkyl chlorides (equation 39). No acidic by-products are

$$P(OR)_3 + CCl_4 + R'OH \rightarrow (RO)_3PO + R'Cl + CHCl_3 \qquad (39)$$

formed and the reaction proceeds at moderate temperatures: phosphines may be used instead of phosphites.

Different mechanisms have been suggested for the phosphine and phosphite reactions however, the more nucleophilic phosphines attacking halogen, and phosphites carbon.

Thus, carbon tetrachloride and trialkyl phosphites react with alcohols by the scheme outlined in equation (40): a tetraalkoxyphosphonium salt is formed by displacement of the trichloromethyl anion from the initially formed salt **35**. (A radical process for the

$$CCl_4 + P(OR)_3 \longrightarrow \underset{\textbf{(35)}}{(RO)_3\overset{+}{P}CCl_3\bar{Cl}} \xrightarrow{R'OH} (RO)_3\overset{+}{P}OR'\bar{Cl} + CHCl_3,$$

$$\begin{matrix} RO & & OR \\ & \diagdown\ \overset{+}{P}\ \diagup & \\ RO & & OR' \end{matrix} \xrightarrow[S_N2]{Cl^-} (RO)_3PO + R'Cl \qquad (40)$$

interaction (in the absence of alcohols) of phosphites with carbon tetrachloride[110], chloroform[111] and bromoform[112] has also been suggested.) The method suffers from the disadvantage that two alkyl halides can be formed, one from the phosphite and one from the alcohol. The ratio of products observed will depend on the relative susceptibilities of R and R′ to nucleophilic attack.

No such ambiguity exists when phosphines are used instead of phosphites, and a different mechanism[113] (equation 41) applies.

$$\begin{array}{l} CCl_4 + PPh_3 \longrightarrow Ph_3\overset{+}{P}Cl\ \bar{C}Cl_3 \xrightarrow{EtOH} Ph_3\overset{+}{P}OEt\ Cl^- \\ \qquad\qquad\quad \downarrow \qquad\qquad\qquad\quad \downarrow \\ \qquad\qquad\quad Ph_3\overset{+}{P}CCl_3\ Cl^- \qquad\quad EtCl + Ph_3PO \\ \qquad\qquad\quad \textbf{(36)} \end{array} \qquad (41)$$

Triphenylphosphine and carbon tetrachloride apparently provide the ylid $Ph_3P{=}CCl_2$ also[114]—ketones undergo the Wittig reaction under these conditions. The phosphite intermediate **35** is known to decompose in the absence of an alcohol to alkyl chloride and the phosphonate, **37**, which, heated in alcohols, gives no further alkyl

$$\underset{\textbf{(37)}}{(RO)_2POCCl_3}$$

halide[115]. Tri(*n*-octyl)phosphine behaves in the same way as triphenylphosphine with carbon tetrachloride and alcohols, using the

halide as solvent, and with carbon tetrabromide and alcohols, when only two equivalents of halide and phosphine are used[116].

Another report[117] on the mechanism of the similar reaction between alcohols and carbon tetrachloride in the presence of tris(dimethylamino)phosphine favours the mechanism of equation (41), as expected for a very nucleophilic reagent. (Aminophosphines are frequently used in place of alkyl or arylphosphines because the basic groups greatly simplify the removal of phosphine oxide from the product mixture[118].)

Evidence for the proposed mechanism (equation 42) comes from three results[117]. The phosphonium salt **38** is not attacked by water,

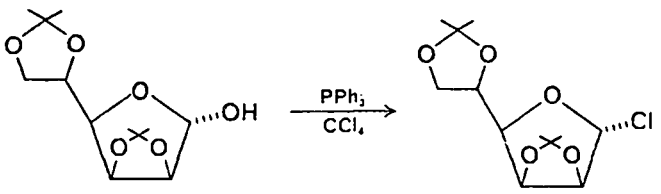
$$(Me_2N)_3P + CCl_4 \longrightarrow (Me_2N)_3\overset{+}{P}Cl\ \bar{C}Cl_3 \xrightarrow{ROH} (Me_2N)_3\overset{+}{P}ORCl^- + CHCl_3$$

$$(Me_2N)_3\overset{+}{P}Cl\ \bar{C}Cl_3 \longrightarrow (Me_2N)_3\overset{+}{P}CCl_3\ Cl^- \quad \textbf{(38)}$$

$$(Me_2N)_3\overset{+}{P}ORCl^- \quad \textbf{(39)} \longrightarrow RCl + (Me_2N)_3PO \qquad (42)$$

and, therefore, not by alcohol in all probability. This was confirmed by adding alcohol to the mixture of phosphine and tetrahalide only after the interaction was complete. No alkyl halide was obtained. The phosphine, tetrahalide and alcohol, mixed in ether at low temperature, gave two layers, a lower oily one, presumably **39**, and an etherial one containing chloroform but no alkyl halide. The alkyl halide was liberated by a slow displacement step as the reagents were warmed.

The stereochemical consequences of the displacement should be configurational inversion. This has been found to be so[119, 120], but examples of reactions with racemization[119] are known, and retention of configuration[121] occurs with alcohols in which S_N2 reactions are prevented by any factor. In this, the reagent resembles the penta-



(40) **(41)**

halides, and the phosphine halides. Thus, the conversion of **40** to **41** occurs with retention of configuration[121].

Halogen sources other than carbon tetrachloride and tetrabromide have been used: bromotrichloromethane[110], chloroform[122], bromocyanacetamide[123] and hexachlorocyclopentadiene[124] have all been employed successfully, but thionyl chloride, sulphuryl chloride, cupric chloride and hexachloroethane proved less efficient[102].

The mechanisms involved are probably similar[125], although Trippett has shown[126] that the phosphonium salts derived from bromocyanacetamide are mixtures of keto-and enol-phosphonium salts (equation 43). Others have reported[127] that, atleast with α-halo-

$$Ph_3P + BrCHCNCONH_2 \longrightarrow Ph_3\overset{+}{P}CH(CN)CONH_2 + Ph_3\overset{+}{P}OC(NH_2)=CHCN \quad (43)$$

ketones, only the enol-phosphonium salts react with alcohols.

Modifications of the phosphite methiodide method for preparing alkyl iodides have been used to synthesize alkyl chlorides (benzyl chloride)[107] and alkyl bromides (benzyl bromide)[107].

Few direct comparisons between the methods of using phosphine dibromide, phosphine in the presence of carbon tetrahalide, and phosphite in the presence of alkyl halide, have been reported. All are mild reactions, and rearrangement products are of only minor importance. Sugar-protecting groups are not attacked by the reagents, and whereas the phosphite methiodides give phosphonates instead of hal es with vicinal diols, triphenylphosphine in carbon tetrachloride gives dihalides[128].

General reviews of the nucleophilic attack by phosphites and phosphines on alkyl halides, and of the reactions of derivatives of tetravalent phosphorus, have appeared recently[13, 129].

b. Derivatives of P^{III}. The standard use[130] of the phosphorus trihalides in the synthesis of alkyl halides from alcohols needs little discussion.

The mechanism of the reaction has been studied most recently by Gerrard and co-workers[3] who showed that both the formation and decomposition of the intermediate phosphite ester proceed (equation 44) in a stepwise manner.

$$PX_3 \xrightarrow{ROH} (RO)PX_2 \xrightarrow{ROH} (RO)_2PX \xrightarrow{ROH} (RO)_3P$$

$$(RO)_3P \xrightarrow{HX} RX + (RO)_2POH \xrightarrow{HX} RX + (RO)P(OH)_2 \xrightarrow{HX} RX + H_3PO_3 \quad (44)$$

Optical purity of the alkyl halide produced is high in each stage of the decomposition, and is lowest in the third stage when S_N1 reactions become increasingly important as the stability of the

$$\overset{}{\underset{}{CHG-X}}$$

phosphite ion increases (equation 45). The earlier stages of the de-

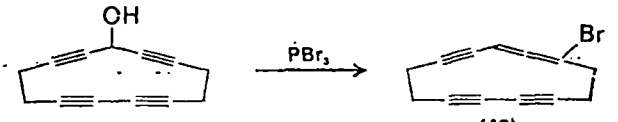
$$(RO)P(OH)_2 \rightleftharpoons R^+ + H_2PO_3^- \quad (45)$$

composition involve S_N2 attack on the protonated phosphite (equation 46). Overall, the optical purity achieved using these

$$(RO)_3\overset{+}{P}H \xrightarrow{X^-} RX + (RO)_2P(OH) \quad (46)$$

phosphorus trihalides is better than when hydrochloric acid or phosphorus and iodine are used to effect the same reactions.

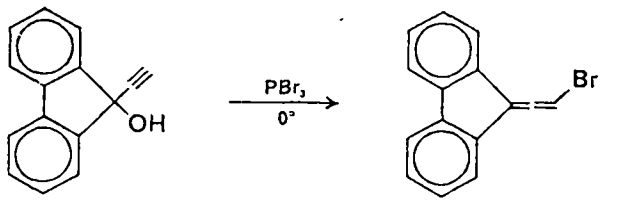
Attempts to prepare the propargyl bromide from alcohol **42** using



(42) **(43)**

phosphorus tribromide gave only **43** [131], and rearrangements in propargylic systems are common with this reagent, particularly with tertiary alcohols (equations 47 [132] and 48 [133]) and probably no tertiary propargyl aryl halides are known. It has been shown[134] that all earlier claims for such halides have given instead the haloallenes.

$$Me_2C(OH)C{\equiv}CH \xrightarrow{PCl_5} Me_2CClC{\equiv}CH\ (47\%) + CH_2{=}CMe{-}CH{=}CHCl\ (23\%) \quad (47)$$

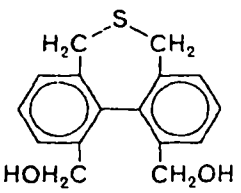


(48)

A curious difference in the reactivity of enantiomers towards phosphorus tribromide in the bridged-diphenyl series has been reported by Mislow[135]. Racemic **44** reacts with the reagent in the solid state to give **45** as expected, whereas the (+) form disproportionates under the same conditions to optically active **46** and **47**. The allylic alcohol **48** reacts with phosphorus tribromide and pyridine in petroleum ether to give the unrearranged bromide[136].

4. Sulphur-containing reagents

Of the many sulphur-containing reagents used to convert hydroxy compounds to halides[137], only thionyl chloride (and bromide) have enjoyed wide application. Thionyl chloride reacts with alcohols to



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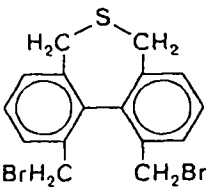

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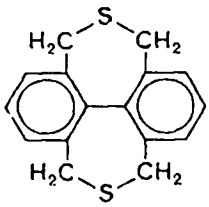

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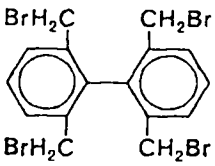

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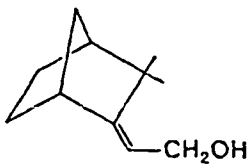


(48)

form intermediate esters (equation 49) but the stereochemical path

$$ROH + SOCl_2 \longrightarrow ROSOCl + HCl \qquad (49)$$

to the final products (and the nature of the products) is determined by the reaction conditions employed. Equimolar proportions of alcohol, chloride and pyridine give the product of S_N2 attack by chloride ion on the chlorosulphite ester (equation 50) with inversion

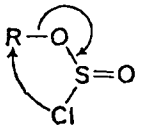
$$ROSOCl \xrightarrow{Cl^-} RCl + SO_2 + Cl^- \qquad (50)$$

of the alkyl group configuration.

Two moles of alcohol and of pyridine to one of chloride give an alkyl sulphite in good yield (equation 51).

$$ROSOCl \xrightarrow{ROH} ROSOOR \qquad (51)$$

In the absence of any base, the S_Ni mechanism operates, and an alkyl chloride of the same configuration as the alcohol is obtained (equation 52), probably through an ion-pair formed by loss of SO_2 from the chlorosulphite.



$$\longrightarrow RCl + SO_2 \qquad (52)$$

A similar difference occurs when allylic alcohols react with thionyl chloride with or without added base, giving either S_N2 attack (equation 53) or S_N2' (equation 54). Propargyl alcohols behave

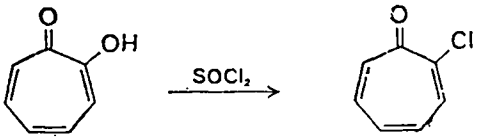
$$CH_3CH{=}CHCH_2OH \xrightarrow[\text{base}]{SOCl_2} CH_3CH{=}CHCH_2Cl \tag{53}$$

$$CH_3CH{=}CHCH_2OH \xrightarrow[\text{no base}]{SOCl_2} CH_3CHClCH{=}CH_2 \tag{54}$$

similarly[138], undergoing direct substitution (equation 55) or rearrangement[139].

$$RC{\equiv}CCH_2OH \xrightarrow{SOCl_2} RC{\equiv}CCH_2Cl \tag{55}$$

Thionyl chloride is the standard reagent for converting carboxylic acids to acid chlorides[140]. It also displaces hydroxyl groups from tropolones[141] (equation 56) and, in dimethylformamide solution, from highly acidic phenols[142] (equation 57). The importance of the



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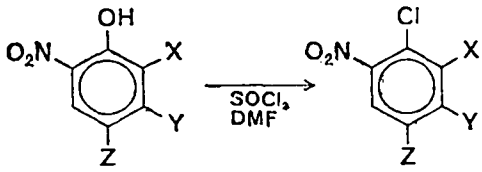

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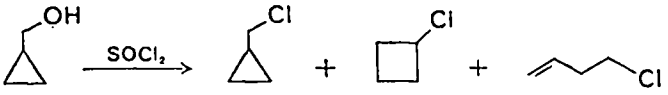
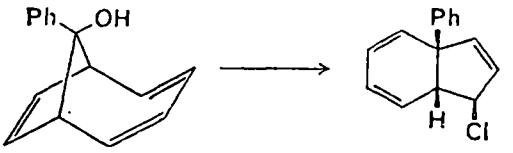


(58)

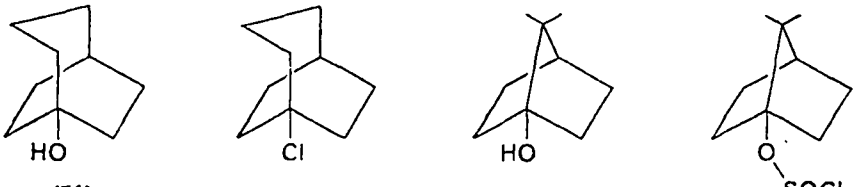
solvent in this reaction is discussed in the following section.

The reagent converts amides to chloroimines[143] and nitroalcohols to nitrochlorides[144, 145] but does not attack phenol esters[146]. In common with other chlorinating reagents it gives rise to rearrangements in cyclopropylcarbinyl systems[147] (equation 58) and in the attempted conversion of aryl and other hindered tertiary propargylic alcohols to halides[139, 148]. Alcohol **49** was converted into the chloro-compound **50** using two moles of thionyl chloride to one of pyri-



(49) (50).

dine[149], and **51** into **52** but **53** into **54** [150, 151], an interesting example of ring-size effects in bicyclic systems.



(51) (52) (53) (54)

Comparisons have been made of the relative usefulness of thionyl chloride and hydrochloric acid[52], and of phosphorus pentachloride and thionyl chloride[152], in converting alcohols to chloro-compounds. In general, however, since the reagents often give rise to different stereochemical results, the choice is not always available.

Shoppee and co-workers have made a particularly extensive study[153] of the 5α-cholestane skeleton and have rationalized the variation in products observed from changing the hydroxyl group position in the molecule.

In general, phosphorus pentachloride is more likely than thionyl chloride to give products from inversion of configuration since the intermediate chlorophosphate ester is more easily ionized than the corresponding chlorosulphite.

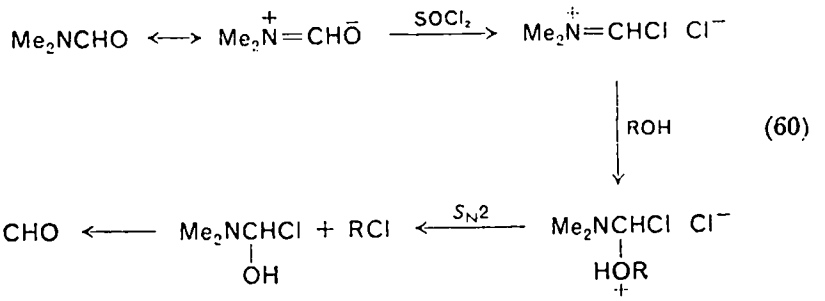
5. Nitrogen-containing reagents

(a) The active intermediates in many displacement reactions (equation 59) which are carried out in dimethylformamide solu-

$$ROH + SOCl_2 \xrightarrow{DMF} RCl + SO_2 + HCl \qquad (59)$$

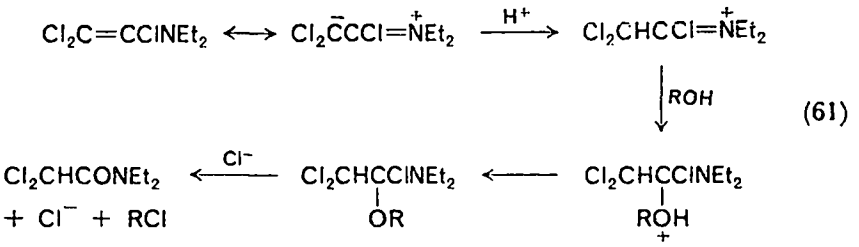
tion[142, 154] are nitrogen-containing salts. A mechanism (equation 60) predicting retention of optical activity but inversion of configuration through an S_N2 reaction is reasonable.

(b) A recent review[155] of polychloroamine compounds dealt only with their preparations and their intramolecular reactions. But



(60)

chlorinated enamines derived from amides are known to effect the conversion of alcohols to optically pure chloro-compounds[156], and of carboxylic acids to their acid chlorides. Picric acid is unaffected by the reagents. The reaction is acid-catalysed, and probably proceeds as shown in equation (61), since alkoxide ions react much less rapidly



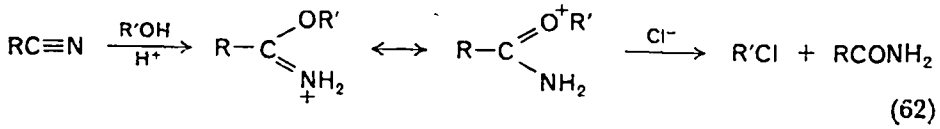
(61)

with the vinyl amine than alcohols do, and, as expected for an S_N2 reaction, the alkyl halide obtained is of the opposite configuration to that of the alcohol.

(Similar halogenations are known to occur using chlorinated vinyl ethers as the reagents, for example **55** [157] and **56** [158].)

$CH_2{=}C(OEt)Cl$ **(55)** $\quad$ $CHCl{=}C(OEt)Cl$ **(56)**

(c) Alkyl cyanides give salts with alcohols (equation 62 [55]). These are susceptible to S_N2 reactions, giving alkyl halides of configuration



(62)

opposite to that found in the alcohol. The effect is similar to that of carbodiimides in activating carboxyl groups towards amide formation in peptide syntheses[58] (equation 63).

$$RN{=}C{=}NR \xrightarrow{R'CO_2H} RNHC(OCOR'){=}NR \xrightarrow{R''NH_2} RNHCONHR + R''NHCOR' \quad (63)$$

6. Organic acid chlorides

Many acid chlorides react with alcohols to form esters, which may either decompose spontaneously to give alkyl chlorides, or which can be converted to them in a subsequent step.

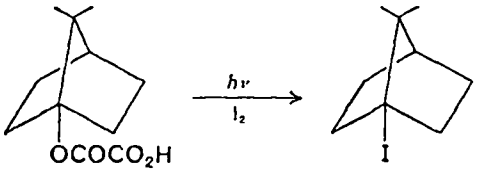
Oxalyl chloride forms chloroxalate esters with alcohols at room temperature (equation 64). The esters decompose when heated

$$ROH + (COCl)_2 \longrightarrow ROCOCOCl + HCl \quad (64)$$

$$ROCOCOCl \xrightarrow[125°]{\text{pyridine}} RCl + CO + CO_2 \quad (65)$$

above 100° in pyridine[159]. Analogous chloroformates also decompose to give alkyl chlorides[160]—a survey of the breakdown of chloroesters in general appears in standard texts on physical organic chemistry.

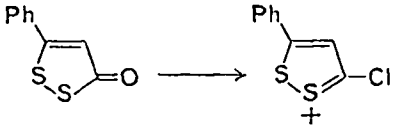
A similar (but multistep) reaction has been used to convert l-apocamphanol to the iodide (equation 66) by irradiating the oxalate in carbon tetrachloride in the presence of iodine and mercuric oxide[33] (section II.A.4) based on earlier work on the de-



(66)

composition of hypoiodites by Barton[161].

Oxalyl chloride[162], like phosgene[163], converts certain carbonyl



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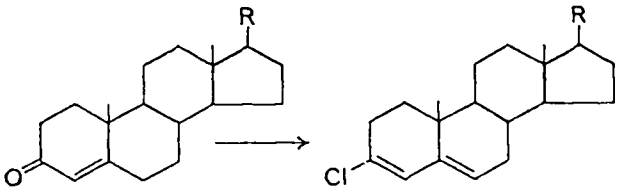
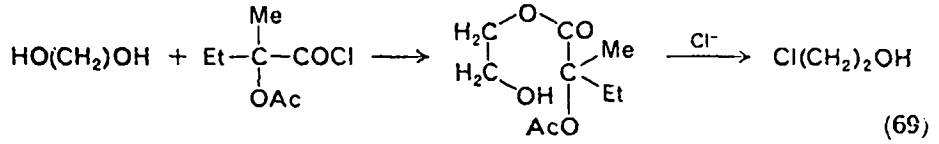


(68)

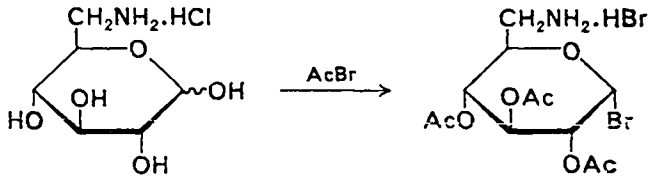
groups to chlorine-substituted salts (e.g., equation 67) and, in the presence of oxalic acid, to vinyl chlorides[164, 165] (e.g., equation 68).

α-Acetoxy acid chlorides effect the conversion shown in equation (69)[166].



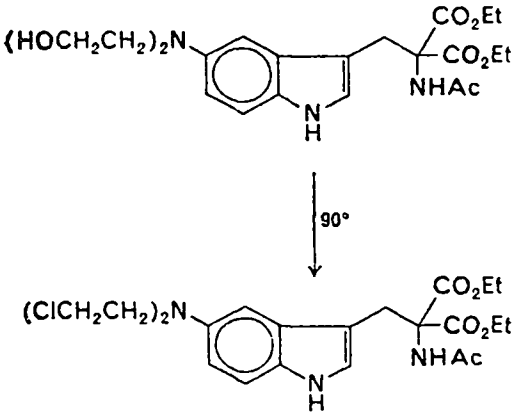
(69)

Acetyl bromide has been used to prepare bromo-compounds from alcohols, but products from acetylation alone, and from dehydration, are common, and the reagent is little used[167]. Thus, carbohydrate hemiacetals are converted to (acetylated) bromoethers:



Halogen acids in acetic acid react with the protected sugars to effect the same result[168].

Methanesulphonyl chloride has also been used as a chlorinating agent in the presence of pyridine[169].



7. Inorganic halides

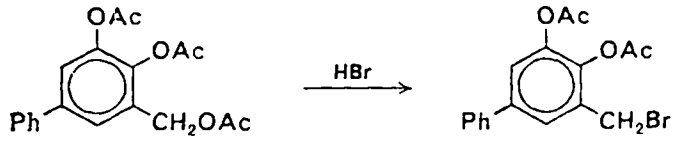
Various inorganic halides have been used to convert alcohols or their derivatives (usually tosylates or acetates) to halo-compounds.

Among these are sodium bromide[170], lithium chloride[171] and bromide[172], calcium chloride in the presence of hydrochloric acid[173, 174], zinc chloride with hydrochloric acid[175] or with dichloromethyl methyl ether[176], magnesium bromide[177], boron and aluminium trichlorides[178, 179], and titanium tetrachloride[180, 181] and tetrabromide[182]. Polar solvents such as dimethylformamide and dimethyl sulphoxide (with which tosylates react reversibly) and acetone are usually used for these displacements. Treatment of a cyclopropylcarbinol with lithium chloride and hydrochloric acid gave ring-opened products[183].

Tosylate displacements in particular provide one of the best methods of converting secondary alcohols to bromides[170] without rearrangement, although inversion of configuration occurs.

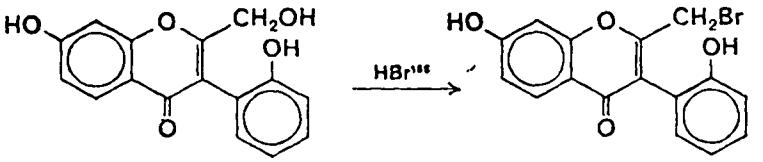
Pyridine hydrochloride has been used on steroid tosylates for the preparation of chloro compounds[184].

Phenol esters are inert to hydrobromic acid in acetic anhydride (equation 70 [185]) whereas benzylic ones are cleaved, and similar



(70)

differentiations are apparent (equations 71, 72) in the preparation of γ-pyrone derivatives, both with free hydroxyl groups and with derivatives.



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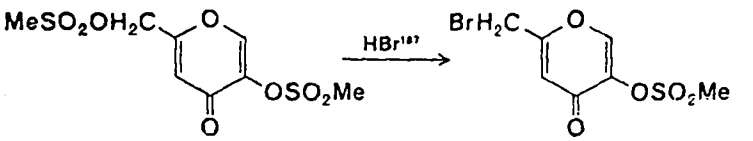


(72)

C. Displacement by Fluorine

1. Direct halogenation

Alcohols do not react with fluorine to give alkyl fluorides. In general, the other halogens can be used directly or indirectly to bring about substitutive halogenation of alcohols under certain conditions

(1-adamantanol with liquid bromine[38], alcohols with iodine in the presence of borohydride[4] or phosphorus[2], alcohols[36] with chlorine), although oxidations occur if labile functional groups are also present in the molecule.

2. Hydrofluoric acid

Despite the reversibility of the reaction (equation 73) and the conclusion[188] that the reaction is of little synthetic value, hydro-

$$ROH + HF \rightleftharpoons RF + H_2O \qquad (73)$$

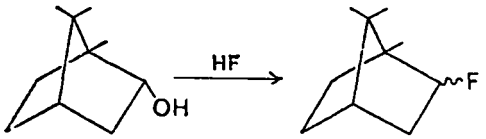
fluoric acid has been used quite widely for preparing fluoro compounds (equations 74 [189], 75 [190] and 76 [191]). The low acidity of

$$Ph_2C(OH)CH_2F \xrightarrow[\substack{1\ \text{minute}\\ -78°}]{HF} Ph_2CFCH_2F \qquad (74)$$

hydrofluoric acid compared with the other halogen acids, and the low nucleophilicity of fluoride ion are here overcome. Very variable

$$R_3SiOH \longrightarrow R_3SiF \qquad (75)$$

yields were obtained with the silanols, (equation 75), from 7% when R = Et, to 100% when R = Ph, but the reaction, using hydrofluoric acid in acetone, has not been used widely for carbon hydroxy compounds.

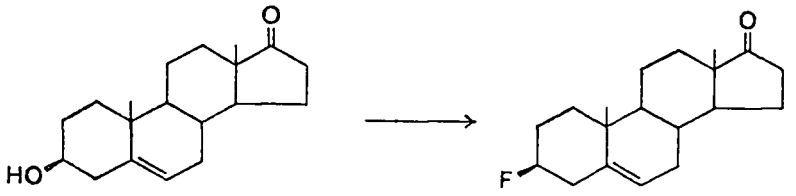


(76)

Alcohols add to diphenylcyanamide, Ph_2NCN, under the influence of potassium butoxide, to give intermediates[192], analogous to those used in section II.B.5c, which react with hydrofluoric acid to give alkyl fluorides.

3. Fluoramines

The fluoramine $FCHClCF_2NEt_2$ has been used to good effect[193] in the example shown (equation 77) and in converting hydroxyamino



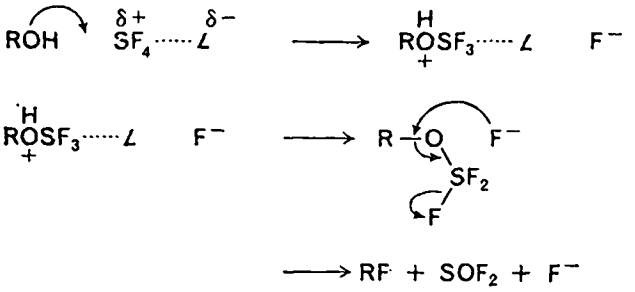
(77)

acids to fluoroamino acids[194], but products resulting from the rearrangement of the intermediate carbonium ion are also found in many cases[195].

4. Sulphur tetrafluoride

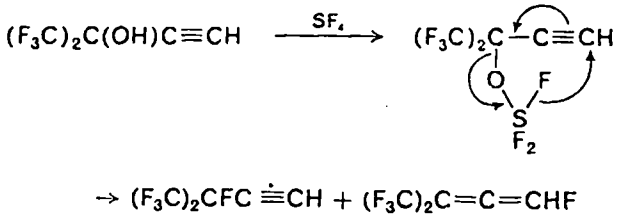
A great many oxygen-containing compounds, including alcohols, are attacked by sulphur tetrafluoride[196, 197]. This toxic gas is perhaps the most efficient reagent for converting alcohols[198] to fluoro compounds, but its great reactivity can be a disadvantage. Carbonyl groups are converted to *gem*-difluorides, and carboxylic acid derivatives to trifluoromethyl groups. Ethers, alkenes and alkynes are not attacked, however.

The conversions are catalysed by Lewis acids (L), and the mechanism is therefore probably as shown (equation 78). With propargylic



(78)

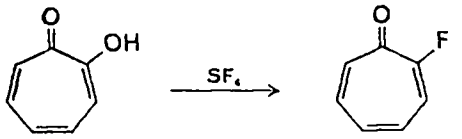
alcohols[81] (equation 79) a mechanism similar to that invoked by



(79)

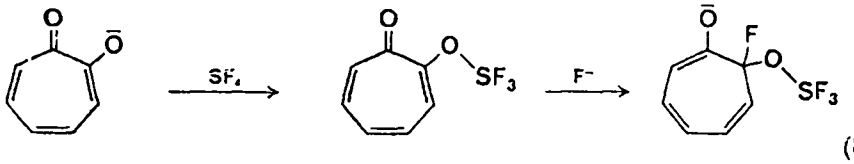
Landor[199] for the rearrangement of sulphinate esters of propargylic alcohols explains the product formation. A similar mechanism was proposed by the same[81] authors for the interaction of PCl_5 with the alcohol[80].

Sulphur tetrafluoride substitutes the hydroxyl group of tropolones by fluorine[196] in benzene solution at 60°, (equation 80) conditions considerably milder than those usually used (ca 150° in a pressure vessel). This very ready reaction is the consequence of the acidity of the enol and also of the increased susceptibility of the intermediate



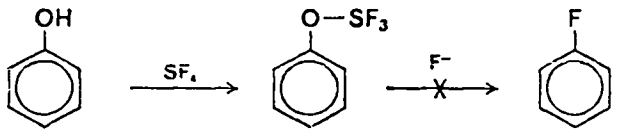
(80)

to attack by fluoride ion due to the presence of the carbonyl group (equation 81). The analogous reaction with simple phenols does not



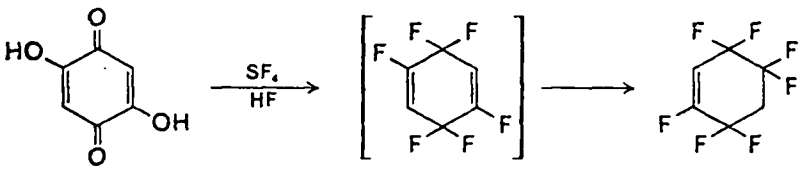
(81)

proceed, a consequence of the resistance of the electron-rich ring in the phenyl ether intermediate to nucleophilic attack (equation 82)



(82)

However, hydroxyquinones are attacked by the reagent[196] (equation 83) and borate esters[200] of alcohols also.



(83)

A recent review[201] has briefly summarized other uses of SF_4 in organic chemistry.

Phenylsulphur trifluoride reacts in many ways as SF_4 [201], but is a milder reagent.

5. Tosylate displacements

Fluoride ion can displace tosyl ion, from sugar derivatives for example[202], and in other molecules also.

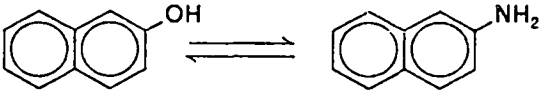
6. Fluoroformate decomposition

Carbonyl fluoride reacts with alcohols to form fluoroformates, and the decomposition of these esters to alkyl fluorides has been described[203].

III. DISPLACEMENT BY NITROGEN

A. Displacement by NH_2

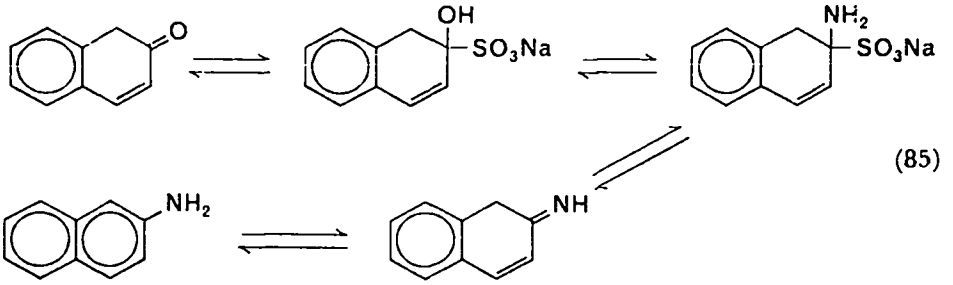
1. Bucherer reaction. The reversible conversion of naphthols to naphthylamines in the presence of aqueous sodium bisulphite and ammonia, the Bucherer reaction[204] (equation 84), has also been



(84)

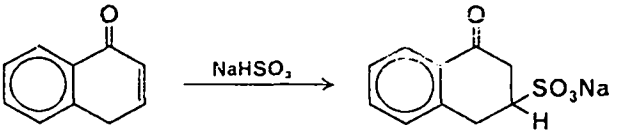
applied[205] to some phenols, to more highly condensed hydroxy-aromatic compounds, and to some heterocyclic systems.

The mechanism of the reaction, for long assumed[205] to involve addition of ammonia to the bisulphite addition compound of the keto-form of the naphthol (equation 85) has been shown erroneous,



(85)

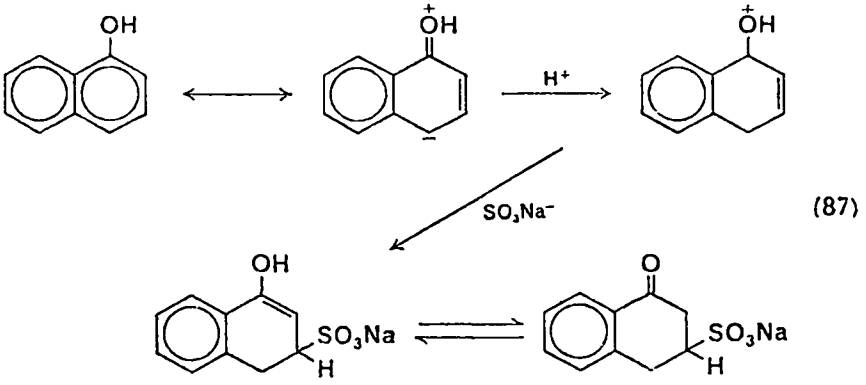
and recent reviews have corrected it[204, 206]. The older formulation of the intermediate as the bisulphite addition product of a ketone was untenable in the light of i.r. evidence[207]. This clearly showed the presence of a ketone, which forms an oxime and a semicarbazone in the usual way. The intermediate may be regarded as the product of 1,4 addition to an α,β-unsaturated ketone (equation 86) or, more



(86)

fully, as the product of the scheme outlined in equation (87). The conversion of the ketone, via an imine, to naphthylamine derivatives then is unexceptional.

2. Ritter reaction[208]. A general method for converting alcohols, rather than phenols (section III.A.1), to amines is that due to Ritter



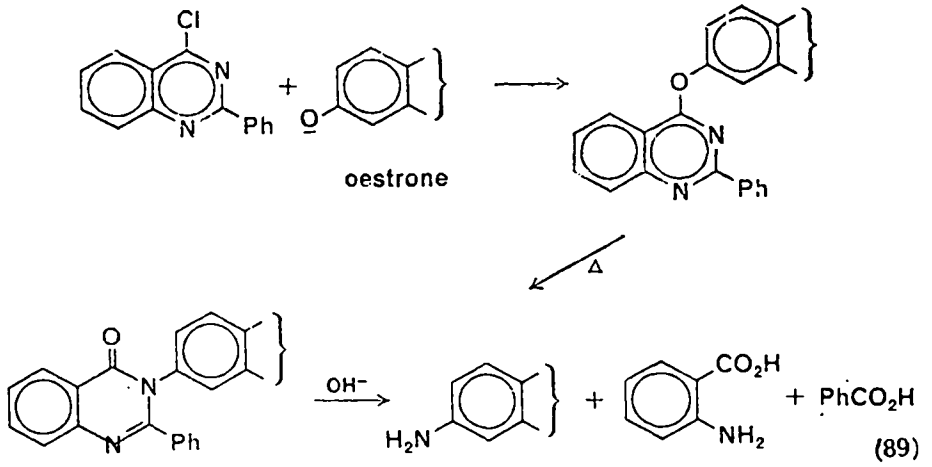
(87)

(equation 88). A review of its application in the synthesis of hetero-

$$ROH \xrightarrow[R'CN]{H_2SO_4} RNHCOR' \longrightarrow RNH_2 \qquad (88)$$

cyclic compounds has appeared[209]. The reaction involves the carbonium ion derived from the alcohol: the same product can also be obtained from an alkene in the presence of nitriles (or inorganic cyanides) and acid. The nucleophilic group which attacks the carbonium ion is a covalent cyanide, using the lone pair on nitrogen, and not cyanide ion.

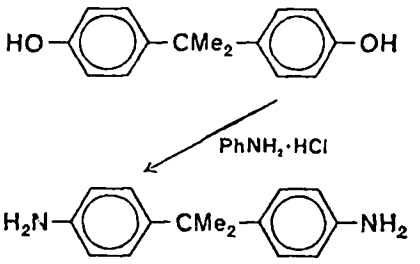
The yield of primary amine is particularly good from tertiary alcohols, and poor from primary ones, as anticipated.



(89)

3. A particularly neat synthetic route to amines from phenols, though not a direct displacement mechanistically, has been reported by Scherrer[210], and applied to oestrone[211] (equation 89).

Another, patented[212] reaction in which the overall conversion is of a phenol to an aniline derivative is shown in equation (90) although it is very unlikely that the mechanism involves any direct displacement of hydroxyl by amine group.



(90)

4. Tosylates can be converted to azides (section III.C.2) and the azides reduced to amines to provide a useful synthetic route from alcohols to amines[213].

B. Displacement by NR_2

The Bucherer reaction can be extended to prepare secondary amines[205] and hydrazines[205] from phenols. Examples of these reactions are included in review articles.

C. Displacement by Azide

1. Direct displacements of hydroxyl by azide are uncommon, but carbonium ions derived from alcohols are attacked by azide ion (compare the Ritter reaction, section III.A.2) to give organic azides[214] (equation 91).

$$Ph_3COH \xrightarrow[H_2SO_4]{NaN_3} Ph_3CN_3 \qquad (91)$$

2. Tosylate displacement by inorganic azide ion provides the principal route to azides from alcohols[215, 216]. The stereochemistry of the product obtained in the displacement of a secondary alcohol depends markedly on the solvent polarity, as anticipated from the inevitable change in mechanism from S_N2 to S_N1 in more polar solvents.

3. Epoxides[217] and halohydrins[218] are attacked by sodium azide and acid, giving hydroxyazides.

IV. DISPLACEMENT BY HYDROGEN

A. Hydrogenolysis

It has long been known that benzylic alcohols[219] (and, more recently, homobenzylic alcohols)[220] are reduced to the parent hydrocarbons by catalytic or chemical hydrogenolysis (equation 92).

$$Ar\ CH_3CH_2OH \xrightarrow{[H]} Ar\ CH_2CH_3 \qquad (92)$$

Cleavage of the carbon–oxygen bond occurs even more rapidly when ester derivatives of alcohols are used, and McQuillin and co-workers have shown[221] that in a series of conversions (equation 93) the rate of hydrogenolysis parallels the stability of X^-, the ease with which

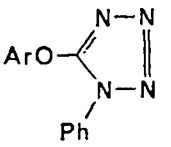
$$R-\underset{\displaystyle X}{\overset{\displaystyle Ph}{\underset{|}{\overset{|}{C}}}}-CO_2Et \xrightarrow{[H]} R-\underset{\displaystyle H}{\overset{\displaystyle Ph}{\underset{|}{\overset{|}{C}}}}-CO_2Et \qquad (93)$$

X^- is eliminated, $OH^- < OCOCH_3^- < OCOCF_3^-$.

The hydrogenolysis of secondary alcohols is characterized by a high degree of stereospecificity[222], different catalysts (and different leaving groups) determining whether retention or inversion of configuration occurs.

Garbisch[223] has discussed the mechanism in terms of a modified Horiuti–Polanyi model[224]. He concludes that whereas homobenzylic hydroxyl groups are lost as water in a β-elimination process involving a benzylic hydrogen (no carbon–oxygen bond cleavage is observed in the absence of such hydrogens) and the final product is therefore produced from an alkene, benzylic hydrogenolysis proceeds by a different and more complex mechanism.

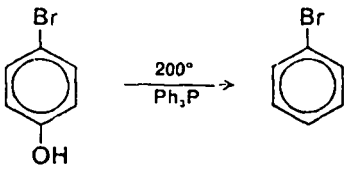
Hydrogenolysis of phenols to benzene derivatives using palladium on carbon can be effected through the derivative **57**[225] (compare equation 89).



(57)

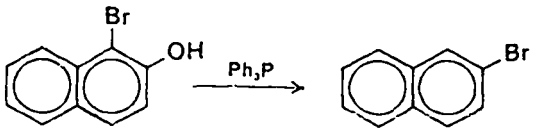
B. Reduction

The apparent reduction observed when *p*-bromophenol is heated with triphenylphosphine[61] (section II.B.3a) (equation 94) is seen



(94)

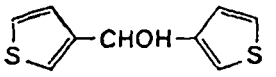
instead as a displacement of hydroxyl by bromine in the light of a similar reaction (equation 95) with 1-bromo-2-naphthol, but several



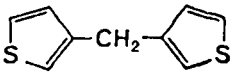
(95)

methods for replacing hydroxyl groups other than by hydrogenolysis are known. Iodides (most conveniently prepared from tosylates) are reduced by zinc and hydrochloric acid in methanol[226] or by bisulphite in dioxan[227].

Triphenylcarbinol is reduced to triphenylmethane by 98% formic acid at 20° [228], 2-naphthol to naphthalene by phosphorus trisulphide in phenol at 400° [229], and the alcohol **58** to **59** by lithium aluminium hydride in the presence of aluminium chloride[230].



(58)



(59)

V. DISPLACEMENT BY OXYGEN

A. Exchange with Labelled Hydroxyl Groups[231] (equation 96)

This topic is discussed in another chapter in this volume.

$$PhOH + H^+ \xrightarrow{H_2O^*} Ph\overset{*}{O}H \qquad (96)$$

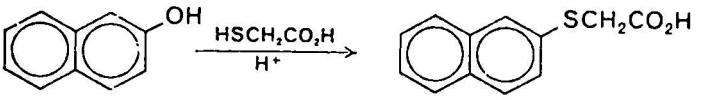
B. Exchange with Alkoxy Groups[232] (equation 97)

$$PhOH + H^+ \xrightarrow{ROH} PhOR \qquad (97)$$

For a discussion of ether formation from alcohols, see an earlier volume in this series[233].

VI. DISPLACEMENT BY SULPHUR

Paralleling the acid-catalysed exchange of hydroxyl for alkoxy groups in the phenols are the reported conversions (equations 98, 99)

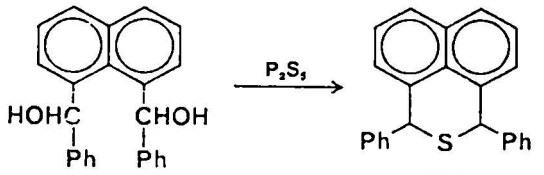


(98)

of β-naphthol to a sulphur ether[234], and of 3-hydroxy-3-methylbut-

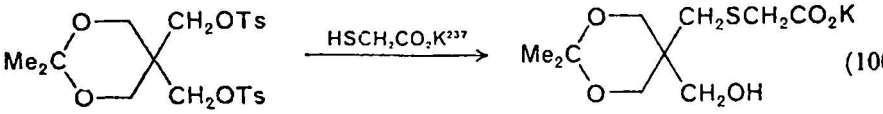
$$Me_2COHC{\equiv}CH \xrightarrow{PhCH_2SH} [PhCH_2SCMe_2C{\equiv}CH] \longrightarrow PhCH_2SCMe_2COMe \quad (99)$$
(61) (60)

1-yne to the ketone **60** via **61** [235]. Phosphorus pentasulphide converts

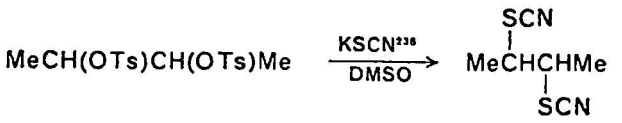


(62) (63)

the diol **62** to the sulphide **63** [236], and thiols and thiocyanates can also be used in the displacement of tosylate groups (equations 100, 101).



(100)



(101)

VII. DISPLACEMENT BY CARBON

The multitudinous reactions in which the carbonium ion derived from an alcohol attacks another carbon atom, as for example in alkene polymerizations, cannot be discussed here. Examples of nucleophilic displacement reactions by alcohol-derived carbanions are included however, in section VII.B.

A. Displacement by Cyanide

High yields of cyanoallenes are obtained from propargyl alcohols in the presence of hydrobromic acid, cuprous cyanide and potassium cyanide. There is no evidence that the acetylenic cyanide is an intermediate in this reaction, and no bromoallene is formed[239].

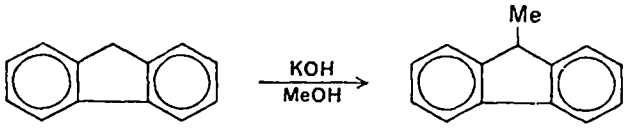
Inorganic cyanides displace tosyl groups from alcohol derivatives[240], usually in dimethylformamide or dimethyl sulphoxide solution, in which the tosylates exist in the equilibrium[241] shown in equation (102). (Displacements by inorganic ions in these polar

$$ROTs + Me_2SO \rightleftharpoons Me_2\overset{+}{S}OR\ \overset{-}{O}Ts \qquad (102)$$

solvents also seem aided by preferential solvation of the cation[242].)

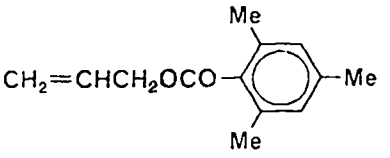
B. Displacement by Alkyl Groups

A great many examples are known of reactions in which carbanions react with alcohols and diols to give alkylated products[243, 244]. The general reaction is represented in equation (103).



(103)

Grignard reagents are sources of potential carbanions, but react with alcohols to remove the acidic proton, usually the basis of the Zerewitinov determination of active hydrogen[245]. Allyl alcohols can, however, be alkylated by treating ester derivatives such as **64** with Grignard reagents[246] (equation 104).



(104)

(64)

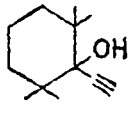
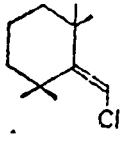
VIII. SURVEY OF DISPLACEMENTS BY HALOGEN ON SPECIFIC HYDROXYL FUNCTIONS

A. Displacements on Propargyl Alcohols

The alcohols are very susceptible to rearrangements during substitution, giving allene derivatives under a wide variety of conditions, often without the intermediacy of propargyl halides. Applications of the rearrangements to the synthesis of allenes have been recently reviewed by Taylor[247].

Reagents which are used on less labile systems to obviate rearrangements work well on propargyl systems generally, although no aryl tertiary propargyl halides have been prepared[134]. In addition to triphenyl phosphite methiodide at low temperature in methylene

TABLE 1. Displacements on propargyl alcohols.

Alcohol	Reagent	Product	Yield %	Ref.
A.				
$CH{\equiv}CCH_2OH$	$(PhO)_3PBr_2$/pyridine	$CH{\equiv}CCH_2Br$	72	248
$CH{\equiv}CCH_2OH$	$(PhO)_3PMeI/CH_2Cl_2$	$CH{\equiv}CCH_2I$	90	18
$CH_3C{\equiv}CCH_2OH$	$SOCl_2$/pyridine	$CH_3C{\equiv}CCH_2Cl$	81	249
$CH{\equiv}CCHMeOH$	$(PhO)_3PMeI/CH_2Cl_2$	$CH{\equiv}CCHMeI$	43	18
$CH{\equiv}CCHMeOH$	$(PhO)_3PBr_2$/pyridine	$CH{\equiv}CCHMeBr$	72	45
$CH{\equiv}CC(OH)Et_2$	$HCl/CuCl/CaCl_2/Cu/Zn$	$CH{\equiv}CCClEt_2$	83	51
$CH{\equiv}CC(OH)Me_2$	PCl_3	$CH{\equiv}CCClMe_2$	47	132
		$+CHCl{=}CHCMe{=}CH_2$	23	
$CH{\equiv}CC(OH)Me_2$	SF_4	$CH{\equiv}CCFMe_2$		81
B. see also References 80, 131, 133				
$CH{\equiv}CC(OH)MeBu\text{-}t$	HBr/CuBr/Cu	$CHBr{=}C{=}CMeBu\text{-}t$		45, 46
	$SOCl_2$/pyridine		83	139
$t\text{-}BuC{\equiv}CC(OH)ArBu\text{-}t$	PBr_3	$t\text{-}BuCBr{=}C{=}CArBu\text{-}t$		134
$t\text{-}BuC{\equiv}CC(OH)ArBu\text{-}t$	$SOCl_2$	$t\text{-}BuCCl{=}C{=}CArBu\text{-}t$		134
$PhC{\equiv}CC(OH)PhAr$	$SOCl_2$	$PhCCl{=}C{=}CPhAr$		250
$HC{\equiv}CC(OH)(CF_3)_2$	SF_4	$CHF{=}C{=}C(CF_3)_2$		81
		$+HC{\equiv}CCF(CF_3)_2$		

chloride[18] and triphenyl phosphite dibromide in the presence of pyridine[248], however, thionyl chloride has been used on primary propargyl alcohols[138, 249], and hydrochloric acid[51], phosphorus trichloride[132] and sulphur tetrafluoride[81] on aliphatic tertiary ones without causing extensive rearrangement. Under different conditions, mineral acid[45, 46], phosphorus tribromide[134], thionyl chloride[134, 148, 250] and sulphur tetrafluoride[81] have all been reported to cause major rearrangements in propargyl alcohols. Propargyl iodides rearrange to iodoallenes in dimethylformamide[18].

B. Displacements on Allylic, Homallylic and Allenic Alcohols

The problems encountered in studying substitutions of allylic alcohols[251] are mainly those of determining whether the mechanism involves double bond participation.

From the synthetic aspect, as with homoallylic systems and, indeed, with simple alcohols, different reagents can be used to give stereochemically or isomerically different products. The different reactions effected by PCl_5 and $SOCl_2$ (7β-cholestanol gives 55% 7α-chlorocholestane with $PCl_5/CaCO_3$ but 59% 7β-chlorocholestane with $SOCl_2$ [152]) have been referred to in section II.B.4. Retention of configuration is found with many reagents on homoallylic alcohols: PCl_5, PX_3, $(PhO)_3PX_2$ and Ph_3PBr_2 all react in this way[74, 75]. An important factor encouraging S_Ni reactions in 3-hydroxy-5-ene steroids is the inability of the rigid molecule to assume the necessary planar transition state configuration for S_N2 reaction. (See also equation 77.)

Allenic alcohols also can be substituted directly by some reagents[79], but rearrange to 1,3-diene derivatives with others[79, 252].

See also References 6, 17, 18, 43, 44, 107, 136, 149, 193 and 248.

C. Reactions of Cyclopropanols[253] and of Cyclopropylcarbinols

No reactions are known in which direct substitution of cyclopropanols occurs; both with the free alcohols and with tosylate derivatives[254], ring opening[255] invariably takes place preferentially.

Cyclopropylcarbinols are also very susceptible to ring opening reactions, although the three-membered ring survives substitution at the adjacent carbon atom to some extent[147]. Earlier speculations on the intermediacy of the tricyclobutonium ion in these reactions are no longer tenable[256]. Halogen acids effect ring opening to give homoallylic halides in good yields[42, 183].

D. Displacements on Phenols (see also section II.B.3.a)

Phenols readily form esters with many of the reagents used for converting alcohols to alkyl halides, but these fail to undergo nucleophilic substitution in a subsequent, halide-forming step, except in a few cases. Phosphorus pentachloride gives poor conversions of phenols to aryl halides because of side reactions: tetraaryloxyphosphonium halides in general are stable at quite high temperatures[69] although their decomposition can be carried out at 140° using the method due to Rydon[70]. The same method allows for the preparation of aryl bromides and iodides by exchanging the chloride ion in the phosphonium salts.

The use of triphenylphosphine dihalides in place of phosphorus pentahalides is preferred because of the easier reaction resulting from making triphenylphosphine oxide the leaving group, and the only disadvantage of the reagent seems to be encountered with very hindered phenols[95] (equation 35).

The hydroxyl group in tropolones can be substituted smoothly with sulphur tetrafluoride or with thionyl chloride[141]. Very acidic phenols react with thionyl chloride in dimethylformamide[142].

The relative inertia of phenolic hydroxyl groups towards displacement enables chemical differentiations to be made between them and, for example, benzylic hydroxyl groups. This has been exploited many times (section II.B.7 and Reference 257).

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The Chemistry of The Hydroxyl Group
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CHAPTER 12

The dehydration of alcohols

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I. INTRODUCTION

The dehydration of alcohols is one example out of a wide spectrum of elimination reactions of the general form

$$RX \longrightarrow \text{olefin} + HX$$

which are of interest for the production of olefins. Furthermore, the bimolecular dehydration of alcohols can often be valuable for the formation of ethers.

The dehydration of alcohols can be observed both in solution and in the gas phase. General rules for elimination reactions have been given in the past[1, 2]. Furthermore, elimination reactions in solution are covered in the chapter by Saunders[3] and those in the gas phase in the chapter by Maccoll[4] in the first volume of this series. Therefore in this chapter the acid- and base-catalysed dehydration of alcohols in solution and the homogeneous pyrolytic elimination of water in the gas phase will be dealt with shortly. The main part of the chapter will subsequently cover the gas phase dehydration over solid catalysts. Excellent reviews on this topic have been published by Winfield[5] in 1960 and recently by Pines and Manassen[6], who treat solely the special aspects of alumina as a dehydration catalyst. Since much information on the heterogeneously catalysed dehydration of alcohols by various solids has been obtained in the last years and since it may now be shown that the principles of organic chemistry, as worked out for homogeneous systems, are also applicable to heterogeneous systems, the author feels justified in spending more than half of the chapter on this last topic.

II. DEHYDRATION IN SOLUTION

A. Acid-Catalysed Dehydration of Alcohols

1. General observations

The dehydration of alcohols proceeds in aqueous acid solutions of either Brønsted or Lewis acids. Product analyses show the formation of mainly Saytzeff-olefins[7, 8]. This is a typical behaviour in *E*1 reactions. Saytzeff products are, however, the thermodynamically most stable olefins, so that under equilibrating conditions the product distribution in principle could be thermodynamically rather than kinetically controlled. The postulation of an *E*1 type reaction is therefore only conclusive if the observed Saytzeff-products prove to be primary, non-rearranged products. Regarding the stereochemical

course of the dehydration a *trans*-elimination was shown to predominate for cyclic alcohols[9, 10]. In the following we will first elucidate the mechanism and the probable reaction intermediates and then turn to some stereochemical aspects of the dehydration of alcohols in acid solutions.

2. Mechanisms of the dehydration of alcohols

The elementary steps of the dehydration in aqueous acid solutions have been investigated most extensively by Taft and co-workers[11–15], in particular for the dehydration of tertiary alcohols. They collected much information for the hydration of olefins, which is a reversible reaction. Thus, conclusions could be drawn on the olefin–alcohol interconversion by applying the principle of microscopic reversibility. Included in these studies were the dependence of rate of hydration and dehydration on the acidity functions H_0 and H_R *, influence of ring size, solvent isotope effects, deuterium exchange with olefins, ^{18}O-exchange, energy and entropy considerations and measurements of olefin solubility. The initial experiments dealt with the dependence of the rate of hydration of olefins on acid concentration[11]. The mechanism of this reaction was then deduced from the experimental results by applying the Zucker–Hammett hypothesis[16]. These authors found that the rates of a number of reactions follow the h_0-function; whereas the rates of another group follow the stoichiometric acid concentration $[H_3O^+]$. Zucker and Hammett formulated the hypothesis that reactions, whose rates follow h_0, do not involve a water molecule before or during the rate-determining step, whereas the second group of reactions involves the participation by a water molecule. Some results from different research groups for the hydration of isobutene in nitric and sulphuric acid solutions at acid concentrations up to 5M are shown in Figure 1. k_c is the rate constant for hydration of dissolved isobutene at unit concentration and $H_0 = -\log h_0$ is the Hammett acidity function. It is clear that the rate constant parallels h_0 satisfactorily, and no direct proportionality between k_c and $[H_3O^+]$ exists. On the basis of this result Taft concluded that the transition state for the hydration of ordinary olefins consists only of the olefin plus a proton, that is, a 'free' carbonium ion. Any hydration of this intermediate should be brought about only by ion–dipole interaction without any strong

* The acidity function H_R is related to the equilibrium $H^+ + ROH \rightleftarrows R^+ + H_2O$ and is defined[15a] as $H_R = -pK_{ROH} - \log \frac{[R^+]}{[ROH]}$.

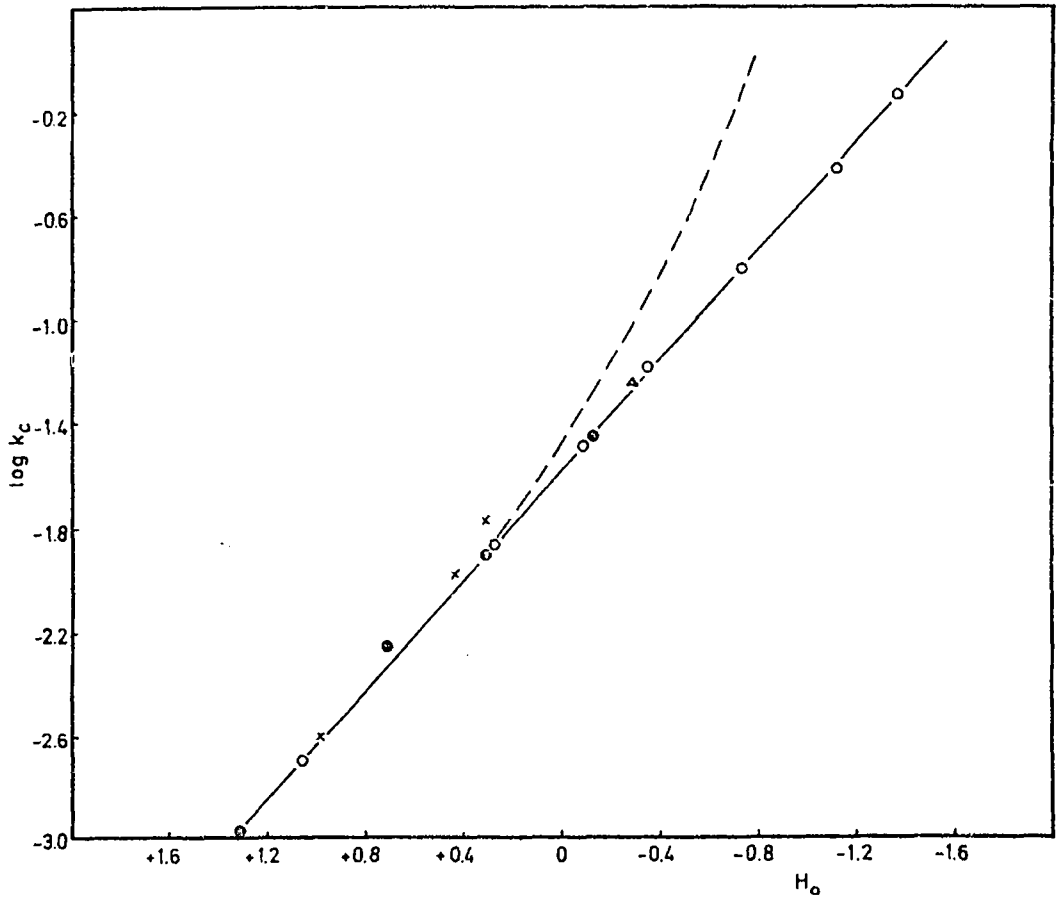
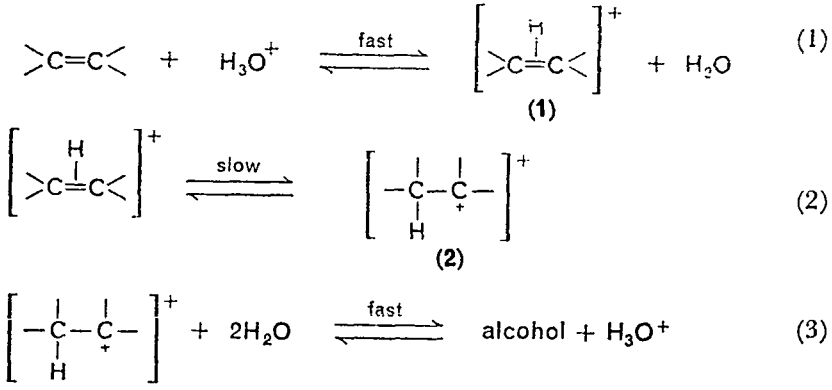


FIGURE 1. The dependence of rate, k_c, of hydration of dissolved isobutene at unit concentration on the acidity function, H_0. ○ Taft[11], HNO_3 solutions; △ Taft[11], H_2SO_4 solutions; ◉ Lucas and Eberz[17], HNO_3 solutions; × Ciapetta and Kilpatrick[18], HCl and $HClO_4$ solutions. (Taken from Reference 11 by permission of the copyright owner.)

covalent interaction between the ion and a water molecule. Therefore, all rate-determining elementary steps of the reaction which require one or more water molecules in the transition state were excluded. The following mechanism for the olefin–alcohol interconversion was proposed:



(1)

(2)

(3)

The species **1** and **2** in this mechanism were thought to be unstable carbonium ions, representing a π-complex and a free carbonium ion, respectively. During the fast formation of the π-complex by addition of a proton the structure of the olefin is preserved, the proton being solely embedded in the π-orbital of the C=C double bond. The bonding of this proton is therefore obviously very weak and different from that of all the other hydrogen atoms which are bonded by the coplanar directed sp^2-orbitals[19]. Except for the embedded proton the structure of this intermediate is essentially that of the olefin, the positive charge being nearly equally shared between the two unsaturated C atoms. In the free carbonium ion, on the other hand, one of the carbon atoms bears the greater portion of the charge. The transformation from **1** to **2** in step (2) is an activated process[19] and is therefore assumed to be rate-determining. The distinctions 'fast' and 'slow' in the above-mentioned mechanism are used according to the rate of material transfer and not with respect to the rate constants. In the former case the principle of microscopic reversibility is directly applicable, so that the reverse of the mechanistic equations represents the mechanism of the alcohol dehydration. For this reaction the rate-determining step cannot be the formation of the carbonium ion in step (3) but rather the isomerization of this intermediate to the π-complex (**1**) in step (2). For this reason the rate of dehydration of an alcohol should also parallel the Hammett acidity

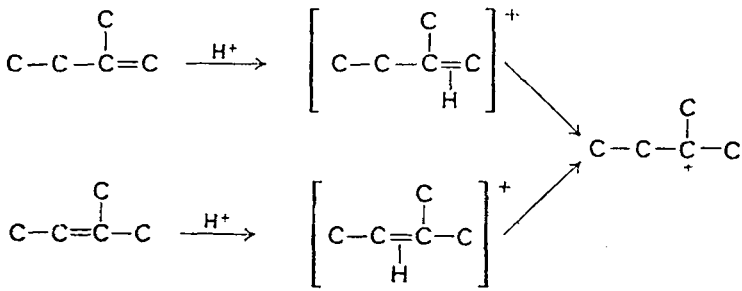
function and not the stoichiometric acid concentration. This behaviour has in fact been found and is illustrated in Table 1 for the dehydration of *t*-amyl alcohol at 25°C in various acidic solutions[15].

TABLE 1. Correlation of the effect of acidity on the rate constant k for the dehydration of tertiary amyl alcohol in aqueous acid media at 25° with the H_0-function[a].

Acid	M	$-H_0$	log k	log k + H_0	log k − log [H_3O^+]
HNO_3	0·97	0·16	−4·19	−4·35	−4·19
H_2SO_4	1·50	0·56	−3·90	−4·36	−3·98
$HClO_4$	1·86	0·71	−3·56	−4·27	−3·83
H_2SO_4	3·00	1·38	−2·58	−4·23	−3·33
H_2SO_4	4·10	1·89	−2·42	−4·31	−3·03

[a] Taken from Reference 15 by permission of the copyright owner.

Analogous results were obtained for the hydration of other olefins and the dehydration of the corresponding tertiary carbinols[12]. For the hydration of small ring olefins the effect of structure on the rate was also consistent with the proposed mechanism[14]. The activation entropies for the hydration of olefins were shown to have low positive or negative values, ranging from about −4 to +1 e.u., whereas for the dehydration of carbinols high positive values between +14 and +19 e.u. were found[12]. These observations are in accord with the above-mentioned mechanism since for steps (1) and (2) no great entropy changes can be expected. In the dehydration of alcohol in step (3) some degrees of translational freedom are gained and therefore the entropy of activation reaches high positive values. The existence of a π-complex as an intermediate is also shown by the fact that 2-methyl-2-butene and 2-methyl-1-butene do not isomerize during hydration[20]. Thus, a reaction sequence with



(4)

carbonium ion formation by a preliminary proton transfer to the olefin must be excluded, since both olefins lead to the same carbonium ion. On the other hand they form different π-complexes. If a carbonium ion, in which all the protons are equivalent, were formed preceding the rate-determining step, this could be detected by the appearance of deuterium in the unreacted olefin, if the reaction were performed in D_2O-enriched solution. No such exchange could be observed, and it must be concluded that the initially added proton remains in an exceptional position, since it is easily lost from the intermediate before a transformation to a carbonium ion can occur. The most probable reaction intermediate is therefore the π-complex. During the reverse reaction, the dehydration of alcohols, an exchange between solvent and substrate should be observed, since the isomerization of the carbonium ion to the π-complex is slow, whereas step (3) is fast. Gold and Gruen[21], however, conclude from their results on the dehydration of *t*-butanol in tritium-enriched acid solutions, that the direct H-exchange in the tertiary butyl cation has to be ruled out. The only acceptable reaction path would then be the exchange via the dehydration–hydration sequence.

Measurements of the solvent isotope effect, on the other hand, are still in favour of Taft's mechanism[13]. The results of the hydration of 2-methyl-2-butene and of 1-methyl-1-cyclopentene in nitric acid solutions at 30° and 35°C, respectively, are illustrated in Figure 2 for various D_2O-concentrations. The Figure shows the dependence on n of the experimentally determined values of k_n/k_H, i.e., the ratio of the rate constants for solutions with a relative deuterium concentration $n = \sum D/\sum (H + D)$ to that for normal aqueous solutions. These values are compared with the theoretical curves which were calculated from a formula derived by Nelson and Butler[22]:

$$\frac{k_n}{k_H} = \frac{(a_{H^+})_n}{(a_{H^+})_H} + \frac{k_D}{k_H}\frac{(a_{D^+})_n}{(a_{D^+})_D} \qquad (I)$$

where $(a_{H^+})_n$ and $(a_{H^+})_H$ are the proton activities in the mixed solvent and in H_2O and analogously $(a_{D^+})_n$ and $(a_{D^+})_D$ are the deuteron activities in the mixed solvent and D_2O, respectively. The derivation of this equation was based essentially on the relative acidities of D_3O^+ and H_3O^+ and on the assumption that a proton transfer from solvent to substrate preceding the rate-determining step is involved. In the case of a rate-determining proton transfer process, on the other hand, the rate should be retarded linearly with increasing mole fraction of D. The fact that the experimental results follow the

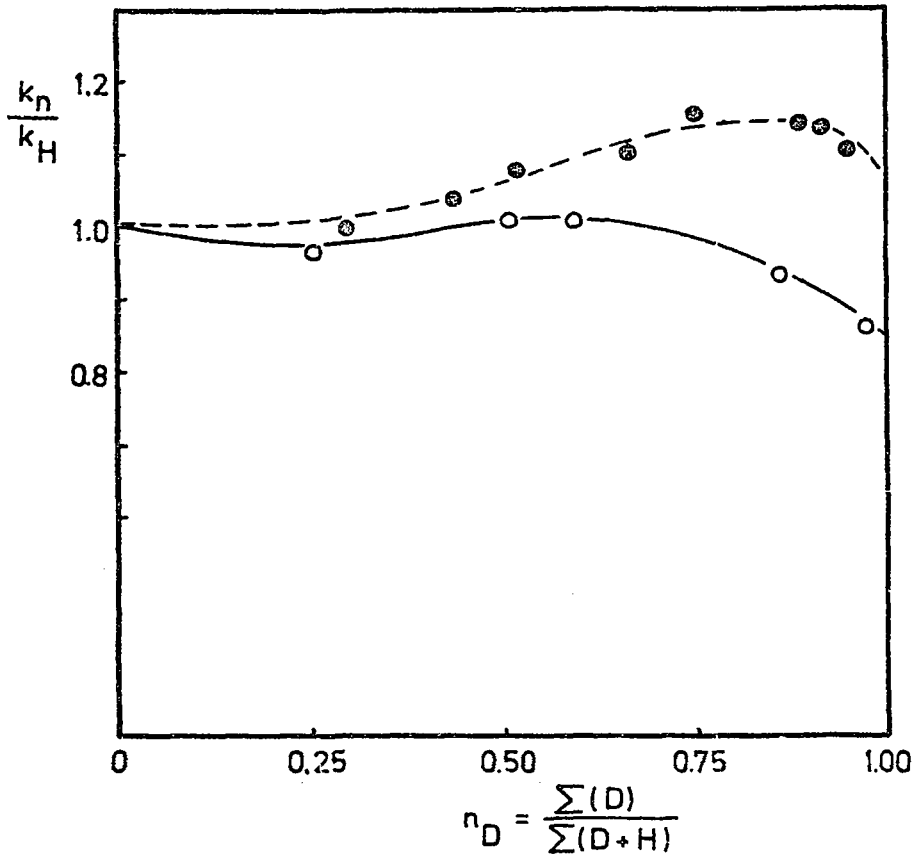


FIGURE 2. Hydration rates of trimethylethylene and 1-methylcyclopentene-1 as functions of H_2O–D_2O content of the solvent. ⊛ 1-methylcyclopentene-1 in 0·0909M nitric acid at 35·2°C. – – – theoretical curve for 1-methylcyclopentene-1. ○ trimethylethylene in 0·973M nitric acid at 30·0°C. —— theoretical curve for trimethylethylene. (Taken from Reference 13 by permission of the copyright owner.)

Butler equation lends further support to the preliminary formation of a π-complex. Step (1) of the reaction scheme must therefore be written in the form

$$>C{=}C< \; + \; D_3O^+ \; \underset{\text{fast}}{\rightleftharpoons} \; \ominus\left[>C(D){-}C< \right]^+ \; + \; D_2O \qquad (1a)$$

so that no D can appear in the unreacted olefin as shown experimentally[20]. The observed isotope effects of near unity were explained as being caused by compensating opposing effects in reaction steps

(1) and (2). The possible occurrence of such low solvent isotope effects for the hydration of olefins has recently been verified by Willi[22a] by means of purely theoretical considerations.

The formation of a π-complex seems now well established, whereas the degree of hydration of the reaction intermediates is still subject to some controversy. With respect to the high solvation energy (ion–dipole interaction) of about 69 kcal/mole for a tertiary butyl cation Taft himself argued that such interactions would probably influence certain aspects of the hydration–dehydration mechanism as, e.g., the stereochemistry. Moreover, Grunwald, Heller and Klein[23], relying on their investigations of racemization and oxygen exchange of 1-phenylethyl alcohol, suggested that the Zucker–Hammett hypothesis is not applicable to the alcohol–olefin interconversion in its simple form. Taft and co-workers arrived at the same conclusion in their later work[15]. If the intermediate carbonium ion were as 'free' as assumed initially, one would expect the reaction rates to parallel the H_R-function. The fact that this suggestion could not be verified by experiment[15] (cf Table 2), whereas the H_0-function

TABLE 2. Correlation of the effect of acidity on the rate constant k for the dehydration of t-amyl alcohol in aqueous HNO_3 solutions at 30°C with the H_0-function[a].

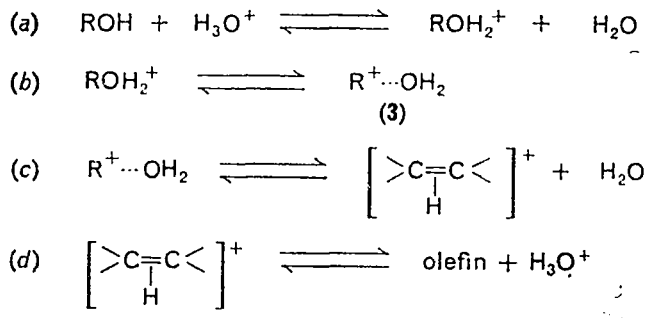
M	$-H_0$	$\log k + H_0$	$\log k + H_R$
0·973	0·16	−4·02	−4·53
1·500	0·45	−3·96	−4·66
2·01	0·67	−3·96	−4·85
2·96	1·00	−3·91	−5·17
4·00	1·32	−4·01	−5·60
4·94	1·56	−4·01	−5·90

[a] Taken from Reference 15 by permission of the copyright owner.

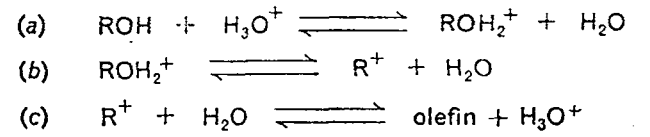
is followed very well, may indicate that the transition state is an oxonium ion rather than a 'free' carbonium ion, i.e., the transition state seems to consist of the substrate plus a proton plus a water molecule rather than the substrate plus a proton. Thus, two possible pathways remain, one in which the ion $R^+ \cdots OH_2$ isomerizes in the rate-determining step to a π-complex, or another in which a 'free' carbonium ion eliminates a β-proton by reaction with a water molecule, to form an olefin. Taft and co-workers[15] have shown that

the ^{18}O exchange rates and the dehydration rates of tertiary alcohols both follow the h_0-function. Since, moreover, the entropies of activation for both reactions show very similar high positive values both reactions are assumed to proceed through the same initial steps. The exchange rates are appreciably faster than the dehydration rates, which shows the rate-determining steps to be different. The following two mechanisms are consistent with all experimental facts.

Mechanism A:

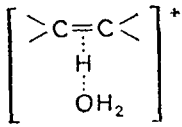


Mechanism B:



In mechanism A, steps (*a*), (*b*) and (*d*) must be fast and step (*c*) rate determining for the dehydration, whereas for the exchange reaction step (*a*) is fast and step (*b*) rate-determining. In mechanism B, on the other hand, step (*c*) determines the rate of elimination of water, and step (*b*) is the slowest reaction for ^{18}O-exchange. In both these mechanisms the transition state is represented by a structure possessing a triple character, i.e., a hybrid with some of the properties of an olefin, a conjugate acid of an alcohol, and a carbonium ion.

An alternative possible description of the π-complex structure is given by Taft[15], who prefers mechanism A.



Very similar results were obtained by Dostrovsky and Klein[24] for the ^{18}O-exchange and dehydration of *t*-butanol under identical conditions in sulphuric acid solutions. However, in their kinetic analysis these authors assume mechanism B to be more likely, with step (*c*) being rate-determining in the dehydration. An exchange

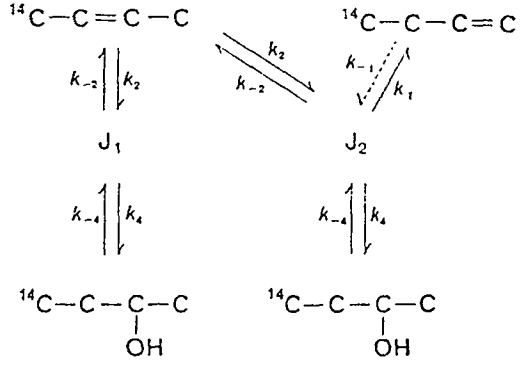
$$H_2{}^{18}O + ROH_2^+ \rightleftharpoons R\,{}^{18}OH_2^+ + H_2O \qquad (5)$$

route could not be rigorously excluded, but is considered as unlikely for tertiary alcohols in highly aqueous media.

Reactions of secondary and primary alcohols have been studied less intensively. The following interrelated reactions of the secondary butyl system were subject to the investigations of Manassen and Klein[25]:

$$\begin{aligned}
EtCH{=}CH_2 + H_2O &\longrightarrow EtCH(OH)CH_3 \quad \text{(Hydration)}\\
CH_3CH_2CH{=}CH_2 &\longrightarrow CH_3CH{=}CHCH_3 \quad \text{(Isomerization)}\\
CH_3CH_2CH(OH)CH_3 &\longrightarrow CH_3CH{=}CHCH_3 + H_2O \quad \text{(Dehydration)}\\
CH_3CH_2CH(^{18}OH)CH_3 + H_2{}^{16}O &\longrightarrow CH_3CH_2CH(^{16}OH)CH_3 + H_2{}^{18}O\\
&\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \text{(Solvolysis)}
\end{aligned} \qquad (6)$$

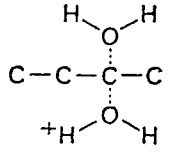
The reactions proceeded in 0·555N perchloric acid at 100°C. By doubly labelling butan-2-ol with ^{18}O and ^{14}C, exchange and isomerization could be followed at the same time under identical conditions. The pathways of the four reactions can be described in the following reaction scheme:



(7)

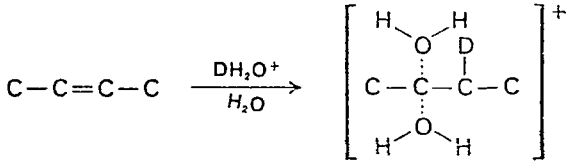
J_1 and J_2 indicate reaction intermediates. It was found that the ratio of elimination to substitution equals $k_{-2}/k_4 = 0{\cdot}5$ and, using a method developed by Grunwald and co-workers[23], that the number of water molecules attached to the reaction intermediate in nearest neighbour sites is two. Since, contrary to the experimental results, as shown by Ingold[26], the elimination to substitution ratio is smaller for secondary carbonium ions than for 'methyl substituted' tertiary

carbonium ions ($k_{-2}/k_1 = 0{\cdot}08$ for tertiary butyl ion[24]), it was concluded that the mechanism for the secondary butyl compound is different from that of the tertiary pentyl compound, i.e., a free carbonium ion is not involved as an intermediate in this case. Furthermore, from calculations of the free energies of formation of carbonium ions one is forced to assume activation energies in the secondary butyl system which are too high to be in accordance with experimental results. Manassen and Klein therefore introduced the idea of a reactive intermediate with two water molecules attached symmetrically to each side of the plane of the carbon skeleton, the bonds between the water molecules and the central carbon atom being of partially covalent character:



The symmetrical position of the water molecules is supported by the comparison of the rates of ^{18}O-exchange and of racemization of optically active *s*-butanol. It was shown by Bunton and Llewellyn[27] that the racemization is almost exactly twice as fast as the exchange, indicating that each exchange of oxygen atoms between alcohol and water gives complete inversion of configuration of the asymmetric C atom.

The high elimination–substitution ratio for the secondary butyl compound can be explained by assuming that the neighbouring water molecule assists in the elimination of the β-proton. The suggested mechanism is furthermore supported by the observed isotope effects. In the *t*-butyl system the deuterium isotope effect of near unity was explained[13] by opposing effects caused by the reaction steps (1) and (2) in Taft's mechanism; in the case of the kinetic isotope effect for secondary compounds only the step in which the the C–H bond is formed during hydration has to be considered:



(8)

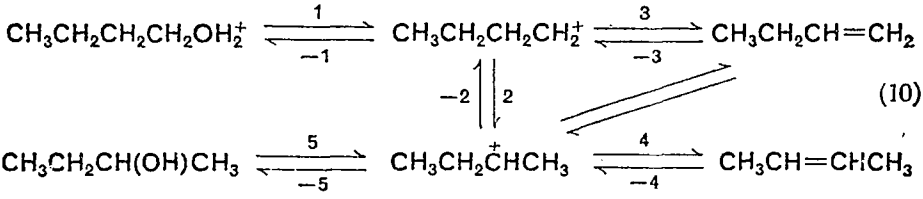
This step is therefore rate-determining.

In the dehydration products of *s*-butanol the thermodynamically less stable *cis*-2-butene predominates over the *trans*-isomer. Manassen and Klein[25] therefore assume some π-complex character of the reaction intermediate, i.e., the β-proton is transferred to the π-orbitals of the developing double bond prior to elimination. Because of the higher stability of *cis*-π-complexes the decomposition of the reaction intermediate leads then preferentially to the *cis* product.

Similar kinetic studies were undertaken by Dostrovsky and Klein[28] for interrelated reactions of the primary butyl compound. As reaction products from treating *n*-butanol with 1N sulphuric acid solution at 125°C, *s*-butanol, di-*n*-butyl ether and a mixture of olefins were found. Assuming a reversible and rapid formation of

$$ROH + H_3O^+ \rightleftharpoons ROH_2^+ + H_2O \tag{9}$$

the conjugate acid of the alcohol the formation of these products could be explained by the following reaction scheme:



(10)

It is known that but-2-ene gives only *s*-butanol on hydration. During the hydration of but-1-ene under the above-mentioned conditions only one part of *n*-butanol in 1000 of the hydrated product was formed, the main product being *s*-butanol. This result must be a consequence of the low stability of the primary carbonium ion, i.e., its minute proportion in equilibrium with the secondary ion even in strong acidic media. Since the ^{18}O-exchange with water has been observed to be faster by a factor of 3 than the decomposition of *n*-butanol under identical conditions, the exchange reaction cannot proceed through reaction steps $1/-1$. The concerted reaction step (5) was therefore suggested to be the preferred reaction path for

$$H_2{}^{18}O + ROH_2^+ \rightleftharpoons H_2O + R\,{}^{18}OH_2^+ \tag{5}$$

the oxygen exchange with primary alcohols. On the same grounds a concerted rather than an ionic mechanism should then be accepted for the direct decomposition of primary alcohols. These conclusions are also in accord with the results observed for exchange and decomposition of neopentyl alcohol.

The ether formation from primary alcohols is assumed by Dostrovsky and Klein[28] to proceed by the bimolecular attack of an alcohol molecule on the oxonium compound. By comparing the conversion with the exchange data, *n*-butanol seemed to be a somewhat more effective nucleophilic reagent than water.

Summarizing the dehydration in aqueous acidic solutions, one comes to the conclusion that tertiary alcohols are dehydrated through more or less free carbonium ions. Secondary alcohols prefer a reaction path midway between a carbonium ion and the transition state of a concerted mechanism, whereas dehydration of primary alcohols proceeds via an almost concerted mechanism. One may assume that with increasing temperature the ionic mechanism participates more and more in the dehydration of secondary alcohols, whereas for primary alcohols the dehydration should occur via the concerted mechanism even in the most acidic media because of the low stability of non-resonance stabilized primary carbonium ions[29].

Taft's mechanism has been questioned by Roček[30], who based his criticism on investigations of the dehydration of 1-methylcyclohexanol in sulphuric acid solutions in acetic acid and mixtures of acetic acid and water as solvents. It has been shown for such relatively nonpolar solvents that the acidity function H_0 in Hammett's definition does not represent a definite physical property of the system[31]. Roček[32] therefore defined a new acidity function $(H_0)_J$ relying on indicator measurements on solutions of various mineral acids in anhydrous acetic acid and acetic acid containing up to 15% of water. This acidity function was shown to be independent of the indicator used in the measurements and it was thought that this function could be useful in correlating kinetic data for acid-catalysed reactions in media of low polarity. The rates of olefin formation were followed in 85 to 100% acetic acid, in the presence of 0·02–1·4M sulphuric acid. The rate constants paralleled the antilogarithm $(h_0)_J$ of the acidity function $(H_0)_J$ rather than the stoichiometric acid concentration. On applying the Zucker–Hammett hypothesis the slow separation of water from the protonated alcohol with a subsequent rapid reaction of the carbonium ion with solvent was suggested to be the reaction path of the dehydration, i.e., mechanism B was assumed to be valid. Especially two points in Taft's argumentation have been criticized by Roček. Firstly, it is mentioned that the application of the principle of microscopic reversibility is justified for a reversible reaction proceeding through the same intermediates in both directions, but that it does not necessarily mean, as assumed

by Taft, that the slowest step in one direction is also the slowest in the reverse reaction. Secondly, it is emphasized that according to Taft's mechanism the rate constants should parallel the H_R-function, which was not the case. Taft, however, contrary to Roček, was led by this finding to the suggestion that the Zucker–Hammett hypothesis is not applicable to the dehydration of alcohols.

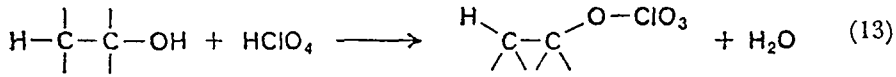
A different reaction path is that through an intermediate ester, which subsequently decomposes either thermally or by the *E*1 or *E*2 mechanisms. Well known for preparative purposes is the dehydration of alcohols in concentrated sulphuric acid[33] whereby, depending on the reaction conditions, the initially formed ester either decomposes to form an olefin

$$ROSO_2OH \longrightarrow \text{olefin} + HOSO_2OH \qquad (11)$$

or gives an ether

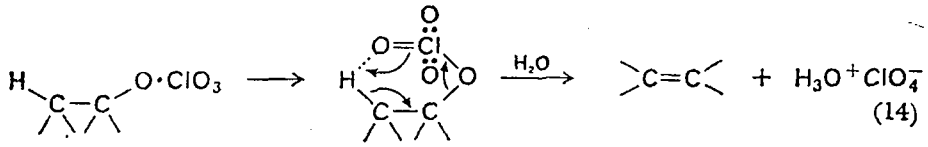
$$ROSO_2OR + ROH \longrightarrow ROR + ROSO_2OH \qquad (12)$$

Similar mechanisms are possible in various other reagents, e.g. *p*-toluenesulphonic, perchloric and oxalic acid, in anhydrides and in $POCl_3$ in pyridine or P_2O_5 in xylene. One example of such dehydration mechanisms was published recently by Gandini and Plesch[34]. For the decomposition of aromatic carbinols, namely $CH_3CHPhOH$, CH_3CPh_2OH, CH_2PhCPh_2OH and $CHPh_2CPh_2OH$, in perchloric and sulphuric acid they observed a very rapid dehydration with a subsequent slow protonation of the resulting olefins. Thus, the dehydration was suggested to be a true acid-catalysed reaction for which a carbonium ion mechanism could not be accepted. The formation of an intermediate ester is suggested.



(13)

This subsequently undergoes a cyclic *cis*-elimination with formation of the olefin and the acid hydrate:



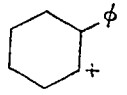
(14)

This pathway is deduced from the Chugaev *cis*-elimination[35]. Similar behaviour was reported for the dehydration of the isomeric 2-benzyl cyclopentanols in phosphoric acid[36].

As noted by Banthorpe[37] this reaction type has not been studied systematically for acyclic systems. Fragmentary information was obtained for the more complicated cyclic structures. In Banthorpe's opinion, ester and oxonium ion formation with stronger acids probably occur simultaneously or within different ranges of conditions with different substrates. Both these intermediates undergo subsequent uni- or bi-molecular decomposition. Further examples for the ether formation through intermediate esters and carbonium ions are presented by Feuer and Hooz[38].

3. Stereochemistry

The stereochemical course of dehydration reactions in solution have mainly been studied with cyclic alcohols. In an early work Vavon[39] showed that *cis*-2-alkylcyclohexanols dehydrate more easily than their *trans*-isomers. From this result a *trans*-elimination* was suggested as likely. Later, using *cis–trans* isomers of 2-phenylcyclohexanol Price and Karabinos[41] arrived at the same conclusion as Vavon because of the almost exclusive formation of 1-phenylcyclohexene from the *cis*-isomer, whereas the *trans*-isomer seemed to produce mainly 3-phenylcyclohexene. The mechanism of the reaction with the *trans*-isomer, however, is much more complicated, since appreciable ring contraction and isomerization was verified by thorough ^{14}C-tracer studies in phosphoric acid, the amount of 1-phenylcyclohexene also predominating in this case[42, 43]. The product distributions are tabulated in Table 3. Since the two isomeric substrates yield the products in widely differing amounts, it may be concluded that a classical carbonium ion (4) cannot be a

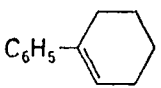
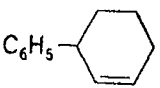
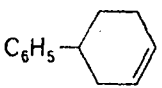
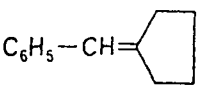
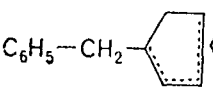
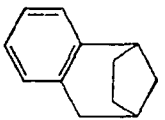


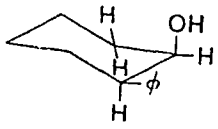
(4)

common intermediate in both reactions. Thus, the participation of an *E*2-like intermediate, at least in the elimination of the elements of water from the *cis*-alcohol, may be suggested. This isomer can achieve a *trans*-planar transition state in conformation (5) with the hydroxyl group axial and the phenyl group equatorial, which is necessary for a *trans*-elimination[44].

* Recently the expressions *anti*- and *syn*-elimination have been proposed as being preferable to *trans*- and *cis*-elimination[40].

TABLE 3. Product distribution in the dehydration of *cis*- and *trans*-2-phenylcyclohexanol in 85% phosphoric acid.

Ref.	$T°$ (C)	Reactant	% Yield					
								
41	250	*cis*	56-62	9-17	—	—	—	—
42			88	2, 4	—	—	—	—
43			97, 4	—	—	—	2, 6	—
41	250	*trans*	10-18	59-68	—	—	—	—
42			21	15		20	32	—
43			20	9	4	17	46	4



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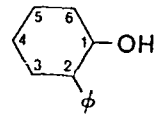
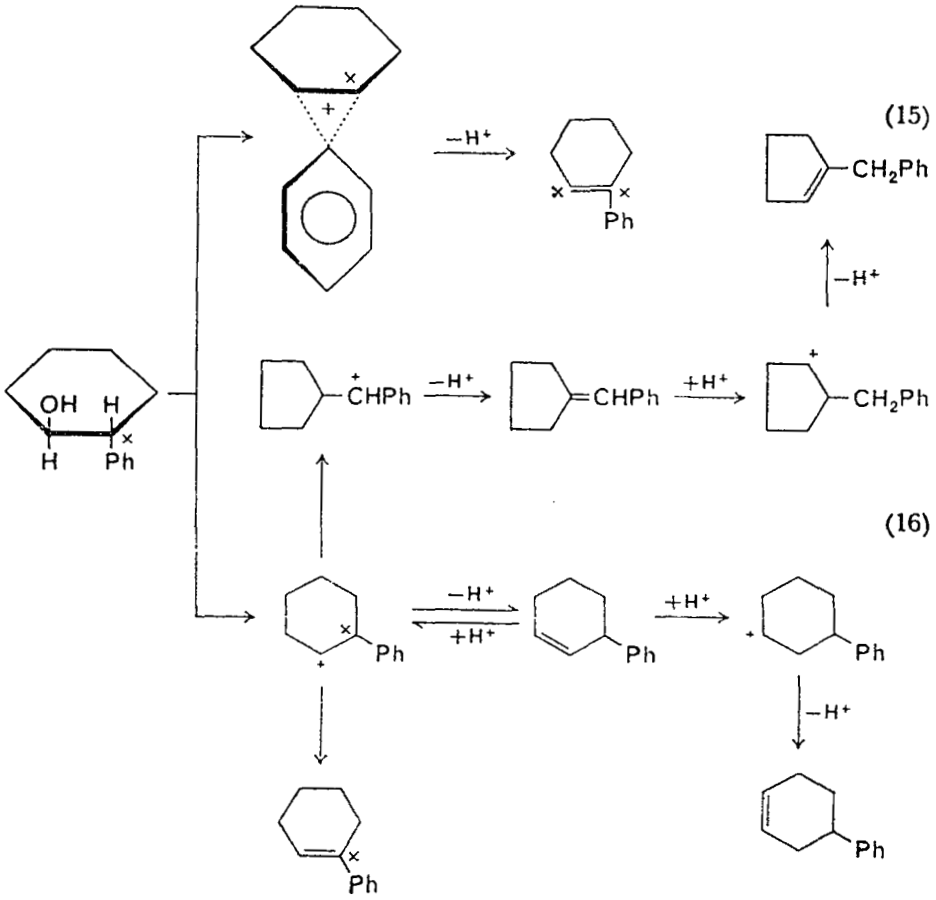


(6)

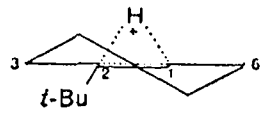
For an *E*2-elimination Hofmann-orientation would be expected rather than the almost exclusively observed Saytzeff-orientation. The suitable *trans*-planar transition state could also be achieved between the hydroxyl group and a β-proton at $C_{(6)}$. (The numbering of C atoms is shown in **6**.) In similar cases in the methyl series both possible products of *trans*-elimination have been observed[43]. The lack of formation of the Hofmann-product may be explained by the phenyl substitution at $C_{(2)}$, which by electron withdrawal favours the acidity of the adjacent proton more than that of the protons at $C_{(6)}$. Assuming the same mechanism for the dehydration of *cis*-2-*t*-butylcyclohexanol one would expect an enhanced formation of the Hofmann-product because of the inductive effect of this group. The only product observed, however, was 1-*t*-butylcyclohexene in 100% yield[45]. Since the substitution of an electron-donating *t*-butyl group at $C_{(2)}$ may favour an *E*1-like reaction intermediate, the exclusive formation of the Saytzeff-product suggests a carbonium ion mechanism. Steric effects of the bulky groups substituted at $C_{(2)}$ may also play a role in the orientation of the elimination products[46]. The explanation given above for the product distribution of *cis*-2-phenylcyclohexanol differs from that of Schaeffer and Collins[42], who include the classical carbonium ion **4** in their scheme.

In *trans*-2-phenyl cyclohexanol a *trans*-planar conformation between the hydroxyl group and either β-proton is precluded and therefore an *E*2-elimination mechanism seems unlikely. Eliel and co-workers[43] assume the observed degree of ring contraction to increase with increasing ionic character of the transition state. Furthermore, with the help of ^{14}C-labelling at $C_{(2)}$ phenyl migration has been found during the elimination of water from the *trans*-alcohol[42]. Thus, the reaction steps in this case may be given by the scheme as shown on the following page by Schaeffer and Collins[42]: It may be pointed out that phenyl migration has also been observed very recently during the dehydration of 3-phenyl-3-methylbutan-2-ol in perchloric and in *p*-toluenesulphonic acid, the Saytzeff-product being formed exclusively[47].

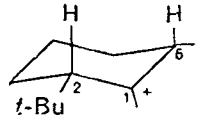


The dehydration of 2-*t*-butylcyclohexanol in phosphoric acid at 130–150°C and in *p*-toluenesulphonic acid at 200°C has been investigated by Goering and co-workers[45]. In this system a conformation with the tertiary butyl group axial is precluded because of steric interactions. The degrees of dehydration of the two isomers were nearly equal, but whereas the *cis*-compound produced 100% 1-*t*-butyl-cyclohexene, the *trans*-isomers produced 60% 1- and 40% 3-olefin. As mentioned above, a concerted mechanism for the dehydration of the *cis*-alcohol can be precluded. The same conclusion is reached for the *trans*-alcohol because of conformational reasons. An *E*1-type elimination is therefore suggested for both isomers. Different reaction intermediates must nevertheless be postulated because of the differing product distributions. A pathway through a bridged carbonium ion **7** is assumed as being the preferred process

in the dehydration of the *cis*- alcohol, whereas in that of the *trans*-alcohol the formation of a classical carbonium ion **8** followed by the loss of an axial proton is postulated. The removal of an axial proton



(7)



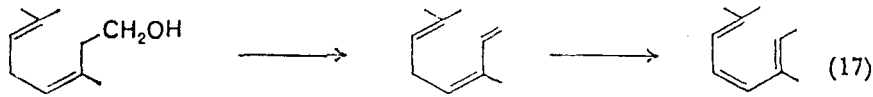
(8)

seems favoured since then the C–H bond of the leaving proton lies in the same plane as the vacant *p*-orbital of the positive carbon $C_{(1)}$. This facilitates *cis*-elimination from *trans*-*t*-butylcyclohexanol, in which the OH group being eliminated is fixed in an equatorial position.

Assuming the formation of an intermediate ester with subsequent *cis*-elimination Banthorpe[48] offers an alternative mechanism for the dehydration of *t*-butyl cyclohexanol.

B. Base-Catalysed Dehydration of Alcohols

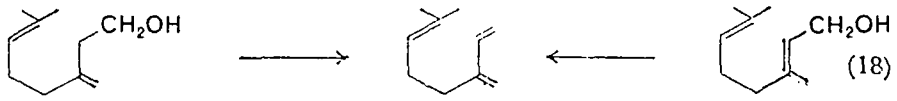
The dehydration of alcohols by concentrated alkaline media is known as a method for the production of dienes[49]. The dehydration can be achieved with alcohols, in which the β-hydrogen is activated by a double bond. Thus, Ohloff[50, 51] succeeded in dehydrating α,β- and β,γ-unsaturated primary alcohols by potassium hydroxide at 200°C, whereas unsaturated tertiary and saturated primary alcohols remained unaltered under these conditions. Ohloff[50] studied the formation of ocimene (**9**) from 3,7-dimethylocta-3,6-



(17)

(9)

dienol (isogeraniol) and of myrcene (**10**) and furthermore the

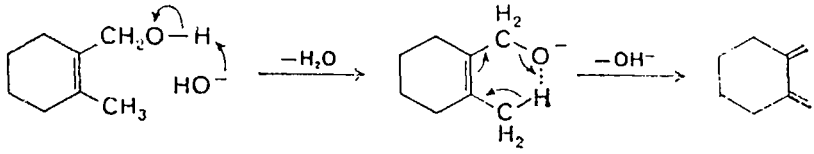


(18)

(10)

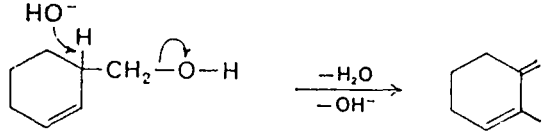
formation of some 1,3-dienes of substituted cyclohexanes and cyclohexenes. The reaction of α,β-unsaturated compounds was suggested

to proceed intramolecularly through a cyclic transition state, as e.g.,



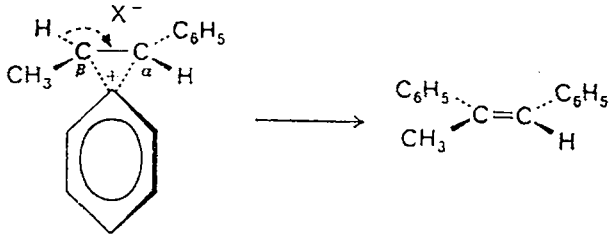
(19)

For the dehydration of β,γ-unsaturated alcohols on the other hand a 1,2-elimination through a polar intermediate was assumed:



(20)

Recently Traynelis and co-workers[52, 53] showed that dimethyl sulphoxide as a solvent facilitates the dehydration of secondary and tertiary benzylic and tertiary aliphatic alcohols and of 1-alkyl-cycloalkanols. The mechanism was elucidated by elimination from *threo*- and *erythro*-1,2-diphenyl-1-propanol. As the olefin composition was the same for both substrates the *trans*-phenonium ion (**11**) was suggested as a common intermediate:



(21)

(11)

This carbonium ion mechanism is supported by the observation of several pinacol rearrangements. Dimethyl sulphoxide appears to serve as a solvent for promoting the ionization of alcohols. Since dimethyl sulphoxide shows unique behaviour in comparison with other bases of similar dielectric properties, one must consider solvating properties other than the extreme dielectric strength ($\varepsilon = 48{\cdot}9$, $\mu = 3{\cdot}95$ D) of this base to be responsible for the dehydration.

Olefinic products, however, are not the only possible products of this reaction type[52, 53]. With smaller amounts of dimethyl sulphoxide present, ether formation predominates over olefin formation and the preparation of cyclic ethers is possible from certain diols.

III. DEHYDRATION IN THE GAS PHASE

A. Homogeneous Dehydration in the Gas Phase

The homogeneous pyrolysis of alcohols has been performed for some straight- and branched-chain aliphatic alcohols. Ethanol, *n*-propanol, *n*-butanol and isopropanol show pyrolytic decomposition at temperatures above 500°C with dehydrogenation products predominating[54–57]. The direct elimination of water plays a minor role in the pyrolysis of these alcohols. On the contrary Kistiakowsky and Schultz[58] found 100% dehydration during pyrolysis of *t*-butanol and *t*-pentanol. Later Barnard[59] reinvestigated the pyrolysis of *t*-butanol. The dehydration proceeds homogeneously and stoichiometrically in the temperature range 487–620°C. The reaction follows a first-order rate law between 20–400 mm Hg at all temperatures. Neither water nor nitric oxide influences the reaction rate. Thus, the reaction must be unimolecular, since otherwise the reaction rate would be affected by the addition of nitric oxide, which is known to be a strong inhibitor of free radical chain reactions. Presumably the elimination of water from *t*-butanol proceeds via a four-centred transition state similar to that suggested for dehydrohalogenation reactions[60, 61].

Alcohols also characteristically split off water under electron impact or photoionization in a mass spectrometer to produce an 'olefin' ion. This phenomenon has been observed with primary alcohols and a 1,2-elimination through a four-membered cyclic intermediate has been proposed[62]. However, no loss of deuterium from *n*-butanol deuterated at C_1, C_2 and C_3 could be detected. Using hexanol-4,4-d_2, -5,5-d_2 and -6,6-d_2 Meyerson and Leitch[63] could show that the hydrogen atom lost as water came from C_4 in more than 90% of the decomposing molecules, a 1,4-elimination thus predominating. From label retentions in secondary decomposition products it must be concluded that elimination of water is accompanied or followed by formation of a new bond between the C atoms from which the elements of water are lost. Similarly, 1,4- and 1,3-elimination processes have been proved to predominate over a 1,2-elimination from cyclohexanol[64]. This behaviour is retained in substituted cyclohexanols. For 4-*t*-butylcyclohexanols a 1,4-elimination induced by photoionization[65] or electron impact[66] has been observed. The elimination of water is more rapid from the *trans*- than from the *cis*-isomer. It must, therefore, be concluded that the *trans*- derivative reacts in the boat form in which the leaving OH-group and the

hydrogen atom in position 4 come closest together. An analogous 1,4-elimination is less likely to occur from the *cis*-isomer. Furthermore, the tertiary butyl group also seems to retain the equatorial conformation in the ionized state.

B. Homogeneous Catalysis of the Dehydration of Alcohols in the Gas Phase

The dehydration of aliphatic alcohols in the gas phase is catalysed by hydrogen halides. Various reactions of this type have been studied systematically by Maccoll and Stimson and co-workers[67–73]. Contrary to the uncatalysed pyrolysis in the presence of hydrogen halides[70] even the decomposition of isopropanol results solely in the elimination of water. The reactions (22) are all homogeneous and

$$\mathrm{ROH} + \mathrm{HX} \longrightarrow \text{olefin} + \mathrm{H_2O} + \mathrm{HX} \qquad (22)$$

stoichiometrical. They follow the rate law

$$-\frac{d[\mathrm{ROH}]}{dt} = k[\mathrm{ROH}][\mathrm{HX}] \qquad (\mathrm{II})$$

in the temperature ranges covered and within several hundreds of mm Hg of partial pressures of both the alcohol and the halide. In Table 4 the frequency factors A and activation energies q are given

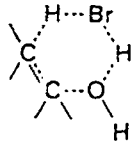
TABLE 4. Arrhenius parameters of the hydrogen halide catalysed dehydration of alcohols.

Alcohol	Catalyst	Temp. range (°C)	$A \times 10^{-12}$ (cm^3/mole sec)	q (kcal/mole)	Ref.
t-BuOH	—	487–620	0·324	54·5	59
t-BuOH	—	487–555	480	65·5	58
t-AmOH	—	487–555	33	60·0	58
i-PrOH	HBr	369–520	1·0	33·2	70
2BuOH	HBr	387–520	5·8	34·9	73
t-BuOH	HCl	328–454	2·0	32·7	69
	HBr	315–425	9·2	30·4	67, 68
t-AmOH	HCl	370–503	6·7	34·0	72
	HBr	308–415	1·0	27·1	71

and compared with the data of the pyrolysis of *t*-butanol and *t*-pentanol. It is clearly seen that the catalysed reactions proceed at temperatures roughly 150°C lower than the pyrolytic dehydration and that the activation energies are reduced by about 20 kcal/mole. The olefinic products from *s*-butanol, i.e., 1-butene, *cis*- and

trans-2-butene, and from *t*-pentanol, i.e., 2-methyl-2-butene, 3- and 1-methyl-1-butene, appear in near equilibrium concentration because of the isomerizing power of the hydrogen halides. The primary product distribution remains therefore unknown.

Cyclohexene, which is an effective inhibitor in chain reactions, does not affect the reaction rates, thus ruling out a free radical chain mechanism even in the case of isopropanol. The elimination of water must therefore proceed unimolecularly. Three possible mechanisms have been discussed by Maccoll and Stimson[68]. They come to the conclusion that the intermediate and rate-determining formation of an alkyl halide, which rapidly decomposes to olefin and hydrogen halide, is unlikely. This suggestion is based on the assumption that formation of the transition state in this case depends merely on the polar conjunction of the alcohol and halide molecule. Since the water molecule is more polar than alcohol molecules, water as a reaction product might destroy such a transition state before reaction could occur. However, no inhibition by water either produced during the reaction or initially added could be verified, so that the intermediate formation of alkyl halides must be excluded. Thus, two possible transition state models remain, namely a six-membered ring **(12)**, which is similar to the transition state assumed for the



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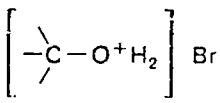


(13)

pyrolysis of esters[74]; or an ion pair **(13)**. During formation of **12** the bromine atom makes a nucleophilic attack at the C_β-proton, the oxygen atom of the alcohol being protonated at the same time. The polarity of hydrogen halides favours such a scheme. Regarding the ion pair **13** formation, the similarity of this heterolytic mechanism with analogous reactions in solution is obvious. No definite decision is possible between these two transition state models, since energy considerations are in neither case convincing. Maccoll and Stimson[68] envisage a continuous range of possible structures between **12** and **13**.

A heterolytic mechanism is also favoured by the influence on reaction rates by the substrate structure and the nature of the hydrogen halide. Generally, methylation at the α-C atom brings about a great increase in dehydration rate, whereas β-methylation

results only in a slight acceleration. Thus, the relative rate for the catalysis by hydrogen bromide is about 60 in the dehydration of *t*-butanol and isopropanol at 420°C [70], and 57 in the case of *t*-pentanol and isopropanol at 400°C [73]. *t*-Pentanol, on the other hand, reacts only 1·6–2 times as fast as *t*-butanol at 360°C [71], and *s*-butanol 1·9 times as fast as isopropanol at 430°C [73]. The influence of the nature of the hydrogen halides is illustrated by the rate ratios 1 : 25 : 200 for the dehydration of *t*-butanol at 320°C with HCl, HBr and HI as catalysts, respectively[67].

C. *Heterogeneous Catalysis of the Dehydration of Alcohols in the Gas Phase*

The gas phase dehydration over solid catalysts is a valuable process for the preparation of olefins and ethers. The direction of the reaction can be governed by proper choice of the catalyst, by selective poisoning of the catalyst surface, by modifying the catalyst's porosity and by selecting favourable temperature ranges. Furthermore, special catalytic properties can be achieved by mixed catalysts. Section 1 of this chapter deals with several classes of dehydration catalysts, a discussion of the selectivity follows in section 2. In the remaining sections the kinetic and mechanistic behaviour for some important and characteristic systems will be presented.

1. Dehydration catalysts

The best investigated dehydration catalysts are the metal oxides. Sulphides, mineral salts and ion exchange resins can also be used. Metals catalyse the dehydration of tertiary alcohols, for which dehydrogenation is impossible without rearrangements of the carbon skeleton. Numerous dehydration catalysts have been tabulated by Sabatier[231, 232] and more recently in a review by Winfield[5]. Therefore in Table 5 only those papers are referred to which appeared after 1960. This table does not claim completeness, but it does give a survey of the important groups of dehydration catalysts.

2. Selectivity of dehydration catalysts

The dehydration of alcohols over various solid catalysts is often accompanied by appreciable degrees of dehydrogenation. The selectivity of these catalysts is a very important, but as yet unsolved problem, though some attempts have been made in correlating selectivity factors and special properties of the solids, such as the width of the forbidden band gap or the differences of electronegativities between anion and cation[233]. Sabatier[231] in his pioneer book

TABLE 5. Dehydration catalysts

Catalysts	Alcohols	Products	Temperature range	References
1. *Oxides:*				
Al_2O_3	C_1–C_5 aliphatic alcs	ethers, olefins	150–400°	75–108
Al_2O_3	long chain aliphatic alcs	olefins	200–400°	109–112
Al_2O_3	cyclohexanol	cyclohexene	250–350°	113–118
Al_2O_3	phenylethanols	styrenes	200°	119
Al_2O_3	2-aminoethanol	piperazine, pyrazine	500°	120
Al_2O_3	furfuryl alcs		220–310°	121
Al_2O_3	unsaturated secondary alcs	dienes	300–320°	122
ThO_2	EtOH	H_2, H_2O + olefin	275–400°	123, 247
ThO_2	*i*-PrOH	propene	165°	107
ThO_2	2-octanol	1-octene	350°	124
ThO_2	RCH(OH)Me	1-olefins	350–450°	125–127
ThO_2	phenols	phenylethers	300–600°	128, 129
ThO_2	decalols	octalins	350°	129a
Cr_2O_3	C_2–C_5 aliphatic alcs	H_2, H_2O + olefins	290–500°	130–132
Fe_2O_3	cyclohexanol *n*-hexanol	cyclohexene various products	100–300°	133
Ga_2O_3	*i*-PrOH	H_2, H_2O + propene	260–320°	134
WO_3, W_2O_5	C_1–C_4 aliphatic alcs	olefins	100–300°	86, 135–139
MoO_2, MoO_3	C_1–C_4 aliphatic alcs	H_2, H_2O + olefins	300–400°	138, 140
TiO_2 (anatas)	*i*-PrOH	H_2, H_2O + propene	280–310°	141
ZrO_2	EtOH	H_2, H_2O + ethylene	300–400°	142
SiO_2	*i*-PrOH	propene		107
NiO	cyclohexanol *n*-hexanol	cyclohexene 1-hexene	100–300°	133
MnO	*t*-BuOH	isobutene	330–380°	143
V_2O_3	EtOH, *i*-PrOH	H_2, H_2O + olefin	450–500°	144
U_3O_8	*i*-PrOH	H_2, H_2O + propene	340–420°	145
Rare earth oxides	C_2–C_4 aliphatic alcs	H_2, H_2O + olefins	320–460°	146–161
Nd_2O_3	cyclic alcs	cyclic olefins	200–500°	162

TABLE 5 (*contd.*)

Catalysts	Alcohols	Products	Temperature range	References
Y_2O_3	EtOH	H_2, H_2O, ethylene + ether	300–340°	163
Sc_2O_3, Y_2O_3	RCH(OH)Me	1-olefins	350–450°	125
2. *Mixed Oxides:*				
SiO_2/Al_2O_3	C_2–C_5 aliphatic alcs	olefins	50–350°	107, 164–171, 182–185
SiO_2/Al_2O_3	long chain alcs	olefins	200–400°	109
SiO_2/Al_2O_3	cyclohexanols	cyclohexenes	350–450°	172
SiO_2/Al_2O_3	unsaturated alcs	dienes	150–300°	122, 173
Cr_2O_3/Al_2O_3	C_3–C_5 aliphatic alcs	H_2, H_2O + olefins	230–320°	174–177
ZnO/Al_2O_3	*i*-PrOH	H_2, H_2O + olefin	280°	178
TiO_2/NiO	*i*-PrOH	propene		179
TiO_2/Fe_2O_3	*i*-PrOH	propene		179
TiO_2/Nd_2O_3	EtOH, *i*-PrOH	H_2, H_2O + olefin		180
Ce_2O_3/La_2O_3	*i*-PrOH	H_2, H_2O + propene	400–500°	181
3. *Zeolites, Molecular Sieves:*				
Mordenite	EtOH	ethylene, ether	250–350°	186, 187
type A	EtOH	ethylene, ether	250–350°	187, 192–194
type X	C_2–C_5 aliphatic alcs	olefins, ethers	240–350°	188–195
type X	long chain and cyclic alcs	olefins	275–300°	196
type Y	C_2–C_4 aliphatic and cyclic alcs	olefins	150–275°	197
cation exchanged zeolites	C_2–C_4 aliphatic alcs	olefins, ethers	240–350°	187, 190–195, 198–200
			140–200°	200a
cation exchanged zeolites	long chain aliphatic and cyclic alcs	olefins	275–300°	196
4. *Sulphides:*				
MoS_2	C_2–C_4 aliphatic alcs	H_2, H_2O + olefins, ethers	230–310°	138, 201–204
MoS_2	cyclohexanol	cyclohexene	260–320°	202
WS_2	C_2–C_4 aliphatic alcs	H_2, H_2O + olefins, ethers	230–310°	138, 201–204

TABLE 5 (*contd.*)

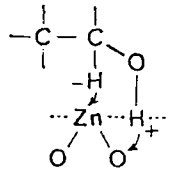
Catalysts	Alcohols	Products	Temperature range	References
WS_2	cyclohexanol	cyclohexene	260–320°	202
WS_2	decanol	decenes		205
5. *Metal Salts:*				
$MgSO_4$	sec. alcohols	olefins		206
$MgSO_4$	C_5–C_{12} alcs	olefins	375°	207–209
$MgSO_4$	cyclohexanol	cyclohexene	375°	208–210
$MgSO_4$/ Na_2SO_4	cyclohexanol	cyclohexene	<400°	211, 212
$CaSO_4$	*s*-BuOH	butenes	270–420°	213
$Ca_3(PO_4)_2$	EtOH	ethylene, ether	370–430°	214
$Ca_3(PO_4)_2$	C_5-alcs	olefins	280–350°	76, 85, 215
$Ca_3(PO_4)_2$	unsaturated alcs	dienes	200–350°	216, 217
$Ca_3(PO_4)_2$	1,4-butanediol	tetrahydrofuran butadiene	260–320° >360°	218
BPO_4	C_2–C_5 aliphatic alcs	olefins	180–450°	76, 84, 85 219
K_3PO_4	2-Me-2-BuOH	olefins	180–450°	84
$ZrO_2 \cdot P_2O_5 \cdot 5H_2O$	C_2–C_5 aliphatic alcs	olefins	100–380°	220, 221
$ZrO_2 \cdot P_2O_5 \cdot 5H_2O$	cyclohexanol	cyclohexene Me-cyclopentene	100–250° 250–400°	221
$AlCl_3$	C_2–C_4 aliphatic alcs	olefins		222
AlF_3	EtOH	ethylene, ether	<500°	223
6. *Ion Exchange Resins:*				
H^+-form	EtOH	ether	120°	224–226
H^+, Li^+, Na^+-form	MeOH, EtOH	ethers	80–120°	227, 227a
H^+-form	C_3–C_{10} aliphatic alcs	olefins, ethers	125–165°	367–370
H^+-form	tertiary alcs	olefins	82°	368
7. *Various Catalysts:*				
active carbon	C_2–C_4 aliphatic alcs	olefins	210–310°	228
α-boron	C_1–C_3 aliphatic alcs	ethers + olefins	275–350°	229
Ni	*t*-BuOH	isobutene	210–360°	230
Ni	C_4–C_5 aliphatic alcs	ethers	150–190°	230a

on catalysis in organic chemistry considered selectivity as an intrinsic property of the solid catalysts. However, activity and selectivity are strongly affected by different modes of preparation[234]. Thus striking difficulties arise in the comparison of various catalysts, especially when data of different research groups must be compared. Nevertheless, some rough correlations could be found, especially on oxide catalysts. Schwab and Schwab-Agallidis[234] showed that the selectivity was changed in favour of dehydrogenation by all preparation methods increasing crystal size and decreasing surface area. In this view the dehydrogenation takes place mainly on the flat surface of the catalyst particles, whereas the dehydration is restricted to the interior of pores, holes or channels, thus being strongly retarded by a decrease in porosity.

By mainly geometrical considerations Eucken[235, 236] and Wicke[237] explained the behaviour of the selectivity factor

$$\left(s = \frac{[H_2]}{[H_2] + [H_2O]}\right)$$

For the dehydrogenation reaction on zinc oxide they postulated a so-called 'Anlagerungsmechanismus', whereby the reaction proceeds via a structure **14**, in which the C–H proton forms a hydride-like bond to a surface metal ion. This is the structural element which



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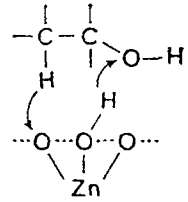


(15)

lends zinc oxide its quasi-metallic dehydrogenation properties. The dehydration on the other hand is explained by means of the hydrogen exchange mechanism, **15**, which proceeds solely on the oxide crystal layer. For the wurtzite lattice of zinc oxide the number of exposed metal ions is equal to the number of exposed oxygen ions. Thus, one might expect a relative selectivity of 0·5. Experimentally, however, almost 100% dehydrogenation is found with zinc oxide. This discrepancy is explained by assuming a poisoning effect of the dehydration centres by water. From these geometrical considerations it was suggested, as a general rule, that metal ions preferentially exposed in the surface are active sites for the dehydrogenation,

whereas the dehydration proceeds on oxide-faces, i.e., oxides in which the ionic radius of the cation is large compared to that of the oxygen ion, should favour dehydrogenation. This correlation could be roughly verified. E.g., calcium oxide which has the NaCl lattice, exposes crystal faces in which Ca^{2+}- and O^{2-}-ions alternate, and is a typical dehydrogenation catalyst. In the surface of the corundum lattice of chromia, however, the oxygen ions predominate, thus making chromia, if appropriately prepared, an effective dehydration catalyst.

Eucken and Heuer[236] made the additional demand that the surface ions or atoms should exhibit high polarity in an effective dehydrogenating catalyst. A different explanation of selectivity has been given by Szabó and co-workers[238, 238a]. They suggest that the dehydrogenation properties increase with an increase in the ionic character of the metal–oxygen bonds and conversely, the dehydrating properties increase with an increase in covalent bond character. Similarly Winfield[239] states two criteria for classifying oxide catalysts: (1) an oxide whose metal ion readily changes its valency state catalyses the dehydrogenation; (2) an oxide with appreciable π-bonding between oxygen and metal is a good dehydration catalyst. Thus the following sequence of catalysts has been presented by Szabó and co-workers[238]:

$$\underset{\text{Dehydration}}{\overset{\text{Dehydrogenation}}{\longleftrightarrow}}$$

$$CaO \quad MgO \quad ZnO \quad FeO \; Fe_2O_3 \quad Cr_2O_3 \quad TiO_2 \quad Al_2O_3 \quad SiO_2 \quad WO_3$$

This suggestion is favoured by the fact that metal salts such as $ZnSO_4$, Zn_2PO_7, $CaSO_4$, $Ca_2(PO_4)_2$ and $MgSO_4$, in which the oxygens are bound mainly covalently, show appreciable dehydrating properties. It must, however, be emphasized that the bond character cannot be the sole factor determining the selectivity. E.g., zinc oxide, ferric oxide and chromia exhibit the same ionic character, i.e., 59% as calculated from the differences of electronegativities by means of Pauling's formula[240]. However, zinc oxide is mainly a dehydrogenation catalyst, whereas ferric oxide and chromia mainly catalyse the dehydration. Hence, additional factors which may be geometrical in nature and may depend on the crystal structure of the solid catalyst, must play a role.

The need for water or surface hydroxyl groups for a catalyst to be active in dehydration has been proved, since a freshly heated oxide catalyst always shows a distinct induction period with respect to its dehydration activity[241–243]. This observation implies the active

participation of the surface hydroxyl groups in the dehydration as proton or hydrogen-bridge donors. The acidity of these hydroxyl protons may govern the reaction mechanism of the olefin formation favouring either the preference of an *E*1- or an *E*2-like elimination. This problem will be discussed later in the chapter.

Another geometrical explanation of the selectivity has been given by Balandin[244, 245] on the grounds of the structure correspondence principle of the multiplet theory. Dehydrogenation as well as dehydration are thought to proceed on an active surface unit consisting of two neighbouring surface atoms, i.e., a duplet. The reaction for which the duplet has the proper spacing will be favoured, or, if two kinds of duplets exist both reactions may be observed. The dehydrogenation can be represented by the following equation, in which the duplet atoms are drawn as dots:

Hydrogen atoms of the methylene and of the hydroxyl group are attracted by one atom of the duplet, the remaining atoms of the molecule by the other. Thus the rupture of a C–H and an O–H bond and formation of a H–H bond and a C–O double bond is assisted. Similarly, the dehydration is explained by attraction of a methyl proton and the hydroxyl group by one duplet atom, the remaining atoms of the alcohol molecule being drawn to the other:

It can be assumed that the geometry of the duplets, which are active for the two reaction types must be different, thus governing the selectivity by their relative occurrence in the catalyst surface. The multiplet theory allows the prediction of selectivity of dehydrogenation and dehydration. In this case the bond strengths of the various reacting atoms attached to the catalyst surface must be known to calculate so-called energy barriers whose relative values determine the selectivity. These parameters have been tabulated for numerous catalysts by Balandin and co-workers[244, 246].

Most of the investigations of the selectivity of dehydrogenation and dehydration were restricted to the decomposition of ethanol or isopropanol at relatively high temperatures. The possible ether

formation at low temperatures was therefore overlooked although it is well known that various aliphatic alcohols and benzyl alcohol produce ethers under dehydrating conditions over alumina[5, 98, 115, 231, 232, 247]. Thoria on the other hand catalyses only the olefin formation even from ethanol at low temperatures[247, 253]. Systematic studies have only been performed for the dehydration on alumina[115]. A rapid formation of surface alkoxide species during the adsorption of several alcohols on alumina has been found by many authors. Thus, the formation of the corresponding surface alkoxide groups is certain for methanol[248], ethanol[248–251], *n*-propanol[250, 251], isopropanol[250], *n*-butanol[251] and benzyl alcohol[115]. During the adsorption of *t*-butanol, isobutanol and cyclohexanol[115] and of methyl cyclohexanols[251a] no such surface compounds could be detected. A close inspection of the experimental facts shows the parallelism that all those alcohols which form a surface alkoxide species on adsorption tend to form ethers at low temperatures. Alcohols which do not show alkoxide formation are purely olefin forming. Furthermore, the thermal stability of aluminium alkoxides[252] is greatest for those derivatives whose corresponding alcohols prefer the ether formation. It was concluded that the occurrence and the thermal stability of the intermediate surface alkoxides are the factors controlling the selectivity over alumina. The active participation of the alkoxide species in the ether formation from ethanol could very recently be proved since the rate of this reaction step has been shown to be directly proportional to the surface concentration of the alkoxide[279]. It was proposed that in ether formation a surface alcoholate group reacts with an alcohol molecule in the adsorbed phase by an electrophilic attack on the hydroxyl oxygen, while the monomolecular olefin formation goes through an *E*1- or *E*2-like reaction intermediate without participation of an alkoxide species. The details of these concepts will be discussed in the section on kinetics and mechanism. The selectivity of ether and ethylene formation from ethanol over silica–alumina catalysts has been explained similarly[254].

If the controlling factors are the same with other catalysts, only those oxide catalysts which react with the alcohol to form a thermally stable surface alkoxide should be active in ether formation. The selective formation of olefin over thoria[247] should therefore be brought about by the lack of this surface compound. No paper on this problem has been published up to now, but it is being studied in the author's laboratory at the moment.

Ross and Bennett[255], studying the dehydration of ethanol on alumina, observed a change of the selectivity in favour of the ether formation with increasing sodium content in the catalyst surface. They assume an exchange of hydroxyl protons by sodium ions, accompanied by a decrease of the overall activity. The increased ether formation is explained by the reaction of two ethanol molecules, one of which is adsorbed on a sodium ion site, the other being held by van der Waals forces. In the light of the above-mentioned selectivity-controlling alkoxide formation, one could alternately propose an increased alkoxide concentration on the sodium containing surface.

3. Influence of structural and surface properties

The influence of the conditions of their preparation on the activity of catalysts is well known. Systematic studies have in particular been published regarding active alumina. An increase in activation energies of the dehydration of isopropanol with an increase of preheating temperature and time was observed by Fricke and Wessing[256]. Differences of the real structure, i.e., structure of the primary particles, lattice defects, structure and dimensions of the secondary particles, as well as the water content of the samples were suggested to contribute to this effect. Similarly, changes in activation energy and frequency factor depending on the preparation conditions of various catalysts were reported by Schwab and Schwab-Agallidis[234], but no direct relationship between these conditions and the activation energies were found. The dependence of the dehydration activity of aluminas on the preheating temperature has often been related to the resulting differences in the water content or the number of surface hydroxyl groups[241–243]. Furthermore, the modes of precipitation and ageing of the hydroxides strongly determine the catalytic properties of the resulting oxides[257–260]. In particular, it has been shown by Rödel and Sonntag[259, 260], that the pH-value and the temperature of precipitation influence the crystal structure and the surface area. For the dehydration of methanol, ethanol and *n*-propanol on aluminas with surface areas ranging from 2·72 to 221 m^2/g Wade and co-workers[261, 262] describe a dependence of the specific activity on the surface area or particle size. In this investigation amorphous samples as well as γ- and α-aluminas were studied. The maximum activity found for the γ-modifications becomes quite understandable, if it is recognized that first of all the spinel structure of γ- or η-alumina always shows higher activity than

α-alumina[236, 237, 263] and that secondly, as Weis[263] and Steinike[265] proved, catalyst samples with the highest degree of crystallinity have the highest specific activity. Weis furthermore stated the predominant importance of the degree of crystallinity over the secondary structure[264]. For samples of similar primary and secondary structures the surface structure, and in particular the distribution and the properties of the surface hydroxyl groups, determine the dehydrating power of the catalyst. Simon and co-workers[266] found that the structure and pore size distribution in the system of micropores is strongly affected by the starting hydroxide (bayerite or böhmite) and the subsequent preparation conditions of the alumina.

Treibmann and Simon[267] investigated the structures of adsorbed isopropanol on aluminas prepared by various methods by means of infrared spectroscopy. They also found that the surface area alone cannot determine the dehydration activity and that the spinel structure and a high degree of crystallinity are necessary for an alumina to be active. While the formation of an isopropylate species was observed during adsorption on every alumina catalyst, no direct relationship was found between catalytic activity with respect to the olefin formation and the appearance of this surface compound. Therefore an olefin formation through dissociation of surface alkoxide groups as sometimes suggested[268, 268a, 268b] is ruled out. These findings are furthermore in favour of the explanation of the selectivity of ether and olefin formation given in the preceding section. A carboxylate structure, which was also found during adsorption of methanol and ethanol[248], of *n*-propanol and *n*-butanol[251, 269] and of isobutanol and benzyl alcohol[115] on alumina, is assumed to inhibit the dehydration rather than to be a reaction intermediate.

The question arises, what kinds of surface sites on alumina, and in general on dehydration catalysts, exist and which of them are catalytically 'active sites'. Regarding alumina, it can be stated from the studies of Peri[270] and of Spannheimer and Knözinger[271] that the (100) crystal face is preferentially exposed and that this surface is partially hydroxylated under catalytical conditions. Thus three kinds of surface sites must exist, namely oxygen ions, hydroxyl groups and incompletely coordinated aluminium ions, which may act as Lewis acid centres. The necessity of the existence of hydroxyl groups on the surface of active aluminas has been stated. Unmodified, high purity aluminas usually give rise to a high degree of isomerization of the primarily formed olefinic products[6, 164, 167, 169, 272]. By a thorough study of the surface properties of aluminas Pines and

Haag[272] could explain the isomerization activity by the presence of strongly acidic Lewis sites. The secondary isomerization of olefins can indeed be suppressed by selective poisoning of the alumina by ammonia[273], pyridine[6, 275] and piperidine[6, 274]; these bases preferentially block the Lewis acid sites. The activity for dehydration to olefins on these modified catalysts on the other hand remains nearly unchanged[276, 277], indicating that the Lewis acid sites apparently do not take part as active centres in the olefin formation from alcohols. Krylov[342, 343] and recently Bremer and Steinberg[344, 344a] on the other hand postulate the active participation of the Lewis acid sites. Using an aluminium trihydroxide (bayerite) as catalyst, which exposes solely hydroxyl groups at the surface, complete inactivity for dehydration was found[277, 278]. Therefore other surface sites must also take part in the olefin formation. This second kind of sites must be the oxygen ions. Pines and co-workers[6, 273] postulate acidic (A) and basic (B) sites as taking part in the reaction. The participation of basic sites has recently been proved by poisoning experiments with tetracyanoethylene[386]. The hydroxyl groups of the alumina surface, however, exhibit only very weak proton or Brønsted acidity[271, 272]. Since H-bond donors and acceptors as active sites must be present on all oxide surfaces and also on metal sulphates, phosphates and sulphides and in the SO_3H groups of ion exchange resins, one might postulate the general necessity for the existence of these two kinds of sites on the surface of an active dehydration catalyst.

A strong decrease in the rate of formation of diethyl ether from ethanol by pyridine poisoning of alumina[277, 279] and silica–alumina[254] has been observed, indicating that the bimolecular ether formation demands incompletely coordinated aluminum ions or Lewis acid sites as active sites in addition to the H-bond donors and acceptors. This result correlates well with the postulate of the ether formation going through an intermediate surface alkoxide stage, since the formation of an alkoxide necessarily proceeds with participation of the incompletely coordinated aluminium ions[250, 251].

As for the participation of surface OH groups, the question arises whether their acidity influences the dehydration activity. Dzisko and co-workers[280, 281] used silica–alumina, silica–zirconia and silica–magnesia catalysts, whose surface acidity was determined by the indicator method and the number of acid sites by *n*-butylamine adsorption[282]. The rate constants of the dehydration of isopropanol on these catalysts for one milliequivalent of acid centres was shown to change symbatically with the acidity of the catalyst. Most of the

methods for the determination of surface acidities described in the literature suffer from not being able to distinguish between Brønsted and Lewis acidity. Only the thermometric titration with dioxan[283] measures the Lewis acidity alone. A further difficulty in the comparison of catalytic activities and surface acid properties arises from the fact that acidities are determined in solution at room temperature, whereas the reactions proceed in the gas phase at elevated temperatures. Pohl and Rebentisch[284] therefore measured the surface acidity of various alumina samples by means of ammonia adsorption at 250°C from the gas phase and obtained good correlation between these acidity data and the catalytic activity observed for the dehydration of isopropanol in the gas phase at 275°C. Bremer and co-workers[174], using chromia–alumina catalysts of varying composition, were able to determine the influence of acid centres on the pre-exponential factor and the activation energy of the dehydration of isopropanol. The number of OH groups was determined by reaction with thionyl chloride, as described by Böhm and Schneider[284a], whereas the acidity was measured using the method of Münzing and co-workers[285b]. In this method the oxide is suspended in dimethylformamide and titrated with potassium methylate against *o*-nitroaniline as indicator. As shown in Figure 3, the logarithms of the pre-exponential factor and the number of OH groups are linearly related and activation energy and acidity change symbatically. Since the catalytic reaction may change the initial surface properties of the catalyst, the two quantities of interest for this correlation were measured after the catalytic activity had been determined.

In a number of investigations[285–292] of Russian research groups the influence of radioactive irradiation during catalysis and the influence of pre-irradiation with slow neutrons and γ-rays was studied. The dehydration of cyclohexanol and long chain normal aliphatic alcohols (C_5–C_{12}) on salt catalysts, such as the sulphates of sodium and magnesium and calcium chloride or phosphate, was thereby investigated. The irradiation was achieved by introducing radioactive isotopes such as ^{35}S, ^{45}Ca or ^{32}P into the catalysts. Generally a strong increase of dehydration activity was observed, and was explained by the ionizing effect of the radiation on the catalyst, which causes the surface to have some activated positively charged centres. These centres are assumed to enhance its capacity for adsorbing OH groups and thus favour carbonium ion formation from the alcohols. However, Krohn and Smith[293] relate the increase

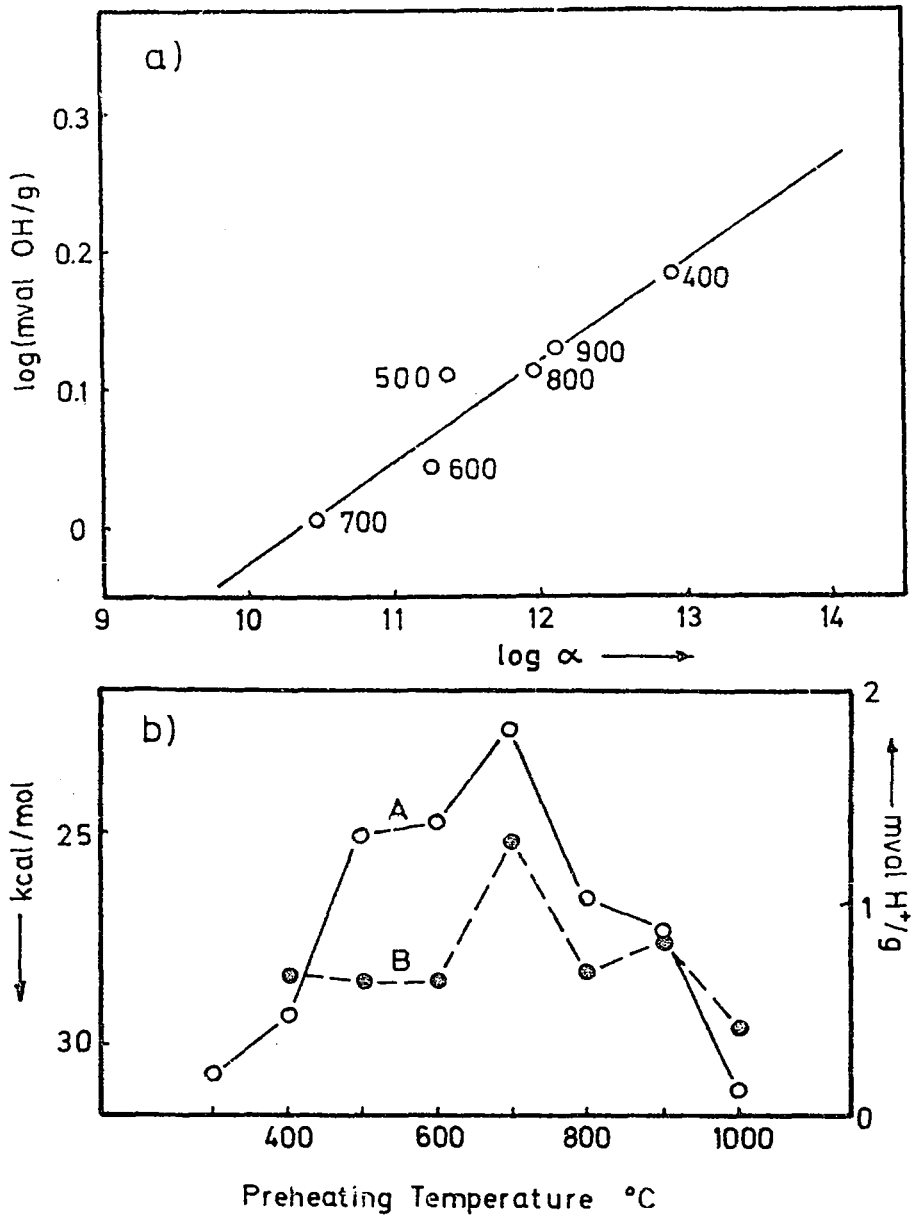
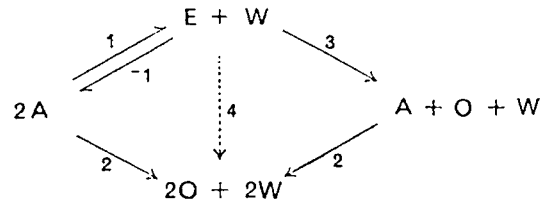


FIGURE 3. (a) Dependence of the pre-exponential factor of the dehydration of isopropanol on Al_2O_3/Cr_2O_3 (7M% Cr_2O_3) on the number of OH groups. The numbers are the pre-heating temperatures. (b) Activation energy of the dehydration of isopropanol on Al_2O_3/Cr_2O_3 (7M% Cr_2O_3), curve A, and surface acidity, curve B, as a function of the pre-heating temperature. (Taken from Reference 174 by permission of the copyright owner.)

in activity to chemical changes of the catalyst surface, i.e., the conversion of sulphur atoms to chlorine during the radioactive decay. In another work the same authors[294] even found a decrease in dehydration activity for the radioactive catalysts when compared on a unit surface area basis.

4. Kinetic investigations and reaction mechanisms

a. The reaction scheme. For a long time the question was subject to controversy whether olefins and ethers which are observed as dehydration products on various catalysts are formed by parallel, consecutive or parallel-consecutive steps. The most extensive work on this problem has been published on the ethanol–alumina system. In early publications consecutive[295–297] and parallel schemes[298–301] were discussed. There were, however, some findings which were not consistent with either of the two schemes, i.e., some aliphatic alcohols of low carbon number at low temperatures form ether exclusively and at higher temperatures the induction period, characteristic for consecutive reactions, is missing in the conversion isotherms for olefin (cf Figure 4a, b). Balaceanu and Jungers[247] therefore proposed a parallel-consecutive scheme which now is generally accepted, and which may be written as follows:



(23)

A, E, W and O representing alcohol, ether, water and olefin, respectively. This scheme was later proved by thorough kinetic analysis[88, 89] and by the use of ^{14}C-labelled ethanol[302, 303]. The primary ether formation (steps 1/–1) may be an equilibrium reaction, whereas for all the other steps the equilibrium is far to the right[304] under conditions normally used. The secondary ether decomposition generally goes through step 3 as shown by the direct decomposition of diethyl ether[88, 98]. At higher temperatures, however, step 4 cannot be excluded. Isagulyants and co-workers[302] assume this step even at low temperatures.

While methanol[98] and benzyl alcohol[305] are dehydrated only bimolecularly to the corresponding ethers, the reaction scheme (23) holds well with unbranched aliphatic alcohols having more than two

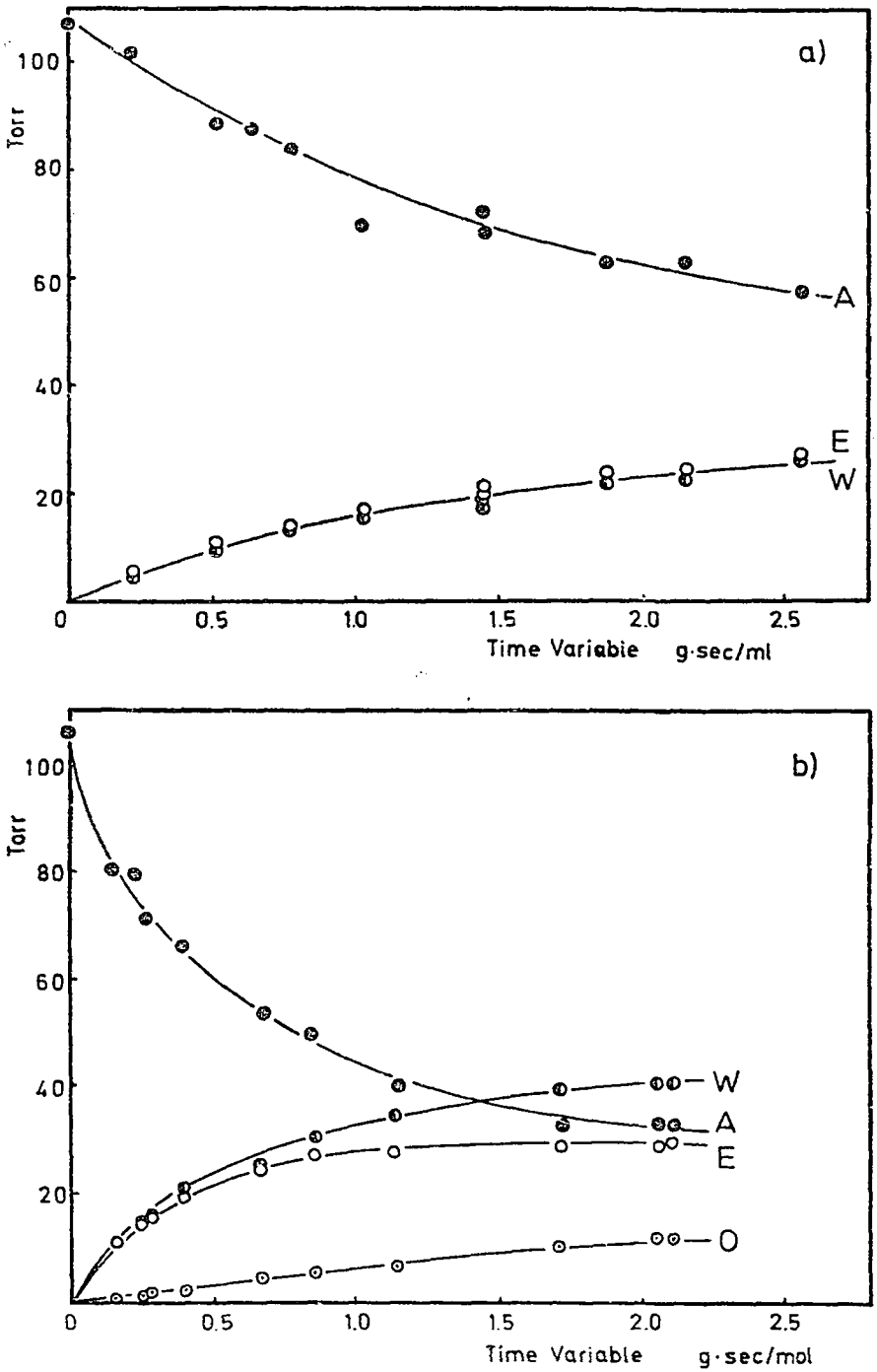


FIGURE 4. (a) and (b). Conversion isotherms for the dehydration of ethanol on alumina at 211°C (Figure 4a) and 256°C (Figure 4b). A = alcohol. E = ether, W = water, O = olefin. (Taken from Reference 98 by permission of the copyright owner.)

carbon atoms. This has been shown for the dehydration of alcohols up to *n*-hexanol by Knözinger and Köhne[98] and for the dehydration of dodecanol by Langer and Walker[306]. The temperature ranges within which only ether formation can be observed decrease with increasing chain length. Thus with *n*-butanol the respective reaction steps (1), (2) and (4) proceed simultaneously even at the lowest possible temperatures. Di-*n*-butyl ether and mainly 1-butene (80%) were also found as reaction products by Isagulyants and co-workers[307] when using ^{14}C-labelled *n*-butanol as substrate. Some mixed ether was detected by the simultaneous dehydration of *s*-butanol and *n*-butanol. Other alcohols such as isopropanol, isobutanol and *t*-butanol have also been investigated[98]. The dehydration of isopropanol results in only small amounts of isopropyl ether with simultaneous formation of propylene. On dehydration the three butanols form only olefins which by secondary isomerization can then give the thermodynamically stable isomer composition. While on dehydration *n*-butanol mainly forms 1-butene as a primary olefinic product, the dehydration of *s*-butanol yields high relative concentrations of the 2-butenes with *cis*-2-butene always kinetically preferred to *trans*-2-butene[308, 338, 339] (cf section III.C.4.b.β).

b. Dehydration of alcohols on alumina. α) *Early mechanisms*: In early investigations on the dehydration of ethanol and isopropanol, an oxonium–carbonium ion mechanism has been postulated by various authors[309–312]. The dehydration equilibria were written by Brey and Krieger[310] as follows, with the carbonium ion $C_2H_5^+$ as a common intermediate:

$$\begin{array}{ccccc} & & C_2H_5OC_2H_5 & & \\ & & \uparrow\downarrow +C_2H_5OH-H^+ & & \\ C_2H_5OH & \underset{}{\overset{-OH^-}{\rightleftharpoons}} & C_2H_5^+ & \overset{-H^+}{\rightleftharpoons} & C_2H_4 \end{array} \qquad (24)$$

These authors assume the removal of a proton from a methyl group to be the rate-determining step in the dehydration of ethanol on alumina. This view, however, disagrees with the concept of a carbonium ion mechanism since in this case the formation of the carbonium ion is rate-determining. Further details of carbonium ion mechanisms are discussed by Winfield[5].

Regarding the necessary presence of water or hydroxyl groups for a catalyst to be active in dehydration (cf section III.C.3) and apply-

ing the principle of least motion Eucken and Wicke[242, 313, 314] proposed a so-called hydrogen exchange mechanism (cf section III.C.2). In this, the substrate is assumed to be adsorbed in a structure which approximates the structure of the reaction products as far as possible. It will be shown later that a hydrogen exchange with the active surface can take place with a carbonium ion mechanism and also with concerted mechanisms.

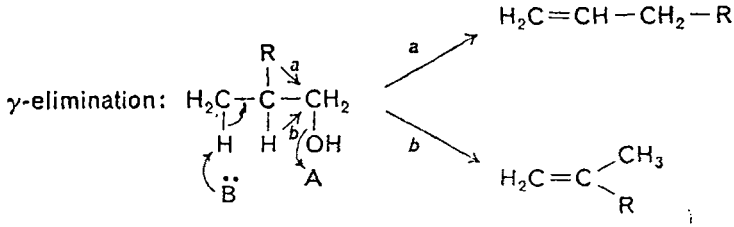
Contrary to ionic mechanisms, Senderens[315] and Ipatieff[316] and later Topchieva, Yun-Pin and Smirnova[268], postulated a covalently bonded adsorption complex in the form of a surface alkoxide. Olefins should be formed by dissociation of this surface compound whereas ether formation is brought about by condensation of two neighbouring surface alkoxide groups. Heiba and Landis[317] tried to prove this type of alkoxide mechanism by a comparison of the product distribution of the dehydration of various alcohols with that of the pyrolytic decomposition of the respective alcoholates. The mechanistic conclusions, however, seem questionable since primary products could hardly be detected at reaction temperatures above 300°C. Furthermore, some evidence has been found which rules out the active participation of surface alkoxide species in the olefin formation (cf section III.C.3).

A radical mechanism was proposed by Vasserberg[323]. Since, however, metal oxide surfaces generally show highly polar properties a dehydration of alcohols through radical intermediates seems unlikely.

Some authors discussed the dehydration as well as the dehydrogenation of alcohols in the light of the electronic theory of heterogeneous catalysis. Thus Volkenshtein[318, 319] and Garner[320] point out that the rate-determining step in the dehydrogenation is an electron acceptor step, in the dehydration, on the contrary, a donor step. Hauffe[321] on the other hand suggests the desorption of acetone as the rate-determining donor step in the dehydrogenation of isopropanol. It seems, however, questionable whether the dehydration of alcohols can be considered to be a donor–acceptor reaction since during the course of the dehydration presumably not single electrons but electron pairs are displaced. Recently Meye[322] found that neither *p*-type nor *n*-type doping of α-Al_2O_3 had a particular influence on reaction rate or activation energy of the dehydration of methanol to dimethyl ether.

β) Stereochemical considerations: Regarding the olefin formation on alumina the question arises whether a simple β-elimination takes

place or whether other elimination routes contribute to the overall reaction. Schwab and co-workers[324, 325], by dehydrating CH_3CD_2OH on alumina in the temperature range 380–430°C found 75% β-elimination and 25% α-elimination. Similarly, the contribution of α-elimination could be observed during the formation of the 2-butenes from $C_2H_5CDOHCH_3$ on calcium sulphate, whereas 1-butene in this case results from a pure β-elimination[213]. As shown by Herling and Pines[327] the dehydration of isobutanol and 2-phenyl-1-propanol at 350°C yields the normal olefins besides isobutene and α-methylstyrene, respectively. Since the formation of *n*-olefins is even enhanced on only weakly acidic alumina catalysts a classical carbonium ion mechanism cannot be responsible for this observation. The authors are thus led to the assumption of the hydroxyl group being removed by an acid site A and of the proton by basic site B. The removal of the elements of water is aided by the anchimeric assistance of neighbouring groups, such as hydrogen or phenyl, and followed by a migration of the respective group. This view may be expressed by the following equations:



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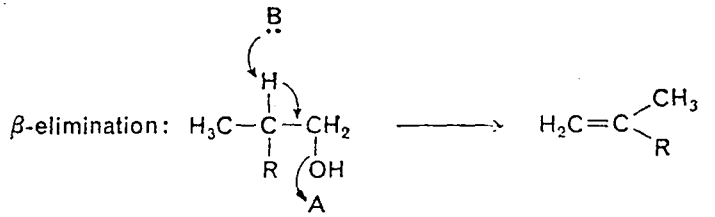
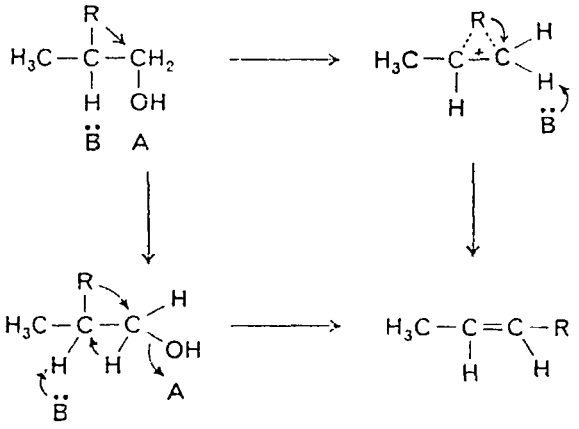


(26)

For the formation of the 2-butenes these authors postulate a non-classical carbonium ion (equation 27).

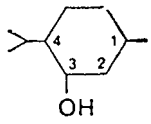
It is not clear which of the two possible pathways is really favoured. The isotope distribution in the dehydration products from 2-phenyl-1-propanol-1-^{14}C lends further support to these stereochemical proposals[328]. Similarly, studies of the ^{14}C-distribution in the dehydration products from labelled substrates over alumina at 348°C showed phenyl migration to occur during the dehydration



(27)

of 2-phenylethanol-1-^{14}C to varying extents between 1·1 and 8·3%, and in the case of 2-*p*-tolylethanol-1-^{14}C between 8·9 and 18·0%[328a]. A maximum of 2·2% γ-hydrogen participation and of 0·3% methyl migration accompanied the dehydration of 1-propanol over alumina at 345°C as evidenced by the ^{14}C-distribution in the propylene formed from 1-propanol-1-^{14}C [328b]. On the other hand, on a γ-alumina sample of different catalytic properties, pure β-elimination from isobutanol $(CH_3)_2CDCH_2OH$ has recently been observed[326] at temperatures between 150–300°C. Since the neopentyl group possesses no β-protons, a γ-elimination with subsequent methyl migration must occur on dehydration. This was confirmed for the dehydration of neopentyl alcohol by the detection of 1,1-dimethylcyclopropane as a product[274]. Analogous results were obtained with 3,3-dimethyl-2-butanol and 3,3-dimethyl-2-pentanol as substrates[274].

As in solutions (cf section II.A.3), *trans*-elimination through a *trans*-planar transition state seems to be preferred also on heterogeneous catalysts. Much information on this problem is obtained by the choice of model substrate alcohols of suitable structure. Thus the dehydration of menthol yields mainly 2-menthene, whereas from neomenthol, 3-menthene is formed preferentially[329]. Both these results suggest a *trans*-elimination of the elements of water. The statistical product distribution in the dehydration of menthol would be 2- and 3-menthene in a 2 : 1 ratio. On the other hand, if a *trans*-planar transition state is required, only the formation of 2-menthene should be observed, since an axial position of the hydroxyl group with a hydrogen in *trans*-position is only achieved with the hydrogen attached to $C_{(2)}$ (see structure on the following page).



The more stable original chair conformation of menthol with the equatorial OH group must therefore flip into the favourable conformation with the OH group axial. Neomenthol on the contrary in its most stable conformation bears the OH group in axial position with β-hydrogens in *trans*-position present both at $C_{(2)}$ and $C_{(3)}$. 2-menthene and 3-menthene can therefore both be formed through *trans*-elimination, with the thermodynamically more stable 3-menthene formed in preference. Since neomenthol is in the conformation required for *trans*-elimination, its dehydration proceeds faster than that of menthol under comparable conditions.

The results of Kochloefl and co-workers[330] for the dehydration of alkylcyclohexanols on alumina also fit *trans*-elimination[331] as does also the product distribution from the dehydration of the four stereoisomeric 1-decalols studied by Schappell and Pines[332]. Similarly *trans*-elimination was shown to be the preferred mode of dehydration using the stereoisomers of 2-alkyl-, 2-phenyl-, 3-*t*-butylcyclohexanols as model substances[332a]. Variances in product distributions from these reactions with the position, size and nature of the group suggested that steric and polar factors play a role in determining the product distribution. The stereochemistry of the dehydration of 1,4-cyclohexanediols[333], 2-*endo*- and 2-*exo*-bornanol[334] and of *endo*- and *exo*-norbornanol[334] has also been studied and the results have been summarized by Pines and Manassen[6]. All these reactions are claimed to proceed in a concerted way, the hydroxyl group of the alcohol being attracted by an acidic site and the proton being removed by a basic site.

For the dehydration of aliphatic alcohols the *trans*-elimination is also the preferred stereochemical course on alumina[6]. Hall[335] used the diastereomeric alcohols *d,l-erythro*- and *d,l-threo*-2-butanol-3-*d* as substrates, and found that their catalytic dehydration over alumina at 200°C proceeds in a nearly stereospecific fashion. The product analysis agreed with *trans*-elimination, which was further supported by the ^{14}C tracer studies of Pines and Herling[328]. Generally speaking, *trans*-elimination clearly predominates when dehydration proceeds by β-elimination.

The explanation of *trans*-elimination on a solid surface is a matter of controversy. Schwab and Schwab-Agallidis[234] postulated on the

grounds of selectivity studies (cf section III.C.4) that the dehydration should proceed in pores of molecular dimensions and in crevices and channels of the catalyst. This idea was taken over by Pines and co-workers[6, 329] with the assumption that the active acidic and basic sites were located at opposite walls of the cavities. This suggestion, however, seems questionable since the dehydrohalogenation of halogenated hydrocarbons on nonporous salt catalysts was also found to proceed by *trans*-elimination[336, 337]. From the occurrence of cyclic olefins in the dehydration of neopentyl type alcohols Pines and co-workers[274] as an alternative assume a non-classical carbonium ion intermediate with a mobile proton being lost to the same surface that also attracts the OH group.

Figure 5 shows the olefin distribution of the dehydration of

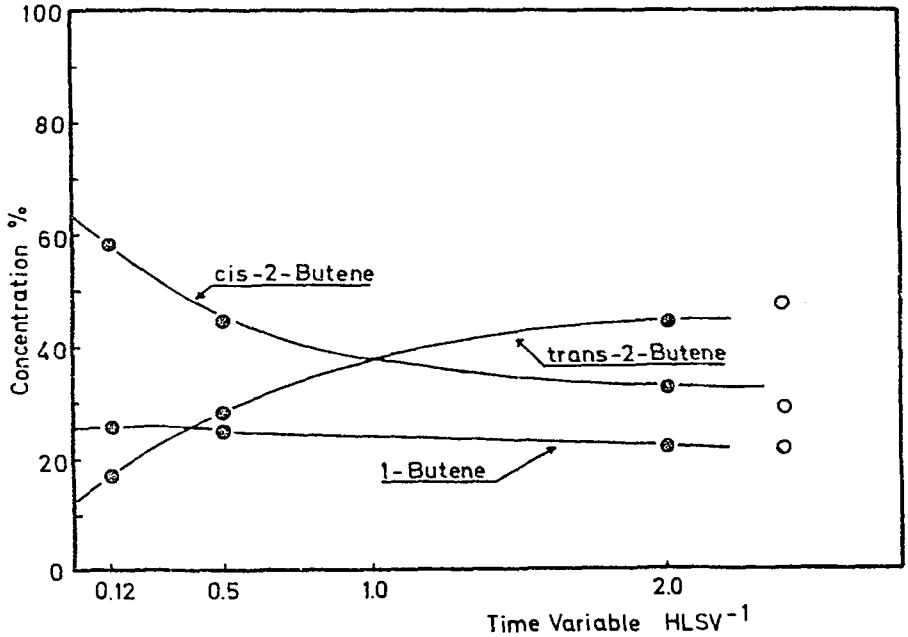
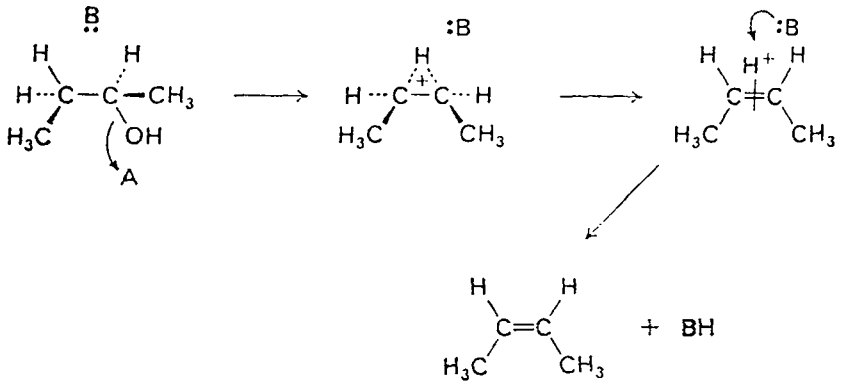


FIGURE 5. Distribution of butene as a function of contact time: 2-butanol over Al_2O_3 at 350°C. ○ Thermodynamic equilibrium. HLSV = Hourly Liquid Space Velocity. (Taken from Reference 339 by permission of the copyright owner.)

s-butanol on alumina. Thermodynamically *trans*-2-butene is the more stable isomer, but *cis*-2-butene as a primary product is being kinetically preferred. A *cis*/*trans* ratio of about 10 : 1 in the primary dehydration products of *s*-butanol at low temperatures (190°C)—only the 2-butenes being formed—has recently been found[338]. Similar

predominance of the *cis*- over the *trans*-olefin has been observed during the dehydration of 2- and 3-pentanol[85, 339]. The primary product distribution in these investigations has been determined either by extrapolation to zero contact time[339] or by preventing secondary isomerization reactions by poisoning with alkali[80, 83, 85], organic bases and ammonia[273, 274]. Such *cis*-preference also occurred in the dehydration of *s*-butanol in acid solution (cf section II.A.2). Pines and Haag[339] propose the same explanation for this phenomenon on solid catalyst surfaces as that given for reactions in solution by Manassen and Klein[25], i.e., formation of a proton–olefin complex. Since *cis*–π-complexes are more stable than *trans*–π-complexes the unusually high *cis*/*trans* ratios become understandable as shown in the following scheme, which is a *trans*-elimination:



(28)

γ) *Kinetic equations*: The olefin formation from alcohols has frequently been explained by a single-site adsorption[243, 310, 340, 341]. The resulting Langmuir-type equations include terms for the inhibition by water and are of the general form:

$$r = \frac{kK_A P_A}{1 + K_A P_A + K_W P_W} \qquad \text{(III)}$$

the surface reaction being suggested as the rate-determining step. In this expression r means the reaction rate, k the rate constant of the surface reaction, K_A and K_W the Langmuir adsorption coefficients and P_A and P_W the partial pressures of alcohol and water, respectively. Krylov[342] suggested that the desorption of water was the slowest step of the overall reaction. Butt and co-workers[88, 89, 345] could describe their conversion isotherms of the parallel-consecutive reaction scheme for the ethanol–ether–ethylene interconversion by

means of the respective single-site rate equations. For the dehydration of cyclohexanol[113], *s*-butanol[226] and iso-propanol[226a] on the other hand a dual-site adsorption is reported. Over wide temperature and pressure ranges the experimental results were best fitted by equations of the type

$$r = \frac{kK_A P_A}{(1 + K_A P_A + K_W P_W)^2} \qquad \text{(IV)}$$

the symbols having the same meaning as in equation (III). There arises, however, a discrepancy to experimental findings in that type (IV) equations do not result in a zero-order reaction at high substrate pressures and negligible inhibition by water, i.e., at low conversions. A zero order, however, has in fact been verified for the dehydration of aliphatic[100, 108, 115] as well as cyclic alcohols[115, 330]. Recently an empirical expression has been found which avoids this difficulty[100, 115]. When r and r_0 are the reaction rates under the given conditions and for the zero-order, respectively, and b is a constant, this equation can be written as

$$r = r_0 \theta_A = r_0 \frac{\sqrt{P_A}}{\sqrt{P_A} + bP_W} \qquad \text{(V)}$$

The value θ_A may be regarded as the fractional coverage of the catalyst surface by alcohol in the presence of inhibiting water. This expression evidently allows a zero-order reaction at low conversions. However, it is difficult to correlate this 'adsorption isotherm' with a simple adsorption model. For the adsorption of only one component isotherms of the type

$$\theta = \frac{(KP)^{1/n}}{1 + (KP)^{1/n}} \qquad \text{(VI)}$$

have been derived[346, 347], where K is the adsorption equilibrium constant and n a constant. With $n = 2$ the equation describes dissociative adsorption[348]. For application to adsorption on energetically heterogeneous surfaces with saturation properties equation (VI) was derived by Sips[349]. The validity of this expression has been proved for various systems[350, 351] and Figure 6 shows some data of the dehydration of cyclohexanol drawn according to the linearized form of equation (V). From infrared investigations of the H-bond systems which form during adsorption of alcohols on alumina[352], a dual-site adsorption of structure **16** was suggested in which the

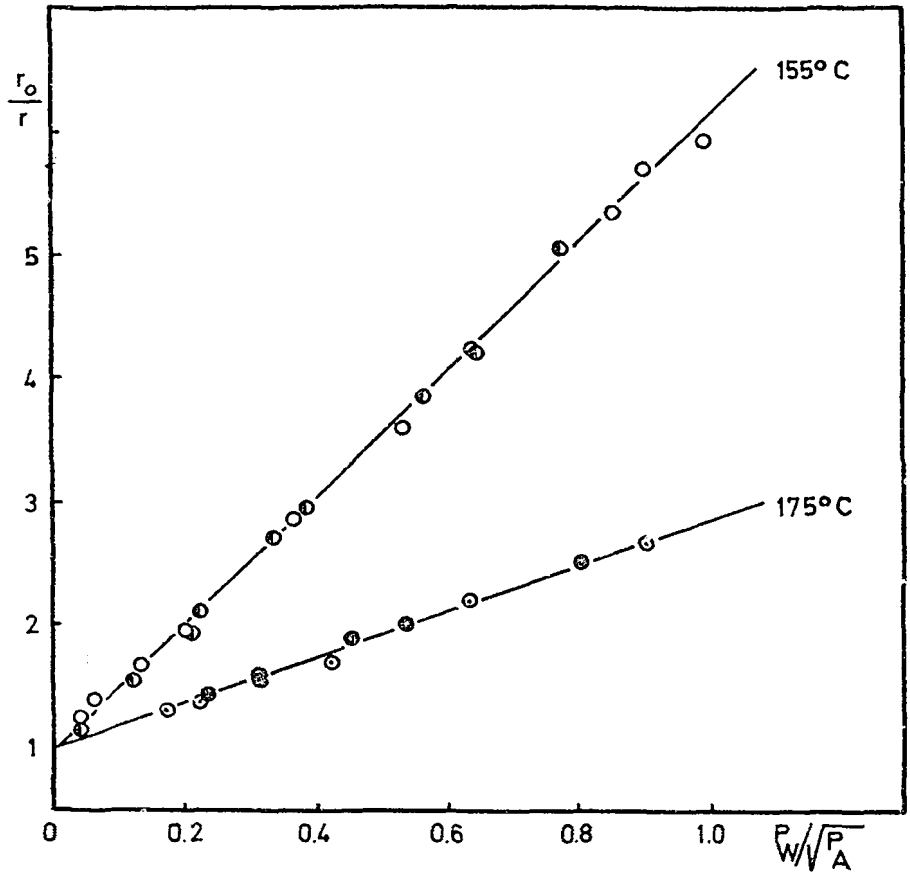
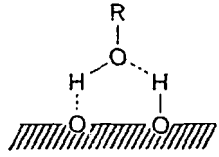


FIGURE 6. Kinetics of the olefin formation from cyclohexanol on alumina at alcohol pressures of 115 (○) and 155 (◐) mm Hg and 100 (●) and 160 (⊙) mm Hg, respectively, at the temperatures indicated.



(16)

alcohol molecule is bonded to the surface by two nonlinear H-bonds*. Such adsorption structures for alcohols also seem highly probable because of sterical aspects[99]. Water on the other hand was shown to

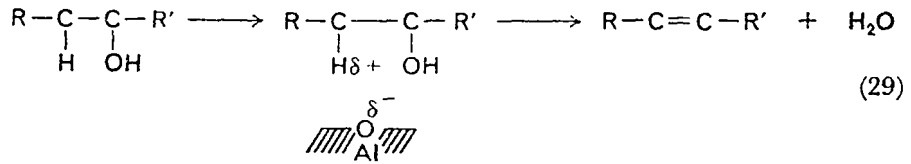
* The existence of nonlinear H-bonds has been proved by Luck[352a]. Alcohols in particular form cyclic dimers with nonlinear H-bonds at low concentrations as shown by the N_2-matrix technique[352b].

block surface hydroxyl groups through single site adsorption by only one linear H-bond for which the water molecule is the acceptor[353]. This picture holds for relatively high ratios of alcohol to water pressures.

Regarding the ether formation, the question arises whether the bimolecular reaction is of the Eley–Rideal or the Langmuir–Hinshelwood type†. De Boer and co-workers[106, 354] suggest a simultaneous ether formation by both reaction types. Zero order has been observed for the ether formation from methanol[101, 108], ethanol[99], isopropanol[108], *n*-propanol[115] and benzyl alcohol[115]. This result clearly indicates a surface reaction with both reaction partners adsorbed, i.e., a Langmuir–Hinshelwood type bimolecular reaction. This conclusion was also reached by Balaceanu and Jungers[247]. The reaction is inhibited by water and the kinetic data are best described by equation (V)[99, 101, 115]. If θ_A in this expression represents the fractional coverage of the catalyst surface by alcohol the reaction rate of the bimolecular ether formation is proportional to the alcohol surface concentration and not to the square of the concentration as one would expect. A second reaction intermediate was therefore postulated whose surface concentration must be constant during the reaction course. This intermediate may be a surface alkoxide, the ether formation thus proceeding through the interaction of this compound with a molecularly adsorbed alcohol.

δ) Mechanisms of ether and olefin formation: The kinetics and stereochemistry of the dehydration of alcohols on alumina has been dealt with in the two previous sections. The timing of the elementary steps will be the subject of this particular section. Mechanistic considerations have often been based on only one of these three equally important factors. For this reason the mechanisms of ether and olefin formation have not yet been fully clarified.

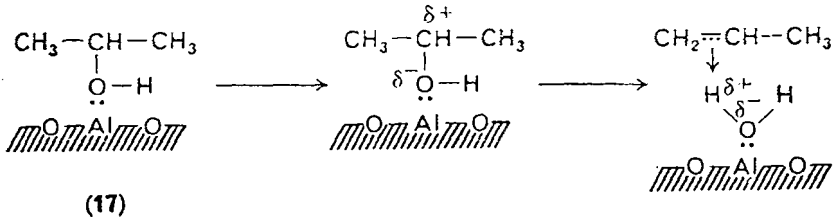
Pisman and co-workers[96] postulated for olefin formation a reaction intermediate which is H-bonded to a surface oxygen ion:



(29)

† For heterogeneously catalysed bimolecular reactions the Langmuir–Hinshelwood mechanism describes the reaction between two chemisorbed species. The Eley–Rideal mechanism on the other hand holds for bimolecular reactions with only one reaction partner being strongly adsorbed, i.e., chemisorbed, the other one being physically adsorbed or pushing from the gas phase (cf. [353a]).

Pines and Haag[339] and later Krylov[342] and Jain and Pillai[108] prefer an adsorption of the alcohol through the oxygen of the alcoholic hydroxyl group on an incompletely coordinated surface aluminium ion. The C–O bond of the alcohol can thereby be polarized, making the OH group a better leaving group. The β-hydrogen can be abstracted by a basic site. In the reaction course, as given by



(30)

(17)

Krylov, for the dehydration of isopropanol the desorption of water is assumed to be rate-determining. The dehydration of C_β-deuterated alcohols gives rise to a primary kinetic isotope effect[326, 355]. This fact disagrees with a rate-determining desorption of water, since deuteration of the alcoholic hydroxyl group does not give rise to an isotope effect. From other experimental facts some contradictions with respect to the above given adsorption complex also arise. It has been shown that selective poisoning of the Lewis centres by pyridine did not affect the olefin formation[276, 277, 279]. Furthermore, H-bonds are not postulated contradictory to the indications of infrared spectroscopy[352]. The adsorption structure **17** may also be objectionable on steric grounds. Spectroscopic investigations of the H-bond systems[352] and steric considerations[99] led to an alternative adsorption complex **16**, in which the alcohol molecule is bound to the surface by two nonlinear H-bonds. The same adsorption complex **16** has been suggested earlier by Winfield[356]. In this structure the alkyl groups are apparently removed from the surface so that no steric interactions will weaken the adsorption bonds. An oxygen ion of the γ-alumina surface occupies an area of 8 Å^2 as given by Peri[270]. With this value a bond angle of about 110° between the nonlinear H-bonds H–O · · · H can be calculated, which agrees very well with the bond angle of a water molecule. If it is accepted that the olefin formation starts from the adsorption complex **16**, the water molecule can thus be preformed in the adsorption complex in accordance with the principle of least motion. By the preformation of the water molecule the C–O bond is polarized and, depending on the ionization energy of the alkyl residue and on the acidity of the surface proton, a car-

bonium ion like species may be formed. A high ionization energy of the alkyl residue and low acidity of the surface proton, on the other hand, would let a concerted elimination of the elements of water be expected. Both in the *E*1-like and in the *E*2-like mechanisms a hydrogen exchange with the surface occurs, according to Eucken and Wicke[242, 313, 314]. Pines and co-workers[6] proposed that tertiary alcohols are dehydrated through more or less free carbonium ions, secondary alcohols through intermediates which may be considered as the transition state of a concerted mechanism containing an ionic contribution, and primary alcohols are dehydrated via a concerted mechanism. Recently, a primary kinetic isotope effect was measured for the dehydration of *t*-butanol-d_9 [355], indicating an *E*2-like mechanism even in the case of tertiary alcohols. As shown in Table 6 this

TABLE 6. The kinetic isotope effect for the dehydration of *t*-BuOH and *t*-BuOH-d_9 [355].

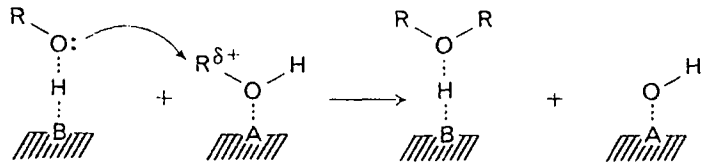
°C	α
120	$3{\cdot}3_5$
140	$2{\cdot}8_3$
160	2·3
180	1·8
200	1·4
220	$1{\cdot}2_3$
240	$1{\cdot}1_5$
260	$1{\cdot}1_5$

isotope effect decreases with increasing temperature. It can be concluded that the transition state is generally that of a concerted mechanism containing ionic contributions, whose size depends primarily on the ionization potential of the alkyl residue. With increasing temperature the ionic character of the mechanism will increase, finally leading to an *E*1-like reaction intermediate, and in accordance with Pines and co-workers[6] the carbonium ion mechanism will dominate at temperatures higher than about 220°C.

Recent investigations of the thermal desorption of ethanol and diethyl ether adsorbed on alumina[104, 105] were assumed to support the alkoxide mechanism (cf section III.C.4.b.α). Using the same experimental techniques Makarov and Shchekochikhin[357] arrive at similar results. These authors, however, suppose a direct or indirect

participation in the olefin formation of the surface acetate which is observed spectroscopically (cf section III.C.3). Because of the high stability of this surface compound this reaction path seems unlikely. Furthermore it seems questionable whether such thermal desorption studies really render conclusions on the dehydration mechanism possible, since the experimental conditions are extremely different in so far as during the catalytic reaction the alcohol and the reaction products are present also in the gas phase and are therefore also physically adsorbed. Tamaru and co-workers[268a] recently presented experimental results by the direct i.r.-spectroscopic observation of the adsorbed species during the course of the dehydration of ethanol and isopropanol which seem to prove the alkoxide mechanism. These experiments are similar to the above mentioned thermodesorption studies in so far as the alcohol was trapped out of the reaction vessel before following the desorption of the reaction products from the adsorbed phase. Generally speaking, it may be stated that there exist experimental results which still lead to contradictory conclusions. Thus, further work will be necessary to clarify the question which intermediate species are taking part in the olefin formation.

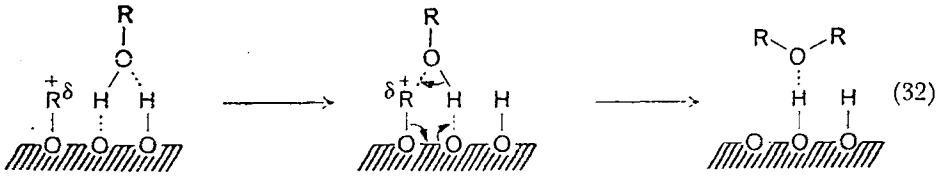
Nevertheless, in ether formation the active participation of an alkoxide species seems proven because of the facts given in the section on selectivity (cf section III.C.2) and because of the form of the kinetic equation (5) and the retardation of the ether formation by selective poisoning of the Lewis centres by pyridine[277]. Jain and Pillai[108, 358], accepting the existence of basic or nucleophilic (B) and acidic or electrophilic (A) sites on the surface of alumina, describe the bimolecular ether formation by the interaction of two types of adsorbed alcohol molecules. This idea was derived from results of the dehydration of various aliphatic alcohols in the presence of phenol, which is assumed to compete with the alcohol for adsorption on the B sites. The alcohol molecule held by the A site represents the adsorption structure responsible for the olefin formation as just mentioned. The polarization of the C–O bond results in a positive charge on the alkyl rest which is considered as being a carbonium ion-like species. The chemisorption of an alcohol molecule on the B site through a H-bond increases the nucleophilicity of the hydroxyl oxygen. The R–O group in this adsorption structure represents an alkoxide-like surface species. The reaction course leading to ether is described by a nucleophilic attack of the alkoxide type species on the positively polarized carbon of the carbonium ion, similar to a S_N2 reaction in homogeneous media.



(31)

Alternately, abstraction of a β-proton from the carbonium ion by the alkoxide or by a basic site on the surface leads to olefin. In this proposal the catalyst induces the suitable polarity in the reactive molecules. The adsorbed phase is therefore considered by Jain and Pillai as being similar to a polar medium, where both nucleophilic substitution and elimination are taking place at the same time and are competing with each other.

In this mechanistic concept oxygen ions and incompletely coordinated aluminium ions of the catalyst surface work as active sites, whereas the hydroxyl groups are not involved. It is, however, known that hydroxyl groups take an active part in the dehydration reaction (cf section III.C.3) and it has been shown by infrared spectroscopy that they form H-bonds during adsorption of alcohols[352]. A mechanism has therefore been proposed which is analogous to that of Jain and Pillai, as it also involves the reaction of an alkoxide type surface species with a molecularly adsorbed alcohol. The adsorption structures of these two species are clearly distinguished[99, 277, 353, 359]. For the molecularly adsorbed alcohol the adsorption structure **16** is assumed, whereas the alkoxide type species is formed by dissociative adsorption of an alcohol molecule. The suitable polarity of the reaction partners is also induced in this case. The alkyl group in the alkoxide species is positively polarized by the electron withdrawal of the underlying Lewis centre, and the attraction of the hydroxyl proton of the alcohol molecule by the basic site increases the nucleophilicity of the hydroxyl oxygen. Ether formation will therefore occur through an electrophilic attack of the α-carbon of the alkoxide species on the hydroxyl oxygen of the molecularly adsorbed alcohol:



(32)

According to this picture water must be formed from the condensasation of two neighbouring hydroxyl groups. The desorption of water as the rate-determining step could be ruled out, since the ether formation from deuterated methanols with the production of heavy water did not give rise to a primary kinetic isotope effect[359]. The overall reaction rate is presumably governed by the rupture of the C–O bond of the alkoxide surface compound. By applying the principle of microscopic reversibility the suggested elementary steps of the reaction can easily be reversed to explain the equilibrium reaction

$$ROR + H_2O \longrightarrow 2\,ROH \qquad (33)$$

c. Dehydration of alcohols on silica–alumina and on molecular sieves. Silica–alumina catalysts of various compositions and pretreatments are active in cracking, isomerization and polymerization. They are also effective dehydration catalysts whose activity may even exceed that of alumina[85]. De Mourges and co-workers[107] report the following activity sequence with respect to the dehydration of isopropanol: $SiO_2 < Al_2O_3$, $ThO_2 < SiO_2$–Al_2O_3. Using the same test reaction Kolesnikov and co-workers[168, 170] studied the influence of the coordination number (cn) of the Al^{3+}-cation in various minerals on their dehydration activity. Catalytic activity decreased in the order sillimanite (cn 4 and 6) > andalusite (cn 5 and 6) > kyanite (cn 6), i.e., the catalyst with the lowest coordination number of the Al^{3+}-cation is the most active. It was therefore concluded that the catalytic effect is primarily due to metal ions with a low coordination number which are able to form polycentric molecular orbitals with the substrate and to undergo a reversible increase of their coordination. From thermal desorption experiments with ethanol it followed that the aluminium ions exposed in the surface of silica–alumina are the sites active in dehydration[104]. De Mourges and co-workers[254] arrived at the same conclusion using catalysts of different alumina contents between 0 and 25% for the dehydration of ethanol and isopropanol. Below about 5% of alumina the dehydration activity increases nearly linearly with the alumina content. Hence Topchieva and Yun-Pin[362] were led to assume a simultaneous reaction scheme for the dehydration of ethanol with a common intermediate of the type of a surface aluminium alcoholate, i.e., the alkoxide mechanism described in section III.C.4.b.α with respect to alumina as catalyst. Two kinds of sites were postulated by de Mourges and co-workers[107] to be active in the formation of ethylene, whereas a third type of active sites is assumed to lead to ether[254],

the alcohol molecule being held to the surface by a dual-site adsorption. The number or efficiency of the active sites must be closely related to the Al–Si ratio. Water was found to inhibit both olefin and ether formation, alcohol and water being adsorbed on different sites and therefore not competing with each other for the same sites. The desorption of water must then be suggested as being rate-determining. By a kinetic analysis of dehydration data of *s*-butanol Kittrell and Mezaki[171, 226, 360] also propose a dual-site mechanism with the surface reaction being rate-determining. A zero-order has been found for the formation of ethylene from ethanol at reasonably low temperatures ($<165°C$)[254], whereas the rate of ether formation is best described by a nearly half-order reaction[254, 361]. Contrary to the above-mentioned dual-site mechanisms Miller and Kirk[166] postulated a single-site surface controlled mechanism, on which, however, a mass transfer effect in the catalyst pellets was superimposed. Under such conditions it appears, however, questionable whether a clear discrimination between various rival reaction models can be achieved.

Besides ether and olefin formation from ethanol and isopropanol, secondary isomerization of the olefinic products from the higher aliphatic alcohols[169] as, e.g., *n*-pentanol[165], 3-pentanol[85] or 2-methyl-2-butanol[84], has been observed. The product distribution is therefore often close to the equilibrium distribution. As with alumina, an exceptionally high *cis/trans* ratio for 2-olefins was found. The stereospecificity of silica–alumina, however, is low compared to alumina, because of its higher surface acidity; its activity is higher for the same reason[85].

A special class of natural and synthetic aluminosilicates are the zeolites or molecular sieves. They show in general a distinct catalytic behaviour[363] and they are, in particular, selective dehydration catalysts. Because of the unique pore structure of this group of catalysts the selectivity is caused by either the molecular shape, which possibly prevents a molecule from penetrating the catalyst interior, or by mass-transfer phenomena within the pores and cavities of the catalyst[364]. Molecular shape selective dehydration of alcohols was reported by Weisz and co-workers[188, 189, 194]. Their results for the dehydration of isomeric butanols on Ca-zeolites 5A and 10X are summarized in Tables 7 and 8, both of which refer to equal contact times. The two zeolites show only slight differences for the dehydration of *n*-butanol which can penetrate both crystals. Isobutanol however is apparently excluded from the crystal interior of the zeolite 5A. This catalyst is therefore shape selective which is

TABLE 7. Dehydration of primary butyl alcohols[a].

°C	Wt % dehydration			
	Ca 10X		Ca 5A	
	n-BuOH	*i*-BuOH	*n*-BuOH	*i*-BuOH
220	—	22	10	<2
230	9	46	18	<2
240	22	63	28	<2
260	64	85	60	<2
290	—	—	—	5

[a] Taken from Reference 189 with permission of the copyright owner.

TABLE 8. Dehydration of *s*-butanol[a].

°C	Wt % conversion	
	Ca 10X	Ca 5A
109	15	~0
116	25	~0
130	82	~0
190	>90	11
205	>90	26
210	>90	45

[a] Taken from Reference 189 with permission of the copyright owner.

proved also in the case of *s*-butanol dehydration (cf Table 8). With increasing temperature zeolite 5A also develops slight dehydration activity, which is due to reaction on the external crystal surface. This could be verified by comparing the external to internal surface area ratio and the relative degrees of conversion of the 5A and 10X zeolites. Analogous results have been obtained for the dehydration of *n*- and isopropanol[365].

In the dehydration of aliphatic alcohols selective formation of olefins has been observed even from substrates which form ethers on dehydration over alumina or amorphous aluminium silicates[186, 197]. This selectivity is caused by a retardation of the diffusion of ether from the active internal surface. Rálek and Grubner[192] found that the apparent activation energy of the diffusion of ethanol in both zeolites 5A and 10X is 1·4 kcal/mole. The apparent activa-

tion energy of the diffusion of ether on the other hand was found to be 2·1 kcal/mole in the zeolite 10X, but 6·4 kcal/mole in the zeolite 5A. This diffusion behaviour is reflected by the conversion data for the two catalysts. The overall activity is nearly identical whereas the molar ratio ethylene–ether ranges from 0–0·5 on zeolite 10X and 1–4 on zeolite 5A at 260°C, depending on the contact time. For comparison this ratio lies between 0 and 1·0 for the dehydration of ethanol on alumina at 240°C. For the same reaction Bryant and Kranich[187] recently showed that the selectivity factor decreases with increasing pore size in the order zeolite A > zeolite Z > zeolite X. This effect is even more pronounced with the longer chain of *n*-butanol.

As far as the effect of cations in the zeolite structures is concerned the H-form was always found to be the most active catalyst in dehydration[187, 190]. The catalytic effect was explained by the presence of protons bonded to the AlO_4 tetrahedrons in the crystal structure[200]. By introducing mono- or di-valent cations by base-exchange the catalytic activity decreases. In the case of Ca ions, the activity was shown to depend on the position of the ions at the surface of the zeolite and on the amount of water adsorbed by surface dipols[199, 200]. Maximum activity was observed for a 1 : 1 ratio of Ca ions and adsorbed water molecules. Thus the catalytic activity can be adjusted to a convenient level by the nature and quantity of the cation used, limited only by the stability of the cation exchanged solids. Usually both size and valence of the exchanging cations show pronounced effects on the catalytic activity. The order LiX > NaX > KX > RbX was observed for the activity in the dehydration of *n*-butanol[195]. The dehydration of ethanol on zeolite X is only slightly affected by low degrees of exchange of Na^+ by Ca^{2+}, but is considerably enhanced at larger degrees of exchange[193]. Higher dehydration activity of zeolites exchanged with bivalent cations was also observed by Bryant and Kranich[187], who explain this phenomenon by geometrical considerations. Cations in the pores and cavities of the zeolites occupy space and only one bivalent ion is required to replace two monovalent ions. Furthermore they could determine limiting ionic radii, i.e., 1·21 Å for monovalent and 1·32 Å for bivalent ions in zeolite A. Catalysts exchanged with ions of radii larger than the limiting values, as e.g., potassium and barium, respectively, were found to be inactive. Similar correlations with large-pore zeolites X could neither be expected nor obtained. The effect of the introduction of divalent cations on the activity of type

X and Y zeolites with respect to the dehydration of iso-propanol has recently been studied by Stone and Agudo[200a]. The activity sequence at 160°C was found to be HY–76 > CaY–78 > MnX–74 > NiY–65 > MnY–77 > Mn–Y–32 > NaY > CaY–27 > NaX, with the attached numbers indicating the percentage replacement of Na^+ by protons and divalent cations, respectively. This activity sequence is discussed with respect to the number, charge and location of the charge balancing cations. Protons located in the supercages are considered to be the active sites. It is suggested that the cations of catalysts containing high percentages of divalent cations exert an indirect specific effect through the reaction

$$M^{2+} + H_2O \longrightarrow MOH^+ + H^+$$

d. Dehydration of alcohols on thoria. Thoria is well known as an active dehydration catalyst[5]. It selectively forms ethylene but not ether from ethanol (cf section III.C.2). The activity and selectivity of dehydration and dehydrogenation strongly depend on the preparation conditions. The most active and selective dehydration catalyst is obtained by pyrolysis of the oxalate at 350–400°C [366]. A less active, but equally selective catalyst is obtained from the decomposition of thorium acetate or carbonate[126, 127]. Appreciable dehydrogenation has been found with thoria samples prepared from the hydroxide[123]. The degree of dehydration of ethanol on these catalysts increased with increasing surface area. These results were explained by associating the dehydration with the interior surfaces or pore walls of the oxide, which are rare in the low-area materials.

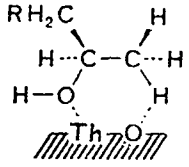
The most striking behaviour of thoria catalysts is the stereospecific formation of 1-olefins from secondary alcohols[124–127]. Asinger and co-workers[124] obtained 88% 1-octene from the dehydration of 2-octanol at 350°C. The selectivity decreased with increasing temperature *cis*- and *trans*-2- or -3-octene being additionally formed. Lundeen and van Hoozer[126, 127] on the contrary found a temperature-independent selectivity factor. Some product distributions are given in Table 9. In a series of isomeric hexanols the 2-alcohols were generally more reactive than the 3-alcohols. Contrary to the dehydration of secondary alcohols the product distribution from the dehydration of *t*-amyl alcohol was found to be temperature-dependent and not selective. The stereochemistry of the dehydration of 2-alcohols over thoria was elucidated using *threo*- and *erythro*-2-methyl-4-deuterio-3-pentanol at 350°C. From the preferred conformations of the substrate alcohols (i.e., methyl and isopropyl groups in *trans*-position) and from the amount of deuterium retained

TABLE 9. Thoria-catalysed dehydration of 2-alcohols[a].

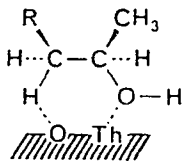
Alcohol	Products % 1-Alkene	2-Alkene
2-Butanol	93–94	6–7
2-Hexanol	95–97	3–5
2-Octanol	95–97	3–5
4-Methyl-2-pentanol	96–98	2–4
1-Cyclohexyl-1-ethanol	96–98	2–4

[a] Taken from Reference 127 with permission of the copyright owner.

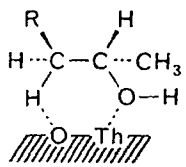
in the main products (*cis*- and *trans*-4-methyl-2-pentene), it was concluded that they are formed by a stereoselective *cis*-elimination. The results are consistent with a structure in which the alcohol is bonded to the surface via the hydroxyl oxygen and a β-proton:



(18)



(19)



(20)

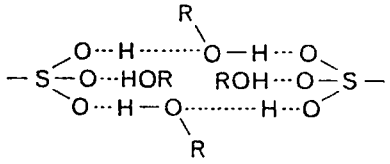
Because of nonbonded interactions between the chemisorbed alcohol and the catalyst surface, structures **19** and **20**, which would lead to the 2-olefins on abstraction of the elements of water, are less stable than structure **18**. The latter requires smaller parts of the chemisorbed molecule to come close to the catalyst surface than **19** and **20**, in which protons of a methylene rather than a methyl group are bonded to the surface. Thus, the stereospecific formation of 1-olefins from 2-alcohols is preferred.

Similar stereoselective action, with 1-olefin yields >85%, has also been observed for several other oxides chosen from Group IIIB, including the lanthanides and actinides[127]. Schappell and Pines[129a] came to the conclusion that, similar to alumina, the preferred reaction course in the dehydration of the stereoisomers of 1-decalol over thoria (prepared from the oxalate) at 350°C is a *trans*-elimination. This follows from the formation of 1,9-octalin as the principal product from the dehydration of *cis*,*cis*-1-decalol, and of *cis*-1,2-octalin as the main product from *cis*-, *trans*-1-decalol. The stereospecificity of the dehydration in the presence of thoria, however, was

found to be not so great as in the presence of alumina. It was assumed that this lower stereospecificity may in part be due to the ease of dehydrogenation of decalols to decalones, with a subsequent epimerization of the alcohols.

e. Dehydration of alcohols on ion exchange resins. The dehydration of alcohols on the H^+-form of ion exchange resins (mainly polystyrene) in liquid phase has been reported in various papers[367–370]. Ethers were observed as the main products from primary alcohols, whereas tertiary alcohols formed olefins. From kinetic measurements[368] the anhydrous sulphonic acid groups or their monohydrates were suggested to represent the active sites in the dehydration of *t*-butanol. In this system the reaction rate was limited by intraparticle diffusion when resins of higher degrees of cross linkage (about 8%) were used.

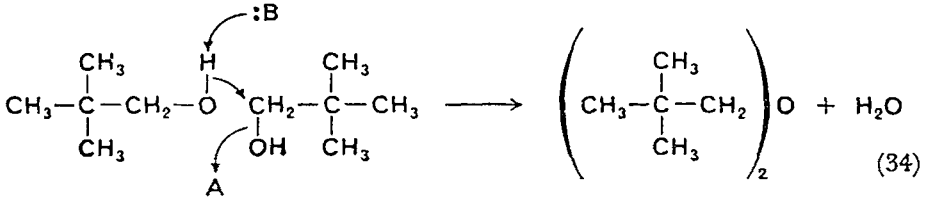
For the vapour phase dehydration on ion exchange resins Kittrell and Mezaki[225, 226], using Kabel and Johanson's[224] kinetic data, postulated an Eley–Rideal mechanism for the ether formation from ethanol, with one alcohol molecule impinging from the gas phase on an adsorbed alcohol molecule to yield adsorbed ether and water. Gates[227, 227a], on the contrary, suggested a Langmuir–Hinshelwood mechanism with both reacting alcohol molecules being adsorbed adjacently, as best fitting the kinetic data. Water strongly inhibits the ether formation from methanol and ethanol. The activity of Li^+ and Na^+ exchanged resins is negligible while increasing with the H^+-content. This indicates the necessity of the H^+-ions for the catalyst to be active in dehydration and suggests that the reaction proceeds through oxonium or carbonium ion intermediates. From measurements of the dielectric constant of the system polystyrene–methanol[372] it could be shown that one SO_3H group adsorbs two alcohol molecules in different structures as shown schematically by:



The same structure was deduced from infrared spectroscopic studies for the adsorption of ethanol, isopropanol and *t*-butanol[371]. This suggestion is consistent with a Langmuir–Hinshelwood mechanism of the ether formation, and the two alcohol molecules held by

different adsorption bonds may be regarded as the respective partners in the bimolecular 'surface' reaction.

f. Dehydration of alcohols on metals. Alcohols such as *t*-butanol which cannot undergo dehydrogenation without rearrangement of the carbon skeleton are dehydrated even on metals[230]. From the preparative point of view the recent investigations of Pines and Steingaszner[230a] have to be considered shortly. These authors observed the formation of ethers from *n*-butanol, *s*-butanol, isobutanol, 2- and 3-methyl butanol and even from neopentanol over nickel/kieselguhr catalysts in the temperature range from 130 to 190°C during the hydrogenolysis of the alcohols. In particular, the formation of neopentyl ethers is a novel reaction and yielded up to 72 mole % of the products formed depending on the preparation conditions of the catalyst. Even unsupported nickel catalysts yield ethers. Mixed ethers were also produced from primary alcohols. The structure of the alcohols seemed to have little influence on the yields of the ethers. The hydrogen present during the course of the reaction seemed not to take part directly in the ether formation, but to prolong the life of the catalyst. The main function of the hydrogen was assumed to be to keep the catalyst surface clean. Surface sites responsible for the ether formation were shown to possess acidic properties since the pre-adsorption of ammonia caused a loss of activity towards the ether formation. Acidic sites A and basic sites B in a nickel catalyst may be attributed to small amounts of nickel oxide which is present in the catalyst surface. This nickel oxide on heating may cause acidic and basic sites in a similar manner as alumina. The increase in the strength and/or number of acidic sites when nickel/kieselguhr is used could be explained by interactions of silica with the nickel as described by Peri[230b]. Since the formation of ethers from alcohols is known to occur on acidic catalysts Pines and Steingaszner formulated an analogous mechanism in which acidic and basic sites of the nickel catalyst participate in the reaction in a concerted manner:



(34)

There is, however, an alternative mechanism which explains the

ether formation under the experimental conditions through the condensation of an aldehyde with an alcohol to form hemiacetal, followed by the hydrogenolysis of the hydroxyl group. This second mechanism seems to be preferable if it is considered that ether formation from neopentanol is not possible over any other acidic oxide catalyst. Furthermore, the occurrence of small amounts of ethers was reported when passing alcohols in the presence of hydrogen over evaporated platinum[230c] or palladium films[230d]. The existence of oxide in the surface of these metals seems unlikely.

5. The effect of the substrate structure on the reactivity

The first attempts to correlate substrate structure and reactivity in dehydration reactions were reported by Dohse[373] and Bork and Tolstopyatova[374], who studied the olefin formation from aliphatic alcohols on bauxite at relatively elevated temperatures. Generally, the observed activation energies decreased on methyl substitution, namely by 5·5 kcal/mole on substitution in α-position, by 2·5 kcal/mole in β- and by 0·5 kcal/mole in γ-position. In agreement with this tendency Stauffer and Kranich[375] found a constant activation energy of 31 kcal/mole for the dehydration of the straight-chain aliphatic alcohols ethanol through *n*-hexanol on γ-alumina. Kraus, Kochloefl and co-workers[118, 330] came to the conclusion that for the dehydration of aliphatic and cyclic secondary alcohols and of stereoisomeric alkylcyclohexanols on alumina steric requirements predominate over the inductive effect with respect to their influence on reactivity. Some recent results on the olefin formation from aliphatic alcohols on alumina[376] are summarized in Table 10. The observed activation energies can be discussed in the picture of an *E*2-like elimination reaction as mentioned in section III.C.4.b.δ. The values of the activation energies increase in the order tertiary, secondary and primary alcohols. This trend is explained by the differing ionic contributions to the transition state and by the inductive effect of the alkyl groups adjacent to the β-C atom. Thus, the ionic contribution is low in the dehydration of isobutanol as compared to *t*-butanol. Furthermore, the two methyl groups in γ-position in isobutanol compensate the positive charge at C_β by their inductive effect. The acidity of the β-proton in isobutanol is therefore much less than the acidity of the β-protons of *t*-butanol so that the activation energies are found in the right order for the rate-determining rupture of the C–H bond.

3-Methyl-2-butanol and 2-methyl-2-butanol both form Hofmann-

and Saytzeff-products in comparable amounts. The inductive effect would predict a lower activation energy for the Hofmann-product.

TABLE 10. 'True' activation energies of the olefin formation from aliphatic alcohols over γ-alumina.

Alcohol	Product	Activation energy[a] (kcal/mole)
i-BuOH	Isobutylene	30·0 ± 0·6
s-BuOH	*cis*-2-butene	27·2 ± 0·7
	trans-2-butene	31·1 ± 1·0
3-Me-2-BuOH	2-Me-2-butene	25·1 ± 0·4
	3-Me-1-butene	27·7 ± 1·0
Cyclohexanol	Cyclohexene	25·7 ± 0·3
t-BuOH	Isobutylene	25·5 ± 0·6
2-Me-2-BuOH	2-Me-2-butene	22·2 ± 0·3
	2-Me-1-butene	23·1 ± 0·3

[a] The errors indicated are maximum errors.

However, the reverse order is found experimentally. An additional contribution of an olefin stabilizing effect must therefore be accepted. This fact supports the *E*2-like reaction intermediate since an olefin stabilizing effect can only work if the double bond is preformed in the transition state, which is true for *E*2-like but not for *E*1-like reaction intermediates.

The applicability of linear free energy relationships (LFER) to heterogeneously catalysed reactions has been proved recently[377–382]. The Hammett equation for aromatic and the Taft equation for aliphatic compounds have now been used to correlate the reactivity of alcohols for dehydration. It can be shown[377] that the reaction constants ρ of these equations are low or even negative for carbonium ion or highly polar mechanisms. Since the mechanism of a heterogeneously catalysed reaction is determined by the substrate structure and by the surface properties of the catalyst, the value of the ρ-constants should reflect both these factors. Some examples have very recently been reported[383], which are shown in Figure 7. The Taft equation was found to be valid for the dehydration of four secondary alcohols (2-methyl-3-butanol: $\sigma^* = 0$; 2-methyl-3-hexanol: $\sigma^* = -0{\cdot}11$; 2,4-dimethyl-3-pentanol: $\sigma^* = -0{\cdot}19$ and 2-methyl-4-ethyl-3-hexanol: $\sigma^* = -0{\cdot}22$) on alumina, zirconia,

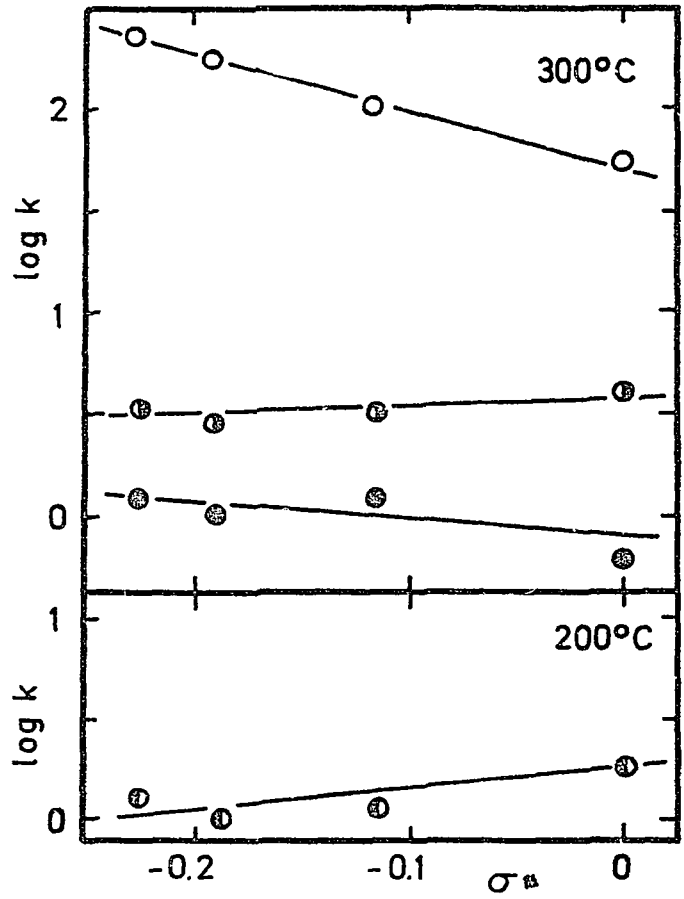
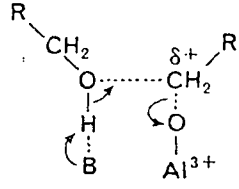


FIGURE 7. Correlation of reaction rate constants of dehydration of secondary alcohols in the coordinates of the Taft equation: ○ SiO_2; ◔ ZrO_2; ◉ TiO_2; ◐ Al_2O_3.

titania and silica. The reaction constants decrease in this order, being negative for titania and silica. An *E*2-like dehydration mechanism on alumina seems therefore indicated by LFER, whereas for the dehydration on titania and silica a more polar mechanism must be assumed. In this case, clearly the surface properties of the catalyst predominantly determine the reaction mechanism. The reaction rate constants of the dehydration of substituted 1-phenyl ethanols on alumina could be correlated by the Hammett equation[119]. The reaction constant in this system was found to be negative and moreover—using the above-mentioned four catalysts—it was independent of the catalyst[384]. Apparently the stabilization of a carbonium ion by the phenyl group is so strong that the influence of the catalyst is

negligible and even on alumina the dehydration proceeds through an *E*1-like reaction intermediate. In this case the substrate structure predominantly determines the mechanism.

The reaction rates of the ether formation from methanol, ethanol, *n*-propanol and benzyl alcohol on alumina could also be correlated by the Taft equation[277, 385]. The activation energies of the four reactions are equal at 25·5 kcal/mole. Thus, the differences of the reaction rates can only arise from differences in the activation entropies. The transition state of the mechanism (32) can be represented by



(21)

The α-C atom in the alkoxide-like species is positively charged because of the electron withdrawal of the Al^{3+}-ion. This positive charge is decreased by the electron-donating power of alkyl groups, while, on the other hand, it is enhanced by the electron withdrawal of the phenyl group in the benzylate. The charge distribution on the hydroxyl oxygen of the alcohol molecule is only slightly affected by R because of the damping effect of the methylene group. The formation of a transition state **21** is therefore to a first approximation the more probable the more positive the α-C atom of the alkoxide species. The activation entropy and the reaction rate are therefore highest for the dehydration of benzyl alcohol. The reaction constant is in fact found to be positive, indicating that the ether formation does not proceed via a strongly polar mechanism. Steric restrictions are apparently negligible despite the widely varying molecular sizes.

IV. CONCLUDING REMARKS

There is a high similarity between the dehydration of alcohols in solutions and on heterogeneous surfaces in the gas phase. All the principles of organic chemistry worked out for reactions in solution hold in heterogeneous catalysis. Thus in both systems the factors determining the course of the elimination reaction and the structure of the transition state are in principle the same. The nature of the

leaving group and the structure of the alkyl residue are intrinsic properties of the substrate molecule, whereas the solid catalyst takes over the role fulfilled by the solvent in liquid phase reactions. The strength of the basic sites of a surface corresponds to the strength of dissolved bases and the interactions between the substrate molecule and the catalyst surface can be compared to the solvating power of the solvent. Even linear free energy relationships are applicable in heterogeneous reactions. The reaction course and reactivity are principally determined by the preponderance of either the intrinsic molecular properties or the surface properties of the catalyst. Due to the adsorption of the substrates on solid surfaces differences with respect to steric aspects may sometimes arise as compared to reactions in the liquid phase. The close similarities between dehydration reactions in solution and on alumina surfaces led Pines and Manassen[6] to the suggestion, which may be generalized for heterogeneous catalysts, that catalysts 'seem to act as *solvating* agents and therefore may be considered as *pseudosolvents* for dehydration reactions'.

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The Chemistry of The Hydroxyl Group
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CHAPTER 13

Uncatalysed rearrangements involving the hydroxyl group

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I. INTRODUCTION

Rearrangements catalysed by acids or bases in which the hydroxyl group plays a determinative role either as a direct participant—as keto–enol tautomerism—or indirectly by exerting a directive influence—as in the pinacol–pinacolone rearrangement—are well known and have been adequately reviewed[1-4]. Uncatalysed rearrangements in which hydroxyl groups play similar roles are less well known and have not been reviewed as a coherent group. Recent formulation of the conservation of orbital symmetry theory by Woodward and Hoffmann[5-12] has permitted an understanding of

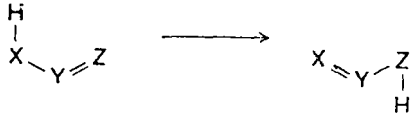
many of these uncatalysed, concerted reactions not possible earlier, and this chapter leans heavily on those ideas.

Primary attention is given to thermal processes, but some related photochemical reactions are included. Certain reactions which are not strictly to be termed rearrangements have been included because of their similarity mechanistically with the rearrangements, and also because the survey would otherwise have been incomplete. It is hoped that the majority of significant material was unearthed from the literature, but apologies are made to the authors of any work inadvertently omitted.

II. SIGMATROPIC REARRANGEMENTS

A. The [1,3] Sigmatropic Shift

Orbital symmetry theory indicates that a concerted thermal 1,3-hydrogen migration must be an unlikely event. The theory pre-

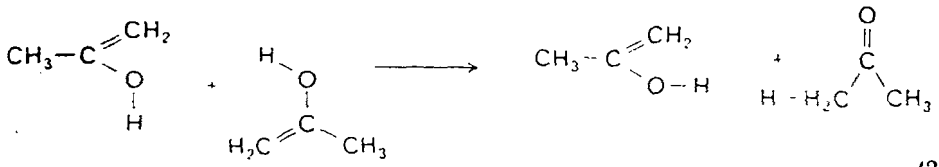


(1)

dicts[5, 7] that the migrating atom must proceed from an initial position on one side of the plane of the other three atoms to a final position on the opposite side of the plane (equation 1). This awkward geometric requirement cannot be achieved in a concerted process. While no clear-cut examples of concerted uncatalysed keto–enol conversions are to be found in the literature, it must be noted that no studies have been made with the objective of testing this possibility.

1. Thermal keto–enol interconversion

A number of reactions are known in which a keto–enol interconversion must occur during a thermal reaction. In no case has any study of the mechanism of this keto–enol tautomerism been carried out. Srinivasan[13] suggested that the enol produced during irradiation of 2-hexanone undergoes ketonization in the gas phase. He considered that one enol molecule could act as a hydrogen transfer agent to convert a second enol to the keto form (equation 2). Studies by



(2)

McMillan, Calvert and Pitts[14] failed to provide support for this idea. When 4-pentenophenone-2-*d* undergoes an enolene rearrangement[15] (see section III) the intramolecular deuterium migration is accompanied by an intermolecular transfer. Since the enolene rearrangement in this case must be preceded by enol formation, the intermolecular exchange is perhaps associated with the keto–enol conversion and might indicate the occurrence of reactions analogous to equation (2).

The oxy-Cope rearrangement (see section II.c) must give an enol directly which then ketonizes. Rearrangement of 1,2-dideuteroxy-1,2-divinylcyclohexane in the gas phase produced facile intermolecular deuterium transfers[16]. Thus once again where a [1,3] hydrogen migration might occur under thermal impetus, intermolecular shifts are observed. It must be concluded that while thermal keto–enol interconversion may be possible, it is very doubtful that these involve concerted [1,3] sigmatropic shifts.

2. Photochemical keto–enol interconversion

A photoinduced [1,3] sigmatropic shift is predicted by orbital symmetry to proceed suprafacially. The prediction should be valid for a concerted reaction from the first excited singlet state, but its relevance to reactions of other excited states is questionable. Experimental observation of direct photoenolization is difficult because of the rapid reversion of the enol to the keto form. Lemaire[17] found that irradiation of biacetyl leads to a product with the spectral and chemical properties of an enol. Enolization occurs via the second excited singlet state and cannot proceed through the first excited singlet or lower vibrational levels of the lowest triplet state.

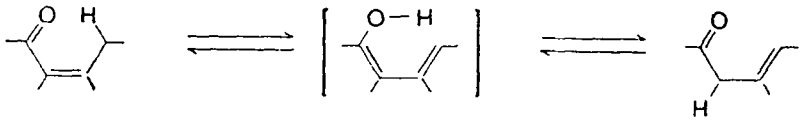
Some observations of McMillan, Calvert and Pitts[14] show that photoenolization is not a general reaction. Irradiation of 2-pentanone in a vessel pretreated with deuterium oxide gave the enol form of acetone via a Norrish type II cleavage. The acetone produced was monodeuterated and recovered 2-pentanone contained no deuterium. Thus under the conditions used neither 2-pentanone nor acetone once ketonized will form an enol. It would appear that despite the expectations based on the theory, concerted photochemical keto–enol interconversions are no easier to find than are the thermal ones.

B. The [1,5] Sigmatropic Shift

Orbital symmetry considerations predict[5, 7] that concerted [1, 5] sigmatropic shifts should be suprafacial if induced thermally and antarafacial when promoted photochemically.

I. Thermal dienol-enone interconversions

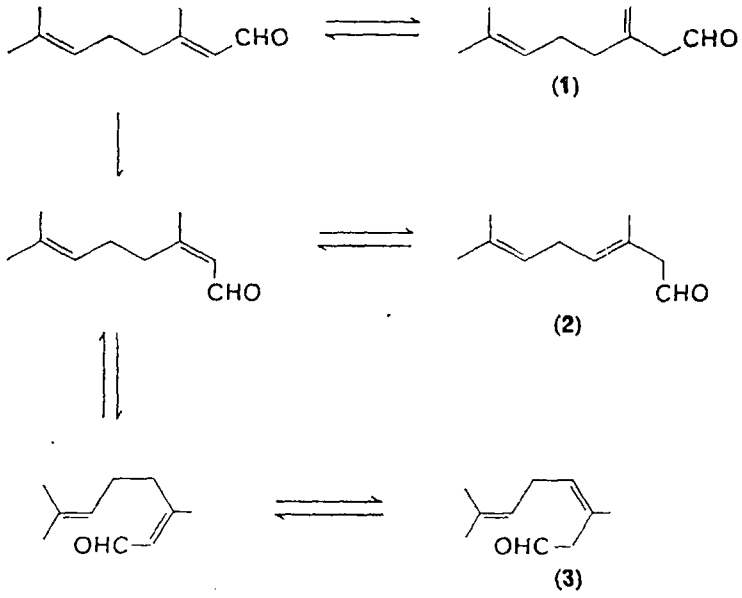
The prediction of a favourable geometry for the concerted thermal 1,5-hydrogen migration does not of itself predict that they will be attainable. However, the thermal dienol–enone interconversion has proved to be a relatively facile process. Experimental observation of the rearrangement (equation 3) cannot normally be made directly since the dienol is only a transient species. Frequently observation is made possible because some alternate hydrogen transfer process permits a formal 1,3-migration to occur (equation 3). Concertedness



(3)

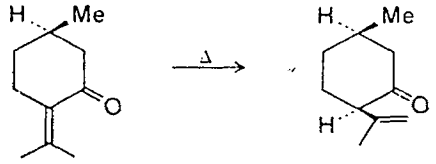
is assumed if the reaction will proceed only when the carbonyl and γ-CH unit are *cis* on the α,β-double bond.

Ohloff[18] found that citral and neral isomerize to unconjugated aldehydes at temperatures as low as 130° (equation 4). The products



(4)

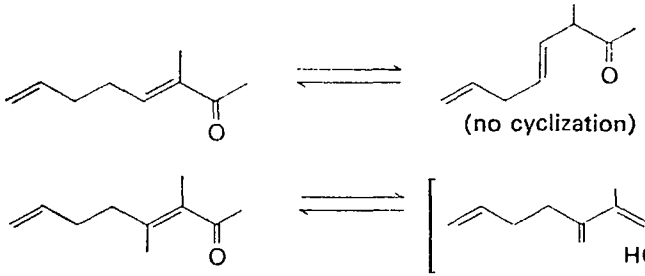
boil at a lower temperature than the reactants so distillation through an efficient column (175° pot temperature) gives a distillate containing 30% **1** and 70% **2** and **3**. Similarly distillation of pulegone[19] gave isopulegone in good yield (equation 5). The stereochemistry of



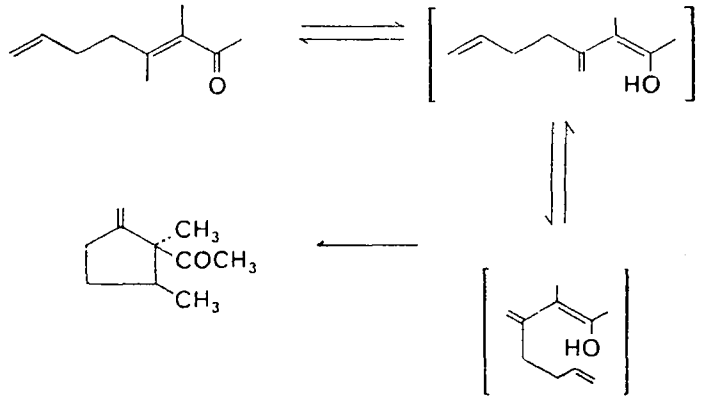
(5)

isopulegone was confirmed by o.r.d. studies.

Similar observations on a deconjugation process were made by Conia and co-workers[20, 21], but the equilibrium between conjugated and unconjugated ketones was altered by an enolene cyclization (see



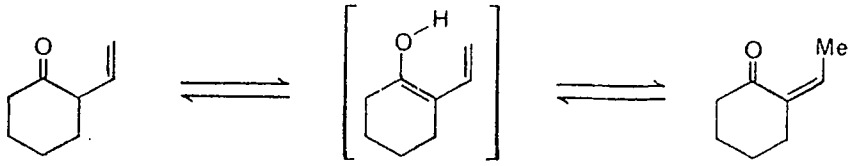
(6)



(7)

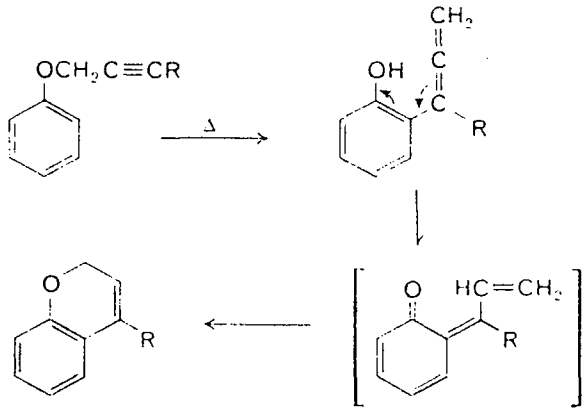
section III). Thus a major difference in the reaction was caused by the presence (reaction 7) or absence (reaction 6) of a methyl group at C_4 on the 3,7-octadien-2-one skeleton. The actual product isolated from the reaction (7) was 2,3,4-trimethyl-3-acetylcyclopentene.

It is possible that the small amount of 4-methyl-4-penten-2-one obtained on pyrolysis of 4-methoxy-4-methyl-2-pentanone[22] has its origin in a similar deconjugative process. Crandall[23] has attributed the formation of a conjugated product from 2-vinylcyclohexanone to a 1,5-hydrogen migration following enolization (equation 8). The nature of the intermediate enol there suggests that *o*-vinylphenols



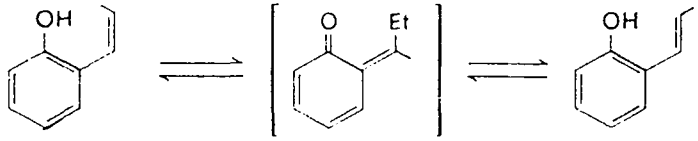
(8)

might react analogously. The intermediacy of such a [1,5] sigmatropic shift in the formation of a benzopyran from phenyl propargyl



(9)

ether has been suggested (equation 9)[24]. The *cis–trans* isomerization of *o*-propenylphenols (reaction 10) has also been attributed[25] to a 1,5-hydrogen migration. Other examples of this general thermal enone–dienol interconversion are probably buried in the literature.



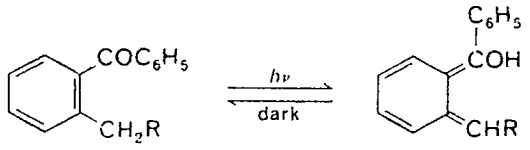
(10)

2. Photochemical dienol–enone interconversions

Perhaps indicative of the tenuous connexion between theory and reaction in photochemistry is the fact that the 1,5-shift which is theoretically less favoured geometrically has many formal examples while the more favourable 1,3-shift is rarely observed. The photochemical 1,5-migrations may, of course, be complex mechanistically, and their occurrence in no way contradicts the theory.

A direct photoenolization invoking a 1,5-hydrogen transfer was first observed by Yang and Rivas[26]. The concentration of enol (equation 11) at the photostationary state was too low for direct

detection. Its presence was confirmed by deuterium exchange, and by trapping the enol with dimethyl acetylenedicarboxylate. Flash photolysis studies[27] showed the reaction involves an $n \rightarrow \pi^*$ triplet state which decays to the enol via a first-order process with $k = 2 \times 10^3$ sec^{-1}. The enol reverts to starting material also by a first-order process with $k = 9 \times 10^{-2}$ sec^{-1}.

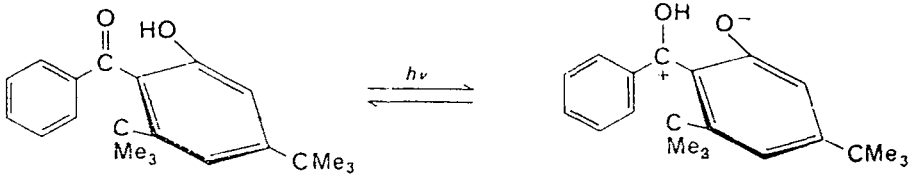


(11)

R = H, CH_3

A more comprehensive study was made by Huffman, Loy and Ullman[28], who found it difficult to predict on a purely structural basis which ketones will react. Thus 1-benzoyl-2-methylnaphthalene and 1-benzoylfluorene do not react, while 6-benzylbenzanthrone, 2-benzyl-3-benzoylbenzofuran and 3-benzyl-2-benzoylbenzofuran do. Of ten 2-alkyl-3-aroylchromones tested six reacted and four did not. Photochromism at low temperature and photoinduced deuterium exchange were used as criteria for the reaction. Generally the enol (coloured form) is longer lived in nonpolar solvents and reverts to the keto form more rapidly when triethylamine is added or in polar protic solvents like ethanol[29]. Therefore the dark reaction is not a thermal 1,5-hydrogen transfer.

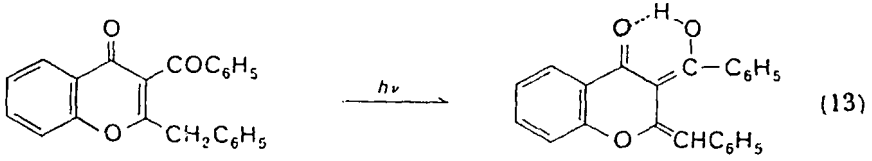
Huffmann, Loy and Ullman showed that photoenolization in these cases proceeds exclusively via the $n \rightarrow \pi^*$ triplet state. It seems probable that reaction occurs only when that is the lowest energy triplet, since ketones which do not enolize frequently phosphoresce[29]. A similar explanation was given by Yang[27] and Beckett and Porter[30]. Pitts, Johnson and Kuwana[31] suggested that the failure of *o*-hydroxybenzophenone to undergo photopinacolization was due to photoenolization. Even though 2,4-di-*t*-butyl-6-hydroxybenzophenone cannot form an enol it apparently undergoes a photoinduced 1,5-



(12)

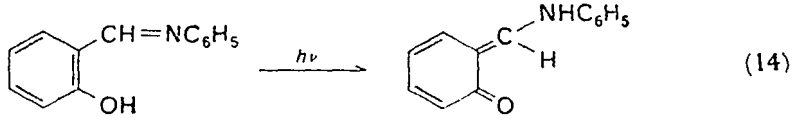
hydrogen transfer[32] (equation 12). The reaction has been attributed to the $n \rightarrow \pi^*$ singlet, but this supposition has not been confirmed.

As equation (12) suggests, coplanarity is not a requirement for hydrogen transfer. The photoenol from 2-benzyl-3-benzoylchromone has the structure indicated in reaction (13), since it shows infrared bands of an internally hydrogen-bonded carbonyl[28]. The photochromism[33] of salicylaldehyde anils[34], which has been attributed to a



(13)

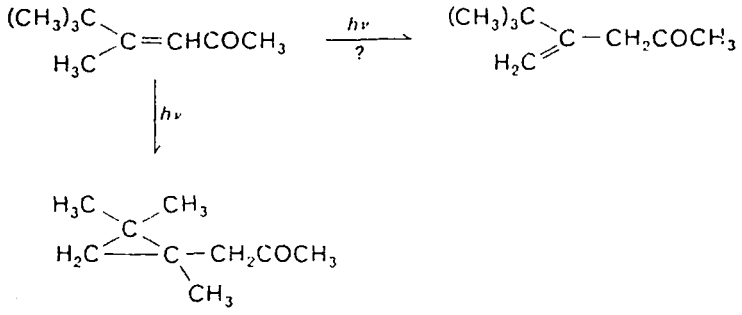
1,5-hydrogen transfer, was shown by Becker and Richey[35] to be due to the *trans*-isomer of the keto-anil (equation 14). Earlier workers[36] assumed the coloured product was the *cis*-keto-anil.



(14)

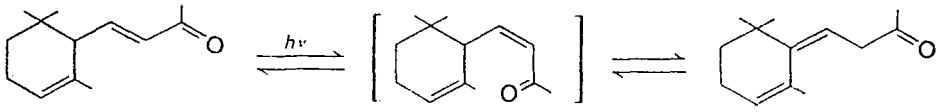
Both 2,4- and 2,5-dimethylacetophenones undergo photoexchange involving the *o*-alkyl group only and show photochromism at low temperature[37], and similar behaviour has been reported for *o*-methylbenzaldehyde[37]. Weller[38] interpreted the spectral changes occurring on irradiation of salicylate esters as indicating a 1,5-hydrogen migration. Both aliphatic α,β-unsaturated carbonyl compounds may undergo a photoenolization with a 1,5-hydrogen shift. Normally the reaction is observed when the proton is then transferred to the α-carbon in a dark reaction and deconjugation results (equation 3). Structure as a criterion for the deconjugation gives results here as erratic as in the photoenolization of aromatic systems. Whether the $n \rightarrow \pi^*$ triplet is implicated is not yet clear, though in certain cases a $\pi \rightarrow \pi^*$ state is the reactive one (see below).

An early report[39] of the photodeconjugation of 3,4,4-trimethyl-3-penten-2-one could not be repeated by Jorgenson and Yang[40], who found only a cyclopropane derivative (reaction 15). Similarly the formation of 3-acetylcyclohexene from 1-acetylcyclohexene[39] could not be confirmed by Pitts and Simonitis[41]. However, irradiation of α-ionone produces a deconjugation reaction (16)[42]. McDowell and Sifniades[43] reported conversion of *trans*-crotonaldehyde to 3-butenal



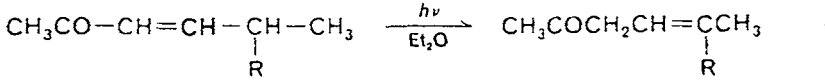
(15)

in low quantum yield (0·1), however, Allen and Pitts[44] failed to detect this product.



(16)

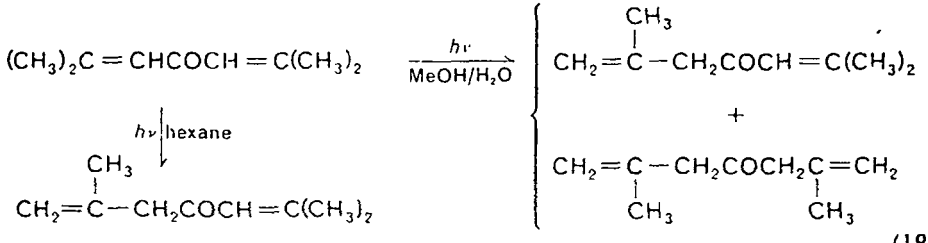
Yang and Jorgenson[45] surveyed the photobehaviour of a series of aliphatic enones. Deconjugation cannot be attained with 3-penten-2-one, 4-methyl-3-penten-2-one, 3,4-dimethyl-3-penten-2-one and 4,5-dimethyl-3-hexen-2-one, but 3-hexen-2-one and 5-methyl-3-hexen-2-one react nicely (reaction 17) when irradiated in Pyrex vessels. A



(17)

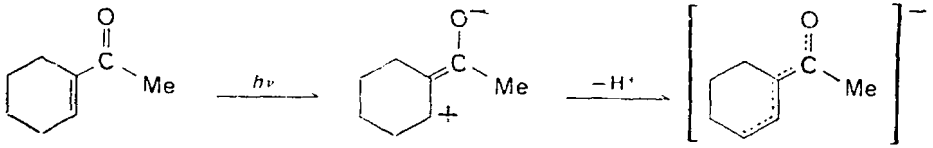
deuterium atom was introduced at the α-carbon if the irradiation was done in CH_3OD. To complete this enigmatic series it was later found[46, 47] that 2,6-dimethyl-2,5-heptadien-4-one undergoes mono or double deconjugation in aqueous methanol, but only mono-deconjugation in hexane (reaction 18).

Commenting on the deconjugation of 1-acetylcyclohexene, a molecule in which a direct 1,5-hydrogen transfer is not possible,



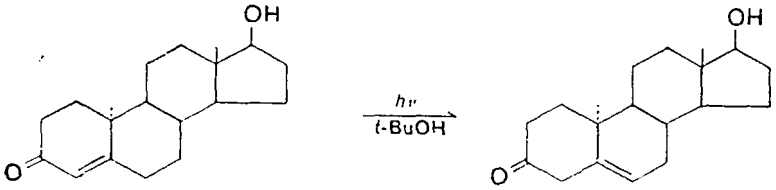
(18)

Hammond and Turro[48] suggested that deprotonation of the polar $\pi \rightarrow \pi^*$ singlet state, followed by reprotonation, could account for the deconjugation (reaction 19). Though the example which evoked the theory is probably not valid, some further cases of a similar type



(19)

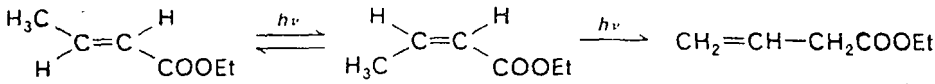
have since been uncovered. Yamada, Uda and Nakanishi[49] found some 3-methylenecyclohexanone in the product of irradiation of cyclohexenone and ethylene in benzene. The double bond in a 10 α-testosterone migrates to a nonconjugated position during irradiation (equation 20)[50]. A direct 1,3-hydrogen migration could account for these results. McDowell and Sifniades[43] had suggested the 1,3-



(20)

migration as a general route for all deconjugative reactions, but exchange reactions[45] had eliminated it from consideration in several cases. Specific incorporation of deuterium at C_4 in 10 α-testosterone[51] showed that 1,3-shifts are not operative in this case either. Kuwata and Schaffner[51] showed that deconjugation in 10 α-testosterone involves the $\pi \rightarrow \pi^*$ excited state. However, that requirement holds only in alcohol solvents since in benzene solution the reaction may proceed upon $n \rightarrow \pi^*$ excitation.

While the results above show that 1,5-hydrogen shifts need not be intramolecular, the stereochemical results in other cases suggest that the direct intramolecular transfer does occur. Photoisomerization of ethyl *trans*-crotonate[52, 53] leads directly to the *cis*-isomer, but ethyl

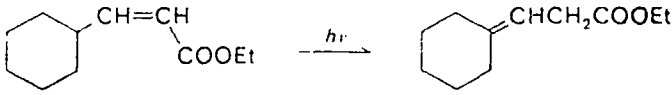


(21)

3-butenoate appears only after an induction period. The *cis*-ester gives both *trans* form and ethyl 3-butenoate without an induction

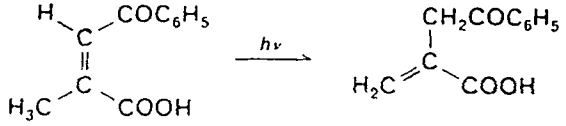
period. Jorgenson and Gundel[54] reported similar observations with ethyl 3,4,4-trimethyl-2-pentenoate. These reactions were not subject to photosensitization, and ethyl crotonate does not react if a Pyrex filter is used. Jorgenson[55] confirmed the stereospecificity of the hydrogen transfer with some rate studies on the geometric isomers of ethyl 3,4-dimethylpentenoate.

Photodeconjugation appears to be more general with unsaturated esters than with enones. Büchi and Feairheller[56] showed that ethyl *cis*-β-cyclohexylacrylate reacts readily (equation 22). Ethyl β,

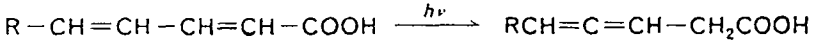


(22)

methylcrotonate undergoes deconjugation while its ketone analogue-mesityl oxide, fails to react[53]. Unsaturated acids also react. Prolonged exposure of *cis*-β-benzoyl-α-methylacrylic acid to sunlight gave β-benzoyl-α-methyleneacrylic acid (reaction 23)[57]. *Trans*-crotonic acid is converted first to the *cis*-isomer and then to 3-butenoic acid[58]. A particularly interesting example was found by Crowley (equation 24)[59]. However, since the methyl esters of the acids gave



(23)

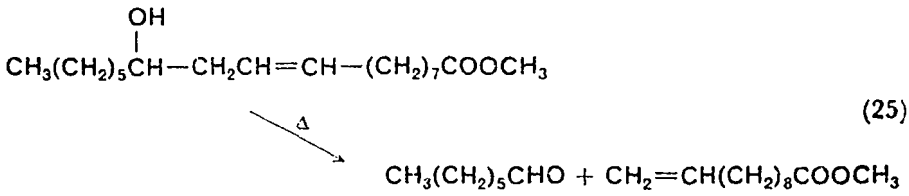


(24)

allene only when formic acid was added to the irradiation mixture, the reaction may involve a more complex process.

3. The β-hydroxy olefin cleavage

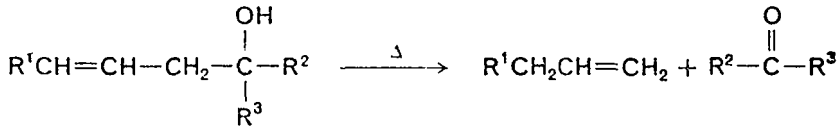
Thermal 1,5-hydrogen migrations via a cyclic transition state are not restricted to *cis*-diene systems. In fact the occurrence of such migrations in molecules containing a 3-butenol grouping has been known for many years. Strictly speaking this reaction does not constitute a rearrangement except in special cases, but it is included here because of its mechanistic relation with the preceding reactions. Krafft[60] observed in 1877 that pyrolytic distillation of castor oil gave an unsaturated fatty acid. Vernon and Ross[61] studied the process in greater detail and isolated heptaldehyde in 85% yield. Barbot[62]



(25)

showed that methyl ricinoleate gives methyl undecylate and heptaldehyde. Gensler and Abrahams[63] obtained 2-octanone from the pyrolysis of methyl 12-methylricinoleate.

Pyrolysis at 600° of a large series of unsaturated tertiary alcohols was made by Grignard[64]. He reported that better yields of ketones from β,γ-olefinic alcohols could be obtained in vacuo at 500° (reaction 26). Apparently he was not aware of the double bond migration or of the special character of the β-hydroxyole fins.

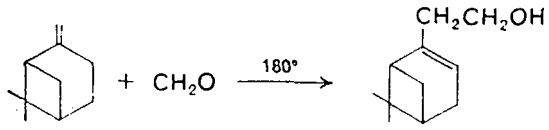


(26)

$R^1 = H \quad R^2 = CH_3 \quad R^3 = n\text{-Pr}, C_6H_5, C_6H_5CH_2$

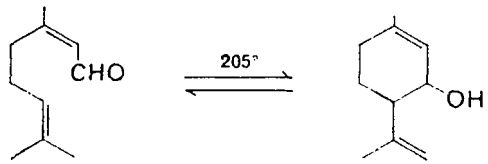
$R^1 = CH_3 \quad R^2 = CH_3 \quad R^3 = n\text{-Bu}, C_6H_5, C_6H_5CH_2$

Bain[65] found that the reaction was reversible at lower temperatures, and he devised the useful synthesis of nopol (equation 27).



(27)

When both the double bond and the carbonyl group are in the same molecule, the reaction becomes a rearrangement (equation 28)[18, 66].



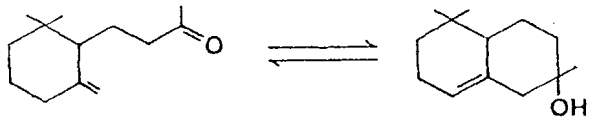
(28)

A number of similar examples (equations 29–31) are to be found in terpene chemistry[18].

The relation between these reactions and the Alder 'ene' synthesis[67] was noted by Arnold and Dowdall[68]. They showed that mono-

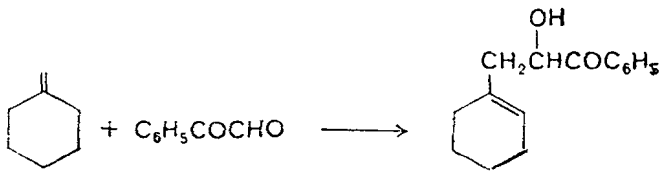
(29)

(30)



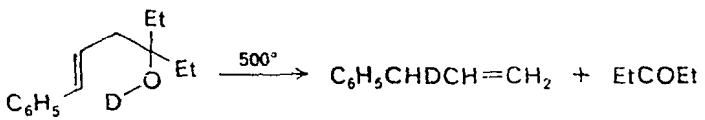
(31)

olefins generally combine with reactive aldehydes with migration of the double bond (equation 32). Young and Roberts[69] drew



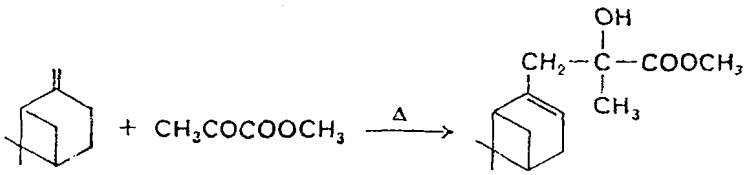
(32)

attention to the relation with the Claisen rearrangement[70] and suggested a cyclic transition state. Substantial evidence in support of the cyclic transition state has been accumulated. Deuterium labelling[71] showed that the hydroxyl proton is transferred intramolecularly to the γ-carbon. Only a single diastereomer is found when β-pinene



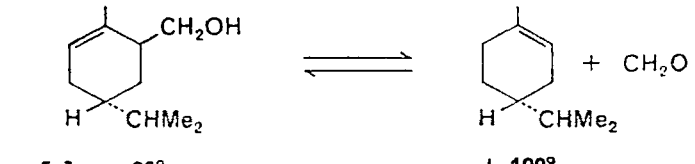
(33)

combines with methyl pyruvate (equation 34)[72]. Similar selectivity



(34)

is found in the 'ene' reaction[73, 74]. A radical reaction is eliminated by use of an optically active alcohol (equation 35)[75]. Optical activity is retained in a product whose asymmetric centre is formed as that in the reactant is destroyed (equation 36)[76]. Activation parameters for



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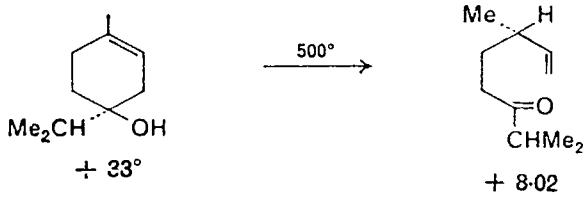
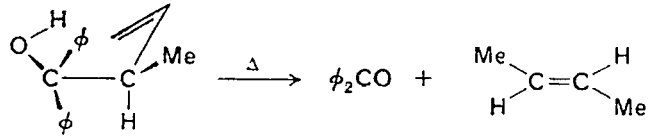


(36)

a number of cleavages have been measured[77] and most $\Delta H^{\ddagger}$ lie near 40 kcal/mole and $\Delta S^{\ddagger}$ are ca −8 e.u.

In the cleavage process a preference normally exists for formation of a *trans* double bond. Thus decomposition of diphenyl α-methallyl carbinol gives 77% *trans*- and 23% *cis*-2-butene (equation 37)[78]. The



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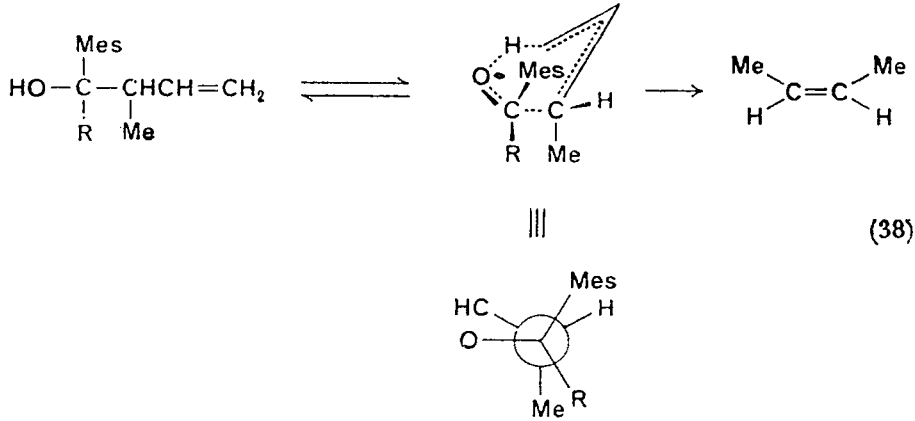
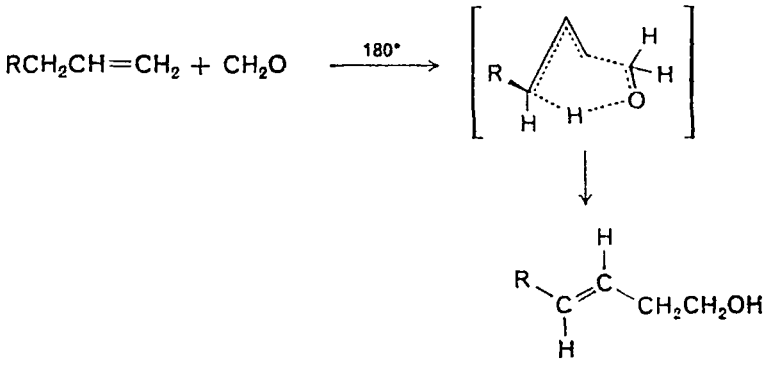


(38)

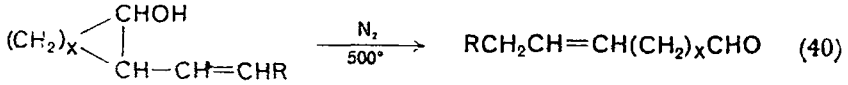
ratio of *cis* to *trans* is similar to that obtained in an E_2 elimination[79]. This contrasts most remarkably with the result achieved when an alkyl mesityl α-methylallyl carbinol is decomposed[65, 78]. If the alkyl group is methyl, 72% *cis*-2-butene is formed[65] and when the alkyl is isopropyl 74% *cis*-2-butene results[78]. A cyclic transition state with the breaking OH and C–C bonds coplanar (equation 38), expected on a stereoelectronic basis, will rationalize these results. In accord with geometry for the transition state the double bond formed during the condensation process is predominantly *trans* (reaction 39)[80].



(39)

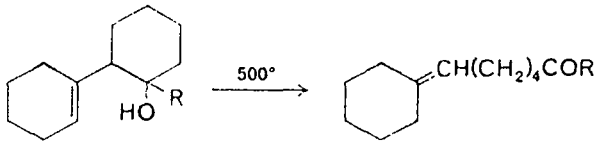
Alkyl and aryl groups have only relatively small influence on the rate of the cleavage[77]. Going from a primary to a tertiary alcohol increases the rate by about fivefold. Phenyl groups have the largest effect and show opposing influences when in the 3- or the 4-position on the butenol chain. Thus 3-phenyl-3-buten-1-ol decomposes about ten times faster than 3-buten-1-ol itself, and the 4-phenyl derivative reacts about five times slower.

Synthetic use of the reaction can be made in either direction. The cleavage reaction has been used in a very clever process for lengthening carbon chains (equations 40, 41)[81, 82]. In equation (41) when R is C≡CH the reaction takes a different course[83]. However, replacing the double bond by a triple bond does not cause the reaction to fail[84, 85, 86]. When it is functionally possible the reaction competes with the oxy-Cope rearrangement (see section II.c)[87]. In



(40)

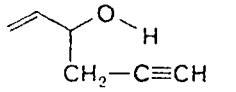
$R = C_6H_{13}, C_5H_{11}, C_4H_9$
$x = 3, 4, 5$



(41)

R = H, CH_3, C_6H_5

cases where the oxy-Cope is geometrically unfavourable the cleavage may be the only observable process (equation 44)[88].



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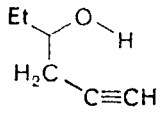

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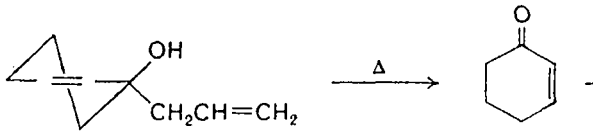
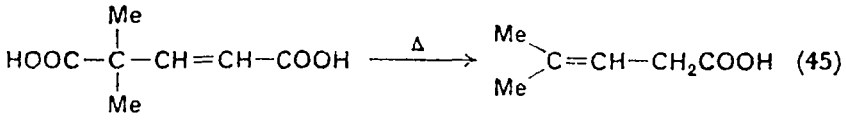


(44)

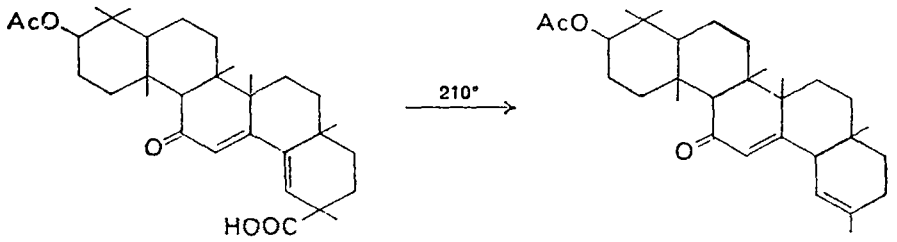
4. Decarboxylation of β,γ-unsaturated acids

A reaction which is directly related to the β-hydroxyolefin cleavage is the rather special thermal decarboxylation of β,γ-olefinic acids. In fact it makes little difference whether the hydroxyl-bearing carbon is the alkyl carbon of the alcohol or the carbonyl group of the acid (equation 45)[89]. The mechanistic relation between these was recognized by Arnold[90], who showed that the decarboxylation of α,β-olefinic acids often occurs via the β,γ-unsaturated acid. A six-



(45)

membered ring transition state is favoured since dienoic acids often give unconjugated dienes (reaction 46)[91, 92, 93]. The special ease of decarboxylation of β,γ-olefinic acids has been utilized in structural studies of morolic acid[93] and of polyporenic acid[94]. The reaction has been employed for the synthesis of exocyclic olefins (equation 47)[95, 96].



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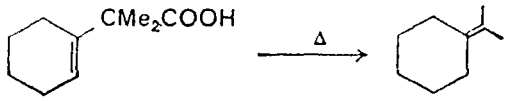
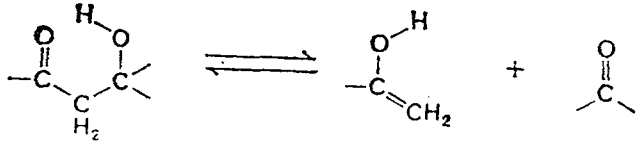


(47)

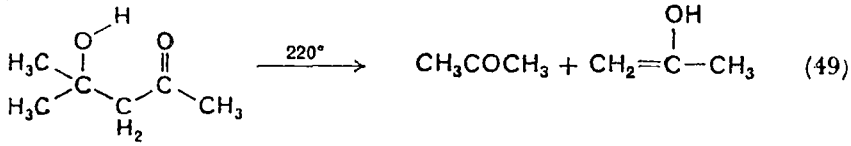
5. Thermal aldol condensation

The aldol condensation which is normally carried out with acids or bases as catalysts does occur as a thermal process. Formally it may be visualized as a β-hydroxy olefin cleavage with the carbon–carbon double bond replaced by a carbonyl group (reaction 48). Generally the retrograde aldol rather than the condensation is more readily observed as a thermal process. Smith and Yates[97] studied the de-



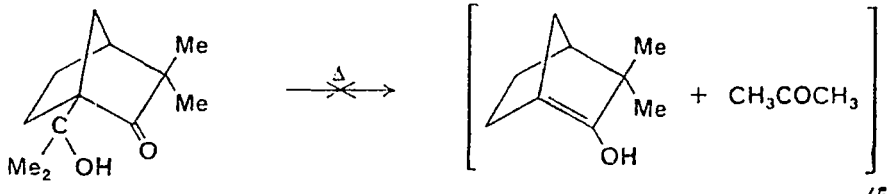
(48)

composition of 4-hydroxy-4-methyl-2-pentanone in the vapour phase at 220–250° (equation 49). The kinetics are first-order with $\Delta H^{\ddagger} = 30$ kcal/mole and $\Delta S^{\ddagger} = -8$ e.u. Mole[98] found that

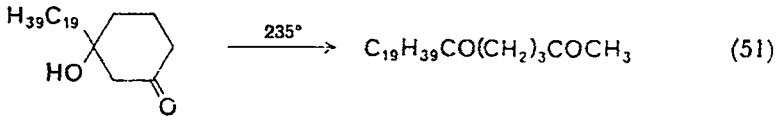


(49)

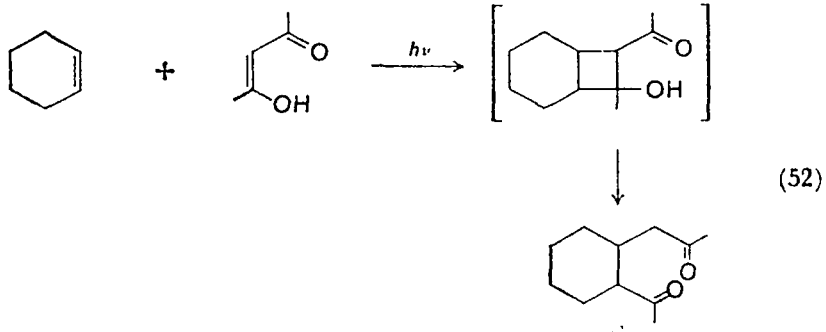
2-methyl-2-(1-hydroxyisopropyl)cyclohexanone undergoes a retrograde aldol condensation, whereas 1-(1-hydroxyisopropyl)-3,3-dimethyl-2-bicyclo[2.2.1]heptanone, which cannot form an enol, is thermally stable (equation 50). Lamberton observed a retrograde aldol condensation when a 3-hydroxycyclohexanone was distilled (reaction 51)[99]. Apparently a thermal retrograde aldol reaction plays a role in the interesting photochemical synthesis of 1,5-diketones (reaction 52) developed by deMayo[100, 101].



(50)

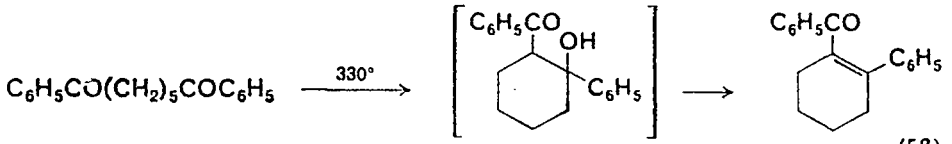


(51)



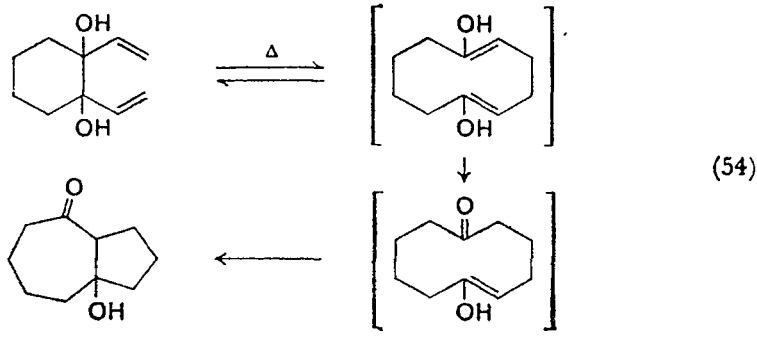
(52)

Diketones may undergo a thermal aldol condensation with cyclization[20, 102]. Thus, for example, 1,7-diphenyl-1,7-heptane-



(53)

dione cyclizes at 330° and the aldol product dehydrates under these conditions (equation 53)[102]. Marvell and Whalley[103] noted that a

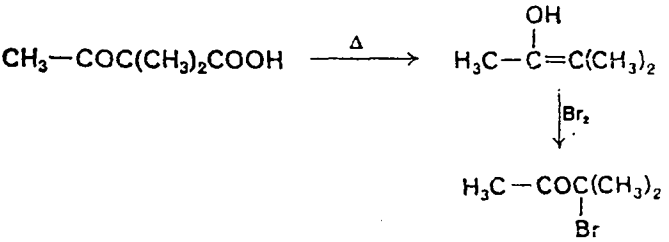


(54)

thermal aldol condensation may provide the route to the formation of 7-hydroxy-2-bicyclo[5.3.0]decanone from 1,2-divinyl-1,2-cyclohexanediol (reaction 54). In this case an alternate possibility exists for formation of this hydroxyketone (see equation 86).

6. Decarboxylation of β-keto acids

The well known decarboxylation of β-keto acids is mechanistically related to the above reactions and involves a six-membered cyclic transition state[104]. In buffered media both the acid and the anion undergo decarboxylation, but the rate constant for the acid is ca 100 times greater than that of the anion[104]. If reaction is carried out in the presence of bromine, an α-bromoketone is found (reaction 55)



(55)

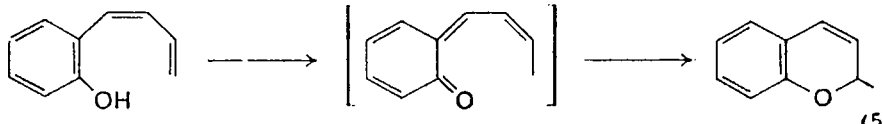
indicating the initial formation of an enol[104]. If enol formation is geometrically impossible the acid will be thermally stable, as is 7,7-dimethyl-2-bicyclo[2.2.1]heptanone-1-carboxylic acid[105]. The rate of decarboxylation of β-keto acids is not markedly influenced by solvent, and the change from alkyl to aryl groups on the β-carbon also has very little influence on the rate[106].

C. *The [1,7]Sigmatropic Shift*

Concerted thermal 1,7-hydrogen migrations are predicted theoretically[5, 7] to be antarafacial. However, the molecule now may have sufficient flexibility to meet this requirement and these reactions have been observed in all carbon systems[107–110]. Not surprisingly, the 1,7-hydrogen migration in a trienol system is rare since the stereochemical requirement that two contiguous double bonds have a *cis*-configuration is rarely met. Heating *cis*-1-(*o*-hydroxyphenyl)-butadiene at 110° is reported to give 2-methylbenzopyran (equation 56)[111]. The OD derivative leads to introduction of a deuterium in the

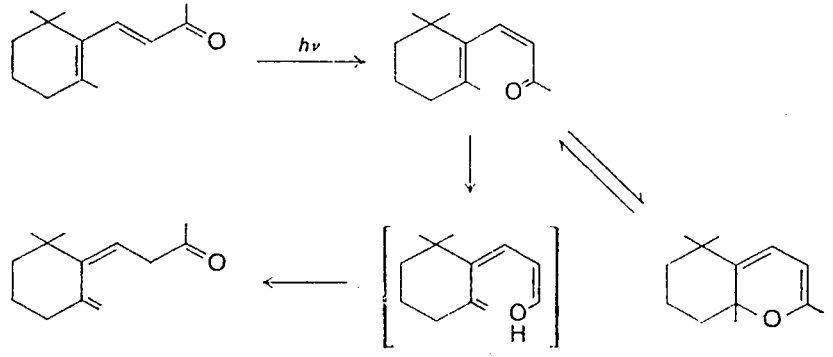
(56)

methyl group of the product. Thus a [1,7] migration is suggested as the first step in the reaction.



(57)

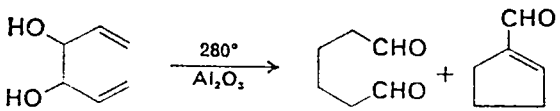
An apparent photochemical 1,7-hydrogen shift is involved in the formation of one of the products of irradiation of *trans*-β-ionone in ether solution[112]. The major product of the irradiation is the pyran[113]. Intermediate formation of *cis*-β-ionone is supported by the evidence for its presence in equilibrium with the pyran[114].



(58)

D. The [3,3] Sigmatropic Shift

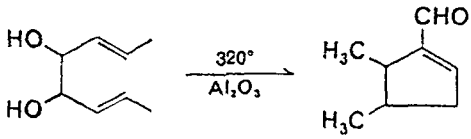
The Cope rearrangement, discovered in 1940[115], is one of the well known and carefully investigated[116] examples of the [3,3] sigmatropic reaction. The course of the rearrangement may be quite profoundly influenced by the presence of hydroxyl groups, and Berson[117] has coined the term oxy-Cope rearrangement for such cases. Oddly enough the first example of an oxy-Cope rearrangement was published some ten years prior to Cope's discovery. Urion[118] found that heating 3,4-dihydroxy-1,5-hexadiene over aluminium oxide gave cyclopentene-1-carboxaldehyde and a trace of 1,6-hexanedial (equation 59). The role of the aluminium oxide is



(59)

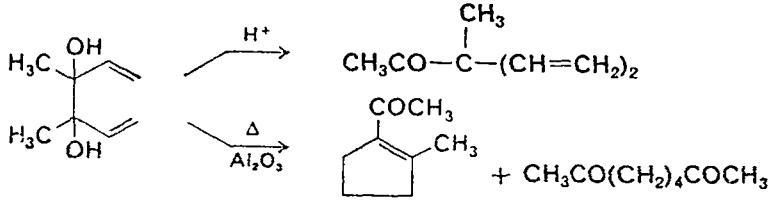
obscure and probably does not alter the reaction (see below). However, it did serve to mask the purely thermal nature of the rearrange-

ment from Urion. In further studies he showed that some acrolein and propionaldehyde were formed in the reaction[119], and that the pinacol–pinacolone rearrangement product, 1,5-pentadiene-3-carboxaldehyde, was not an intermediate. The homologous 4,5-dihydroxy-2,6-octadiene gave a mixture of *cis*- and *trans*-4,5-dimethylcyclopentene-1-carboxaldehyde (reaction 60)[120].



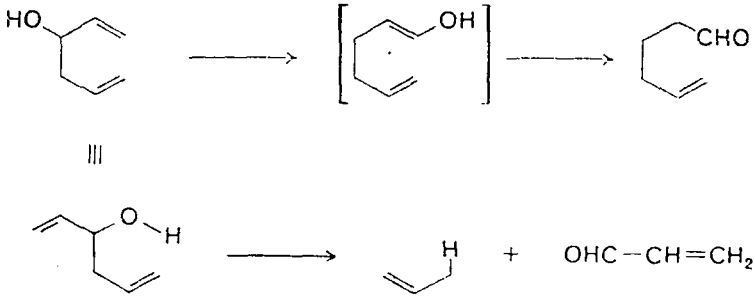
(60)

Following Cope's early work there was a period of relative inactivity in this field, and no studies of hexadienes with functional substituents other than nitrile or ester groups were made until 1959. Wiemann and Thuan[121], in a continuation of Urion's work, reported that the thermal and acid catalysed reactions of 3,4-dimethyl-3,4-dihydroxy-1,5-hexadiene gave different products. They suggested aluminium oxide was acting as a surface active catalyst.



(61)

Generally simple aliphatic hexadienes having one or more hydroxyl groups at C_3 or C_4 rearrange in a concerted process giving a carbonyl compound. Thus 1,5-hexadien-3-ol gives 5-hexenal[122]. The β-hydroxyolefin cleavage is the main competitive reaction (equation 62). Viola and co-workers[87] have made a thorough study of the effect of methyl substitution on the ratio of cleavage versus rearrangement. Replacement of a hydrogen by a methyl at C_2, C_3

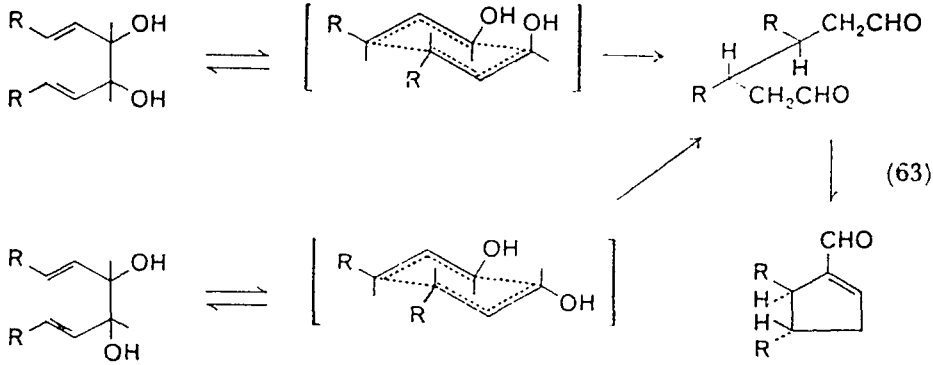


III

(62)

or C_4 alters the ratio very little, while substitution at C_1, C_5 or C_6 favours the cleavage. The ratio is solely dependent on the relative free energies of the two transition states (Curtin–Hammett principle)[123, 124] and apparently more than a pure steric problem is involved.

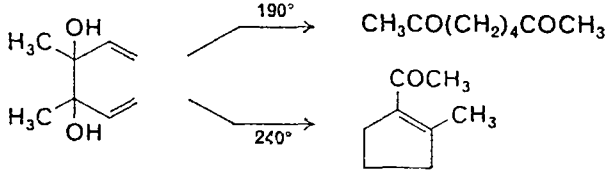
It has been shown theoretically[6] that the Cope rearrangement prefers a chair-like to a boat-like transition state. This has been confirmed experimentally[125]. With a diol having both double bonds *trans* application of the principles of conformational analysis shows that both *dl* and *meso* forms of the diol must give the *dl* form of the



(63)

product (equation 63). Ring closure should lead exclusively to the *trans*-4,5-dialkylcyclopenten-1-carboxaldehyde. Chuche and Wieman[126] found that for R = phenyl the product was purely *trans*, but where R = methyl the product contained 76% *trans*- and 24% *cis*-4,5-dimethylcyclopenten-1-carboxaldehyde. The latter result confirms Urion's earlier study[120]. Either the reactant in this latter case must contain some mono-*cis* isomer, or a most unexpectedly high percent of reaction occurs via the boat-like transition state.

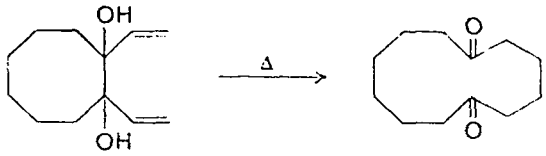
Conia and students[127, 128] have shown the synthetic value of the rearrangement of the readily accessible 1,2-divinyl-1,2-diols. Reaction may lead either to a dione or a cyclized product (equation 64)



(64)

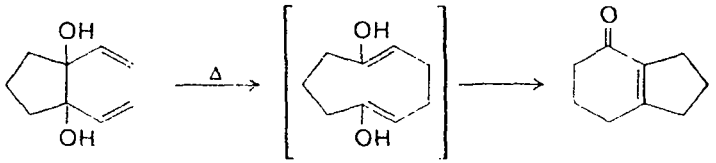
depending on the conditions. The reaction might be expected to be useful for ring expansion by four carbons. In some cases it is indeed[129]

useful in this way (equation 65), but in the most valuable region, i.e. formation of medium rings from the common ring derivatives, cyclization of the bis-enol is apparently unavoidable[103, 127]. Under



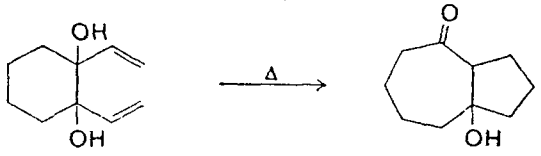
(65)

controlled conditions the hydroxy ketone can be isolated[103] (equal tion 67). Formation of the ketone is stereospecific since the *trans*-dio-



(66)

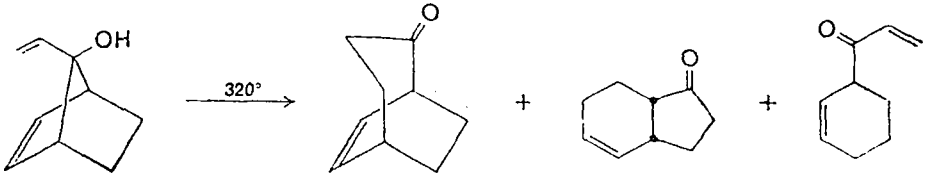
gives one isomer of the ketone, while the *cis*-diol forms a mixture



(67)

containing mainly the other isomer[103]. The result is nicely rationalized via a stereospecific Cope rearrangement followed by an aldol condensation (equation 54) or by an enolene rearrangement (equation 86).

If the molecular geometry permits the ends of the hexadiene system



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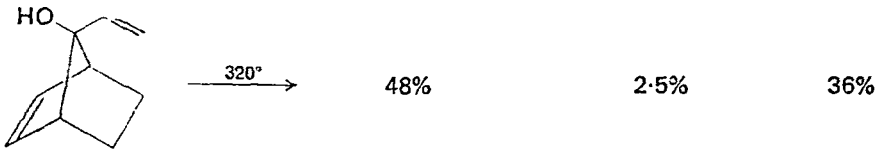
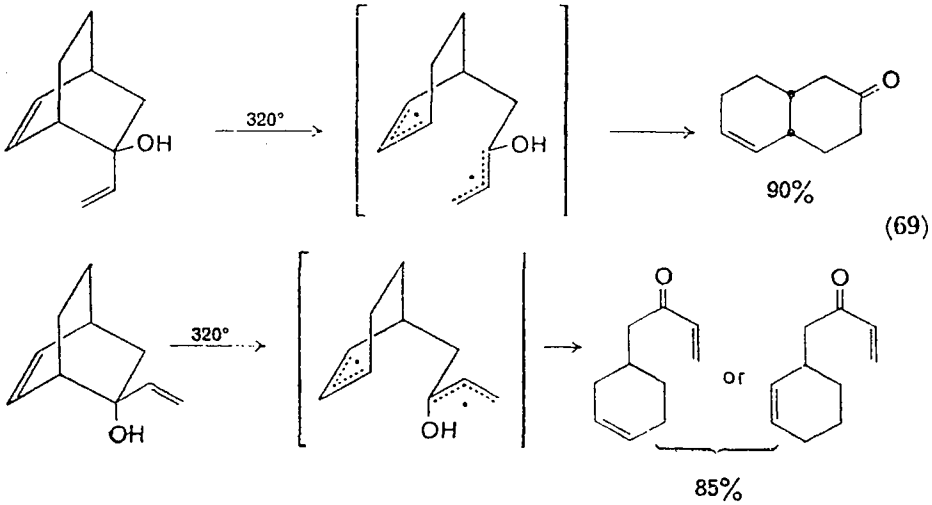


to approach one another properly, the Cope rearrangement is a concerted reaction[116]. When this condition is not met fission to two allylic radicals and recombination occur[130]. Examples of the oxy-Cope reaction which proceed by a biradical mechanism have been reported by Berson and students[117, 131–133]. Both epimers of 7-vinyl-2-bicyclo[2.2.1]hepten-7-ol rearrange at the same rate giving mixtures of the same products but in differing amounts (reaction 68)[131]. Radical recombination with both single inversion and double inversion of the allyl groups occurs. The monocyclic ketone is derived from a reaction which is a formal analogue of the β-hydroxy olefin cleavage. Since *syn*-7-vinylnorbornenol is the major product (75%) from 7-norbornenone and vinyl Grignard, this thermal process is an effective synthetic entrée to the bicyclo[3.2.2]nonane ring system.

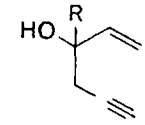
A second epimeric pair (equation 69) shows quite a different



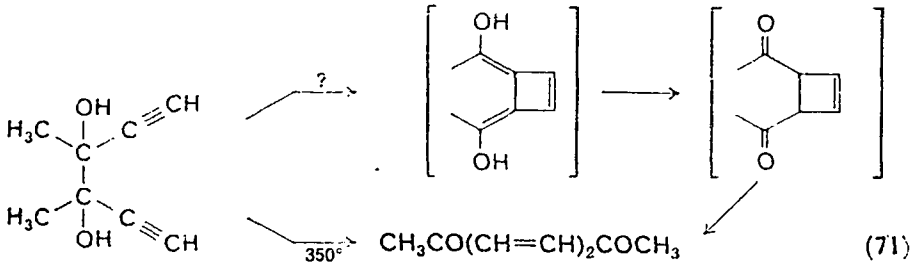
behaviour despite the fact that they react at the same rate. In this case the radical recombinations or hydrogen abstractions are so much faster than internal rotations that no crossover results. That the reaction is intramolecular was confirmed by the use of optically active reactants[132]. The hydroxyl group lowers the bond dissociation energy of the central bond of the biallylic system by 2·4 kcal/mole[133].

Use of a triple bond in place of a double bond apparently causes no alteration in the course of the rearrangement[84–86]. Both the Cope rearrangement and the β-hydroxy olefin cleavage (equations 42 and 43) occur. Some enolene rearrangement products are also observed

(see section III). The mechanism has not been investigated, but no products derived from a single inversion radical recombination were observed. Even 3,4-dimethyl-3,4-dihydroxy-1,5-hexadiyne gave the



$$\xrightarrow{\Delta} \quad RCOCH_2CH_2CH{=}C{=}CH_2 + RCOCH{=}CH_2 + CH_2{=}C{=}CH_2 \qquad (70)$$

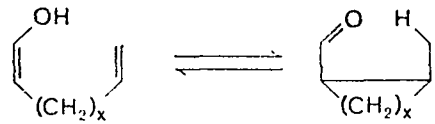


$$\xrightarrow{350^\circ} \quad CH_3CO(CH{=}CH)_2COCH_3 \qquad (71)$$

product expected of a normal oxy-Cope rearrangement (equation 71)[86]. An alternative route via formation of a dimethylenecyclobutene[134] and electrocyclic ring opening of the ketonized cyclobutene[135] is a distinct possibility.

III. THE ENOLENE REARRANGEMENT

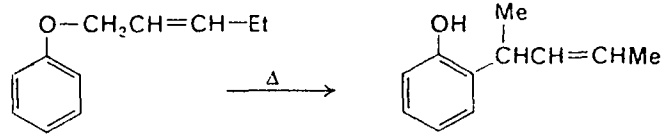
The term 'enolene' rearrangement was coined by Roberts[15] to cover the general rearrangement (equation 72). In the reverse direction



(72)

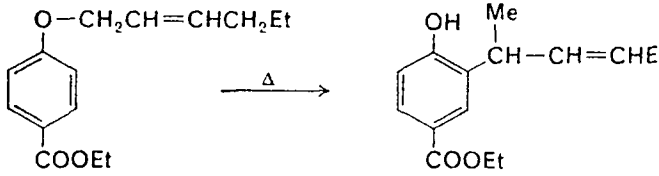
this is formally a 1,5-hydrogen shift, and where x = 1 Winstein[136] called such rearrangements homodienyl hydrogen shifts. The forward reaction is clearly an intramolecular 'ene' reaction[67]. To emphasize this diversity of character, these rearrangements have been put in a separate section.

Historically the enolene rearrangement is an offspring of the Claisen rearrangement. Lauer and Filbert[137] observed that γ-ethylallyl phenyl ether gave *o*-(α,γ-dimethylallyl)phenol (equation 73) rather than the expected *o*-(α-ethylallyl)phenol. The normal product was identified in the product mixture by later workers[136]. Rearrangement with isomerization in the allylic moiety was termed the abnormal Claisen rearrangement. Some of the structural requirements for



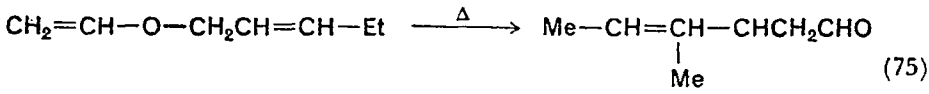
(73)

abnormal rearrangement were quickly established. Only the normal product was obtained from α-alkylallyl phenyl ethers[137, 139, 140]. A γ-methyl or phenyl on the allyl group led only to normal reaction[141]. *Para*-Claisen rearrangement of the γ-ethylallyl ether of methyl cresotinate was completely normal[142]. An abnormal product was obtained[139] from γ-propylallyl 4-carbethoxyphenyl ether (equal tion 74), and a chroman clearly derived from an abnormal product



(74)

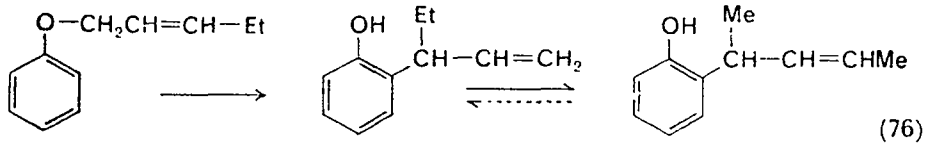
was isolated from a γ,γ-dimethylallyl ether[143]. An acyclic case was provided by the isolation of a small amount of 3-methyl-4-hexena- from γ-ethylallyl vinyl ether[138]. Eventually use of C^{14} showed that



(75)

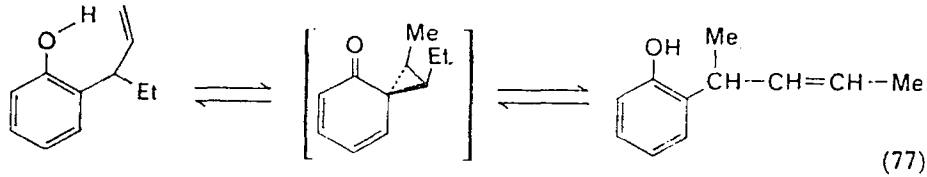
an abnormal product was also formed from a crotyl ether[144].

Finally, a careful investigation revealed that the abnormal product was not a direct descendant from the ether, but resulted from further reaction of the normal product[145]. The methyl ether of the normal



(76)

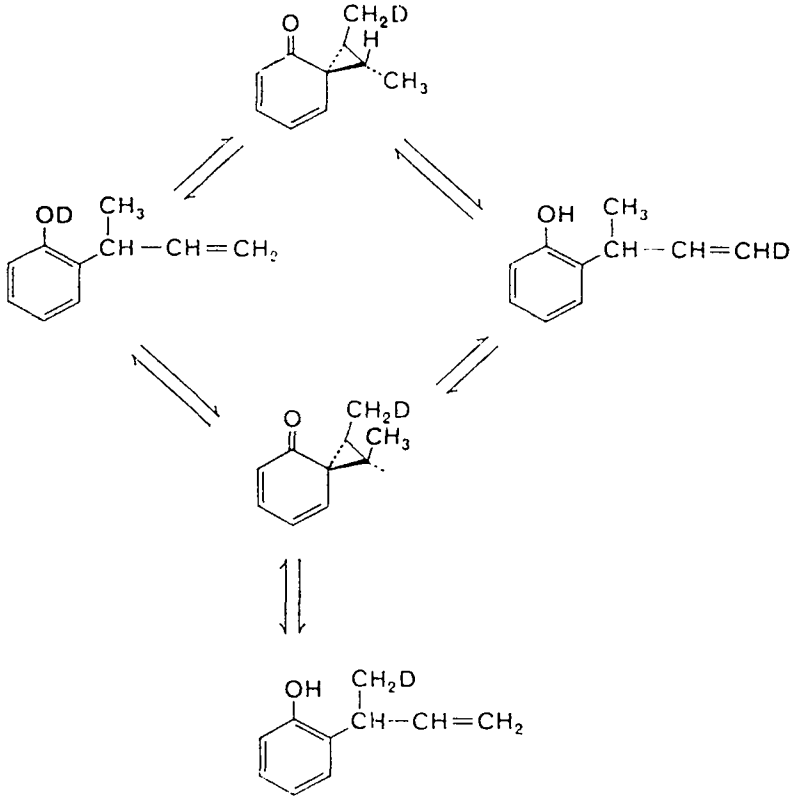
product is thermally stable alone or in the presence of phenol. *Para*-Claisen products are also thermally stable. Rearrangement is limited



(77)

to *o*-(α-alkylallyl)phenols, and is a rather complex example of the enolene rearrangement[145].

A significant body of data has been accumulated in support of this mechanism. Further studies with *o*-(2-C^{14}-methylallyl)phenol showed that the label was equilibrated between the α-methyl and γ-allyl carbons only[146, 147]. Heated in deuterium oxide the phenol incorporated deuterium on the same two carbons[148]. However the rate of incorporation was faster at the γ-carbon than in the methyl group. This observation is in accord with the expectation that the methyl groups on the cyclopropane ring of the intermediate may be either

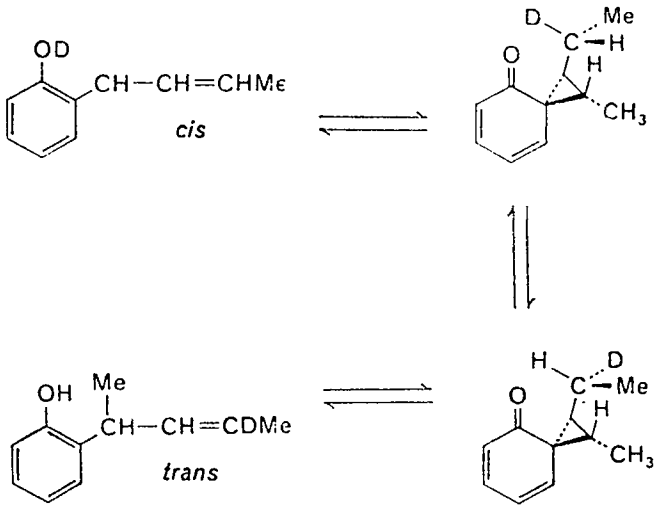


(78)

cis or *trans* (reaction 78). Only the *cis* orientation can lead to deuteration of the methyl. Both deuterium incorporation and *cis–trans* isomerization of the double bond were used[149] to demonstrate reaction of an *o*-crotylphenol.

The rates of *cis–trans* isomerization and of deuterium incorporation at the γ-carbon of *o*-(α,γ-dimethylallyl)phenol are identical[150]

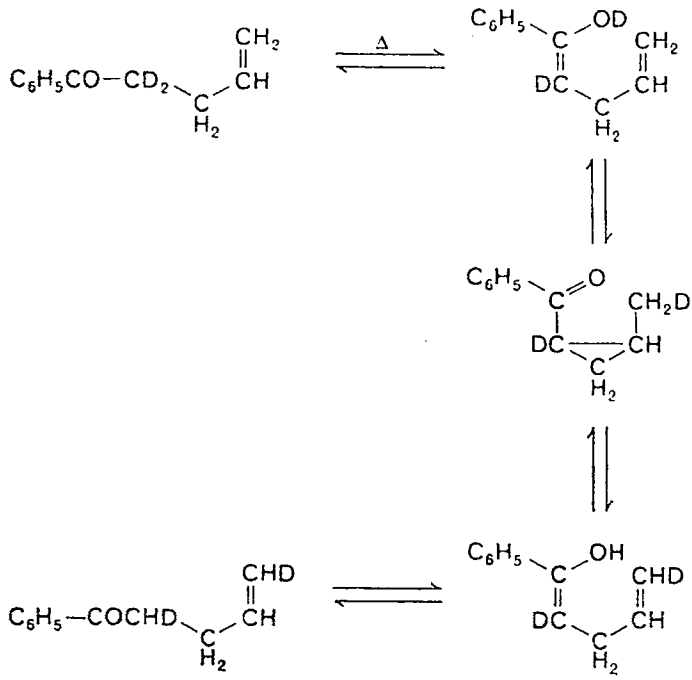
and the *trans*-product obtained from a pure *cis*-isomer contained only deuterium at the γ-carbon (reaction 79). The proton transfer is thus



(79)

stereospecific. The theoretical basis for the specificity was suggested by Winstein[151].

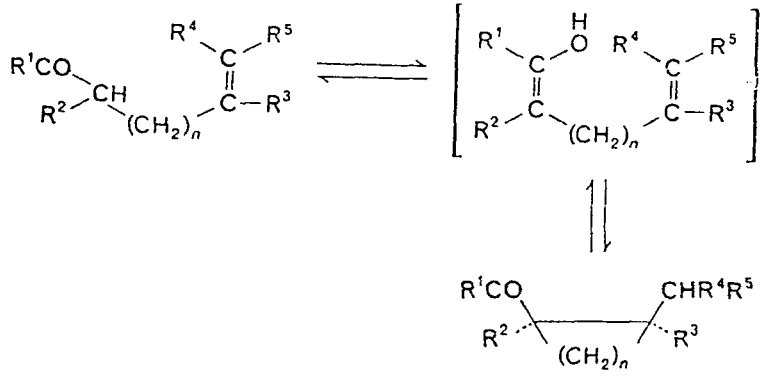
As these results would suggest, *cis*-1-acyl-2-alkylcyclopropanes



(80)

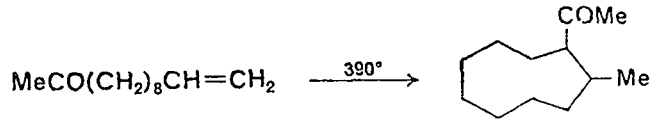
undergo facile thermal ring opening accompanied by a hydrogen shift[15, 152–154]. *Trans*-isomers are thermally stable at temperatures where the *cis*-isomers react readily. Rearrangement of 1-acetyl-2,2-dimethylcyclopropane was kinetically first-order ($\Delta S^{\ddagger} = -10$ e.u.)[152, 153]. Though the enol appropriate to reversal of this ring opening is not stable in a nonphenolic system, it is apparently formed readily in situ since 4-pentenophenone-2*d* exhibits the appropriate deuterium migration (equation 80)[15].

Conia and students have demonstrated that the enolene rearrangement is of great generality[20, 21, 155–164]. Examples of the type (reaction 81) have been studied with $n = 1$, 2, 3, 4 and 7. When $n = 1$ or 2 ring opening occurs and when $n = 3$, 4 or 7 cyclization is the spontaneous process[159]. The stereochemistry of the cyclized product is as shown but if $R^2 = R^3 = H$ further reaction leads to



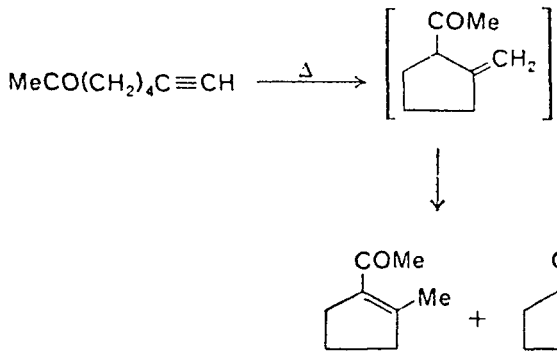
(81)

the *trans*-isomer. Yields in the ring formation reach a maximum with $n = 3$ and decrease as n increases. However, even when $n = 7$ the yield is 30% (equation 82)[158].



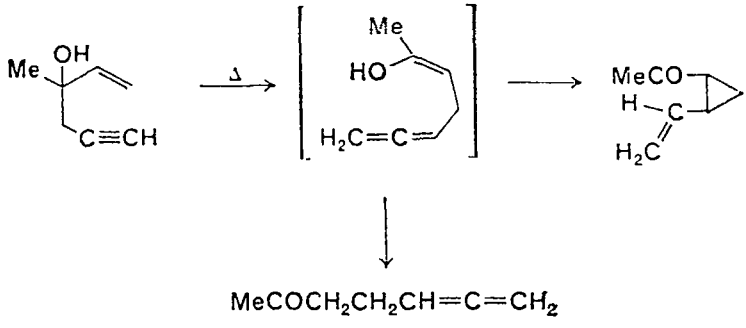
(82)

Doubly-unsaturated ketones with an α,β-enone system will react (equation 7) if the proper structural conditions are satisfied[21, 160], but the α,β-double bond is deconjugated during reaction. Acetylenic ketones like 7-octyn-2-one cyclize in good yield[20]. If the acetylenic group is in a terminal position the initially formed exocyclic double bond migrates to an endocyclic position (equation 83).

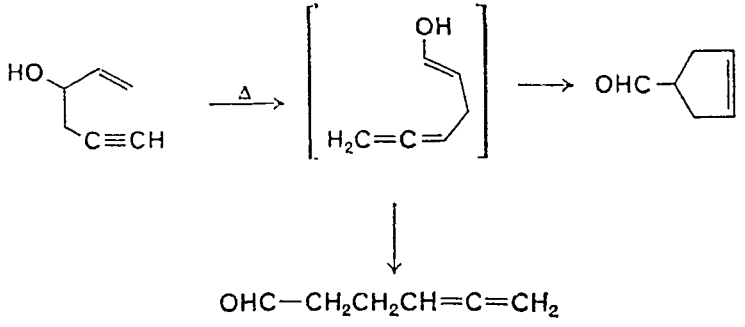


(83)

In all of these aliphatic or alicyclic cases the enol must be formed initially from the ketone. As was noted earlier the mode of this process is not yet clear. In some other reactions, notably the oxy-Cope, an enol is formed directly and under the proper conditions an enolene rearrangement could follow this step. When 3-methyl-3-hydroxyhex-1-ene-5-yne is heated the expected result occurs (equation 84)[85]. Apparently the allenic enol rearranges rapidly to the 1-acetyl-2-vinylcyclopropane which survives the conditions of the reaction. This is the first example of a ring closure in the enolene



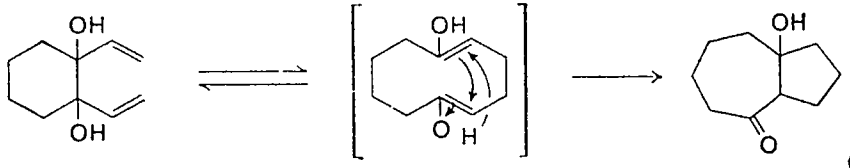
(84)



(85)

case where $n = 1$. A most unusual ring closure is observed when the methyl group is missing (equation 85)[84]. It would appear that the 3-cyclopenten-1-carboxaldehyde could not be the product of a concerted ring closure like the enolene process. The enol is expected to be predominantly *trans*, if the oxy-Cope rearrangement is concerted in this case, and in any event direct transfer of the hydrogen to the central carbon of the allene would give a *trans* double bond rather than the *cis* one needed to form a five-membered ring.

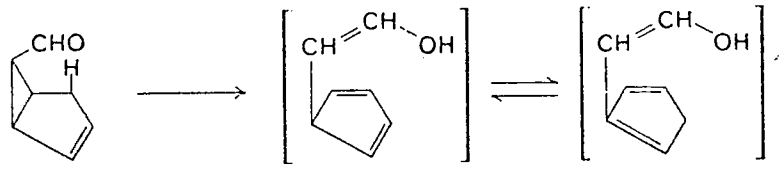
The enolene rearrangement may also be the terminal step in oxy-Cope reactions leading to initial formation of medium ring bisenols[103]. In accord with this suggestion, which gives a role only to



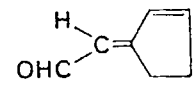
(86)

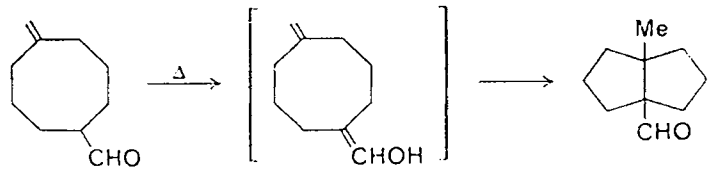
one of the hydroxyl groups (equation 86), the mono methyl ether of 1,2-divinyl-1,2-cyclohexanediol reacts in the same way to give a bicyclic product[103].

Though the final step in most ring openings by the enolene process is a formal 1,3-hydrogen shift, the theoretically expected greater facility of a 1,5-shift is illustrated by one case (reaction 87)[105]. Note



(87)





(88)

that the very facile 1,5-hydrogen shifts in the cyclopentadiene ring[166, 167] apparently proceed more rapidly than that involving the enol. A ring closure of an interesting type which may also belong to the enolene group has been reported (equation 88)[168], although the authors do not attribute the ring closure to this mechanism.

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The Chemistry of The Hydroxyl Group
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CHAPTER 14

Biological formation and reactions of the hydroxyl group

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I. INTRODUCTION

The purpose of this chapter is to discuss the formation and reactions of hydroxyl groups in compounds found in biological systems. If one looks at the large number of organic molecules found in the plant and animal kingdoms, it is quickly apparent that the majority contain hydroxyl groups, for example, all sugars, some amino acids, some fatty acids, steroids, pigments, etc. Since it would be difficult to try and describe completely the synthesis of all of these compounds, only the general principles of hydroxyl group formation will be discussed here.

Although compounds with hydroxyl groups may vary structurally and chemically, there are surprisingly few general reactions which lead to their biosynthetic formation. In organic chemistry, hydroxyl groups are introduced into molecules by one of the following reactions:

1. Reduction of a carbonyl group. 2. Group transfer reactions including ester hydrolysis and hydrolysis of glycosidic bonds. 3. Aldol or ketol condensations. 4. Addition of water at a double bond. 5. Monooxygenation or mixed function oxygenation.

These reactions have been extensively investigated and the mechanisms are relatively well understood.

The same reaction types are found in biological systems with the important difference that they are catalysed by enzymes. The enzymes have been divided into groups according to the reaction which they catalyse[1]. Reactions of the hydroxyl group in biological systems are in most cases implied in the enzymatic reactions for their formation since most of these are reversible.

The importance of reactions involving hydroxyl groups in biological systems can be indicated as follows: Hydroxylated compounds formed by the addition of water to a double bond or by reduction of a carbonyl group can act as hydrogen donors for dehydrogenases. These can transfer their reducing equivalents to the respiratory chain resulting in the formation of ATP, which is the major energy source for all biochemical reactions. Hydroxyl groups can also act as acceptors in group transfer reactions. These are important in photosynthesis and in the metabolism of carbohydrates.

The hydrophobicity of organic compounds can be diminished by introduction of hydroxyl groups. This enables the specific transfer of compounds between systems of varying hydrophilicity.

Hydroxylations are important in steroid metabolism where the presence of hydroxyl groups plays an important role in biological hormone activity. The metabolism of xenobiotics (see section VIII. A.4) also involves hydroxylation reactions. Secondary metabolism reactions such as those involved in the synthesis of alkaloids, terpenoids, etc., also utilize hydroxyl group formation.

In summary, the processes leading to biological formation of hydroxyl groups and their subsequent reactions will be discussed, giving representative examples of each group to illustrate the mechanism involved. Special emphasis has been placed on some of the monooxygenases which have been extensively investigated only in the last few years.

II. SOME CONCEPTS OF ENZYMOLOGY AND A LIST OF ABBREVIATIONS

In a discussion of the biological formation and reactions of hydroxyl groups, it may be well to define some of the more common biochemical terms and concepts.

An enzyme is defined as 'a protein with catalytic properties due to its power of specific activation'[2].

Purification of enzymes led to determinations of molecular weight and shape as well as various other physical and chemical properties. In addition to protein, many enzymes also contain bound metal ions, flavins, pyridine nucleotides, pterins, etc.

Enzyme reactions can be studied by investigations of the substrates and products using the usual methods of general chemistry; spectrophotometry, manometry, electrode methods, polarimetry, chromatography, isotopes.

In interpretation of such investigations, three definitions are particularly useful in biochemistry:

1. Coenzyme. Functions as a biological catalyst only when it is activated by a specific enzyme. An example is NAD.
2. Substrate. Substance on which an enzyme acts and which is activated by it.
3. Active centre. Part of the enzyme at which the substrate is bound and at which the enzymatic reaction occurs.

Enzyme reactions involve the formation of an intermediate enzyme–substrate complex:

$$E + S \rightleftharpoons ES \rightleftharpoons EP \rightleftharpoons E + P \qquad (1)$$

where E = enzyme; S = substrate; ES = enzyme–substrate complex; EP = enzyme–product complex; P = product.

Enzyme activities are usually expressed in the following terms[1]:

One unit of an enzyme is that amount which will catalyse the transformation of 1 μmole substrate/minute at optimal pH and substrate concentration at a given temperature. The specific activity is defined as units of enzyme/mg of protein.

Excellent reviews on mechanisms of enzyme catalysis are those of Westheimer[3] and Rose[4].

For easier reference, the classification ('EC') numbers as set forth by the Enzyme Commission of the International Union of Biochemistry[1] have been included whenever possible.

A list of some abbreviations commonly used in biochemistry follows.

Abbreviations

NAD = oxidized nicotine adenine diphosphopyridine nucleotide

$NADH_2$ = reduced nicotine adenine diphosphopyridine nucleotide

NADP = oxidized nicotine adenine diphosphopyridine nucleotide phosphate

$NADPH_2$ = reduced nicotine adenine diphosphopyridine nucleotide phosphate
ATP = adenosine triphosphate
FAD = flavin adenine nucleotide
UDP = uridine diphosphate
DOPA = dihydroxyphenylalanine

III. REDUCTION OF A CARBONYL GROUP

These important reactions in biochemistry are catalysed by a group of enzymes belonging to the oxidoreductases, subgroup dehydrogenases. Those of interest here catalyse the following reversible reaction:

$$R^1R^2C{=}O \rightleftharpoons R^1R^2CHOH \qquad (2)$$

Substrates for these enzymes are alcohols, sugars, hydroxy acids and hydroxy steroids and the corresponding ketones. They require a pyridine nucleotide, NAD or NADP, as co-factor. Recent reviews of dehydrogenase reactions are given by Sund, Diekman and Wallenfels[5] and by Strittmatter[6].

A. Alcohol Dehydrogenase

One of the best known and most thoroughly investigated reactions of this type is that of alcohol dehydrogenase (ADH, EC 1.1.1.1.). It catalyses the following reaction:

$$RCHO + NADH_2 \rightleftharpoons RCH_2OH + NAD \qquad (3)$$

This enzyme can be isolated from many different sources.

The stereochemistry of this reaction has been studied particularly by Vennesland and co-workers[7] using deuterium labelled ethanol. The enzyme is stereospecific for both the alcohol and pyridine nucleotide; the reaction occurring by direct transfer of hydrogen atoms. The mechanism probably involves the formation of intermediate ternary complexes whose interconversions are rate-limiting. Zinc and thiol groups are necessary for binding of substrate and coenzyme to the enzyme.

A dehydrogenase with a different mechanism is illustrated by hypoxanthine dehydrogenase, a NAD requiring flavoprotein[8], important in purine base metabolism. Here, hydrogen atoms are probably transferred from the pyridine nucleotide to substrate via the flavoprotein, instead of directly.

Table 1 lists a few of the dehydrogenases which are important in the biochemistry of hydroxyl groups.

TABLE 1. Some examples of dehydrogenase reactions.

Name	Reaction	Reference
Malate dehydrogenase EC 1.1.1.37	Malate + NAD $\rightleftarrows$ oxaloacetate + $NADH_2$	9
Glycerol phosphate dehydrogenase EC 1.1.1.8	L-Glycerol-3-phosphate + NAD $\rightleftarrows$ dihydroxyacetone phosphate + $NADH_2$	10
Lactate dehydrogenase EC 1.1.1.27	Lactate + NAD $\rightleftarrows$ pyruvate + $NADH_2$	11
17-β-Hydroxysteroid dehydrogenase EC 1.1.1k	Testosterone + NAD $\rightleftarrows$ Δ^5-androstene-3,17-dione + $NADH_2$	12

IV. GROUP TRANSFER REACTIONS

There are many examples in biochemistry in which a group is transferred to an acceptor resulting in formation of a hydroxylated compound. Enzymes which catalyse these reactions include the transferases and hydrolases. For a review of transferase reactions see Reference 13.

A. Transferases

1. Transaldolases and transketolases

Transaldolase (EC 2.2.1.1) is an enzyme of the nonoxidative glycolytic pathway. Discussions of this enzyme as well as transketolase are given in Reference 14. This enzyme catalyses the transfer of a dihydroxyacetone moiety from a ketose. For example, from D-seduheptolose-7-phosphate to an aldose, D-erythrose-4-phosphate. It does not need co-factors for the reaction. The same mechanism for both the aldolase (see below) and transaldolase reactions has been postulated. A structure for the enzyme-bound intermediate can be depicted as in Figure 1.

Transketolase (EC 2.2.1.2) is a second enzyme of the nonoxidative

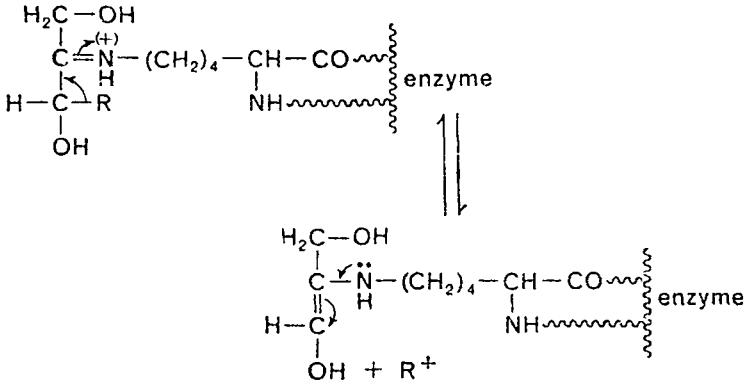

FIGURE 1. Structure of the enzyme-bound intermediate in the transaldolase reaction.

degradation pathway. An example of the reactions catalysed by this enzyme is

$$\text{Xylulose-5-phosphate} + \text{erythrose-4-phosphate} \rightleftharpoons \text{fructose-6-phosphate} + \text{glyceraldehyde-3-phosphate} \quad (4)$$

As co-factors, transketolase requires thiamine pyrophosphate (TPP) and a divalent cation, Mg(II)[15, 16]. The enzyme has been isolated from cells of various types; mammalian liver, green plants, bacteria. The reaction can be regarded as a reversible transfer from a ketose donor to an aldose acceptor. The condition for the reaction is that the ketose have the L-configuration.

2. Glycosyltransferases

The glycosyltransferases or transglycosidases may be divided into two groups, the hexosyl transferases and the pentosyl transferases. An example of these enzymes which is widely distributed is sucrose glucosyltransferase (EC 2.4.1.7) which catalyses the reaction

$$\alpha\text{-Glucose-1-phosphate} + \text{fructose} \rightleftharpoons \text{sucrose} + \text{phosphate} \quad (5)$$

From studies with ^{32}P labelled phosphate[17] and ^{14}C labelled fructose[18], it was shown that an intermediate glucose–enzyme complex is formed. In contrast, the mechanism of the reaction catalysed by maltose phosphorylase (EC 2.4.1.8)

$$\alpha\text{-Glucose-glucose} + \text{phosphate} \rightleftharpoons \beta\text{-glucose-1-phosphate} + \text{glucose} \quad (6)$$

does not involve an intermediate complex but rather a direct group transfer.

Other important types of enzyme are those requiring an UDP-sugar as substrate. These enzymes synthesize polysaccharides by

transfer of sugar residues to polysaccharide chains. An example is UDP-glucose-glycogen glucosyltransferase (EC 2.4.1.11) which catalyses the following reaction:

$$\text{UDP-glucose} + (\text{glycogen})_n \rightleftharpoons \text{UDP} + (\text{glycogen})_{n+1} \qquad (7)$$

A transferase catalysing esterification of a hydroxylamine or carboxylic group is UDP-glucuronyltransferase (EC 2.4.1.17). This enzyme is acceptor-unspecific and catalyses the transfer of a glucuronate group to a wide range of phenols, alcohols, amines and fatty acids:

$$\text{UDP-glucuronate} + \text{acceptor} \rightleftharpoons \text{UDP} + \text{acceptor-glucuronide} \qquad (8)$$

The enzyme has been isolated from liver. Its mechanism has been investigated and the reaction leads to inversion[19].

Hydroxyl groups give an ether linkage; carboxyl groups, an ester linkage.

3. Glycosidases

The transglycosidases are also active as glycosidases. In this case they catalyse the hydrolysis of glycosidic bonds in simple glycosides, oligo- and poly-saccharides. They are all water-soluble, slightly acid proteins with the exception of lysozyme which is basic. They do not appear to have any usual coenzyme or functional prosthetic group with the exception of α-amylase which is a metalloenzyme[20]. A discussion of these enzymes is found in Reference 21. The overall reaction can be written as follows:

$$\text{Glycosyl-OR} + \text{EH} \rightleftharpoons \text{glycosyl-E} + \text{ROH} \qquad (9)$$

$$\text{Glycosyl-E} + \text{H}_2\text{O} \rightleftharpoons \text{glycosyl-OH} + \text{RH} \qquad (10)$$

where EH = enzyme.

For each type of glycosidic bond, there is a more or less specific glycosidase. A list of some of these enzymes is given in Table 2.

4. Phosphotransferases

These enzymes transfer phosphate groups from a nucleotide, usually ATP, to alcohol groups, especially sugar alcohols. They are also known as kinases.

One of the best-known examples is hexokinase (EC 2.7.1.1.). It catalyses the following reaction:

$$\text{ATP} + \text{D-hexose} \longrightarrow \text{ADP} + \text{D-hexose-6-phosphate} \qquad (11)$$

These enzymes require Mg(II) for activation. The mechanism has been investigated using ^{32}P and ^{18}O labelled ATP (Reference 31).

TABLE 2. Enzymes hydrolysing glycosidic bonds.

Enzyme	Substrate or reaction	Source	Reference
α-Amylase (EC 3.2.1.1)	α-1,4-Glucan links of starch, glycogen and related polysaccharides	Pancreas, saliva, plants, moulds, bacteria	20–22
β-Amylase (EC 3.2.1.2)	β-1,4-Glucan links in polysaccharides removing successive maltose units from the nonreducing ends of the chain	Same as above	21, 23
Dextranase (EC 3.2.1.11)	α-1,6-Glucan links	Intestinal mucosa, moulds, bacteria	20, 24
α-Glucosidase (EC 3.2.1.20)	α-D-Glucoside + H_2O→ an alcohol + D-glucose	Widely distributed	25
β-Glucosidase (EC 3.2.1.21)	Acts on β-glucopyranosides and α-D-galactosides in animals	Animals, plants, moulds, bacteria	25, 26
α-Galactosidase (EC 3.2.1.22)	Hydrolyses α-D-galactosides to an alcohol + D-galactose	Yeast, plants, bacteria	27
β-Galactosidase (EC 3.2.1.23)	Hydrolyses β-galactosides to an alcohol + D-galactose; also catalyses galactotransferase reactions	Plants, moulds, bacteria	28
Trehalase (EC 3.2.1.28)	Hydrolyses trehalose to D-glucose	Yeast, moulds	29
Lysozyme (EC 3.2.1.17)	Hydrolyses β-1,4-links in mucopoly-saccharides and -peptides	Egg white, spleen, nasal mucus, latex	30

Mg(II) combines with ATP to form a complex which then combines with the enzyme. This complex then binds a hexose alcohol group. Thiol groups are involved in the enzyme binding. The hexokinases are important in activation of sugars for entrance into the glycolytic pathway.

A special type of transfer reaction is involved in the biosynthesis of serine from cysteine[32]. Serine is produced by a transsulphonation of cysteine with aminoethanol. This is illustrated in Figure 2.

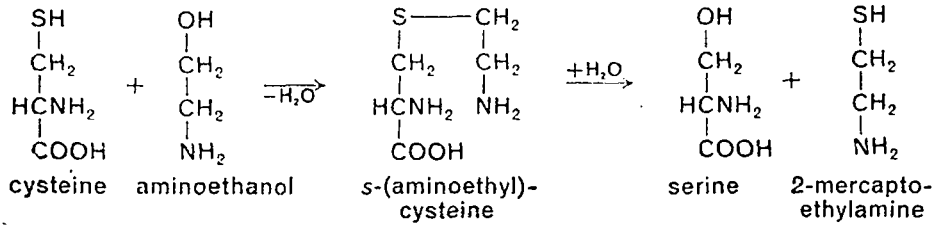

FIGURE 2. Biosynthesis of serine.

B. *Esterases*

These enzymes are found widely distributed in living cells. They are active in the metabolism of zenobiotics. They may be called carboxylic ester hydrolases or carboxylic acid esterases. The enzyme group is EC 3.1.1.1.

1. Carboxylic acid esterases

Recently, highly purified and well characterized carboxyl esterases have been isolated from liver and kidney microsomes. They hydrolyse not only numerous carboxylic esters but also several aromatic amides, such as acetanilide or acetophenetidine[33–35]. The molecular weights of these enzymes are 163,000–170,000 [34–38]. Titration experiments with organophosphate inhibitors indicate the presence of two active sites per molecule[37, 39].

The carboxylic acid esterases can be divided into two groups based on their degree of specificity. The first, called 'group specific esterases' includes enzymes with a relatively narrow substrate specificity, lipases and esterases in a narrower sense. The second group includes esterases with very strict substrate specificity. This group includes the phosphorylases which catalyse the splitting of carboxylic acids from phospholipids.

The esterases have been divided into three groups: A-esterases, hydrolysing aromatic esters; B-esterases, hydrolysing both aliphatic and aromatic esters; C-esterases, hydrolysing choline esters. A discussion of these enzymes has appeared[40].

One of the best-known choline esterases is acetylcholine esterase (EC 3.1.1.7), which plays an important role in functions of the nervous system[41–43]. It hydrolyses acetylcholine to choline and acetic acid:

$$(CH_3)_3N^+CH_2CH_2OCOCH_3 + H_2O \rightleftharpoons (CH_3)_3N^+CH_2CH_2OH + CH_3COOH \quad (12)$$

This enzyme has also been found in blood erythrocytes where it has

the same function. The catalytic mechanism for acetylcholine esterase can be described as follows. Only a small portion of the substrate reacts with the active centre of the enzyme, which can be divided into two sites; an anionic site determining the substrate specificity which binds the quaternary nitrogen of the choline moiety, and an esterifying site determining the hydrolytic process[44, 45]. The sites and enzyme–substrate complex can be pictured as in Figure 3.

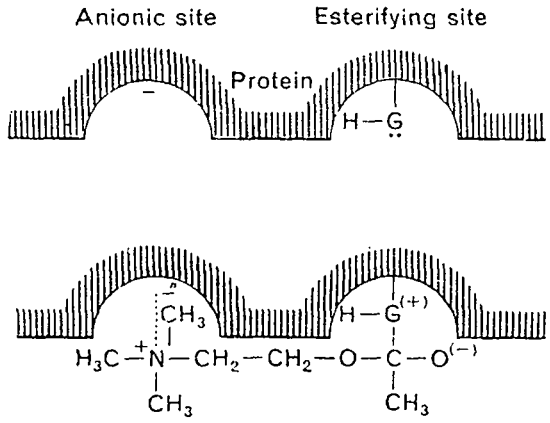

FIGURE 3. The active site of acetylcholine esterase and its enzyme–substrate complex.

2. Phosphoesterases

These enzymes can be divided into two groups, the phosphomonoesterases and the phosphodiesterases.

They catalyse the following reactions:

$$\begin{matrix} RO \\ HO \end{matrix}\!\!>\!P(O)O^- + H_2O \longrightarrow ROH + (HO)_2P(O)O^- \qquad (13)$$

$$(RO)_2P(O)O^- + H_2O \longrightarrow ROH + (HO)_2P(O)O^- \qquad (14)$$

Table 3 lists some of the important phosphomonoesterases.

In the last few years, the phosphodiesterases have become important in analytical identification and characterization of natural products, especially in degradation mixtures of nucleic acids. Many investigations of the properties of phosphodiesterases isolated from different bacteria, animals and plants have been made. For reviews, see References 55–57.

TABLE 3. Phosphomonoesterases.

Enzyme	Reaction	Co-factor	Reference
Alkaline phosphatase (EC 3.1.3.1)	Orthophosphoric monoester + $H_2O \rightarrow$ alcohol + H_3PO_4	Mg(II)	46
Acid phosphatase (EC 3.1.3.2)	Same as above	Mg(II)	46
Glucose-6-phosphatase (EC 3.1.3.9)	D-Glucose-6-phosphate + $H_2O \rightarrow$ D-glucose + H_3PO_4	—	47
Phosphatidate phosphatase (EC 3.1.3.4)	Hydrolyses L-phosphatidates to diglycerides	—	48
Phosphoserine phosphatase (EC 3.1.3.3)	Hydrolyses phosphoserine	Mg(II)	49–51
D-Fructose-1,6-diphosphatase (EC 3.1.3.11)	Hydrolyses fructose diphosphate to fructose monophosphate	Mg(II), Mn(II)	52–54

3. Sulphuric acid esterases

These enzyme reactions have been reviewed by Gregory and Robbins[58]. They have been classified as follows[59]:

1, aryl sulphatases; 2, steroid sulphatases; 3, glycosulphatases; 4, mucopolysaccharide sulphatases including chondrosulphatases; and 5, myrosulphatases.

They catalyse the following reaction:

$$ROSO_3H + H_2O \longrightarrow ROH + H_2SO_4 \qquad (15)$$

in which the O–S bond is broken during the hydrolysis[60]. They are widely distributed in nature and those from molluscs and mustard seed have been well investigated.

V. ALDOL OR KETOL CONDENSATION REACTIONS

A. *Aldolase*

Condensation reactions are catalysed by enzymes belonging to the group, lyases. One of the well-known reactions of this group is that catalysed by the enzyme, aldolase (EC 4.1.2.7). It catalyses the following reaction:

$$\text{Ketose-1-phosphate} \rightleftharpoons \text{dihydroxyacetone phosphate} + \text{aldehyde} \qquad (16)$$

It is an intracellular enzyme found in the soluble fraction of the cytoplasm. It has been isolated from different sources[61–63]. A discussion is found in Reference 64. Two different types have been found which differ in molecular weight and in specificity towards cofactors and divalent metals. Class I are found in vertebrates, invertebrates, higher plants, green algae and protozoa; Class II, in bacteria, fungi and blue-green algae. Horecker[65, 66] has investigated aldolase-catalysed reactions and suggests a mechanism involving formation of a Schiff base between dihydroxyacetone phosphate and an ε-amino group of lysine at the active centre of the enzyme. The stereochemistry of the reaction has been studied by Rose and coworkers[67, 68]. The enzyme differentiates between the two hydrogen atoms of dihydroxyacetone phosphate. For a review see Rose[4].

B. Other Condensation Reactions

1. Citrate synthase

Another example of the synthesis of hydroxyl compounds by condensation reactions is the synthesis of citric acid from oxalacetate and acetyl CoA by citrate synthase (EC 4.1.3.7)[69].

$$\text{Acetyl CoA} + \text{oxalacetate} + H_2O \longrightarrow \text{citrate} + \text{CoASH} + H^+ \qquad (17)$$

This condensation is a key reaction in the Krebs citric acid cycle. It is found in all cells with aerobic metabolism.

2. Acetyl CoA production

Hydroxymethylglutaryl CoA lyase (EC 4.1.3.4) catalyses the production of acetyl CoA from 3-hydroxy-3-methylglutaryl CoA. The enzyme has been isolated from animal tissues[70] and plays an important role in intermediary metabolism since acetyl CoA is a key product for many reactions. The reaction is as follows:

$$\text{3-Hydroxy-3-methylglutaryl CoA} \rightleftarrows \text{acetyl CoA} + \text{acetoacetase} \qquad (18)$$

A second enzyme, hydroxymethylglutaryl CoA synthase (EC 4.1.3.5), isolated from both animal tissues and yeast catalyses the formation of acetyl CoA in a different way[71]:

$$\text{3-Hydroxy-3-methylglutaryl CoA} + \text{CoA} \rightleftarrows \text{acetyl CoA} + \text{acetoacetyl CoA} + H_2O \qquad (19)$$

3. Sphingosine biosynthesis

A condensation reaction of importance in higher animals is involved in the biosynthesis of sphingosine, a component of ganglioside

in brain[72]. The mechanism has been investigated both in vivo and in vitro[73–75]. The biosynthesis is illustrated as follows:

$$\text{Palmityl CoA} + \text{NADPH}_2 \longrightarrow \text{palmityl aldehyde} + \text{NADP} + \text{CoASH} \quad (20)$$

$$\text{Serine} + \text{Mn(II)} + \text{pyridoxal phosphate} \longrightarrow \text{serine–Mn–pyridoxal phosphate complex} \quad (21)$$

$$\text{Serine–Mn–pyridoxal phosphate complex} + \text{palmityl aldehyde} \longrightarrow \text{sphingosine} + \text{Mn(II)} + \text{CO}_2 + \text{pyridoxal phosphate} \quad (22)$$

VI. ADDITION OF WATER AT A DOUBLE BOND

The addition (or elimination) of water to (at) a double bond is a reaction commonly found in biochemical processes:

$$>C{=}C< + H_2O \rightleftharpoons -\overset{H}{\underset{|}{C}}-\overset{OH}{\underset{|}{C}}- \quad (23)$$

These reactions are catalysed by enzymes called hydratases. They are key enzymes in the metabolism of carbohydrates and fats as well as some amino acids. The hydratases can be divided into four groups according to their co-factor.

i. those not requiring a co-factor
ii. those requiring a divalent cation
iii. those requiring a metal ion and reduced co-factor
iv. those requiring pyridoxal phosphate.

Examples of these enzyme types are given in Table 4.

TABLE 4. Addition reactions.

Enzyme	Reaction	Co-factor	Reference
Aconitase (EC 4.2.1.3)	*cis*-Aconitaste + H_2O → citrate	Fe(II)	76
Enolase (EC 4.2.1.11)	Phosphoenolpyruvate + H_2O→ 2-phospho-D-glycerate	Mg(II)	77–79
Crotonase (EC 4.2.1.17)	2,3-(or 3,4-) *trans*-Enoyl-CoA + H_2O → L-3-hydroxy-acyl CoA		80–82
5-Dehydroquinase (EC 4.2.1.10)	5-Dehydroshikimate + H_2O → 5-Dehydroquinate		83, 84
Threonine synthase (EC 4.2.99.2)	*O*-Phosphohomoserine + H_2O → threonine + phosphate	Pyridoxal phosphate	85

A. Fumarase

In investigations of the reaction mechanisms, it was shown that the addition of water is in many cases stereospecific. For example, fumarase (EC 4.2.1.2) catalyses the *trans*-addition of water to fumarate yielding L-malate[86–88] (Figure 4).

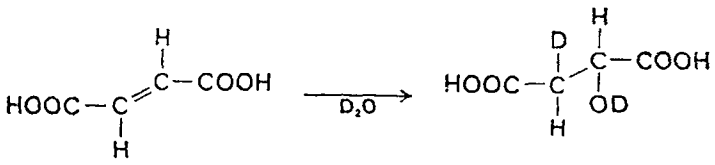

FIGURE 4. Mechanism of the fumarase reaction.

B. Others

1. Biosynthesis of threonine

A somewhat different mechanism is found in the biosynthesis of threonine from homoserine. Investigations of this synthesis in *Neurospora* and in yeast showed that pyridoxal phosphate is a requisite co-factor[89]. Two different enzyme fractions are necessary for the synthesis; one containing a kinase which phosphorylates the hydroxyl group of homoserine with ATP; the other, an enzyme which catalyses the elimination of orthophosphate. From investigations with ^{18}O and deuterium labelled compounds, Flavin and Slaughter[90] postulated the scheme illustrated in Figure 5.

2. Oxidation of nicotine and nicotinic acid

Water can also be added at a carbon–nitrogen double bond via a similar mechanism. This is found in bacterial oxidations of nicotine and nicotinic acid[91]. The hydroxylation occurs at a pyridine ring, i.e., in an aromatic system. Hochstein and co-workers[92, 93] showed by investigations with ^{18}O labelled water that the oxidation of nicotine to 6-hydroxynicotine involves the oxygen of water (Figure 6). Hunt and co-workers[94] found the same reaction mechanism for the hydroxylation of nicotinic acid in *Pseudomonas fluorescens*.

VII. ISOMERIZATIONS

This class of reactions involving hydroxyl groups is catalysed in biochemistry by the isomerases (EC 5). The ones of interest in a discussion of reactions of the hydroxyl group are those catalysing

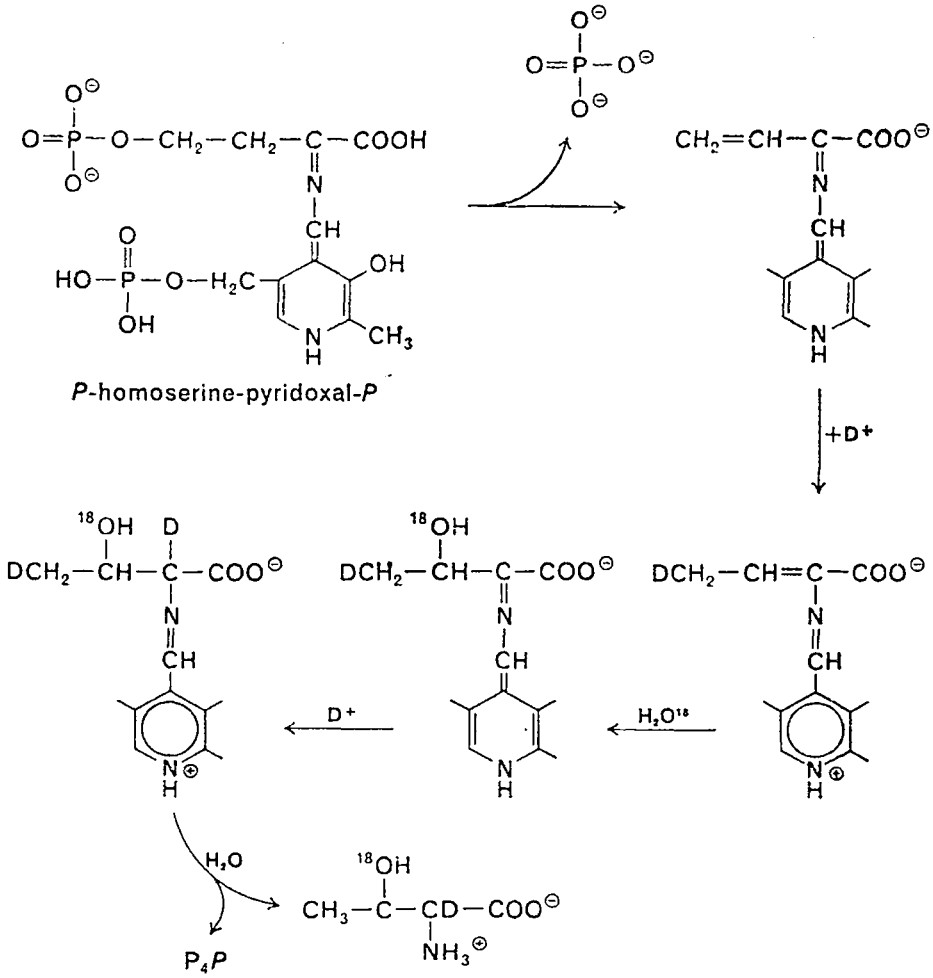

FIGURE 5. Biosynthesis of threonine.

intramolecular oxidoreductions, for example, triosephosphate isomerase, and those catalysing stereochemical changes, for example, lactate racemase.

A. Triosephosphate Isomerase

This enzyme (EC 5.3.1.1) catalyses the intramolecular reduction of an aldehydic or ketonic group by the adjacent hydroxyl group. It is an important enzyme in the Embden–Meyerhof pathway of carbohydrate metabolism. It catalyses the stereospecific interconversion of dihydroxyacetone phosphate and glyceraldehyde phosphate. The mechanism of the reaction has been studied by Rose and

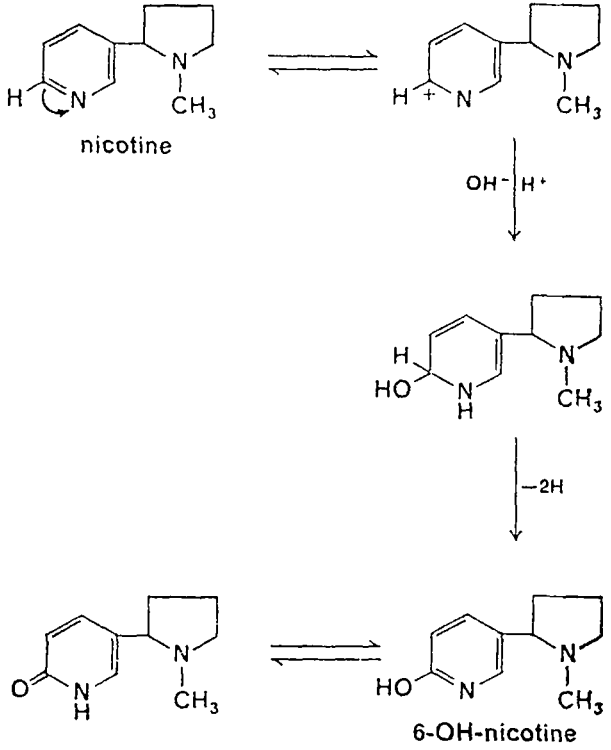

FIGURE 6. Bacterial oxidation of nicotine.

Rieder[95]. The reaction involves the formation of an intermediate enzyme-bound *cis*-enediol. Apparently a direct intramolecular transfer of hydrogen is involved (see Figure 7). A similar mechanism has

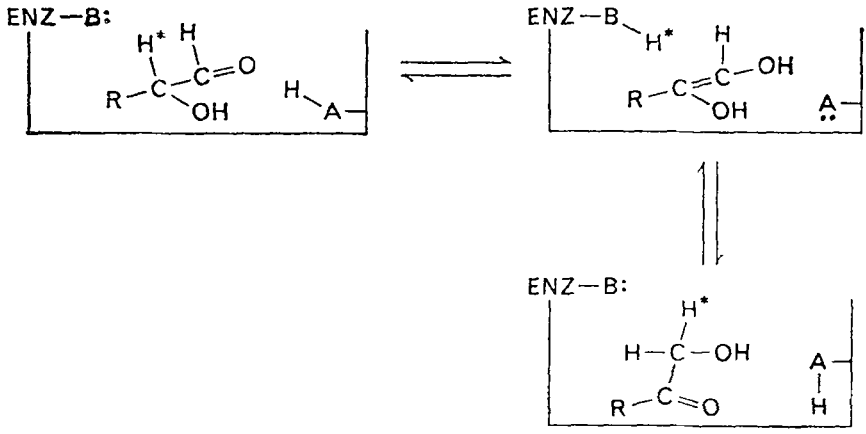

FIGURE 7. Mechanism of the triosephosphate isomerase reaction.

been suggested for glucosephosphate isomerase (EC 5.3.1.9) which catalyses the interconversion of glucose-6-phosphate and fructose-6-phosphate[96, 97].

B. Lactate Racemase

This enzyme (EC 5.1.2.1) catalyses the interconversion of D- and L-lactate. The mechanism of the reaction has been studied by Dennis and co-workers[98, 99]. They suggest that a direct internal hydride shift is involved as shown in Figure 8.

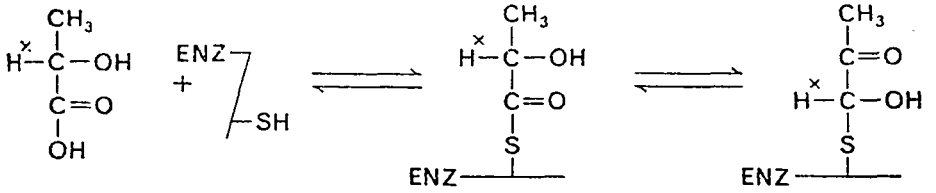

FIGURE 8. Mechanism of the lactate racemase reaction.

Isomerase reactions have been reviewed by Rose[4]. Some representative examples of these reactions are given in Table 5.

TABLE 5. Isomerase reactions.

Enzyme	Reaction	Source	Reference
Ribulose-phosphate-3-epimerase (EC 5.1.3.1)	D-Ribulose-5-phosphate ⇌ D-xylulose-5-phosphate	Widely distributed	100, 101
Mannose isomerase (EC 5.3.1.7)	D-Mannose ⇌ D-fructose	Bacteria	102
Glucosephosphate isomerase (EC 5.3.1.9)	D-Glucose-6-phosphate ⇌ D-fructose-6-phosphate	Widely distributed	103–104

VII. MONOOXYGENATION OR MIXED FUNCTION OXYGENATION

Since the dehydrogenation of aromatic amino acids and aliphatic compounds such as alicyclic steroids is energetically unfavourable, an enzymatic hydroxylation occurs utilizing molecular oxygen.

These reactions are catalysed by the monooxygenases or mixed

function oxygenases. Mason and co-workers[105] in investigations with ^{18}O labelled oxygen gas showed that molecular oxygen is incorporated into organic substrates in the cell. Since two electrons were required for the activation of oxygen, Mason[106] suggested the following stoichiometry:

$$RH + DH_2 + O_2 \longrightarrow ROH + D + H_2O \qquad (24)$$

where RH = substrate to be oxidized; DH_2 = electron donor.

From this equation it is apparent that two types of reaction occur: hydroxylation of the substrate and oxidation of the electron donor. The monooxygenases also often catalyse epoxidations, dealkylations and oxidations of nitrogen and sulphur. Because of these multifunctions, the enzymatic properties and the mechanisms of reaction of monooxygenases are of special interest. A review by Mason appeared in 1965 [107].

A. Monooxygenases in Mammals

I. Steroids

Monooxygenase enzyme systems have a predominant position in the synthesis and metabolism of steroids, since in biological systems only mixed function oxygen is available for introduction of a hydroxyl group into the aliphatic steroid ring. In addition to specifically introduced hydroxyl groups which are important for hormone activity, hydroxylated compounds also serve as intermediates for other reactions such as elimination of a side chain or aromatization of the ring.

Many such hydroxylating enzyme systems are known and some have been isolated and investigated. Steroid monooxygenase reactions have been reviewed by Hayano[108].

Table 6 lists some of the sterol monooxygenases which are involved in the early steps leading to steroid synthesis. The enzyme systems outlined in the table have been shown by in vitro investigations to be monooxygenases requiring the physiological electron donor, $NADPH_2$, and molecular oxygen.

Table 7 lists the hydroxylations of testosterone and androstenedione found in mammalian tissues. Steroid positions 2, 6α, 6β, 7α, 7β, 15α, 16α, 16β are hydroxylated in the liver.

During the past five years, considerable progress has been made in the elucidation of the mechanism of microsomal monooxygenation. In 1958, the occurrence of a second microsomal cytochrome in addition to cytochrome b_5 was reported by Klingenberg[124]. Its spectral properties were similar to a *b*-type cytochrome, but it

TABLE 6. Sterol monooxygenases.

Enzyme	Source	Remarks	Reference
Squalene-2,3-epoxy-monooxygenase (EC 1.14.1.3)	Liver microsomes	Oxidation at $C_{(2)}$ and $C_{(3)}$ leads to epoxide intermediate allowing ring closure giving steroid skeleton in a further enzymatic step	109, 110
Lanosterol demethylase	Liver microsomes	Demethylation occurs via hydroxylated intermediates which are then oxidized and decarboxylated anaerobically using NAD as co-factor	111
Cholesterol-7-monooxygenase	Rat and rabbit liver microsomes	In vivo investigations indicated similar hydroxylation steps at 6α, 6β and 12α. The elimination of the side chain at $C_{(24)}$ probably also occurs via an oxygenation mechanism	112
	Snake liver	Hydroxylates at 16α	113
Cholesterol-20-monooxyogenase	Mitochondria from adrenals, testis, ovary, placenta	Side chain elimination via a 20,22-dehydroxy intermediate. Contains cytochrome P 450. Vitamin A apparently a necessary co-factor	114

showed a characteristic and unusual absorbance of its reduced carbon monoxide complex at 450 nm, and was therefore tentatively called cytochrome P 450. Since most microsomal hydroxylations are inhibited by carbon monoxide, it was suggested that this new cytochrome might be the oxygen-reducing and activating species of the microsomal monooxygenation system.

The most thoroughly investigated systems to date are the 11β- and 21-steroid hydroxylating systems isolated from adrenal glands. Estabrook and co-workers[125, 126] were able to show that cytochrome P 450 is the terminal oxidase for the 21-monooxygenase system. The carbon monoxide inhibited hydroxylation could be reactivated in the presence of oxygen and light. The photochemical action spec-

TABLE 7. Hydroxylations of testosterone or androstendione by mammalian tissues.

Position hydroxylated	Source of enzyme	Reference
2β	Microsomes	115–118
6α	Microsomes	119
6β	Microsomes	115–118
11β	Adrenal mitochondria	120
16α	Microsomes	116–118
19	Liver and placental microsomes	119, 121
15α, 18α	Liver microcomes	122
7α	Liver microsomes	111, 118
7β	Liver microsomes	119, 123

trum (removal of CO inhibition by illumination with monochromatic light) proved to be identical with the absorption spectrum of the carbon monoxide complex of cytochrome P 450. A cytochrome P 450–substrate complex was observed in this system as indicated by a spectral shift of the Soret peak for the oxidized cytochrome from 420 nm to 390 nm on the addition of substrate[127]. Steroids hydroxylated in the 21-position did not show this effect. This monooxygenase is relatively substrate specific; $C_{(19)}$ and $C_{(18)}$ steroids react more slowly than $C_{(21)}$. Steroids esterified at $C_{(21)}$ react only after hydrolysis; substrates with a double bond at $C_{(9)}$–$C_{(11)}$ are not hydroxylated although traces of a 9,11-epoxy derivative are found.

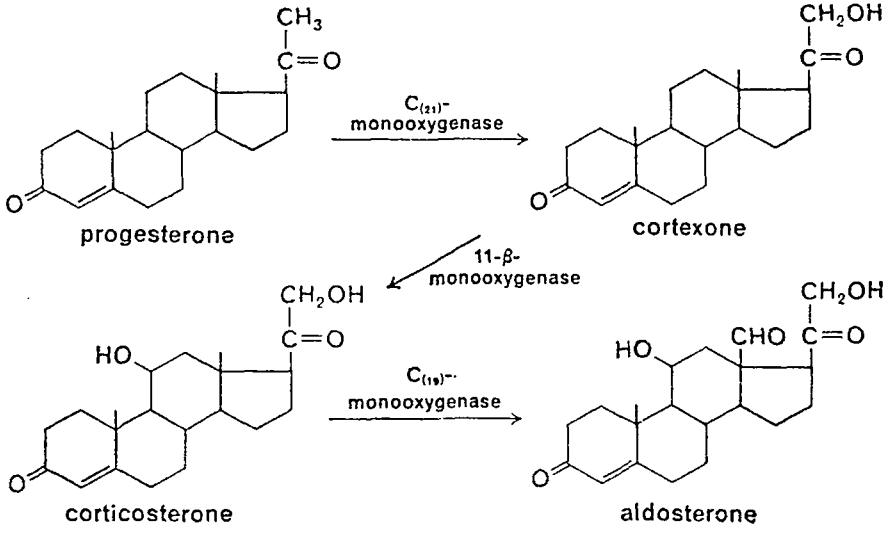

FIGURE 9. Synthesis of aldosterone.

A nonhaem iron protein, adrenodoxin, has been found in adrenal gland microsomes[128]. Recent experiments in which attempts to recombine isolated fractions of the electron transport chain by Omura and co-workers[129] showed that a $NADPH_2$-dependent flavoprotein and adrenodoxin were necessary for electron transfer.

Studies of 11β-hydroxylation were first done with perfused adrenals and later with a mitochondrial fraction isolated from tissue homogenates[125].

In contrast to the system described above, Mattijssen and Mandel[130] found a 21-hydroxylating system in adrenals which did not involve P 450.

Figure 9 shows the 21- and 11β-steroid hydroxylations.

2. Aromatic amino acids

Monooxygenations play an important role in the degradation of aromatic amino acids. These reactions are important in secondary metabolism as illustrated by reactions involving phenylalanine as the starting substrate. Figure 10 shows some of the products formed from this amino acid via hydroxylation reactions.

Phenylalanine monooxygenase (EC 1.14.3.1), which hydroxylates phenylalanine in the *para* position to tyrosine, is dependent on molecular oxygen and tetrahydropteridine. The tetrahydropteridine $\rightleftharpoons$ dihydropteridine system is NADP dependent[131]. If *p*-tritiophenylalanine is used as substrate, a *m*-tritiotyrosine is found as product. This migration of substituent (the so-called NIH shift[132]) is characteristic for monooxygenation of aromatic compounds.

The tyrosine produced in the above reaction can react further in secondary metabolic pathways as follows.

In liver, the product resulting from transamination of tyrosine, *p*-hydroxyphenyl pyruvate, is hydroxylated at $C_{(1)}$ by a monooxygenase (EC 1.14.2.2). The side chain is then oxidatively decarboxylated and migrates to the *ortho* position, giving homogentisic acid as a final product. The electrons necessary for the monooxidation are provided by the decarboxylation of the side chain. Ascorbate is a co-factor[133].

In insects, in melanin synthesis in the skin and in melanoma, tyrosine is hydroxylated in the *meta* position to give DOPA. This product acts as electron donor for the tyrosine hydroxylation since it can be oxidized to DOPA quinone. This quinone is the starting substrate for melanin synthesis. In insects, this enzyme is activated by the metamorphosis hormone ecdyson[134].

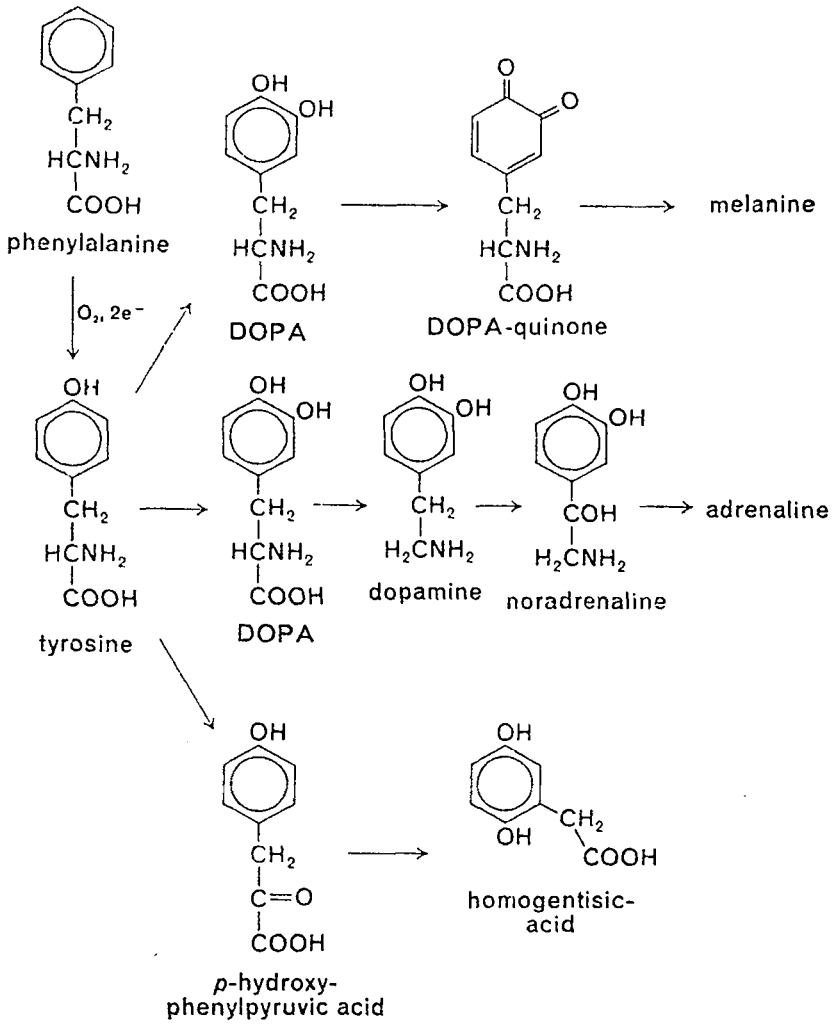

FIGURE 10. Hydroxylation of aromatic amino acids.

In adrenal glands, tyrosine can be hydroxylated in the *meta* position by a tetrahydropteridine-dependent enzyme[135]. The DOPA produced in this reaction is hydroxylated to noradrenalin after a decarboxylation at the β-carbon. This enzyme (EC 1.14.2.1) contains copper. It was shown by electron spin resonance studies that two atoms of copper can be reduced by ascorbate and are oxidized during the monooxygenation step[136].

Table 8 lists some other aromatic aminooxygenases. For a review of these reactions, see Kaufman[140].

Table 8. Aromatic amino acid monooxygenases.

Enzyme	Source	Co-factors	Remarks	Reference
Tryptophan-5-monooxygenase	Liver, brain, small intestine, poison glands of toad	Ascorbate, Cu(II)	5-Hydroxytryptophan is decarboxylated to serotonin	137
Kynurenine-3-monooxygenase (EC 1.14.1.2)	Liver mitochondria, insects	$NADPH_2$	—	138
Butyrobetaine monooxygenase	Rat liver	$NADPH_2$, Fe(II)	Product is carnitine	139

Another interesting enzyme of this series is proline monooxygenase[141]. The enzyme requires ascorbate, Fe(II) and α-ketoglutarate for activity. It hydroxylates proline and possibly lysine residues in the protocollagen peptide chain but not free proline or lysine.

3. Others

Another monooxygenase reaction has been reported recently, catalysed by a haem monooxygenase from liver microsomes[142]. This enzyme, which is $NADPH_2$ and oxygen dependent and is inhibited by carbon monoxide, catalyses the physiologically important conversion of haem to bilirubin.

4. Xenobiotic monooxygenases

The term xenobiotic includes all nonphysiological compounds normally not found in living organisms. They include a variety of drugs, solvents, etc. Most of them are highly lipid soluble and therefore dissolve and accumulate in the hydrophobic regions of tissue and cells, especially in adipose tissue; for example, DDT.

There is a well-known detoxification system for these compounds in higher vertebrates which converts them to more hydrophilic derivatives which can be readily excreted through the kidney as the glucuronate or sulphate.

This system is located primarily in the liver[143, 144], although minor activities have also been found in the kidney, lung and small intestine. It is a monooxygenase system requiring $NADPH_2$ and molecular oxygen.

By techniques used in studying adrenal steroid hydroxylations, it

was established that cytochrome P 450 also functions in the oxygen activation process in liver microsomal xenobiotic hydroxylations[145]. An $NADPH_2$ flavoprotein reductase has been isolated from liver microsomes and studied in vitro[146]. Nonhaem iron protein has not been found in the mammalian liver microsomal system and it is not known whether electrons in this system are transferred directly to cytochrome P 450 from the reductase or whether an unknown intermediate factor is involved.

The interaction of substrate with cytochrome P 450 has been studied recently in liver microsomes[147, 148].

The system has an unusually broad substrate specificity; only a certain lipid solubility seems to be necessary for the monooxygenation of an organic compound. Table 9 shows a number of organic substrates and their oxidation products formed by the monooxygenation system from rat liver microsomes. Similar results have been obtained with liver microsomes from other species. Hydroxylation at an aliphatic carbon atom is the most favoured enzyme reaction as illustrated by experiments with alkyl-substituted aromatic rings in which the aliphatic side chain is preferentially hydroxylated. With alkylated heteroatoms, hydroxylation occurs at the α-carbon atom, leading to formation of an unstable semiacetal which decomposes as shown in Figure 11.

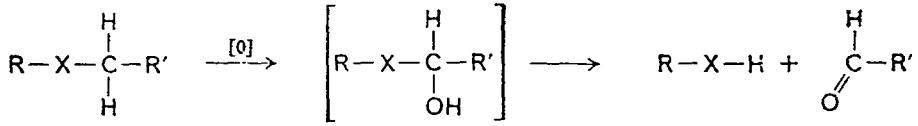

FIGURE 11. Monooxygenation of alkylated heteroatoms.

Much information on the mechanism of hydroxylation has been obtained by studying the monooxygenation of aromatic substrates. Studies on the monooxygenation of naphthalene suggested that an epoxide is an intermediate in these systems. The main product of the reaction was identified as the 1,2-dihydronaphthalene-1,2-diol with only minor quantities of the 1- and 2-naphthol being formed. Although naphthalene-1,2-oxide is extremely unstable, its isolation in small quantities from a microsomal incubation mixture has been reported[166]. The 'NIH shift' also occurs in this system as illustrated by the hydroxylation of tetrachloroethylene to chloral hydrate[167].

The two-electron activation of the oxygen molecule is mediated by cytochrome P 450. Although many attempts to elucidate the

TABLE 9. Products of microsomal monooxygenation.

Substrate	Products	Remarks	Reference
Cyclohexane	Cyclohexanol	Induced by phenobarbital	149
n-Heptane	*n*-Heptanol-1	Induced by phenobarbital	150
Stearate	18- and 17-Hydroxystearates, octadecane-1,18-dioic acid		151
Benzene	Phenol		152
Acetanilide	*o*-, *m*- and *p*-Hydroxyacetanilide (501094)	Induced by benzpyrene	153
4-Fluoroacetanilide	2- and 3-Hydroxy-4-fluoroacetanilides, 4-hydroxyacetanilide	Induced by benzpyrene competitively inhibited by acetanilide	106
4-Chloro- and 4-bromoacetanilide	Similar to fluoro derivative		154
4-Methylacetanilide	4-Hydroxy-3-methylacetanilide		154
N-Acetylphenetidine	*N*-Acetyl-2-hydroxyphenetidine *N*-Acetyl-3-hydroxyphenetidine 4-Hydroxyacetanilide	*O*-Dealkylation	155
6-Methylthiopurine	Thiopurine + formaldehyde	*S*-Demethylation	156
Trimethylamine	Trimethylamine-*N*-oxide	*N*-Oxidation	157
Indene	Indane-2,3-diol	Epoxide intermediate?	158
Amphetamine	Phenylacetone + ammonia	Deamination	159
Chlorpromazine	Chlorpromazine sulphoxide, demethylchlorpromazine + formaldehyde	Sulphoxidation	160, 161
N-Methyl-4-nitroaniline	4-Nitroaniline + formaldehyde	*N*-Demethylation	162
Aniline	2- and 4-Aminophenol Phenylhydroxylamine	*C*-Hydroxylation *N*-Hydroxylation	163
Coumarin	Umbelliferone	—	164
Naphthalene	1-,2-Naphthol 1,2-Dihydronaphthalene-1,2-diol	—	165

nature of the active oxygen species have been made, its nature is still unknown.

The pattern of phenolic products formed, the occurrence of the 'NIH shift' and the production of epoxide compounds in xenobiotic microsomal monooxygenase reactions suggest that an oxygen atom species may be involved. Studies with nonenzymatic model systems indicated that as intermediate[168] an 'oxenoid' complex may be involved which is defined by its ability to transfer an oxygen atom with six electrons.

Figure 12 summarizes the scheme of electron transport in liver microsomes as postulated to date[129].

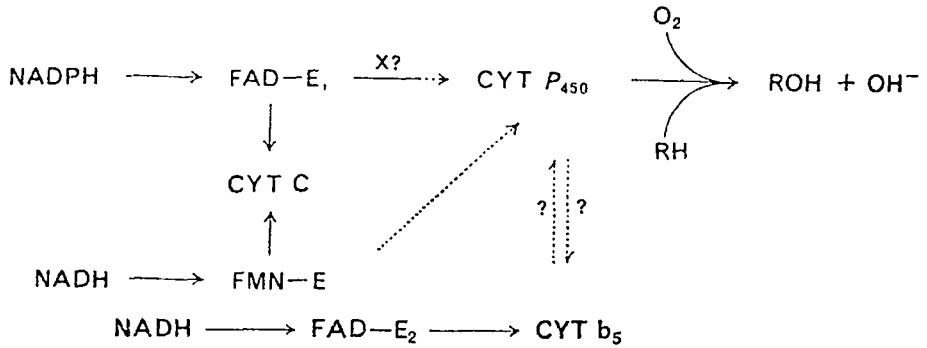

FIGURE 12. Proposed scheme of electron transport in liver microsomes[129].

The subject of xenobiotic hydroxylation has been reviewed by Conney[169] and by Staudinger and co-workers[170].

B. Monooxygenases of Higher Plants

Although hydroxylation processes in higher plants are widely distributed, the enzymes catalysing these reactions and the mechanisms are for the most part unknown.

An example of the importance of hydroxylations in secondary metabolism is given in Figure 13 [171–174].

Hydroxylation of the phenyl group in different positions is the first step in many important synthetic pathways. These lead to the synthesis of lignin[175, 176], flavonoids[177, 178], ubiquinone[179], alkaloids[180, 181], coumarins and other compounds. In later steps of biosynthesis, the compounds can undergo still further hydroxylations which, for example as with the alkaloid colchicine, play an important role as intermediates in ring expansion. The type of ring formation in alkaloid synthesis is dependent on the position of free phenolic

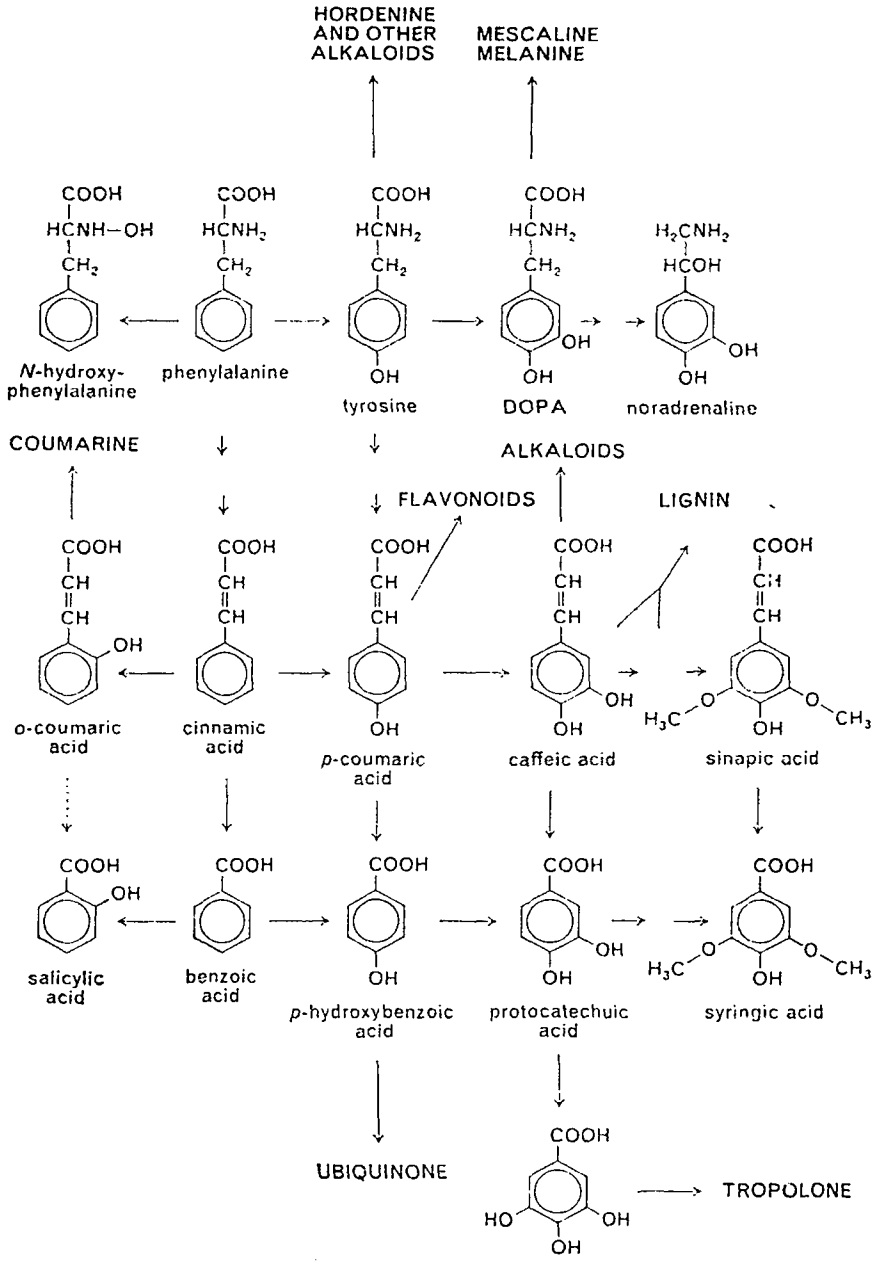

FIGURE 13. Some examples of hydroxylation in secondary metabolism in higher plants.

groups. Methylations can protect hydroxy groups thereby inactivating their influence on ring formation. Occasionally, hydroxylation (for example in the alkaloid series) takes place at a nonactivated position on the aromatic ring. This seldom occurs in vitro, and can only be explained by a specific enzyme effect. Only two of the above hydroxylations have been investigated; the *para*-hydroxylation of cinnamic acid, and the introduction of an hydroxyl group at $C_{(2)}$ and $C_{(3)}$ in the aromatic ring by the phenolase system.

1. Cinnamic acid-4-hydroxylase

Cinnamic acid, which is formed by ammonia elimination from phenylalanine, has an important position in secondary metabolism. It is hydroxylated to *p*-coumaric acid by cinnamic acid hydroxylase. The evidence that this enzyme is probably a monooxygenase was presented by Zenk[182], who was also the first to observe the 'NIH shift' in hydroxylations by an enzyme from higher plants (*Catalpa hybrida*).

p-Tritiocinnamic acid was transformed to *m*-tritiocoumaric acid, and by a simultaneous β-oxidation to *m*-tritio-*p*-hydroxybenzoic acid.

$NADPH_2$ and tetrahydrofolic acid were found to be the electron donors in a microsome fraction from pea seedlings[183]. A similar system from spinach leaves uses $NADH_2$ as co-factor; it also can hydroxylate phenylalanine to tyrosine[184].

2. The phenolase system

The introduction of a second and third hydroxyl group, e.g., tyrosine → caffeic acid, probably occurs in many cases via the phenolase system which is widely distributed in plants and animals. It is active in many different biosynthetic pathways. The animal phenolase system is generally specific for tyrosine and DOPA; that from plants utilizes a wide variety of mono- and di-phenolic substrates. The new hydroxyl group is introduced in a position *ortho* to the hydroxyl groups already present (phenol-*ortho*-hydroxylase, cresolase). The reaction seldom stops at the *o*-diphenols (or polyphenols) but usually the product is further oxidized by the phenolase complex to *o*-quinone (*o*-diphenol dehydrogenase, catecholase).

The electrons necessary for *o*-hydroxylation are in most cases provided by a coupled oxidation to the diphenol–quinone system. Phenolase contains copper (two neighbouring copper atoms forming an enzymatic functional unit) which forms a complex with molecular

oxygen with accompanying valence change. From this, one can formulate the reaction as follows[171]:

$$\text{Enz-}(Cu^{+})_2 + O_2 \longrightarrow \text{Enz-}(Cu^{+})_2\text{—}O_2 \quad (25)$$

$$\text{Enz-}(Cu^{+})_2\text{—}O_2 + \text{monophenol} + 2\,H^{+} \longrightarrow \text{Enz-}(Cu^{2+})_2 + o\text{-diphenol} + H_2O \quad (26)$$

$$\text{Enz-}(Cu^{2+})_2 + 2e \longrightarrow \text{Enz-}(Cu^{+})_2 \quad (27)$$

$$o\text{-Diphenol} \longrightarrow o\text{-quinone} + 2\,H^{+} + 2e \quad (28)$$

The active hydroxylating agent is probably the reduced $(Cu^{+})_2$–O_2 complex (CuO^{+}) [185]. See Figure 14.

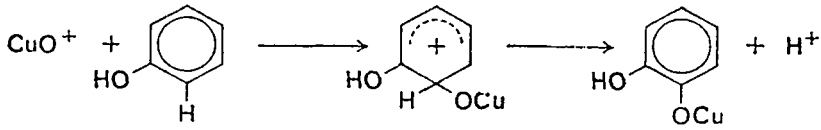

FIGURE 14. Electrophilic attack on an aromatic system by cuprylion ion.

The phenolase complex can be characterized as a single enzyme with two active centres[171] or as a system containing two very similar proteins, one, an *o*-hydroxylase, and the other, an *o*-diphenyl dehydrogenase[185]. The latter concept is favoured by the fact that the phenolase complex can be split into two protein fractions; one possessing a high catecholase activity, and the other, cresolase and catecholase activities. However, these results may also be interpreted differently. It appears possible that hydroxylation and dehydrogenation occur at two different sites since cresolase does not exchange Cu^{2+} ions during the reaction in contrast to catecholase. The former enzyme is also less stable. In addition, cresolase and catecholase can be differentially inhibited: ferulic acid inhibits the dehydrogenation of chlorogentic acid by a plant phenolase more strongly than the hydroxylation of *p*-coumaric acid[186].

Although a large number of publications on the phenolase system have appeared, one still does not have a detailed knowledge of the reaction, partially because, in most cases, unpurified enzyme preparations were used. Of the many further hydroxylation reactions in higher plants, only a few other types have been studied.

3. Others

Investigations on the incorporation of ^{18}O during carotenoid hydroxylation showed that molecular oxygen is found in the hydroxyl groups of the leaf xanthophylls, lutein, violaxanthin and neoxanthin in the alga *Chlorella vulgaris*[187, 188] as well as in the epoxide group of anthraxanthin in the legume *Phaseolus lunatus*[189].

This is a strong indication that a monooxygenase system is involved. However, other groups found incorporation of oxygen from $H_2{}^{18}O$ in the epoxide or hydroxyl groups.

Other monooxidations occurring in higher plants are hydroxylation of phenylalanine[184] and anthranilic acid[190], squalene epoxidations[191], *N*-hydroxylation of tryptophan[192] and hydroxylations involving steroids[193].

C. Monooxygenases of Microorganisms

In contrast to higher plants, microorganisms are especially suitable for enzyme investigations because the *de novo* synthesis of a fixed enzyme can be induced by growing on a fixed substrate (adaptive induction).

In addition to those monooxygenases induced by substrate, those found in the metabolic pathways of plants and animals are also found in bacteria. Although the functions of induced monooxygenases are essentially catabolic, they often take part in anabolic pathways, for example, tyrosine synthesized via an induced phenyle alanine hydroxylase can be used in protein synthesis[194]. Sombacterial monooxygenases are listed in Table 10.

1. Phenylalanine hydroxylase

The phenylalanine hydroxylase isolated from *Pseudomonas*[195, 202] which transforms phenylalanine to tyrosine in the presence of O_2, $NADH_2$, tetrahydropteridine and metal ions, was investigated with regard to the 'NIH shift'. The group which migrates from the *para* to *meta* position can be hydrogen or its isotopes, chlorine, bromine or a methyl group[203]. The hydroxylation of *p*-methylphenylalanine is of special interest since not only is *m*-methyltyrosine found, but also a large amount of *p*-hydroxymethylphenylalanine[204]. This illustrates a monooxygenase which can hydroxylate both an aromatic ring and an aliphatic side chain. This indicates that there are no basic differences in the enzymes for these two types of reactions.

The transformation of *p*-hydroxyphenylpyruvic acid to homogentisic acid which occurs in phenylalanine degradation in bacteria and higher plants, can also be explained by a 'NIH shift' if one assumes that in the hydroxylation, other organic groups in addition to the methyl group can migrate to a neighbouring ring position, in this case with accompanying decarboxylation.

2. Salicylate hydroxylation

Salicylic acid is hydroxylated at $C_{(1)}$ by salicylate monooxygenase

TABLE 10. Some monooxygenases of bacteria.

Enzyme	Reaction	Co-factors	Remarks	Reference
p-Hydroxy-benzoate monooxygenase	*p*-Hydroxybenzoate → 3,4-dihydroxybenzoate	Fe(II) NADPH FAD	Isolated from *Pseudomonas putida* substrate specific	195, 196
Melilotate hydroxylase	*O*-Hydroxyhydrocinnamate → 2,3-dihydroxyhydrocinnamate	FAD NADH	Isolated from *Arthrobactor*	197
Imidazolacetate monooxygenase	Imidazolacetate → Imidazoloneacetate	NADH FAD	Isolated from *Pseudomonas* The product is hydrolysed to *N*-formimino-L-aspartate	198, 199
Vanillate-*O*-demethylase	4-Hydroxy-5-methoxybenzoate → 4,5-dihydroxybenzoate	NADH	Isolated from *Pseudomonas* Methoxy group eliminated as formaldehyde	200
Thiamine-7-hydroxylase	5-Methyluracil → 5-hydroxy-methyluracil	Fe(II) Ascorbate α-Ketoglutarate NADPH	Isolated from *Neurospora crassa*	201

from *Pseudomonas* with simultaneous decarboxylation to catechol. The oxygen of the hydroxyl group comes from molecular O_2 [205, 206]. Spectrophotometric investigations[207, 208] indicated the following sequence:

$$\text{Enz-FAD} + \text{salicylate} \longrightarrow \text{Enz-FAD-salicylate} \quad (29)$$

$$\text{Enz-FAD-salicylate} + \text{NADH}_2 \longrightarrow \text{Enz-FADH}_2\text{-salicylate} + \text{NAD} \quad (30)$$

$$\text{Enz-FADH}_2\text{-salicylate} + \text{O}_2 \longrightarrow \text{Enz-FAD} + \text{catechol} + \text{CO}_2 + \text{H}_2\text{O} \quad (31)$$

One mole of the holoenzyme (formed from an equimolar amount of the isolated apoenzyme and FAD) reacts with one mole of salicylate in the absence of O_2 with the formation of a ternary complex of salicylate hydroxylase–apoenzyme–FAD–salicylate. This complex is stoichiometrically reduced by $NADH_2$ and then reacts with molecular oxygen to give the end products, catechol, CO_2, H_2O and unchanged holoenzyme.

3. ω-Hydroxylase

The enzymatic oxidative attack of the methyl carbon atom of aliphatic compounds[209] or fatty acids[210, 211] is widely distributed in nature. It is probably catalysed by monooxygenases. An oxidation by dehydrogenation is energetically unfavourable. The ω-hydroxylase from *Pseudomonas oleovorans* catalyses the formation of *n*-octanol from octane (hexane and decane are also oxidized, but less) and the ω-hydroxylation of fatty acids ($C_{(8)}$ to $C_{(18)}$ with optimal chain length $C_{(12)}$). Molecular oxygen and $NADH_2$ are necessary. The enzyme consists of three components which have been separated and partially purified[211]: (1) rubredoxin, (2) $NADH_2$ rubredoxin reductase, (3) ω-hydroxylase. Rubredoxin is a nonhaem iron protein containing two atoms of iron per molecule and, in contrast to ferredoxin, does not contain labile sulphide. Its molecular weight is about 12,800 and its reduction potential is −0·037 volts[211]. The amino acid sequence of rubredoxin from *Peptostreptococcus elsdenii* has been determined; the iron is bound at four cysteine sulphurs[212]. Rubredoxin is an electron carrier which receives electrons from $NADH_2$ and $NADPH_2$ (catalysed by $NADH_2$ rubredoxin reductase from *Pseudomonas* and $NADPH_2$ ferredoxin reductase from spinach) and transfers them to the ω-hydroxylase or added cytochrome *c*. The electron transport chain consists of three components as shown in Figure 15. The introduction of the hydroxyl group occurs in the yeast, *Torulopsis gropengiesseri*, in the ω and ω − 1 positions and is stereospecific through direct exchange of a hydrogen atom by an oxygen species which is easily transformed to a hydroxyl group[213].

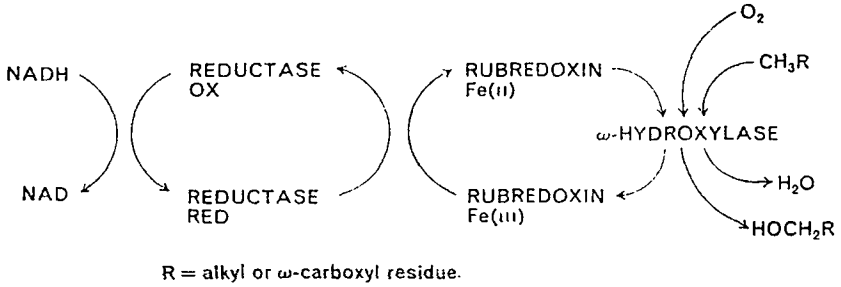

FIGURE 15. The ω-hydroxylase system of *Pseudomonas*.

It is probable that hydroxylation of *p*-xylene and toluene to *p*-methylbenzyl- and benzyl alcohols in *Pseudomonas aeruginosa* occurs by a similar mechanism using a similar electron transport chain[214].

4. Methylene hydroxylase

A mechanism comparable to the ω-hydroxylase is assumed for the camphor-induced methylene hydroxylase system from *Pseudomonas putida*, which contains a nonhaem iron protein, putidaredoxin, as electron carrier. This system hydroxylates the methylene $C_{(5)}$ of (+)-camphor stereospecifically to 5-*exo*-hydroxycamphor[215, 216]. The electron transport goes from $NADH_2$ via a putidaredoxin reductase to putidaredoxin which involves one electron reduction and differs significantly from rubredoxin in possessing two moles of labile sulphide[217, 218]

The hydroxylase itself has been more thoroughly investigated. It contains cytochrome P 450, and therefore gives typical absolute and difference spectra with substrate in the oxidized state and with carbon monoxide in the reduced state. The hydroxylation process has been postulated as shown in Figure 16 [216, 219].

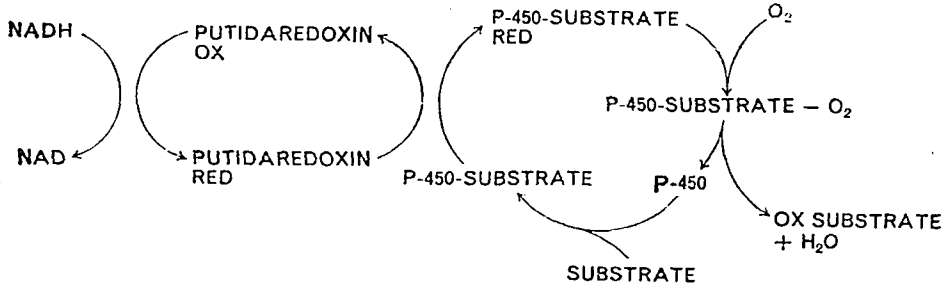

FIGURE 16. The methylene hydroxylase system of *Pseudomonas putida*.

The hydroxylation mechanisms of bacterial methylene- and ω-hydroxylases are similar to steroid hydroxylations in mammals which

contain a nonhaem iron protein, adrenodoxin, as electron carrier. It is possible that the countless microbial steroid monooxygenases which stereospecifically replace a hydrogen atom with a hydroxyl group[220, 221, 222] have a similar reaction mechanism. Microorganisms can hydroxylate steroids in all positions with the exception of $C_{(4)}$, $C_{(5)}$ and $C_{(13)}$ [223], and $C_{(3)}$ and $C_{(20)}$ which usually already contain a hydroxyl or ketone group.

The steroid monooxygenases are very important in industry since intermediates necessary in the production of medicinal analogues to the steroid hormones can be easily synthesized using microorganisms. Often these intermediates cannot be synthesized chemically, or only uneconomically. Microbial and chemical steps are often combined as, for example, in the synthesis of cortisone from progesterone. This involves three microbial hydroxylations and a chemical oxidation with chromate[220].

5. Others

a. Anthranilic acid hydroxylase. In contrast to the hydroxylases discussed above, anthranilic acid hydroxylase hydroxylates two neighbouring carbon atoms forming catechol. From experiments with ^{18}O in *Pseudomonas*, both oxygen atoms were shown to originate from one molecule of oxygen[224]. A cyclic intermediate 1,2-peroxide has been suggested which then is reduced by $NADH_2$ followed by CO_2 and NH_3 elimination to catechol. Taniuchi and co-workers[225] believe, however, that this enzyme is a monooxygenase catalysing the formation of a 1,2-epoxide which is nonenzymatically hydrolysed with accompanying NH_3 elimination followed by decarboxylation. However, a *cis*-benzene glycol is involved as intermediate in the oxidation of benzene to catechol by *P. putida*[226].

The enzyme isolated from *Pseudomonas fluorescens* required $NADH_2$ or $NADPH_2$ as co-factor, and after purification, Fe(II) ions for activation.

The hydroxylation of anthranilic acid in the mould *Aspergillus niger*[227] and in chloroplasts of *Tecoma stans*[190] apparently does not involve any of the above reaction types. Anthranilic acid is hydroxylated at $C_{(3)}$ (some $C_{(2)}$). In *A. niger* 2,3-dihydroxybenzoic acid is produced which can be decarboxylated by a carboxylase to catechol. $NADPH_2$ is the sole electron donor. In *T. stans*, 3-hydroxyanthranilic acid is synthesized which can be transformed to catechol. This enzyme is extremely substrate specific and has an absolute requirement for tetrahydrofolic acid; $NADH_2$ ($NADPH_2$) increases the

activity. The pH optimum at pH 5·0 is similar to that of cinnamic acid hydroxylase and phenylalanine hydroxylase isolated from spinach leaves.

b. Kynurenate hydroxylase. This enzyme (EC 1.14.1.3) isolated from *Pseudomonas*[228] transforms kynurenate to kynurenate-7,8-dihydrodiol. It also introduces two hydroxyl groups in the *ortho* position and possibly forms a 7,8-epoxide as intermediate. The enzyme requires $NADH_2$ ($NADPH_2$) flavins (especially FAD) and Fe(II) ions as co-factors. The dihydrodiol formed can be further dehydrogenated to 7,8-dihydroxykynurenate by a dehydrogenase.

The dihydroxylation of naphthalene in *Pseudomonas* dependent on O_2 and $NADH_2$ apparently also involves a 1,2-epoxide intermediate which is hydrolysed by water to the dihydrodiol[209, 229].

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CHAPTER 15

Syntheses and uses of ^{18}O-labelled hydroxylic compounds

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I. INTRODUCTION

Oxygen occurs in nature as an isotopic mixture of ^{16}O (99·759%), ^{17}O (0·037%), and ^{18}O (0·204%). When a compound contains more than 0·2 atom % of ^{18}O it is called an ^{18}O-labelled compound. The amount of ^{18}O-label is usually expressed as the excess atom % of ^{18}O which is obtained by subtracting 0·2 atom % from the actual amount of ^{18}O present.

The main use of ^{18}O-labelled compounds, and especially of hydroxylic compounds described in this article, is for tracer studies for the elucidation of reaction mechanisms.

Heavy oxygen-labelled compounds differ in physical behaviour from the light ones although their chemical behaviour is identical. Careful fractional distillation is one of the methods to obtain ^{18}O-enriched hydroxylic compounds. $H_2{}^{18}O$ [1], methanol-^{18}O [2] or ethanol-^{18}O [3] can be obtained in this way from ordinary water or alcohols. However, in compounds of large molecular weights, the difference of the molecular weight due to the isotopes becomes relatively small. At present ^{18}O-water and gaseous $^{18}O_2$ are commercially available. The usual ^{18}O-labelled organic compounds are readily derived from ^{18}O-enriched water.

The oxygen exchange of alcohols in the presence of concentrated sulphuric acid is a drastic method for preparation of ^{18}O-labelled alcohols, applicable only for a limited number of alcohols.

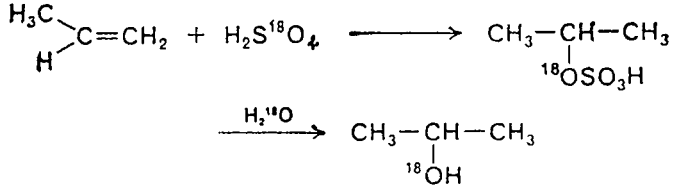
$$R^{16}OH + H_3{}^{18}O^+ \longrightarrow R^{18}OH + H_3{}^{16}O^+$$

^{18}O-Labelled phenols, however, can be produced readily by the acid-catalysed exchange reaction.

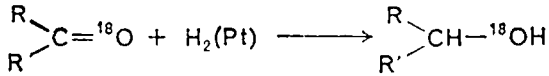
Higher alkanols are readily synthesized by the nucleophilic substitution of the corresponding alkyl halides with hydroxyl group:

$$RX + {}^{18}OH^- \longrightarrow R\text{-}{}^{18}OH + X^-$$

The hydration of alkenes is a useful method. Usually the alkenes are absorbed in ^{18}O-labelled sulphuric acid and then treated with boiling ^{18}O-water. The branched alcohols are produced preferentially.



Catalytic hydrogenation of aldehydes and ketones is a convenient method of the synthesis of ^{18}O-labelled alcohols, since the enriched carbonyl compounds are easily prepared by both acid- and base-catalysed exchange reactions:



The reduction of ^{18}O-labelled carbonyl compounds by lithium aluminium hydride for the preparation of the corresponding ^{18}O-labelled alcohols is usually quantitative.

Base-catalysed aldol condensation of aldehydes in the presence of

^{18}O-enriched water may also be useful for the preparation of ^{18}O-labelled unsaturated alcohols. For instance, *n*-butenol-^{18}O may be produced by treatment of acetaldehyde with $K^{18}OH$ in $H_2{}^{18}O$.

Among various methods for the determination of oxygen-18 content in organic compounds a modified Rittenberg–Ponticorvo procedure has been most convenient[4]. ^{18}O-containing organic compounds are mixed with mercuric chloride and then pyrolysed in a sealed tube at 450–530° to yield carbon dioxide which is collected and its ^{18}O-content measured mass-spectrometrically.

II. OXYGEN EXCHANGE

A. Alcohols

The exchange reactions of hydroxyl groups of alcohols are catalysed by acids such as hydrochloric and sulphuric. Concentrated sulphuric acid is known to exchange its oxygen atoms with water[5], and therefore, ^{18}O-labelled sulphuric acid can be readily prepared by the reaction with ^{18}O-enriched water[6].

Tertiary alcohols undergo oxygen exchange most readily and hence are the easiest to prepare:

$$PhMe_2COH + H_2{}^{18}O \longrightarrow PhMe_2C^{18}OH$$

$$Ph_2CHOH + H_2{}^{18}O \longrightarrow Ph_2CH^{18}OH$$

In the case of the acid-catalysed exchange reactions of primary and secondary alcohols, rearrangement to more stable secondary or tertiary alcohols takes place very often and dehydration also takes place simultaneously in most cases.

For instance, in a strong acidic media *n*-butyl alcohol gives *s*-butanol, di-*n*-butyl ether and butene, while neopentyl alcohol affords *t*-pentyl alcohol and pentenes. The rate of the oxygen exchange reaction of *n*-butanol is higher than that of the dehydration to butene, as indicated in Table 1.

TABLE 1. Rate constants for exchange and decomposition.

Alcohol	H_2SO_4(M)	$k_{ex} \times 10^8$ (sec^{-1})	$k_{dec} \times 10^8$ (sec^{-1})
n-Butyl alcohol	0·917	56	16·4
n-Butyl alcohol	0·092	7	—
neo-Pentyl alcohol	0·960	1·4	51

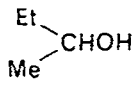
Temperature: 125°, Solvent: aqueous acid

This observation suggests that the reaction takes place through S_N2 type transition state[7].

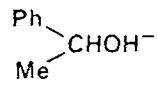
It has been assumed that the oxygen exchange of *s*-alcohols proceeds through the initial formation of carbonium ions and the subsequent hydration, since the rate is known to be correlated with the Hammett acidity function. However, when the reaction was carried out with an optically active secondary alcohol, the rate of oxygen exchange was roughly a half of that of racemization, similar to the S_N2 process[8].

Bunton accounted for this result as follows; when an alcohol (**1**) produces a relatively unstable and short-lived carbonium ion, the incipiently formed cation would be shielded rather tightly in the front by the leaving water molecule and hence approach of other water molecules from the same side would be hindered. In other words, the carbonium ion formed is not stable enough to be free from the leaving water molecule.

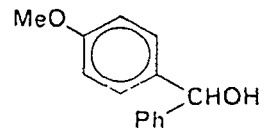
Accordingly, the rate of racemization becomes twice that of the exchange reaction, as in the S_N2 reaction of a typical Finkelstein reaction[9]. This theory was supported by testing other alcohols producing relatively more stable carbonium ions[10, 11].



(1)



(2)



(3)

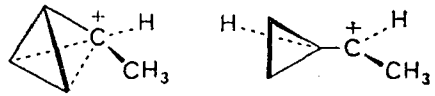
	(1)	(2)	(3)
k_{ex}/k_{rac}	0·5	0·8	1
Reference:	8	10	11

In compound **3** which can form a stable carbonium ion stabilized by the strong electron-donating *p*-methoxyphenyl group, the ratio k_{ex}/k_{rac} is near unity, since the carbonium ion has a sufficiently long lifetime to equilibrate completely before it recombines with a water molecule.

Optically active α-methyl cyclopropyl carbinol also produces a stable carbonium ion, and the value of k_{ex}/k_{rac} becomes unity. Richey[12] suggested in this case that the carbonium cation has a symmetric structure (**5**) [13] rather than an unsymmetrical one (**4**).

Bunton[14] reported that k_{ex}/k_{rac} of exchange reactions depends not only upon the structure of alcohols, but also on the nature of solvent and attempted to elucidate the role of the water molecule in the

exchange reaction. Based on the observation that in solvents of low water content and high acidity k_{rac}/k_{ex} is larger than unity, it was concluded that an internal return is involved in this reaction. The



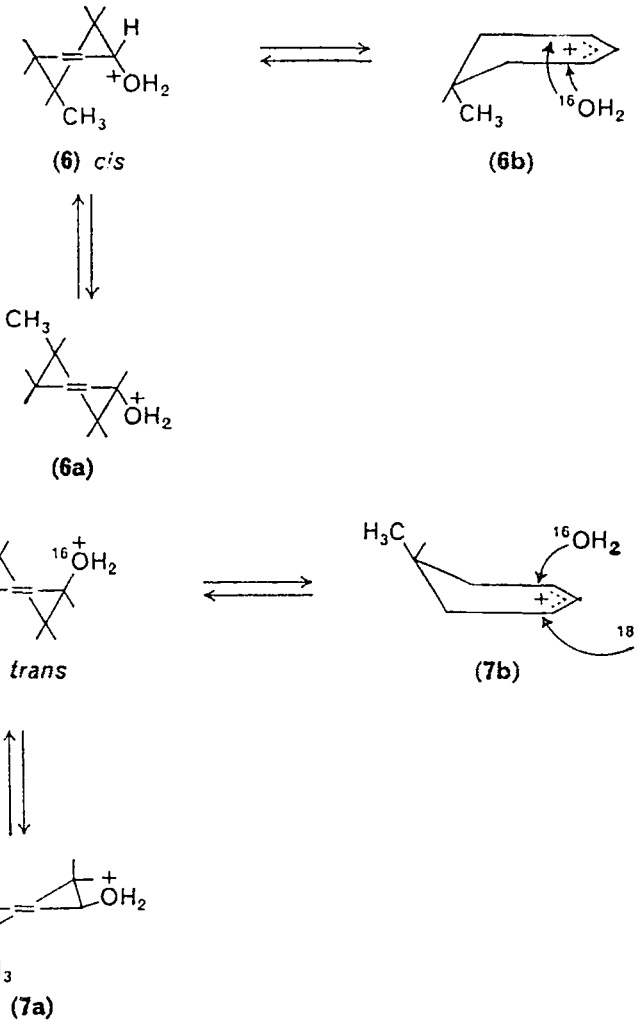
(4) (5)

stereochemistry of the oxygen exchange depends on both the lifetime of the incipiently formed carbonium ion intermediate and on the time required for the expelled water molecule to migrate from the solvation shell, losing its identity in the solvent. In aqueous media the carbonium ion is captured by a water molecule attacking from either the front or rear side of the leaving group. However, as the water content of the solvent is decreased, the water molecule expelled will be pulled away by the solvent, and the carbonium ion will lose its stereochemical identity. The presence of nucleophilic solvents such as dioxane also leads to interesting results. For example, when the activity of water is decreased by the addition of acid, the carbonium ion will be solvated by dioxane molecules and the recapture of the ion will be stereochemically non-specific and k_{rac}/k_{ex} will become larger than unity.

Goering[15] investigated the acid-catalysed oxygen exchange reaction of *cis*- (**6**) and *trans*- (**7**)-5-methyl-2-cyclohexenol in solvent water and observed that with the *cis*-compound, the major path of the racemization is through an intramolecular process ($k_{ex}/k_{rac} = 0{\cdot}03$), while with the *trans*-isomer the interconversion of the enantiomers results in almost complete exchange of ^{18}O ($k_{ex}/k_{rac} = 0{\cdot}4$).

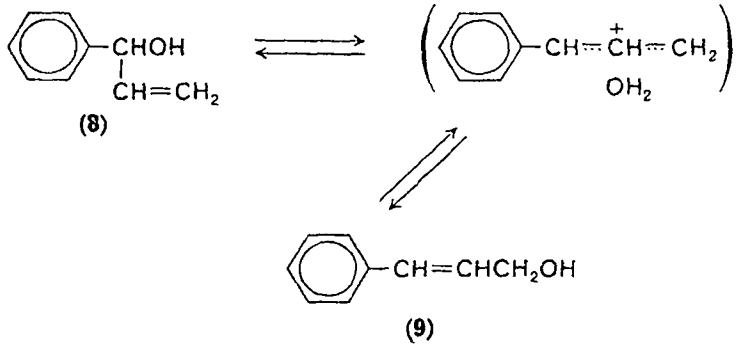
In these reactions the quasi-axial conformation **6** and **7** may be more favoured in the transition state because of the maximum overlap between a developing *p*-orbital and a double bond. On the other hand, the quasi-equatorial conformers **6a** and **7a** can attain this orientation only with considerable distortion of the ring. Thus the 5-methyl-2-cyclohexyl-carbonium ion conformers (**6b** and **7b**) are believed to react with a water molecule preferentially so as to form the quasi-axial bond according to the microscopic reversibility principle. Once the carbonium ion **7b** is formed, not only the leaving water molecule but also the water molecules originating from the medium will participate in the formation of solvation shell. Therefore, concurrent occurrence of both exchange and racemization gives a large value of k_{ex}/k_{rac}. On the other hand, in the carbonium ion **6b**

the reaction centre is solvated only by the leaving water molecule, and hence the product is found to have exchanged oxygen very little, yet undergone complete racemization.



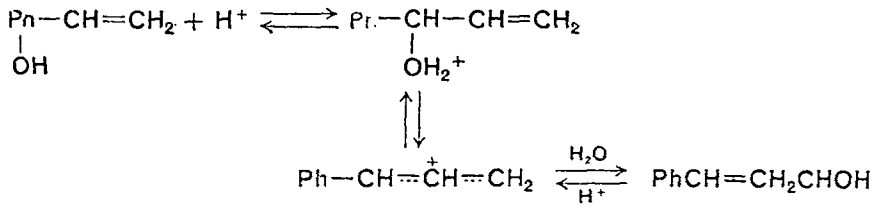
The exchange reaction of α-phenylallyl alcohol (8) was studied also by Goering and co-workers who found that in the acid-catalysed exchange, racemization and rearrangement of the optically active alcohol in 60 : 40 (v/v) aqueous dioxane take place without oxygen exchange[15].

Bunton[16a] reported that the rate of the $HClO_4$-catalysed rearrangement of 1-phenylallyl alcohol into 3-phenylallyl alcohol in



(8) (9)

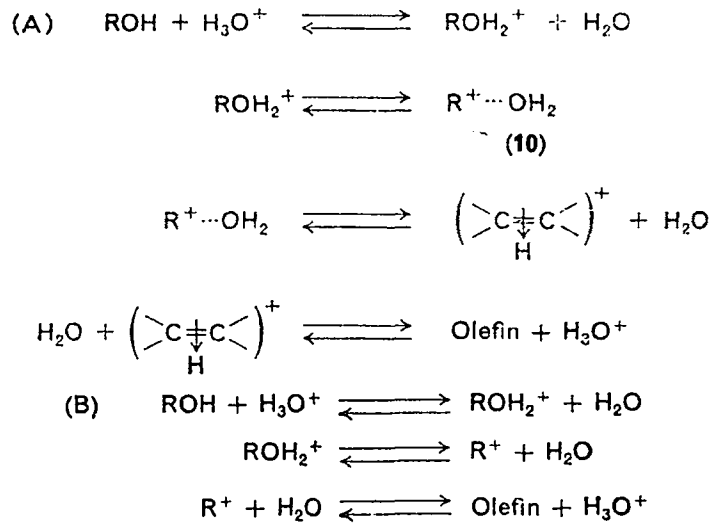
60 : 40 dioxane–water is proportional to the Hammett acidity function rather than to $[H_3O^+]$. The compound **8** recovered after intercepting the rearrangement in $H_2{}^{18}O$ is found to have partially exchanged its oxygen with ^{18}O of $H_2{}^{18}O$ and the alcohol **9** isolated had the same ^{18}O-content as that of the solvent water. The mechanism is depicted as shown below:



Dostrovsky and Klein[17] carried out the dehydration of *t*-butyl alcohol in sulphuric acid and Taft and co-workers[17] also studied the same reaction. The similarity of enthalpy and entropy values for the dehydration and exchange seems to show that both reactions proceed through the same or quite similar transition states. On the basis of these considerations, Taft[18] proposed two possible mechanisms (A) and (B). The intermediate called 'encumbered carbonium cation' (**10**) is proposed in the mechanism (A). This is different from the π-complex in nature.

The exchange reactions of other miscellaneous alcohols such as *trans*-1,2-dimethylcyclohexane-1,2-diol[19], bicyclic alcohol[20] and pinacol[21] have also been reported.

Among these an interesting finding is the ^{18}O-exchange reaction[22] of the alcoholic oxygen with carbon dioxide. This is based upon the observation that an isotopic equilibrium between the oxygen atom of an alcohol and carbon dioxide is attained when the two are heated in a sealed tube with a small amount of sulphuric acid. Incidentally,



as shown in Table 2, the equilibrium reaction between water and carbon dioxide has long been used for the determination of the ^{18}O-content in the water derived from ^{18}O-containing organic compounds[23].

TABLE 2. Percentage of equilibrium attained by CO_2 and oxygen-exchange in hydroxyl compounds.

Hydroxyl compound	Temp. °C	Time hr	Equilibrium % of CO_2	Equilibrium % of hydroxyl oxygen
Ethyl	200	3	99	90
n-Butyl	200	3	95	65
n-Octyl	200	3	94	60
Benzyl	200	1	99	90
Neopentyl	230	3	97	97
Isopropyl	120	3	100	100
Phenol	200	3	0	0

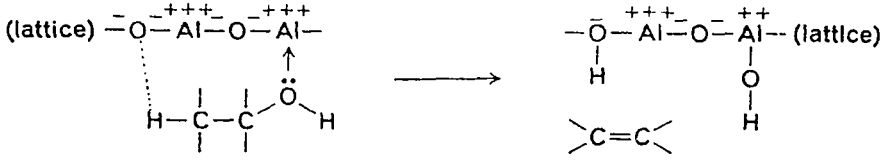
B. Exchange Reactions on Solid Surfaces

Lewis acids such as aluminium oxide or zinc chloride are good catalysts for the dehydration of alcohols. Aluminium oxide also catalyses the oxygen exchange of alcohols. The reactions are usually carried out at around 200–300°C and the catalytic ability is believed to be associated with the nature of the surface and hence markedly

dependent upon the method used for the preparation of the sample. In a certain temperature range, aldehyde, ether, or rearranged products may predominate. However, at about 300°C the dehydration reaction becomes the main pathway:

$$RCH_2CH_2OH \xrightarrow[Al_2O_3]{} RCH{=}CH_2$$

The reaction is accompanied by oxygen exchange between the solid and ethanol vapour. The first step of the reaction is probably the formation of a complex between ethanol and aluminium oxide. Exchange of ^{18}O between ethanol and the catalyst is also observed at 300° on kaolin, $Al_2O_3 + Cr_2O_3$, and zinc oxide. Carbonium ions have been postulated as intermediates in the reaction; however, these could not be free carbonium ions, because the dehydration on the solid surface does not always lead to the orientation according to the Saytzeff rule[24].



Isomerization and dehydration usually accompany the ^{18}O-exchange reaction under such drastic conditions. However, an excellent method to give ^{18}O-labelled alcohols under mild conditions is the rapid ^{18}O-exchange between alcohols and ^{18}O-labelled alumina in a nonpolar solvent such as benzene at room temperature[25]. In this case neither rearrangement nor dehydration takes place. For instance, neopentyl alcohol which, in other methods, easily isomerizes and dehydrates to pentenes, in this method exchanges its oxygen without any accompanying rearrangement.

TABLE 3. ^{18}O-Exchange on unlabelled alumina at room temperature, after 72 hours.

Labelled compound	Solvent	Starting material atom %	Product atom %
Benzoic acid	benzene	10·8	6·20
Cholestenone	benzene	44·0	0·74
Triphenylmethanol	benzene	44·65	22·0
Neopentyl alcohol	hexane	1·90	0·37

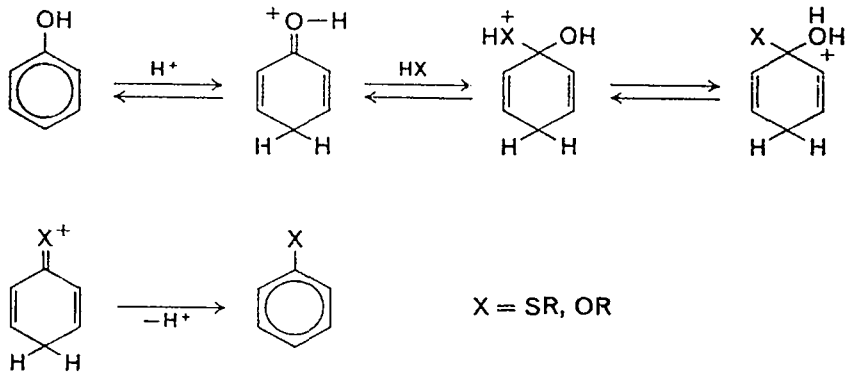
This may indicate that the molecule is held very tightly on the surface of the alumina and the isotopic exchange takes place without inversion at the α-carbon atom and without the formation of free carbonium ions which would allow rearrangement.

C. Exchange Reaction of Phenols

When phenols, resorcinol, α- and β-naphthols were heated 6–24 hours at 180° in 10N HCl in ^{18}O-enriched water, complete exchange took place[26]. The ease of exchange falls in the following order: *p*-nitrophenol, *p*-cresol, *m*-aminophenol, *p*-bromophenol, 2,4,6-trimethylphenol, 2,4,6-tribromophenol. The presence of *o*- and *p*-substituents apparently hinders either prior protonation or nucleophilic attack of water molecule at the reaction centre or both. The hydroxyl group of these phenols can be replaced by other nucleophiles such as ethanol and *n*-butanethiol under the same conditions.

The exchange reaction of substituted phenols and α,β-naphthols with ^{18}O-water was carried out under various conditions, and the rate of the reaction (except in the case of *p*-bromo- and *p*-aminophenols) was shown to be correlated with the Hammett equation with the value of $\rho = 0{\cdot}47$.

A pre-equilibrium protonation followed by an aromatic nucleophilic substitution reaction is suggested, although with *p*-nitrophenol only the latter stage is important. The mechanism presented by us is formulated as shown below;



However, in neutral[27] and basic solutions[28], no exchange takes place between water and phenol, naphthol or even *o*- and *p*-nitrophenols[29].

Hydroquinone is known to undergo oxygen exchange in neutral,

alkaline and acidic aqueous media with rate constants of 0·22, 0·24, and $1{\cdot}0 \times 10^{-5}$ sec^{-1}, respectively, at 140°C.

III. NUCLEOPHILIC SUBSTITUTION

A. Alkyl Halides

In nucleophilic substitution reactions of alkyl halides, when ^{18}O-labelled hydroxide or water is used, the ^{18}O-labelled alcohol is the product of the hydrolysis as shown by the following equation[30]:

$$t\text{-BuCl} + H_2{}^{18}O \longrightarrow t\text{-Bu}{}^{18}OH + HCl$$

$$CH_3CH_2CH_2Br + K^{18}OH \longrightarrow CH_3CH_2CH_2{}^{18}OH + KBr$$

Alkyl sulphate and sulphonate are also often used as the substrate.

The reactivity of the leaving group is in the order; bromide > chloride > fluoride in most protic solvents such as water and alcohols.

The reactivity of various alkyl halides varies in the order: tertiary > secondary > primary alkyl halides in S_N1 type solvolysis. Under S_N2 solvolytic conditions, however, steric hindrance due to bulky alkyl groups may retard the reaction rate. For instance, neopentyl halide reacts very slowly due to steric hindrance by the bulky tertiary group present around the carbon centre. The S_N2 type solvolytic reaction is quite effective in the preparation of optically active ^{18}O-labelled alcohols from the corresponding optically active alkyl halides, since the reaction involves stereochemical inversion at the saturated carbon centre. The rate of the reaction is small in the neutral media, but large in alkaline media. For example, ^{18}O-labelled ethyl alcohol is readily prepared in the reaction of an ethyl halide with an aqueous solution of ^{18}O-labelled KOH:

$$CH_3CH_2Cl + K^{18}OH \longrightarrow CH_3CH_2{}^{18}OH + KCl$$

The reactivities of alkyl halides fall in the order: primary > secondary > tertiary. Usually, the solvolysis is accompanied by elimination, caused by the attack of hydroxide ion at the β-hydrogen of alkyl halides, especially in branched tertiary halides.

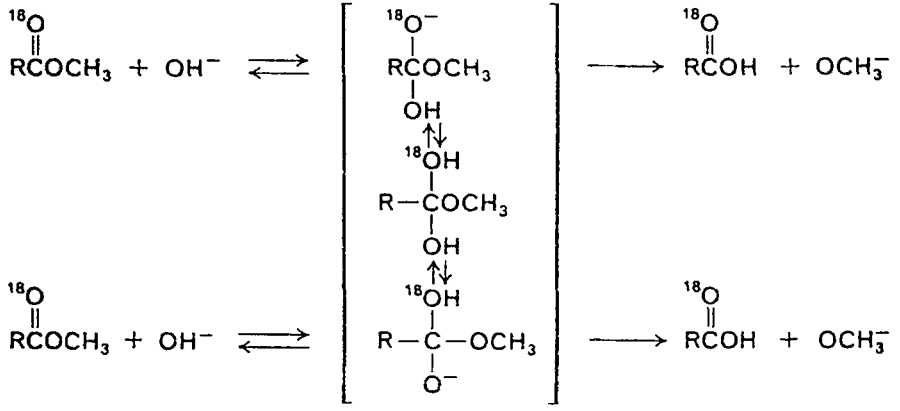
$$ROH + TsCl \longrightarrow ROTs + HCl$$

$$ROTs + CH_3C(={}^{18}O)({}^{18}ONa) \longrightarrow R-{}^{18}O-C(=O)-CH_3 \xrightarrow{KOH} R-{}^{18}OH$$

A better preparative method of ^{18}O-labelled alcohols is the reaction shown on p. 807 which involves initial tosylation of alcohols[31].

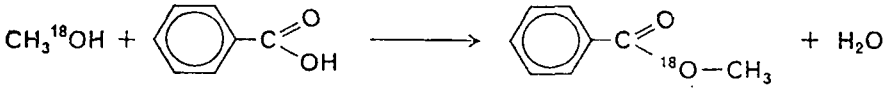
B. Carboxylic Esters

The hydrolysis of esters has been thoroughly investigated by Bender and co-workers[32]. The alkaline hydrolysis involves a tetrahedral addition complex. ^{18}O-tracer experiments revealed that ester recovered before the completion of the reaction shows considerable incorporation of ^{18}O during the reaction. Hence, the intermediate is partitioned between reversal to the initial ester and the product[32].



This mechanism is applicable for the hydrolysis of ethyl, isopropyl and *t*-butyl benzoates. Similar tetrahedral intermediates have been proposed in the acid-catalysed hydrolysis of the same esters and also in the hydrolyses of benzamides and acid chlorides. In the hydrolysis of *p*-substituted methyl benzoates the ratio, k_{hyd}/k_{exch}, was found to be 11 for the unsubstituted compound while the Hammett ρ-value for the hydrolysis was $+1{\cdot}93$. The k_{hyd}/k_{exch} value varies widely with substituents, and it was suggested that the proton transfer in the tetrahedral intermediate is kinetically important.

In an early study Roberts and Urey[33] examined the esterification of benzoic acid with ^{18}O-labelled methanol and found that the methyl benzoate obtained was labelled with an excess ^{18}O, but the water formed was not. They proved that esterification proceeds through the following scheme:



This means that the hydrolysis of the ester under similar conditions also takes place by acyl–oxygen fission, according to the microscopic reversibility principle. Accordingly, hydrolysis by $H_2{}^{18}O$ of ordinary esters is not a suitable procedure for the preparation of ^{18}O-labelled alcohols[34]. Acetals of ^{18}O-labelled benzaldehyde and propionaldehyde also hydrolyse by way of aldehyde C–O bond cleavage, although the ^{18}O-content of allyl alcohol obtained upon hydrolysis of diallyl acetal indicates a slight enrichment in the alcohol moiety[35]. Alkyl–oxygen fission takes place in the A-1 type hydrolysis of esters. These reactions involve the formation of stable carbonium ions. *t*-Butyl acetate is one of these examples which undergo alkyl–oxygen bond cleavage[36].

$$(CH_3)_3COCCH_3 + H_2{}^{18}O \xrightarrow{H^+} (CH_3)_3C{}^{18}OH + CH_3COOH$$

Isotopic tracer experiments using ^{18}O-enriched water confirmed that alkyl–oxygen fission occurs also in the hydrolysis of methyl 2,4,6-tri-*t*-butylbenzoate and 2,6-di-*t*-butylbenzoate in aqueous sodium hydroxide. Alkyl–oxygen cleavage predominates only with hindered esters[37].

TABLE 4. Isotopic analysis in the fission of methyl esters.

Methyl ester	Solvent	Atom % of water	Atom % of $C^{16}O^{18}O$ from acid
2,4,6-Trimethylbenzoate	65% dioxane	0·75	0·7
2,5,Di-*t*-butylbenzoate	65% dioxane	0·75	0·8
2,6-Di-*t*-butylbenzoate	90% dioxane	0·5	0·0
2,4,6-Tri-*t*-butylbenzoate	65% dioxane	0·9	0·0

Sometimes, hydrolysis occurs through both acyl–oxygen and alkyl–oxygen fission concurrently. In the acid-catalysed hydrolysis of *t*-butyl acetate, two modes of hydrolysis contribute: namely, A_{al} in which protonation of the ester leads to rate-determining expulsion of the *t*-butyl cation, and A_{ac} in which the protonated ester undergoes a slow rate-determining attack by water molecule at the carbonyl group. The ^{18}O-content of *t*-butyl alcohol obtained in the hydrolysis of *t*-butyl acetate in ^{18}O-labelled water at 25–85° was measured and the reaction was found to involve 85% and 99%

alkyl–oxygen fission at 25° and 85° respectively. The activation parameters for these fissions are[38];

$$E_a = 27{\cdot}5 \text{ kcal/mole} \qquad \log A = 16{\cdot}1 \text{ for } A_{al}$$
$$E_a = 17{\cdot}3 \text{ kcal/mole} \qquad \log A = 7{\cdot}9 \text{ for } A_{ac}$$

The steric course[39] of the hydrolysis of optically active *p*-methoxydiphenylmethyl acetate was determined in both acid and neutral conditions. Under both conditions studied the alkyl–oxygen bond is broken with complete loss of optical activity. The addition of azide or acetate ion reduces the hydrolytic rate by capturing the generated carbonium cation, but does not change the rate of loss of optical activity during the hydrolysis.

$$\begin{array}{l} ROAc \longrightarrow R^+ + OAc^- \\ \qquad\quad \downarrow H_2{}^{18}O \\ \qquad\quad R^{18}OH + H^+ \end{array}$$

In a similar manner, the hydrolysis of triphenylmethyl acetate[40] has been examined in aqueous dioxane containing ^{18}O-enriched water, and it was shown that in initially neutral, weak alkaline and acid media, the reaction follows the following mechanistic course:

$$CH_3COOCPh_3 \longrightarrow CH_3COO^- + {}^+CPh_3 \xrightarrow{H_2{}^{18}O} CH_3COOH + H^{18}OCPh_3$$

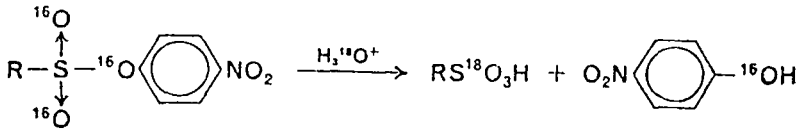
Diphenylmethyl formate[41], however, undergoes acyl–oxygen bond fission under both acidic and basic conditions, although in initially neutral solution, alkyl–oxygen fission occurs:

$$HC(=O^{16})-{}^{16}OCHPh_2 \xrightarrow{\text{in neutral solution}} Ph_2CH^{18}OH$$
$$HC(=O^{16})-{}^{16}OCHPh_2 \xrightarrow{\text{in acidic or basic solution}} Ph_2CH^{16}OH$$

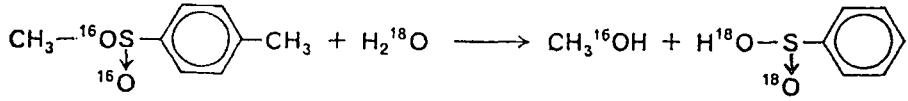
C. Sulphonate and Sulphate Esters

The hydrolysis of sulphonate esters, unlike that of carboxylic esters, has been shown to occur without the formation of an addition intermediate. For example, when the acid hydrolysis was carried out by heating *p*-nitrophenyl benzenesulphonate with hydrochloric acid in ^{18}O-enriched water in a sealed tube at 180°, the overall

reaction was found to be irreversible and there was no exchange of oxygen in the recovered ester. The benzenesulphonic acid isolated incorporated one atom equivalent of ^{18}O [42]:



The hydrolysis of methyl *p*-toluenesulphinate in acidic dioxane–water-^{18}O was also shown to proceed through acyl–oxygen cleavage[43].



It was shown that *p*-nitrophenol formed by the hydrolysis of *p*-nitrophenyl *p*-toluenesulphonate in $H_2{}^{18}O$ always contains an excess ^{18}O. The hydrolysis undoubtedly proceeds via an S_N2 process involving nucleophilic attack by water on the sulphur atom. Under the same condition *p*-nitrophenol itself also undergoes facile oxygen exchange.

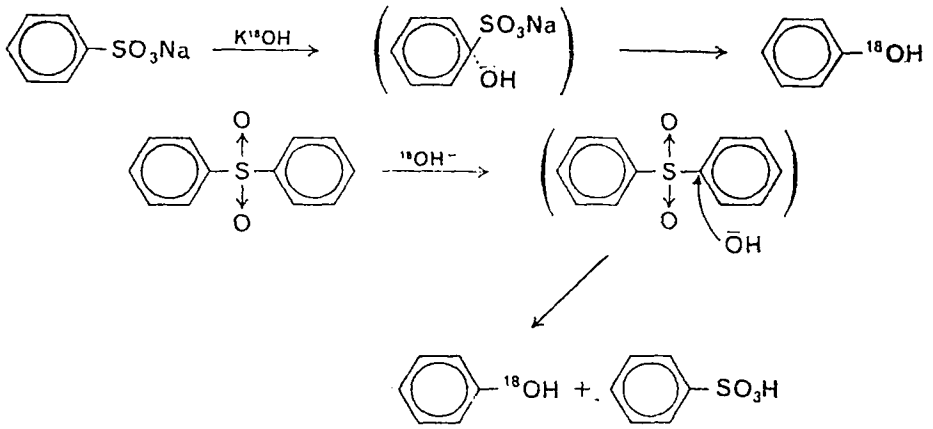
The alkaline hydrolysis of *p*-nitrophenyl toluenesulphonate in ^{18}O-enriched water containing potassium hydroxide is also an irreversible reaction. However, the ^{18}O-incorporation is somewhat lower than that in the case of sulphuric acid. Apparently, a portion of the reaction proceeds via an aromatic nucleophilic substitution process involving C–O bond cleavage, though the process involving nucleophilic attack on the sulphur atom is the major path.

$$ArSO_3Ar' + {}^{18}OH^- \longrightarrow \underset{\text{(minor process)}}{ArSO_3H + A'r{}^{18}OH}$$

The C–S bond cleavage is also observed in the alkaline fusion of aromatic sulphonic acids and diaryl sulphones. With these compounds, the 'benzyne' route is ruled out by ^{14}C tracer experiments, and a direct aromatic substitution mechanism is favoured for the fusion of the sulphonic acid[44], while with the sulphones the attack appears to occur at both benzene carbon and sulphur atoms[45].

Bender and Dewey[46] examined the mechanism of the hydrolysis of sulphonate esters and found that phenyl methanesulphonate, when hydrolysed in aqueous 80% dioxane containing isotopically enriched water, gives phenol with a normal isotopic abundance of ^{18}O:

$$MeSO_3OPh + {}^{18}OH^- \longrightarrow MeS{}^{18}O_3H + Ph{}^{16}OH$$



On the other hand, methanol with 0·82 atom % of ^{18}O is obtained when heating dimethyl sulphate with sodium hydroxide in water containing 1·2% of ^{18}O. The use of a large excess of aqueous solution[46] leads to the formation of methanol labelled with 1·10 atom % of ^{18}O [47]:

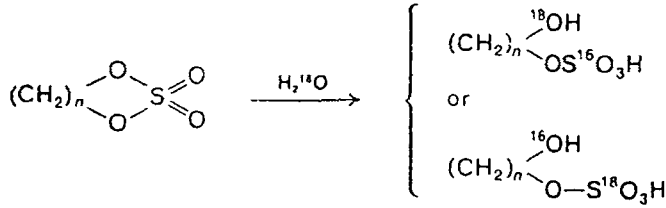
$$(CH_3O)_2SO_2 + H_2{}^{18}O \longrightarrow CH_3{}^{18}OH + CH_3OSO_3H$$

Heating dimethyl sulphate with $H_2{}^{18}O$ containing a trace of sulphuric acid results in the formation of methanol with 1·08% of ^{18}O. Accordingly, the hydrolysis of dimethyl sulphate does not involve S–O bond cleavage, but proceeds via the cleavage of the C–O linkage in both acidic and alkaline media. Other sulphate esters, such as diethyl and diisopropyl sulphate, undergo nearly 100% alkyl–oxygen fission[48]. Thus, the hydrolysis of dialkyl sulphate may be a useful method to prepare the corresponding ^{18}O-labelled alcohol.

The hydrolysis of cyclic sulphates has been investigated in some detail. In the hydrolysis of the esters of cyclohexane-*cis*- and -*trans*-diols in $H_2{}^{18}O$, the cyclic *cis*-diol sulphate is hydrolysed either with net inversion to give *trans*-diol or C–O and S–O bond cleavages to afford *cis*-diol, while *trans*-diol sulphate affords the diol via C–O bond fission mainly with retention accompanying partial racemization, or gives the *trans*-diol via both S–O and C–O bond cleavages forming the incipient epoxide intermediate[49].

Westheimer[50] found that ethylene sulphate, trimethylene sulphate, and dimethylene sulphate undergo first-order solvolysis. In aqueous solvents of pH range of 2 to 9 the relative rate ratio is 12 : 1 : 6. In a more alkaline solution the predominant reaction is the saponification following the second-order rate equation with relative rate

ratio of 103 : 1 : 5·5. The ^{18}O-analysis indicates that the first step in the solvolysis of all those sulphates in either neutral or alkaline solution is the C–O bond cleavage; however, in the case of ethylene sulphate ($n = 2$) a partial S–O bond fission (about 14%) is also detected.

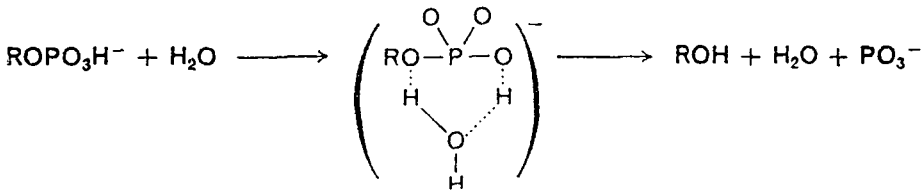


D. Phosphorus Esters

The hydrolysis of mono esters of phosphoric acid, for instance, 1-methoxy-2-propyl phosphate, proceeds under various conditions in water enriched with ^{18}O. At pH 4, or at pH 8·5 in the presence of lanthanum hydroxide, the cleavage of phosphate esters takes place at the P–O (and not at the C–O) bond and leads to the formation of normal alcohols:

$$R^{16}OPO_3H^- + H_2{}^{18}O \longrightarrow R^{16}OH + H_2P^{18}O_4^-$$

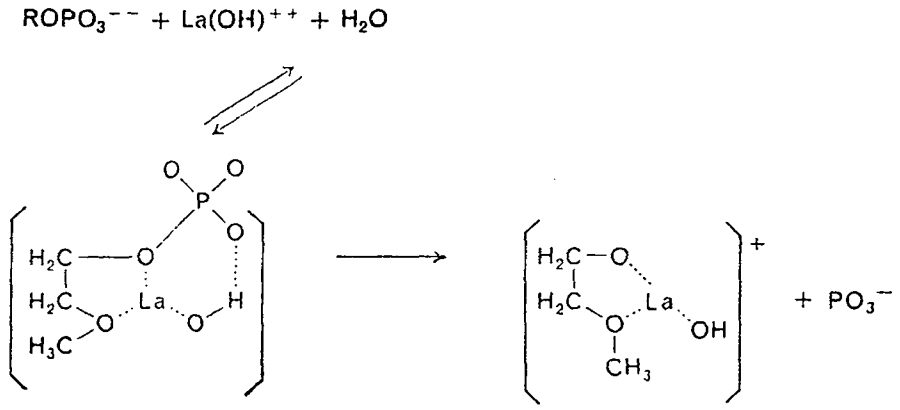
The stereochemical result, namely, the complete retention of configuration, also confirms the ^{18}O-results[51], while the alcohol and monomeric metaphosphate ion, PO_3^-, are postulated as primary products.



The hydrolysis of methyl phosphate in acid solution containing $H_2{}^{18}O$ gives ^{18}O-labelled methyl alcohol[52]; however, the alcohol acquires only a small fraction of ^{18}O enrichment.

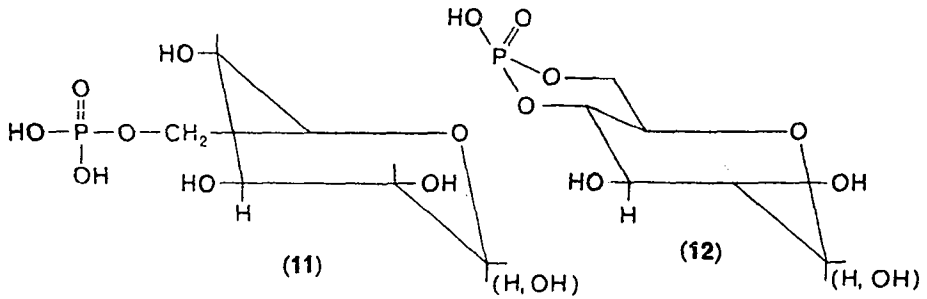
A plausible mechanism for the hydrolysis of 1-methoxy-2-ethyl phosphate is considered to involve the transition state, as shown on the following page.

The rate of the hydrolysis of D-glucose-6-dihydrogen phosphate[53] was measured in aqueous solution at 72–100°. By the use of ^{18}O-enriched water, the hydrolysis of the neutral molecule and the monoanion were found to involve complete P–O bond fission.



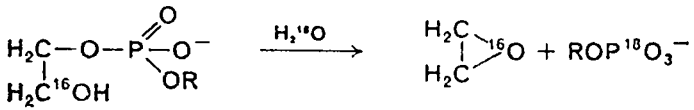
The dianion is found to generate orthophosphate mainly through cleavage of the C–O bond. In solutions of 1–5M of NaOH, the rate of release of orthophosphate is proportional to the concentration of sodium hydroxide. In a strongly acidic solution, D-glucose-6-phosphate undergoes rapid reversible ring closure to afford a cyclic sugar phosphate via P–O bond fission. In this case the hydrolysis proceeds via C–O bond fission with ^{18}O-exchange, with the solvent.

Glucose-6-phosphate exists in the pyranose form and cyclization may occur between the phosphate group and the equatrial hydroxyl function on C-4 leading to a six-membered cyclic phosphate. The isotopic exchange in **11** is considered to proceed through the formation of such a cyclic intermediate **12**, which undergoes exclusively rapid P–O bond fission.

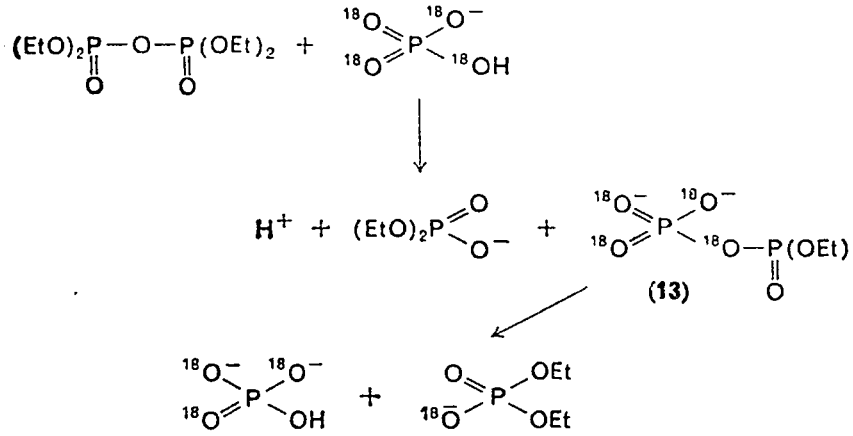


The esters of vicinal diols[54] exhibit a different behaviour in the hydrolysis. The hydrolysis of cyclohexyl *erythro*-3-hydroxy-2-butyl hydrogen phosphate in aqueous NaOH at 100° gives stereochemically pure *meso*-butane-2,3-diol. When the hydrolysis is conducted in H_2O enriched with ^{18}O, the product formed is isotopically natural.

A mechanism involving the formation of an epoxide is suggested, as shown below.



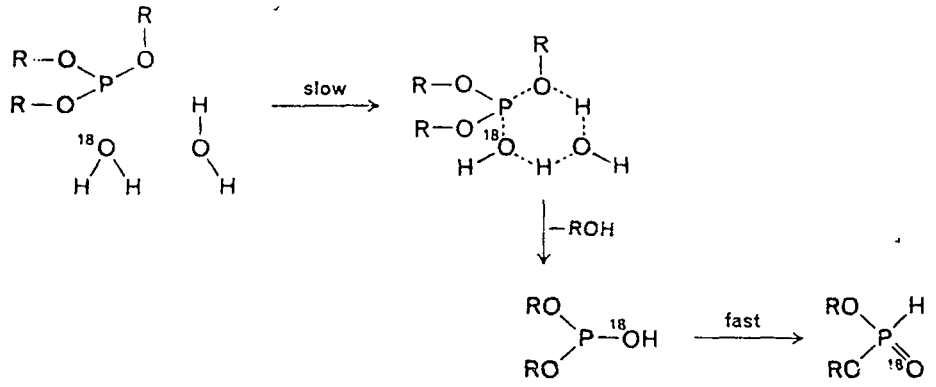
The phosphate ion[55] acts as a nucleophile, for example, when the hydrolysis of tetraethyl pyrophosphate in the presence of ^{18}O-labelled phosphate ion is performed, tetraethyl pyrophosphate produces two molecules of diethyl phosphate, one of which is ^{18}O enriched. The percentage enrichment agrees with that expected on the basis of a catalysed path involving the formation of a diethyl pyrophosphate ion[13] as an intermediate;



Haake and Westheimer[56] investigated the hydrolysis of ethylene phosphate at room temperature and found that the rate ratio k_{hyd}/k_{exch} in acid media is 5. They stated that both the hydrolysis and the oxygen exchange take place simultaneously through a complex which has either a trigonal bipyramidal or a square pyramidal structure.

The hydrolysis of triphenyl phosphite[57] was studied and the rate was found to be of first-order in phosphite and second-order in H_2O. The experiment in ^{18}O-enriched water–acetonitrile shows that the P–O bond is broken and the kinetic isotope effect k_{H_2O}/k_{D_2O} is as large as 8. These results suggest that O–H bond weakening occurs in the rate-determining step.

A five-membered cyclic ester of a phosphonic acid, lithium propylphostonate (**14**), and a 6-membered analogue, lithium butyl

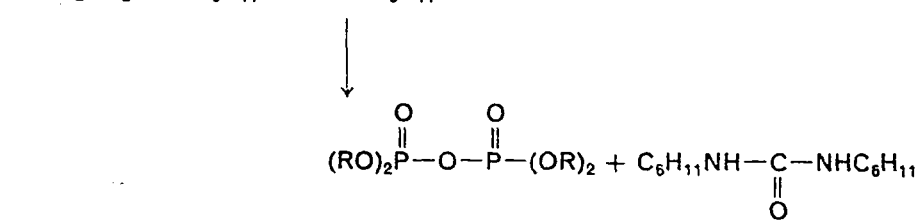


phostonate (**15**) have been synthesized and the hydrolysis rates of these compounds relative to that of sodium ethyl ethylphosphonate in acid solution were found to be $5 \times 10^4 : 3 : 1$[58].

The ^{18}O tracer study shows that the ethyl phostonates are cleaved at the P–O bond, whereas the hydrolysis of the open chain phosphonate occurs with about equal cleavage of both P–O and C–O bonds.

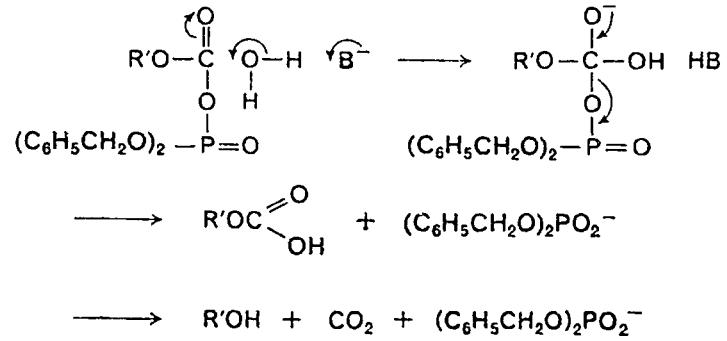
(14) **(15)**

The hydrolysis of the triesters of phosphoric-carbonic anhydride[59] gives dialkyl phosphate, carbon dioxide and alcohol. The dialkyl phosphate was isolated and allowed to react with dicyclohexyl carbodiimide.



The m/e ratio of 226/224 in the mass spectrum of dicylcohexylurea was determined with the results reported in Table 5.

It is evident that the reaction proceeds predominantly through carbon–oxygen bond cleavage with a minor contribution of P–O bond cleavage.



Consequently, though the hydrolysis of the phosphate ester is convenient for the preparation of ^{18}O-labelled alcohols it is not a satisfactory procedure due to the contamination by C–O (alkyl) bond cleavage.

TABLE 5. Tracer study

^{18}O-content of dicyclohexylurea

Urea	R(226/224)
Natural abundance[a]	0·0141
^{18}O-enriched[b]	0·0358
Sample 1[c]	0·0143
Sample 2[c]	0·0142

[a] Prepared by hydrolysis of dicyclohexylcarbodiimide with ordinary distilled water.

[b] Prepared by hydrolysis of dicyclohexylcarbodiimide with 1·56 atom % ^{18}O water.

[c] Samples derived from dibenzyl hydrogen phosphate produced by the hydrolysis of anhydride in 1·56 atom % ^{18}O water.

E. Other Esters

^{18}O-labelled alcohols can also be prepared by hydrolysis of inorganic esters of alcohols[60].

The acid-catalysed hydrolyses of *n*-propyl, *t*-butyl and diphenylmethyl nitrites were studied at 0° in 72·5% (w/w) dioxane–water. ^{18}O tracer experiments showed that the reactions proceed exclusively by acyl–oxygen cleavage. Even in the hydrolysis of *t*-butyl nitrite in $H_2{}^{18}O$ the *t*-butanol obtained did not contain any ^{18}O.

The alkaline hydrolysis proceeds through nucleophilic attack by the hydroxide ion on the nitrogen atom of the esters, and is again not suitable to prepare ^{18}O-labelled alcohols. Other esters of inorganic oxyacids have been studied to determine the site of cleavage in the hydrolysis with ^{18}O-enriched water[61]. Triphenylmethyl perchlorate, sulphate and nitrate, and *t*-butyl nitrate are among the few which undergo hydrolysis via alkyl–oxygen fission, while *n*-butyl and *n*-octyl sulphates are hydrolysed only partly through this pathway.

IV. ADDITIONS

A reliable method of preparation of ^{18}O-labelled alcohols is the acid-catalysed addition of ^{18}O-enriched water to alkenes[62].

$$H_2S^{18}O_4 + CH_3CH_2CH{=}CH_2 \longrightarrow CH_3CH_2\underset{\displaystyle {}^{18}OSO_3H}{\underset{|}{C}}H{-}CH_3 \longrightarrow CH_3CH_2\underset{\displaystyle {}^{18}OH}{\underset{|}{C}}HCH_3$$

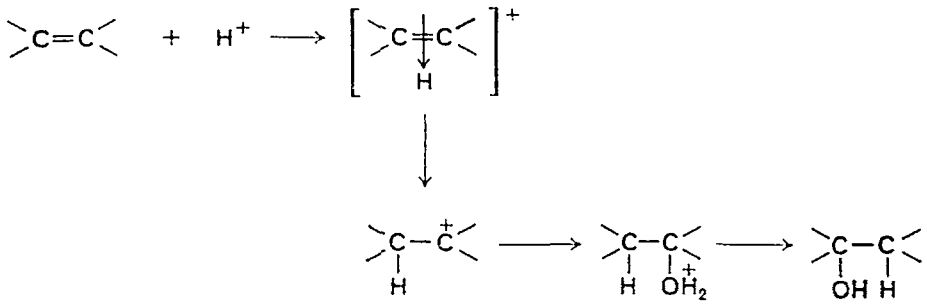
A commonly accepted mechanism of alkene hydration is shown below (a). Levy and Taft studied the acid-catalysed hydration of isobutene[63] and found that the rate is proportional to the H_0 function. This seems to indicate that water is not involved in the activated complex (route b):

(a) $$\rangle C{=}C\langle + H_3O^+ \longrightarrow \rangle\underset{\displaystyle H_2O^+}{\underset{|}{C}}-\underset{\displaystyle H}{\underset{|}{C}}\langle \longrightarrow \rangle\underset{\displaystyle HO}{\underset{|}{C}}-\underset{\displaystyle H}{\underset{|}{C}}\langle$$

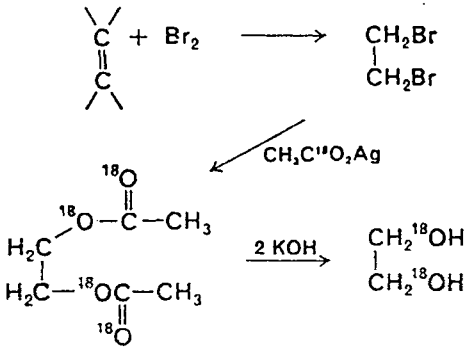
(b) $$\rangle C{=}C\langle + H_3O^+ \longrightarrow \rangle\underset{\displaystyle H}{\underset{|}{C}}-\overset{+}{C}\langle + H_2O$$

$$\rangle\underset{\displaystyle H}{\underset{|}{C}}-\underset{\displaystyle {}^+OH_2}{\underset{|}{C}}\langle \longrightarrow \text{product}$$

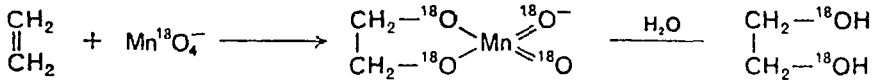
In mechanism (b) the formation of carbonium ion is considered to be rate-determining, but a mechanism assuming the second step to be rate-controlling is also compatible with the experimental results. Considering also other observations, such as the lack of deuterium exchange during the addition[64], the following mechanism, involving the formation of a π-complex, was suggested.



Other addition reactions are also useful for the preparation of ^{18}O-labelled alcohols. Catalytic hydration of acetylene by $H_2{}^{18}O$ provides ^{18}O-labelled acetaldehyde, which upon reduction gives ethanol. Glycols can be prepared, when two hydroxyl groups are introduced into an alkene, or by the reaction of dihalides with silver acetate-^{18}O.



The oxidation of an olefin by ^{18}O-labelled potassium permanganate affords a cyclic intermediate **16**, which decomposes to an ^{18}O-labelled glycol upon hydrolysis[66], with cleavage of the Mn–O bond:



(16)

For example, the oxidation of oleic acid is effected at about pH 12 with an excess of permanganate, which is permissible since the oxidation of the diol by permanganate is very slow (Table 6).

The addition of a Grignard or other metalorganic reagent can also be used for the synthesis of ^{18}O-labelled alcohols from ^{18}O-labelled aldehydes or ketones.

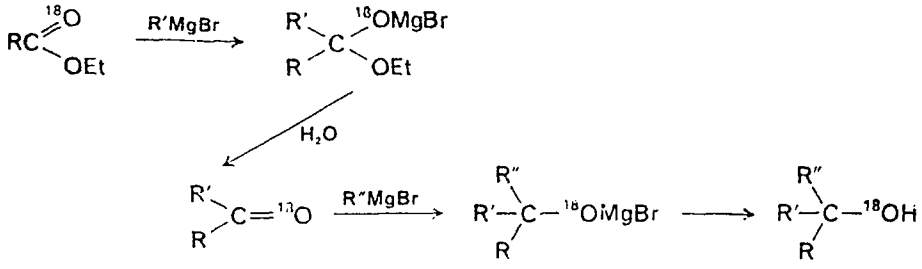


TABLE 6. Oxidation of oleic acid[66].

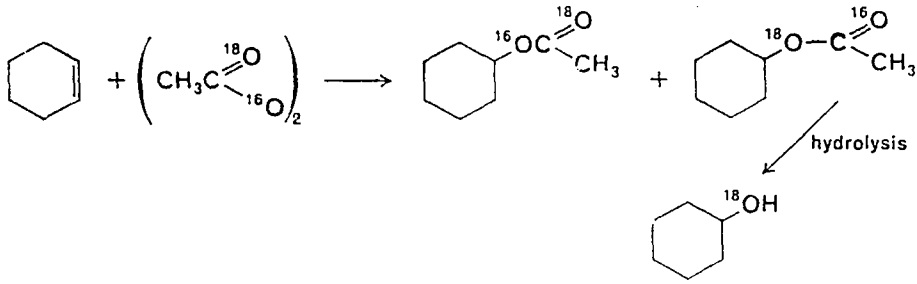
Excess atom % in $KMnO_4$	$KMnO_4$/oleic acid	Excess atom % in CO_2 from diol	Atoms oxygen from $KMnO_4$
0·910	1·45	0·117	1·03
0·910	2·00	0·176	1·55

V. OXIDATIONS

A number of oxidations by various reagents can be used for the preparation of ^{18}O-labelled alcohols. Careful oxidation of alkanes by ^{18}O-labelled potassium permanganate affords partially ^{18}O-labelled alcohol[65], while alkenes yield glycols[66].

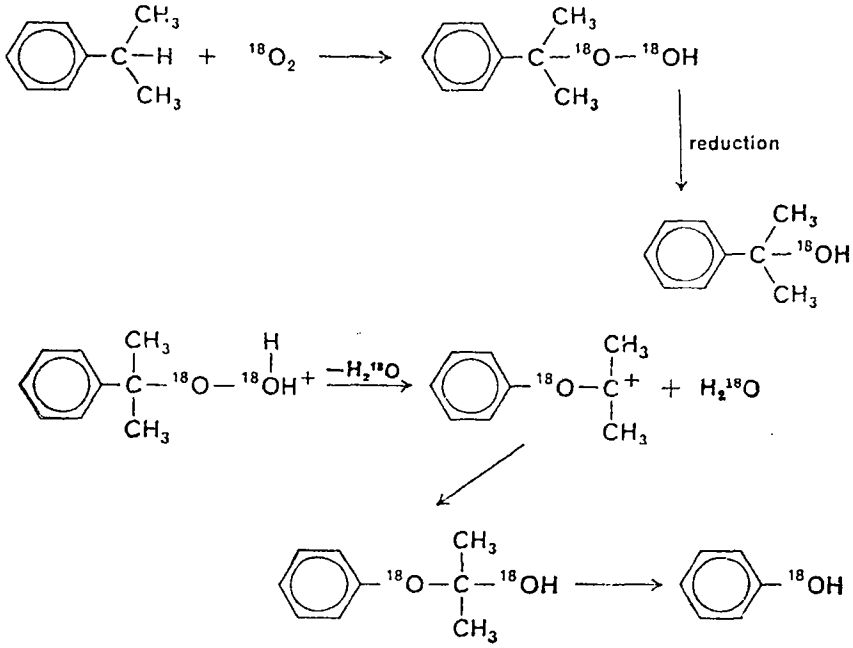
$$R_3CH + Mn^{18}O_4^- \longrightarrow R_3C^{18}OMn^{18}O_3 \longrightarrow R_3C^{18}OH$$

Peroxides such as acetyl peroxide oxidize alkenes to the corresponding acetate ester which is easily converted to the labelled alcohol upon hydrolysis[67].



Hydroperoxides, which are formed by auto-oxidation, might also be used in some cases[68].

The rearrangement of the hydroperoxide is catalysed by acid to afford phenol.



3,4-Dimethylphenol is enzymatically oxidized to 4,5-dimethyl catechol by action of 'phenolase enzyme'; all the oxygen atoms introduced as hydroxyl groups into benzene ring are derived from molecular oxygen[69].

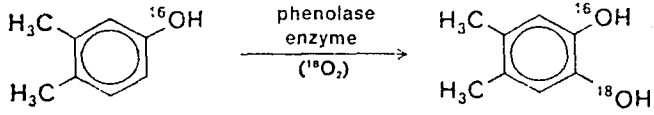


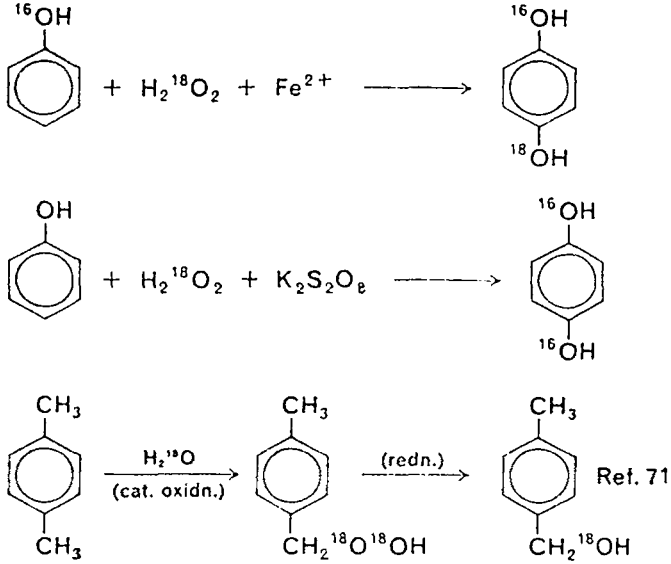
TABLE 7. ^{18}O-Experiments of the reaction of 'phenolase enzyme' with 3,4-dimethylphenol in $^{18}O_2$[a] and H_2O; and in O_2 and $H_2{}^{18}O$[b].

System	Found excess atom %	Theoretical value for uptake of one excess atom %
$^{18}O_2 + H_2O$	0·52	0·59
	0·51	0·59
$O_2 + H_2{}^{18}O$	0·00	0·59
	0·00	0·59

[a] Prepared electrolytically; [b] containing 1·4 atom %

Hydrogen peroxide can convert olefins to the corresponding hydroperoxides which can be reduced to alcohols, while aromatic compounds are directly oxidized to phenols.

In the presence of acetic acid, phenol is hydroxylated by means of a mixture containing $H_2{}^{18}O_2$ and Fe^{2+} ion to ^{18}O-labelled pyrocatechol. With $K_2S_2O_8$ and $H_2{}^{18}O_2$ in alcohol solution phenol is oxidized also to hydroquinone, containing the persulphate oxygen in the new hydroxyl group[70].



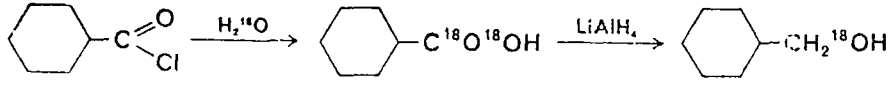
A convenient method for the preparation of aliphatic alcohols is the treatment of alkyl Grignard reagents with ^{18}O-enriched oxygen[81].

$$MeMgBr + {}^{18}O_2 \xrightarrow{H_2O} Me{}^{18}OH$$

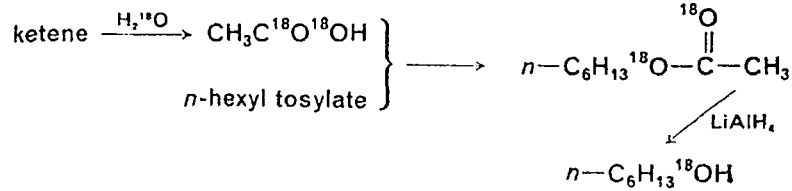
Oxygen enriched with ^{18}O can be readily obtained by electrolysis of $H_2{}^{18}O$ containing 20% sulphuric acid.

VI. REDUCTIONS

^{18}O-labelled alcohols can be obtained by the reduction of carbonyl compounds, such as aldehydes, ketones, esters, acid chlorides and anhydrides[72]. For example, cyclohexyl carbinol enriched with ^{18}O is prepared by the reduction of cyclohexanoic acid with lithium aluminium hydride.



Similarly, esters which are tagged with ^{18}O are easily reduced to the corresponding alcohols[73].



The use of sodium borohydride is also effective for the reduction of ^{18}O-tagged carbonyl groups of aldehydes and ketones to give corresponding ^{18}O-labelled alcohols.

$$NaBH_4 + 4\,CH_2{}^{18}O + 3\,H_2O \longrightarrow 4\,CH_2{}^{18}OH + NaH_2BO_3$$

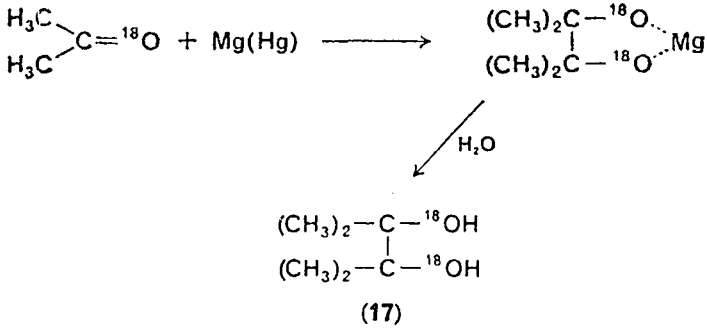
The platinum- or nickel-catalysed hydrogenation is a convenient and important procedure suitable for large-scale reductions of aldehydes and ketones. An aldehyde can be labelled by ^{18}O by equilibrating it with ^{18}O-labelled water, and subsequently reduced to ^{18}O-labelled ethanol[74].

$$CH_3C(=O)H + H_2(Ni) \longrightarrow CH_3CH_2{}^{18}OH$$

Ketones or aldehydes can be reduced to the corresponding primary or secondary alcohols, e.g., by using aluminium isopropoxide:

$$R_2C=^{18}O \xrightarrow{Al[OCH(CH_3)_2]_3} [R_2CH^{18}O]_3Al \longrightarrow R_2CH^{18}OH$$

Pinacols (**17**) are made available by reduction of various ketones with magnesium amalgam in benzene[75].



(**17**)

Since in these reductions ^{18}O-labelled carbonyl compounds are the starting materials it is appropriate briefly to mention their preparation.

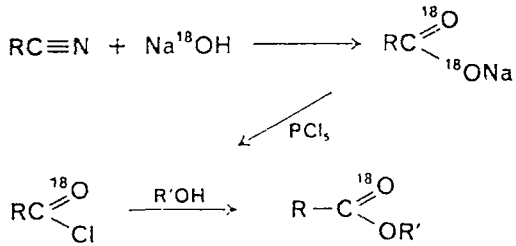
The aldehydes and ketones enriched with ^{18}O are readily made

available by simple treatments of the carbonyl compounds with ^{18}O-enriched water[76], in the presence of a strong acid or base.

Bryn and Calvin[77] investigated the oxygen-exchange reaction of aldehydes and ketones with $H_2{}^{18}O$ by means of infrared spectroscopy and measured the times required for the establishment of equilibrium. They found that in acidic tetrahydrofuran the times required for the oxygen exchange of aldehydes increase in the following order: acetaldehyde < benzaldehyde < 2-naphthaldehyde < 1-naphthaldehyde < 9-anthraldehyde < 9-phenanthraldehyde < indolealdehyde. The relative rates of ^{18}O-exchange of benzophenone, acetophenone and acetone were found to be 1 : 60 : 1200. At 20°, the equilibrium constants for these ketones are 7·8, 8·3 and 12·3 respectively.

VII. REARRANGEMENTS

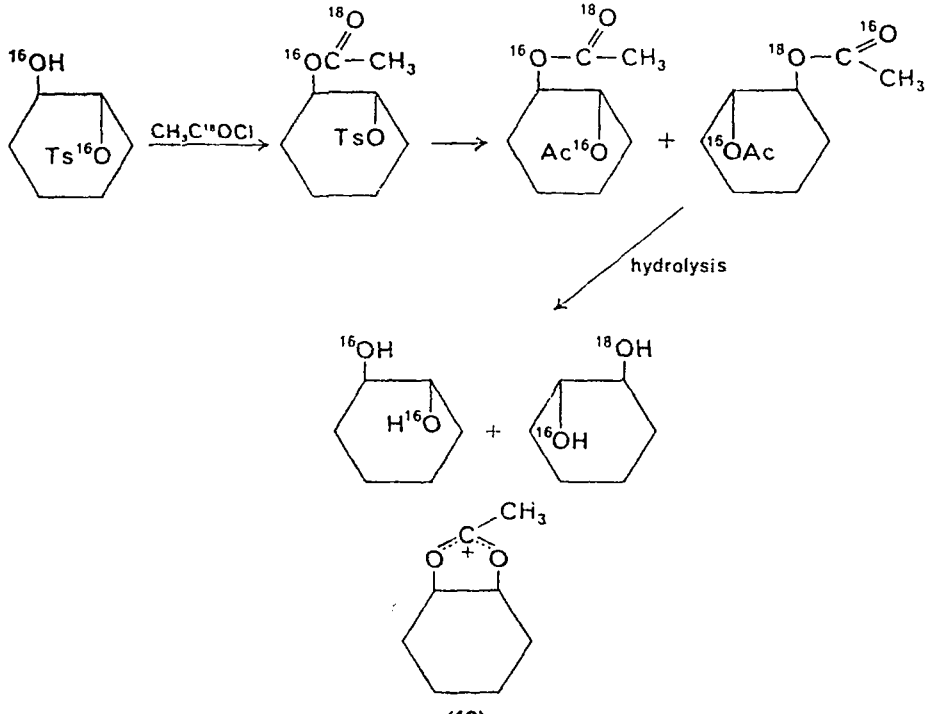
It is easier to introduce an excess ^{18}O into carbonyl oxygen than into alcoholic oxygen in esters. The carbonyl portion of an ester is usually derived from the corresponding carboxylic acid, while the doubly ^{18}O-labelled carboxylate is available by acid-catalysed hydrolysis of the nitrile.



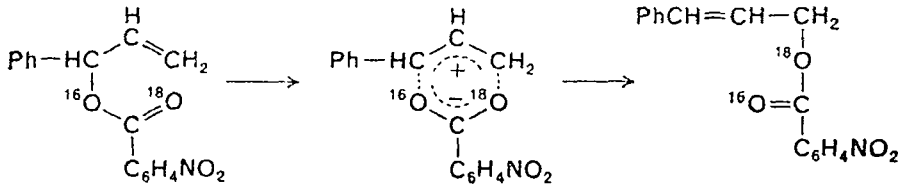
In some rearrangements occurring through cyclic intermediates (e.g., **18**) the labelled oxygen atom of the original carbonyl group turns into the alcoholic oxygen. When 2-acetoxy-(carbonyl-^{18}O)-cyclohexyl tosylate is solvolysed in acetic acid, two isotopically isomeric alcohols are produced via the formation of two acetates[78].

Similarly, the carbonyl oxygen of 1-phenylallyl *p*-nitrobenzoate (**19**) upon rearrangement turns exclusively to the ether oxygen of 3-phenylallyl *p*-nitrobenzoate (**20**). This result is in full accord with a synchronous cyclic mechanism[79].

The reaction of an acid chloride with ^{18}O-labelled alcohol is known to give the ester exclusively labelled at the ether oxygen. When



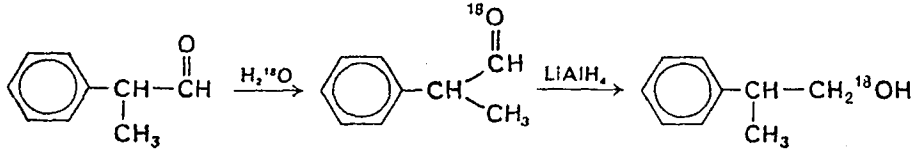
(18)

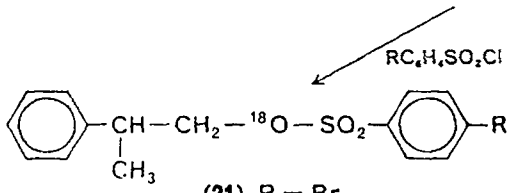


(19) (20)

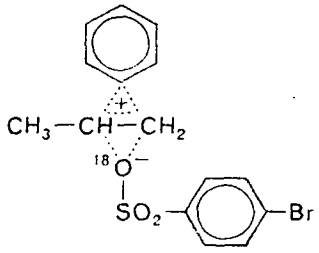
2-phenyl-1-propyl *p*-bromobenzenesulphonate (**21**) thus prepared is allowed to rearrange in acetic acid, it gives 1-phenyl-2-propyl *p*-bromobenzenesulphonate which can be reduced with sodium in ammonia to afford benzylmethylcarbinol. The ^{18}O content of this carbinol indicates that during the rearrangement a partial equilibration of the labelled oxygen takes place (**21a**). In the solvolytic rearrangement of 2-*p*-methoxyphenyl-1-propyl *p*-toluenesulphonate (**22**), all three oxygen atoms of the sulphonate group become completely equilibrated[80].

The thermal rearrangement of methyl benzoate (**23**) at high temperatures leads to migration of the methyl group from one oxygen to the other. The rearrangement can already be observed at 250°,



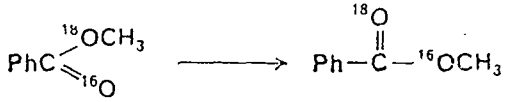


(21) R = Br
(22) R = OMe



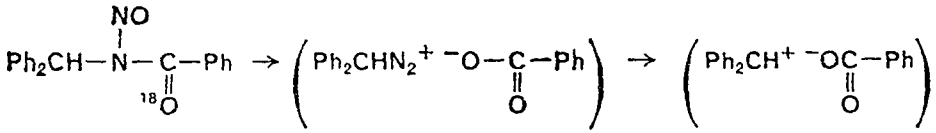
(21a)

and it proceeds smoothly and at a moderate rate at 400–405°, giving a yield of 66% after 3 hours[81]:



(23)

The nitrosoamide **24** in which the carbonyl group is labelled with ^{18}O is suggested to decompose in the following manner[81]:



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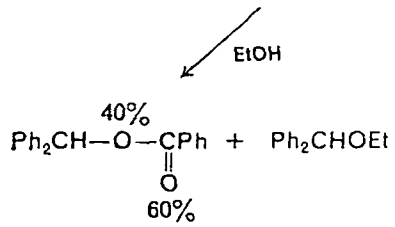


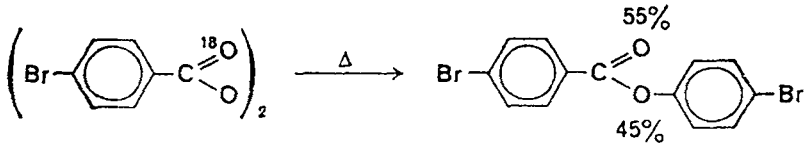
The ^{18}O experiment shown in Table 8 indicates that when the reaction is performed in refluxing ethanol 60% of ^{18}O is retained in the carbonyl oxygen of the benzoate[82]. The decomposition of carbonyl-^{18}O-labelled acetyl peroxide gives ^{18}O-scrambled methyl acetate. The cage recombination of acetoxy and methyl radicals is believed to be the mechanistic path[83].

TABLE 8. ^{18}O-Analytical data for the decomposition of diacetyl peroxide.

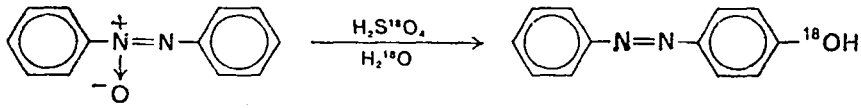
Compound	^{18}O-content
Deacetyl peroxide	0·630% label in carbonyl oxygen
Methyl acetate	0·627 excess atom % in one oxygen
Methanol[a]	0·314 excess atom %
Ethanol[a]	0·312 excess atom %

[a] Obtained by LAH reduction of methyl acetate.

The other diacyl peroxides also decompose to form the corresponding esters with partial scrambling of ^{18}O-labelling[84–86]:

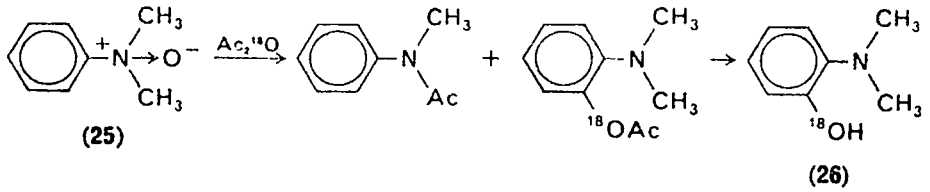


Rearrangements of tertiary amine *N*-oxides have been investigated by means of ^{18}O-tracer in some detail. Azoxybenzenes in concentrated sulphuric acid are converted to *p*-hydroxyazobenzenes in good yields[87].



The phenolic oxygen introduced into the *para* position originated always from the ^{18}O-enriched water applied. Tertiary amine *N*-oxides bearing alkyl groups have been found to react with ^{18}O-labelled acetic anhydride giving either ^{18}O-labelled phenolic or alcoholic compounds. Thus, *N*,*N*-dimethylaniline *N*-oxide (**25**) yields ^{18}O-labelled 2-(*N*,*N*-dimethylamino)phenol (**26**) and *N*-methylacetanilide on reaction with ^{18}O-labelled acetic anhydride[88].

Table 9 together with the earlier findings suggests that a radical



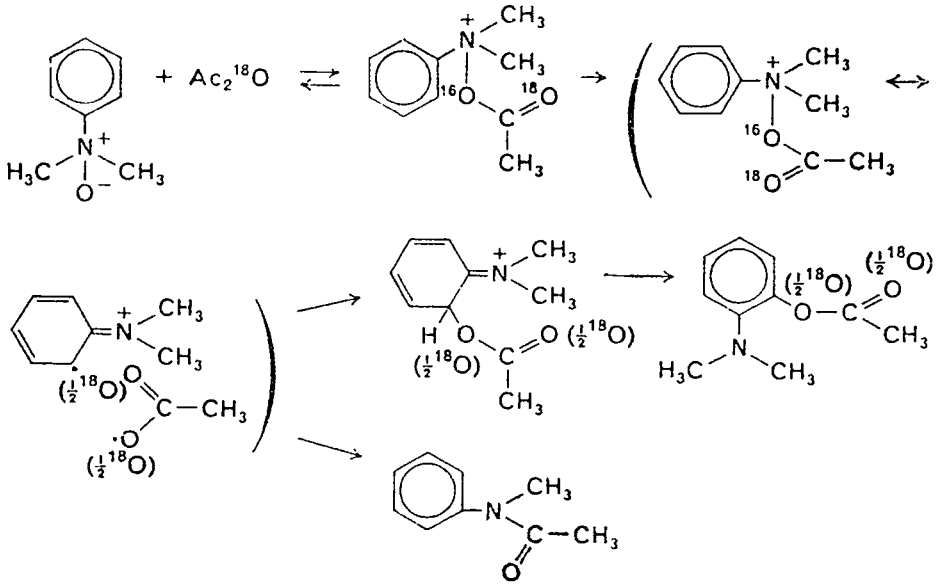
(25) (26)

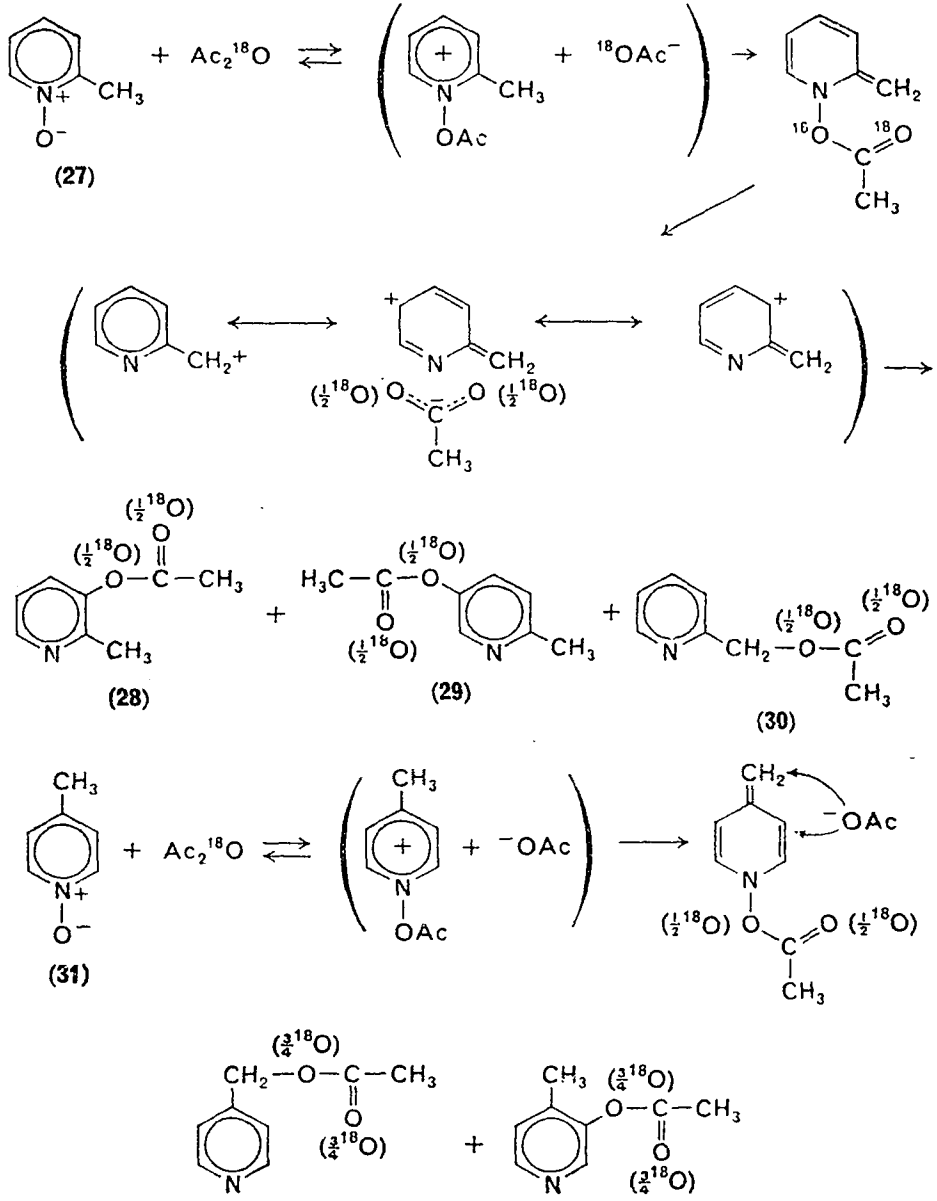
pair mechanism is reasonable for the initial formation of both compounds:

TABLE 9. ^{18}O-Analytical results for the reaction of *N,N*-dimethylaniline *N*-oxide with $Ac_2{}^{18}O$.

Compound	Atom %
$CH_3COOCOCH_3$	0·91
$O(CH_3)_2NC_6H_4OCOCH_3$	0·53
$O(CH_3)_2NC_6H_4OH$	0·49
$C_6H_5N(CH_3)COCH_3$	0·85

A similar treatment of 2-picoline *N*-oxide (**27**) gives ^{18}O-labelled acetates of 3- and 5-hydroxy-2-picoline (**28** and **29**) and 2-pyridynemethanol (**30**)[89]. 4-Picoline-*N*-oxide (**31**) reacts similarly[90]. The mechanisms of these reactions are shown below. The modes of the reactions of alkylpyridine and quinoline *N*-oxides with various

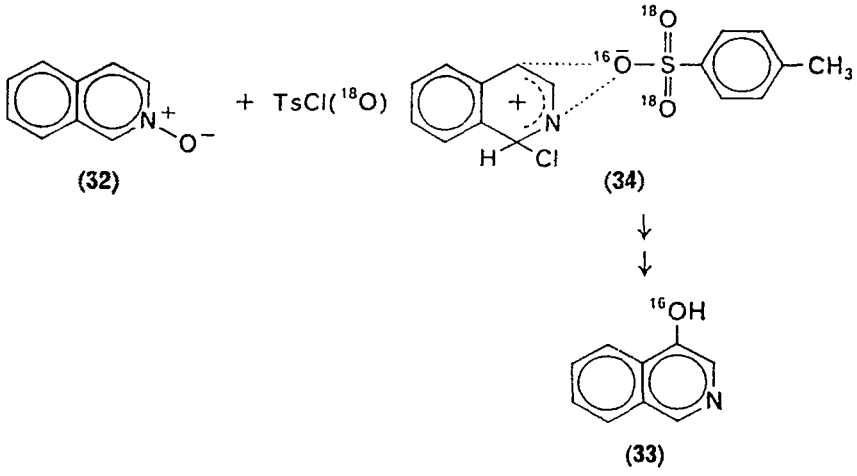




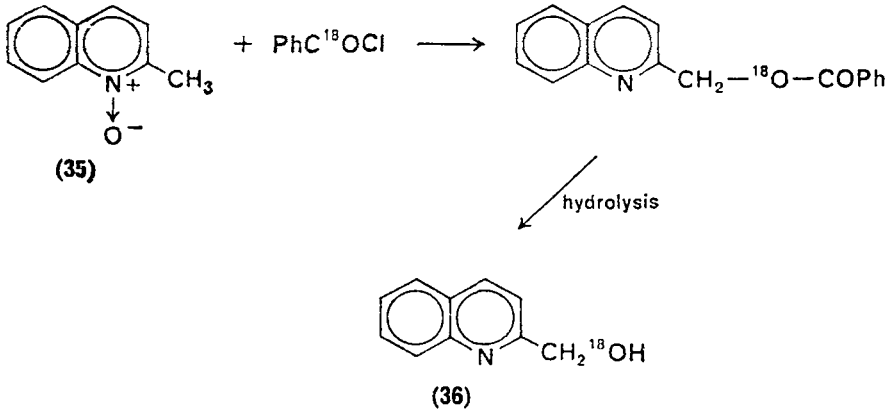
^{18}O-labelled acylating agents have been investigated extensively in our laboratories[91].

In the reactions of isoquinoline (**32**) and pyridine *N*-oxides with ^{18}O-labelled toluenesulphonyl chloride, the 4-hydroxyisoquinoline (**33**) and 2-pyridone formed are found to contain only little ^{18}O.

The reaction is known to proceed via the formation of an oxygen bridged-ion pair **34** as shown below[92].



Instead of acetic anhydride, benzoyl chloride can be used to prepare similar products[93]. Thus, when quinalidine *N*-oxide (**35**) is treated with ^{18}O-labelled benzoyl chloride and the ester obtained is hydrolysed, ^{18}O-labelled 2-quinolylmethanol (**36**) is formed in a fair yield.



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CHAPTER 16

Photochemistry of alcohols and phenols

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I. INTRODUCTION

This chapter deals with photochemical reactions involving alcohols, enols and phenols. The discussion includes both chemical deactivation processes of photoexcited hydroxyl compounds, and reactions in which the hydroxyl compounds either participate as reactants or contribute to the course of a photoinduced conversion.

Not discussed here are obsolete photochemical results on hydroxyl compounds, often of dubious reproducibility, which have been summarized elsewhere[1], and photochemical reactions which involve photoexcitation of metalorganic and inorganic compounds. A discussion of the photochemistry of carbohydrates in this chapter was precluded by a comprehensive review on this subject published previously[2]. Also, in view of the numerous recent textbooks[3–6] and review articles[7–11] on organic photochemistry, it was deemed unnecessary to reprint the Jablonski diagram or to explain the principal terms of photochemistry in an introductory section.

The great interest in organic photochemistry is probably best reflected by the significant contributions to the understanding of photochemical processes of alcohols and phenols, made when the manuscript for this chapter was in preparation.

II. PHOTOCHEMICAL REACTIONS INVOLVING ALCOHOLS

A. Photolysis of Alcohols

1. The absorption spectrum

Within the limits of the ultraviolet spectrum generally considered by the organic chemist, i.e., between 4000Å and 2000Å, simple hydroxyl compounds do not display any absorption maxima, but show structureless end absorption[12, 13]. Water vapour, for example, has its longest wavelength absorption maximum at 1667Å, with an ε value of 1440 (Figure 1). Replacement of one hydrogen in the water molecule by an alkyl group does not alter the shape of the

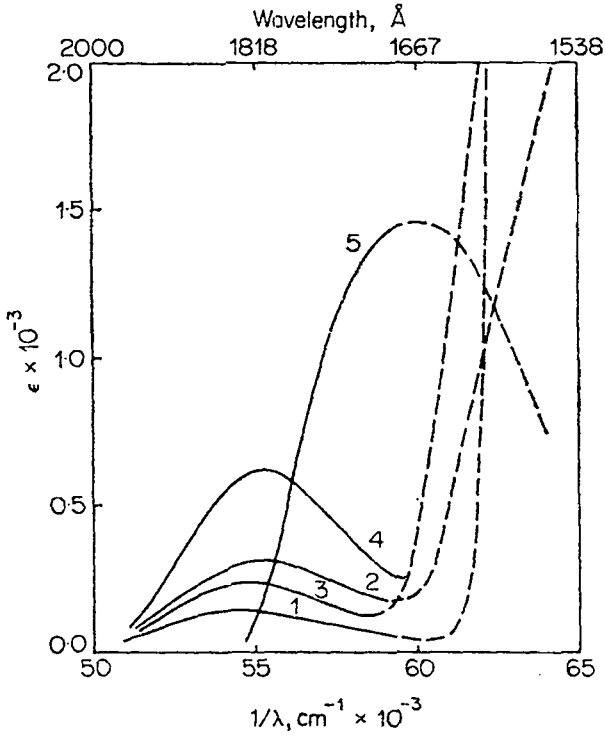


FIGURE 1. Vapour-phase absorption spectra of methanol (1), ethanol (2), propanol (3), isopropanol (4) and water (5). [Reproduced, by permission, from reference 14.]

absorption maximum but results in a decrease of its intensity and a shift of its position towards longer wavelengths. Thus, methanol in the gas phase exhibits a continuum with a longest wavelength absorption maximum at 1835Å and a molar extinction coefficient of 150[14, 15]. Ethanol, propanol and isopropanol have been found to have similar spectral properties. At shorter wavelengths around 1600Å, 1470Å and 1250Å, methanol exhibits structured absorption maxima of greater intensity[16a]. For the three primary alcohols investigated, their ionization potential does not parallel the position of their longest wavelength absorption maximum. However, their ionization potential has been found to correlate with the position of the first absorption minimum, which may correspond to the O–O transition of the next shorter-wavelength maximum (Table 1).

TABLE 1. Longest wavelength absorption maxima and minima of hydroxyl compounds[14].

Hydroxyl compound	λ_{max} (Å)	ε	λ_{min} (Å)	ε	Ionization potential (e.v.)
Water	1667	1480	(1449)	120	12·59
Methanol	1835	150	1647	52	10·85
Ethanol	1815	320	1681	190	10·50
Propanol	1832	240	1706	130	10·15
Isopropanol	1808	620	1678	260	(10·09)

According to Mulliken[17], the longest wavelength absorption maximum of alcohols is to be attributed to a n–σ^* transition, i.e., absorption of a photon results in the excitation of a nonbonding electron of the hydroxyl oxygen to an antibonding σ^* orbital of the alcohol. In the liquid state, the longest wavelength absorption maximum undergoes a blue shift, thus indicating the involvement of the nonbonding electrons in the excitation process.

2. Primary and secondary processes in the gas phase

Upon irradiation in the gas phase with light of the wavelength of 1849Å, methanol decomposes to give mainly hydrogen and ethylene glycol, as well as formaldehyde[18–21]. Minor products are methane, water and carbon monoxide (Figures 2 and 3). The quantum yield has been found to increase with increasing pressure; however, its numeric value is always smaller than 1. The pressure dependence

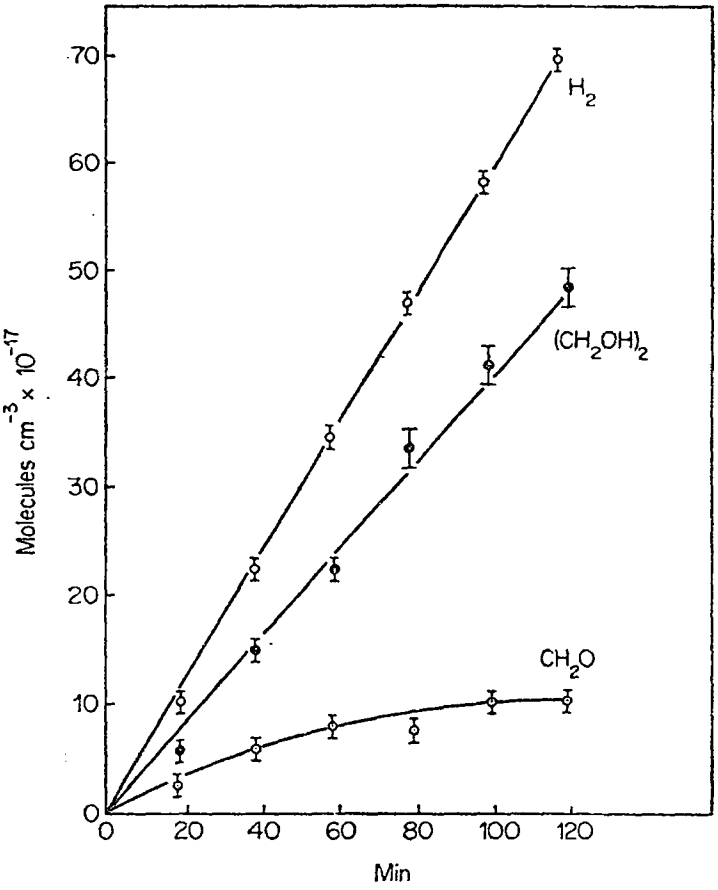


FIGURE 2. The formation of hydrogen, ethylene glycol and formaldehyde during the photolysis of methanol vapour at 1850Å. [Reproduced, by permission, from reference 19.]

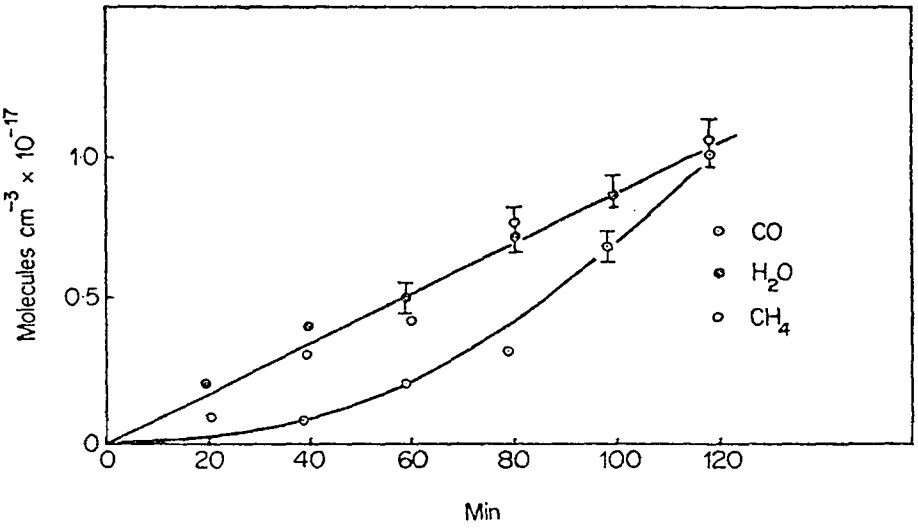


FIGURE 3. The formation of water, methane and carbon monoxide during the photolysis of methanol vapour at 1850Å. [Reproduced, by permission, from reference 19.]

of the quantum yield suggests the involvement of a collision-induced predissociation[16a, 16b].

Based on scavenging experiments and on results obtained in the photolysis of deuterium labelled methanol described below, the formation of all observed products can be explained by a sequence of primary and secondary processes (reactions 1–10).

Primary processes:

$$CH_3OH + h\nu \longrightarrow CH_3OH^* \begin{cases} \longrightarrow CH_3O^{\cdot} + H^{\cdot} \ (\sim 75\%) & (1) \\ \longrightarrow CH_2O + H_2 \ (\sim 20\%) & (2) \\ \longrightarrow {}^{\cdot}CH_3 + {}^{\cdot}OH \ (\sim 5\%) & (3) \end{cases}$$

Secondary reactions:

$$H^{\cdot} + H^{\cdot} \longrightarrow H_2 \quad (4)$$

$$H^{\cdot} + CH_3OH \longrightarrow H_2 + {}^{\cdot}CH_2OH \quad (5)$$

$$CH_3O^{\cdot} + CH_3OH \longrightarrow CH_3OH + {}^{\cdot}CH_2OH \quad (6)$$

$$CH_3^{\cdot} + CH_3OH \longrightarrow CH_4 + {}^{\cdot}CH_2OH \quad (7)$$

$${}^{\cdot}OH + CH_3OH \longrightarrow H_2O + {}^{\cdot}CH_2OH \quad (8)$$

$$2\,{}^{\cdot}CH_2OH \longrightarrow (CH_2OH)_2 \quad (9)$$

$$CH_2O + h\nu \longrightarrow CO + H_2 \quad (10)$$

Reaction (1) is supported by the formation of HD as the major product in the photolysis of CH_3OD[18]. Likewise, irradiation of CD_3OH gives hydrogen which was found to consist of 71% HD, 25% H_2 and 4% D_2 [19]. When the photolysis of methanol is carried out in the presence of ethylene as a hydrogen atom scavenger, the amount of liberated hydrogen decreases by about 80%, thus indicating that about 20% of the total amount of hydrogen is liberated as molecular hydrogen (reaction 2). It should be pointed out, however, that no hydrogen atoms were detectable by the *para*-hydrogen method[21]. Reaction (3) accounts for the observed formation of equal amounts of water and methane (via reactions 7 and 8). However, contrary to an earlier suggestion[3] based on the spectroscopic detection of hydroxyl radicals[22], there is no evidence that reaction (3) proceeds preferably when methanol is excited with light of shorter wavelength. According to recent investigations, vapour-phase photolysis of methanol at both 1849Å and 1236Å results in an identical product distribution, rather than in an increased formation of methane and water[19]. This is remarkable, since irradiation at 1849Å leads to methanol in the first excited singlet state (S_1) while irradiation at 1236Å gives rise to the second

excited singlet (S_2). It appears improbable that decomposition of methanol in the second excited singlet state does proceed by the same bond breaking reactions as decomposition of methanol in the first excited singlet state. It has been suggested, therefore, that internal conversion from the S_2 state to the S_1 state is an efficient process, and that decomposition of photoexcited methanol proceeds primarily from the lowest excited singlet state[19]. As for the formation of ethylene glycol in the photolysis of methanol, secondary hydrogen atom abstraction reactions (5–8) give rise to the $^{\bullet}CH_2OH$ radical which then dimerizes (reaction 9). Carbon monoxide undoubtedly originates from the photochemical decomposition of formaldehyde.

The gas-phase photolysis of the next higher homologues of methanol has been reported[20, 21]; however, those investigations were carried out before modern analytical methods were available[20]. Thus, ethanol has been reported to decompose upon irradiation between 1800Å and 2000Å, giving hydrogen with a quantum yield of 0·65 [19], as well as acetaldehyde and ethane[21]. Photolysis of ethanol with light of wavelength >1520Å gives ethylene, acetaldehyde and formaldehyde[20]. Propanol reportedly gives ethylene, propionaldehyde and formaldehyde[20]. *t*-Butanol has been found to give acetone[20]. Presumably, secondary photochemical decomposition reactions are responsible for the formation of most of these products. Recent results obtained in liquid-phase photolysis of alcohols strongly suggest the predominant fission of the O–H bond to give alkoxy radicals and hydrogen atoms, both of which could abstract the α-hydrogen atom from primary or secondary alcohols thus giving rise to the precursors of pinacols.

3. Liquid-phase photolyses

a. Photolysis of pure alcohols. The photolysis of alcohols in the liquid phase and in solution has been the subject of early investigations; however, proper product identification was not possible until modern analytical methods such as gas chromatography became available. Though it had been known that liquid ethanol upon irradiation between 2000 and 1800Å eliminates hydrogen with a quantum yield of about 0·6, it was generally assumed that acetaldehyde was formed as the second major product. However, in 1958 it was shown[23] that photolysis of liquid alcohols mainly results in a dehydrodimerization to give hydrogen and diols according to reaction (11).

$$RCH_2OH + h\nu \longrightarrow H_2 + RCH(OH)CH(OH)R \qquad (11)$$

R = a: H; b: CH_3; c: C_2H_5; d: n-C_3H_7; e: iso-C_3H_7; f: C_6H_5

In a more recent communication[24], describing the photolysis of alcohols at reflux temperature, the formation of hydrogen and diols as the major products has been confirmed, but substantial amounts of other products, presumably deriving from secondary photochemical reactions, were detected as well (Table 2). The photo-

TABLE 2. Liquid-phase photolysis of alcohols at reflux temperature[24].

Alcohol	Products (mmole/hr)
Methanol	Hydrogen (2·97); Ethylene glycol (1·92); Formaldehyde (0·32); Glycerol (0·26); Carbon monoxide (0·098); Methane (0·012)
Ethanol	Hydrogen (2·54); 2,3-Dihydroxybutane (1·63); Methane (0·81); Carbon monoxide (0·75); Acetaldehyde (0·1)
Isopropanol	Hydrogen (1·72); Pinacol (1·52); Methane (1·27); Carbon monoxide (0·68); Acetone (0·23); Ethane (0·05)
t-Butanol	Methane (5·10); 2,5-Dihydroxy-2,5-dimethylhexane (1·74); Pinacol (1·25); Carbon monoxide (0·42); Acetone (0·35) 3-Hydroxy-3-methyl-2-butanone (0·33)

lysis of *t*-butanol (cf Table 2) has also been reported[23] to give 2,5,8-trihydroxy-2,5,8-trimethylnonane. The predominant formation of methane in the photolysis of *t*-butanol strongly suggests that reactions (12–15) are the important primary and secondary processes.

$$(CH_3)_3COH + h\nu \longrightarrow {}^{\bullet}CH_3 + (CH_3)_2\dot{C}OH \quad (12)$$

$${}^{\bullet}CH_3 + (CH_3)_3COH \longrightarrow CH_4 + {}^{\bullet}CH_2(CH_3)_2COH \quad (13)$$

$$2(CH_3)_2\dot{C}OH \longrightarrow \text{Pinacol} \quad (14)$$

$$2{}^{\bullet}CH_2(CH_3)_2COH \longrightarrow \text{2,5-Dihydroxy-2,5-dimethylhexane} \quad (15)$$

Interestingly, the photolysis of alcohols in the presence of about 5% cyclohexene does not lead to any gaseous products, presumably because the olefin acts as a radical scavenger[24]. Thus, photolysis of isopropanol in the presence of cyclohexene leads to acetone as the major product (2 mmole/hr). Other identified products formed (in mmole/hr) are cyclohexane (0·6), cyclohexyldimethylcarbinol (0·51), cyclohexenyldimethyl carbinol (0·40), bicyclohexyl (0·12), pinacol (0·09) and cyclohexenylcyclohexane (0·05).

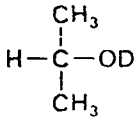
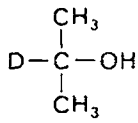
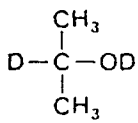
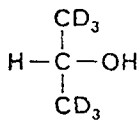
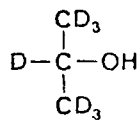
It was first[24] suggested that photoexcitation of primary and secondary alcohols in the liquid phase results in homolytic fission

(reaction 16) of the α–C–H bond which has a lower bond energy than the OH bond and which is known to be most easily attacked in

$$R_2CHOH + h\nu \rightarrow R_2\dot{C}OH + H^{\cdot} \qquad (16)$$

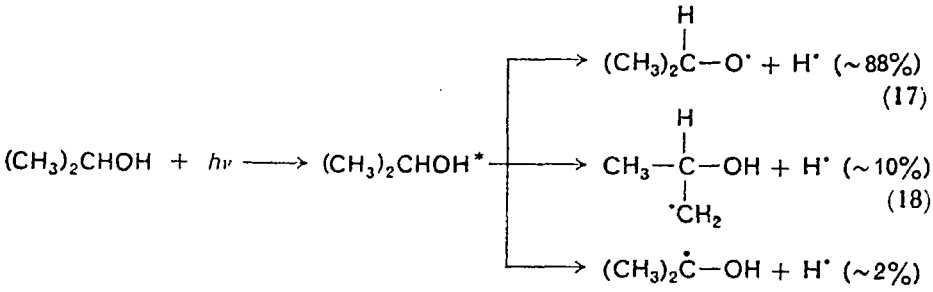
free radical oxidation reactions. However, it was demonstrated in a recent[25] study of five different deuterium labelled isopropanols that only about 2% of the total amount of hydrogen liberated during the photolysis originated from primary fission of the α–C–H bond (Table 3). About 88% of the total hydrogen derived from cleavage of the O–H bond, while about 10% originated from the CH_3 group, as indicated by the isotope composition of the eliminated hydrogen listed in Table 3. The photochemical elimination of hydrogen from

TABLE 3. Isotope composition of hydrogen formed in the liquid-phase photolysis of deuterated isopropanols (2537/1849Å)[25].

Alcohol	% H_2	% HD	% D_2
	11·0	88·0	1·0
	22·4	77·0	1·6
	2·3	22·5	75·2
	91·0	9·0	0
	6·5	90·5	3·0

isopropanol (at 2537/1849Å) which proceeds with a quantum yield of about 0·75, can thus be rationalized by a sequence of primary and secondary reactions (reactions 17–24).

Primary processes:

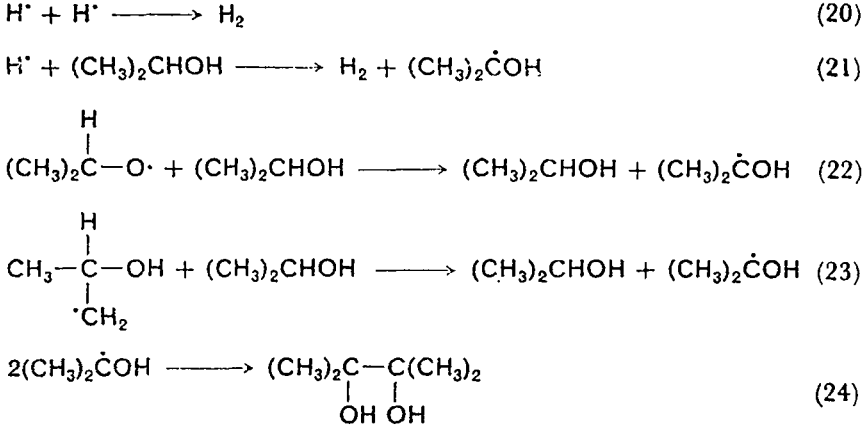


(17)

(18)

(19)

Secondary reactions:



(20)

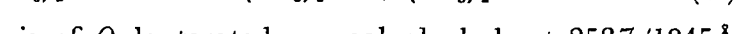
(21)

(22)

(23)

(24)

It had also been assumed[25] that dimethylhydroxymethyl radicals can disproportionate into acetone and isopropanol (reaction 25); however, evidence for such a reaction has not yet been presented.



(25)

The photolysis of *O*-deuterated normal alcohols at 2537/1845Å leads to hydrogen which consists mainly of HD (Table 4) although the ratio of CH/OD increases from three, in the case of methanol, to eleven, in the case of pentanol[26]. This finding strongly suggests that the liquid-phase photolysis as well as the gas-phase photolysis of alcohols results in preferential homolytic fission of the O–H bond, apparently because the energy introduced by photochemical n–σ^* excitation will be located mainly at the O–H bond.

Recently the photolysis at 1849Å (25°C) of secondary and tertiary alcohols has been reinvestigated and found to give epoxides in

TABLE 4. Isotope composition of hydrogen liberated in the liquid-phase photolysis of alcohols at 25°C.

Alcohol	% H_2	% HD	% D_2
CH_3OD	14·3	84·7	1·0
C_2H_5OD	10·5	88·8	0·7
n-C_3H_7OD	16·3	82·9	0·8
n-C_4H_9OD	11·4	87·2	1·4
n-$C_5H_{11}OD$	18·7	80·6	0·7

a low-quantum yield process[27]. Thus, *s*-butanol gives a mixture of butylene oxides with a quantum yield of 0·043 (reaction 26).

$$CH_3CHOHCH_2CH_3 + h\nu \longrightarrow H_2C(O)CHCH_2CH_3 + CH_3HC(O)CHCH_3 + H_2 \quad (26)$$

t-Butanol upon irradiation at 25°C has been found to give hydrogen with a quantum yield of 0·11, isobutylene oxide with a quantum yield of 0·08, and *t*-butoxy-2-hydroxy-2-methylpropane with a quantum yield of 0·027 (reaction 27). It is worth noting that, in this case,

$$(CH_3)_3COH + h\nu \longrightarrow (CH_3)_2C(O)CH_2 + (CH_3)_3COCH_2\overset{\displaystyle CH_3}{\overset{|}{\underset{\displaystyle OH}{\underset{|}{C}}}}CH_3 + H_2 \quad (27)$$

the sum of the quantum yields of the other two products is equal to the quantum yield of hydrogen formation. Irradiation of *O*-deuterated *t*-butanol gives hydrogen which consists mainly (95%) of HD. Apparently, the hydrogen is eliminated as molecular hydrogen rather than atomic hydrogen since reaction (27) is not affected by the presence of radical scavengers.

The formation of propylene oxide (reaction 28) in the photolysis of isopropanol proceeds with a quantum yield of 0·016, thus contributing only about 2% to the total quantum yield for the elimination of hydrogen (0·75).

$$(CH_3)_2CHOH + h\nu \longrightarrow CH_3HC(O)CH_2 + H_2 \quad (28)$$

It has been suggested that a favourable steric position of the hydroxyl group with respect to the β–C–H group in secondary and

tertiary alcohols is responsible for the formation of epoxides. However, a detailed mechanism has not yet been presented.

b. Photolysis of alcohols in aqueous solution. The photolysis of water at 1849Å results in the homolytic cleavage of the O–H bond to give hydrogen atoms and hydroxyl radicals[28–31] according to reaction (29).

$$H_2O + h\nu \longrightarrow H^{\cdot} + {}^{\cdot}OH \qquad (29)$$

Interestingly, irradiation of water containing small amounts of aliphatic alcohols seemingly leaves the water unattacked[32, 33]. For example, when a 5×10^{-3}M solution of methanol in water is irradiated at 1849Å, the alcohol smoothly decomposes to give ethylene glycol and hydrogen with a quantum yield of about 0·6, although 99% of the incident light is absorbed by water[28]. In view of the photoinduced homolysis of water, the photochemical decomposition of alcohols in aqueous solution appears well explained by the sequence of reactions (30–33).

$$H_2O + h\nu \longrightarrow H^{\cdot} + {}^{\cdot}OH \qquad (30)$$

$$H^{\cdot} + CH_3OH \longrightarrow H_2 + {}^{\cdot}CH_2OH \qquad (31)$$

$${}^{\cdot}OH + CH_3OH \longrightarrow H_2O + {}^{\cdot}CH_2OH \qquad (32)$$

$$2\,{}^{\cdot}CH_2OH \longrightarrow (CH_2OH)_2 \qquad (33)$$

At methanol concentrations greater than 5×10^{-3}M, the quantum yield for the liberation of hydrogen increases slowly, presumably because the absorption of light by methanol becomes important. This result may indicate that the liberation of hydrogen from photoexcited methanol proceeds with a quantum yield of larger than 0·6 [28].

4. Low-temperature studies

The photolysis of methanol at low temperature (75°K) was first carried out in order to determine the *ortho–para* ratio of the hydrogen liberated during the irradiation[34]. It was anticipated that an increased amount of *para*-hydrogen would be indicative of a bimolecular process in the formation of molecular hydrogen. Since the photolysis of methanol at 75°K and 85°K gave (contrary to a recent[3] statement) only normal hydrogen (i.e., 25% *para* H_2 and 75% *ortho* H_2), it was concluded that the two hydrogen atoms forming a hydrogen molecule originated from the same alcohol molecule. However, recent hydrogen atom scavenging experiments and proper product analysis show that this conclusion, at least for the photolysis in the gas phase and the liquid phase, is incorrect[18, 19, 24].

More recently, low-temperature photolyses of alcohols have been studied in conjunction with electron spin resonance spectroscopy[35–37]. Thus, irradiation of methanol at 77°K, using a Vycor filter in order to prevent excitation by the 1849Å mercury emission, reportedly leads to $CH_3O^{\bullet}$, $^{\bullet}CH_2OH$, $^{\bullet}CH_3$, and $^{\bullet}CHO$ radicals[35, 36]. Likewise, irradiation of ethanol under similar conditions results in the formation of $C_2H_5O^{\bullet}$, $^{\bullet}C_2H_5$ and $CH_3\dot{C}HOH$ radicals[37]. In view of the results obtained in the gas-phase and liquid-phase photolysis of alcohols, secondary photochemical reactions most likely are responsible for the formation of all radicals other than the alkoxy radicals. It is known[38], for instance, that photolysis of the hydroxymethyl radical ($^{\bullet}CH_2OH$) gives rise to hydrogen and the formyl radical (reaction 34).

$$^{\bullet}CH_2OH + h\nu \longrightarrow H_2 + {}^{\bullet}CHO \qquad (34)$$

Irradiation of methanol adsorbed on alumina has been found[39] to give rise to an e.s.r. spectrum which was ascribed to the radical Al–O–$\dot{C}H_2$. Irradiation of ethanol adsorbed on alumina gave the analogous α-carbon radical Al–O–$\dot{C}HCH_3$. It is assumed that these radicals are formed by photochemical decomposition of the corresponding aluminium alkoxides.

B. Photochemical Dehydrogenation of Alcohols

In this section, attention will be focused mainly on the role of the alcohols as hydrogen donors for photoexcited molecules, particularly carbonyl compounds, rather than on the light-absorbing species. This limitation appears justified in view of the previously published chapter on the photochemistry of ketones and aldehydes[40]. Also, the photochemical dehydrogenation of alcohols by nitrogen heterocycles will be considered in a separate section (II.C.1.b) where only the addition reactions of alcohols will be discussed. The photoinduced addition reactions of alcohols to quinones will be discussed from a mechanistic point of view in the section on photoenolization (III.A.1).

1. Reactions of alcohols with photoexcited carbonyl compounds

The photochemical dehydrogenation of primary and secondary alcohols by photoexcited ketones and aldehydes generally proceeds according to reaction (35)[41, 42].

Large differences in the rate of dehydrogenation of various alcohols have been observed. Tertiary alcohols are not readily

attacked by photoexcited carbonyl compounds. Secondary alcohols generally react faster than primary alcohols (cf section II.D for similar results on the dehydrogenation by photoexcited quinones).

$$R^1R^2CO + R^3R^4CHOH + h\nu \longrightarrow R^1R^2C(OH)-CR^1R^2(OH) + R^3R^4CO \qquad (35)$$

However, large differences in the reactivity have been observed within the series of secondary alcohols. Thus, the photochemical dehydrogenation of *cis*-4-*t*-butylcyclohexanol by photoexcited benzophenone proceeds faster than that of the *trans*-isomer[43]. It has been concluded from a series of competitive hydrogen abstraction experiments (Table 5) that steric hindrance in secondary alcohols reduces the rate of photochemical dehydrogenation[44].

TABLE 5. Relative reactivities of secondary alcohols towards photoexcited benzophenone[44].

Alcohol	Reactivity[a, b]	Material balance (%)
Cyclohexanol[b]	1·6 ± 0·06	95
Cyclopentanol[a]	1·3 ± 0·04	94
Isopropanol	1·0	
2-Octanol[a]	1·05 ± 0·03	95
2-Heptanol[a]	1·0	92
Methyl-*t*-butylcarbinol[b]	0·9 ± 0·02	
3-Heptanol[a]	0·67 ± 0·02	96
Methylneopentylcarbinol[b]	0·18 ± 0·01	95

[a] Compared to isopropanol.
[b] Compared to 2-octanol.

The mechanism of the photochemical reduction of benzophenone by alcohols has been studied for many years. On the basis of the results obtained in numerous investigations[45–54], the photochemical dehydrogenation of alcohols by carbonyl compounds is now understood to proceed in several consecutive steps as exemplified for the oxidation of isopropanol by photoexcited benzophenone (reactions 36–40). (For an important recent result on the photochemical reduction of benzophenone see Reference 54a.) It is important to note that the earlier proposed mode of acetone formation by disproportionation of dimethylhydroxymethyl radicals (reaction 25) has not been verified. Optically active secondary alcohols when recovered

after irradiation in the presence of benzophenones do not show any change in optical activity[51, 55].

$$(C_6H_5)_2CO + h\nu \xrightarrow{\text{excitation}} (C_6H_5)_2CO^{*(1)} \text{ (singlet state)} \quad (36)$$

$$(C_6H_5)_2CO^{*(1)} \xrightarrow[\text{crossing}]{\text{intersystem}} (C_6H_5)_2CO^{*(3)} \text{ (triplet state)} \quad (37)$$

$$(C_6H_5)_2CO^{*(3)} + (CH_3)_2CHOH \longrightarrow (C_6H_5)_2\dot{C}OH + (CH_3)_2\dot{C}OH \quad (38)$$

$$(CH_3)_2\dot{C}OH + (C_6H_5)_2CO \longrightarrow (C_6H_5)_2\dot{C}OH + (CH_3)_2CO \quad (39)$$

$$2(C_6H_5)_2\dot{C}OH \longrightarrow (C_6H_5)_2C(OH)-C(OH)(C_6H_5)_2 \quad (40)$$

The proposed transfer of a hydrogen atom from the dimethylhydroxymethyl radical $(CH_3)_2\dot{C}OH$ to ground-state benzophenone accounts for the theoretical limiting quantum yield of 2, as actually observed[51, 52, 54] at high benzophenone concentrations (Table 6), but may be more complicated than depicted in reaction (39).

TABLE 6. Quantum yields of disappearance of benzophenone in degassed isopropanol[a, 54].

Benzophenone concentration (mole/litre)	Quantum yield
8×10^{-6}	$0{\cdot}84 \pm 0{\cdot}06$
7×10^{-5}	$1{\cdot}02 \pm 0{\cdot}03$
5×10^{-4}	$1{\cdot}35 \pm 0{\cdot}05$
1×10^{-2}	$1{\cdot}70 \pm 0{\cdot}08$
1×10^{-1}	$1{\cdot}90 \pm 0{\cdot}08$

[a] Excitation at 2537Å.

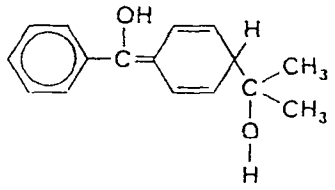
The quantum yield of the photoreduction not only varies with the benzophenone concentration but also depends on the isopropanol concentration (Table 7). Surprisingly, the quantum yield of reduction in neat isopropanol (13 mole/litre) was found to be smaller than that of the reduction in dilute isopropanol (1 mole/litre) in benzene or isooctane[56, 57]. This unexpected effect has been attributed[58] to the presence of a long-lived transient involved in photochemical dehydrogenation of isopropanol by benzophenone. Structure **1** has been assigned to this intermediate whose molar extinction coefficient at its longest wavelength absorption maximum (322 mμ)

TABLE 7. Photoreduction of benzophenone by isopropanol in benzene[a, b, 56].

Isopropanol concentration (mole/litre)	Quantum yield
13	1·16
5·0	1·32
3·0	1·71
1·0	1·57
0·7	1·60
0·5	1·41
0·27	1·16
0·1	0·71
0·05	0·45

[a] Benzophenone concentration 10^{-1} mole/litre.
[b] Excitation at 3130Å.

is at least ten times as large as that of benzophenone in that region of the spectrum (Figure 4)[58]. Thus, the intermediate **1**, which seems to be more stable in isopropanol solution than in nonhydroxylic solvents, may reduce the rate of the dehydrogenation of isopropanol by impairing the absorption of light by benzophenone.



(1)

Spectroscopic evidence for a strongly absorbing intermediate in the photochemical dehydrogenation of isopropanol by benzophenone was first published in 1958 [59] and, independently, in 1959 [51]. Subsequently, the nature of the intermediate has been the subject of several investigations[60–65]. However, only the recently proposed[58, 64] structure **1** seems to be in agreement with all chemical and spectroscopic properties of the intermediate. Its formation can be explained in terms of a coupling reaction of the dimethylhydroxymethyl radical with the resonance contributor of structure **2** to the diphenylhydroxymethyl radical. Interestingly, spectroscopic studies suggest that the intermediate **1** transfers a hydrogen atom to ground-state benzophenone to give acetone and the diphenylhydroxymethyl

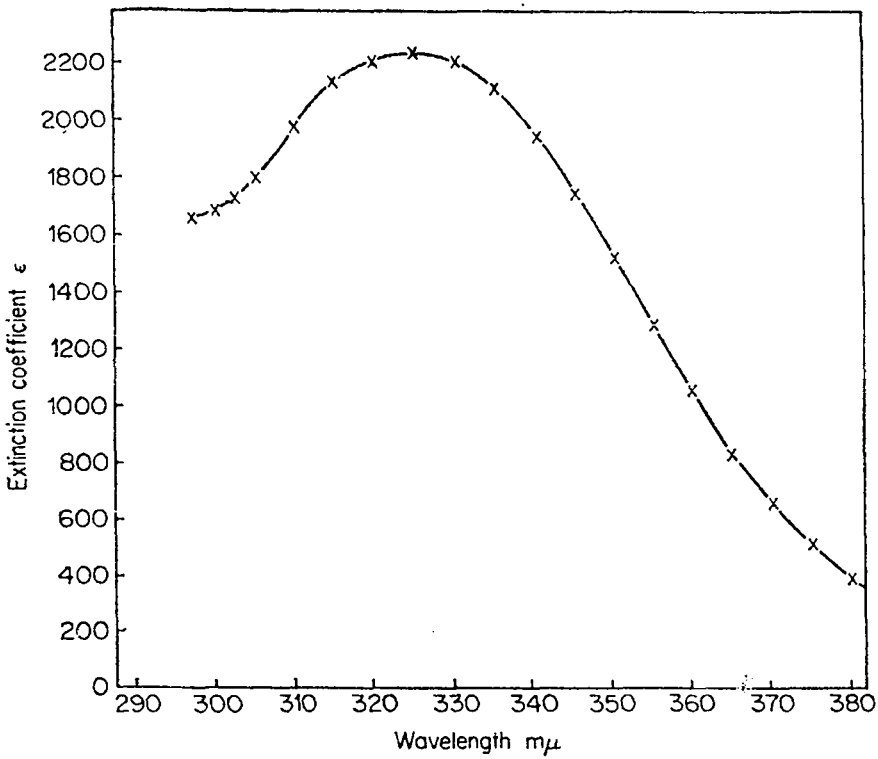
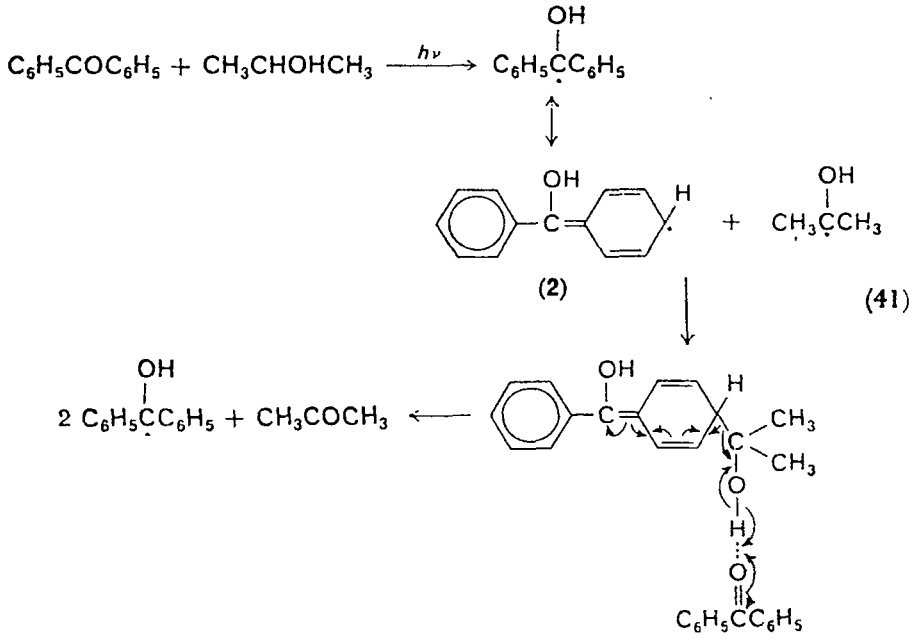


FIGURE 4. Absorption spectrum of compound **1** calculated from multicomponent spectroscopy and verified actinometrically. [Reproduced, by permission, from reference 58.]

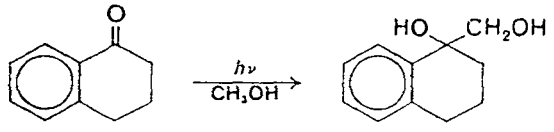


radical in a nonphotochemical process[58] (reaction 41). The intermediate **1** thus plays an important role in the photochemical dehydrogenation of isopropanol by benzophenone since it appears to be responsible for the observed quantum yield of larger than unity. Evidence has been presented for the formation of structurally similar intermediates in the photochemical dehydrogenation of isopropanol by substituted benzophenones[64, 65]. Likewise, strongly absorbing intermediates have been observed spectroscopically in the analogous photochemical dehydrogenation of other aliphatic alcohols[64, 65]. Attempts to isolate the intermediate **1** have not been successful yet, mainly because it reacts with molecular oxygen (to give hydrogen peroxide, acetone and benzophenone), and because of its capability of transferring a hydrogen atom to benzophenone (which was not known until recently[58]). Thus, incomplete photochemical conversion of benzophenone will result in subsequent destruction of the intermediate in a spontaneous dark reaction. However, the intermediate may also have a photochemistry of its own.

The intermolecular coupling reaction of the diphenylhydroxymethyl radical with the dimethylhydroxymethyl radical to give an asymmetric glycol has not been observed. It has been found, however, that the photochemical dehydrogenation of methanol with aromatic ketones does lead to asymmetric glycols if the irradiation is carried out at low ketone concentrations[66, 67]. For instance, irradiation of a 0·017M solution of benzophenone in methanol gives benzpinacol in only 10% yield, while 1,1-diphenylethane-1,2-diol (**3**, R = C_6H_5) is formed in 60% yield (reaction 42). Similar results have been obtained with 4,4′-disubstituted benzophenones and with acetophenone. Also, the irradiation of α-tetralone (**4**) at low concentration in methanol was found to give fairly high yields of the asymmetric glycol **5** (reaction 43).

$$C_6H_5COR \xrightarrow[CH_3OH]{h\nu} C_6H_5-\underset{\displaystyle CH_2OH}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}-R \qquad (42)$$

R = CH_3 or C_6H_5 (3)



(4) (5) (43)

The photochemical reaction of benzophenone in alkaline isopropanol solution does result in the dehydrogenation of the alcohol, but gives excellent yields of benzhydrol instead of benzpinacol[68]. It had been suggested originally that the role of the base is that of a catalyst for the disproportionation of benzpinacol. Although this disproportionation reaction is known[69, 70] to occur, it has not been shown yet that benzpinacol actually is the primary product when the photolysis of benzophenone is carried out in isopropanol solution containing isopropoxide. According to a recent suggestion[71], the formation of benzhydrol can be explained by a reaction sequence which involves hydrogen atom abstraction from isopropoxide ion by photoexcited benzophenone as well as subsequent proton and electron transfer steps (reactions 44–47). (See, however, Reference 71a.)

$$(CH_3)_2CHOH + RO^- \rightleftarrows (CH_3)_2CHO^- + ROH \quad (44)$$

$$(C_6H_5)_2CO^* + (CH_3)_2CHO^- \longrightarrow (C_6H_5)_2\dot{C}OH + (CH_3)_2\dot{C}O^- \quad (45)$$

$$(C_6H_5)_2\dot{C}OH + (CH_3)_2\dot{C}O^- \longrightarrow (C_6H_5)_2\bar{C}OH + (CH_3)_2CO \quad (46)$$

$$(C_6H_5)_2\bar{C}OH + (CH_3)_2CHOH \longrightarrow (C_6H_5)_2CHOH + (CH_3)_2\dot{C}HO^- \quad (47)$$

The photochemical dehydrogenation of alcohols in solution by 1,4-benzoquinone and 9,10-anthraquinone has been found to proceed with optimal quantum yields of about 0·8 to 1·0[72–78]. The proposed mechanism for the dehydrogenation (reactions 48–53) is similar to that proposed for the dehydrogenation by benzophenone. Again, evidence for reaction (53) remains to be presented. The

$$Q + h\nu \longrightarrow Q^{*(1)} \text{ (singlet state)} \quad (48)$$

$$Q^{*(1)} \longrightarrow Q^{*(3)} \text{ (triplet state)} \quad (49)$$

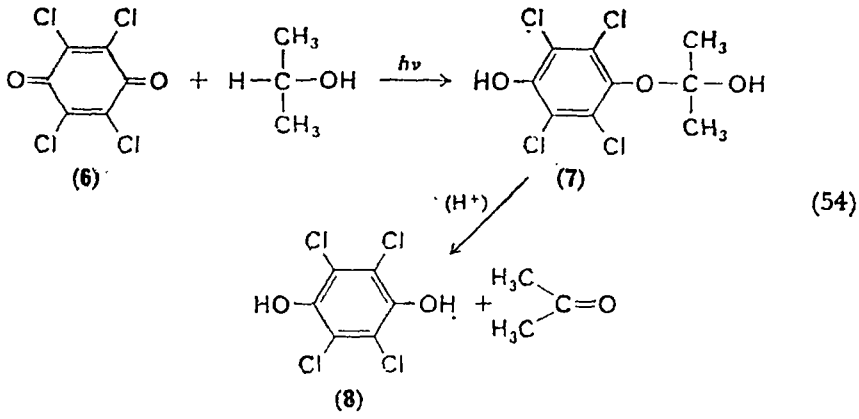
$$Q^{*(3)} + R_2CHOH \longrightarrow {}^{\cdot}QH + R_2\dot{C}OH \quad (50)$$

$$R_2\dot{C}OH + Q \longrightarrow R_2CO + {}^{\cdot}QH \quad (51)$$

$$2\,{}^{\cdot}QH \longrightarrow QH_2 + Q \quad (52)$$

$$2\,R_2COH \longrightarrow R_2CO + R_2CHOH \quad (53)$$

involvement of a hemiketal (**7**) has been suggested[79] for the photochemical dehydrogenation of isopropanol by chloranil (**6**) which leads to tetrachlorohydroquinone (**8**) and acetone (reaction 54). The formation of **7** can be rationalized in terms of a coupling reaction of ${}^{\cdot}QH$ with $R_2\dot{C}OH$; however, evidence for the intermediary formation of hemiketals in the photochemical dehydrogenation of alcohols by quinones has not been published. (For a recent comprehensive review of light-induced reactions of quinones see Reference 80.)



(54)

2. Photochemical reduction of nitro- and nitroso compounds by alcohols

Irradiation of nitrobenzene at 3660Å in degassed isopropanol solution leads to phenylhydroxylamine and acetone as the primary products according to the following proposed mechanism (reactions 55–59)[81].

$$C_6H_5NO_2 \xrightarrow[2.\ \text{intersystem crossing}]{1.\ n\text{–}\pi^*\ \text{excitation}} C_6H_5NO_2{}^{*(3)} \quad (55)$$

$$C_6H_5NO_2{}^{*(3)} + CH_3CHOHCH_3 \longrightarrow C_6H_5\dot{N}O_2H + CH_3\dot{C}OHCH_3 \quad (56)$$

$$C_6H_5\dot{N}O_2H + CH_3\dot{C}OHCH_3 \longrightarrow C_6H_5\dot{N}(OH)_2 + CH_3COCH_3 \quad (57)$$

$$C_6H_5\dot{N}(OH)_2 + CH_3CHOHCH_3 \longrightarrow C_6H_5\dot{N}OH + CH_3\dot{C}OHCH_3 + H_2O \quad (58)$$

$$C_6H_5\dot{N}OH + CH_3\dot{C}OHCH_3 \longrightarrow C_6H_5NHOH + CH_3COCH_3 \quad (59)$$

The quantum yield for the photochemical reduction of nitrobenzene by isopropanol has been found to be only 0·01. Apparently rapid deactivation of n–π^* triplet state nitrobenzene is responsible for the low efficiency of the oxidation of isopropanol[82]. In isopropanol–water mixtures containing hydrochloric acid the quantum yield for the disappearance of nitrobenzene increases to 0·3 [83]. The main products formed in this reaction are aniline and 4-chloroaniline. It has been suggested that protonation of nitrobenzene in the excited state may account for the difference in products and quantum yields; however, the mechanism of the photoreaction remains to be elucidated. Recent results indicate that aniline can also be formed, though in very low yield, by irradiation of nitrobenzene in neutral isopropanol[84]. It was also suggested that nitrosobenzene is the precursor of phenylhydroxylamine and that the π–π^* triplet state nitrobenzene is the hydrogen abstracting species[85].

The photolysis of nitrosobenzene in both neutral, alkaline and acidified methanol solution has been found to give azoxybenzene and 2-hydroxyazobenzene as the major products[86]. Although a complete product analysis has not been carried out, it appears reasonable to assume that the primary reaction of photoexcited (triplet) nitrosobenzene in neutral and acidified solution is hydrogen abstraction from the alcohol. However, secondary dark reactions will depend on the reaction medium and the pH of the solution. Also, most likely, a secondary photoreaction is responsible for the formation of 2-hydroxyazobenzene[87, 88].

3. Photosensitized reductions by alcohols

The photosensitized reduction of unsaturated compounds generally involves the abstraction of a hydrogen atom from an alcohol by a photoexcited carbonyl compound. The ketyl radicals thus formed may then transfer a hydrogen atom to the unsaturated acceptor A to give a new radical $^{\bullet}AH$. As to whether $^{\bullet}AH$ will be reduced further by another ketyl radical to give AH_2, or will disproportionate, or will dimerize to give HAAH largely depends on the nature of the acceptor A. Schematically, the sensitized reduction by hydrogen atom transfer from isopropanol via ketyl radicals can be described by reactions (60–65). Several examples of this type of

$$R_2CO + h\nu \longrightarrow R_2CO^* \quad (60)$$

$$R_2CO^* + (CH_3)_2CHOH \longrightarrow R_2\dot{C}OH + (CH_3)_2\dot{C}OH \quad (61)$$

$$(CH_3)_2\dot{C}OH + A \longrightarrow (CH_3)_2CO + {}^{\bullet}AH \quad (62)$$

$$R_2COH + {}^{\bullet}AH \longrightarrow R_2CO + AH_2 \quad (63)$$

$$2\,{}^{\bullet}AH \longrightarrow A + AH_2 \quad (64)$$

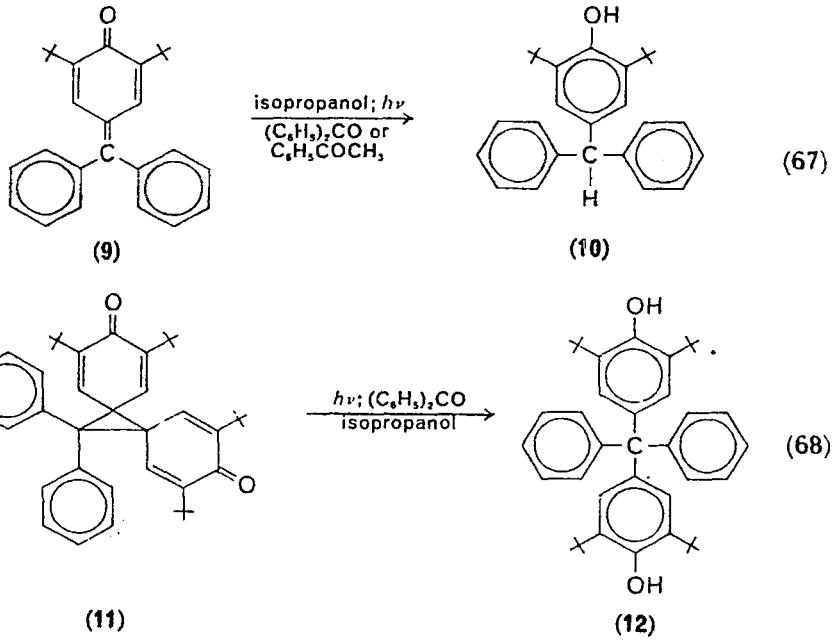
$$2\,{}^{\bullet}AH \longrightarrow HAAH \quad (65)$$

sensitized reduction have been reported. The quantum yields for the truly sensitized reactions are always smaller than unity[89, 90]. Thus, azomethines upon irradiation in alcohol solution containing aromatic carbonyl compounds (or in benzene solution containing benzhydrol and benzophenone) are smoothly reduced to the corres-

$$RCH{=}N{-}R^1 + (CH_3)_2CHOH \xrightarrow[\text{benzophenone}]{h\nu} RCH_2NHR^1 + (CH_3)_2CO \quad (66)$$

ponding amines (reaction 66)[89, 90]. Similarly, the benzophenone-sensitized reduction of 3,5-di-*t*-butylfuchsone (**9**) in isopropanol solution smoothly leads to 3,5-di-*t*-butyl-4-hydroxytriphenylmethane (**10**) (reaction 67[91]). Likewise, bispirocyclohexadienone **11** is reduced

in isopropanol containing benzophenone to give the tetraphenylmethane **12** in high yield (reaction 68)[92, 301].



Interestingly, some photosensitized reductions in isopropanol have been found to proceed according to a radical chain-mechanism[93, 94]. Thus, the photochemical reduction of benzoylazide in isopropanol solution containing benzophenone as a sensitizer results in the elimination of nitrogen and the quantitative formation of benzamide and acetone (reactions 69 and 70). The quantum yield of this

$$(CH_3)_2\dot{C}OH + C_6H_5CON_3 \longrightarrow N_2 + C_6H_5\dot{C}ONH + CH_3COCH_3 \quad (69)$$

$$C_6H_5\dot{C}ONH + (CH_3)_2CHOH \longrightarrow C_6H_5CONH_2 + (CH_3)_2\dot{C}OH \quad (70)$$

reaction has been found to be as high as 500 [93]. It seems likely that the ketyl radicals, formed according to reactions (61) and (70), induce the decomposition of azides, thus initiating the chain-reaction. A similar mechanism may be operative in the photochemical reduction of sulphonyl azides and diazoketones in isopropanol solution[94, 95].

Not all benzophenone-sensitized reductions of unsaturated compounds necessarily involve hydrogen atom transfer via ketyl radicals. For instance, it has been suggested[96] that the benzophenone-sensitized reduction of dibenzoylethylene to dibenzoylethane in isopro-

panol solution proceeds by an energy transfer mechanism (reactions 71–73). However, in retrospect, the participation of ketyl radicals

$$(C_6H_5)_2CO + h\nu \longrightarrow (C_6H_5)_2CO^{*(3)} \quad (71)$$

$$(C_6H_5)_2CO^{*(3)} + C_6H_5COCH{=}CHCOC_6H_5 \longrightarrow (C_6H_5)_2CO + [C_6H_5COCH{=}CHCOC_6H_5]^{*(3)} \quad (72)$$

$$[C_6H_5COCH{=}CHCOC_6H_5]^{*(3)} + (CH_3)_2CHOH \longrightarrow C_6H_5COCH_2CH_2COC_6H_5 + (CH_3)_2CO \quad (73)$$

in this reduction cannot be excluded with certainty.

Sensitized reductive dimerizations according to reactions (60), (61), (62) and (65) are known for azo compounds and for azomethines. Thus, irradiation of diethyl azodicarboxylate in isopropanol containing benzophenone has been reported to give tetraethyl tetrazotetracarboxylate[97] (reaction 74). The photochemical reduc-

$$C_2H_5OOC{-}N{=}N{-}COOC_2H_5 + (CH_3)_2CHOH + h\nu \xrightarrow{\text{benzophenone}} C_2H_5COOC{-}NH{-}\underset{\displaystyle C_2H_5OOC}{\overset{}{\underset{|}{N}}}{-}\underset{\displaystyle COOC_2H_5}{\overset{}{\underset{|}{N}}}{-}NH{-}COOC_2H_5 + (CH_3)_2CO \quad (74)$$

$$C_6H_5CH{=}N{-}R + R_2CHOH + h\nu \longrightarrow \underset{\displaystyle C_6H_5CH{-}NHR}{\overset{}{\underset{|}{C_6H_5CH{-}NHR}}} + R_2CO \quad (75)$$

tive dimerization of benzaldehyde *N*-alkylimines (reaction 75) in alcohol solution has been found to be sensitized by benzaldehyde which is formed by inadvertent partial hydrolysis of the azomethine[98].

C. Photochemical Addition Reactions of Alcohols

1. Free-radical addition of alcohols

a. Additions to alkenes and alkynes. Primary and secondary alcohols can undergo light-induced additions to olefins according to reaction (76)[99]. For example, ultraviolet irradiation of hexene-1 in ethanol

$$R_2CHOH + CH_2{=}CHR^1 + h\nu \longrightarrow \underset{\displaystyle OH}{\overset{}{\underset{|}{R_2C{-}CH_2{-}CH_2R^1}}} \quad (76)$$

solution leads to octanol-2. Likewise, isopropanol has been found to add to octene-1 to give 2-methyldecanol-2. The additions most likely proceed by a chain-mechanism. However, little is known about the nature of the initially formed radicals. As expected, this type of

addition reaction can also be initiated by thermal decomposition of peroxides[99].

More interesting photochemical additions of alcohols to alkenes and alkynes are those which involve aromatic ketones as sensitizers. The role of the sensitizer is best described as that of a hydrogen abstracting reagent and a hydrogen atom carrier, as exemplified by reactions (77–80) describing the photochemical synthesis of terebic acid (**15b**)[100].

$$(C_6H_5)_2CO + h\nu \longrightarrow \longrightarrow (C_6H_5)_2CO^{*(3)} \tag{77}$$

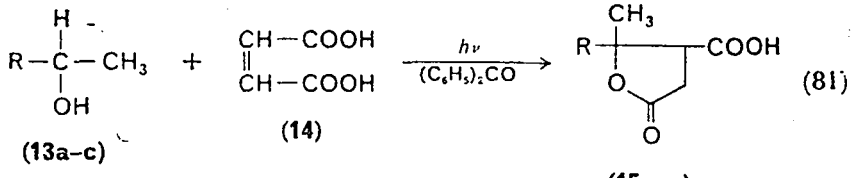
$$(C_6H_5)_2CO^{*(3)} + (CH_3)_2CHOH \longrightarrow (C_6H_5)_2\dot{C}OH + (CH_3)_2\dot{C}OH \tag{78}$$

$$(CH_3)_2\dot{C}OH + HOOC{-}CH{=}CH{-}COOH \longrightarrow HOOC{-}\underset{\displaystyle HOC(CH_3)_2}{\underset{|}{CH}}{-}\dot{C}H{-}COOH \tag{79}$$

$$\begin{array}{l} HOOC{-}\underset{\displaystyle HOC(CH_3)_2}{\underset{|}{CH}}{-}\dot{C}H{-}COOH + (C_6H_5)_2\dot{C}OH \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \downarrow \\ HOOC{-}\underset{\displaystyle HOC(CH_3)_2}{\underset{|}{CH}}{-}CH_2{-}COOH + (C_6H_5)_2CO \end{array} \tag{80}$$

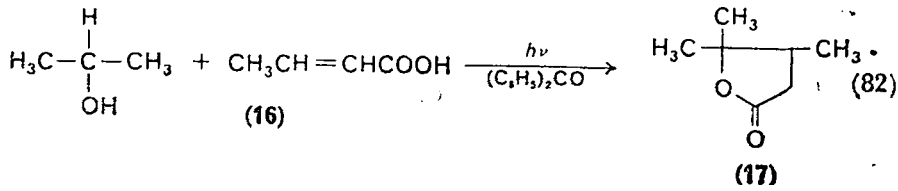
$$HOOC{-}\underset{\displaystyle (CH_3)_2COH}{\underset{|}{CH}}{-}CH_2{-}COOH \longrightarrow H_2O + \textbf{(15b)} \tag{80a}$$

The corresponding substituted paraconic acids **15a** and **15c** were obtained by irradiation of a mixture of maleic acid (**14**) and benzophenone in ethanol (**13a**) and 2-octanol (**13c**) solution, respectively (reaction 81)[101]. Likewise, the benzophenone-sensitized addition of isopropanol to crotonic acid (**16**) gives β,γ-dimethyl-γ-valerolactone



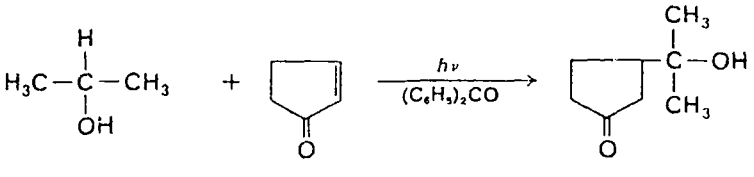
(81)

R = a: H, b: CH_3, c: n-C_6H_{13}

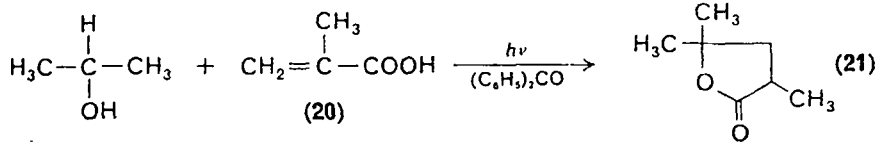


(82)

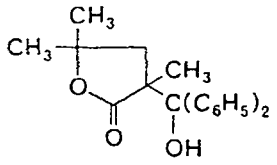
(**17**) (reaction 82)[101]. It should be pointed out that the lactonization is a secondary reaction due to the presence of the carboxyl group. Thus, irradiation of cyclopentenone (**18**) in isopropanol containing benzophenone leads to the tertiary alcohol **19** (reaction 83)[102]. The major product in the benzophenone-sensitized addition of isopropanol to methacrylic acid (**20**), however, is not the corresponding lactone **21**, but the lactone **22** (reaction 84), which conceivably derives from attack of **21** by photoexcited benzophenone[103].



(18) **(19)** (83)



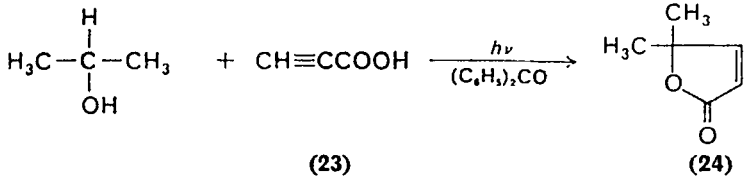
(20) **(21)** (84)



(22)

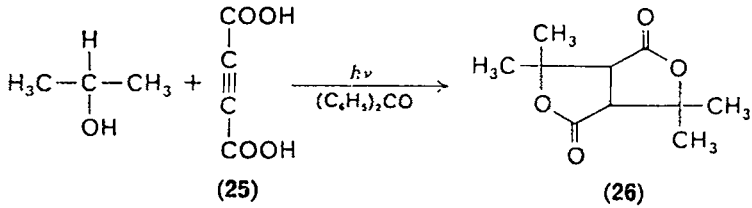
Acetylenes have been found to undergo ketone-sensitized additions of alcohols as well. Thus, the unsaturated lactone **24** is formed by the benzophenone-sensitized addition of isopropanol to propiolic acid (**23**) (reaction 85)[104]. Irradiation of acetylene dicarboxylic acid (**25**) in isopropanol containing benzophenone gives a mixture of the addition products **26** and **27** (reaction 86)[105]. Photolysis of acetone in ethanol solution saturated with acetylene has been found to lead to 1-butene-3-ol (**28**) (reaction 87)[106]. This addition reportedly proceeds with a quantum yield greater than unity, indicating that the ketone-sensitized addition of alcohols to alkenes and alkynes may also proceed according to a chain-mechanism in which the photoexcited ketone serves predominantly as a radical initiator.

The photochemical reactions competing with the addition of the



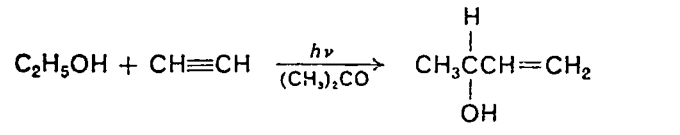
(85)

(23) (24)



(86)

(26) (27)



(87)

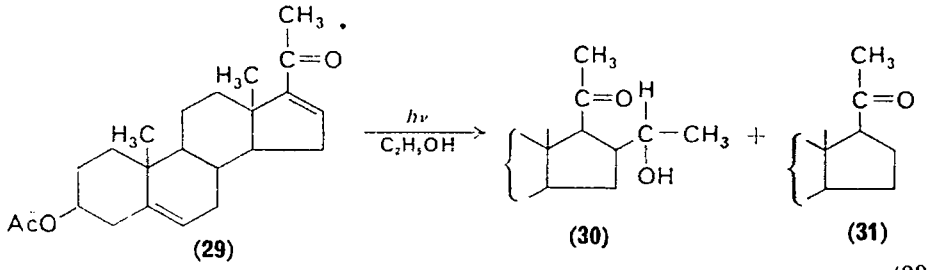
(28)

alcohol to the double bond may be those resulting in reduction of the olefinic double bond. In such a process, the alcohol merely serves as a hydrogen donor.

The stability of the radicals involved probably influences the yields of addition and reduction products. Thus, irradiation of the 3β-acetoxy pregna-5,16-diene-20-one (**29**) in ethanol solution results both in reduction of the C-16 double bond to give pregnenolone acetate (**31**) and in the free-radical addition of the alcohol to give **30** (reaction 88)[107]. Both products are formed in about equal yields. Analogous results are obtained when the photolysis is carried out in isopropanol. However, the reduction product was the only identifiable compound when the irradiation was performed in *t*-butanol solution. It appears that the photoexcited carbonyl group in **29** induces the addition and reduction reactions by abstracting a hydrogen atom from the solvent.

b. Additions to azomethines and nitrogen heterocycles. Azomethines and

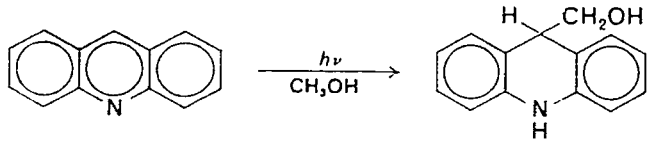
nitrogen heterocycles undergo photochemical reactions with alcohols in essentially the same manner as has been described for carbonyl compounds (section B.1). Thus, irradiation in alcohol solution may



(29) (30) (31)

(88)

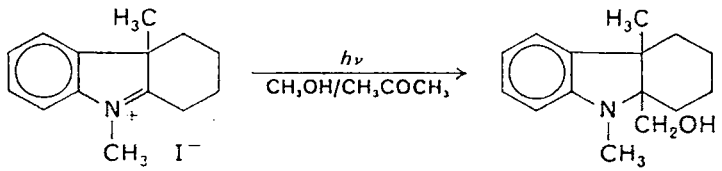
result in the reduction of the C=N bond, in reductive dimerization, and in the addition of the alkylhydroxymethyl radical to the hydrogen atom abstracting azomethines and nitrogen heterocycles. For example, the photolysis of acridine (**32**) in methanol gives the reductive dimerization product biacridan (46%), the reduction product acridan (3%) and the methanol addition product 9-hydroxymethylacridan (**32a**) in about 9% yield (reaction 89)[66, 108, 109]. Many other nitrogen heterocycles have been found to undergo



(89)

(32) (32a)

similar addition reactions of alcohols in far better yield, though the reduction of the C=N bond generally occurs as a competing process. The addition reactions of alcohols can be brought about either by direct photoexcitation of the azomethine and nitrogen heterocycle, or by sensitization by ketones in a similar fashion to that described for the sensitized addition of alcohols to olefins (section C.1.a). For instance, the acetone-sensitized addition of methanol to the substituted tetrahydrocarbazolenium iodide **33** leads to the hydroxymethyl substituted hexahydrocarbazole **34** in about 40% yield, but

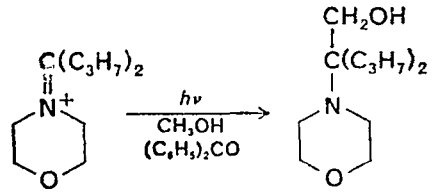


(90)

(33) (34)

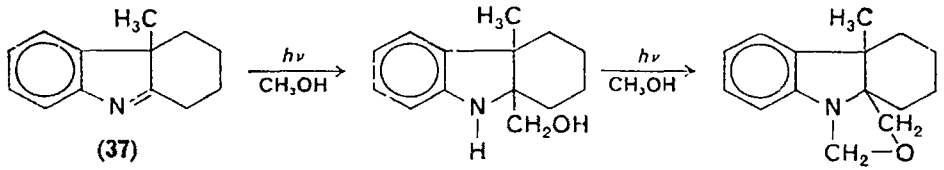
only a small amount of reduction product is formed (reaction 90)[110]. (For a recent example of a photochemical addition of alcohols to an amidine C=N bond, see Reference 110a.)

Numerous examples of benzophenone-sensitized additions of alcohols to nitrogen heterocycles have been reported as well[111]. Thus, irradiation of iminium salt **35** in methanol containing benzophenone leads to the addition product **36** in good yield (reaction 91).

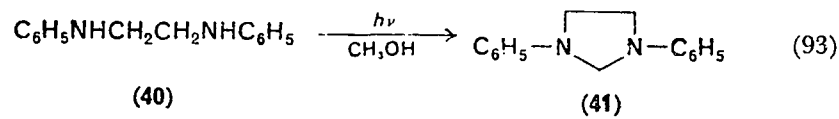


(35) (36) (91)

In many cases, photochemical addition of alcohols proceeds smoothly in the absence of sensitizers. Irradiation of the tetrahydrocarbazolenine **37** in methanol gives the addition product **39** in 51% yield via the intermediate **38** (reaction 92)[110]. The formation of **39** from **38** is apparently analogous to the photochemical formation of *N,N'*-diphenyl-tetrahydroimidazole (**41**) from 1,2-dianilinoethane (**40**) (reaction 93)[110]. The mechanism of this reaction is not understood.



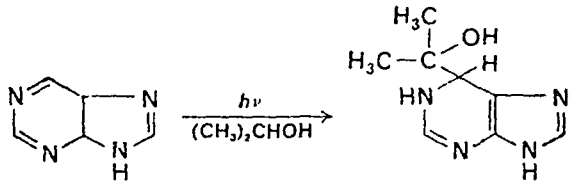
(37) (38) (39) (92)



(40) (41) (93)

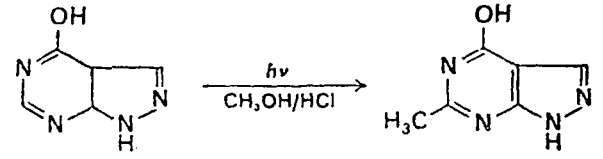
Alcohols other than methanol have been found to undergo photochemical additions to nitrogen heterocycles as well. Thus, irradiation of purine (**42**) in isopropanol solution in the absence of oxygen leads to the tertiary carbinol **43** with a quantum yield of 0·2 (reaction 94)[112, 113]. The addition of methanol and ethanol to purine proceeds with the same ease[113]. Spectroscopic observations suggest that similar photochemical additions of ethanol to other heterocycles,

including pyridine, pyrazine, benzimidazole, benzoxazole, may be possible[112].

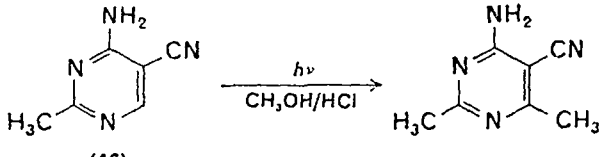


(42) (43) (94)

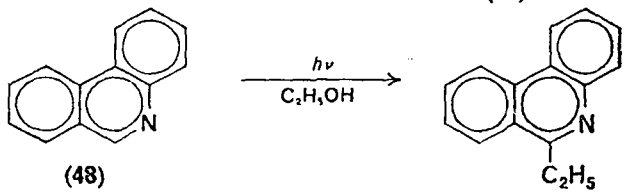
Photochemical additions of alcohols to nitrogen heterocycles may be preparatively useful, since the primary addition products may eliminate water under the conditions of irradiation. The overall reaction thus is a photoinduced alkylation, as has been observed, albeit in low yield, for quinoline and isoquinoline[114]. Excellent yields of alkylation products from other heterocycles have been obtained when the irradiations were carried out in acidified alcohol solution. Thus, irradiation of the pyrazolopyrimidine **44** in methanol containing 2% hydrochloric acid gave the $C_{(6)}$-methylated product **45** in 67% yield (reaction 95)[115, 116]. Photolysis of 2-methyl-4-amino-5-cyanopyrimidine (**46**) under these conditions afforded 2,6-dimethyl-4-amino-5-cyanopyridine (**47**) in 80% yield (reaction



(44) (45) (95)



(46) (47) (96)



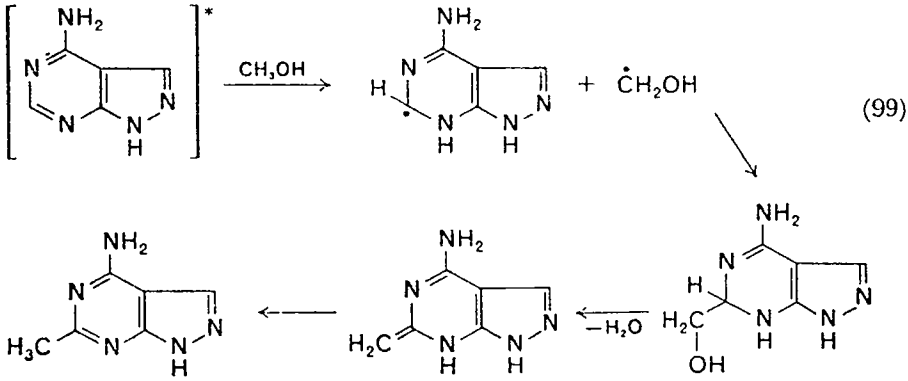
(48) (49) (97)

96). Likewise, irradiation of phenanthridine (**48**) in acidified ethanol has been found[117] to give 6-ethylphenanthridine (**49**) (reaction 97).

It has been suggested[116] that the photoexcited heterocycle (A*) induces the homolysis of methanol according to reaction (98), and

$$A^* + CH_3OH \longrightarrow A + {}^{\cdot}CH_2OH + H^{\cdot} \qquad (98)$$

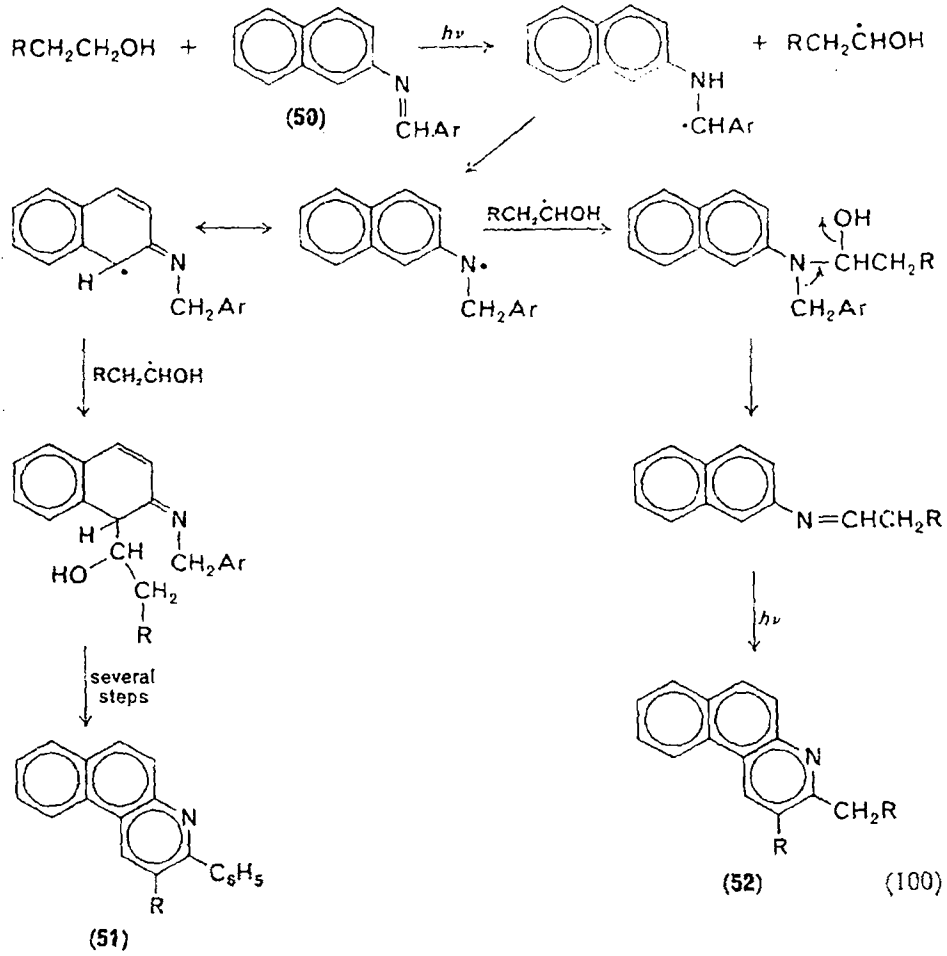
that the hydroxymethyl radical will attack the ground-state heterocycle. It appears more reasonable to assume, however, that the mechanism of the photoalkylation involves a radical combination reaction as outlined in reaction (99). A similar mechanistic approach has been used[117] in order to explain the incorporation of alcohols in the photochemical formation of phenanthridines **51** and **52** from benzal-β-naphthylamine[118] (**50**) (reaction 100). Ultraviolet irradiation of azomethine **53** in ethanol solution leads to **54** in a similar fashion[119] (reaction 101).

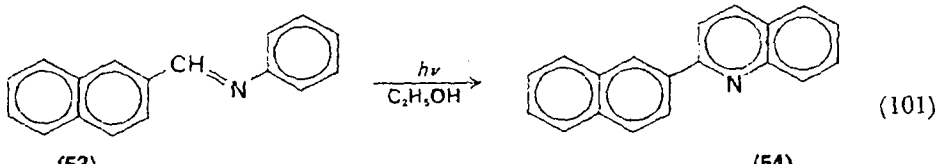


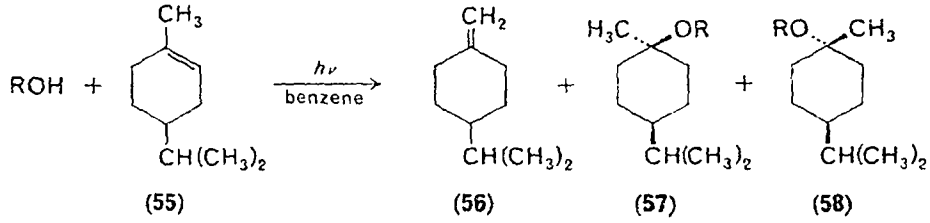
(99)

2. Ionic addition of alcohols

a. Additions to olefins. Certain olefins have been found to undergo a photoinduced addition of alcohols to give ethers in a reaction which competes with isomerization or dimerization of the olefin. The addition proceeds in Markovnikov direction and can be sensitized by aromatic hydrocarbons such as benzene, toluene or xylene. For example[120, 121], irradiation of 1-menthene (**55**) in methanol containing 1% of benzene gives the isomer **56** (which does not undergo the addition reaction), and the methanol addition products **57** and **58** (reaction 102). Ethanol, isopropanol and water were added to **55** in a xylene-sensitized reaction to give the corresponding alcohol adducts. No ethers were formed when the irradiation was carried out in *t*-butanol. Methanol, however, has been found to add to (+)-3-carene, 1-methylcyclohexene, 1-methoxycyclohexene and

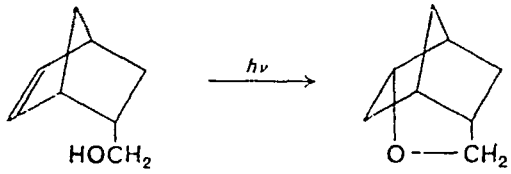






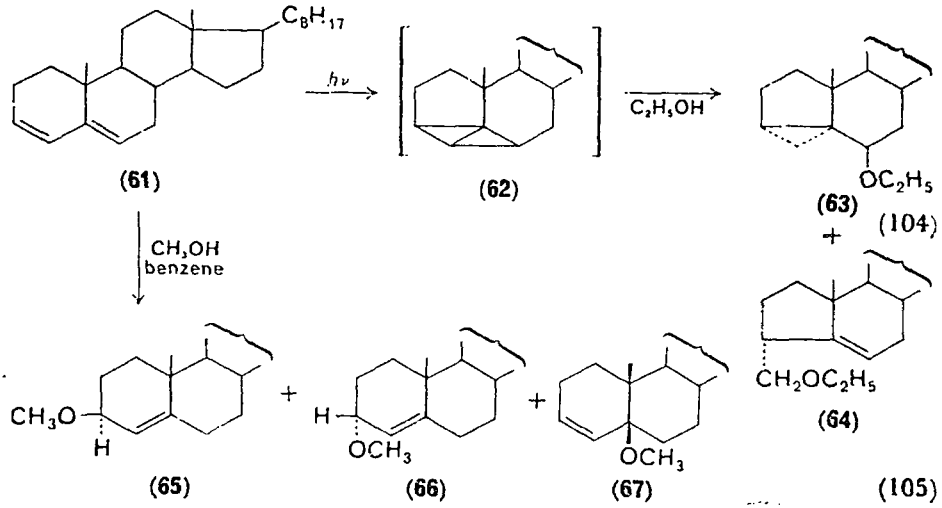
R = CH_3, CH_3CH_2, $(CH_3)_2CH$, H (102)

1-methylcycloheptene[120, 122]. Irradiation of 1-methylcyclopentene or 1-methylcyclooctene under similar conditions does not afford any ethers but leads to reduction products instead[122, 123]. This seems to indicate that ring strain may be an essential prerequisite for the addition reaction. Evidence has been presented that protonation of the excited state olefin leads to a cationic intermediate which then reacts with the hydroxyl compound to give the observed addition products whose stereochemistry is determined by the steric environment of the ionic precursor[124]. In the case of the more rigid norbornene, the photochemical addition of alcohols proceeds by a free radical mechanism[123]. However, 5-norbornene-2-methanol (**59**), where ionic addition is sterically favoured, does undergo photoinduced intramolecular addition reaction to give **60** (reaction 103)[125]. (For a more recent discussion, see Reference 125a.)



(59) (60) (103)

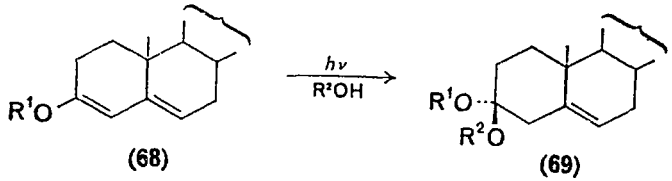
Photoinduced ionic additions to conjugated dienes have been observed in steroids[126–132]. Thus, irradiation of 3,5-cholestadiene (**61**) in a benzene–methanol mixture (1 : 4) gives the addition products **65**, **66** and **67** (reaction 105)[129]. The nature of the products indicates that the benzene-sensitized reaction does not proceed via



(61) (62) (63) + (64) (104)

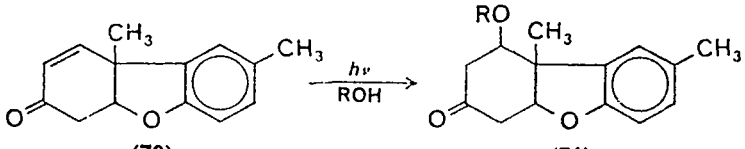
(65) (66) (67) (105)

the bicyclobutane intermediate **62** whose involvement has been established[130–132] in the addition of ethanol to 3,5-cholestadiene to give the ethoxy compounds **63** and **64**. Ionic addition of alcohols to 3-alkoxy-substituted steroids **68** proceeds in the absence of a sensitizer to give ketals of structure **69** [126–128] (reaction 106).



(68) (69) (106)

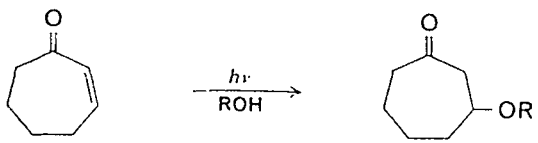
Ionic addition of alcohols, proceeding in the absence of any aromatic hydrocarbon sensitizer, has been observed in the photolysis of certain unsaturated cyclic ketones[133–137]. Methanol generally adds more easily than less acidic alcohols. For example[133], methanol and isopropanol add to Pummerer's ketone (**70**) to give the alkoxy compounds **71a–b** (reaction 107). Likewise, irradiation of 2-cyclo-



(70) (71) (107)

R = a: CH_3, b: $(CH_3)_2CH$

heptenone (**72**) in methanol, ethanol or isopropanol leads to the corresponding 3-alkoxycycloheptanones (**73a–c**) (reaction 108)[134].

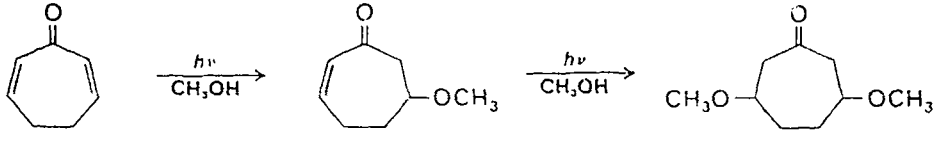


(72) (73) (108)

R = a: CH_3; b: C_2H_5; c: $(CH_3)_2CH$; d: $(CH_3)_3C$

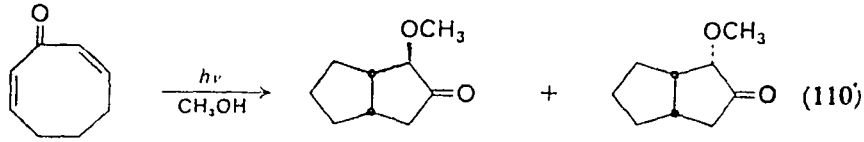
However, irradiation of **72** in *t*-butanol gives the *t*-butoxy compound **73d** in low yield only, apparently because the cyclodimerization of 2-cycloheptenone competes favourably with the ionic addition reaction. Photolysis of 2,6-cycloheptadienone (**74**) ultimately leads to the dimethoxy compound **76** via the monoaddition product **75** (reaction 109)[135]. Interestingly, irradiation of 2,6-cycloheptadienone in *t*-butanol containing a small amount of sulphuric acid leads to a

bicyclic addition product[135]. An analogous addition reaction resulting in the formation of the bicyclic compounds **78** and **79** (ratio 8 : 1)



(74) **(75)** **(76)** (109)

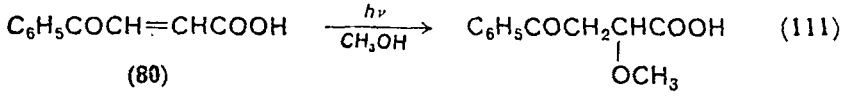
was recently observed when 2,7-cyclooctadienone (**77**) was irradiated in methanol solution (reaction 110)[136]. It has been suggested



(77) **(78)** **(79)** (110)

that photoexcitation of dienone **77** leads to a polar species. Protonation, followed by ring contraction, would then give rise to a bicyclic cationic intermediate which can undergo attack by the solvent.

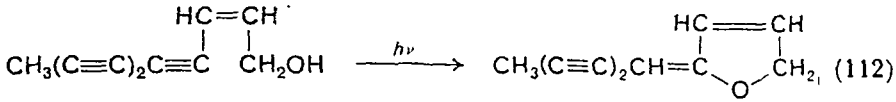
Photoinduced ionic additions of alcohols to simple acyclic olefins apparently have not yet been reported. However, methanol has been found[138, 139] to add to *trans*-β-benzoylacrylic acid (**80**) to give β-benzoyl-α-methoxypropionic acid (**81**) (reaction 111). Similar addition reactions of methanol were accomplished by irradiating the



(80) **(81)** (111)

analogous *p*-methyl-, *p*-methoxy- and *p*-bromo-benzoylacrylic acids[139]. In the latter two cases, not only methanol addition to the carbon–carbon double bond but also simultaneous esterification of the carboxylic acid was observed (see also section II.G). According to a recent[140] reinvestigation, the earlier[141] reported photochemical addition of methanol to crotonic acid has not been verified.

An example of an ionic addition of an alcohol to an acetylenic bond is the photoinduced intramolecular cyclization of dec-2-ene-



(82) **(83)** (112)

4,6,8-triyn-1-ol (**82**) which leads to the dihydrofuran **83** (reaction 112)[142].

The photochemical methoxylation of styrene by irradiation in methanol solution containing cupric ions has been reported to give a mixture of the dimethyl ethers **84** and **85** (reaction 113)[143]. The

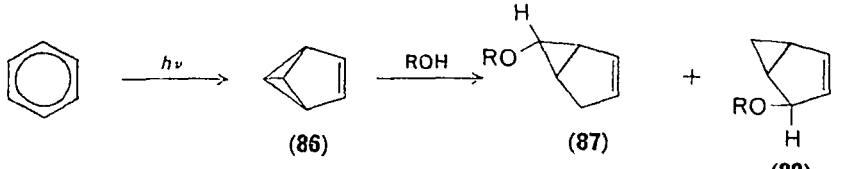
$$C_6H_5CH{=}CH_2 + CH_3OH \xrightarrow[h\nu]{Cu^{++}} C_6H_5CH(OCH_3)CH_2OCH_3 \quad (\mathbf{84}) + CH_3OCH_2CH(C_6H_5)CH(C_6H_5)CH_2OCH_3 \quad (\mathbf{85}) \qquad (113)$$

mechanism of the methoxylation is not readily understood. Apparently, both ionic and radical intermediates are involved in this reaction.

Ionic additions of hydroxyl compounds also have been observed in the photochemistry of riboflavin model compounds[144, 145] and in the photochemistry of nucleic acid[146–150]. A detailed discussion of those reactions and of the photoinduced hydrations are considered to be beyond the scope of this chapter. (For a recent review, see Reference 150.)

b. Additions to photochemically generated strained rings, carbenes, nitrenes, ketenes, isocyanates and ozonides. It is virtually impossible to describe or mention in this section all those photochemical reactions which have been carried out in alcohol solution and in which the alcohol has served as a trapping agent for a photochemically generated reactive intermediate in its ground state. Therefore, only a few representative examples have been selected here.

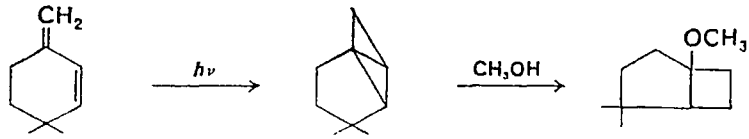
The photolysis of benzene in trifluoroethanol[151, 152] or in methanol[153] containing a trace of hydrochloric acid gives the bicyclic ethers **87** and **88** by addition of the alcohols to ground-state benzvalene (**86**) (reaction 114). Similarly, irradiation of diene **89** in methanol gives (besides other products) the methyl ether **91** by



(**86**) (**87**) (**88**) (114)

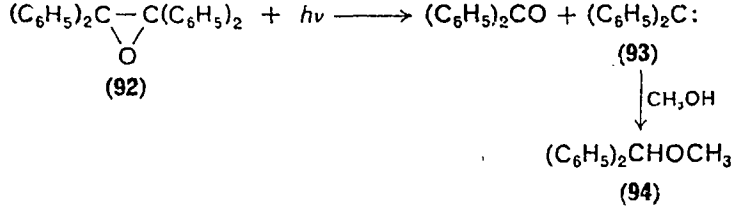
$R = CH_3,\ CF_3CH_2$

addition of the solvent to the bicyclobutane intermediate **90** (reaction 115)[154, 155].



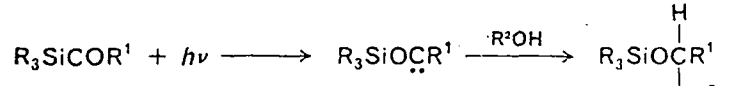
(89) (90) (91) (115)

Photolysis of tetraphenyloxirane (**92**) in methanol gives benzophenone and benzhydryl methyl ether (**94**) via the intermediate carbene **93** [156, 157] (reaction 116). Irradiation of silyl ketones (**95**)



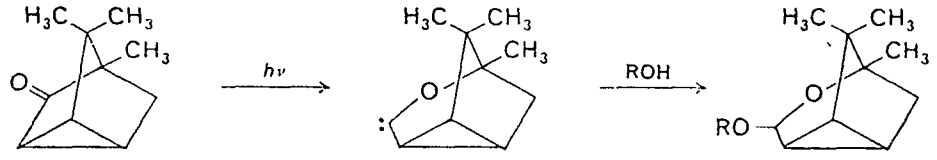
(92) (93) (94) (116)

in alcohol solution has been found to give the mixed acetals **97** presumably by addition of the solvent to the siloxycarbene **96** [158] (reaction 117). Other recent examples of addition of alcohols to



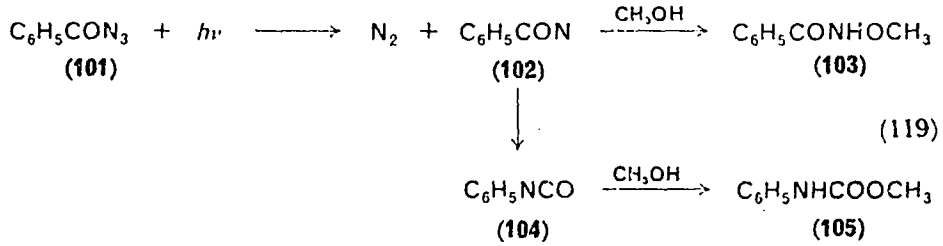
(95) (96) (97) (117)

intermediate carbenes have been observed in the photolysis of bicyclic ketones[159–161], such as cyclocamphenone (**98**) which leads to **100** via the oxacarbene **99** (reaction 118).



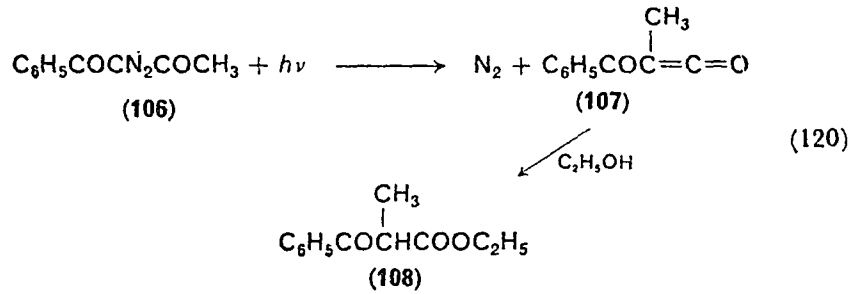
(98) (99) (100) (118)

The photolysis of benzoylazide (**101**) in methanol has been found to give a mixture of the urethane **105**, formed by addition of the alcohol to phenylisocyanate (**104**), and *O*-methyl-*N*-benzoylhydroxylamine (**103**), formed by addition of the alcohol to the intermediate benzoylnitrene (**102**) (reaction 119)[162].



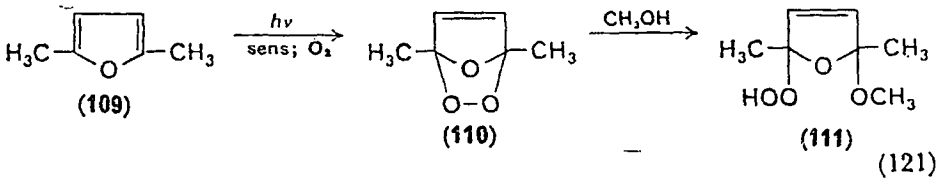
(119)

The formation of ethyl-α-methyl-α-benzoylacetate (**108**) by irradiation of diazobenzoylacetone (**106**) in ethanol involves the addition of solvent to the intermediate ketene **107** (reaction 120)[163].



(120)

The photochemical autoxidation of 2,5-dimethylfuran (**109**), sensitized by Rose Bengal, in methanol solution gives 2,5-dimethyl-2-methoxy-5-hydroperoxydihydrofuran (**111**) by addition of the solvent to the intermediate ozonide **110** (reaction 121)[164]. Numerous similar additions of alcohols have been observed in the dye-sensitized autoxidation of other furans[164].



(121)

D. Photosensitized Autoxidation of Alcohols

Aliphatic alcohols undergo rapid autoxidation upon irradiation only in the presence of compounds which absorb the incident light and which initiate a free radical reaction. Both quinones and aromatic carbonyl compounds have been found to be effective sensitizers for the photochemical reaction of alcohols with molecular oxygen.

Bolland and Cooper[165] have carried out a detailed kinetic investigation of the photochemical autoxidation of aqueous ethanol in the

presence of sodium anthraquinone-2,6-disulphonate which leads to acetaldehyde, acetic acid and hydrogen peroxide. Evidence has been presented for three significant features of this reaction: (1) the autoxidation does not proceed by a chain-mechanism; (2) acetic acid does not derive from the simultaneously formed acetaldehyde, but is a primary reaction product; and (3) the photoexcited sensitizer (Q*) reacts by abstracting the α-hydrogen atom from the alcohol to give a semiquinone radical (·QH) which reacts with oxygen, whereby the sensitizer is regenerated. The formation of the observed oxidation products of ethanol has been described in terms of the following mechanism (reactions 122–129) which should be

$$Q + h\nu \longrightarrow Q^* \tag{122}$$

$$Q^* + C_2H_5OH \longrightarrow {}^{\cdot}QH + CH_3\dot{C}HOH \tag{123}$$

$$CH_3\dot{C}HOH + O_2 \longrightarrow CH_3CH(OO^{\cdot})OH \tag{124}$$

$${}^{\cdot}QH + O_2 \longrightarrow Q + HO_2{}^{\cdot} \tag{125}$$

$$CH_3\dot{C}HOH + Q \longrightarrow {}^{\cdot}QH + CH_3CHO \tag{126}$$

$$2\,CH_3CH(OO^{\cdot})OH \longrightarrow 2\,CH_3COOH + H_2O_2 \tag{127}$$

$$2\,HO_2{}^{\cdot} \longrightarrow H_2O_2 + O_2 \tag{128}$$

$$CH_3CH(OO^{\cdot})OH + HO_2{}^{\cdot} \longrightarrow CH_3CHO + H_2O_2 + O_2 \tag{129}$$

applicable to primary alcohols in general. The conceivable regeneration of the sensitizer according to reactions (130) and (131) was dismissed because the reaction of ·QH with molecular oxygen was considered to be the more efficient one.

$$CH_3CH(OO^{\cdot})OH + {}^{\cdot}QH \longrightarrow CH_3CH(OOH^{\cdot})OH + Q \tag{130}$$

$$HO_2{}^{\cdot} + {}^{\cdot}QH \longrightarrow H_2O_2 + Q \tag{131}$$

Wells[166, 167] has compared the reactivity of numerous alcohols with that of ethanol by measuring the rate of oxygen uptake upon

irradiation in the presence of sodium anthraquinone-2-sulphonate. For primary and secondary alcohols it has been concluded[167] from the results shown in Table 8 that increasing alkylation on the

TABLE 8. Photochemical oxidation of alcohols sensitized by sodium anthraquinone-2-sulphonate[167].

Alcohol	Reactivity[a]	Reactivity per OH group
Methanol	0·12	0·12
Ethanol	1·00	1·00
n-Propanol	1·53	1·53
n-Butanol	2·07	2·07
Isopropanol	2·14	2·14
s-Butanol	2·85	2·85
t-Butanol	0·01	0·01
Ethylene glycol	0·58	0·29
1,2-Propylene glycol	1·26	0·63
Trimethylene glycol	2·38	1·19
2,3-Butylene glycol	2·98	1·49
Glycerol	0·84	0·28
Erythritol	0·82	0·21
Cyclohexanol	5·18	5·18
cis-1,2-Cyclohexanediol	10·90	5·45
trans-1,2-Cyclohexanediol	3·78	1·89
cis-1,4-Cyclohexanediol	8·13	4·25
Myo-inositol	0·90	0·15

[a] Reactivity relative to that of ethanol.

α-carbon atom increases their activity, and that the reactivity per CHOH-group decreases with increasing number of hydroxyl groups. It should be kept in mind, however, that in the oxidation of many hydroxyl compounds, most likely, one specific hydroxyl group will be oxidized. For instance, the photochemical autoxidation (though in the absence of a sensitizer) of myo-inositol gives predominantly myo-inos-2-ose and aldaric acids[168].

The benzophenone-sensitized autoxidation of alcohols has received attention repeatedly. It had been suggested originally that the photochemical autoxidation of alcohols in the presence of benzophenone yields water (and the carbonyl compound derived from the alcohol)[169, 170]. However, Bäckström, in 1944, reinvestigated the benzophenone-sensitized autoxidation of isopropanol and found that acetone and hydrogen peroxide (rather than water) were

formed quantitatively[171]. The reactions (132–134) were proposed

$$(C_6H_5)_2CO + h\nu \longrightarrow (C_6H_5)_2\dot{C}-\dot{O} \quad (132)$$

$$(C_6H_5)_2\dot{C}-\dot{O} + (CH_3)_2CHOH \longrightarrow (C_6H_5)_2\dot{C}OH + (CH_3)_2\dot{C}OH \quad (133)$$

$$(C_6H_5)_2\dot{C}OH + (CH_3)_3\dot{C}OH + O_2 \longrightarrow (C_6H_5)_2CO + (CH_3)_2CO + H_2O_2 \quad (134)$$

to explain these results. According to a later suggestion[51], reaction (134) can be described by reactions (135–138).

$$(C_6H_5)_2\dot{C}OH + O_2 \longrightarrow (C_6H_5)_2CO + HO_2^{\cdot} \quad (135)$$

$$(CH_3)_2\dot{C}OH + O_2 \longrightarrow (CH_3)_2CO + HO_2^{\cdot} \quad (136)$$

$$HO_2^{\cdot} + (CH_3)_2\dot{C}OH \longrightarrow H_2O_2 + (CH_3)_2CO \quad (137)$$

$$HO_2^{\cdot} + (C_6H_5)_2\dot{C}OH \longrightarrow H_2O_2 + (C_6H_5)_2CO \quad (138)$$

The mechanism presented above is based on the assumption that hydrogen peroxide is the primary product in the oxidation of isopropanol. Results obtained in a later reinvestigation indicate, however, that the benzophenone-sensitized autoxidation of isopropanol gives the hydroxyhydroperoxide **112** as the primary reaction product, which readily decomposes in the presence of small amounts of

$$H_3C-\underset{\displaystyle OOH}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-OH \longrightarrow (CH_3)_2CO + H_2O_2 \quad (138a)$$

(112)

water to give acetone and hydrogen peroxide[172, 173]. One conceivable mode of formation for **112** would involve the reaction of oxygen with the dimethylhydroxymethyl radical (reaction 139) and subsequent transfer of a hydrogen atom from the diphenylhydroxymethyl radical to the peroxy radical **112a**, whereby benzophenone will be regenerated (reaction 140). It is worth pointing out that the

$$(CH_3)_2\dot{C}OH + O_2 \longrightarrow \underset{\displaystyle (CH_3)_2C-OH}{\overset{\displaystyle OO^{\cdot}}{\underset{|}{\overset{|}{}}}} \quad (139)$$

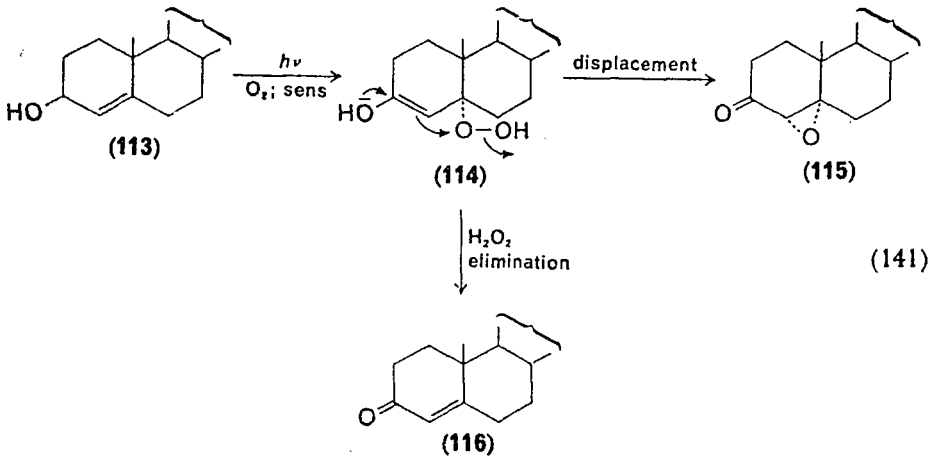
(112a)

$$\underset{\displaystyle (CH_3)_2\dot{C}OH}{\overset{\displaystyle OO^{\cdot}}{\underset{|}{\overset{|}{}}}} + (C_6H_5)_2\dot{C}OH \longrightarrow \underset{\displaystyle (CH_3)_2COH}{\overset{\displaystyle OOH}{\underset{|}{\overset{|}{}}}} + (C_6H_5)_2CO \quad (140)$$

benzophenone-sensitized autoxidation of isopropanol does not proceed in a chain-reaction as its quantum yield has been found to be about 0·5 [171]. The rate of oxidation was found to decrease with

increasing oxygen pressure. This surprising result has been attributed to quenching of photoexcited benzophenone by oxygen.

Fluorescent dyes, such as Rose Bengal, do not sensitize the photochemical autoxidation of saturated aliphatic alcohols[174]. However, an interesting example of a Type II photooxygenation[175] of an allylic alcohol has been observed in the steroid series. Thus, irradiation of cholest-4-en-3β-ol (**113**) in the presence of oxygen and hematoporphyrin gives the epoxyketone **115** and the unsaturated ketone **116**, presumably via the hydroxyperoxide **114** (reaction 141)[176].

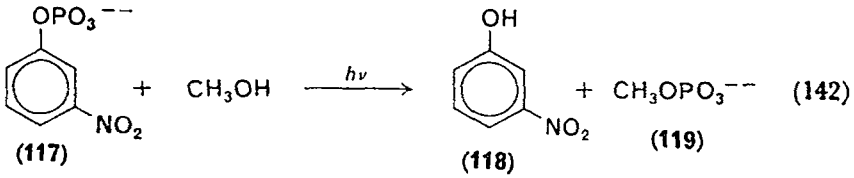


(141)

Benzylic alcohols have been reported to undergo a photochemical autoxidation in dimethyl sulphoxide solution[177]. However, the unique role of the solvent apparently is not understood.

E. Photoinduced Alcoholysis

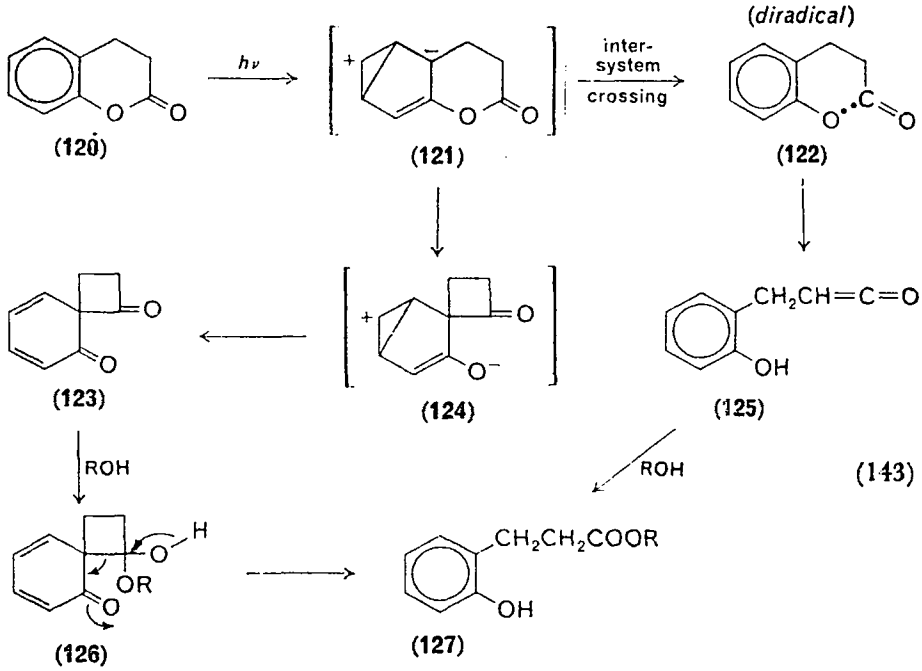
Most photoinduced solvolyses known today have been carried out with aromatic compounds in which absorption of light causes the excitation of the π-electrons of the aromatic system. Thus, irradiation of 3-nitrophenyl phosphate (**117**) in methanol results in a smooth transesterification to give 3-nitrophenol (**118**) and monomethyl phosphate (**119**) (reaction 142)[178, 179]. It has been suggested that the reaction proceeds from a low vibrational level of the first



(142)

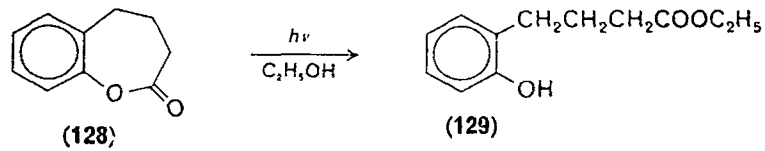
excited π–π^* singlet state in which electron distribution is favourable for heterolytic dissociation of the ester linkage. A detailed discussion of the mechanism of this type of photosolvolysis is beyond the scope of this section and has been presented elsewhere[179, 180].

Solvolysis of phenolate esters derived from carboxylic acids generally occurs as a minor side-reaction in the photoinduced Fries rearrangement[181, 182]. However, photolysis of alcohol solutions of certain lactones does not give any Fries rearrangement products but results in a smooth alcoholysis. For instance, irradiation of dihydrocoumarin (**120**) in ethanol gives methyl β-(2-hydroxyphenyl)propionate (**127**; R = methyl) in 86% yield (reaction 143)[183]. The



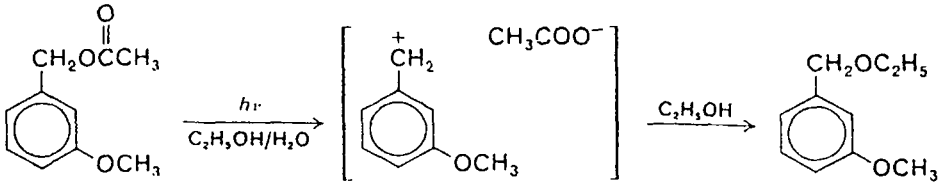
(143)

photolysis of **120** in methanol and isopropanol gives the methyl ester and isopropyl ester, respectively[183, 184]. Likewise, irradiation of the seven-membered lactone **128** in ethanol solution leads to ethyl γ-(2-hydroxyphenyl)butyrate (**129**) (reaction 144)[183]. It had been



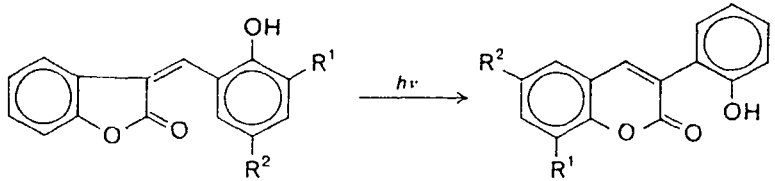
(144)

suggested previously[185] that the photolysis of **120** leads to the ketene* **125** via the diradical **122**. According to a more recent proposal, however, the photoinduced alcoholysis of lactones proceeds via the ionic intermediate **124** to the bicyclic intermediate **123** [183]. A similar mechanistic approach had been applied previously to explain the facile photochemical solvolysis of 3-methoxybenzyl acetate (**130**) in aqueous ethanol which leads to a mixture of 3-methoxybenzyl alcohol and the corresponding ethyl ether **132** via the ionic intermediate **131** (reaction 145)[186].



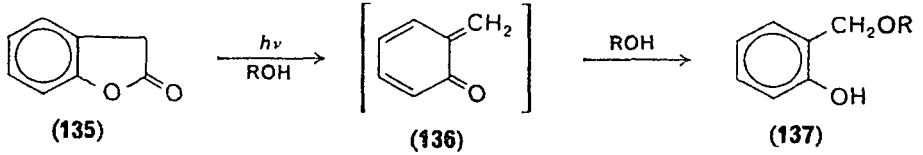
(130) (131) (132) (145)

The photochemical alcoholysis of lactones, apparently, cannot be considered a general reaction. For instance, irradiation of 3-(2-hydroxybenzylidene)-2(3H)-coumaranone (**133**, R^1, R^2 = H) in ethanol solution has been found to result in an intramolecular transesterification to give 3-(2-hydroxyphenyl)coumarin(**134**) (reaction 146)[187]. Interestingly, photolysis of coumaranone (**135**) in methanol



(133) (134) (146)

or ethanol leads to the corresponding alkyl ethers of 2-hydroxybenzyl alcohol (**137a**, **137b**). Although details of these reactions have not



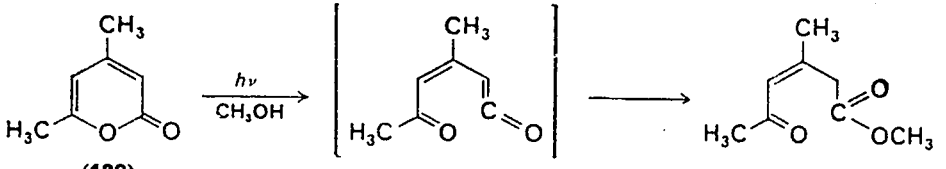
(135) (136) (137) (147)

R = a: CH_3, b: C_2H_5

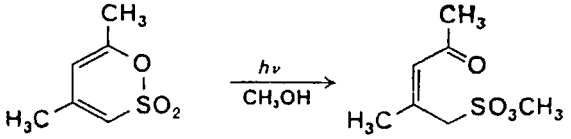
* After completion of the manuscript, the formation of a ketene in the photolysis of dihydrocoumarin was established by spectroscopic means[185a].

been published yet, it appears reasonable to assume that the formation of **137** involves a photoinduced decarbonylation and proceeds via the *ortho*-quinone methide **136** (reaction 147)[183].

The photolysis of the unsaturated lactone **138** in methanol has been found to lead to the δ-keto ester **140** (reaction 148)[188]. It has been suggested that the solvolysis proceeds via the ketene **139**; however, spectroscopic evidence for the ketene remains to be presented. It should be noted that the previously[189] suggested involvement of a sulphene in the photoinduced alcoholysis of the sultone **141** (reaction 149) has not been substantiated[190]. The simplest explanation



(138) (139) (140) (148)



(141) (142) (149)

for the formation of **140** and **142** would thus be the direct attack of the solvent on the photoexcited cyclic esters*.

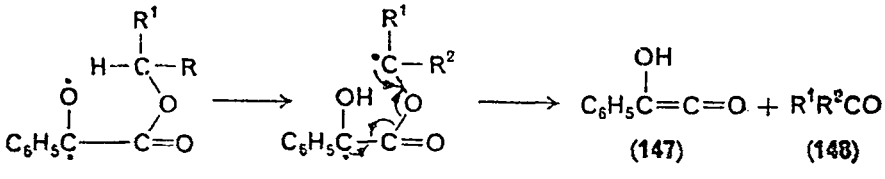
The photolysis of esters of phenylglyoxylic acid in alcohol solution and elevated temperature has been found to result in an apparent alcoholysis and simultaneous oxidation–reduction reaction. For instance, irradiation of isopropyl phenylglyoxalate (**143**) in ethanol at 78° gives ethyl mandelate (**144**) and acetone (reaction 150)[191].

$$\underset{\textbf{(143)}}{C_6H_5COCOOCH(CH_3)_2} + C_2H_5OH + h\nu \longrightarrow \underset{\textbf{(144)}}{C_6H_5CHOHCOOC_2H_5} + (CH_3)_2CO \qquad (150)$$

The mechanism proposed for this unique reaction involves the intramolecular hydrogen abstraction by the photoexcited carbonyl group,

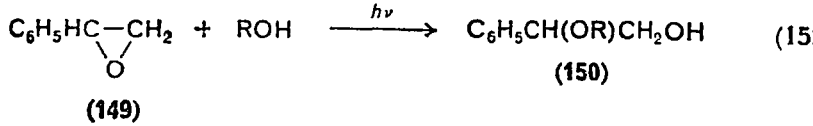
* Since completion of the manuscript, a new mechanism for the photo-induced alcoholysis of 2-pyrones involving the intermediate formation of a β-lactone has been proposed[190a].

followed by a fragmentation reaction to give the oxidation product **148** (R^1R^2CO) and the ketene **147** which will be attacked by the solvent alcohol (reaction 151).



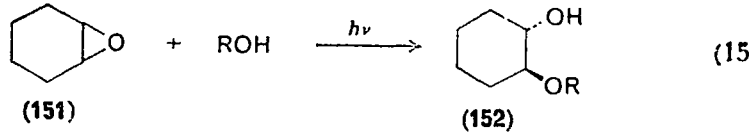
(151)

A remarkably smooth alcoholysis of certain epoxides has been accomplished by photochemical means. For example, irradiation of styrene oxide (**149**) in methanol gives 2-methoxy-2-phenylethanol (**150**, R = CH_3) in 60% yield[192]. Ethanol was found to add in the same fashion (reaction 152). Likewise, photolysis of cyclohexene



(152)

oxide (**151**) in methanol and ethanol yields the corresponding *trans*-2-alkoxycyclohexanols (**152**) in 50% and 76% yield, respectively. It has been suggested that the alcoholysis of epoxides involves the attack of the photoexcited oxirane system by the solvent.

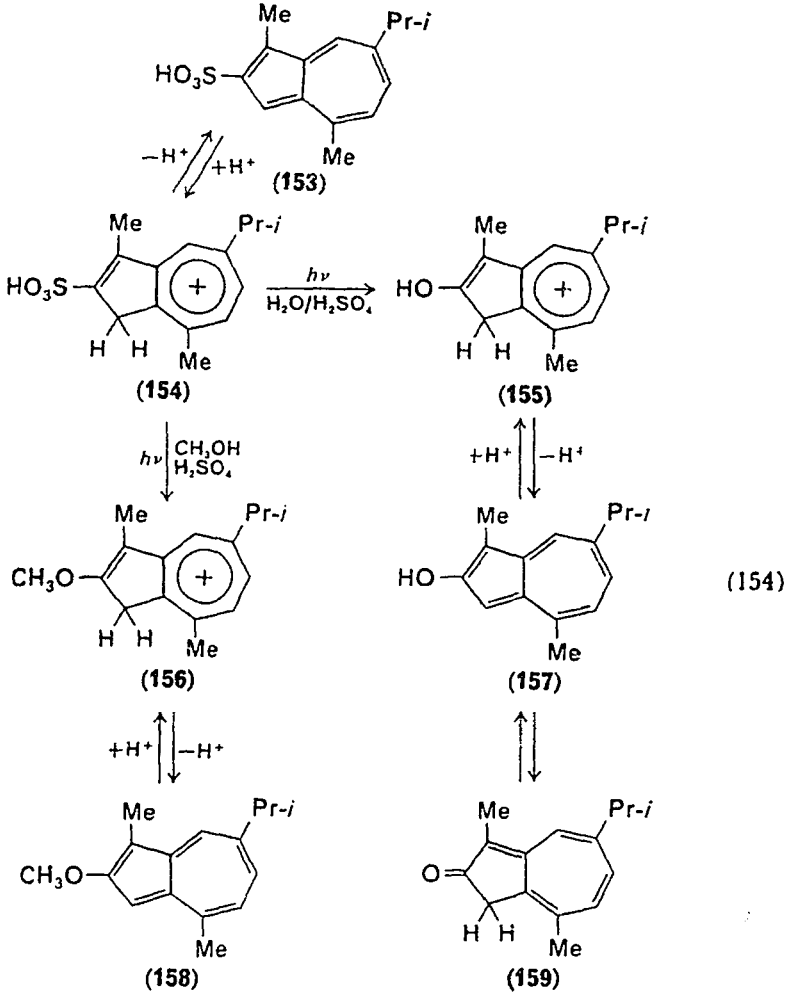


(153)

F. Photoinduced Substitution by Alcohols

Although the subject of substitution of aromatic compounds by hydroxyl ions has received considerable attention[179, 180], little is known about substitution by alcohols. One interesting example has been reported only recently. Irradiation of guaj-azulene-2-sulphonic acid (**153**) in a methanol–sulphuric acid mixture gives 2-methoxy-guaj-azulene (**158**) in 38% yield (reaction 154)[193]. Photolysis of **153** in aqueous sulphuric acid correspondingly gives a 50% yield of 2-hydroxy-guaj-azulene (**157**) which has been found to be in equilibrium with its keto-tautomer **159**. The mechanism of the substitution reaction has not been elucidated. It has been suggested that photoexcitation of the azulenium cation **154** results in either expulsion of

HSO_3^- or transfer of an electron from the solvent. Spectroscopic evidence has also been presented for a photoinduced protolytic



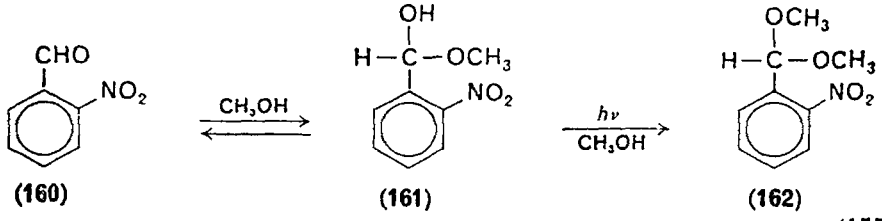
(154)

reaction of azulenium cation involving a hydrogen of the methylene group[194].

G. Photoinduced Acetalization, Ketalization and Esterification

Several examples of photochemical acetalization and ketalization of carbonyl compounds have been reported; however, there is still justified doubt as to whether the addition of alcohols to the carbonyl group is a true photochemical process or is due to inadvertent acid catalysis.

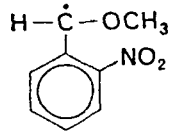
The earliest example of a photoinduced acetalization was reported in 1910 by Bamberger and Elger who isolated 2-nitrobenzaldehyde dimethylacetal (**162**) from a methanol solution of 2-nitrobenzaldehyde (**160**) which had been exposed to sunlight (reaction 155)[195].



(160) **(161)** **(162)**

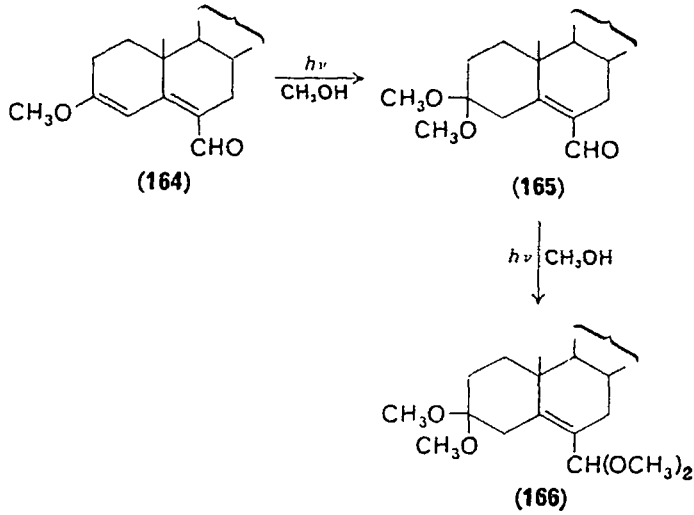
(155)

Ethanol, propanol, isopropanol and isobutanol, as well as 3,6-dichloro-2-nitrobenzaldehyde, 4,5-dimethoxy-2-nitrobenzaldehyde, 3-nitrobenzaldehyde and 4-nitrobenzaldehyde were found to react similarly. It was pointed out by Bamberger and Elger that the acetalizations, conceivably, were brought about by acids formed during the photolysis, rather than by direct catalysis by light. According to a recent investigation, the formation of the acetal **162** from the aldehyde **160** proceeds in two consecutive steps via the hemiacetal **161**. Only the last step was found to be photoinduced[196]. Its mechanism, however, is not readily understood. Spectroscopic (e.s.r.) evidence has been presented for the formation of a radical intermediate. Also, the quantum yield of the acetalization reaction reportedly is larger than unity[196]. It has been suggested, therefore, that the acetalization proceeds via the intermediate **163** in a radical chain reaction. However, the proposed[196] mechanism most likely is not correct because the formation of acetal **162** can hardly be rationalized in terms of homolytic processes.



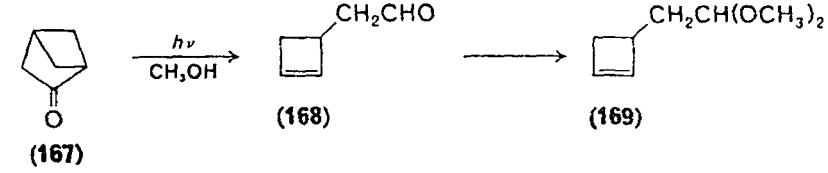
(163)

Acetalizations have also been encountered in the photolysis of steroidal aldehydes such as **164** [197, 198]. Kinetic evidence indicates that the photochemical addition of methanol to the 3,4-carbon–carbon double bond to give **165** precedes the acetalization of the aldehyde to give **166** (reaction 156). Other examples of photoinduced acetalization have been observed in the photolysis of bicyclic



(156)

ketones **167**, **170** and **173** in methanol solutions which leads to the acetals **169**, **172** and **175** via the aldehydes **168**, **171** and **174**, respectively (reactions 157–159)[199]. The role of the light in the acetalization reaction is still subject to discussion.



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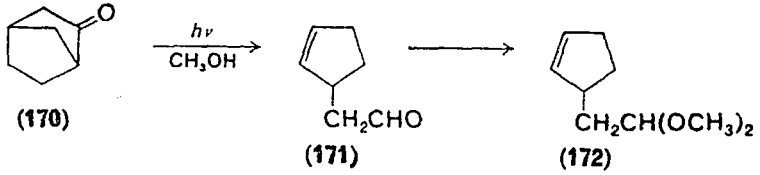

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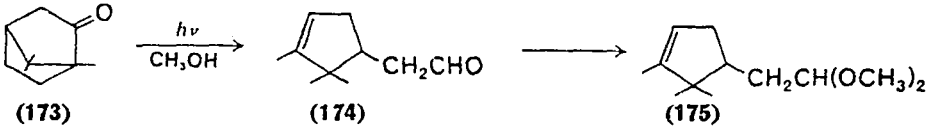
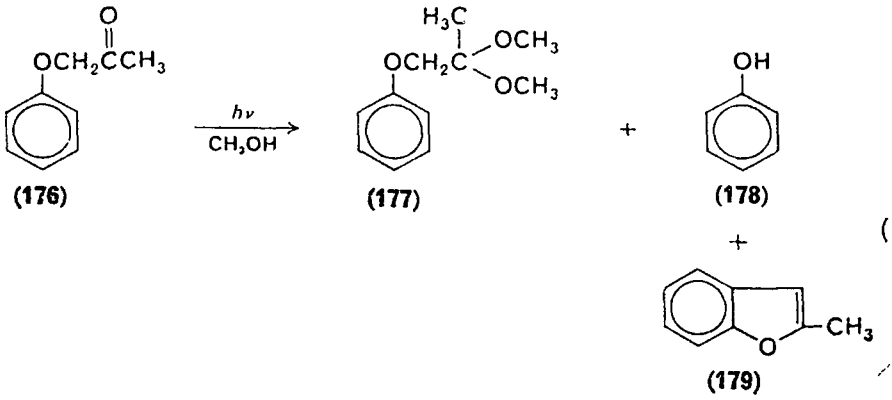


(159)

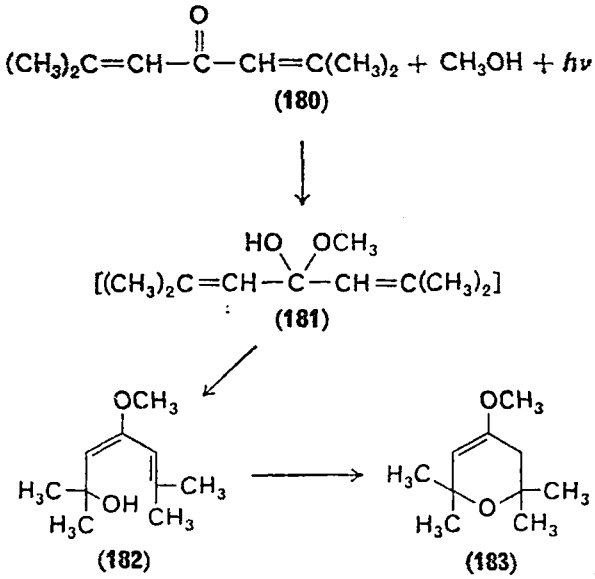
The photolysis of phenoxyacetone (**176**) (reaction 160) in methanol solution has been found to give the dimethylketal **177** in 56% yield besides phenol (5%) and 2-methylbenzofuran (**179**, 5%)[200]. Fair yields of dimethylketals were obtained from a variety of 3-substi-



(176) (177) (178) (179) (160)

tuted and 4-substituted aryloxyacetones. It has been suggested that ketalization represents one mode of deactivation of photoexcited aryloxyacetones, while fission of the ether bond (which gives rise to the phenol and **179**) was considered another possible path of energy dissipation.

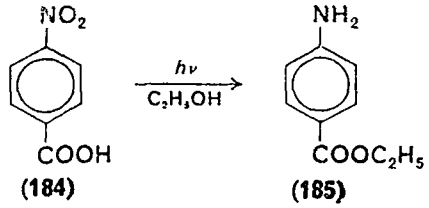
The photochemical formation of the hemiketal **181** has been invoked in order to explain the formation of the methoxy compound **183** by irradiation of phorone (**180**) in methanol (reaction 161)[201]. The intermediate **182** is believed to be formed by an allylic migra-



(182) (183) (161)

tion of the hydroxyl group of the hemiketal. It is not clear, however, as to whether the acetalization indeed is a photochemical reaction.

The esterification of carboxylic acids, apparently, has only been observed concomitant with other photochemical processes. One example[139] has been mentioned in section C.2.a. Recently, irradiation of 4-nitrobenzoic acid (**184**) in ethanol (reaction 162) was found to give ethyl-4-aminobenzoate (**185**)[202]. A plausible mechanism for the esterification reaction has not yet been presented. The involvement of nitric acid catalysis cannot be excluded.



(184) (185) (162)

III. PHOTOCHEMICAL FORMATION AND REACTIONS OF ENOLS

A. Photoenolization

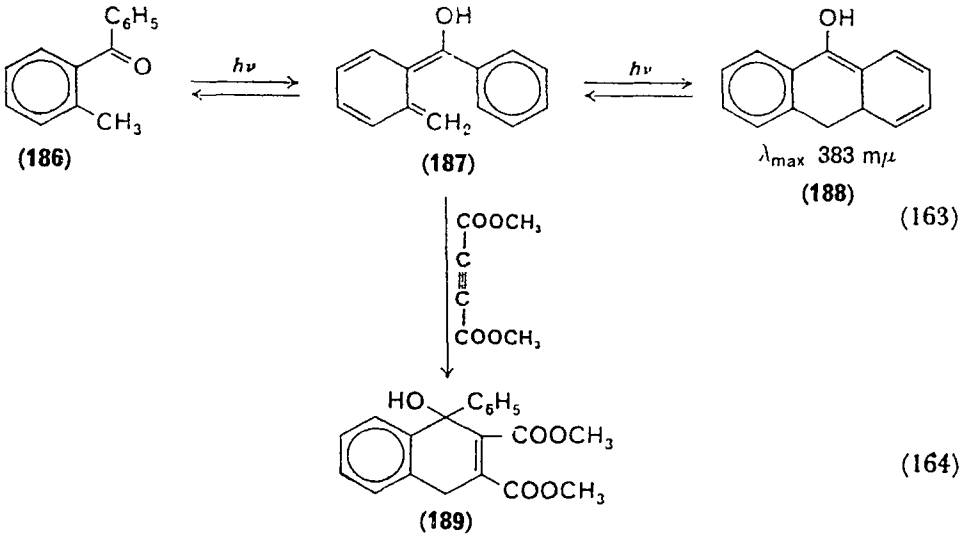
1. Photoenolization involving intramolecular hydrogen abstraction

The photochemical reductive dimerization of *ortho*-alkyl-substituted aromatic ketones to give pinacols proceeds with quantum yields of only 0·01 to 0·05 [203, 204]. By means of deuterium exchange experiments, Yang and Rivas have demonstrated that an intramolecular hydrogen abstraction reaction leading to an enol of the aromatic ketone competes efficiently with the intermolecular hydrogen abstraction from the alcohol[205]. When 2-methylbenzophenone (**186**) is irradiated in the presence of a dieonophile such as maleic anhydride[206] or dimethyl acetylenedicarboxylate[204, 207], the photoenol **187** can be trapped (reaction 164) to give high yields of a

TABLE 9. Photoenolization of 2-methyl-substituted benzophenones.

	Yield of trapped enol	Reference
2-Methylbenzophenone	82%	207
2,4-Dimethylbenzophenone	81%	207
2,5-Dimethylbenzophenone	86%	207
2-Methyl-4′-methoxybenzophenone	82%	207
2-Methyl-4′-chlorobenzophenone	79%	207
2,3′,4′-Trimethylbenzophenone	62%	207
2-Methylacetophenone	Poor yield	208

Diels–Alder adduct, such as **189**[205]. Using this technique, the formation of photoenols could be verified for a variety of 2-alkyl-substituted benzophenones (Table 9). It should be noted, however, that the yield of Diels–Alder adduct is no indication of the actual photoenolizability of a ketone. No adduct is formed from the spectroscopically detectable[209] photoenol of 2-benzylbenzophenone, probably for steric reasons.

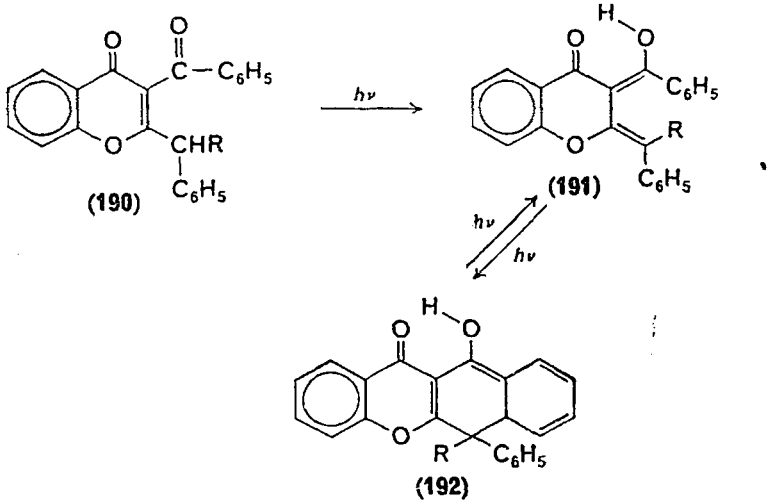


(186) **(187)** **(188)** (163)

(189) (164)

Reketonization of the 2-methylbenzophenone enol **187** is a thermal process proceeding rapidly at room temperature. The ultraviolet spectra of some photoenols have been measured by flash photolysis and found to exhibit a long-wavelength maximum around 400 mμ[209]. Initiated by conflicting reports about the lifetime of transient species observed in flash-photolysis experiments, Ullman and Huffman discovered that the photoenol **187** upon electronic excitation cyclizes (reaction 163) to give 4a,10-dihydro-9-anthrol (**188**)[210]. Compound **188** has an absorption maximum at 383 mμ and reverts to the enol **187** upon photoexcitation. The enol **191** formed by irradation of the photochromic 2-benzyl-3-benzoyl chromone (**190**) undergoes a similar photoinduced cyclization (reaction 165) to give **192** [211]. The mechanism of the photoenolization of 2-alkylbenzophenones probably involves an n–π^* triplet excitation. Details on the scope and mechanism of photoenolization of photochromic ketones have been discussed elsewhere[212].

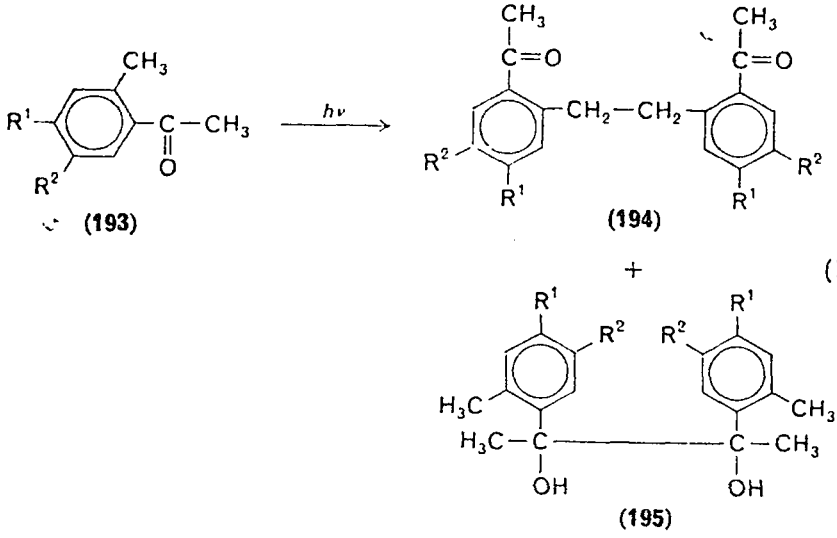
In the series of 2-alkylsubstituted phenylalkylketones both spectroscopic[213] and chemical[208, 214] evidence for photoenolization has been obtained. Irradiation of 2,4-dimethylacetophenone and 2,5-dimethylacetophenone in CH_3OD was found to result in the partial



(165)

$R = H, C_6H_5$

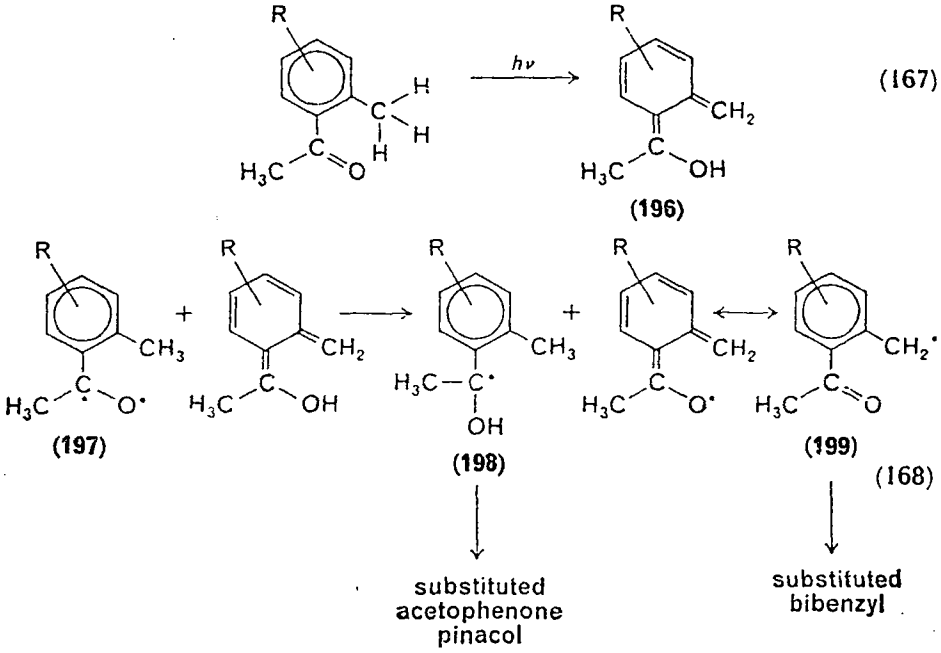
exchange of hydrogen for deuterium exclusively in the 2-methyl group. Photolysis of these acetophenones in ethanol at near liquid



(166)

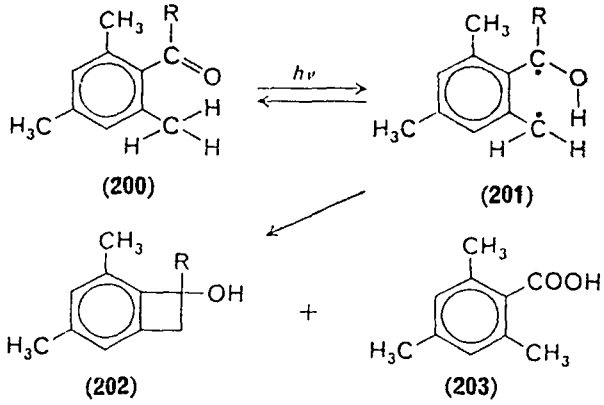
a: $R^1 = CH_3$; $R^2 = H$ b: $R^1 = H$; $R^2 = CH_3$

nitrogen temperature also produced reversibly a yellow colour which disappeared upon warming and which was attributed to the enol. Chemical evidence for the photoenolization was obtained by irradiation of neat 2,4-dimethylacetophenone (**193a**) at room temperature through Pyrex (reaction 166) which leads to 2,4-dimethylacetophenone pinacol (**195a**) and 2,2′-diacetyl-5,5′-dimethylbibenzyl (**194a**)[214]. 2,5-Dimethylacetophenone (**193b**) behaves similarly, giving pinacol **195b** and the substituted bibenzyl **194b.** The mechanism proposed for the simultaneous formation of **194** and **195** involves the oxidation of the photoenol **196** by triplet state acetophenone (**197**) to give the ketyl radical **198** and the radical **199** (reactions 167 and 168).



Interestingly, 2,4,6-trimethylacetophenone (**200a**) upon irradiation in isopropanol does not seem to undergo reversible photoenolization but gives the cyclobutanol **202a** in 70% yield instead, mesitoic acid **203** being formed as a by-product (reaction 169)[215]. Cyclobutanols **202b** (63%) and **202c** (61%) are formed in the photolysis of 2,4,6-trimethylpropiophenone (**200b**) and 2,4,6-trimethylisobutyrophenone **200c**, respectively. The amount of mesitoic acid increases with the degree of alkylation of the ketone. No cyclobutanol but mesitoic acid is formed in 48% yield by ultraviolet

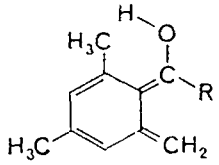
irradiation of 2,4,6-trimethylpivalophenone (**200d**). The mechanism of its formation is not known. As for the formation of cyclobutanols, it is conceivable that steric hindrance in the *trans*-isomer **204** of the



(169)

R = a: CH_3, b: C_2H_5, c: $CH(CH_3)_2$, d: $C(CH_3)_3$

photoenol is responsible for the intramolecular coupling in structure **201**. It is worth noting that *cis*- and *trans*-enol structures have been assigned to different transients observed upon photoexcitation of 2,4,6-trialkyl-substituted benzophenones[216] (cf, however, Reference 210).

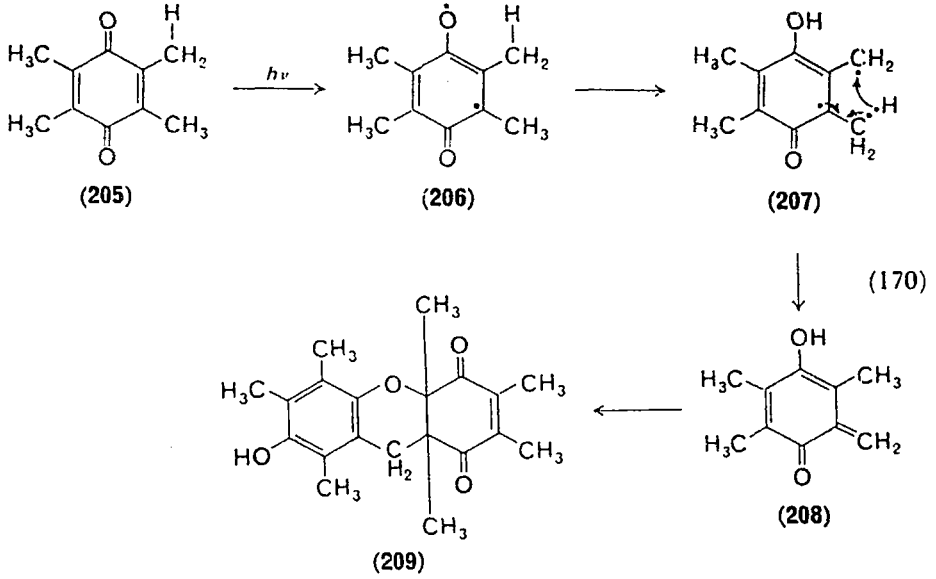


(204)

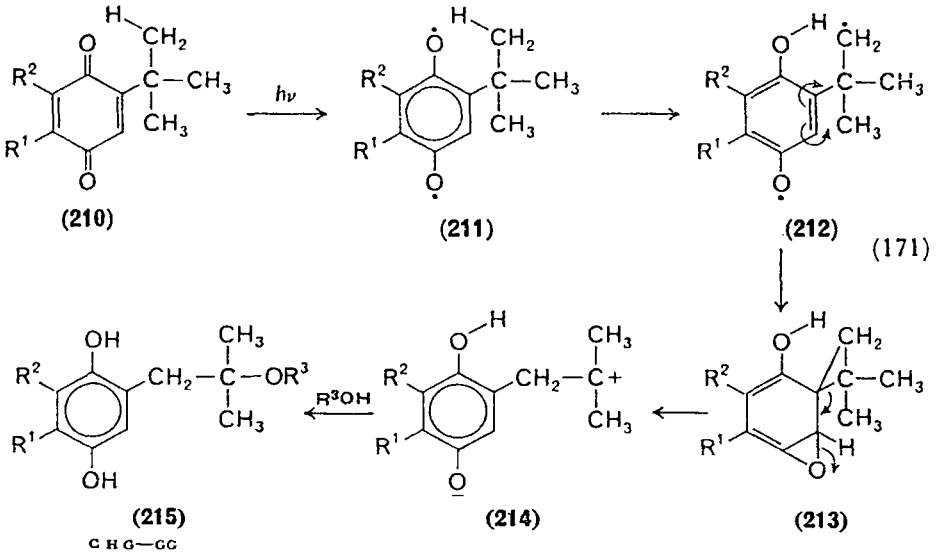
Enolization reactions involving intramolecular hydrogen atom transfer from an alkyl substituent to a carbonyl group also have been encountered in the photochemistry of quinones. Thus irradiation of duroquinone (**205**) in ethanol leads to diduroquinone (**209**) (reaction 170)[217]. The dimerization probably proceeds by Diels–Alder addition of **205** to a photochemically generated duroquinone enol (**208**), rather than by a proposed[217] attack of duroquinone by a diradical. It has been suggested that the ultraviolet absorption maximum at 495 mμ of a transient observed upon photoexcitation of **205** which disappears by a first-order process may be due to the diradical **206** [78, 218, 219].

Ultraviolet irradiation of higher alkyl-substituted benzoquinones

in alcohol solution not only leads to the corresponding hydroquinones (cf section B.1) but results in an addition reaction involving the solvent [219–221]. Thus, *t*-butyl-substituted benzoquinones (**210**) give



the substituted hydroquinones (**215**) in which the side-chain has undergone a rearrangement reaction. Methanol, ethanol, isopropanol and *t*-butanol have been found to add to alkyl-substituted benzoquinones in this fashion. The involvement of radicals in this

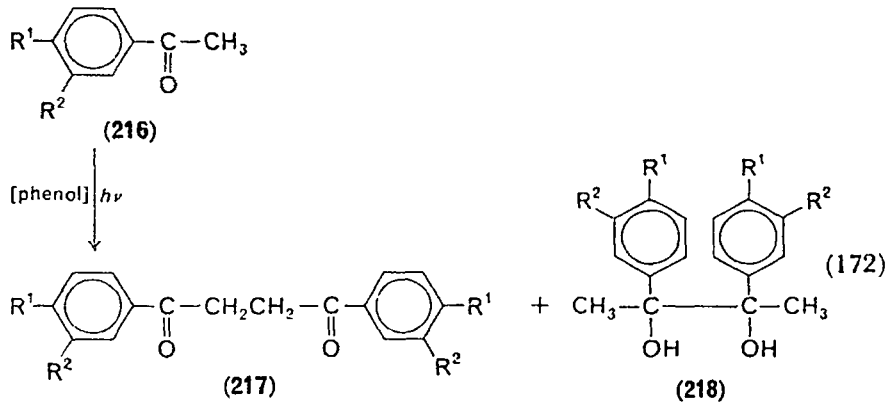


reaction is supported by the appearance of an e.s.r. signal during irradiation[219].

The mechanism for the formation of **215**, however, cannot involve only radical intermediates. The primary reaction apparently proceeds through an n–π^* triplet state of the quinone resulting in intramolecular hydrogen atom abstraction from the alkyl substituent to give the biradical **212**. The rearrangement of the side-chain as observed in product **215** conceivably proceeds through the intermediates **213** and **214** [221] since the formation of an ether from an alcohol requires the involvement of a heterolytic step and cannot be explained by a pure homolytic mechanism as had been suggested[219].

2. Photoenolization involving intermolecular hydrogen abstraction

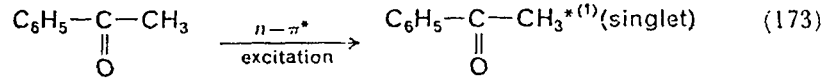
Phenols have been found to induce a unique photochemical reaction of acetophenone[214]. Irradiation of neat acetophenone (**216a**) containing a small amount of phenol (advantageously adsorbed on silica gel) smoothly leads to acetophenone pinacol (**218a**) and 1,2-dibenzoylethane (**217a**) in excellent yields (reaction 172). 4-Methylacetophenone (**216b**) and 3,4-dimethylacetophenone (**216c**) undergo



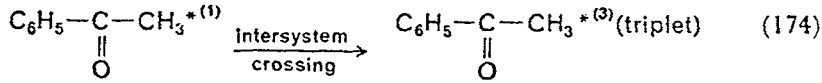
a: $R^1 = H$; $R^2 = H$ b: $R^1 = CH_3$; $R^2 = H$ c: $R^1 = CH_3$; $R^2 = CH_3$

this oxidative–reductive dimerization in the same manner. The reaction obviously involves the acetophenone enol. Attempts to bring about the photochemical oxidative–reductive dimerization in the presence of mineral acids, however, have failed. Therefore, the enolization of acetophenones by phenol appears to be a true photochemical process (reactions 173–176). The catalytic role of phenol in the photochemical enolization is depicted in the six-membered

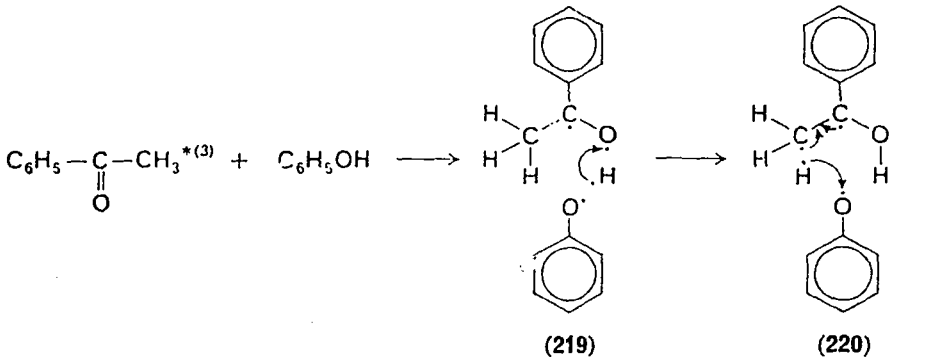
transition states **219** and **220**. Oxidation of acetophenone enol (**221**) by triplet state acetophenone then leads to radicals **222** and **223**, each of which will dimerize to give acetophenone pinacol and 1,2-dibenzoylethane, respectively.

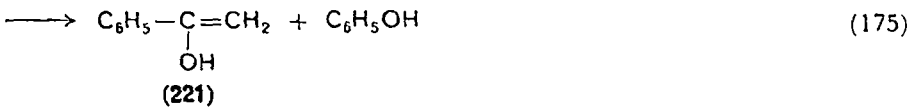


(173)

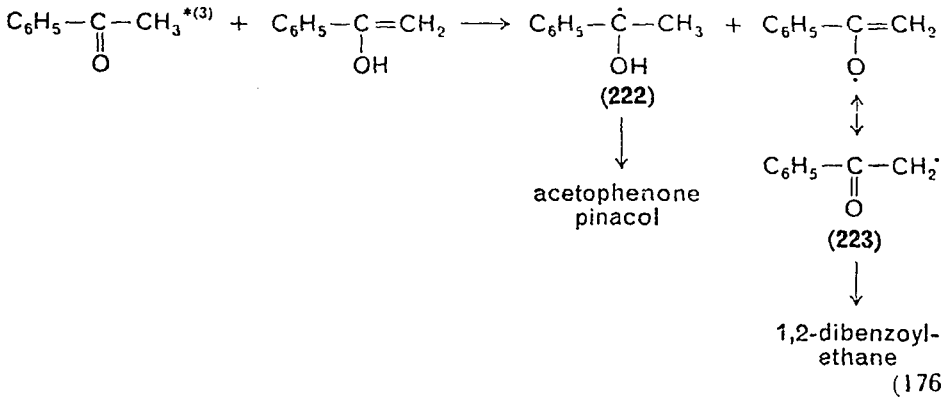


(174)



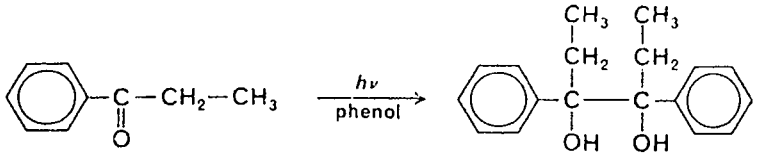


(175)



(176)

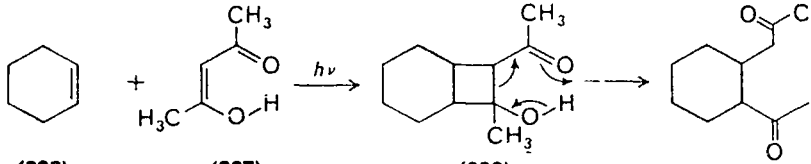
In the photochemical reaction with propiophenone (**224**) phenol does not seem to induce the enolization reaction but apparently serves as a hydrogen donor for the reductive dimerization leading to propiophenone pinacol (**225**) (reaction 177).



(224) (225) (177)

B. Cycloaddition of Enols to Olefins

Irradiation of acetylacetone (**227**) in cyclohexene solution yields the 1 : 1 addition product acetonyl-2-acetylcyclohexane (**229**) in 78% yield (reaction 178)[222]. The formation of **229** probably pro-

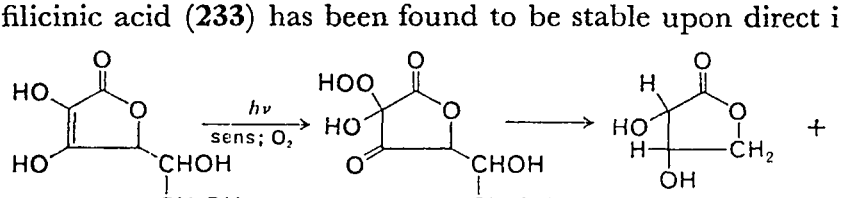


(226) (227) (228) (229) (178)

ceeds via the intermediate **228**. Photolysis of acetylacetone in *cis,cis*-1,5-cyclooctadiene and *cis*-cyclooctene gives similar 1 : 1 addition products[223]. Other enolizable diketones such as dimedone or 2-acetylcycloalkanones have been found to undergo the photocycloaddition reaction with cyclohexene in the same fashion[223, 224]. However, attempts to extend the reaction to styrene or conjugated dienes have been unsuccessful. It has been suggested that the addition reaction involves the triplet state of the enolizable ketone.

C. Photochemical Reactions of Enols with Molecular Oxygen

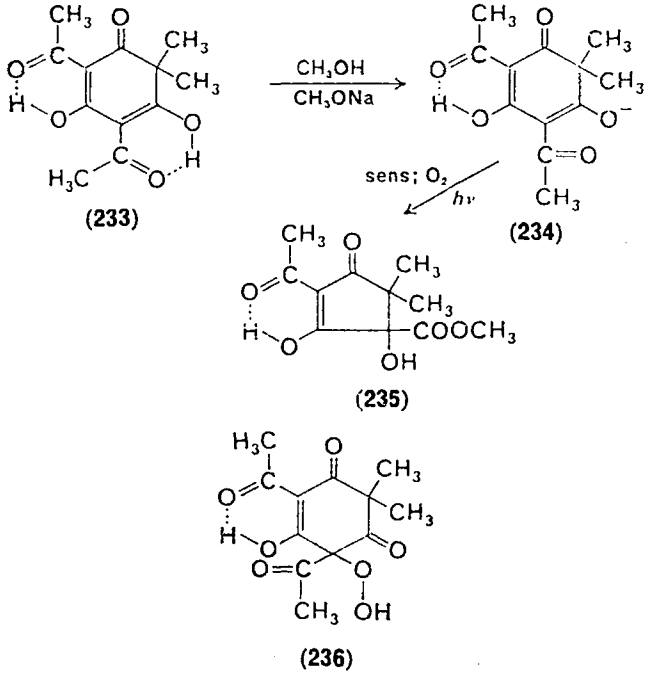
Photosensitized autoxidation of ascorbic acid (**230**) in the presence of Rose Bengal, chlorophyll or eosin[79] gives the hydroperoxide **231** which decomposes in a subsequent dark-reaction into oxalic acid and the lactone **232** (reaction 179). Interestingly, the enol diacetylfilicinic acid (**233**) has been found to be stable upon direct irradia-



(230) (231) (232) (179)

tion in the presence of oxygen, possibly because of strong intramolecular hydrogen bonding. Its enolate ion (**234**), however, under-

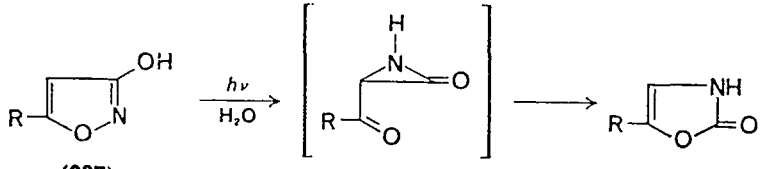
goes photochemical autoxidation to give **235** (reaction 180)[225]. Irradiation in the presence of Rose Bengal greatly enhances the rate of autoxidation, suggesting the participation of singlet oxygen in this reaction. Analogous to the photosensitized autoxidation of ascorbic acid, the hydroperoxide **236** may be an intermediate in the reaction leading to **235**.



(233) (234) (235) (236) (180)

D. Photoinduced Rearrangement of Enols

Several five-membered heterocycles are known to undergo photochemical rearrangement reactions in which two ring atoms interchange their position. This type of reaction has also been found to proceed in the case of the 3-hydroxy-substituted isoxazoles[226]. For

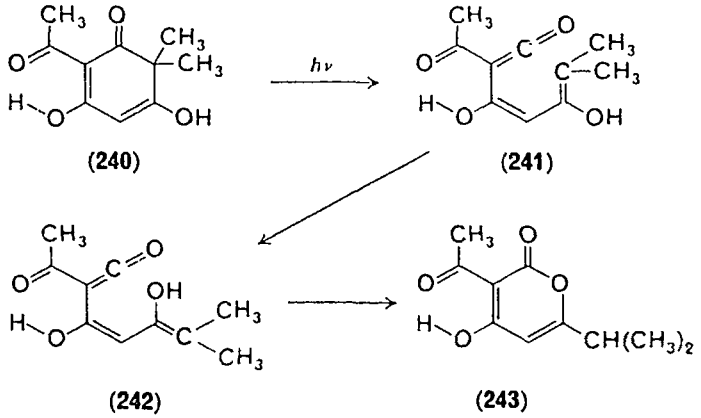


(237) (238) (239) (181)

a: R = CH_3 b: R = $CH(COO^-)NH_3^+$

example, irradiation at 2537Å of 3-hydroxy-5-methylisoxazole (**237a**) in aqueous solution under nitrogen gives 5-methyl-2(3H)-oxazolone (**239a**). Likewise, photolysis of ibotenic acid (**237b**) in water has been found to give muscazone (**239b**) in about 35% yield (reaction 181). The mechanism of the photochemical conversion of 3-hydroxy-substituted isoxazoles into 2(3H)-oxazolones presumably proceeds by valence tautomerization via the intermediate **238**, analogous to the photoinduced rearrangement of 3,5-diphenyl-isoxazole[227].

A remarkably smooth rearrangement of a hydroxydienone into a pyrone was reported recently[228]. Irradiation of monoacetylfilicinic acid (**240**) in ether or methanol solution was found to give the α-pyrone **243** in about 80% yield (reaction 182). It has been sug-



(182)

gested that the isomerization proceeds via the intermediate **241** (= **242**) which undergoes an intramolecular reaction with the enolic hydroxyl group. There is no indication that an intermolecular addition of the hydroxylic solvent to the ketene competes with the rearrangement reaction.

IV. PHOTOCHEMICAL REACTIONS INVOLVING PHENOLS

A. Photolysis of Phenols

1. Electron ejection and homolysis

The ultraviolet spectrum of phenol (Figure 5) exhibits three long wavelength maxima at 278, 270 and 265 mμ, which are attributable to π-electron transitions from vibrational levels of the benzene nucleus. In order to explain the photochemical behaviour of phenol, however, it is necessary to assume that absorption of a photon results

in the promotion of a nonbonding electron on the oxygen to an antibonding molecular orbital.

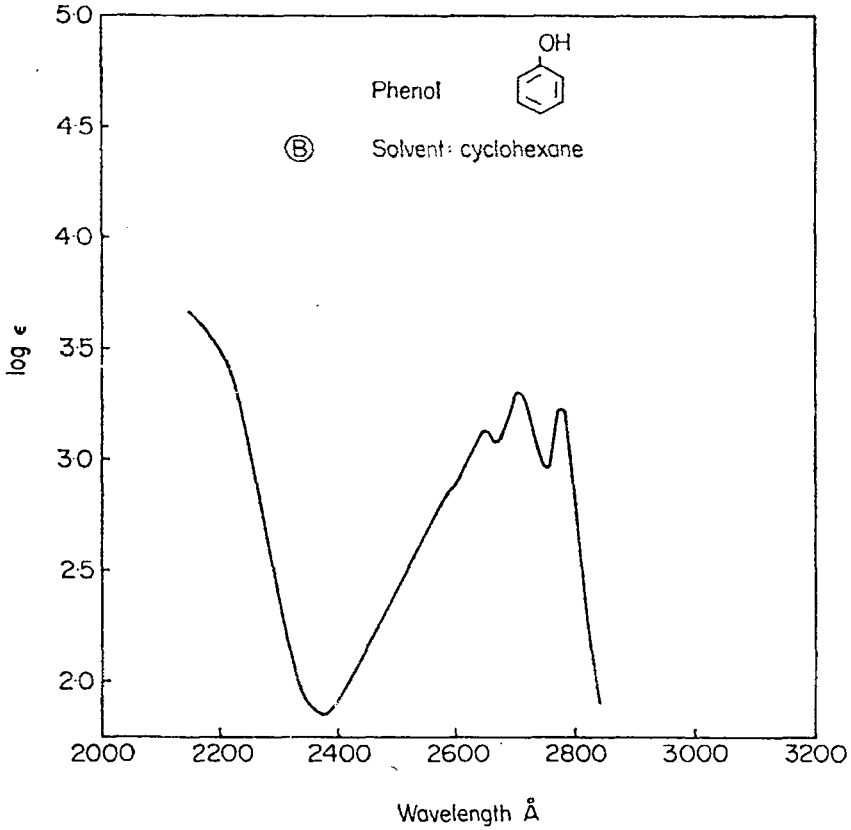


FIGURE 5. The ultraviolet spectrum of phenol. [Reproduced, by permission, from reference 229.]

Photolysis of phenol in the gas phase, in solution, or at low temperature in glassy media results in the homolytic cleavage of the O–H bond to give phenoxy radicals with a quantum yield of about 0·01 (reaction 183)[230–232]. Phenoxy radicals are also generated

$$C_6H_5OH + h\nu \longrightarrow C_6H_5O^{\cdot} + H^{\cdot} \quad (183)$$

$$C_6H_5O^- + h\nu \longrightarrow C_6H_5O^{\cdot} + e_{aq} \quad (184)$$

photochemically by electron ejection from phenolate ions (reaction 184)[233, 234]. Spectroscopic evidence has been presented that the photolysis of phenols in aqueous solution gives the hydrated electron[235, 236], and it has been found that electron ejection occurs as the predominant process in the photolysis of 4-aminophenol at

77°K [237]. Photolysis of 2-naphthol in aqueous solution was reported to give both the hydrated electron and 2-naphthoxy radicals[238]. Interestingly, the observed pH dependence of the quantum yield for the generation of the hydrated electron was found to be similar to the pH dependence of the fluorescence yield. It has been concluded, therefore, that electron ejection and phenolate fluorescence are competing deactivation processes of the first excited state.

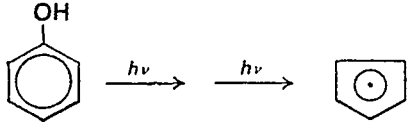
The ultraviolet spectra of photochemically generated phenoxy radicals derived from a large number of substituted phenols have been reported[230, 231]. Homolytic fission of the O–H bond was observed in the photolysis of even such substituted phenols where ground state considerations would suggest rupture of obviously weaker bonds as, for example, in bromophenols (see, however, References 236 and 239).

Electron ejection and homolytic cleavage of the O–H bond generally have been considered to be two distinctly different primary processes in the photolysis of phenols. This concept, however, is not readily comprehensible in terms of chemical oxidation mechanisms. More likely, electron ejection from photoexcited phenols to give radical cations may be the only primary process leading to products. The phenoxy radical could then be formed in a consecutive step involving expulsion of a proton (reaction 185). The rate of the

$$C_6H_5OH \xrightarrow[-e]{h\nu} [C_6H_5OH]^{\cdot +} \longrightarrow C_6H_5O^{\cdot} + H^+ \qquad (185)$$

second step will depend on the nature of the solvent and on the stability of the radical cation and phenoxy radical. Such a mechanism would readily explain the results obtained in the photolysis of amino-substituted phenols.

It has been reported recently[240] that phenol in the gas phase can, to a very limited extent, undergo a biphotonic process (reaction 186) leading to the cyclopentadienyl radical **244**. Gas-chromato-

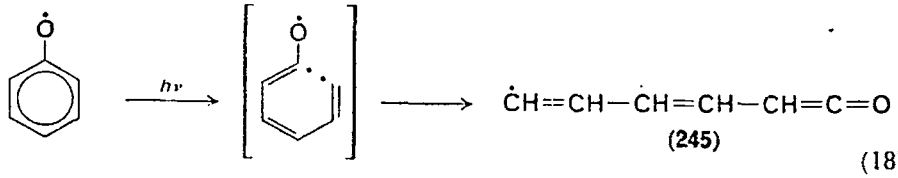


(186)

(244)

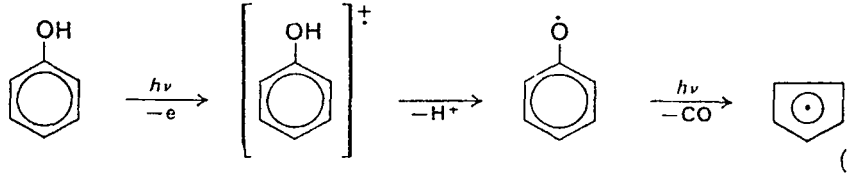
graphic analysis also showed the presence of carbon monoxide and hydrogen in about equal quantities. It is worth noting that the formation of carbon monoxide in the photolysis of the phenoxy radical (reaction 187) at 4·2°K had been found previously[241]. It was suggested that carbon monoxide derived by decomposition of

an excited 6-oxo-1,3,5-hexatrienyl radical (**245**). It is conceivable that **245** actually is the precursor of the cyclopentadienyl radical and carbon monoxide in reaction (186). Thus, the biphotonic de-



(187)

composition of phenol also could be a two-step photolysis involving the primary formation of the phenoxy radical (reaction 188).



(188)

2. Intermolecular proton transfer

Since chemical conversion of photoexcited phenols into products is a low quantum yield process, most of the excited molecules return to the ground state by either radiationless processes or by emission of light (fluorescence) from the first excited singlet state. The same is true for photophysical deactivation of phenolate ions whose fluorescence maximum is observed at longer wavelengths because of the smaller energy difference between the ground state of the anion and its first excited state.

Förster reported in 1950 that photoexcitation of phenols in aqueous solution results in the fluorescence of both the neutral phenol and the phenolate ion, even over a pH range where no phenolate ion exists under ground state conditions[242]. This means that phenols are significantly stronger acids in their first excited singlet state than in their ground state. The two-component fluorescence spectrum of the 2-naphthol : 2-naphtholate ion system obtained at different pH values is shown in Figure 6. The photochemical excitation and deactivation processes for phenols in the presence of water as a proton acceptor can be described by reactions (189–192).

$$\mathrm{ArOH} \xrightarrow{h\nu} \mathrm{ArOH}^* \tag{189}$$

$$\mathrm{ArOH}^* + \mathrm{H_2O} \rightleftarrows \mathrm{ArO^-}^* + \mathrm{H_3O^+} \tag{190}$$

$$\mathrm{ArO^-}^* \longrightarrow \mathrm{ArO^-} + h\nu' \tag{191}$$

$$\mathrm{ArO^-} + \mathrm{H_3O^+} \longrightarrow \mathrm{ArOH} + \mathrm{H_2O} \tag{192}$$

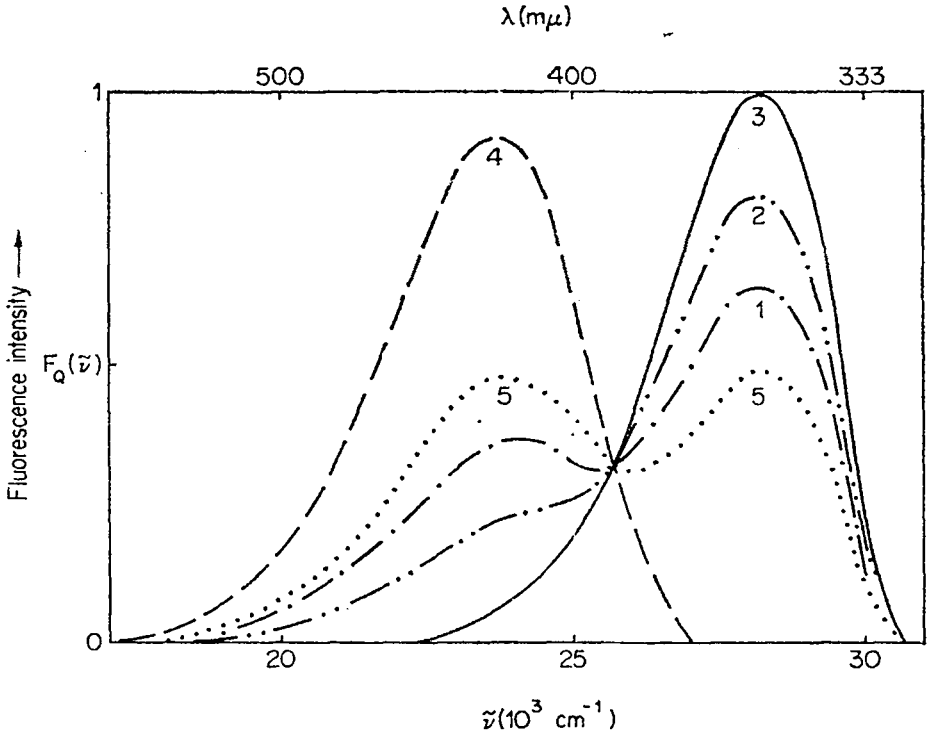


FIGURE 6. Fluorescence spectra of 2-naphthol in water at 25°. (1) pH 5–6; (2) 0·004M $HClO_4$; (3) 0·15M $HClO_4$; (4) 0·02M NaOH; (5) 0·02M CH_3COONa + 0·002M CH_3COOH (pH = 5·7). [Reprinted with permission from reference 243.]

A detailed treatment of the photoinduced reversible deprotonation of phenols, known as the Förster cycle (schematically depicted in

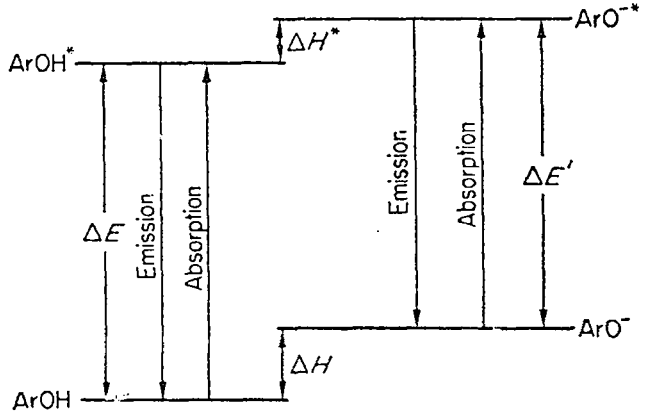


FIGURE 7. Schematic representation of the Förster cycle.

Figure 7), has been published by Weller[243]. A fundamental result of the investigations by Förster and Weller is the estimation of excited state acidity constants (pK^*) according to the equation:

$$pK - pK^* = (\Delta E - \Delta E')/2{\cdot}303RT$$

Another method for the determination of pK^* is based on the observed fluorescence intensities. The excited state pK^*'s for a large number of phenols have been determined by these two methods[243–248]. Some examples are given in Table 10. Generally,

TABLE 10. Acidity constants on phenols in the ground state and in the first excited singlet state.

ArOH	pK	pK^*	ΔpK	Reference
Phenol	10·00	4·1	5·9	246
4-Bromophenol	9·35	2·9	6·45	246
3-Methoxyphenol	9·62	4·6	5·0	246
4-Methoxyphenol	10·24	5·7	4·54	246
2-Naphthol	9·46	2·82	6·66	243

the difference in acidity between ground state and excited singlet state phenols is about six orders of magnitude. Ground state substituents constants have been found to correlate with the excited state pK's [245, 247, 248]. The deuterium isotope effect on the excited state dissociation of phenols also has been investigated and found to be smaller than that for the ground state dissociation[246].

The increased acidity of phenols in the first excited singlet state has also been found to enhance hydrogen bond formation with suitable proton acceptors such as ethers or esters. This effect can manifest itself in a characteristic red-shift of the longest-wavelength absorption maximum of the phenol (Figure 8), or in pronounced effects on the fluorescence intensity[249–252].

Regarding the acidity of excited states, it is worth noting that the pK of triplet state phenols is very similar to that of ground state phenols. For example, the pK of 2-naphthol in the triplet state is 8·1 [253]. On the basis of molecular orbital theory, the enhanced acidity of phenol in the excited state can be calculated as the charge distribution shown for the ground state (**246**) and the first excited singlet state (**247**) indicate[254, 255]. In terms of classical resonance structures, the first excited singlet state of phenol may then be

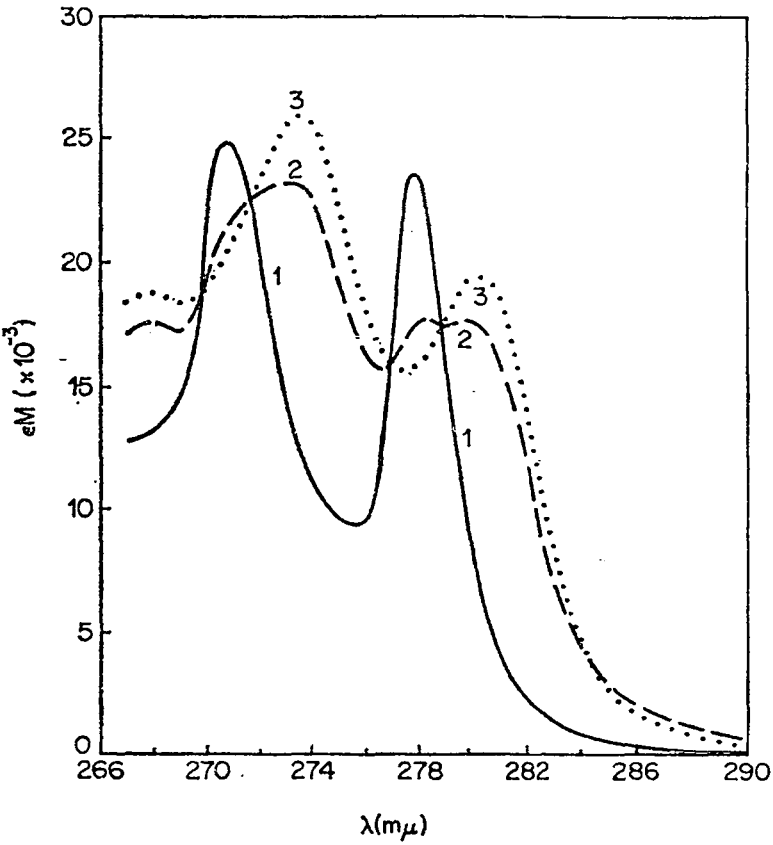
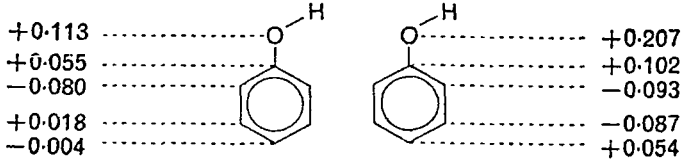


FIGURE 8: The effect of hydrogen bonding on the ultraviolet absorption spectrum of phenol. 1: in petroleum ether, 2: in petroleum ether containing 0·182 mole/l of dioxan, 3: in petroleum ether containing 0·597 mole/l of dioxan. [Reproduced, by permission, from reference 249.]

Charge distribution originating from π—π^* *transactions*[255]



(246) (247)

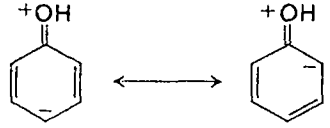
represented as the ionic resonance form **248**, while the triplet state may be depicted as the radical resonance contributor **249**.

3. Intramolecular charge-transfer

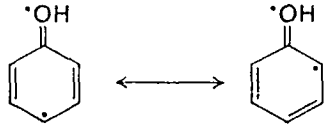
The introduction of a hydroxyl group into the 4-position of an

aromatic ketone or aldehyde has a pronounced inhibiting effect on the photoreactivity of the carbonyl group. Some of the primary processes involved in and responsible for this lack of reactivity may be understood in the light of the preceding discussion on photo-induced acid-base reactions of phenols.

Two examples of hydroxy-substituted carbonyl compounds,

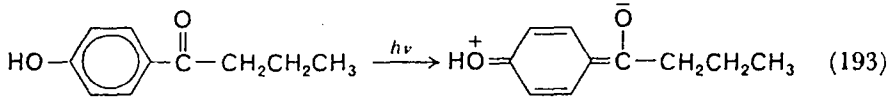


(248)

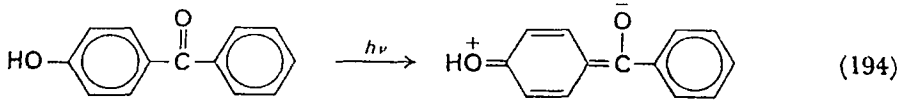


(249)

namely 4-hydroxybutyrophenone (**250**) and 4-hydroxybenzophenone (**252**), have been studied in detail since their photochemical behaviour appeared anomalous in comparison with that of their parent compounds. Thus the quantum yield for the formation of ethylene in the photolysis of unsubstituted butyrophenone is 0·42 [256, 257]. However, the quantum yield for the same process is zero in the case of 4-hydroxybutyrophenone[257]. Pitts has suggested that the lack of reactivity is to be attributed to the 'charge-transfer character' of the lowest π–π^* triplet state. If the reactive (hydrogen atom abstracting) n–π^* triplet of unsubstituted butyrophenone can be depicted as a diradical $R_2\dot{C}$—$O^{\cdot}$, the unreactive state of photo-excited 4-hydroxybutyrophenone may be represented by the ionic resonance structure **251** (reaction 193).



(250) (251) (193)



(252) (253) (194)

Both the photochemistry and the ultraviolet absorption spectrum of 4-hydroxybenzophenone (**252**) have been found to be highly

solvent dependent[258]. In alcohol solution where its absorption spectrum (Figure 9) is similar to that of the 4-benzoylphenolate ion, 4-hydroxybenzophenone does not react photochemically (i.e., the quantum yield of its disappearance is less than 0·01). In cyclohexane solution, however, where its ultraviolet absorption spectrum is

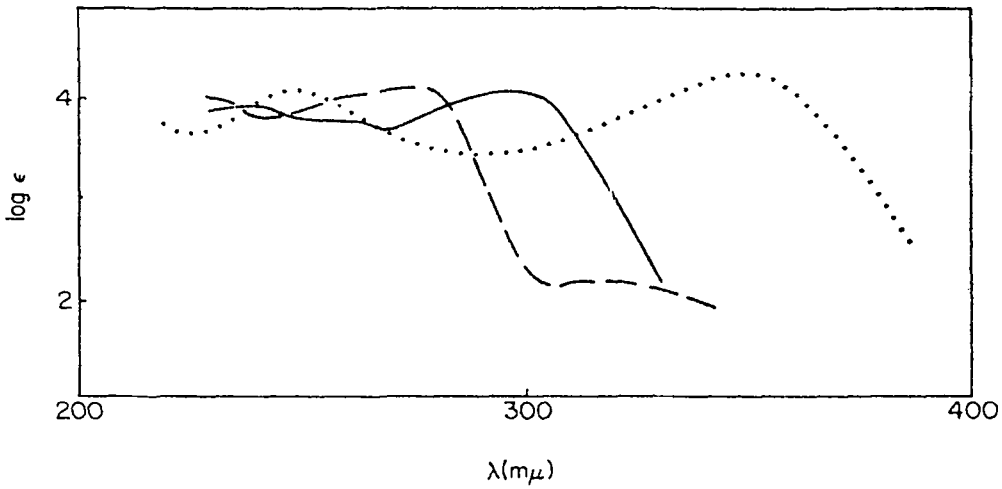


FIGURE 9. Ultraviolet spectra of 4-hydroxybenzophenone ———— in alcohol ····· in alkaline solution — — — — in cyclohexane

[Reprinted from reference 258, by permission of the International Union of Pure and Applied Chemistry and Butterworths Scientific Publications.]

similar to that of unsubstituted benzophenone[259] (i.e., the long-wavelength n–π^* transition is separated from the π–π^* transition), 4-hydroxybenzophenone disappears upon irradiation with a quantum yield of 0·9 [260]. It should be pointed out, however, that nothing is known about the nature of the products formed. It is possible that the disappearance of 4-hydroxybenzophenone is due to decomposition reactions, rather than the claimed pinacolization process.

As for the effect of solvent on the ultraviolet absorption spectrum of 4-hydroxybenzophenone, it has been suggested that the high-intensity long-wavelength band in alcohol solution should be assigned to a charge-transfer transition (CT) rather than a π–π^* transition[261]. The pK of 4-hydroxybenzophenone, determined spectroscopically, was found to be −4 in the first excited singlet, 3 in the first excited triplet and 6·5 in the ground state. Thus, deprotonation in the excited state as described in section IV.A.2 may be responsible for the lack of reactivity in alcohol solution. Based on

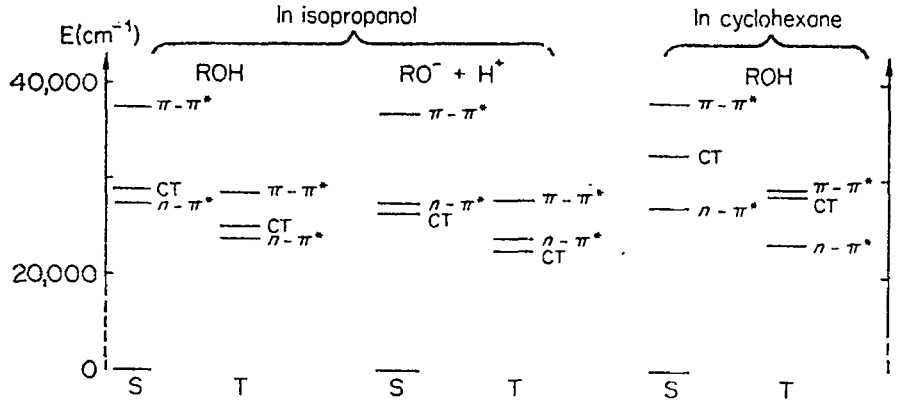


FIGURE 10. Energy levels of 4-hydroxybenzophenone, S = singlet state, R = 4-benzoyl phenyl, T = triplet state. [Reproduced, by permission, from reference 260.]

the positions of the energy levels for the n–π^* and CT states of neutral and deprotonated 4-hydroxybenzophenone (Figure 10), it has been suggested[261] that reactions (195–201) are involved in the photochemistry of 4-hydroxybenzophenone. Since hydrogen atom abstraction can only occur if the lowest triplet state is n–π^* in nature, reprotonation of the anion [$RO^{-*(3)}CT$] would have to precede the internal conversion to give [$ROH^{*(3)}n$–π^*].

Deactivation processes in photoexcited 4-hydroxybenzophenone (R = 4-benzoylphenyl)

$$ROH \longrightarrow ROH^{*(1)}(CT \text{ and } n\text{–}\pi^*) \quad \text{(excitation)} \tag{195}$$

$$ROH^{*(1)}(CT;\ n\text{–}\pi^*) \longrightarrow RO^{-*(1)}(CT) + H^+ \quad \text{(deprotonation)} \tag{196}$$

$$RO^{-*(1)}(CT) \longrightarrow RO^{-*(3)}(CT) \quad \text{(intersystem crossing)} \tag{197}$$

$$RO^{-*(3)}(CT) \longrightarrow RO^- \quad \text{(deactivation)} \tag{198}$$

$$RO^{-*(3)}(CT) \underset{-H^-}{\overset{+H^+}{\rightleftharpoons}} ROH^{*(3)}(CT) \quad \text{(protonation)} \tag{199}$$

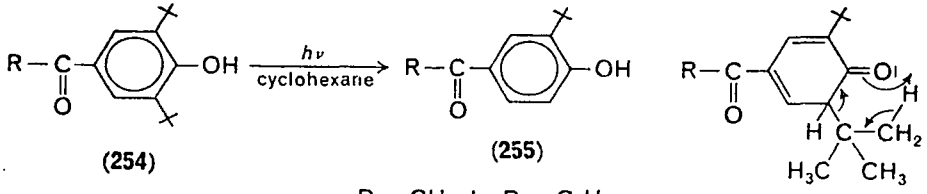
$$ROH^{*(3)}(CT) \longrightarrow ROH^{*(3)}(n\text{–}\pi^*) \quad \text{(internal conversion)} \tag{200}$$

$$ROH^{*(3)}(n\text{–}\pi^*) \longrightarrow \text{hydrogen abstraction reaction} \tag{201}$$

In this scheme the assumption has been made that alcohol will act as a proton acceptor in the deprotonation reaction. It should be considered, however, that the basicity of the carbonyl group is greatly enhanced in the first excited singlet state. It is, therefore, conceivable that intermolecular hydrogen bond formation in the excited state may be involved in the photostability of 4-hydroxybenzophenone in protic solvents.

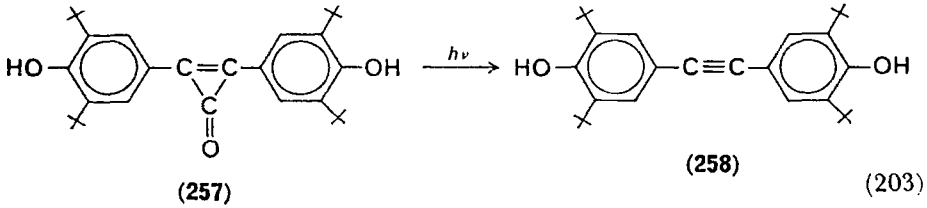
A recent report indicates that the hydroxyl group in the *para* position not only influences the reactivity of photoexcited aromatic ketones but may also have an effect on the products obtained when

the reaction does proceed in cyclohexane[262]. Irradiation of 3,5-di-*t*-butyl-4-hydroxyacetophenone (**254a**) or 3,5-di-*t*-butyl-4-hydroxybenzophenone (**254b**) in cyclohexane solution has been found not to result in the expected pinacolization reaction, but gives the debutylated ketones 3-*t*-butyl-4-hydroxyacetophenone (**255a**) and 3-*t*-butyl-4-hydroxybenzophenone (**255b**), respectively (reaction 202). No reaction is observed in isopropanol solution, where, however, the methyl ethers of **254a** and **254b** do pinacolize photochemically. It is possible that the tautomer **256** may be involved in the photo-



(202)

chemical dealkylation of **254**, though the involvement of phenoxy radical intermediates cannot be excluded. It is worth noting, however, that irradiation of bis-(3,5-di-*t*-butyl-4-hydroxyphenyl)-cyclopropenone (**257**) where intramolecular charge-transfer is not feasible,



(203)

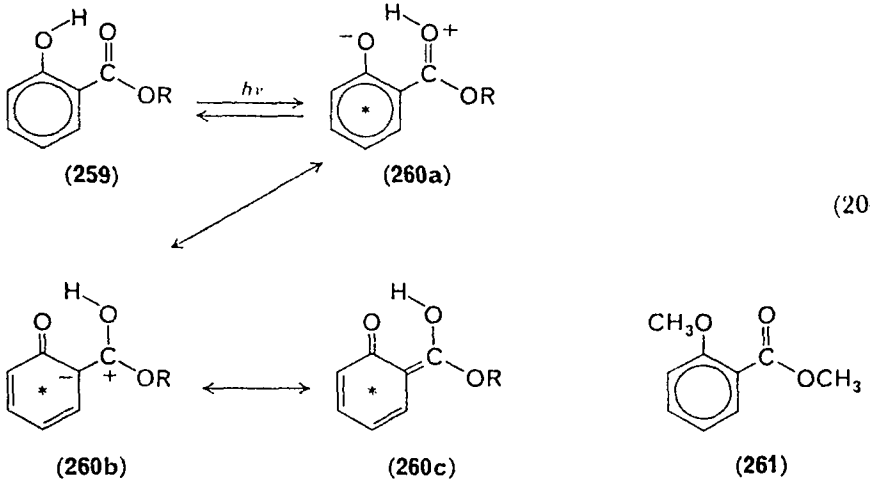
smoothly leads to the decarbonylated product **258** (reaction 203) in the same fashion as the unsubstituted diphenylcyclopropenone[263].

B. Photoinduced Reversible Tautomerization of Phenols

1. *Ortho*-Hydroxycarboxylic acids

Spectroscopic investigations by Weller have revealed that photoexcitation of *ortho*-hydroxy-substituted carboxylic acids and their esters results in a reversible tautomerization reaction[243]. Salicylic acid (**259**, R = H) in methanol solution was found to exhibit a fluorescence maximum (at 435 mμ) of an abnormally large Stokes shift. The fluorescence maximum of methyl salicylate is found at the same position, while that of methyl 2-methoxybenzoate (**261**) (at 360 mμ) shows a normal Stokes shift. This phenomenon has been observed with other *ortho*-hydroxycarboxylic acids and their esters,

but not in *meta*- and *para*-hydroxycarboxylic acids[264a]. Weller has suggested that the long-wavelength fluorescence of *ortho*-hydroxycarboxylic acids is due to emission from the excited state tautomer **260** which is formed by intramolecular proton transfer. Ionization



(204)

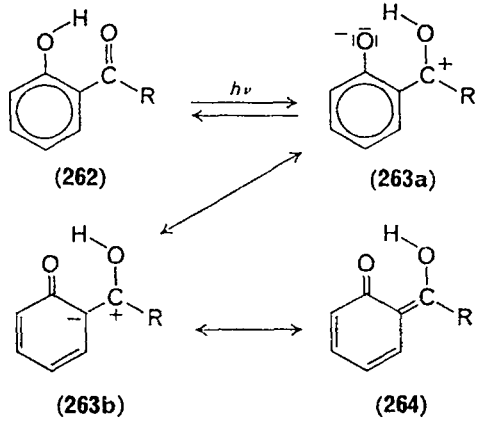
R = H, R = CH_3

of the phenol is facilitated in the excited state; however, in the case of *ortho*-hydroxy carbonyl compounds the proton transfer is favoured by a six-membered transition state and enhanced by the increased basicity of the aromatic carboxylic acids in the excited state. The proton transfer must be rapid since the equilibrium is established during the lifetime of the excited state tautomer **260**. Interestingly, in nonpolar solvents such as methylcyclohexane or benzene a low-intensity fluorescence maximum around 360 mμ is observed besides the long-wavelength maximum and is attributed to emission from excited state salicylic acid. It is remarkable that in suitable solvents the photoinduced intramolecular proton transfer occurs at temperatures as low as $-180°C$ [264b]. (For recent results on the effect of intramolecular hydrogen bonding on the acidity in the lowest excited singlet state of salicylic acid, see Reference 265.)

2. *Ortho*-Hydroxycarbonyl compounds

Introduction of a hydroxyl group into the *ortho* position drastically influences the photoreactivity of aromatic carbonyl compounds. For example, 2-hydroxybenzophenone in isopropanol solution is photostable, while 2-methoxybenzophenone under the same conditions undergoes photoreduction with a quantum yield of unity[266].

While 4-hydroxybenzophenone sensitizes the photochemical *cis–trans* isomerization of 1,3-pentadienes very efficiently, 2,4-dihydroxybenzophenone does not act as a sensitizer, nor does 2-hydroxy-4-methoxybenzophenone or salicylaldehyde[267]. Butyrophenone upon irradiation in benzene solution gives ethylene and acetophenone in a Norrish Type II process, but 2-hydroxybutyrophenone does not react under identical conditions[257]. Chemical and ultraviolet spectroscopic evidence for the photochemical transformation of *ortho*-hydroxycarbonyl compounds of structure **262** into their tautomers of structure **263** or **264** has not been obtained yet (reaction 205); however, rapid reversible intramolecular hydrogen transfer (either heterolytically or homolytically) from the phenol to the carbonyl group followed by rapid thermal reketonization appears to be



(262) (263a) (263b) (264) (205)

responsible for the total lack of reactivity of *ortho*-hydroxy carbonyl compounds. Similar arguments have been used to explain the lack of photochemical reactivity of 2-hydroxy-4,6-di-*t*-butylbenzophenone[268].

2-Hydroxybenzophenone does not show phosphorescence in solution at room temperature, which means that no triplet species are detectable[269]. At low temperature (77°K) in 3-methylpentane 2-hydroxybenzophenone phosphoresces only very weakly probably because photoexcitation will mainly result in the intramolecular hydrogen transfer reaction. It has been found, however, that 2-hydroxybenzophenone exhibits a strong long-lived phosphorescence at 77°K in hydrogen bonding solvents, such as alcohols, indicating that photoexcitation under these conditions does give the triplet state. The lack of photochemical reactivity of *ortho*-hydroxy-substituted benzophenones in alcohol solution where intermolecular

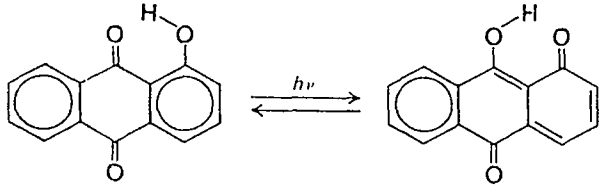
hydrogen bonding would permit normal carbonyl photochemistry has been attributed to very short lifetimes of the triplets produced at room temperature[269]. However, compared with the ground state, the pK* of 2-hydroxybenzophenone has been found to be significantly lower (see Table 11). This suggests that a deprotonation reaction in

TABLE 11. Dissociation constants of some 2-hydroxybenzophenones in the ground state (pK) and the first excited singlet state (pK*) (Solvents 50% ethanol in water) [from Reference 270].

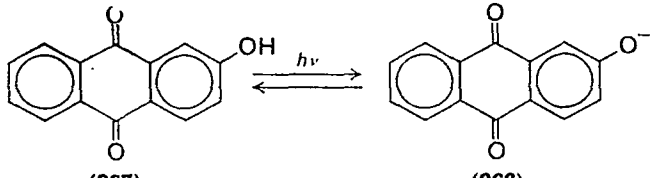
	pK	pK*	ΔpK
2-Hydroxybenzophenone	10·83	3·78	7·05
2-Hydroxy-4-nitrobenzophenone	8·23	−3·54	11·77
2-Hydroxy-5-nitrobenzophenone	6·69	−8·36	15·05
2-Hydroxy-4-methoxybenzophenone	10·68	2·70	7·98
2-Hydroxy-5-methoxybenzophenone	11·03	5·59	5·44
2-Hydroxy-4-methylbenzophenone	11·10	4·20	6·90
2-Hydroxy-5-methylbenzophenone	11·30	3·70	7·60

which the hydroxylic solvent acts as proton acceptor (as discussed in section IV.A.2) may represent an alternate mode of deactivation involved in the photochemistry of *ortho*-hydroxy carbonyl compounds.

The deactivating effect of *ortho*-hydroxy substitution has also been observed in the photochemistry of 9,10-anthraquinones[76]. Unsubstituted 9,10-anthraquinone undergoes photochemical reduction in aqueous isopropanol with a quantum yield of 0·94, and 1-chloro-9,10-anthraquinone is reduced with a quantum yield of



(265) (266) (206)

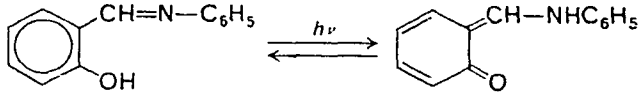


(267) (268) (207)

unity. However, 1-hydroxy-9,10-anthraquinone (**265**) is not reduced photochemically, presumably because of the reversible tautomerization (reaction 206) leading to **266**. 2-Hydroxy-9,10-anthraquinone (**267**) is not reduced either under these conditions. In this case, not the tautomerization reaction, but photoinduced deprotonation (reaction 207) to give the photostable 2-hydroxy-9,10-anthraquinone anion (**268**), may be responsible for the lack of reactivity.

3. Photochromic hydroxyl compounds

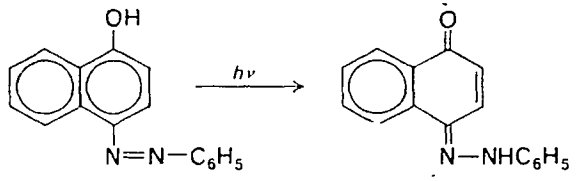
A large number of *ortho*-hydroxy-substituted anils[271] have been found to exhibit photochromic behaviour which has been attributed to an intramolecular hydrogen transfer in the excited state[272]. Photolysis of *ortho*-hydroxybenzylidene aniline (**269**) at low temperature in solution indeed gives rise to a transient species (λ max, 470 mμ), which has a lifetime in the millisecond region, and to which the *ortho*-quinone methide structure (**270**) has been assigned (reaction 208)[273a,b]. Other spectral changes observed in photo-



(208)

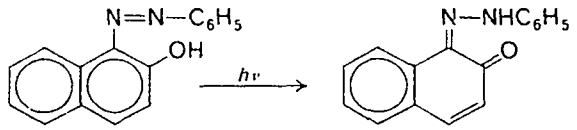
(269) (270)

chromic systems of this type are caused by *cis–trans* isomerism[273b]. A detailed discussion of photochromic *ortho*-hydroxy compounds such as **271** and **273** is beyond the scope of this section. A comprehensive review on this subject has been published recently[274].



(209)

(271) (272)

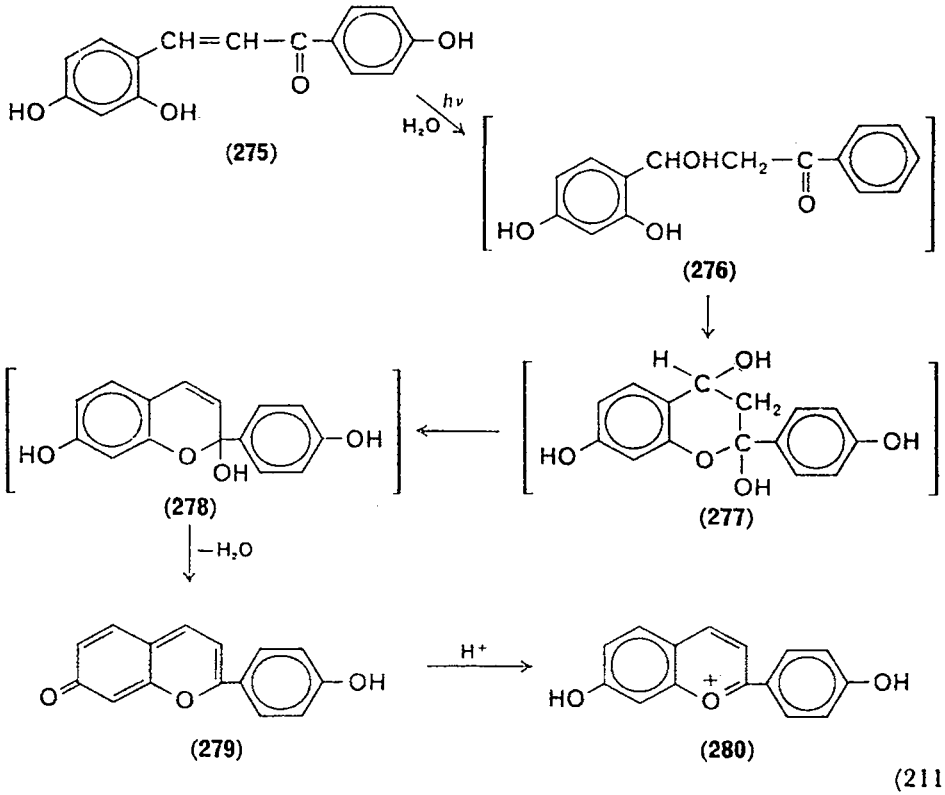


(210)

(273) (274)

It is worth pointing out that a multi-step mechanism may be involved in seemingly simple photochemical conversions of *ortho*-

hydroxyl compounds. For example, irradiation of the *ortho*-hydroxychalcone (**275**) leads to the coloured flavylium ion (**280**) in an overall reaction (211) consisting in the elimination of water from the



(211)

cyclized intermediate **278**. However, spectroscopic and kinetic evidence has been presented, which shows that the conversion of **275** into **280** also involves the intermediates **276** and **277**, suggesting that the hydration of the carbon–carbon double bond is a prerequisite for the cyclization reaction[275].

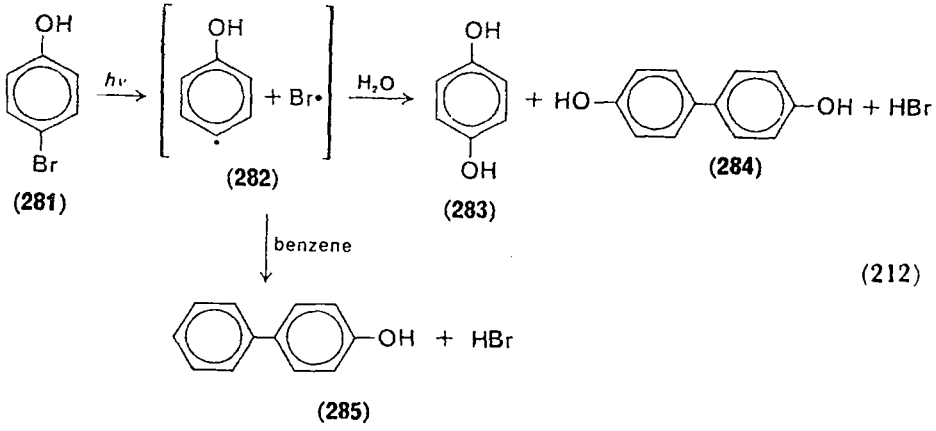
C. *Photolysis of Halogen-containing Phenols*

(For photochemical reactions of chlorophenols see References 275a and 275b which appeared after completion of this manuscript.)

1. Bromophenols and iodophenols

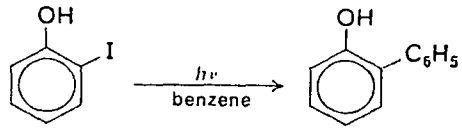
Photoexcitation of bromo- and iodo-phenols in solution results in the homolytic cleavage of the carbon–halogen bond rather than in the cleavage of the O–H bond. Product analysis provides no evidence for a conceivable rearrangement of hydroxyphenyl radicals into

phenoxy radicals. Thus, ultraviolet irradiation of 4-bromophenol (**281**) at 2537Å in water gives hydroquinone, 4,4'-dihydroxybiphenyl and hydrogen bromide (reaction 212)[239b]. Irradiation of 2-bromophenol and 3-bromophenol gives the analogous products. Photolysis of 4-bromophenol in benzene solution gives 4-hydroxybiphenyl (**285**) as the major product which obviously derives from attack of the solvent by the 4-hydroxyphenyl radical (**282**)[276].



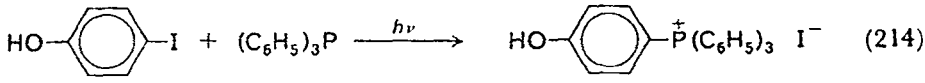
(281) (282) (283) (284) (285) (212)

Cleavage of the carbon–halogen bond appears to be the predominant reaction of photoexcited iodophenols[277]. This feature has been successfully exploited for the synthesis of arylated phenols. Thus, 2537Å irradiation of 2-iodophenol (reaction 213) in benzene solution gives 2-hydroxybiphenyl (**287**) in 60–70% yield[278]. The



(286) (287) (213)

photochemical arylation of similar iodosubstituted phenols is summarized in Table 12. Irradiation of 4-iodophenol (**288**) in the presence of triphenylphosphine results in a smooth substitution reaction leading to 4-hydroxytetraphenylphosphonium iodide (reaction 214)[283].



(288) (289) (214)

TABLE 12. Photolysis of iodophenols in benzene.

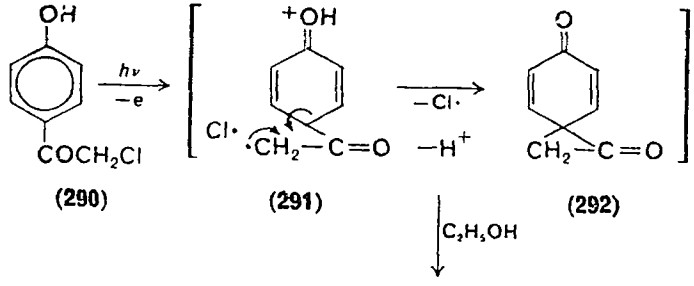
Starting phenol	Product (yield)	Reference
4-Cyano-2-iodophenol	4-Cyano-2-phenylphenol (25%)	279
4-Cyano-2,6-diiodophenol	4-Cyano-2,6-diphenylphenol (71%)	279
2,6-Diiodo-4-formylphenol	2,6-Diphenyl-4-formylphenol (20–30%)	280
2,4,6-Triiodophenol	2,4,6-Triphenylphenol	280
6-Iodo-2,4,5-triphenyl-resorcinol	Tetraphenylresorcinol (53%)	281
2,4,6-Triiodoresorcinol	Triphenylresorcinol (12%)	281
4,6-Diiodoresorcinol	Diphenylresorcinol	281
2,6-Dimethyl-4-iodophenol	2,6-Dimethyl-4-phenylphenol	282

2. Phenolic acyl halides

Irradiation of 4-hydroxyphenacyl chloride (**290**) in ethanol solution has been found to give a mixture of 4-hydroxyacetophenone and ethyl (4-hydroxyphenyl)acetate (**293**)[284]. Apparently, two distinct primary processes are involved in the photolysis of **290**, one of which results in the homolytic cleavage of the carbon–halogen bond to give the dehalogenated reduction product via hydrogen atom abstraction by chlorine atoms from the solvent and hydrogen atom transfer from the thus generated hydroxyalkyl radicals to the 4-hydroxyphenacyl radicals. The other primary process leading to **293** most likely involves electron ejection from the phenolic site to give the radical cation **291**. Displacement of the chlorine atom and proton expulsion may then lead to the spiro ketone **292** whose attack by the solvent would give the observed rearranged product **293** (reaction 215).

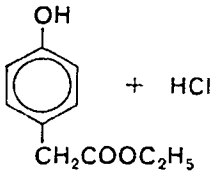
Photolysis of 2-hydroxyphenacyl chloride (**294**) in ethanol gives coumaran-3-one (**295**) as the major product[284], while the reductive dehalogenation process becomes negligible (reaction 216). Conceivably, the cyclization reaction proceeds by a similar displacement mechanism as suggested for the formation of the intermediate **292**. Interestingly, the photolysis of the seemingly related hydroxy-substituted phenacyl bromide **296** results in the formation of flavone hydrobromide **299** (reaction 217) most likely by a mechanism which first involves a photochemical reductive debromination step[285]. The cyclization reaction can then be explained by nonphotochemical intramolecular proton transfer from the phenol to the carbonyl group, and hydrogen bromide catalysed elimination of water.

Recently, the photocyclization of some *N*-chloroacetyl derivatives of pharmacodynamic amines has been investigated[286, 287]. Thus, irradiation of *N*-chloroacetyl-*m*-tyramine (**300**) in aqueous ethanol solution smoothly gives hydrogen chloride and the cyclization product **301** (reaction 218). Analogous cyclization products were obtained by photolysis of *N*-chloroacetyl-3,4-dihydroxyphenethylamine (**302**) and *N*-chloroacetyl-4,5-dimethoxy-3-hydroxyphen-



(290) (291) (292)

(215)



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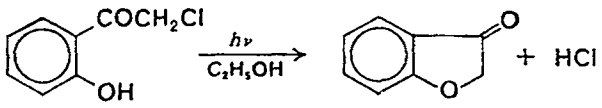
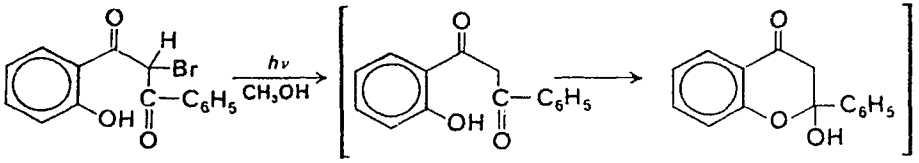


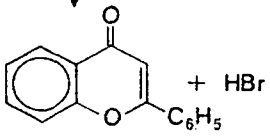
(294) (295)

(216)



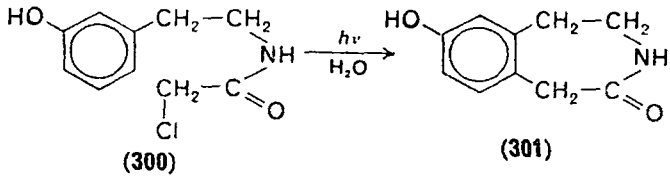
(296) (297) (298)

(217)

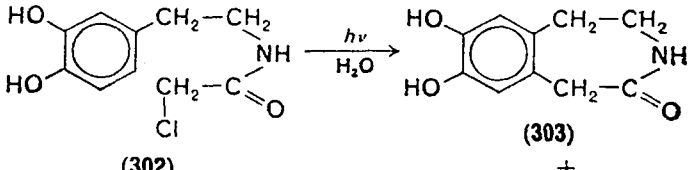


(299)

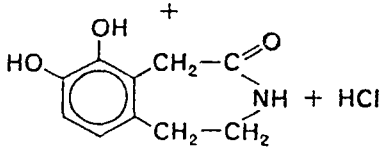
ethylamine (**305**). Remarkably, irradiation of *N*-iodoacetyl-*m*-tyramine results mainly in the reductive elimination of hydrogen iodide, rather than in the cyclization reaction[286]. Presumably the



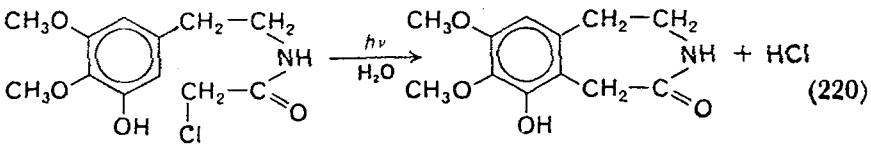
(300) (301) (218)



(302) (303)



(304) (219)



(305) (306) (220)

reductive dehalogenation reaction and the cyclization reaction are competing processes. The reductive dehalogenation probably results from photoinduced homolytic cleavage of the carbon–halogen bond and hydrogen atom abstraction from the solvent. The cyclization reaction, however, does not necessarily involve a photoinduced primary fission of the carbon–halogen bond as has been suggested. The reaction may proceed by electron ejection from the excited aromatic nucleus. Displacement of the halogen would result in intramolecular coupling by overall loss of chloride ions. The final step of proton expulsion would lead to the observed cyclization products. Since electron ejection has also been observed in the photolysis of anisole, the proposed mechanism would explain the

photocyclizations of the *N*-chloroacetyl derivatives of 3,4-dimethoxyphenethylamine as well.

D. Photochemical Reactions of Phenols with Hydrogen Peroxide and with Molecular Oxygen

1. Hydroxylation of phenols

Irradiation of phenols in aqueous solution containing hydrogen peroxide has been found to give *ortho*- and *para*-hydroxylated products[288]. Some examples of the preparatively interesting reactions are listed in Table 13. The mechanism of hydroxylation probably

TABLE 13. Photochemical hydroxylation of phenols in aqueous hydrogen peroxide.

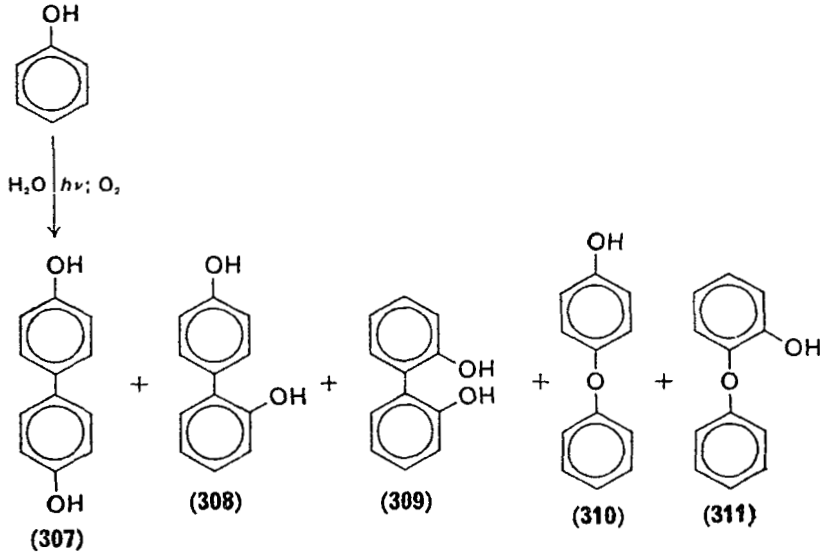
Phenol	Products (% yield, based on consumed phenol)
Phenol	Catechol (26); hydroquinone (14); pyrogallol (5); 1,2,4-trihydroxybenzene (3)
4-Methylphenol	3,4-Dihydroxytoluene (25)
4-Methoxyphenol	4-Methoxycatechol (9); hydroquinone (5)
4-Hydroxybenzoic acid	3,4-Dihydroxybenzoic acid (38); hydroquinone (10)
3-(4-Hydroxyphenyl)-propanoic acid	3-(3,4-Dihydroxyphenyl)-propanoic acid (28)
Tyrosine	3,4-Dihydroxyphenylalanine (20)

involves the oxidation of phenols by photochemically generated OH-radicals, and coupling of OH-radicals with phenoxy radicals. Small amounts of dimeric oxidative coupling products derived from the starting phenols have been detected in the photochemical hydroxylation. Since not only the hydrogen peroxide but also the phenols absorb in the wavelength region (2537Å) employed, the involvement of photochemically generated phenoxy radicals must be considered.

2. Oxidative coupling of phenols

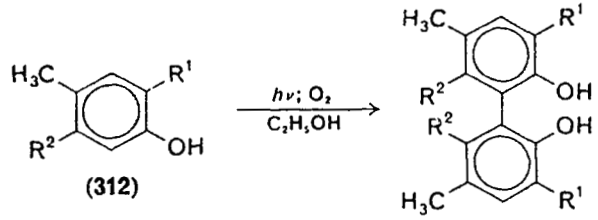
The irradiation at 2537Å of phenols, cresols and dihydroxybenzenes in oxygenated aqueous solution has been studied in detail[239a]. A multitude of products deriving from homolytic carbon–carbon coupling, carbon–oxygen coupling and hydroxylation reactions, is formed under these conditions. Thus, phenol gives 4,4-di-hydroxybiphenyl (**307**), 2,4-dihydroxybiphenyl (**308**), 2,2′-dihydroxybiphenyl (**309**), as well as traces of *p*-phenoxy-phenol (**310**), *o*-phenoxyphenol (**311**), hydroquinone and catechol (reaction 221).

Synthetically more interesting results were obtained with higher substituted phenols[289, 289a]. Photochemical autoxidation of 2,6-dimethylphenol in alcohol solution gives 4,4′-dihydroxy-3,3′-5,5′-tetramethylbiphenyl in 45–75% yield. The formation of 3,3′-5,5′-tetramethyldiphenoquinone under these conditions has not been observed, probably because diphenoquinones can be photochemically



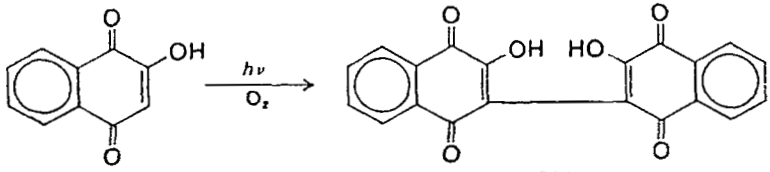
(307) (308) (309) (310) (311) (221)

reduced, even in the presence of oxygen[239a]. Substituted 2,2′-dihydroxybiphenyls (**313a**) and (**313b**) have been obtained in good



(312) (313) (222)

a: $R^1 = CH(CH_3)_2$; $R^2 = CH_3$ b: $R^1 = CH_3$; $R^2 = H$



(314) (315) (223)

yield by photochemical autoxidation of phenols **312a** and **312b**, respectively (reaction 222). Likewise, irradiation of 2-hydroxy-1,4-naphthoquinone (**314**) in water in the presence of oxygen gives the dehydrodimer **315** (reaction 223)[290]. The reaction apparently involves *ortho* carbon–carbon coupling of a photochemically generated enoxy radical.

3. Dye-sensitized oxidation of phenols

Photochemical autoxidation of phenols in the presence of sensitizers such as fluorescein, eosin, Rose Bengal or erythrosin are generally carried out under conditions where only the dye absorbs the light. These oxidations often are rather complex. It has been shown that the photoexcited triplet state dye D* can react with the phenol to give the phenoxy radical in a straightforward homolytic dehydrogenation (reaction 224)[291, 292]. D* can also react with

$$D^* + C_6H_5OH \longrightarrow DH^{\cdot} + C_6H_5O^{\cdot} \qquad (224)$$

molecular oxygen to give singlet oxygen (reaction 225)[293]. However,

$$D^* + O_2{}^{(3)} \longrightarrow D + O_2{}^{(1)} \qquad (225)$$

published data strongly suggest that singlet oxygen does not react efficiently with simple phenols.

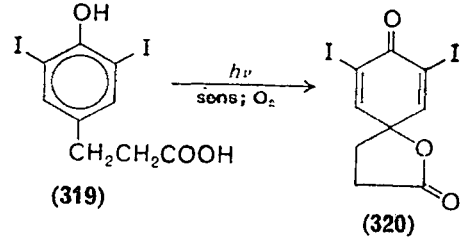
The only products obtained in very low yield in the dye-sensitized oxidation of 2,6-di-*t*-butyl-4-methylphenol (**316**) in methanol solution are the α-methoxy-*p*-cresol (**317**) and the hydroperoxy compound **318** (reaction 226)[294]. The formation of **317** most likely in-

(316) (317) (318) (226)

volves the ground state addition of methanol to the quinone methide, suggesting that the disproportionation of the phenoxy radical competes with the addition of molecular oxygen which leads to **318**. The photosensitized oxidation of 3-(3,5-diiodo-4-hydroxyphenyl)-propanoic acid (**319**) in the presence of erythrosin gives a moderate yield of the spirolactone **320** (reaction 227)[295], presumably by a process which involves the dehydrogenation of **319** by the photoexcited dye, and reaction of the phenoxy radical with ground state oxygen. Thus, there is no evidence that singlet oxygen is involved

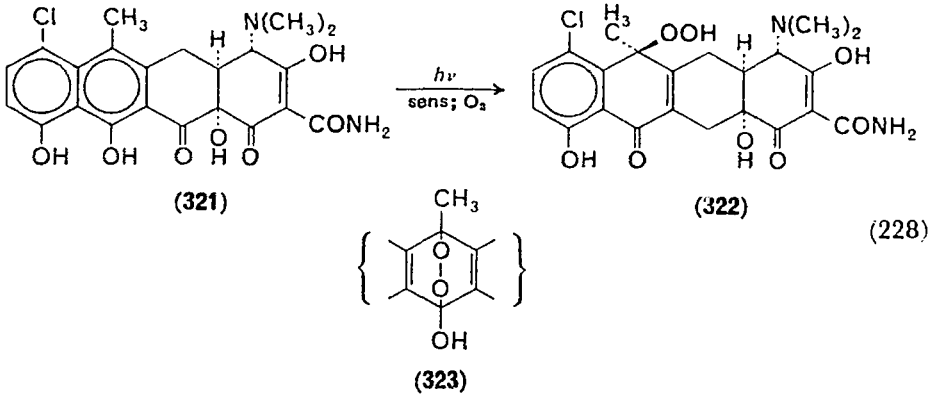
in the photochemical autoxidation of simple phenols. (See References 295a and 295b for recent results.)

Remarkably clean dye-sensitized oxidations obviously involving singlet oxygen have been observed with phenols of the tetracycline series[296, 297]. For instance, tetracycline **321** upon photooxidation in



(319) (320) (227)

benzene solution containing 3,4-benzopyrene gives the hydroperoxide **322** in high yield and high stereospecificity (reaction 228). It is conceivable that **322** is formed by rearrangement of an intermediate peroxide (**323**) which could be the product of a photochemical diene synthesis with singlet oxygen.



(321) (322) (228)

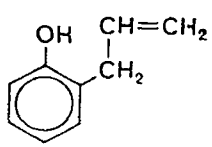
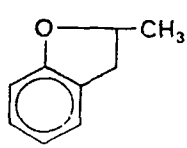
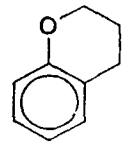
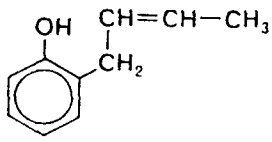
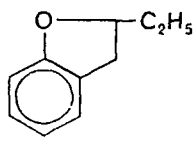
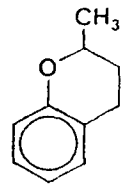
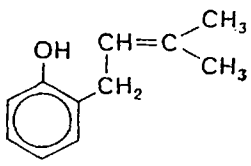
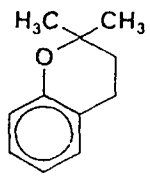
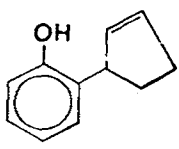
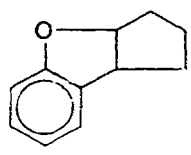
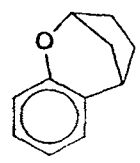
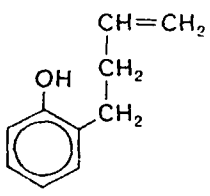
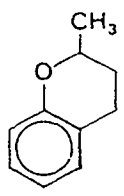
(323)

E. *Photochemical Addition Reactions of Phenols*

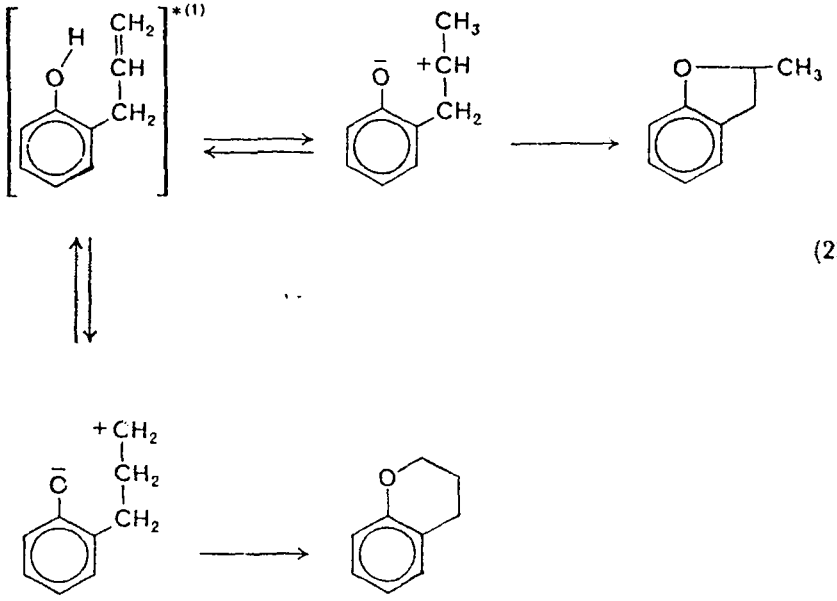
1. Intramolecular addition of phenols to carbon–carbon double bonds

The intermolecular photochemical addition of phenols to olefins apparently is a very inefficient process[298]. However, upon irradiation in benzene, 2-allylphenols (see Table 14) undergo an intramolecular addition reaction to give fair yields of coumarans and chromans[298, 299]. Ring-substituted 2-allylphenols as well as 2-(but-3-enyl)phenol also react photochemically[299]. However, 2-propenylphenol cannot be cyclized by irradiation under similar conditions.

TABLE 14. Intramolecular photochemical addition of phenols to olefins

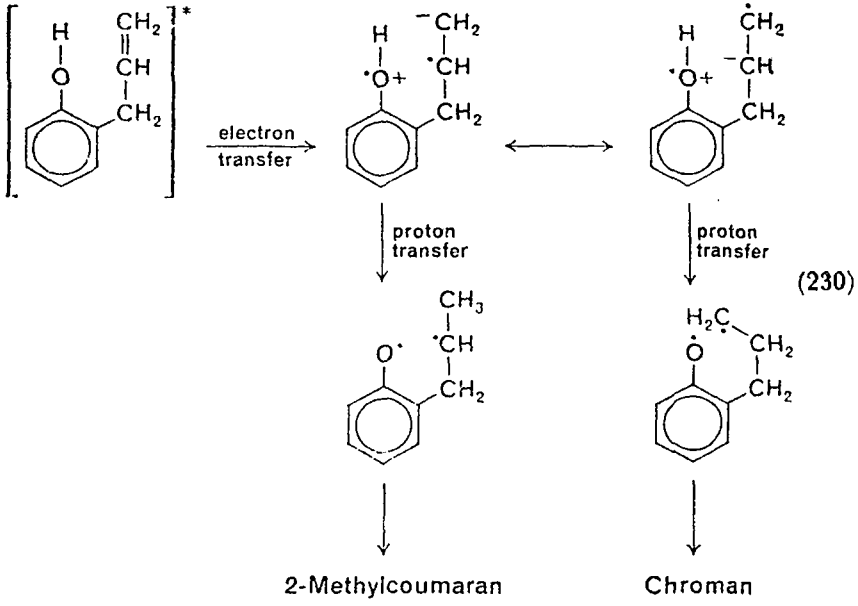
Starting phenol	Products A	Products B	Ratio Yield (%)	Ratio A : B
			35	90:10
			52	30:70
		Unidentified	33	90:10
			30	66·5:33
		Unidentified	31.5	80:20

All photochemical cyclization reactions have been found to occur predominantly in Markovnikov direction. Photolysis of deuterium labelled 2-allylphenol revealed that the hydroxyl hydrogen is transferred to the olefinic side-chain. It has been suggested[299] that cyclization proceeds by intramolecular transfer of a proton to the olefin from the excited singlet state phenol (reaction 229). Although this mechanism has the virtue of simplicity, the protonation of an olefin



(229)

by such a weak acid is doubtful. The participation of phenoxy radicals in the cyclization reaction should be considered instead. Thus a homolytic mechanism (reaction 230), involving electron transfer from the photoexcited phenol to the carbon–carbon double bond, followed by proton transfer and subsequent intramolecular

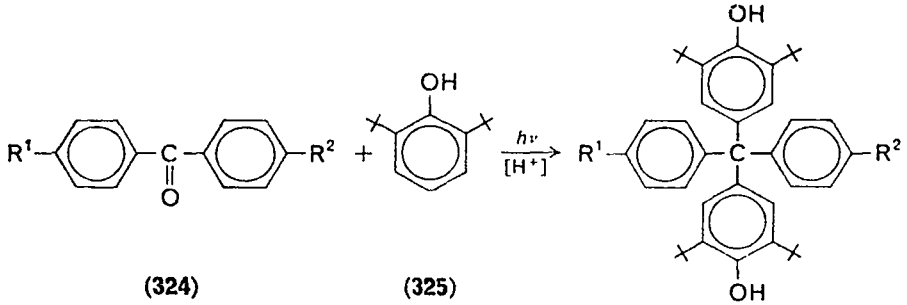


(230)

radical coupling, explains the observed products and related results obtained on the photolysis of 2-allyl-substituted aryl formates[298] equally well.

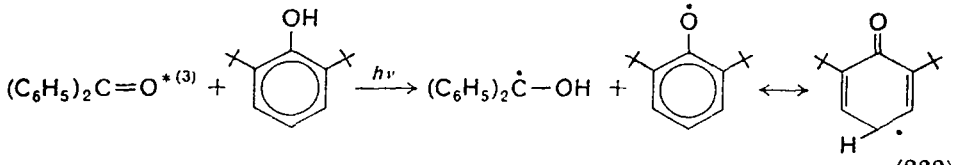
2. Sensitized addition of phenols to quinone methides

The reaction of photoexcited benzophenones **324** with 2,6-di-*t*-butylphenol (**325**) in methanol solution containing a small amount of mineral acid leads to 4,4'-dihydroxytetraphenylmethanes (**326**) (reaction 231)[300]. The mechanism of this reaction involves the

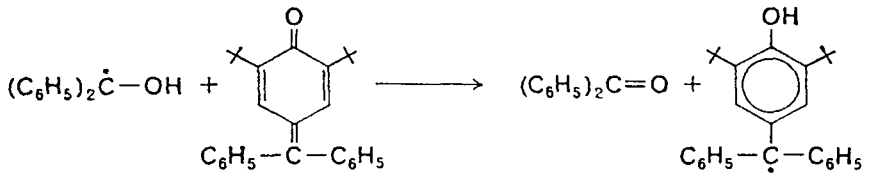


(324) **(325)** **(326)** (231)

benzophenone-sensitized addition of 2,6-di-*t*-butylphenol to the intermediately generated quinone methide 3,5-di-*t*-butylfuchsone probably according to reactions (232–234)[301].

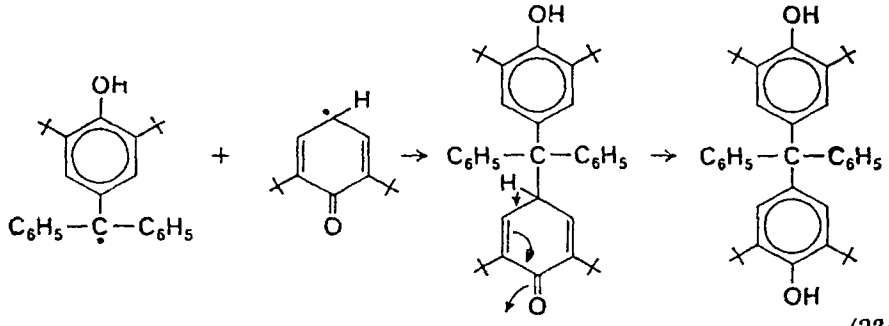


(232)



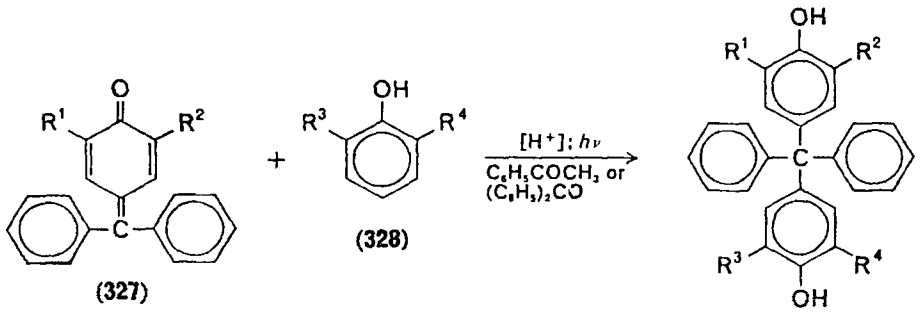
(233)

Apparently, in the presence of quinone methides, the hydrogen atom transfer reaction from diphenylhydroxymethyl radicals regenerating benzophenone competes favourably with intermolecular coupling and dimerization reactions. In the addition reaction, benzophenone can be replaced by acetophenone as a sensitizer[302].



(234)

A variety of 2,6-disubstituted phenols and substituted α,α-diphenylquinone methides have been applied in reaction (235) leading to tetraphenylmethanes **329** (see Table 15). The noted advantageous effect of mineral acid presumably consists in the catalysis of the



(235)

TABLE 15. Photosensitized addition of phenols to quinone methides according to reaction (235).

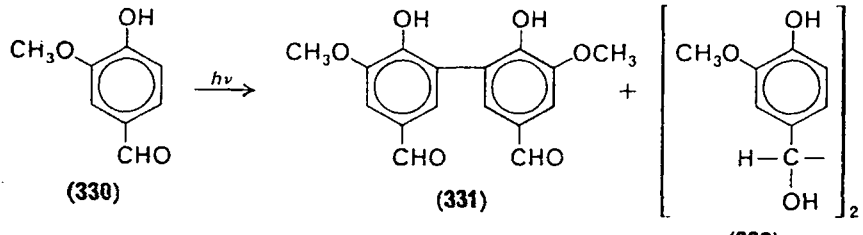
R^1	R^2	R^3	R^4	Yield (%)
-*t*Butyl	*t*-Butyl	*t*-Butyl	*t*-Butyl	94
Cyclohexyl	Cyclohexyl	*t*-Butyl	*t*-Butyl	80
Cyclohexyl	Cyclohexyl	Cyclohexyl	Cyclohexyl	65
Isopropyl	Isopropyl	*t*-Butyl	*t*-Butyl	73
Isopropyl	Isopropyl	Isopropyl	Isopropyl	74
Methyl	Phenyl	*t*-Butyl	*t*-Butyl	90
Phenyl	Phenyl	*t*-Butyl	*t*-Butyl	90
Phenyl	*t*-Butyl	*t*-Butyl	*t*-Butyl	91
Phenyl	*t*-Butyl	Phenyl	*t*-Butyl	89
Phenyl	Phenyl	Phenyl	*t*-Butyl	88
Phenyl	Phenyl	Phenyl	Phenyl	60

final tautomerization step in reaction (234) and possibly in the suppression of the photochemical reaction of the aromatic ketone with the alcohol used as solvent.

The limitation of the reaction to 3,5-di-substituted α,α-diphenylquinone methides and the good yields of 4,4'-dihydroxytetraphenyl methanes obtained when 2,6-di-*t*-butylphenol is employed suggest that the stability of both the 4-hydroxytriphenylmethyl radical and the phenoxy radical are essential factors in the photosensitized addition of phenols to quinone methides[301].

F. Photochemical Reactions of Aryl Ketones with Phenols

Although the photochemical reactions of aromatic carbonyl compounds with alcohols have been the subject of numerous studies ever since the appearance of the classical paper by Ciamician and Silber[41] in 1901, the photolysis of carbonyl compounds in the presence of phenols had received little attention. This is surprising since Ciamician and Silber reported that irradiation of a solution of vanillin (**330**) in ethanol, ether or acetone leads to dehydrodivanillin



(330) (331) (332)

(236)

(**331**). The fate of the hydrogen remained unknown. It appears reasonable to assume that the reaction involves the intermolecular oxidative attack on the phenolic hydroxyl group by the photoexcited aldehyde, and that hydrovanilloin (**332**) accompanies the formation of **331** (reaction 236). The reaction suggests that phenols are better hydrogen donors for photoexcited carbonyl compounds than alcohols. This assumption is supported by the spectroscopic investigation by Bäckström and Sandros[303], who found that phenols quench the phosphorescence of biacetyl in benzene solution about ten thousand times more efficiently than alcohols (see Table 16). (For a more recent spectroscopic investigation see References 304 and 305.)

Photochemical reactions of aromatic ketones with phenols have been investigated recently[91, 92, 214, 300, 301, 302]. The dehydrogenation of the phenol by the photoexcited ketone appears to be a general

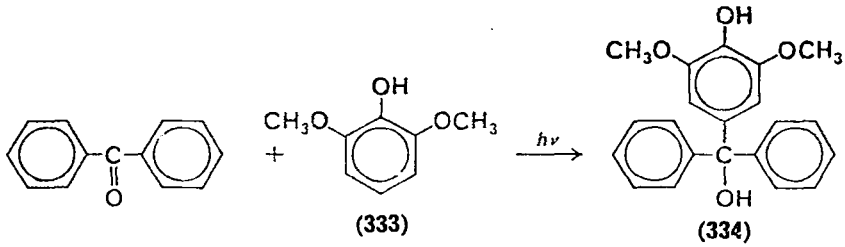
reaction. The type of product obtained, however, has been found to depend on both the structure of the ketone and the phenol participating in the dehydrogenation reaction.

TABLE 16. Quenching constants for the photochemical reaction of biacetyl with hydroxyl compounds.

Hydroxyl compound	Quenching constant in l $mole^{-1}$ sec^{-1}
Methanol	$2{\cdot}6 \times 10^2$
Isopropanol	$2{\cdot}7 \times 10^3$
Benzyl alcohol	$6{\cdot}9 \times 10^3$
Phenol	$8{\cdot}9 \times 10^7$
Resorcinol	$2{\cdot}7 \times 10^8$
Hydroquinone	$5{\cdot}3 \times 10^9$

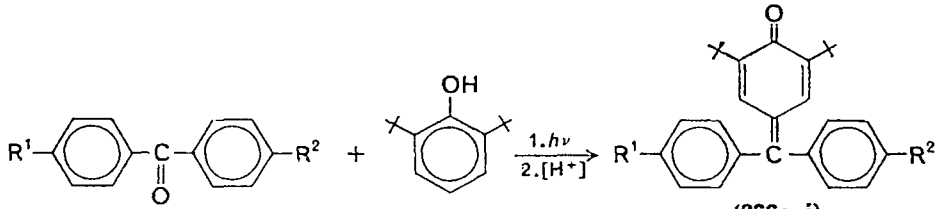
I. Intermolecular coupling reactions

Photoexcitation of benzophenone in acetone containing 2,6-dimethoxyphenol (**333**) smoothly leads to 3,5-dimethoxy-4-hydroxytriphenylcarbinol (**334**)[302]. Other 2,6-disubstituted phenols, such as



(237)

diisopropyl-, dicyclohexyl- or di-*t*-butylphenol, react with benzophenone and many substituted benzophenones (**335a–i**) in the same manner. The 4-hydroxytriphenylcarbinols thus formed readily eliminate water in an acid-catalysed dark-reaction (reaction 243) to give substituted fuchsones (**336a–i**) in good yields (reaction 238 [302]).



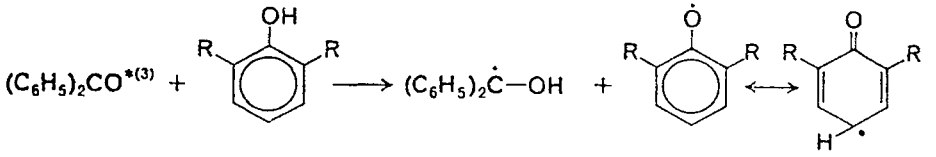
(238)

	R^1	R^2	Yield %
a	H	H	47
b	H	CH_3	57
c	H	Cl	52
d	H	Br	65
e	H	OH	51
f	H	$COOCH_3$	54
g	CH_3	CH_3	41
h	Cl	Cl	50
i	CH_3COO	CH_3COO	63

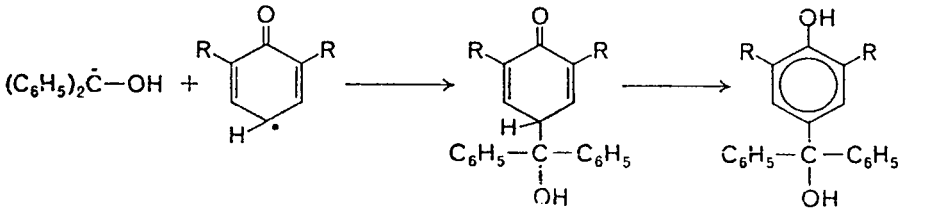
The formation of the 4-hydroxytriphenylcarbinols (reactions 239–242) can be rationalized in terms of hydrogen atom abstraction from the phenol by triplet state ketone to give a phenoxy radical and a

$$(C_6H_5)_2CO + h\nu \xrightarrow[\text{excitation}]{n-\pi^*} (C_6H_5)_2CO^{*(1)} \tag{239}$$

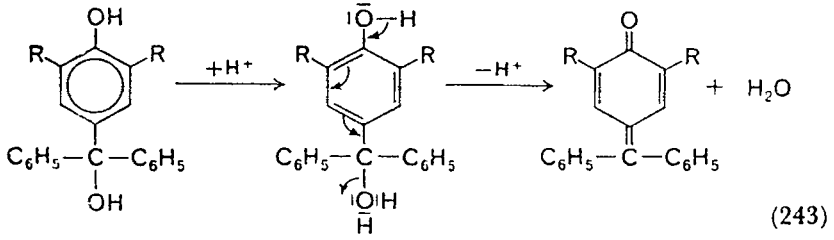
$$(C_6H_5)_2CO^{*(1)} \xrightarrow[\text{crossing}]{\text{intersystem}} (C_6H_5)_2CO^{*(3)} \tag{240}$$



(241)



(242)

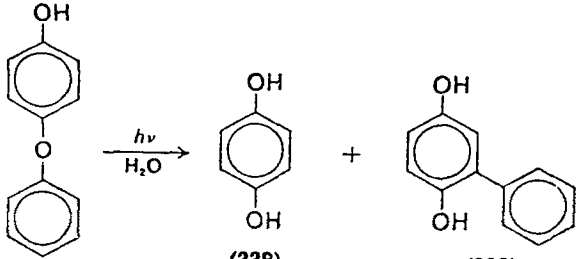


(243)

diphenylhydroxymethyl radical which undergo a coupling reaction. By-products in the photochemical reaction of benzophenones with 2,6-disubstituted phenols may be benzpinacol and 3,3',5,5'-tetra-substituted 4,4'-dihydroxydiphenyls. The photochemical reaction leading to 4-hydroxytriphenylcarbinols proceeds smoothly only with phenols having bulky substituents in the 2,6-position. This suggests that a long lifetime of the phenoxy radicals is essential for good yields of mixed coupling products. Less stable phenoxy radicals formed by oxidation with photoexcited benzophenones could dimerize or polymerize by either C–C or C–O coupling.

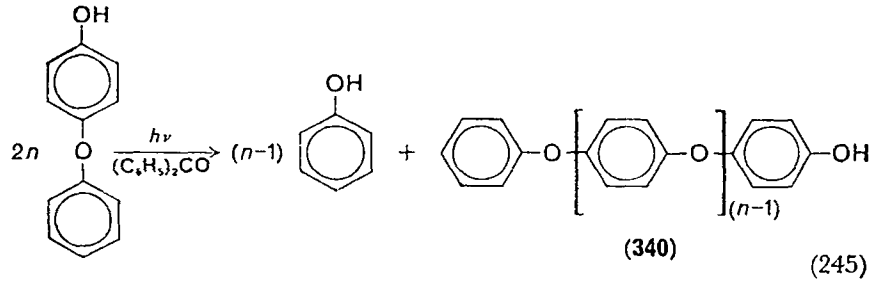
2. Photosensitized disproportionation of 4-phenoxyphenols

Direct irradiation of 4-phenoxyphenol (**337**) at 2537Å in aqueous solution leads to hydroquinone (**338**) and 2,5-dihydroxydiphenyl (**339**; reaction 244). Thus, excitation of **337** results in scission of the diphenyl ether linkage rather than in cleavage of the O–H bond[239b].



(337) (338) (339) (244)

The reaction of photoexcited benzophenone with *p*-phenoxyphenol takes an entirely different course, obviously involving the formation of *p*-phenoxyphenoxy radicals[92]. Irradiation of benzophenone (20 mole %) in a solution of *p*-phenoxyphenol in benzene, using only light of wavelengths >2900Å results in a smooth disproportionation reaction (245) leading to phenol and a poly-*p*-phenylene ether **340** (see Figure 11). Other hydroquinone monoaryl ethers



(340) (245)

such as *p*-(*p*-phenoxyphenoxy)-phenol and *p*-(2,6-dimethylphenoxy)-2,6-dimethylphenol react in the same manner, giving monomer and oligomer in excellent yields. The disproportionation can be explained

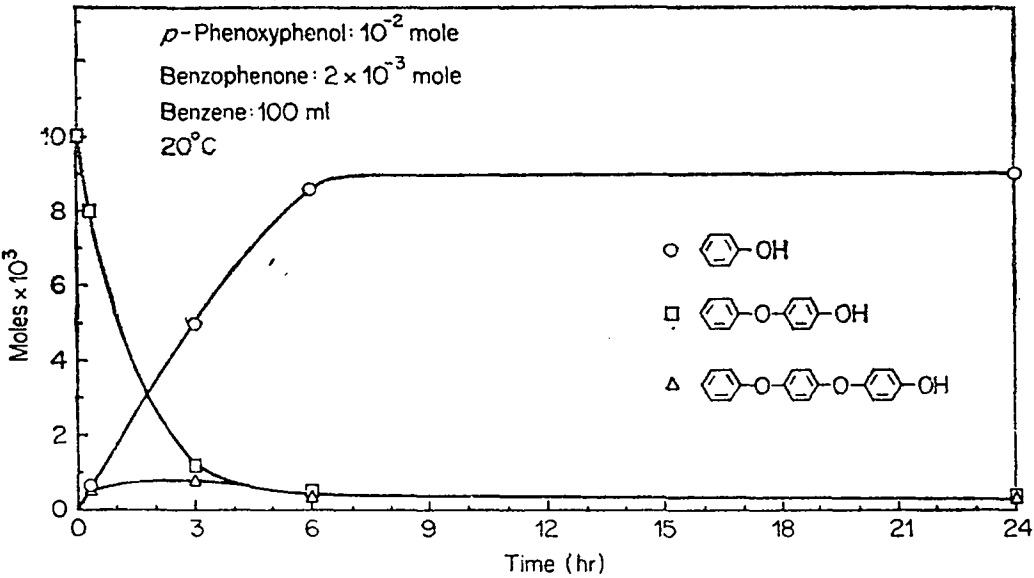


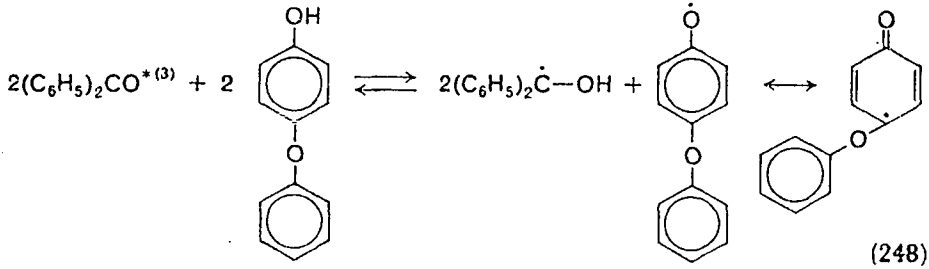
FIGURE 11. Benzophenone-sensitized disproportionation of 4-phenoxyphenol. [Reproduced, by permission, from reference 92.]

by a mechanism (reactions 246–252) in which photoexcited benzophenone abstracts a hydrogen atom from **337** to give the diphenylhydroxymethyl radical and a phenoxy radical. Two phenoxy radicals

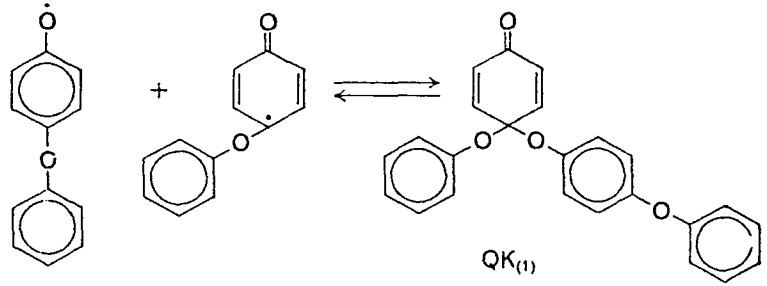
$$(C_6H_5)_2CO + h\nu \xrightarrow[\text{excitation}]{n-\pi^*} (C_6H_5)_2CO^{*(1)} \qquad (246)$$

$$(C_6H_5)_2CO^{*(1)} \xrightarrow[\text{crossing}]{\text{intersystem}} (C_6H_5)_2CO^{*(3)} \qquad (247)$$

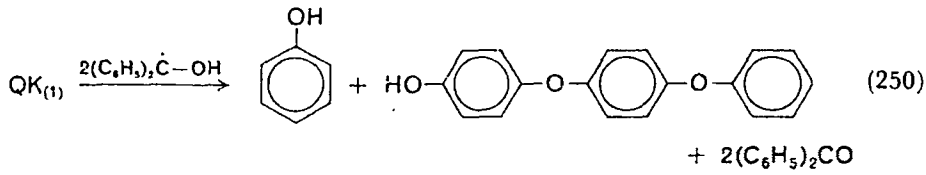
couple to give a quinone ketal (QK_1) which is reduced by the diphenylhydroxymethyl radical to give phenol and a trimer, benzophenone being regenerated (reaction 250). Oxidation of the trimer then would lead to monomer and tetramer. Termination steps not regenerating benzophenone conceivably involve *ortho* C–C or C–O coupling of phenoxy radicals. It was originally suggested that an energy transfer from photoexcited ketone to the quinone ketal QK_1 precedes the reduction reaction; however, recent results[301] suggest that the ground state quinone ketal can be reduced by diphenylhydroxymethyl radicals.



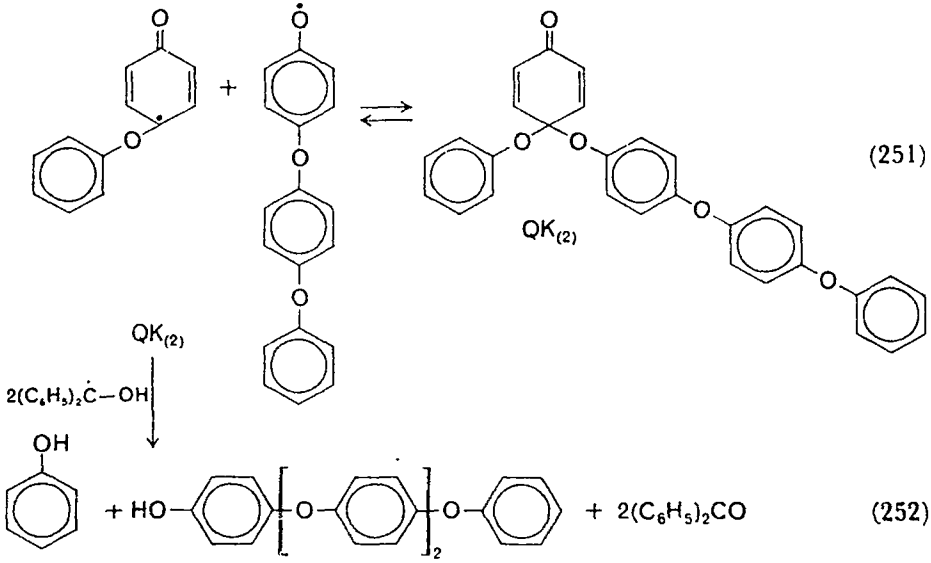
(248)



(249)



(250)



(251)

(252)

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The Chemistry of The Hydroxyl Group
Edited by Saul Patai

CHAPTER 17

The radiation chemistry of the hydroxyl group

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I. INTRODUCTION

Some 300 papers have been devoted to the study of the effects of ionizing radiation on pure compounds containing the hydroxyl group and several more to aqueous solutions of such compounds. In this review we shall only consider pure organic compounds and consequently treat neither water nor aqueous solutions.

The growth of the subject has been extremely rapid in the last five years (Figure 1) and more than three-quarters of the published

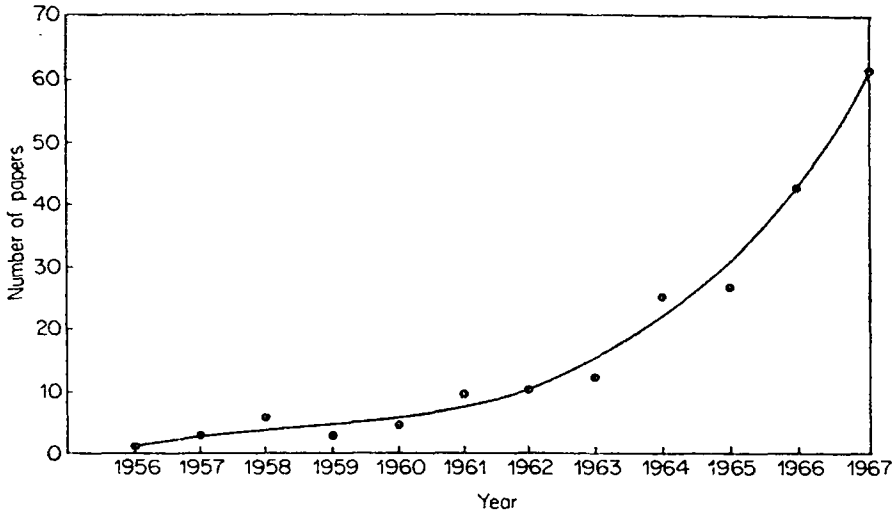


FIGURE 1. Annual publications on the radiation chemistry of the hydroxyl group.

data has appeared since 1962. The main area of exploration has been the radiolysis of saturated aliphatic alcohols which accounts for more than 90% of the papers which have appeared. Furthermore the overwhelming majority of studies have been carried out in the liquid phase at room temperature. Consequently, what follows is essentially a review of the radiation chemistry of pure, liquid, aliphatic alcohols. The effect of phase is treated under a separate heading and short sections are devoted to unsaturated alcohols, polyhydric alcohols and aromatic hydroxyl compounds.

This chapter may be subdivided into three main parts:

(i) Phenomenological observations of the eventual end products.
(ii) Studies of the reactive intermediates involved in the reactions.
(iii) The effects of variation of certain parameters on the mechanism.

It is felt that this is a logical sequence which follows the chronological development of the subject and which also seems to provide answers to the initiate in the order in which he might be expected to ask questions. What are the overall effects of irradiation; how are they brought about; how do environmental factors affect them.

II. HISTORICAL DEVELOPMENT

As early as 1913 Kailan[1] showed that 'the chemical action of the penetrating radium radiation' on ethanol in the presence of air led to the production of water, acids and peroxides. Some years later he extended this study to isobutyl and benzyl alcohols[2]. At about the same time McLennan and Patrick[3] published their findings on the action of high-speed cathode rays on the simpler alcohols. The most important liquid products were formaldehyde in the case of methanol and acetaldehyde in the case of ethanol. As gaseous products they identified hydrogen, carbon monoxide, carbon dioxide, methane and, in the case of ethanol, ethane.

In the next 20 years only two more articles appeared[4] and it was only in the middle fifties that momentum began to build up. Breger[4] showed that the principal gaseous product in the α-particle and deuteron irradiation of alcohols was hydrogen and Skraba and coworkers[5] studied the decomposition of $^{14}CH_3OH$ under the influence of its own radiation.

The first comprehensive investigation of the radiolysis of alcohols was that of McDonell and Newton[6], and even today it may be considered as the most extensive study yet undertaken. They established the important principle that the major products from *n*-alcohols are hydrogen, aldehyde and glycol; *s*-alcohols give both aldehydes and ketones and *t*-alcohols give ketones but not aldehydes.

This investigation was followed by studies on the effect of dose[7], linear energy transfer[8], oxygen[9, 10] and other solutes[11, 12] so that by 1960 a rough picture of the reaction mechanism had evolved. Since then the radiolysis of alcohols has been intensively studied and many aspects of the mechanism are well established although some problems remain to be solved.

III. METHODOLOGY AND DEFINITIONS

The approach towards an understanding of the processes underlying the radiation chemistry of the hydroxyl group has undergone a considerable change in the past fifteen years. Where earlier workers

aimed at determining the complete product distribution the accent has been shifted to study only one or two products and their dependency on certain parameters in an endeavour to characterize the elementary reactions in which they are produced. Although the latter approach has decided advantages, it is nevertheless true that a knowledge of product distribution should be available before mechanistic interpretations are undertaken. Thus, in the study of a new compound, or one for which conflicting data have been obtained, the following approach should be followed:

(a) The compound should be purified as rigorously as possible and irradiated in the absence of air at the lowest practical dose to avoid secondary effects.

Definition: Dose refers to the amount of energy absorbed by the compound and is expressed in eV/gm (ml) or rads where 1 *rad* $= 6 \times 10^{13}$ *eV/gm.*

(b) A careful study should be made to identify *all* the products of the radiolysis employing a variety of analytical conditions.

(c) The absolute yields should be established under these conditions.

(d) The effect of dose and the concentration of potential impurities on these yields should be established in order to derive initial yields.

Definition: Initial yields refer to values obtained from a pure compound at conversions which are too low for the products to enter into secondary reactions. Radiation chemical yields are expressed in molecules formed per 100 *eV of energy absorbed by the pure compound and are referred to as G-values.*

(e) The effect of added solutes which are known to scavenge suspected intermediates should be followed.

Definition: A scavenger is a solute which reacts rapidly with intermediates (ions or free radicals) in such a way as to change the yield of products which are formed in reactions of these intermediates in the absence of solute. Product yields, which are affected by the addition of solutes, are referred to as 'radical or scavengeable yields' and those which are independent of added solutes, as 'molecular or unscavengeable yields'.

(f) The results should then be interpreted making use of thermochemical data for bond strengths and heats of reaction, photochemical data for postulating possible free radical reactions, mass spectrometry for suggesting possible ionic reactions, etc. The results of this interpretation should be summarized in a plausible reaction mechanism which explains the formation of all products.

(g) The validity of the various elementary reactions should be rigor-

ously established. The methods involved are usually kinetic, such as the determination of rate constants and comparing these with known values, or observing the decay of an intermediate and the simultaneous growth of a product. Both direct and indirect methods are available, some examples of the former being pulse radiolysis[13] and electron paramagnetic resonance[14] and of the latter competition kinetics[15] and kinetic salt effects[16].

IV. STABLE END PRODUCTS

A. Primary Alcohols

The production of hydrogen, aldehyde with the same carbon number as the alcohol and vicinal glycol with double the carbon number is characteristic of all the normal alcohols investigated. In the case of methanol and ethanol these three products are found in greater yields than any other products but as the chain length of the alcohol is increased a larger number of 'major' products are formed.

The addition of solutes which act as traps for free radicals (scavengers) drastically reduces the hydrogen yield and completely suppresses the glycol yield but has a much less pronounced effect on the aldehyde yield. The residual yields of aldehyde and hydrogen are approximately equal which indicates that these contributions to the total yield are due to the same process which may be formulated as follows:

$$RCH_2OH \xrightarrow{\sim\sim} RCHO + H_2 \qquad (1)$$

The remaining yields and the whole of the glycol yield must then be attributed to free radical intermediates. A mechanism consistent with the observation that vicinal glycols are formed is scission of an α-carbon–hydrogen bond with the formation of a hydrogen atom and an α-hydroxyalkyl radical.

$$RCH_2OH \xrightarrow{\sim\sim} RCHOH^{\cdot} + H^{\cdot} \qquad (2)$$

From studies of aqueous solutions of deuterated alcohols it is known that hydrogen atoms abstract hydrogen readily from the α-carbon atom[17].

$$H + RCH_2OH \longrightarrow H_2 + RCHOH^{\cdot} \qquad (3)$$

The consequence of reactions (2) and (3) is thus the formation of 1 molecule of hydrogen and 2α-hydroxy radicals which cannot react with the substrate and must react with each other. Combination (dimerization) will then explain the vicinal glycol yield (4); and

exchange of a hydrogen atom (disproportionation) accounts for the scavengeable aldehyde yield (5).

$$2\ RCHOH^{\cdot} \longrightarrow \begin{matrix} RCHOH \\ | \\ RCHOH \end{matrix} \qquad (4)$$

$$2\ RCHOH^{\cdot} \longrightarrow RCHO + RCH_2OH \qquad (5)$$

The stoichiometry of reactions (2) to (5) requires that the scavengeable hydrogen yield must equal the sum of the scavengeable aldehyde plus glycol yields. Furthermore, as the unscavengeable hydrogen and aldehyde yields are equal a similar equality is required for the total hydrogen yield and the total aldehyde plus glycol yields. This mechanistic requirement has already been demonstrated experimentally in the radiolyses of methanol, ethanol and propanol as shown in Table 1.

TABLE 1. Total (T) and scavengeable (S) yields of products in the radiolysis of *n*-alcohols.

Alcohol	$G(H_2)^T$	$G(ald)^T$	$G(glycol)^T$	$G(H_2)^S$	$G(ald)^S$	$G(glycol)^S$
Methanol[18]	5·4	2·15	3·7	3·7	0	3·7
Ethanol[19]	5·0	3·2	1·7	3·25	1·5	1·7
Propanol[20]	4·4	2·9	1·5	2·60	1·0	1·5

Inspection of the last two columns of the table shows that, in contrast to ethanol and propanol, the aldehyde yield from irradiated methanol is unscavengeable. The glycol yield, on the other hand, is scavengeable which indicates that the α-hydroxymethyl radical dimerizes but does not disproportionate while the higher homologues appear to undergo both processes at approximately the same rate. The reasons for these differences are not apparent and further work in this direction would be most interesting.

Data on the higher alcohols regarding total yields is sketchy and nonexistent for the radical yields. It does, however, seem that the stoichiometry for the total yields is not obtained any longer, as shown in Table 2.

These results should however be treated circumspectly as they all refer to high dose irradiation unlike the data in Table 1. As will be shown later, certain product yields are dose dependent and initial yields can only be determined at low doses. The aldehyde yields, in particular, are very sensitive to dose and it seems likely that the

TABLE 2. Product yields in the radiolysis of higher *n*-alcohols.

Alcohol	$G(H_2)$	G(ald)	G(glycol)	Radiation	Ref.
Butanol	4·18	0·62	0·10	γ	21
Butanol	3·59	1·5	0·92	α	6
Octanol	3·48	0·7	0·56	α	6
Decanol	3·47	1·0	0·51	α	6

values in Table 2 are substantially lower than the initial yields. The glycol yields, on the other hand, are much less affected by dose variation and it seems as if the decrease in yields with increasing chain length may be a true effect.

There are two possible explanations for this effect. In the first place it might be due to increasing importance of reaction (5) at the expense of reaction (4), as it seems to be a general phenomenon that large radicals disproportionate rather than dimerize while the converse is true for small radicals[21]. Secondly, it may be possible that hydrogen abstraction (reaction 3) from the higher alcohols is not specifically confined to the α-carbon atom and that a range of hydroxy-alkyl radicals are formed. This is consistent with the observation that with increasing chain length the influence of the hydroxyl group on the α-carbon–hydrogen bonds is lessened and the C–H bond strengths at the various carbon atoms are not very different. The consequence of the formation of a number of isomeric hydroxy-alkyl radicals is the formation of a range of glycols other than vicinal glycols. As it has not been demonstrated that the measured yield refers to total glycols it is possible that the values quoted only refer to the vicinal glycol contribution.

In addition to the three products referred to in the preceding section, hydrocarbons are also produced when alcohols are irradiated. They are found in low yields in methanol and ethanol but with increasing chain length these yields increase as shown in Table 3.

Table 3 shows that the hydrocarbon occurring in highest yield always contains one carbon atom less than the alcohol from which it was produced. Thus the major hydrocarbon product from ethanol is methane, from propanol it is ethane and from butanol it is propane. This indicates that cleavage of the α-carbon–carbon bond is an important process. Furthermore the yield for the cleavage reaction increases with increasing chain length; the effect being most pronounced on going from ethanol to propanol. Thus $G(C_2H_4) + G(C_2H_6) = 2{\cdot}35$ in the case of propanol.

TABLE 3. Hydrocarbon yields in the radiolyses of alcohols.

Alcohol	CH_4	C_2H_4	C_2H_6	C_3H_6	C_3H_8	C_4H_8	C_4H_{10}	Ref.[a]
Methanol	0·43	0·004	0·006	—	—	—	—	22
Ethanol	0·6	0·14	0·24	—	0·01	—	0·004	23
Propanol	0·14	0·35	2·0	0·13	0·25	0·01	0·01	24
Butanol	0·10	0·18	0·09	0·29	1·87	0·09	0·28	25
Octanol	0·02	0·03	0·03	0·01	0·02	0·01	0·01	6
Decanol	0·02	0·05	0·04	0·01	0·03	0·01	0·01	6

[a] Other values for these yields are to be found in the literature, for the C_1–C_4 alcohols. The present data refer to low dose yields from carefully purified material which we consider to be more reliable. The C_8 and C_{10} data refer to high dose α-irradiation but represent the only available results.

The cleavage of a terminal methyl group from the rest of the molecule does not appear to be an important effect when higher alcohols are irradiated as indicated by the low methane yields in propanol, butanol, octanol and decanol. The yield in ethanol is substantially higher but of course this removal of the terminal methyl group also corresponds to α-C–C scission. The high methane yield in methanol cannot be compared to yields in other alcohols as no C–C bonds exist in this material.

It may be that cleavage of C–C bonds, in general, is relatively unimportant when the α-carbon bond is not involved but complete hydrocarbon analyses for a wider range of alcohols are needed before this suggestion can be confirmed.

Cleavage of the C–O bond to yield hydrocarbon fragments with the same carbon number as the alcohol from which they are produced takes place to some extent. There is no indication that increasing chain length decreases the importance of this process—$G(C_4)$ from butanol is 0·37, $G(C_3)$ from propanol is 0·38, $G(C_2)$ from ethanol is 0·38 and $G(CH_4) = 0·43$ in methanol.

The formation of hydrocarbons with a higher carbon number than the parent alcohol occurs only to a very limited extent. Thus, for example, the yield of ethane in methanol—probably due to reactions (6) and (7)—is only 0·006 indicating that (7) does not compete favourably with other reaction possibilities such as (8).

$$CH_3OH \longrightarrow\!\!\!\!\sim\!\!\!\!> CH_3^{\cdot} + OH^{\cdot} \qquad (6)$$

$$2\,CH_3^{\cdot} \longrightarrow C_2H_6 \qquad (7)$$

$$CH_3^{\cdot} + CH_3OH \longrightarrow CH_4 + CH_2OH^{\cdot} \qquad (8)$$

Complementary to the formation of hydrocarbons by C–C and C–O scission is the production of oxygenated minor products. These

can be attributed to the hydroxyl and hydroxy-alkyl fragments produced in the scission. If these fragments are capable of reaction with the substrate by hydrogen abstraction the products are water (equations 9, 10) or alcohols of lower carbon number than the parent alcohol (equations 11, 12).

$$CH_3CH_2OH \longrightarrow\!\!\!\!\sim\!\!\!\!> CH_3CH_2^{\cdot} + OH^{\cdot} \quad (9)$$

$$OH^{\cdot} + CH_3CH_2OH \longrightarrow CH_3CHOH^{\cdot} + H_2O \quad (10)$$

$$CH_3CH_2OH \longrightarrow\!\!\!\!\sim\!\!\!\!> CH_3^{\cdot} + CH_2OH^{\cdot} \quad (11)$$

$$CH_2OH^{\cdot} + CH_3CH_2OH \longrightarrow CH_3OH + CH_3CHOH^{\cdot} \quad (12)$$

The production of water and lower alcohols has been demonstrated in a number of cases as shown in Table 4 (overleaf) and it is to be expected, as more complete product analyses become available, that this will be shown to be a general effect. The high values reported for water in some cases should be treated with caution as recent work has shown that, because of the hygroscopic nature of anhydrous alcohols, the accurate measurement of $G(H_2O)$ is difficult.

The formation of aldehydes and glycols shown in Table 4 shows that hydrogen abstraction is not the only fate of hydroxy-alkyl radicals, formed by C–C cleavage, in these systems. These products can be ascribed to reactions between the various radicals produced—disproportionation leading to aldehydes (13) and dimerization to glycols (14).

$$CH_2OH^{\cdot} + CH_3CHOH^{\cdot} \longrightarrow HCHO + CH_3CH_2OH \quad (13)$$

$$CH_2OH^{\cdot} + CH_3CHOH^{\cdot} \longrightarrow \begin{matrix} CH_2OH \\ | \\ CH_3CHOH \end{matrix} \quad (14)$$

The hydroxy-methyl radical, in particular, does not seem to undergo abstraction (reaction 12) at all as the product of this reaction, methanol, is only found in low yield in irradiated ethanol and not at all in the higher alcohols. Thermochemical calculations[26] show that the abstraction reactions are endothermic and thus unlikely. This observation, taken in conjunction with the appreciable yields of formaldehyde found in all cases, suggests that if this radical is formed it reacts only in disproportionation reactions such as (13). Contradictory to this is the observation, discussed above, that in methanol the disproportionation reaction between two hydroxymethyl radicals does not take place.

The high yields of formaldehyde from propanol and butanol are noteworthy and support the suggestion, based on hydrocarbon yields,

TABLE 4. Yields of oxygenated minor products in the radiolysis of alcohols.

Alcohol	H_2O	CH_3OH	C_2H_5OH	C_3H_7OH	HCHO	CH_3CHO	C_2H_5CHO	Glycols[a]	Ref.
Methanol	0·93	—	—	—	2·2[b]	—	—	—	6, 22
Ethanol	0·5	0·06	—	—	0·3	3·2[b]	—	0·2	19, 23
Propanol	0·93	—	—	—	1·9	—	2·09[b]	—	6, 20
Butanol	0·37	—	1·47	0·25	1·44	—	—	—	21

[a] Glycols other than vicinal glycols.
[b] Major products in these two alcohols not due to C–O or C–C scission.

that C–C cleavage involving the α-carbon increases with increasing chain length.

In addition to the products listed in Table 4, CO is frequently found in irradiated alcohols. There does, however, seem to be some doubt as to whether this is a primary product as experiments at low doses[28] have failed to reveal its presence and reported yields nearly all refer to high dose irradiation.

B. Branched Alcohols

The only branched alcohols to have received attention are isopropanol and the isomeric butanols. Product yields are listed in Tables 5 and 6 (overleaf).

Comparison of *n*- and iso-butanol values in Table 6 shows that, with the exception of hydrogen and C_3 compounds, product distribution is very similar. Furthermore, the sum $G(H_2) + G(C_3) = 4{\cdot}3$ is the same for both alcohols indicating that the increase in $G(C_3)$ in isobutanol is at the expense of the hydrogen yield. It seems thus that isomeric *primary* alcohols behave very similarly with the exception that α-C–C cleavage is more favoured when the resulting fragment is branched and that this process is in competition with α-C–H cleavage.

The results for isopropanol show that a distinct difference exists between primary and secondary alcohols; the most prominent features being a greatly increased methane yield, the production of acetone and a diminished aldehyde yield, but this should be viewed with caution as more recent results at low doses[29, 30] indicate that $G(H_2)$ values in *n*- and iso-propanol are not significantly different.

The differences between the methane yields from the primary and secondary alcohols can be ascribed to the increased ratio of alkyl groups to hydrogen atoms at the α-carbon atom leading to increased α-C–C cleavage (reaction 15). The radical produced is α-hydroxyethyl which apparently does not abstract hydrogen from the substrate to produce ethanol (reaction 16) but rather disproportionates to acetaldehyde (reaction 17).

$$(CH_3)_2CHOH \longrightarrow CH_3^{\bullet} + CH_3CHOH^{\bullet} \qquad (15)$$

$$CH_3CHOH^{\bullet} + (CH_3)_2CHOH \longrightarrow CH_3CH_2OH + (CH_3)_2COH^{\bullet} \qquad (16)$$

$$CH_3CHOH^{\bullet} + R^{\bullet} \longrightarrow CH_3CHO + RH \qquad (17)$$

($R^{\bullet}$ = any radical in the system)

Despite the increased importance of α-C–C cleavage the scission of the α-C–H bond is still a dominant process (reaction 18) leading

TABLE 5. Product yields in the γ-radiolysis of branched alcohols[21].

Alcohol	H_2	CH_4	C_2	CO	Ether	CH_3CHO	Higher aldehydes	Acetone	MeCOEt	Alcohols	H_2O	Glycol
Isopropanol	3·7	1·5	0·5	0·2	0·3	0·3	—	1·5	—	—	trace	0·2
s-Butanol	2·6	0·5	2·4	0·6	—	0·5	0·1	0·2	0·4	—	trace	0·1
t-Butanol	1·0	3·0	2·9	0·6	0·2	—	—	1·1	—	0·2	0·3	trace
n-Butanol	4·2	0·1	0·7	0·1	--	—	0·6	—	—	1·5	0·4	0·1

TABLE 6. Product yields in the α-radiolysis of branched alcohols[6].

Alcohol	H_2	CO	CH_4	C_2H_4	C_2H_6	C_3H_6	C_3H_8	C_4H_8	C_4H_{10}	H_2O	CH_3CHO	Total aldehyde	Total ketone	Glycol
Isopropanol	2·7	0·1	1·1	—	0·2	0·3	0·1	—	—	0·9	1·0	—	2·0	0·4
Isobutanol	2·8	0·1	0·1	—	—	0·8	0·7	0·1	0·2	0·6	—	1·7	0	0·9
s-Butanol	2·6	0·1	0·4	0·4	0·9	—	0·1	0·2	0·2	0·6	—	1·8	1·1	0·6
t-Butanol	1·2	0·05	1·6	0·1	0·5	—	—	0·3	0·1	1·0	—	—	2·8	0·1
n-Butanol	3·6	0·1	0·1	0·1	—	0·2	0·5	0·1	0·1	0·6	—	1·5	0	0·9

to formation of hydrogen and hydroxy-isopropyl radicals. The predominant fate of the latter is then presumably disproportionation to acetone (reaction 19).

$$(CH_3)_2CHOH \longrightarrow H^{\cdot} + (CH_3)_2COH^{\cdot} \quad (18)$$

$$2\,(CH_3)_2COH^{\cdot} \longrightarrow (CH_3)_2C{=}O + (CH_3)_2CHOH \quad (19)$$

Another striking feature of the isopropanol system is the considerably lower glycol yield as compared to *n*-propanol. This is almost certainly due to steric hindrances in the case of the secondary alcohol and it seems reasonable to expect that this phenomenon is common to all α-branched alcohols.

s-Butanol resembles isopropanol in many respects although the similarity might not be immediately apparent. The methane yield, for example, is much smaller in the former case but this is compensated by the greatly increased $G(C_2)$ yield. Thus, cleavage of a C–C bond is an important process in both cases and it would seem that where the two alkyl groups, attached to the α-carbon, are not identical cleavage of the larger fragment is favoured. A similar effect has been noted in the fragmentation patterns of α-branched alcohols in the mass spectrometer[31].

The oxygenated fragment resulting from the removal of an ethyl radical is, of course, again the α-hydroxy-ethyl radical (reaction 20) which produces acetaldehyde by disproportionation (reaction 17). Intuitively it might then be expected that the CH_4/acetaldehyde ratio in isopropanol and the $C_2H_4 + C_2H_6$/acetaldehyde ratio in *s*-butanol should be the same and this in fact is demonstrated in the γ-radiolysis data.

$$CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HOH \longrightarrow CH_3CH_2^{\cdot} + CH_3CHOH^{\cdot} \quad (20)$$

The total ketone yield is lower in the case of *s*-butanol and this may be partly attributed to the lower yield of hydrogen (Table 5). If this is ascribed to reaction (21) having a lower yield than the corresponding reaction in isopropanol (18) the lower yield of hydroxy-isobutyl radicals will account for the lower yield of methyl

$$CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HOH \longrightarrow CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}OH^{\cdot} + H^{\cdot} \quad (21)$$

$$2\,CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}OH^{\cdot} \longrightarrow CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}{=}O + CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HOH \quad (22)$$

ethyl ketone (reaction 22) in *s*-butanol as compared to acetone (reaction 19) in isopropanol.

The close similarity between the low glycol yields from the secondary alcohols supports the suggestion that dimerization of branched hydroxy-alkyl radicals is subject to steric hindrance.

The only tertiary alcohol investigated, *t*-butanol, represents a further departure from the pattern obtained with *n*-alcohols. Here we find a much lower hydrogen yield, substantial C_1 and C_2 yields and acetone as the only carbonyl compound. These effects can be attributed to the lack of α-C–H bonds and α-C–C cleavage becomes the dominant process (reaction 23).

$$(CH_3)_3COH \longrightarrow CH_3^{\bullet} + (CH_3)_2COH^{\bullet} \qquad (23)$$

The hydroxy isopropyl radical so formed apparently undergoes disproportionation to acetone (reaction 19) almost exclusively, as isopropanol (the product of abstraction) is not found and the yield of glycol (the product of dimerization) is negligible.

It seems possible that methyl radicals abstract both hydrogen atoms (reaction 24) and methyl groups (reaction 25) from *t*-butanol. If these are the only processes responsible for methane and ethane formation, the γ-radiolysis data indicate that the two processes are of equal importance.

$$CH_3^{\bullet} + (CH_3)_3COH \longrightarrow CH_4 + \underset{\displaystyle CH_2}{\overset{\displaystyle (CH_3)_2COH^{\bullet}}{|}} \qquad (24)$$

$$CH_3^{\bullet} + (CH_3)_3COH \longrightarrow C_2H_6 + (CH_3)_2COH^{\bullet} \qquad (25)$$

The further reactions of the radical formed in equation (24) may only be guessed at but the production of small amounts of *s*-butanol may offer a clue, namely that rearrangement may take place. The following mechanism is then possible:

$$\underset{\displaystyle CH_2}{\overset{\displaystyle (CH_3)_2COH^{\bullet}}{|}} \longrightarrow \underset{\displaystyle CH_3CH_2}{\overset{\displaystyle CH_3COH^{\bullet}}{|}} \qquad (26)$$

$$2\ \underset{\displaystyle CH_3}{\overset{\displaystyle CH_3CH_2COH^{\bullet}}{|}} \longrightarrow \underset{\displaystyle CH_3}{\overset{\displaystyle CH_3CH_2C{=}O}{|}} + \underset{\displaystyle CH_3}{\overset{\displaystyle CH_3CH_2CHOH}{|}} \qquad (27)$$

The formation of an equivalent amount of methyl ethyl ketone, which has not been reported, is required to test this suggestion. It is clear, however, that if all the radicals formed in reaction (24) react via reactions (26) and (27) then a much higher yield of *s*-butanol

would be expected. An alternative fate for these radicals is therefore required if reaction (24) is the sole source of *s*-butanol.

V. INTERMEDIATES

The primary processes in the radiolysis of alcohols can be described by the following scheme:

$$\text{Excitation:} \quad ROH \longrightarrow ROH^* \tag{28}$$

$$\text{Ionization:} \quad ROH \longrightarrow ROH^+ + e^- \tag{29}$$

$$\text{Ion dissociation:} \quad ROH^+ \longrightarrow A^{\cdot +} + B^{\cdot} \tag{30}$$

$$ROH^+ \longrightarrow X^+ + Y \tag{31}$$

$$\text{Ion-molecule reaction:} \quad ROH^+ + ROH \longrightarrow RO^{\cdot} + ROH_2^+ \tag{32}$$

$$\text{Neutralization:} \quad ROH^+ + e^- \longrightarrow ROH^{**} \tag{33}$$

$$\text{Dissociation:} \quad ROH^* \text{ and } ROH^{**} \longrightarrow A^{\cdot} + B^{\cdot} \tag{34}$$

$$ROH^* \text{ and } ROH^{**} \longrightarrow X + Y \tag{35}$$

Where A·, B· are free radicals and X, Y are stable molecules.

Until 1960 it was generally accepted that ion-neutralization was extremely rapid and that reaction (33) was the only fate of the primary ions (the so-called Samuel–Magee model[32]). The scheme thus reduced to reactions (28), (29) and (33) followed by dissociation of the excited molecule products. Consequently reaction mechanisms were drawn up in which free radicals were the only reactive intermediates. The discovery of the solvated electron as a short-lived intermediate in the radiolysis of alcohols[33] showed, however, that this was an over-simplification and that reactions involving ions should also be taken into account. The existence of free ions suggested that the Samuel–Magee hypothesis of rapid neutralization was not applicable to these liquids and that, as in the case of water, the alternative Lea–Platzmann[34] model of slow neutralization and electron solvation should be used. Recently it has been pointed out[35] that liquids of intermediate dielectric constant do not obey either formulation and that a more general model should be used in the case of the alcohols. Before considering the ramifications of this model let us first consider the evidence for the various intermediates which have been postulated in various reaction mechanisms describing alcohol radiolysis.

A. Ions

1. Electrons

The first specific reference to electrons, as chemically distinguishable intermediates in the radiolysis of alcohols, was by Hayon and Weiss[36], who postulated positive and negative polarons (the latter may be considered to be solvated electrons) as the primary intermediates in the radiolysis of methanol.

$$2\,CH_3OH \rightsquigarrow CH_3OH^+ + CH_3OH^- \quad (36)$$

$$CH_3OH^+ \longrightarrow CH_2OH + H^+ \quad (37)$$

$$CH_3OH^- \longrightarrow CH_3O^- + H \quad (38)$$

According to this formulation the solvated electron (polaron) is a precursor of molecular hydrogen via reaction (38) and the subsequent known reaction of hydrogen atoms (reaction 39)[17].

$$H + CH_3OH \longrightarrow H_2 + CH_2OH \quad (39)$$

These workers implicitly accepted the electron escape mechanism of Platzmann[34] but did not offer experimental evidence to substantiate this. It had in fact been pointed out in an earlier paper[11] that the formation of the major products in the radiolysis of methanol could be interpreted in terms of either theory.

An interesting observation made by Hayon and Weiss was that certain solutes reduced the hydrogen yield from irradiated ethanol in *two* distinct stages separated by a well-defined plateau. They failed to comment on the significance of this and it was left to later workers[18, 27, 28] to introduce the concept of two reactive precursors of hydrogen, namely the solvated electron and the hydrogen atom. Kinetic studies of the effect of a number of solutes in irradiated methanol[18] substantiated the suggestion that two precursors were involved and competitive studies involving anthracene and sulphuric acid were interpreted in terms of the electron being the more reactive species.

This argument was applied to the radiolysis of ethanol in two simultaneous but separate investigations. At Cambridge it was pointed out[28] that the reduction of $G(H_2)$ by low concentrations of acetaldehyde could be interpreted in terms of electron but not hydrogen atom scavenging. The solvated electron yield was deduced to be $G(e^-_{solv}) = 0{\cdot}9$ from these studies. Adams and Sedgwick[27] arrived at similar conclusions and obtained a value of $G(e^-_{solv}) = 1{\cdot}02$.

Credence was lent to these arguments by the unequivocal demonstration of the solvated electron as the principal species in neutral irradiated water by kinetic salt effect[37] and pulse radiolysis[38] ex-

periments. The existence of the solvated electron as an intermediate in alcohol radiolysis was finally proved by the demonstration of its absorption spectrum in pulse-irradiated ethanol by Taub, Sauer and Dorfman in 1963[33]. This was followed by experiments in methanol, *n*-propanol, *i*-propanol and ethylene glycol, in all of which the transient absorption of the electron was noted[39]. In the case of ethanol the yield was determined as $G(e^-_{solv}) = 1$ in agreement with the earlier kinetic data. The determination of absolute rate constants likewise justified the contention that the electron is the more reactive of the hydrogen precursors.

a. Solvated electron yields. The yields of solvated electrons have been determined for a number of alcohols by spectroscopic and kinetic methods. The spectroscopic determinations are more reliable, in principle, providing that the extinction coefficient of e^-_{solv} is known. $\xi(e^-_{solv})$ has been determined for ethanol by an indirect method[40] and the values for other alcohols derived from it. The method requires a knowledge of the extinction coefficient of the diphenylide ion. This is known in ethanol[41] but not in other alcohols and the assumption has been made that it is independent of the solvent. The values given for $G(e^-_{solv})$ by spectroscopic methods are thus dependent on the validity of this assumption.

The kinetic method is indirect and is based on the effect of added solutes which compete with the substrate for the electron[35]. Thus the effect of acetone in reducing $G(H_2)$ in the radiolysis of ethanol (Figure 2) can be interpreted in terms of the following competition.

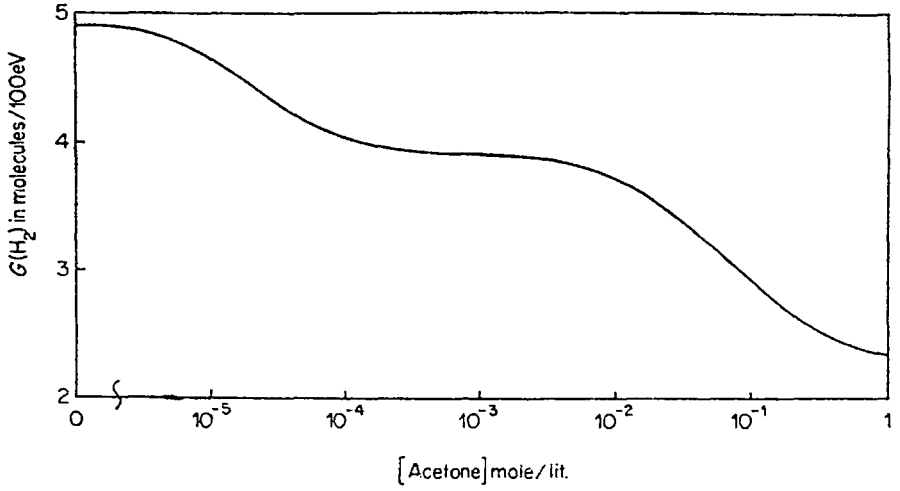


FIGURE 2. Effect of acetone on the hydrogen yield in the radiolysis of ethanol.

(This assumes that the initial reduction in $G(H_2)$ is due to scavenging of solvated electrons which normally lead to hydrogen production. The subsequent reduction in $G(H_2)$ is assumed due to H-atom scavenging.)

$$e^-_{solv} + C_2H_5OH \xrightarrow{k_A} H_2$$

$$e^-_{solv} + (CH_3)_2CO \xrightarrow{k_S} \text{products other than } H_2$$

Kinetically this competition may be expressed as follows:

$$1/\Delta G(H_2) = 1/G(e^-_{solv}) + k_A[C_2H_5OH]/k_S[(CH_3)_2CO]G(e^-_{solv}) \quad (1)$$

where $\Delta G(H_2) = [\text{Initial } G(H_2)] - [G(H_2)]$ at any given $[(CH_3)_2CO]$ and k_A and k_S are the reaction rate constants.

Thus a plot of $1/\Delta G(H_2)$ against $1/[(CH_3)_2CO]$ should be linear with the intercept equal to $1/G(e^-_{solv})$. A number of determinations of $G(e^-_{solv})$ have been made in this way[35]. The competition plot derived from the data in Figure 2 is shown in Figure 3 from which a value of $G(e^-_{solv})$ in ethanol of approximately 1·0 is obtained.

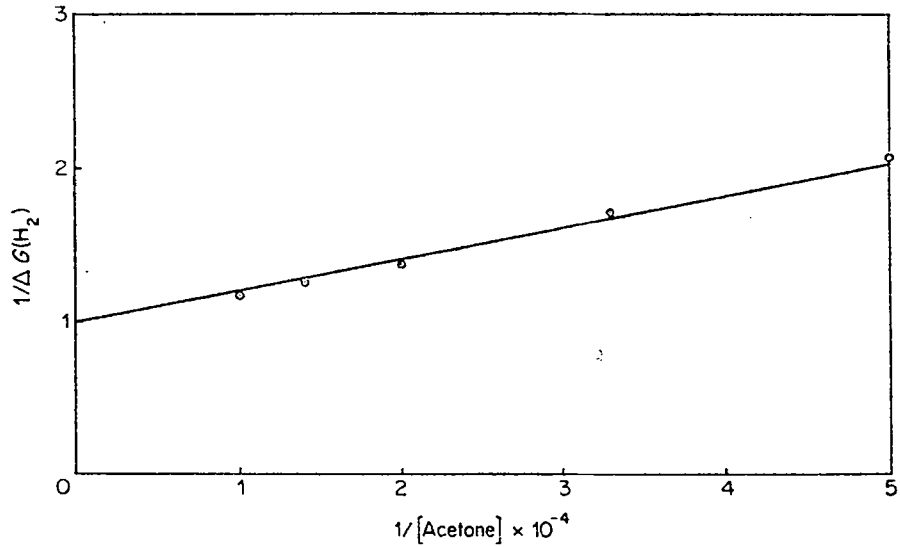


FIGURE 3. Plot of equation (1) for the data in Figure 2.

Values for $G(e^-_{solv})$ in various alcohols obtained by kinetic as well as spectroscopic methods are given in Table 7.

Some values for methanol (2·0)[47], ethanol (1·50)[45] and *i*-propanol (1·20)[29] appear to be rather high and it is interesting to note that nitrous oxide was the solute in all three cases. This suggests an effect specific to this scavenger which merits further investigation.

TABLE 7. $G(e^-_{solv})$ in various alcohols.

Alcohol	$G(e^-_{solv})$												
Methanol	1·30	—	1·10	—	1·05	—	—	—	—	2·0	—	1·1	—
Ethanol	0·90	1·00	1·00	1·02	0·90	1·20	1·50	0·90	—	—	—	1·0	—
n-Propanol	0·65	—	1·00	—	—	—	—	—	—	—	—	—	—
i-Propanol	—	—	1·00	—	—	—	—	—	0·90	—	1·20	—	0·7
n-Butanol	0·55	—	—	—	—	—	—	—	—	—	—	—	—
n-Pentanol	—	0·37	—	—	—	—	—	—	—	—	—	—	—
n-Hexanol	—	0·33	—	—	—	—	—	—	—	—	—	—	—
Ethylene glycol	—	—	1·20	—	—	—	—	—	—	—	—	—	—
Reference	35	42	39[a]	27	43	44	45	23	46	47	29	49	30

[a] Spectroscopic determination.

b. Solvated electron rate constants. Although the technique of pulse radiolysis followed by fast spectroscopy has been applied to the determination of a large number of rate constants involving the hydrated electron[48], relatively little has been published on the kinetics of solvated electron reactions in alcohols.

Table 8 lists some rate constants which have appeared in the literature.

TABLE 8. Rate constants of some reactions of solvated electrons in various media ($mole^{-1}\ sec^{-1}$).

Reaction \ Medium	H_2O	CH_3OH	C_2H_5OH
$e^- + H^+$	$2{\cdot}2 \times 10^{10}$	$3{\cdot}9 \times 10^{10}$	$2{\cdot}0 \times 10^{10}$
$e^- + O_2$	$2{\cdot}0 \times 10^{10}$	$1{\cdot}9 \times 10^{10}$	$1{\cdot}9 \times 10^{10}$
e^- + biphenyl	—	—	$4{\cdot}3 \times 10^{9}$
e^- + naphthalene	$5{\cdot}4 \times 10^{9}$	—	$5{\cdot}4 \times 10^{9}$
e^- + *p*-terphenyl	—	—	$7{\cdot}2 \times 10^{9}$
e^- + naphthacene	—	—	$1{\cdot}0 \times 10^{10}$
$e^- + C_6H_5CH_2Cl$	$5{\cdot}5 \times 10^{9}$	$5{\cdot}0 \times 10^{9}$	$5{\cdot}1 \times 10^{9}$
$e^- + (C_6H_5)_3COH$	—	—	$2{\cdot}0 \times 10^{8}$

An important observation from this table is that rate constants of solvated electrons are relatively independent of the medium. This finding makes it possible to derive values for $k(e^-_{solv} + \text{alcohol})$[35] and also to obtain rate constants from relative rate constant data. Apart from these rate constants obtained by spectroscopic methods, a number of relative rate constants have been determined by competition kinetics. The method involves the use of equation (1), inspection of which shows that the slope of a plot of $1/\Delta G(H_2)$ against [alcohol]/[solute] is equal to $k(e^-_{solv} + \text{alcohol})/k(e^-_{solv} + \text{solute})Ge^-_{solv}$.

A list of some relative rate constants which have appeared in the literature is given in Table 9.

c. Structure and optical properties of solvated electrons. The nature and structure of e^-_{solv} is still the subject of conjecture. A detailed analysis of models which have been proposed is beyond the scope of this review. The reader is referred to the excellent article by Walker[50] on the hydrated electron, most of which is relevant to electrons solvated in other media. For the purpose of the present discussion the following remarks are sufficient to give some indication of the nature of this novel reaction intermediate.

TABLE 9. Relative rate constants of the solvated electron given as $k(e^- + \text{solute})/k(e^- + \text{alcohol})$.

Solute \ Alcohol	MeOH	EtOH	*n*-PrOH	*i*-PrOH	*n*-BuOH
Acetone	$1{\cdot}5 \times 10^6$	4×10^5	$7{\cdot}7 \times 10^4$	$3{\cdot}4 \times 10^3$	$1{\cdot}4 \times 10^4$
$CH_2ClCOOH$	8×10^5	$1{\cdot}0 \times 10^5$	—	$2{\cdot}1 \times 10^4$	—
Fe^{3+}	—	—	$5{\cdot}6 \times 10^4$	—	—
Cr^{3+}	—	—	$3{\cdot}0 \times 10^5$	$3{\cdot}0 \times 10^4$	—
NO_3^-	6×10^6	$2{\cdot}4 \times 10^5$	—	—	—
Co^{2+}	—	$1{\cdot}0 \times 10^5$	—	—	—
Anthracene	5×10^6	$2{\cdot}4 \times 10^6$	—	—	—
CH_3CHO	—	$1{\cdot}6 \times 10^5$	—	—	—
C_2H_5CHO	—	—	$1{\cdot}0 \times 10^5$	—	—
CCl_4	—	$1{\cdot}1 \times 10^4$	—	$1{\cdot}3 \times 10^4$	—
N_2O	$5{\cdot}7 \times 10^5$	—	—	$5{\cdot}9 \times 10^3$	—
H^+	$1{\cdot}7 \times 10^6$	$1{\cdot}7 \times 10^6$	—	—	—

Solvated electrons are excess electrons solvated in the alcohols. The process of solvation can be considered due to the polarization of neighbouring solvent molecules as the result of electron dipole interactions. The electrostatic field of the excess electron induces a potential well which traps and stabilizes the electron. It is thus bound in a self-induced stable quantum state of the polarized dielectric. A necessary condition for electron solvation therefore appears to be that the dielectric constant of the medium should be substantially greater than unity.

Electrons solvated in the alcohols exhibit a broad absorption spectra extending throughout the visible[40]. The maximum is found in either the visible or near infrared and exhibits a red shift with decrease in the static dielectric constant of the alcohol[40]. A collection of some optical properties due to Dorfman and co-workers[40] is given in Table 10.

TABLE 10. Optical absorption data for the solvated electron in some alcohols.

Alcohol	Abs. maximum (Å)	E_{10}^{max} (mole^{-1} cm^{-1})	Oscillator strength
Ethylene glycol	5800	14,000	0·7
Methanol	6300	17,000	0·8
Ethanol	7000	15,000	0·9
1-Propanol	7400	13,000	0·6
2-Propanol	8200	14,000	0·7

2. Positive ions

There is little or no absolute evidence for the participation of positive ions in the radiolysis of liquid alcohols. Nevertheless, it must be abundantly clear that a necessary corollary of the existence of the solvated electron is the existence of positive ions with a sufficiently long lifetime to undergo reaction if this is possible. Vapour phase data[51–53] has shown that these ions are very reactive and ion-molecule reactions in the liquid phase are a very real possibility. In addition, ionic fragmentation analogous to that observed in the mass spectrometer may also take place[54, 55] although it must be remembered that the excess energy required for these reactions will be rapidly dissipated by molecular collisions in condensed phases.

a. Ion-molecule reactions. Liquid phase ion-molecule reactions of the anthracenide and diphenylide anions with a number of aliphatic alcohols have been observed in pulse radiolysis studies[56, 57]. The ions are formed by attachment of the solvated electron to the aromatic compound in solution (reaction 40) and react by proton transfer from the substrate.

$$e^-_{solv} + Ar \longrightarrow Ar^- \quad (40)$$

$$Ar^- + ROH \longrightarrow ArH + RO^- \quad (41)$$

Although these reactions are not relevant to the ions formed in the radiolysis of *pure* alcohols it is an unequivocal demonstration that ion-molecule reactions do take place in the liquid phase.

Chemical evidence for ion-molecule reactions in liquid alcohols has recently been offered by Ward and Hamill[58]. In hydrocarbon–alcohol mixtures they found products expected from conventional carbonium ion reactions in small yields. For example, they found anisole from benzene–methanol and cyclohexyl–ethyl ether from cyclohexane–ethanol. They also found evidence for proton transfer from cyclo-$C_6H_{12}^+$ to ethanol.

The existence of ion-molecule reactions in the radiolysis of pure liquids has been proposed[59, 60] on theoretical grounds and it has been pointed out that an evaluation of the role of ions as reactive intermediates hinges on the lifetime of a positive molecular ion before neutralization. Williams[61] states that all substantiated ion-molecule reactions are exothermic with negligible activation energy. Furthermore, they often have large cross-sections and there should be a high probability of reaction at every collision encounter. He concludes that reactions of the parent molecule ion involving low activation energies probably precede neutralization even in the liquid state.

In the case of the alcohols Williams[59] points out that the threshold ionization refers to the loss of a nonbonding electron with the result that the unpaired electron is highly localized on the oxygen atom (e.g., $CH_3{}^{+\bullet}OH$). The ensuing reactions of the parent molecule ion are strongly directed by the tendency of the oxygen atom to complete its valence shell of electrons. One important pathway for achieving this is by hydrogen abstraction:

$$CH_3OH^{\bullet +} + CH_3OH \longrightarrow CH_3OH_2{}^+ + CH_2OH^{\bullet} \qquad (42)$$

He also suggests that the generality of this reaction is indicated by the repeated observation of ions corresponding to mass = parent + 1 in mass spectra recorded at elevated pressure. Proton transfer from the ion to the substrate could, of course, also explain this finding.

There does seem to be a strong case for suggesting that ion-molecule reactions observed in the vapour phase may also take place in the liquid phase. It is thus important to consider the available vapour phase data when setting up a liquid-phase reaction mechanism.

Wilmenius and Lindholm[62] investigated ion-molecule reactions in a tandem mass spectrometer in which the ions produced in the first one were allowed to react with an alcohol in the collision chamber of the second and the product ions subsequently mass analysed. In the case of methanol the following proton transfer reactions were observed:

$$CH_3OH^+ + CH_3OH \longrightarrow CH_3O^{\bullet} + CH_3OH_2{}^+ \qquad (43)$$

$$CH_2OH^+ + CH_2OH \longrightarrow CH_2O + CH_3OH_2{}^+ \qquad (44)$$

With $CH_3{}^+$ as the bombarding ion, hydride ion transfer occurred.

$$CH_3{}^+ + CH_3OH \longrightarrow CH_4 + CH_2OH^+ \qquad (45)$$

It was, however, concluded that hydride ion transfer is usually of minor importance compared with the competitive process, charge exchange, and that it is of importance only when charge exchange cannot take place. Charge transfer is always possible when the ionization potential of the molecule is lower than the neutralization energy of the ion.

The very large cross-sections for proton transfer reactions in alcohols have prompted a number of investigations. Hamill and co-workers have investigated the dependence of cross-sections on field strength[63] and electron energy[64], in the latter case showing a significant dependence. In these and other[65, 66] high-pressure mass spectra the ion at mass P + 1 is observed and has been attributed to the reactions below as well as to reactions (43) and (44):

$$CH_3OH^+ + CH_3OH \longrightarrow CH_3OH_2{}^+ + CH_2OH^{\bullet} \qquad (46)$$

$$CHO^+ + CH_3OH \longrightarrow CH_3OH_2{}^+ + CO \qquad (47)$$

By working at low electron energies, Futrell[51] and co-workers have separated the parent ion contribution to the formation of $CH_3OH_2^+$ and have shown that a proton may be transferred from either the hydroxyl (reaction 43) or the carbon position (reaction 43a).

$$CD_3OH^+ + CD_3OH \longrightarrow CD_3O^{\cdot} + CD_3OH_2^+ \quad (43)$$

$$CD_3OH^+ + CD_3OH \longrightarrow \dot{C}D_2OH + CD_3OHD^+ \quad (43a)$$

The relative transfer probabilities were found to be 1·00 for reaction (43) and 0·81 for reaction (43a). It is interesting to note that (43a) corresponds to the hydrogen atom abstraction mechanism proposed by Williams[59].

Reaction (44) was also found to be an important source of $CH_3OH_2^+$ but reaction (47) has been eliminated by other workers[62]. An interesting finding[51] was that proton transfer from the parent ion is not an important source of $CH_3CH_2OH_2^+$ in ethanol which has only CH_3CHOH^+ as its precursor (reaction 48).

$$CH_3CHOH^+ + CH_3CH_2OH \longrightarrow CH_3CHO + CH_3CH_2OH_2^+ \quad (48)$$

Later work[53], however, indicated that this finding was incorrect and that several simultaneous processes take place. In addition to reaction (48) the following reactions are important:

$$CH_3CH_2OH^+ + CH_3CH_2OH \longrightarrow CH_3CH_2OH_2^+ + CH_3\dot{C}HOH \quad (49)$$

$$CH_3CH_2OH^+ + CH_3CH_2OH \longrightarrow CH_3CH_2OH_2^+ + CH_3CH_2\dot{O} \quad (50)$$

$$CH_2OH^+ + CH_3CH_2OH \longrightarrow CH_3CH_2OH_2^+ + CH_2O \quad (51)$$

The reaction rates for these reactions are extremely rapid, as shown in Table 11.

TABLE 11. Rate constants for some ion-molecule reactions.

Reaction	Rate constant (mole^{-1} sec^{-1})	
	Ref. 51	Ref. 52
$CH_3OH^+ + CH_3OH \longrightarrow CH_3OH_2^+ + CH_3O^{\cdot}$	$6{\cdot}6 \times 10^{11}$	$8{\cdot}8 \times 10^{11}$
$CH_3OH^+ + CH_3OH \longrightarrow CH_3OH_2^+ + CH_2OH^{\cdot}$	$8{\cdot}1 \times 10^{11}$	
$CH_2OH^+ + CH_3OH \longrightarrow CH_3OH_2^+ + CH_2O$	$4{\cdot}1 \times 10^{11}$	$5{\cdot}0 \times 10^{11}$
$CH_3CHOH^+ + CH_3CH_2OH \longrightarrow CH_3CH_2OH_2^+ + CH_3CHO$	$3{\cdot}6 \times 10^{12}$	—

b. Ion fragmentation. There is no direct evidence for fragmentation of excited parent ions in the liquid phase and some workers have

suggested that collisional deactivation precludes this possibility. Ion fragmentation is of course the predominant process in gases at low pressures (i.e., in the mass spectrometer) and there are strong indications that even at atmospheric pressure it plays an important role.

In recent years several workers have met with a considerable measure of success in calculating gas-phase radiolysis yields from mass spectral data[67-72]. This success has prompted other workers[54,55] to attempt to calculate yields in the liquid phase and, in the case of the aliphatic alcohols, it was concluded[55] that fragmentation might well play an important role. Despite the lack of experimental evidence on the subject it is, nevertheless, worthwhile considering the argument which has been presented in favour of the extrapolation of mass spectrometric data to condensed phases:

It is reasonable to assume that the primary product of ionization in liquid-phase radiolysis, as in the mass spectrometer, is the parent ion in either the ground or an excited state. In the MS-source at 10^{-6} mm Hg pressure, the excited parent ions are isolated and undergo fragmentations. The fragment ions, if formed in excited states, can undergo further fragmentations, and so on until electronic equilibrium is attained. In competition with the fragmentation process are collisional deactivation and ion collection, the latter being substantially more important and taking place within 10^{-6} sec. Thus reactions with unimolecular rate constants lower than 10^{6} sec^{-1} are not observed in the MS. In other words, the observed mass spectrum corresponds to the ionic distribution 10^{-6} sec after the initial ionization act.

A parent ion formed in the liquid phase, on the other hand, undergoes some 10^{7} collisions in 10^{-6} sec, so that many of the dilute gas-phase fragmentations will not take place. What is thus needed is the mass spectrum 10^{-13} sec after initial ionization. An instrument capable of providing this is purely hypothetical and consequently the ionic distribution before the first collision must be derived theoretically.

One method of deriving ionic distributions as a function of time involves the use of the quasi-equilibrium theory of mass spectrometry[73] to calculate rate constants for individual fragmentations. Attempts at predicting gas-phase radiolysis yields by this method have met with varying degrees of success, but even predicted mass spectra do not agree with experiment in many cases. Furthermore, the theory assumes a unimolecular decomposition of *isolated* molecules and is not strictly applicable to the liquid phase[74]. Therefore it would seem that this approach must remain a future objective.

The alternative is to use actual ionic distributions as measured in the MS after microseconds, and to extrapolate these to picosecond intervals in a semi-empirical fashion. The most important assumption made in this approach is that the fragmentation pattern is only modified by collisional deactivation. Thus the most rapid unimolecular reactions ($k > 10^{12}$ sec^{-1}) will take place in the liquid phase in exactly the same manner as in a dilute vapour. This assumption cannot be rigidly defended but does seem reasonable.

The second assumption concerns a decision as to which decompositions compete successfully with collisional deactivation, and, in the absence of known rate constants, this is necessarily somewhat arbitrary. For want of anything better it is assumed that dissociations involving complex rearrangements of the parent ion are excluded in the liquid phase, as are secondary dissociations of first-generation fragment ions.

A number of additional assumptions have also to be made and these will be discussed as they occur in the following outline of the method:

(a) The mass spectrum obtained is simplified by including only the most abundant mass numbers in a reduced mass spectrum. This is justifiable as ions occurring in very low yield correspond to dissociations with low-frequency factors which may be excluded in the liquid phase. Furthermore, if included in the calculations, they lead to radiation chemical yields too small to be meaningfully compared with experiment.

(b) Ionic structures corresponding to the various mass numbers are assigned, making use of high-resolution data in cases of ambiguity.

(c) Plausible fragmentation patterns are formulated, and unlikely steps eliminated, by comparing the measured appearance potential of the ion under study with thermochemically calculated values for the reaction proposed for its formation. Only in cases of close agreement are possible fragmentation steps included in the final fragmentation pattern.

(d) On the assumption that secondary fragmentation is excluded in the liquid phase (*vide supra*) this pattern is modified by intensifying primary fragment yields at the expense of secondary fragments derived from them.

(e) The ionic yields in the modified fragmentation pattern, expressed as a percentage of the total ionization, are converted to G-values using an appropriate value of G(total ionization).

(f) The likely ion-molecule reactions of the fragments are written down making the following assumptions, which have been justified by various authors[54, 72]:
  (i) Fragment ions which are protonated forms of stable molecules transfer a proton to the alcohol substrate.
  (ii) The ions of stable molecules with suitable ionization potentials transfer their charge to the substrate.
  (iii) All other ions give rise to hydride ion transfer from the substrate.

(g) The yields of free radical and stable products formed in these ion-molecule reactions are established.

(h) The further reactions of the free radicals are written down where known, or postulated, and the stable product yields established.

(i) Mass balance is set up and final end-product yields are calculated.

(j) The calculated yields are compared with those experimentally determined, bearing in mind that the theoretical values do not include any contributions from the decomposition of excited neutral molecules. Thus, where known, such contributions are first deducted from the experimental values.

The method has been applied to the calculation of radiolysis yields in methanol, ethanol and propanol with considerable success[55]. In the case of methanol the agreement between calculated and experimental values is almost perfect, which is probably fortuitous (Table 12), and in the other alcohols the agreement is very

TABLE 12. Calculated and experimental yields in methanol radiolysis[55].

	$(H_2)_M$	H	H_2O	CH_4	CH_2O	$(CH_2OH)_2$
Calculated	1·92	3·20	0·42	0·42	2·34	3·20
Experimental	1·90	3·20	—	0·40	2·20	3·20

satisfactory. There does, therefore, seem to be a strong case for considering ion fragmentation when setting up liquid-phase radiolysis mechanisms.

B. Radicals

Direct evidence for the participation of free radicals in the reaction mechanism, when alcohols are irradiated, is available. The greater

portion of this evidence is based on electron spin resonance spectroscopy of samples irradiated in the solid state and the direct application of these data to the liquid phase should be treated with some caution[75]. Nevertheless, much valuable information has been obtained from these experiments.

The radicals from methanol and ethanol were originally identified[76] as CH_2^+ and $C_2H_4^+$ respectively but subsequent workers[77-79] have established the intermediates, $CH_2OH^{\cdot}$ and $CH_3CHOH^{\cdot}$. As mentioned in section IV, the formation of hydrogen and vicinal glycols as final products also strongly indicated the presence of α-hydroxy-alkyl radicals. Confirmation that these radicals are important in liquid-phase radiolysis has recently been obtained[13] in pulse radiolysis experiments in which the absorption spectrum of α-hydroxy-ethyl in ethanol was obtained. The CH_2OH radical has also been observed in the pulse radiolysis of methanol[95]. The major sources for these radicals are the following reactions:

$$RCH_2OH^+ + RCH_2OH \longrightarrow RCH_2OH_2^+ + RCHOH^{\cdot} \quad (52)$$

$$RCH_2OH^* \longrightarrow RCHOH^{\cdot} + H^{\cdot} \quad (53)$$

$$H + RCH_2OH \longrightarrow RCHOH^{\cdot} + H_2 \quad (54)$$

Of these three reactions, (54) is the best substantiated as it has been shown that the hydrogen atoms formed in the radiolysis of water react with ethanol almost exclusively by hydrogen abstraction from the α-carbon atom[17]. Reaction (53) is rather unlikely to take place in the liquid phase due to collisional deactivation and, even if it does occur, the radicals, formed in the same liquid cage, will tend to recombine[35]. Reaction (52) occurs in the gas phase[62] and it is reasonable to expect that it is also important in the liquid phase as suggested by Williams[59].

Gas phase results[51] indicate, however, that reaction (52) is in competition with reaction (55) which leads to the production of alkoxyl radicals.

$$RCH_2OH^+ + RCH_2OH \longrightarrow RCH_2O^{\cdot} + RCH_2OH_2^+ \quad (55)$$

Other data including photolysis results[80-82] and the effect of carbon monoxide on ethanol radiolysis[75] also indicate that ethoxyl production is an important process. Recently it was established[83] that in the radiolysis of solid methanol–benzene mixtures the cyclohexadienyl radical is formed by addition of a hydrogen atom to benzene and that the hydrogen atom originates from the hydroxyl group. This result is compatible with the following mechanism:

$$CH_3OD^+ + CH_3OD \longrightarrow CH_3O^{\cdot} + CH_3OD_2^+ \quad (56)$$

$$CH_3OD_2^+ + e^- \longrightarrow CH_3OD + D^{\cdot} \quad (57)$$

$$D + C_6H_6 \longrightarrow C_6H_6D^{\cdot} \quad (58)$$

By deuterating both the benzene and the methanol in various positions Leone and Koski[83] were able to verify this explanation. Nevertheless they also observed the hydroxy-methyl radical which indicated that both radicals are produced in the radiolysis. In a recent kinetic approach it was concluded[19], in agreement with this finding, that reactions (52) and (55) are of equal importance in the radiolysis of liquid ethanol. This is also in agreement with the equality of the rate constants for reactions (52) and (55) which has been demonstrated in the vapour phase[51].

Although the primary production of alkoxyl radicals is not yet universally accepted, the evidence in favour of this event is mounting. The failure to detect these radicals by kinetic methods in earlier work is directly related to their reactivity towards the substrate leading to the production of hydroxy-alkyl radicals[84] (reaction 59).

$$RCH_2O^{\cdot} + RCH_2OH \longrightarrow RCH_2OH + RCHOH^{\cdot} \qquad (59)$$

Thus it is that in most systems the results are compatible with the production of hydroxy-alkyl radicals only. In one case however, the presence of alkoxyl radicals seems certain. When carbon monoxide saturated solutions of ethanol are irradiated a major product is ethyl formate[19, 75], which may be explained by reactions (60) and (61).

$$CH_3CH_2O^{\cdot} + CO \longrightarrow CH_3CH_2OCO^{\cdot} \qquad (60)$$

$$CH_3CH_2OCO^{\cdot} + CH_3CH_2OH \longrightarrow CH_3CH_2OCHO + CH_3CHOH^{\cdot} \qquad (61)$$

Other radicals formed during radiolysis have not been observed directly although there can be little doubt that hydrogen atoms are produced. Ethyl radicals have been observed in u.v.-irradiated solid ethanol[78] and are almost certainly also formed during radiolysis. Thus it is found that most free radical scavengers reduce the ethane yield in irradiated alcohols which may be explained by the competition between reactions (62) and (63). Other alkyl radicals are also likely intermediates.

$$C_2H_5^{\cdot} + RCH_2OH \longrightarrow C_2H_6 + RCHOH^{\cdot} \qquad (62)$$

$$C_2H_5 + S \longrightarrow \text{Other products} \qquad (63)$$

Another product which has been identified[78] in u.v.-irradiated solid ethanol is CHO but it is thought that this is due to secondary processes involving the decomposition of hydroxy-alkyl radicals (64)[85, 86] which would not occur in the liquid phase.

$$RCHOH^{\cdot} \longrightarrow RH + CHO^{\cdot} \qquad (64)$$

It thus appears that the most important radicals formed in the radiolysis of alcohols are hydrogen atoms, alkoxyl, hydroxy-alkyl

and alkyl radicals. With the exception of the hydroxy-alkyl radical the predominant fate of these radicals is hydrogen abstraction from the substrate at the α-carbon position (reactions 54, 59 and 62). The result of each reaction is the production of additional hydroxy-alkyl radicals. These do not react with the substrate but disappear in inter-radical reactions, the most important of which are reactions between each other. Two possibilities exist, namely disproportionation (reaction 65) and dimerization (reaction 66), the two processes being in competition.

$$2\ RCHOH^{\cdot} \longrightarrow RCHO + RCH_2OH \qquad (65)$$

$$2\ RCHOH^{\cdot} \longrightarrow (RCHOH)_2 \qquad (66)$$

The overall rate constant for the disappearance of hydroxy-ethyl radicals has been established[13] for the case of ethanol as

$$2[k(65) + k(66)] = 1{\cdot}4 \times 10^9\ \text{mole}^{-1}\ \text{sec}^{-1}.$$

Furthermore, the ratio of the rate constants for the two processes has been determined for the lower alcohols. These are shown in

TABLE 13. Ratio of rate constants for dimerization and disproportionation of hydroxy-alkyl radicals.

Radical	k(dimer)/k(disp)
Hydroxy-methyl	10 [87], 15 [88] (in methanol); 5 [89] (in water)
Hydroxy-ethyl	1 [92] (in ethanol); 2 [90], 4 [13] (in water)
Hydroxy-propyl	1·6 [91] (in propanol)

Table 13. There appears to be a decrease in the ratio with increasing chain length; a finding which is more clearly brought out by the ratio of the glycol yield (product of dimerization) to the aldehyde yield (product of disproportionation) (Table 14).

TABLE 14. Ratio of G(glycol) to G(aldehyde) for several alcohols[21, 85].

Alcohol	Methanol	Ethanol	n-Propanol	n-Butanol
G(glycol)/G(aldehyde)	2·1	2·3	1·3	0·2

The decreasing importance of dimerization with increasing chain length may be ascribed to steric hindrances in the case of the larger molecules. In support of this suggestion it can be shown that a large difference exists between G(glycol) = 1·6 [20] in n-propanol in which

the unpaired electron on the α-carbon atom is relatively accessible, and G(glycol) = 0·4 [93] in isopropanol in which the unpaired electron is more effectively shielded.

In addition to dimerization and disproportionation the dissociation of α-hydroxy-alkyl radicals has also been considered. McDonell and Newton[8] suggested that the formation of formaldehyde in high LET (Linear Energy Transfer) irradiation (see section X) may be due to reaction (67) taking place in the small, highly energized regions of the initial energy absorption.

$$CH_2OH^{\bullet} \longrightarrow CH_2O + H^{\bullet} \qquad (67)$$

In support of this suggestion they point out that formaldehyde formation in the photolysis of methanol vapour is a high activation energy process competing substantially with glycol formation only above 400°C [94].

The dissociation of hydroxy-alkyl radicals under the influence of u.v. light has been demonstrated by Johnsen in a number of frozen alcohols[21, 85]. The e.p.r. spectrum due to hydroxy-alkyl radicals was found to disappear after exposure to u.v. light, and, on warming the frozen sample, product analysis showed large yields of hydrogen and carbon monoxide which may be explained by reactions (64) followed by (68).

$$RCHOH^{\bullet} \xrightarrow{h\nu} RH + CHO^{\bullet} \qquad (64)$$

$$CHO^{\bullet} \xrightarrow{h\nu} CO + H^{\bullet} \qquad (68)$$

C. Molecular Products

The concept of molecular products was introduced in the radiolysis of water to differentiate between radicals which diffuse out of the spurs (localized regions in which the primary intermediates are initially distributed in high concentration) and those which undergo reaction within the spur[96]. Thus hydrogen and hydrogen peroxide are molecular products formed in spurs:

$$H + H \longrightarrow H_2 \qquad (69)$$

$$OH + OH \longrightarrow H_2O_2 \qquad (70)$$

As in the case of water the primary intermediates formed in the radiolysis of alcohols will be initially distributed nonhomogeneously in small volume elements of high local concentration. These are not quite the isolated spurs of irradiated water as, in contrast to that case, the intermediates are capable of reaction with the substrate. Some of these reactions have already been treated under ion-molecule reactions and these are substantially completed before

diffusion controlled 'spur' expansion takes place. It can also be assumed that electron solvation and ion neutralization precede 'spur' expansion. The ionic and radical species so produced react rather more slowly so that the concept of a 'spur' containing the following species at about 10^{-10} sec after the initial ionization may be accepted:

$RCH_2OH_2^+$, e^-_{solv}, H, $RCH_2O^\cdot$, $RCHOH^\cdot$, Ion-molecule products

In the case of water spur expansion involves a competition between diffusion of the intermediates into the bulk medium, on the one hand, and reaction between the intermediates on the other[32]. In the alcohols a third possibility, reactions with the substrate, must be added. If the rate constants of the latter reactions are large compared to reactions between intermediates then the concept of molecular products formed in intra-spur reactions cannot be applied*. If, on the other hand, they are relatively small the situation approximates that of water.

$RCH_2OH_2^+$, e^-_{solv} and $R\dot{C}HOH$ either react very slowly or not at all with the substrate and may be considered 'spur' intermediates in the sense applied to water. $RCH_2O^\cdot$, however, is thought[84] to react rapidly with the substrate (reaction 59) but as the product is RCHOH this merely leads to a simplification of the 'spur' population. The absolute rate constants of H-atoms with alcohols are not particularly high in aqueous medium (10^7–10^8 $mole^{-1}$ sec^{-1})[97] and there is a strong indication that they are even lower in alcohol medium[35]. Reactions of H-atoms with other 'spur' species are, however, probably very rapid. It thus seems reasonable to propose the following reactions leading to molecular products in alcohol spurs:

	Rate constants ($mole^{-1}$ sec^{-1})	
$e^-_{solv} + e^-_{solv} \longrightarrow H_2 + 2\,RCH_2O^-$	1×10^{10} [99]	(71)
$e^-_{solv} + H^\cdot \longrightarrow H_2 + RCH_2O^-$	$2{\cdot}5 \times 10^{10}$ [99]	(72)
$e^-_{solv} + RCHOH^\cdot \longrightarrow RCH_2OH + RCH_2O^-$	$3{\cdot}0 \times 10^{10}$ [99]	(73)
$e^-_{solv} + RCH_2OH_2^+ \longrightarrow RCH_2OH + H^\cdot$	2×10^{10} [98]	(74)
$H^\cdot + H^\cdot \longrightarrow H_2$	2×10^{10} [100]	(75)
$H^\cdot + RCHOH^\cdot \longrightarrow RCH_2OH$	2×10^{10} [101]	(76)

* This statement is not strictly true, as products of ion-molecule reactions can be classified as intra-spur molecular products. It is however correct if we consider the 'spur' behaviour of only those intermediates which have survived 10^{-10} sec after the initial ionization. The situation then parallels the definition of a spur in water.

[Rate constants are those obtained for the analogous reactions in water. Thus $k_{73} = k(e^-_{solv} + OH)$ and it is tacitly assumed that this is not much different from $k(e^-_{solv} + RCHOH)$.]

Disproportionation and dimerization of hydroxy-alkyl radicals might also be included as spur reactions but as their rate constants are by more than an order of magnitude lower[13] than reactions (71–76) they are probably of less importance. In support of this it may be pointed out that the product of dimerization, glycol, does not show a molecular yield in the presence of scavengers.

Recent proof of the existence of regions of high ion and radical concentrations in irradiated alcohols has come from Thomas and Bensasson[102], who have shown that after electron-beam irradiation with nano-second pulses, solvated electrons disappear rapidly immediately after the pulse followed by a slower decay. They suggest that the rapid decay is due to reactions (73) and (74) in the spurs. In support of this, rough calculations[26] of the competition between the various reactions indicate that (73) and (74) account for 80% of the decay of solvated electrons.

It therefore seems reasonable to expect a molecular yield of hydrogen due to reactions (71), (72) and (75) in the spurs. According to reactions (71–76) hydrogen appears to be the only product which is formed by molecular processes in the sense applied in water radiolysis. In the broader sense of scavengeable products we may include other molecular processes such as ion-molecule reactions (77) and molecular elimination from excited molecules. The latter type of reactions have not been unequivocally demonstrated but there is no reason to doubt the possibility of reactions such as (78).

$$RCHOH^+ + RCH_2OH \longrightarrow RCHO + RCH_2OH_2^+ \quad (77)$$

$$RCH_2OH^* \longrightarrow RCHO + H_2 \quad (78)$$

The occurrence of reactions such as (77) and (78) explains the observation of molecular yields of aldehydes, for example.

A final mechanism which leads to molecular yields involves hydrogen abstraction by radicals possessing excess kinetic energy (so-called hot atom reactions). For example, the hydrogen atom formed in reaction (78a) will receive a large fraction of the excess energy of the parent ion in the form of kinetic energy. Consequently, it will react readily with the substrate by abstraction and will not be as readily scavenged as thermal energy hydrogen atoms.

$$RCH_2OH^+ \longrightarrow RCHOH^+ + H \quad (78a)$$

Experiments on deuterated alcohols led Myron and Freeman[103] to

the conclusion that the unscavengeable hydrogen found in the radiolysis of ethanol was formed from a very reactive species such as a hot hydrogen atom. Other evidence for hot hydrogen atoms is rather speculative but there does seem to be good reason to believe that they do form in irradiated alcohols, particularly in the lower homologues[55].

VI. GENERAL REACTION MECHANISM

As previously discussed, the discovery of the solvated electron in water and other polar liquids strongly supports the Lea–Platzman[34] model of slow thermalization of subexcitation electrons followed by solvation. Nevertheless, it is clear that electron solvation is precluded in nonpolar liquids and furthermore that electron escape from the parent ion is not favoured in liquids with small dielectric constants (ε). The ε for the aliphatic alcohols decreases with increasing chain length and a corresponding decrease in the yields of solvated electrons might be expected.

The above arguments have been used as the basis of a general theory[35, 104] to describe the fate of subexcitation electrons in irradiated liquids. In broad outline the theory states that the Lea–Platzman[34] and Samuel–Magee[32] models are special cases of the general theory; the former being applicable when ε is large (>80) and the latter applicable in nonpolar systems ($\varepsilon < 10$). The intermediate region is then characterized by competition between subexcitation electron escape on the one hand and geminate recombination on the other.

Quantitatively the theory may be expressed as follows:

(i) When an electron-ion pair is formed in a spur the electron will possess excess kinetic energy and will move a certain distance from the parent ion before this energy is degraded and the electron is thermalized. The actual distance γ depends on the initial energy of the electron for which there is a whole spectrum of values, and, hence, there will be a spectrum of γ-values.

(ii) The probability that an ion-pair of initial separation γ will escape geminate recombination is given by the Onsager[105] relationship:

$$\Phi(\gamma) = \exp(-r/\gamma) \qquad \text{(A)}$$

where r = the effective recombination radius of a pair of thermal energy ions in a medium with dielectric constant ε; e is the charge

on an ion ($4{\cdot}80 \times 10^{-10}$ e.s.u.) and

$$r = \frac{e^2}{\varepsilon kT} \tag{B}$$

(iii) If N(Y) is the relative number of electrons that attain a distance Y from their parent ion, then the fraction of electrons which escape is given by the expression

$$F = \int N(Y)\, \phi(Y)\, dy \tag{C}$$

The yield of free ions (or in the alcohols, solvated electrons) per 100 eV is then given by

$$G(\text{free ions}) = F.G(\text{ionization}) \tag{D}$$

where G(ionization) = number of ion-pairs initially produced per 100 eV.

Equation (C) may be solved by constructing a histogram of the relative number of electrons in each of a series of energy intervals followed by numerical integration.

The theory has been applied to the aliphatic alcohols using the following mechanism:

$$RCH_2OH \rightsquigarrow RCH_2OH^+ + e^- \tag{79}$$

$$RCH_2OH^+ + RCH_2OH \longrightarrow RCH_2O^{\cdot} + RCH_2OH_2^+ \tag{80}$$

Escape $$e^- + n\,RCH_2OH \longrightarrow e^-_{solv} \tag{81}$$

Recapture $$e^- + RCH_2OH_2^+ \longrightarrow RCH_2OH + H \tag{82}$$

It is assumed that reaction (80) precedes neutralization and recent data on reaction rates of ion-molecule reactions substantiate this. Thus free electrons become solvated electrons and recaptured electrons become hydrogen atoms. If reactions (81) and (82) are the only sources of these intermediates, the theory may be tested by experimentally determining $G(e^-_{solv})$ and G(H). The significance of these values is that $G(e^-_{solv}) = G$(free ions), the quantity to be compared, and $G(e^-_{solv}) + G(H) = G(e^-_{TOTAL}) = G$(ionization) which is required for the calculations.

It has been shown that it is possible to determine $G(e^-_{solv})$ and G(H) experimentally and we may now compare these values with the theoretical ones derived from the electron escape theory. The values are given in Table 15 for a number of alcohols and plotted as a function of the dielectric constant in Figure 4.

The agreement is quite satisfactory and points to the general validity of the theory which may be reiterated as follows:

When a liquid is irradiated ion-electron pairs are produced in

TABLE 15. Comparison of experimental[35, 42] and theoretical yields of the precursors of hydrogen.

Alcohol	Methanol	Ethanol	Propanol	*i*-Propanol	Butanol	Pentanol	Hexanol
ε	32·6	24·3	20·1	18·3	17·1	13·9	13·3
$G(e^-_{solv})$							
Expt	1·3	1·00	0·7	0·7	0·55	0·40	0·40
Theor	1·5	1·15	0·9	0·75	0·65	0·55	0·50
$G(H)$							
Expt	2·4	2·3	1·9	1·9	2·00	2·30	2·30
Theor	2·2	2·15	1·7	1·85	1·90	2·15	2·20
G(ionization)	3·7	3·3	2·6	2·6	2·55	2·70	2·70

isolated volume elements called spurs. Depending on its kinetic energy, such an electron will travel a certain distance from its parent ion before becoming thermalized. The subsequent fate of the electron is determined by the polarity of the medium.

If the dielectric constant of the medium is large the coulombic attraction between the electron and the counter ion is weak and the electron tends to escape the electrostatic sphere of interaction. Furthermore, if the dielectric relaxation time is short the substrate molecules tend to orientate their dipoles about the electron forming

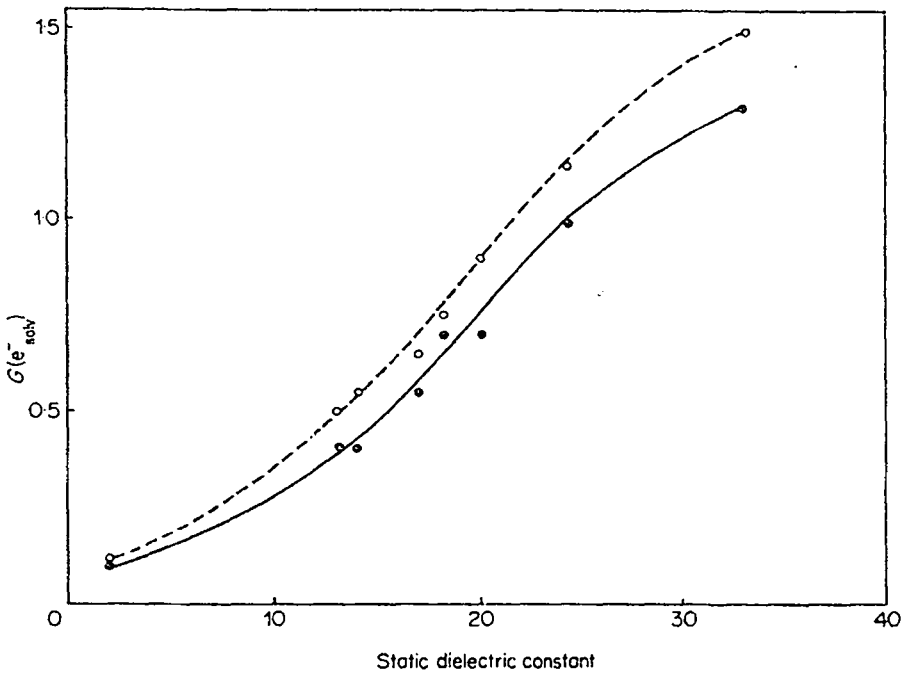


FIGURE 4. Effect of dielectric constant on solvated electron yields.

a solvation sheath which further lessens the probability of geminate recombination. Under these conditions the counter ion and solvated electron react independently, giving rise to an ionic mechanism. This corresponds to the Lea–Platzman formulation of the primary process.

If the dielectric constant of the medium is small the coulombic attraction is strong and the probability of recapture is high. Furthermore, if the time required for recapture is short, the positive ion will not have reacted with the substrate and the product of the neutralization reaction is an excited molecule. Under these conditions the

electron and the counter ion do not react independently and dissociation of the excited molecule gives rise to a free radical mechanism. This corresponds to the Samuel–Magee formulation of the primary process.

Intermediate dielectric constants give rise to competition between escape and recapture and the mechanism is both ionic and free radical. Neither of the earlier formulations cover this situation.

Freeman has calculated[106] that the time required for thermalization of the major portion of subexcitation electrons is between 10^{-11} and 10^{-10} sec. Thus in terms of the arguments proposed in section V.A.2.b there is sufficient time for ion fragmentation and ion-molecule reaction to take place before electron solvation. Accordingly we may now write down the following general reaction scheme for the primary ionic reactions:

Ionization	$RCH_2OH \rightsquigarrow RCH_2OH^{+*} + e^-$	(A)
Fragmentation	$RCH_2OH^{+*} \longrightarrow RCH_2OH^+$	(B)
	$\longrightarrow RCHOH^+ + H$	(C)
	$\longrightarrow R^\cdot + CH_2OH^+$	(D)
	$\longrightarrow R^+ + CH_2OH^\cdot$	(E)
H-atom abstraction	$RCH_2OH^+ + RCH_2OH \longrightarrow RCH_2OH_2^+ + RCHOH^\cdot$	(F)
Proton transfer	$RCH_2OH^+ + RCH_2OH \longrightarrow RCH_2O^\cdot + RCH_2OH_2^+$	(G)
Proton transfer	$RCHOH^+ + RCH_2OH \longrightarrow RCHO + RCH_2OH_2^+$	(H)
Proton transfer	$CH_2OH^+ + RCH_2OH \longrightarrow CH_2O + RCH_2OH_2^+$	(I)
Charge transfer	$R^+ + RCH_2OH \longrightarrow R^\cdot + RCH_2OH^+$	(J)
Hydride ion transfer	$R^+ + RCH_2OH \longrightarrow RH + RCHOH^+$	(K)

The product ions formed in (J) and (K) will, of course, react further via (F), (G) and (H) so that all primary ions will be converted to alkyl-hydroxonium ions and the only neutralization reaction will be (L).

Electron recapture	$RCH_2OH_2^+ + e^- \longrightarrow RCH_2OH + H$	(L)
Electron escape	$e^- + n\,RCH_2OH \longrightarrow e^-_{solv}$	(M)

The period required for reactions (A–M) covers the time scale 10^{-17}–10^{-10} sec. During this time neutral excited molecules may also decompose and although the following reactions are, at the present time, rather speculative they can conveniently be included for the sake of completeness.

Excitation	$RCH_2OH \rightsquigarrow RCH_2OH^*$	(N)
Collisional deactivation	$RCH_2OH^* \longrightarrow RCH_2OH$	(O)

Dissociation $RCH_2OH^* \longrightarrow RCHOH^{\cdot} + H^{\cdot}$ (P)

$\longrightarrow R^{\cdot} + CH_2OH^{\cdot}$ (Q)

Molecular elimination $RCH_2OH^* \longrightarrow RCHO + H_2$ (R)

$\longrightarrow RH + CH_2O$ (S)

The intermediates formed in the above reactions will still be contained in the original spur at this point in time [10^{-10} sec after the primary steps (A) and (N)]. Spur reactions and spur expansion now take place. We shall only consider the most important spur reactions although it must be remembered that other possibilities also exist.

Spur reaction $e^-_{solv} + H^{\cdot} \longrightarrow H_2 + RCH_2O^-$ (T)

Spur reaction $e^-_{solv} + e^-_{solv} \longrightarrow H_2 + 2\,RCH_2O^-$ (U)

Spur reaction $e^-_{solv} + RCH_2OH_2^+ \longrightarrow RCH_2OH + H^{\cdot}$ (V)

Spur reaction $H^{\cdot} + H^{\cdot} \longrightarrow H_2$ (W)

The following two reactions also take place in the spurs but as they lead to no net reaction are considered separately:

Back reaction $e^-_{solv} + RCHOH^{\cdot} \longrightarrow RCH_2OH + RCH_2O^-$ (X)

Back reaction $H^{\cdot} + RCHOH^{\cdot} \longrightarrow RCH_2OH$ (Y)

It should be pointed out that the production of RCH_2O^- ions does not represent decomposition of the alcohol as they are stable and do not react further except in the neutralization step.

Neutralization $RCH_2OH_2^+ + RCH_2O^- \longrightarrow 2\,RCH_2OH$ (Z)

The spur reactions are in competition with diffusion out of the spurs which results in a uniform distribution of the intermediates, e^-_{solv}, $H^{\cdot}$, H^*, $R^{\cdot}$, $CH_2OH^{\cdot}$, $RCH_2O^{\cdot}$ and $RCHOH^{\cdot}$ in the bulk medium. With the exception of H^* (hot hydrogen atom) which will react within the first few collisions, the products of the further reactions of these species will all be scavengeable.

Bulk reactions $e^-_{solv} + RCH_2OH \longrightarrow H_2 + RCHOH^{\cdot} + RCH_2O^-$ (AA)

(H-abstraction) $H^{\cdot} + RCH_2OH \longrightarrow H_2 + RCHOH^{\cdot}$ (BB)

(H-abstraction) $H^* + RCH_2OH \longrightarrow H_2 + RCHOH^{\cdot}$ (CC)

(H-abstraction) $R^{\cdot} + RCH_2OH \longrightarrow RH + RCHOH^{\cdot}$ (DD)

(H-abstraction) $CH_2OH^{\cdot} + RCH_2OH \longrightarrow CH_3OH + RCHOH^{\cdot}$ (EE)

(H-abstraction) $RCH_2O^{\cdot} + RCH_2OH \longrightarrow RCH_2OH + RCHOH^{\cdot}$ (FF)

(Disproportionation) $2\,RCHOH^{\cdot} \longrightarrow RCHO + RCH_2OH$ (GG)

(Dimerization) $2\,RCHOH^{\cdot} \longrightarrow (RCHOH)_2$ (HH)

VII. EFFECT OF PHASE

Throughout this review we have dealt specifically with irradiation effects in liquid alcohols. Work has also been done on radiolyses in the solid and vapour phases and we shall consider these in some detail in the present section.

A. Vapour Phase

The vapour-phase radiolysis of methanol was studied by Baxendale and Sedgwick[107], who found a twofold increase in $G(H_2)$ and $G(CH_2O)$ as compared to the liquid phase (Table 16). More methanol is decomposed (cf column $-CH_3OH$) in the vapour phase which may be due to the following factors: dissociation of excited species competes with collisional deactivation and the decreased collision frequency in the gas phase will favour increased decomposition; the Franck–Rabinowitch[108] 'cage effect' which tends to promote the recombination of ion and radical pairs in the liquid phase does not apply in the vapour phase. The effect may be even more pronounced as the vapour-phase results were obtained at much higher total doses than those used in the liquid-phase experiments.

TABLE 16. Product yields in the vapour- and liquid-phase radiolysis of methanol.

Product	H_2	CH_2O	$(CH_2OH)_2$	CO	CH_4	$(-CH_3OH)$
G-gas	10·4	5·6	3·1	0·84	0·26	12·9
G-liquid[18]	5·4	2·2	3·7	0·15	0·80	10·6

Myron and Freeman[103] have compared gas- and vapour-phase results in the radiolysis of ethanol at comparable doses and, as seen in Table 17, there is a much more pronounced difference in $G(-C_2H_5OH)$ between the phases than observed in the case of methanol.

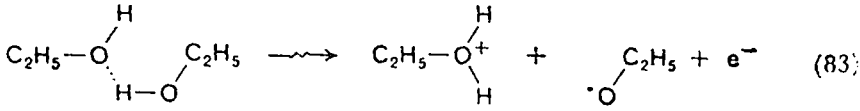
TABLE 17. Product yields in the vapour-phase radiolysis of ethanol.

Product	H_2	CH_3CHO	Glycol	CH_4	CO	$(-C_2H_5OH)$
G-gas[a]	7·6	4·5	1·35	1·70	1·1	9·4
G-gas[b]	7·5	3·5	4·0	2·3	0·6	13·9
G-liquid[b]	4·2	1·8	2·5	0·5	0·04	7·5

[a] ^{210}Po-rays [b] ^{60}Co-rays.

As pointed out by Myron and Freeman[103], even these results obtained at the same dose cannot be rigidly compared as the gas-phase experiments were conducted at 100°C and the liquid-phase data apply to 28°C. Nevertheless, as we shall see later, the gas-phase yields do not seem to be significantly dependent on temperature below 100°C and the values in Table 17 are probably representative.

The mechanism is probably very similar to that operative in the liquid phase except where solvation effects play a role. One such exception, suggested by Myron and Freeman[103], is the proton transfer reaction (83) which is probably favoured over other possibilities in the liquid phase because of hydrogen bonding.



(83)

Electron solvation, as such, is precluded in the vapour phase although it is possible that clusters of neutral molecules associated with positive ions may occur[66, 109–111]. Thus it is possible that the neutralization reaction will be rather different in the vapour phase[107].

$$RCH_2OH_2^+ + e^- \longrightarrow RCH_2OH^* + H \quad (84)$$

$$RCH_2OH^* \longrightarrow RCHO + H_2 \quad (85)$$

The latter dissociation has been substantiated in the vapour-phase photolysis of methanol[80]. The decomposition of excited molecules in the primary act is also thought[103] to proceed via reaction (85). These reactions account for the increased hydrogen and aldehyde yields in the vapour phase.

Myron and Freeman[103] point out that in addition to overall increases, the ratio $G(CH_4)/G(H_2)$ is much higher in the vapour than in the liquid phase. They explain this in terms of 'caging' in the liquid phase being more important for radical pairs such as ($CH_3^\bullet$, $CH_2OH^\bullet$) than for pairs containing a hydrogen atom which diffuses much more freely ($CH_3CHOH^\bullet$, $H^\bullet$).

Meaburn and Mellows[112] have studied the effect of solutes on the hydrogen yield and derived values for the precursors as follows: $G(e^-) = 4{\cdot}1$, $G(H) = 4{\cdot}9$, $G(H_2)_m = 2{\cdot}1$. Assuming that all the electrons formed in the primary ionization act are scavenged we may write

$$G = 4{\cdot}1 \quad RCH_2OH \rightsquigarrow RCH_2OH^+ + e^- \quad (86)$$

$$G = 4{\cdot}9 \quad RCH_2OH \rightsquigarrow RCHOH^\bullet + H^\bullet \quad (87)$$

As in the liquid phase, values for $G(H_2)$ vary considerably from investigation to investigation. Values of 6·4 [113], 7·5 [103], 8·9 [114], 10·4 [107], 11·0 [115] and 11·1 [112] have been reported. The variation is partially due to a dose-effect[115] similar to that observed in the liquid phase and there may be a post-irradiation effect[107] with borate in pyrex glass. Meaburn and Mellows[112], however, found no difference in $G(H_2)$ from soft glass and from pyrex vessels.

The effect of temperature and pressure on the vapour-phase radiolysis of several alcohols has been studied by Anderson and Winter[113]. They found that, at sufficiently high pressures, the hydrogen yields fall in two plateau regions separated by a small temperature range in which yields change markedly for small differences in temperature. The onset of the increase in $G(H_2)$ is between 120°C and 150°C for methanol, ethanol and *n*-propanol. Above 200°C a further rapid increase in $G(H_2)$ and $G(CH_4)$ is observed in all three alcohols and the effect appears to be more marked in ascending the homologous series. At constant temperature the yields of H_2 and CH_4 appear to decrease with increasing pressure, reaching limiting yields at pressures greater than 2 atmospheres.

They suggest that the initial increase in $G(H_2)$ is due to the breaking down of ion clusters of the type $ROH_2^+(ROH)_n$ which stabilize the ion with respect to dissociative charge neutralization.

The concept of ion clusters has also been invoked by Freeman[116] to explain high yields of diethyl ether and methanol in the radiolysis of ethanol at 350°C. At these temperatures radiation-sensitized pyrolysis of ethanol takes place.

B. *Solid* State

The primary effects of radiation on frozen alcohols are probably similar to those produced in the liquid state, though the rigid structure of the solid will affect subsequent chemical reactions. Thus subexcitation electrons might be expected to be trapped in the matrix in a similar fashion to their solvation in liquid alcohols. A distinction should, however, be drawn between trapped and solvated electrons depending on whether or not the trap existed before the electron arrived at the site and whether or not orientational polarization can occur.

As opposed to the liquid state the mobility of free radicals is low and the probability of recombination close to the track is high. Thus it is generally found that hydrogen yields are lower in the solid than in the liquid state as shown in Table 18.

TABLE 18. $G(H_2)$ in the radiolysis of alcohols in the liquid and solid states[21, 85].

Alcohol	Methanol	Ethanol	*n*-Propanol	*i*-Propanol	*n*-Butanol
Liquid	5·66	5·53	4·09	3·74	4·18
Solid	3·60	4·60	4·42	3·63	3·54

The effect of phase on other radiolysis products is more complicated and conflicting reports are to be found in the literature. In the case of methanol, for example, Hayon and Weiss[117] found no aldehyde at −196°C whilst the glycol yield increased by 0·9*G* units. Johnsen[85], however, found only a slight reduction in aldehyde and a decrease in glycol yield. This finding was corroborated by Teply and co-workers[118] but even in cases of qualitative agreement, there are large discrepancies in quoted values at −196°C. Some of the variation might be due to a dose-effect although this parameter has not been thoroughly studied.

At the present time, the most reasonable description of solid-state methanol radiolyses points to a considerable reduction in G(HCHO) and a much less pronounced decrease in G(glycol) as compared to the liquid state. If we assume that glycol formation is a free radical process and aldehyde a molecular process, as in the liquid state, the following explanations seem reasonable:

Enhanced recombination of unlike radicals in the spurs reduces G(glycol).

The lower temperature (−196°C) decreases the importance of radical dissociation, which is a process of high activation energy (88), leading to formaldehyde production[117].

$$CH_2OH^{\cdot} \longrightarrow CH_2O + H^{\cdot} \qquad (88)$$

In the case of liquid ethanol there is qualitative agreement between reported values[36, 85, 119] and taking average values it seems that $G(CH_3CHO)$ is 30% higher and G(glycol) is 50% lower than in the liquid phase. The reduction in the glycol yield is as expected but the increase in G(aldehyde) is completely incompatible with the explanation offered for formaldehyde formation in methanol. Any explanation is, at present, speculative but a tentative suggestion is that reaction (89), which reduced acetaldehyde yields at doses above 10^{18} eV/ml in the liquid phase, is not important in the solid state.

$$e^-_{solv} + CH_3CHO \longrightarrow CH_3CHO^- \qquad (89)$$

The radiolysis of higher alcohols in the solid state leads to even

more complicated results with hydrogen yields increasing in some cases and decreasing in others[21]. In general, the effect of going to the liquid state on the production of carbonyl compounds and glycols is similar to that observed for ethanol. Yields of carbonyls are slightly increased but the already low glycol yields essentially vanish.

VIII. EFFECT OF TEMPERATURE

The effect of temperature on the hydrogen yield from −72°C to 20°C in irradiated ethanol was studied by Basson[120], who found $G(H_2)_o$ to be independent of temperature over this range. Studies of scavenger effects, however, showed that the yields of the precursors, $G(e^-_{solv})$ and $G(H)$, were strongly temperature dependent as shown in Table 19.

TABLE 19. Temperature dependence of hydrogen precursor yields in the radiolysis of liquid ethanol.

Temp. °C	$G(H_2)_o$	$G(e^-_{solv})$	$G(H)$	$G(H_2)_m$
25	5·0	0·95	2·33	1·72
0	4·9	1·05	2·22	1·73
−20	5·0	1·15	2·15	1·70
−72	5·1	1·30	2·00	1·70

The constancy in $G(H_2)_o$, the initial yield, is explained by the fact that although the ratio $G(e^-_{solv})/G(H)$ increases with decreasing temperature the sum $G(e^-_{solv}) + G(H)$ remains constant as does the molecular yield, $G(H_2)_m$. If the formation of e^-_{solv} and H in reactions (92) and (93) is the sole fate of the subexcitation electrons produced in (90) then the experimental results indicate that G(ionization) $= G(90)$ is independent of temperature

$$CH_3CH_2OH \longrightarrow CH_3CH_2OH^+ + e^- \quad (90)$$

$$CH_3CH_2OH^+ + CH_3CH_2OH \longrightarrow CH_3CH_2O^{\cdot} + CH_3CH_2OH_2^+ \quad (91)$$

$$e^- + n\,CH_3CH_2OH \longrightarrow e^-_{solv} \quad (92)$$

$$e^- + CH_3CH_2OH_2^+ \longrightarrow CH_3CH_2OH + H^{\cdot} \quad (93)$$

The results indicate furthermore that reactions (92) and (93) are competitive and that the extent of the competition is temperature dependent. This was interpreted in terms of the increase in dielectric constant with decreasing temperature. Increasing the dielectric constant increases the probability of electron escape and solvation according to the expression $\phi(\text{escape}) = \exp(-e^2/\varepsilon kTy)$ where

ε = dielectric constant. The relationship between $G(e^-_{solv})/G(H)$ at different temperatures (and ε) closely resembles that obtained for a number of liquids of different dielectric constant which may be taken as evidence of the validity of this explanation.

A similar study was undertaken independently by Russell and Freeman[44] who also found $G(H_2)_o$ constant between -112°C and 25°C. Above this temperature, however, $G(H_2)_o$ began to increase from 5·0 at 25°C to about 6·0 at 100°C, then remaining constant up to 150°C. This increase has been tentatively attributed to an excited molecule (Y) which is deactivated at low temperatures but, with the additional increment of thermal energy acquired at high temperatures, can decompose to yield H_2 or H (reaction 94). A crude estimate of the activation energy of reaction (94) was made and was of the order of 10 kcal/mole.

$$Y \longrightarrow H \text{ or } H_2 + \text{products} \qquad (94)$$

Their data on N_2O-scavenging taken in conjunction with theoretical considerations indicates that $G(e^-_{solv})$ decreases with increasing temperature from 1·5 at -112°C to 1·1 at 25°C in reasonable agreement with Basson's findings.

In a reinvestigation of the system the same authors[45] showed that certain anomalies existed in their earlier work. These could be related to the formation of ethyl chloride in studies of the acid effect at high temperatures, when HCl was used. Taking account of this effect required certain changes in the values of parameters used in the calculation of $G(e^-_{solv})$. In particular, a value of G(ionization) = 4·0 instead of the earlier 3·0 was used giving $G(e^-_{solv}) = 1·9$ at -112°C, 1·5 at 25°C, 1·5 at 90°C and 1·6 at 145°C.

Russell and Freeman[29] have also studied the effect of temperature on the hydrogen yield in irradiated 2-propanol. Their results do not appear to fit the pattern observed in the case of ethanol, which is rather surprising. Thus, for example, $G(H_2)$ increased roughly linearly with temperature from $G(H_2) = 3·6$ to 5·5 between -85°C and 140°C. Higher temperatures up to 225°C caused no further increase in yield. They concluded that the increase was due to temperature and acid-dependent precursors. In ethanol these precursors are thought to be different and are denoted Y and X, but in 2-propanol the additional species are not invoked and solvated electrons are postulated as the precursors in both cases. The explanation for the differences between ethanol and 2-propanol are not entirely convincing and further studies are clearly indicated.

IX. EFFECT OF DOSE

The effect of total energy input on product yields was first studied by Newton and McDonell[7], who found significant reductions for all products as the dose was increased. The effect was ascribed to a 'protective' action on the part of aldehydes, glycols and unsaturated compounds either by energy transfer from the alcohol to the product without subsequent reaction or by acting as radical traps. The radical trap mechanism was proposed as follows:

$$H^{\cdot} + CH_3CH_2OH \longrightarrow H_2 + CH_3CHOH^{\cdot} \quad (95)$$

$$H^{\cdot} + CH_3CHO \longrightarrow CH_3CHOH^{\cdot} \quad (96)$$

$$H^{\cdot} + (CH_3CHOH)_2 \longrightarrow CH_3CHOH^{\cdot} + C_2H_5OH \quad (97)$$

$$H^{\cdot} + RCH = CH_2 \longrightarrow RCH_2CH_2^{\cdot} \quad (98)$$

The mechanism was extremely plausible and as we shall see the concept of internal scavenging was later proved correct.

Further work showed, however, that product yields began decreasing at very much lower doses than used in the above work. In ethanol, for example, $G(H_2)$ began to decrease as the dose was increased above 10^{18} eV/ml. Now if we assume that acetaldehyde, for example, is acting as a radical trap, then we have a competition between reactions (95) and (96) which is described by equation A

$$G(95) = G(H_2) = \frac{G(H)}{1 + \dfrac{k_2[CH_3CHO]}{k_1[CH_3CH_2OH]}} \quad (A)$$

Taking $G(CH_3CHO) = 3$ and $D = 10^{18}$ eV/ml we find

$$[CH_3CHO] = 5 \times 10^{-5}\text{M}.$$

Furthermore,

$$k_1 \sim 1 \times 10^9 \text{ mole}^{-1} \text{ sec}^{-1}, k_2 \sim 7 \times 10^8$$

and

$$[CH_3CH_2OH] \sim 18\text{M}.$$

Thus

$$G(95) = G(H_2) = \frac{G(H)}{1 + \dfrac{7 \times 10^8 \times 5 \times 10^{-5}}{1 \times 10^9 \times 18}} = \frac{G(H)}{1{\cdot}000002} \sim G(H)$$

It is thus clear that at such low doses the product concentration is far too low significantly to affect the hydrogen yield. (This is also true if glycols or unsaturated compounds are invoked as radical traps.) It can, in fact, be shown that for $G(H) = 2$, a reduction of

$G(H_2)$ by only 0·2 would require $[CH_3CHO] = 5M$, a condition only met at very high doses.

A careful study[28] of the dose effect at doses between 10^{18}–10^{21} eV/ml (Figure 5) revealed that $G(H_2)$ and $G(CH_3CHO)$ decrease

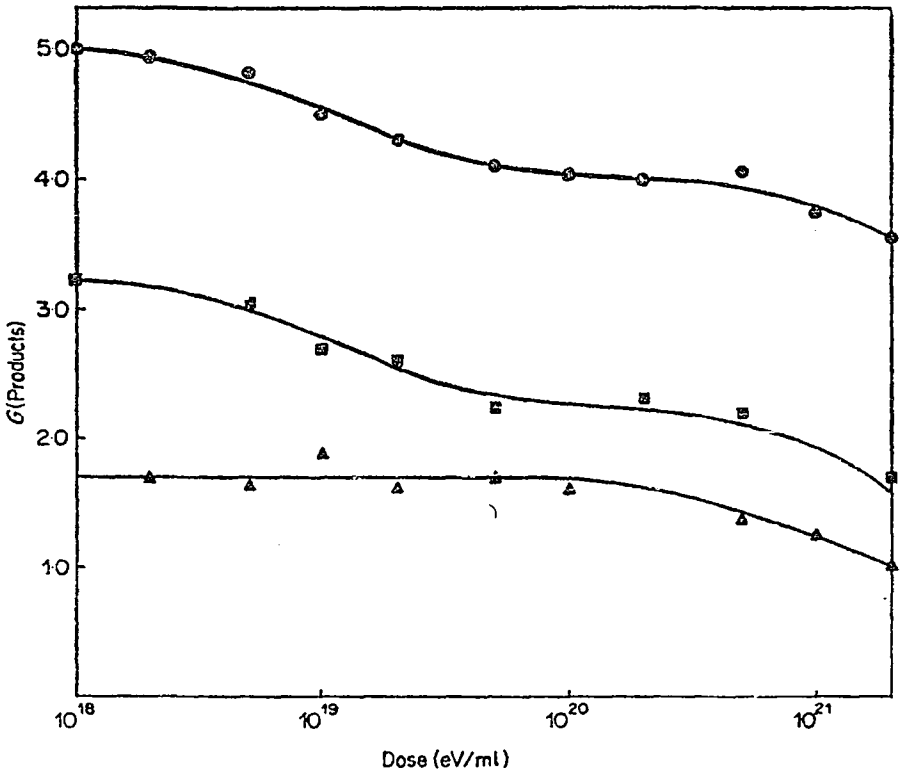


FIGURE 5. Product yields as a function of dose in the radiolysis of ethanol.
● Hydrogen ■ Acetaldehyde ▲ 2,3-Butanediol

in parallel fashion to a plateau value and at very high doses decrease again. G(glycol) on the other hand is independent of dose up to 10^{20} eV/ml. The twofold decrease in $G(H_2)$ was similar to that obtained with increasing concentration of added scavenger and suggested that two precursors of hydrogen, viz e^-_{solv} and H were being scavenged by a reaction product. The initial decrease in $G(H_2)$ was interpreted as due to the scavenging of solvated electrons by acetaldehyde according to the following mechanism:

$$e^-_{solv} + CH_3CH_2OH \longrightarrow H_2 + CH_3CHOH^{\cdot} + CH_3CH_2O^- \quad (99)$$

$$e^-_{solv} + CH_3CHO \longrightarrow CH_3CHO^- \quad (100)$$

$$CH_3CHO^- + CH_3CH_2OH_2^+ \longrightarrow CH_3CHOH + CH_3CH_2OH \quad (101)$$

This requires that $G(H_2) = G(CH_3CHO)$ and that as $G(CH_3CHOH)$ remains constant the yield of glycol due to the dimerization of these radicals will remain constant in agreement with the experimental findings.

Justification for invoking solvated electrons as the precursor scavenged by acetaldehyde was that hydrogen atoms react[121] with acetaldehyde both by addition (reaction 96) and abstraction (reaction 102). Thus the required stoichiometry cannot be obtained and a mechanism invoking H-atoms would predict a decrease in G(glycol) at low doses.

$$H + CH_3CHO \longrightarrow H_2 + CH_3C{=}O^{\cdot} \quad (102)$$

Furthermore, kinetic analysis of the data in Figure 5 gave ratios of k_{100}/k_{99} in agreement with values calculated from absolute rate constants of the solvated electron as obtained by pulse radiolysis.

The further decrease in product yields at high doses is probably due to H-atom scavenging by acetaldehyde and/or other products as suggested by the earlier workers.

The dose-effect offers an explanation to some of the variation in yields obtained by different workers. The yield of acetaldehyde in the radiolysis of ethanol, for example, can be correlated with the dose at which the determination was made (Table 20).

TABLE 20. $G(CH_3CHO)$ in the radiolysis of ethanol at different doses.

Dose $\times 10^{18}$ eV/ml	0·3	0·4	3·5	11·0	72	200
$G(CH_3CHO)$	3·14	3·20	2·05	1·90	1·88	1·40
Reference	36	19	27	23	13	85

In contrast to the effect of total dose, the dose-rate[28] does not seem to affect yields significantly (Table 21). This indicates the

TABLE 21. Effect of dose-rate on the yields of the major products in the radiolysis of ethanol. (Total dose 10^{19} eV/ml.)

Dose-rate in eV/ml/min $\times 10^{16}$	3·2	8	13	32
$G(H_2)$	3·90	4·08	3·88	3·72
$G(CH_3CHO)$	2·24	2·36	2·02	2·14
$G(CH_3CHOH)_2$	1·68	1·62	1·46	1·73

absence of chain reactions in agreement with the proposed mechanism. Furthermore, the range explored is too narrow significantly to affect the local concentration of primary intermediates although it might be expected that very high dose-rates would produce effects characteristic of radiations of high LET (see section X).

X. EFFECT OF LINEAR ENERGY TRANSFER

In the previous sections we have considered the effects of γ-radiation from the isotope cobalt-60. Some studies have also been made using other kinds of radiation and we shall now consider these.

The processes of ionization and excitation along the particle track are common to all kinds of radiation. On the other hand it has been demonstrated that the chemical consequences of irradiation by various kinds of radiation are dissimilar. These differences can be attributed almost solely to one effect: differences in the density of ionization along the particle track. The quantity used to describe the ionization density produced by a given radiation is referred to as Linear Energy Transfer (LET). LET is defined as the linear rate of energy loss by an ionizing particle traversing a material medium. LET increases with decreasing particle energy, with increasing particle charge and with increasing electron density of the medium.

The higher the LET the higher the initial local concentration of free radicals and ions about the particle track will be. Thus reactions between intermediates are favoured over reactions with the substrate or solutes. It can, therefore, be expected that high LET radiations will lead to higher unscavengeable yields and lower radical yields. Furthermore the greater probability of geminate recombination of ion and radical pairs should decrease overall product yields.

The effect of LET on methanol was studied by McDonell and Gordon[8], who determined product yields in irradiations with 28 MeV cyclotron accelerated helium ions (LET = 3·0 eV/Å) and ^{60}Co γ-rays (LET = 0·03 eV/Å). Their results are summarized in Table 22.

$G(-CH_3OH) = G(CH_2O) + 2(CH_2OH)_2 + G(CO) + (CH_4)$ is derived from the following stoichiometric equations which describe the radiolytic decomposition of methanol:

$$CH_3OH \longrightarrow CH_2O + H_2 \quad (103)$$

$$2\,CH_3OH \longrightarrow (CH_2OH)_2 + H_2 \quad (104)$$

$$2\,CH_3OH \longrightarrow CH_4 + CO + H_2O + H_2 \quad (105)$$

TABLE 22. Products in the decomposition of methyl alcohol by ^{60}Co γ-radiation and by 28 MeV He-ions.

Product	G-^{60}Co	G-He-ions	G-He-ions (corrected)
Hydrogen	4·0	3·46	4·10
Formaldehyde	1·3	1·67	2·26
Glycol	3·0	1·74	2·30
CO	0·16	0·23	0·20
CH_4	0·24	0·36	0·36
$G(-CH_3OH)$	7·7	5·74	7·42

Comparison of the first two columns shows that the overall yields decrease significantly with increasing LET. The values are, however, not strictly comparable as they were obtained at different total doses. The ^{60}Co yields apply to a dose of $1{\cdot}5 \times 10^{19}$ eV/ml whereas the helium ion irradiation was 6×10^{21} eV/ml. As seen in section IX, product yields are strongly dose-dependent and it can be expected that the values given for the helium ion irradiation are significantly lower than the initial yields. The effect of dose on product yields in the helium ion irradiation of ethanol has been studied[7] and the results may be somewhat arbitrarily applied to the data in Table 22 to obtain values corrected for the dose effect. The derivation of the correction factors is given in Table 23.

TABLE 23. Dose-effects in the 28 MeV helium ion irradiation of ethanol.

G-values	H_2	CO	CH_4	Aldehyde	Glycol
$D_1 = 6 \times 10^{21}$ eV/ml	3·46	0·11	0·43	2·2	1·05
$D_2 = 3 \times 10^{20}$ eV/ml	4·10	0·093	0·43	3·0	1·40

The corrected yields show a less pronounced LET effect on $G(-CH_3OH)$ and G(glycol) but G(HCHO) is very much larger in the case of the high LET irradiation. It was suggested[8] that formaldehyde formation is a high activation energy process taking place only in the small, highly energized regions of the initial energy absorption (spurs). The observed increase in G(HCHO) could then be explained by the increasing importance of reaction (106) with increasing ionization density:

$$CH_2OH^{\cdot} \longrightarrow CH_2O + H^{\cdot} \qquad (106)$$

Increasing the importance of reaction (106) would then decrease the probability of the formation of glycol, assumed due to the dimerization of CH_2OH radicals which diffuse out of the spurs and react in the bulk medium (107).

$$2\,CH_2OH \longrightarrow (CH_2OH)_2 \qquad (107)$$

Lichtin and co-workers[22, 122] have also examined LET effects employing the α- and ^7Li recoils, of total energy 2·35 MeV per nuclear event, resulting from the absorption of thermal neutrons by boron present in the form of dissolved methyl borate. The LET characteristic of these recoils is approximately 30 eV/Å, i.e., ten times higher than 28 MeV–helium ions. They compared the results of these irradiations with ^{60}Co results obtained at comparable doses. These are given in Table 24.

TABLE 24. Product yields in methanol at different LET values.

Product	G-^{60}Co	G-recoils	G-fission fragments
Hydrogen	4·98	5·5	9·7
Formaldehyde	2·20	3·2	3·6
Ethylene glycol	3·20	0·7	0·8
CO	0·06	1·0	3·0
CH_4	0·43	0·6	0·9

Landsman and Butterfield[123] have reported yields for the ^{235}U fission fragment irradiation of methanol as shown in the fourth column of Table 24. Comparison of these results with those of Lichtin and co-workers should be made with caution, as the fission fragment work was carried out under conditions of high temperature (100°C) and dose (8×10^{20} eV/ml).

Assuming that the data in Tables 22 and 24 are comparable we have plotted product yields as a function of LET in Figure 6. The following observations may be made:

(a) The overall decomposition of methanol, as expressed by $G(-CH_3OH)$, decreases with LET over most of the range as might be expected on the basis of increased probability of back reactions with increasing radical and ion density. Above LET values of 30 eV/Å, however, an abrupt increase in $G(-CH_3OH)$ takes place similar to the behaviour of $G(-H_2O)$ in the radiolysis of water[124]. This suggests a source of increased methanol decomposition in tracks of high ionization density.

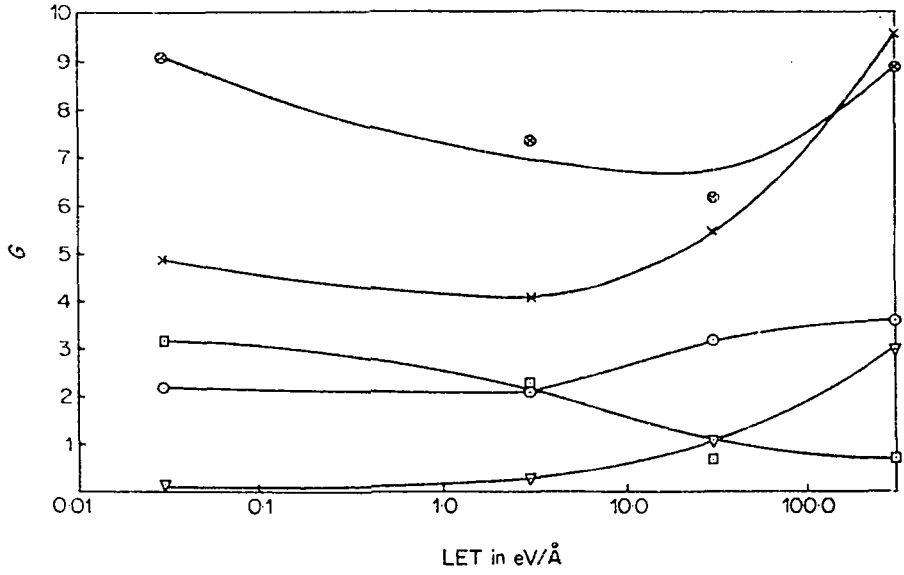


FIGURE 6. LET effect in the radiolysis of methanol.
⊗ (—CH_3OH) × H_2 ⊙ HCHO ⊡ $(CH_2OH)_2$ ▽ CO

(b) The yields of hydrogen and CO increase rapidly with increasing LET above 3 eV/Å with $\Delta G(H_2) = 5{\cdot}6$ and $\Delta G(CO) = 2{\cdot}8$. This may be stoichiometrically expressed by reaction (108) which could be the source of the increased methanol decomposition

$$CH_3OH \longrightarrow\!\!\!\!\!\sim\!\!\!\!\!\sim 2\,H_2 + CO \qquad (108)$$

(c) The increase in the formaldehyde yield over the entire range and the decrease in the glycol yield are, roughly speaking, mirror images. This suggests that their formation involves competing reactions and that the extent of the competition is LET dependent. If reactions (106) and (107) take place as suggested by Gordon and McDonell[8], they could account for the observed effects.

The effect of LET on radical and molecular yields in the radiolysis of methanol has also been investigated[22] (Table 25). These yields were derived using oxygen as solute and are dependent on the validity of the reaction mechanism.

As expected, and in agreement with aqueous radiation chemistry, the ratio of molecular products to radical products increases greatly

TABLE 25. Radical and molecular yields in the radiolysis of methanol by ^{60}Co γ-rays and $^{10}B(n,\alpha)^{7}Li$ recoils[22].

Species	H_2^M	H	CH_4^M	CH_3	CO	CH_2O^M	CH_2OH	$(CH_2OH)_2^M$
G-^{60}Co	1·9	3·1	0·2	0·2	0·08	2·2	6·2	0·1
G-Recoils	2·4	1·4	0·6	0·1	0·80	2·1	1·0	0·4

with increasing LET. Thus we find values of $G(M)/G(R)$ of 0·6 (H_2), 1·0 (CH_4) and 0·02 $(CH_2OH)_2$ for ^{60}Co-rays increasing to 1·7, 6·0 and 0·4 respectively, for recoil radiolysis.

No differentiation between H-atoms and solvated electrons was made in the above work. Imamura and Seki[125] investigated the effect of nitrous oxide, a specific electron scavenger, on the radiolysis of methanol by $^{10}B(n,\alpha)^{7}Li$ recoils and showed that the yield of solvated electrons was about one-tenth of that in γ-radiolysis. They concluded that the much higher density of ions and electrons in the recoil tracks results in a marked reduction in the average separation distance between ion-pairs and in an increased probability of electron recapture.

An LET effect in the vapour phase has been noted by Myron and Freeman[103], who compared ^{60}CO irradiation results with those obtained with ^{210}Po α-rays. The conditions of pressure, temperature, dose-rate, dose and surface to volume ratio of the reaction vessel were similar in both cases so that the differences shown in Table 26 must be attributed to differences in radiation quality.

TABLE 26. LET effects in the vapour-phase radiolysis of ethanol.

Product	H_2	CH_4	CO	C_2H_4	C_2H_6	CH_3CHO	1,2-Propane diol	2,3-Butane diol
G-^{60}Co	7·5	2·3	0·6	1·2	0·2	3·5	0·9	3·1
G-^{210}Po	7·6	1·7	1·1	0·7	0·2	4·5	0·15	1·2

The most striking difference between the γ- and α-radiolyses is the acetaldehyde/butanediol ratio, namely 1·1 for γ's and 3·8 for α's. The effect may be partially explained by the greater probability of reaction[109] in the densely ionized α-ray tracks.

$$e^-_{solv} + CH_3CH_2OH_2^+ \longrightarrow CH_3CH_2OH + H^\cdot \qquad (109)$$

If the greater part of the electron yield reacts in this way and the

H-atoms give rise to reactions (110–112) then each solvated electron produces a molecule of hydrogen and $\frac{1}{2}$ molecule of aldehyde or glycol.

$$H^{\cdot} + CH_3CH_2OH \longrightarrow H_2 + CH_3CHOH^{\cdot} \quad (110)$$

$$2\,CH_3CHOH^{\cdot} \longrightarrow CH_3CHO + CH_3CH_2OH \quad (111)$$

$$2\,CH_3CHOH^{\cdot} \longrightarrow (CH_3CHOH)_2 \quad (112)$$

In the case of γ-radiolysis, however, the probability of reaction (109) is greatly reduced and solvated electrons which diffuse out of the tracks disappear in reactions (113) and (114), which is their predominant fate at high doses (see section IX) such as used in this investigation[103] ($\sim 10^{20}$ eV/ml).

$$e^-_{solv} + CH_3CHO \longrightarrow CH_3CHO^- \quad (113)$$

$$CH_3CHO^- + CH_3CH_2OH_2^+ \longrightarrow CH_3CHOH + CH_3CH_2OH \quad (114)$$

Reaction (113) decreases the acetaldehyde yield and could explain the lower $G(CH_3CHO)$ in the γ-radiolysis.

This explanation can only be partially true as the occurrence of reaction (113) rather than (109) should also lead to a lower $G(H_2)$ in the γ-radiolysis, which is not observed, and should not affect the glycol yield which is almost three times lower.

The explanation offered by Newton and McDonell[7] for the higher $G(CH_3CHO)/G(\text{glycol})$ ratio in α- than in γ-irradiated liquid methanol can be applied to the present case and it may be that reaction (115) occurs in the dense tracks of α-particles rather than reactions (111) and (112)

$$CH_3CHOH \longrightarrow CH_3CHO + H \quad (115)$$

However, this requires a greater hydrogen yield in α-radiolyses which again is not observed.

Other reasons have been suggested by Myron and Freeman[103] but these are at present speculative and more work on the subject is clearly indicated; preferably at low doses where secondary reactions such as (113) do not complicate the interpretation.

XI. EFFECT OF OXYGEN

The presence of oxygen has a profound effect on the radiolysis of alcohols. In oxygen-saturated solutions the hydrogen yield is three times lower than in degassed solutions, the glycol yield is completely suppressed, the aldehyde yield increases several-fold and acids and peroxides are produced in high yield. Some values are shown in Table 27.

TABLE 27. Product yields in the radiolytic oxidation of aliphatic alcohols.

Alcohol	Hydrogen	Aldehyde	Glycol	Acid	Peroxide
Methanol[22]	1·9	8·7	0·1	1·5	3·1
Ethanol[19]	1·7	6·2	0	2·0	4·5
1-Propanol[126]	1·9	11·0	0	3·5	9·2
2-Propanol[127]	—	28·0[a]	0	—	19·0

[a] G(acetone) + G(aldehyde).

The reduction in $G(H_2)$ and G(glycol) is consistent with the scavenging of solvated electrons, hydrogen atoms and α-hydroxyalkyl radicals by oxygen. The increase in G(aldehyde) and the production of acids and peroxides must then be due to the reactions of the peroxy-radicals so formed. A mechanism capable of explaining the observed effects is the following:

$$(e^-_{solv})H^\cdot + O_2 \longrightarrow HO_2^\cdot \quad (116)$$

$$RCHOH^\cdot + O_2 \longrightarrow RCH(OH)O_2^\cdot \quad (117)$$

$$2\,HO_2^\cdot \longrightarrow H_2O_2 + O_2 \quad (118)$$

$$2\,RCH(OH)O_2^\cdot \longrightarrow RCH(OH)OOH + RCHO + O_2 \quad (119)$$

$$HO_2^\cdot + RCH(OH)O_2^\cdot \longrightarrow RCH(OH)OOH + O_2 \quad (120)$$

$$HO_2^\cdot + RCH_2OH \longrightarrow RCHOH^\cdot + H_2O_2 \quad (121)$$

$$RCH(OH)O_2^\cdot + RCH_2OH \longrightarrow RCH(OH)OOH + RCHOH^\cdot \quad (122)$$

$$RCH(OH)OOH \longrightarrow RCHO + H_2O_2 \quad (123)$$

$$RCH(OH)OOH \longrightarrow RCOOH + H_2O \quad (124)$$

Reactions such as (118–119) are thought to occur in aqueous solution[128, 129] and it seems reasonable to propose their occurrence in the alcohols. Reactions (121) and (122) are endothermic, however, and many workers do not consider them as possible steps in the mechanism. If they do take place a chain reaction must ensue and the yields of products should be dose-rate dependent. The evidence regarding the influence of dose-rate is rather contradictory with some workers finding a dependency and others not.

Choi and Lichtin[22] concluded that product yields in the radiolytic oxidation of methanol are not dependent on dose-rate and explained their results in terms of a nonchain mechanism. Habersbergerova[130] and co-workers, on the other hand, varied the dose-rate systematically over a wide range and showed that peroxide and aldehyde yields are dependent on the square root of the intensity as would be expected from a chain reaction. A dose-rate dependence in ethanol has also been found by Bach[9], and other workers have suggested

that a chain mechanism is required to explain the radiolytic oxidation of *n*-propanol[126] and of *i*-propanol[127].

Recently a systematic investigation[131] of dose-rate effects in some of the lower alcohols has been undertaken. Preliminary results indicate that the chain reaction does not take place in methanol but is important in all of the higher homologues. In the case of isopropanol, for example, *G*-values of over a hundred have been obtained.

Reactions (123) and (124) may take place after irradiation as hydroxy-hydroperoxides are known to decompose easily[132]. It has, for example, been shown[28] that pure samples of dihydroxy-diethyl peroxide decompose quantitatively to acetaldehyde and other products when injected into a gas chromatography column. The spectrophotometric determination of peroxides also involves the use of mineral acids[133] which are known to initiate hydrolysis of hydroxy-hydroperoxides. Thus, it is fairly certain that such compounds are frequently determined as their decomposition products.

Habersbergerova and co-workers[130] used a method of peroxide analysis[134] which differentiated between H_2O_2 and organic peroxides and concluded that the latter were produced in appreciable yield. Using paper chromatography, they identified the peroxide formed in methanol as hydroxymethyl-hydroperoxide and specifically excluded methyl hydroperoxide as a possible product. They found the yield of the hydroxymethyl-hydroperoxide to be strongly dose-rate dependent varying from 1 at high dose-rate to 15 at low values.

In complete contradiction to these results are the findings of Ladygin[135], who concluded that hydroxymethyl-hydroperoxide is absent in irradiated methanol and implied that methyl hydroperoxide is a product. To further complicate the picture it has been shown[136] that no peroxide is obtained when very dry methanol is irradiated. Addition of water before irradiation produces an abrupt change at 0·3% by weight with $G(H_2O_2)$ rising to 2·8, at which value it then remains constant, independent of further increases in (H_2O). Clearly the whole question of peroxide formation is complicated and more work is required to explain inconsistencies.

XII. EFFECT OF ACID

The addition of acid increases the yields of a number of products from irradiated alcohols and parallels the effect observed in the

radiolysis of water. Baxendale and co-workers[11, 18] studied the effect of sulphuric acid on methanol and found increases in $G(H_2)$ and $G(CH_2O)$ with increasing acid concentration. $G(CH_4)$ decreased while $G(CO)$ and G(glycol) remained constant. Yields were independent of concentration above 10^{-2}M. Similar results were obtained by Lichtin[137] at 10^{-2}M H_2SO_4, who, however, also observed an increase in G(glycol). This increase in the glycol yield has recently been confirmed by Seki and Imamura[47] although in this case the concentration of acid was ten times higher. These results are summarized in Table 28 and are given as the difference in the yield between acid and neutral radiolyses for each investigation.

TABLE 28. Effect of acid on methanol radiolysis.

Ref.	$\Delta G(H_2)$	$\Delta G(CH_2O)$	ΔG(glycol)	$\Delta G(CH_4)$	$\Delta G(CO)$	$[H_2SO_4]$
18	0·65	0·40	0·1	−0·2	−0·03	10^{-2}M
37	0·37	0·46	0·71	0	−0·01	10^{-2}M
47	0·72	1·09	0·34	−0·03	0·02	10^{-1}M

The agreement between the data sets is poor and it is difficult to arrive at a definite conclusion regarding the stoichiometry of the acid effect. It does, however, seem contrary to Baxendale and Mellows' suggestion, that the glycol yield does increase with acid concentration and that neither the methane nor the CO yield are dependent on this parameter.

The results have been interpreted in terms of solvated electrons which do not lead to the production of hydrogen in the absence of acid. If it is assumed that the increase in $G(H_2)$ is accompanied by an equivalent increase in G(HCHO), a possible explanation is that these electrons are normally captured by the ion CH_2OH^+ (reaction 125).

$$CH_2OH^+ + e^- \longrightarrow CH_2OH^{\cdot} \qquad (125)$$

In the presence of acid the methyl hydroxonium ion competes with the hydroxy-methyl ion for the electron (reaction 126) leaving the latter free to react with the substrate by proton transfer.

$$CH_3OH_2^+ + e^- \longrightarrow CH_3OH + H^{\cdot} \qquad (126)$$

$$CH_2OH^+ + CH_3OH \longrightarrow CH_2O + CH_3OH_2^+ \qquad (127)$$

The hydrogen atom reacts with the substrate to produce a molecule of hydrogen and the hydroxy-methyl radical (reaction 128). The net result, at sufficiently high acid concentration, is the production of one molecule of hydrogen and one of formaldehyde per electron.

The glycol yield, on the other hand, remains constant as reaction (129) is unaffected by the competition between reactions (125) and (126).

$$H^{\cdot} + CH_3OH \longrightarrow H_2 + CH_2OH^{\cdot} \quad (128)$$

$$2\,CH_2OH \longrightarrow (CH_2OH)_2 \quad (129)$$

Reactions (125) and (126) are thought to occur in the spurs and the relatively high concentration of acid required to produce an effect supports this suggestion.

This explanation, whilst very plausible, must be regarded with some doubt in view of the increase in G(glycol) found in other experiments. Furthermore it has not been established with any certainty that $\Delta G(H_2) = \Delta G(HCHO)$.

Adams and Sedgwick[27] have found that the effect of acid on the radiolysis of ethanol is similar to that noted by Baxendale and Mellows for methanol. $G(H_2)$ increases with (H_2SO_4) but G(glycol) remains constant—$G(CH_3CHO)$ was not measured but was assumed to increase in parallel fashion to $G(H_2)$. In a more recent investigation Ackerman and Basson[138] found increases in both acetaldehyde and glycol with $\Delta G(H_2) \sim 2\Delta G(CH_3CHO) \sim 2\Delta G$(glycol). They also showed that the presence of acid complicated the analysis of glycol by gas chromatography and suggested that this might account for the difference between their work and the earlier study[27]. The results are summarized in Table 29.

TABLE 29. Effect of acid on ethanol radiolysis.

Ref.	$\Delta G(H_2)$	$\Delta G(CH_3CHO)$	ΔG(glycol)	$\Delta G(CH_4)$	Acid
27	0·60	—	0	0	10^{-1}M H_2SO_4
138	0·65	0·40	0·35	—	10^{-1}M H_2SO_4
44	0·80	—	—	—	10^{-2}M HCl

On the basis of these results it has been suggested[138] that the earlier interpretations[10, 27] of the acid effect require reformulation to account for the increase in G(glycol). The reactions involved are thought to occur in the spurs in agreement with the suggestion of Baxendale and Mellows and may be formulated as follows: The species originally present in the spurs are ethyl hydroxonium ions, hydroxy-ethyl radicals—both formed in reaction (130)—and solvated electrons and the following intraspur reactions are expected in the absence of acid (reactions 131–135)

$$C_2H_5OH^+ + C_2H_5OH \longrightarrow CH_3CHOH^\cdot + C_2H_5OH_2^+ \quad (130)$$

$$e^-_{solv} + e^-_{solv} \longrightarrow H_2 \quad (131)$$

$$e^-_{solv} + C_2H_5OH_2^+ \longrightarrow C_2H_5OH + H^\cdot \quad (132)$$

$$e^-_{solv} + CH_3CHOH^\cdot \longrightarrow C_2H_5O^- \longrightarrow C_2H_5OH \quad (133)$$

$$2\,CH_3CHOH^\cdot \longrightarrow CH_3CHO + C_2H_5OH \quad (134)$$

$$2\,CH_3CHOH^\cdot \longrightarrow (CH_3CHOH)_2 \quad (135)$$

The addition of acid will serve to increase the concentration of alkyl hydroxonium ions so that reaction (132) proceeds to the exclusion of reactions (131) and (133). Reaction (131) is a source of molecular hydrogen but as (132) is probably followed by (136) in the spurs which also produces hydrogen no net effect is expected.

$$H + H \longrightarrow H_2 \quad (136)$$

On the other hand inhibition of reaction (133), which is a back reaction to alcohol, will lead to the production of additional hydrogen atoms and hydroxy-methyl radicals. For each electron scavenged one molecule of hydrogen is produced via reaction (137) and two hydroxy-ethyl radicals are made available—one from the scavenging of (133) and one from (137).

$$H + CH_3CH_2OH \longrightarrow H_2 + CH_3CHOH^\cdot \quad (137)$$

The rates of disproportionation (reaction 134) and dimerization (135) are approximately equal[92] so that for each electron scavenged one half molecule of aldehyde and one half molecule of glycol are produced in reasonable agreement with the experimental findings.

The concept of an additional yield of solvated electrons, scavenged from the spurs, being responsible for the increased hydrogen yield is fundamental to all three investigations and the differences in interpretation hinge around which reaction is being interfered with by the acid. Ackerman and Basson[138] believe it is reaction (133), Baxendale and Mellows[18] suggest (125) (in the case of methanol) and Adams and Sedgwick[27] prefer (138).

$$CH_3CH_2OH^+ + e^-_{solv} \longrightarrow (CH_3CH_2OH)^* \longrightarrow CH_3CHOH^\cdot + H \quad (138)$$

Apart from the fact that the last two explanations do not account for the increased glycol yield, there also seems to be a case for suggesting that the ions involved in reactions (125) and (138) undergo reaction with the substrate before neutralization can take place[23, 35]. Thus reactions (139) and (130), respectively, precede (125) and (138). This leaves (133) as the only reaction in the spurs which could lead to differences in product distribution on the addition of acid. This reaction and the effect of acid on it is analogous to that proposed to explain similar effects in the radiolysis of water[139].

$$CH_2OH^+ + CH_3OH \longrightarrow CH_2O + CH_3OH_2^+ \quad (139)$$

XIII. OTHER COMPOUNDS CONTAINING THE HYDROXYL GROUP

Although, as pointed out in section I, very little work has been done on compounds, apart from aliphatic alcohols, containing the hydroxyl group, we shall deal with a few exceptions, very briefly, in this section.

A. Polyhydric Alcohols

The action of γ-radiation of liquid ethylene glycol has been studied by Barker and co-workers[140]. A large number of products was determined at a dose of $2{\cdot}6 \times 10^{21}$ eV/ml, the more important contributions being shown in Table 30.

TABLE 30. Product yields in the radiolysis of ethylene glycol.

Product	*G*-value
Glycolaldehyde	1·70
Acetaldehyde	2·30
Formaldehyde	4·90
2-Methyl-1,3-dioxolane	15·90
Methanol	1·90
Ethanol	0·77
Glycerol	2·80
Formic acid	3·70
Acetic acid	7·50
Ethylene glycol	−51·00

Although it is difficult to distinguish between primary and secondary products at this high dose, the high yield of 2-methyl-1,3-dioxolane and the large value for ethylene glycol decomposition indicate a chain reaction.

B. Aromatic Alcohols

Van Sikle and Redeker[141] have studied the radiolysis of various aromatic alcohols. Three dihydroxydiphenylmethanes and three related phenolic compounds were subjected to 1 MeV electron bombardment in the solid state (−70°C to −30°C). The principal product in all cases is a 'polymer' of the starting material. *G*(Polymer) ranges from 0·5–0·8 in all cases except *o*-hydroxy-benzyl alcohol which gave 2·7. Gaseous products, of which 90% is hydrogen, are

produced with G-values ranging from 0·06–0·27. The low product yields are characteristic of aromatic compounds—the benzene ring exhibiting a protective effect.

C. Hydroxyl Acids

Pure hydroxyl acids have not been irradiated except in conjunction with electron paramagnetic resonance experiments[142] but C^{14}-labelled calcium glycolate appears to be decomposed in high yield $G \sim 170$ under the influence of its own β-particles[143]. The products include formic and oxalic acids. In aqueous solutions the principal organic product is dimer, thus glycollic acid, $CH_2OHCOOH$, gives tartaric acid, $(CHOHCOOH)_2$ [144]. This is presumably due to dimerization of $\dot{C}HOHCOOH$ and it seems that this class of compounds behaves very similarly to the aliphatic alcohols.

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The Chemistry of The Hydroxyl Group
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CHAPTER 18

Protection of the hydroxyl group

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I. INTRODUCTION

A. General Remarks

In polyfunctional compounds containing one or more hydroxyl groups, it is often necessary to protect these groups selectively, leaving the other functions available for reaction. The incipient hydroxyl groups in the product can then be regenerated at will. Several criteria are necessary for the satisfactory protection of specific hydroxyl groups.

1. The protected derivative must be easily prepared in satisfactory yield.

2. The reagent used must react selectively without affecting other portions of the molecule; it is often necessary to protect certain hydroxyl groups specifically, in the presence of other such groups which are left free for further reaction.

3. The derivative formed must be stable to the sequence of chemical reactions undergone by the protected molecule.

4. The original hydroxyl function may be regenerated in high yield without simultaneous attack elsewhere in the molecule.

B. Limitations of Study

It is intended to limit this discussion to a study of the protection of alcoholic and phenolic hydroxyl groups. Carboxylic acids, enols and the hydroxyl groups of inorganic acids will not be considered.

Examples of the protection of these groups abound in the literature of organic chemistry and an examination of all, or even of a large proportion, of the reactions involved would extend much beyond the space available. It is, however, planned to consider generally

the type of reactions involved in a diversity of compounds ranging from phenols and simple aliphatic polyols, such as glycol and glycerol, to the more complex polyols, such as carbohydrates and sterols. We shall differentiate between reactions involving isolated hydroxyl functions and those in which two or more such functions are converted to a cyclic derivative. Differences in the reactivity of alcohols and phenols will be pointed out. The reactions of hydroxyl groups in polyols are analogous to those occurring in simple alcohols and phenols with the additional complication of neighbouring-group effects and the possibility of production of optical isomers at asymmetric centres.

The intervention of steric and electronic factors often causes the differential reactivity of different hydroxyl groups in a polyol, enabling the selective protection of such groups. A study of these differences in reactivity has been of great assistance in the elucidation of the configuration and conformation of many complex molecules. It has even, at times, enabled an evaluation of the relative weight of steric and electronic factors in the reactions of compounds. Our illustration of the use of protecting groups will be then mainly from compounds with more than one hydroxyl group. This will afford the possibility of discussing the general methods available for the protection of such groups, which are applicable also to simpler molecules, and enable an analysis of the additional problems involved in the more complicated cases. Study of the reactions of the alcoholic functions in carbohydrates and sterols has especially advanced our knowledge of the importance of steric and electronic factors in the reactivity of molecules and their effect on the nature of the products obtained.

C. Types of Protecting Groups

Three principal types of derivatives have been employed: (1) ethers and hemiacetals, (2) esters, (3) heterocyclic rings, including those containing, in addition to oxygen and carbon, such atoms as nitrogen, sulphur or boron.

D. Indirect Protection

It has, occasionally, been found expedient to convert a hydroxyl to a different functional group (e.g., ketone) which can be reconverted to the required hydroxyl at the end of the sequence of reactions. Complications may arise in this approach, since the tetragonal sp_3-hybridized C–OH bond is converted to a trigonal sp_2

C=O bond. In the case of an asymmetric alcohol, the configuration of the final product may thus not be identical with that of the starting material.

A number of articles have previously appeared dealing directly or indirectly with part of the material of this chapter. They include studies of the reactivities of hydroxyl groups in steroids[1, 2], and a general article on the protection of reactive groups[3]. Much relevant information in carbohydrate chemistry is available in the recent edition of an encyclopaedic study of organic chemistry[4].

II. ETHERS AND GLYCOSIDES

A. Alkyl Ethers

1. Preparation

(i) The most general approach to the formation of ethers is by reaction of a nucleophilic oxygen with RX, where X is a 'good leaving-group' (halide, sulphonate, sulphate or sulphite being common examples).

$$ROH + MeX \longrightarrow ROMe + X^- + H^+ \qquad (1)$$

The resonance-stabilized phenoxide ion is more readily obtained than the alkoxide ion and phenols are thus readily alkylated in alkaline solution with a variety of reagents (equation 2):

$$RO^- + MeX \longrightarrow ROMe + X^- \qquad (2)$$

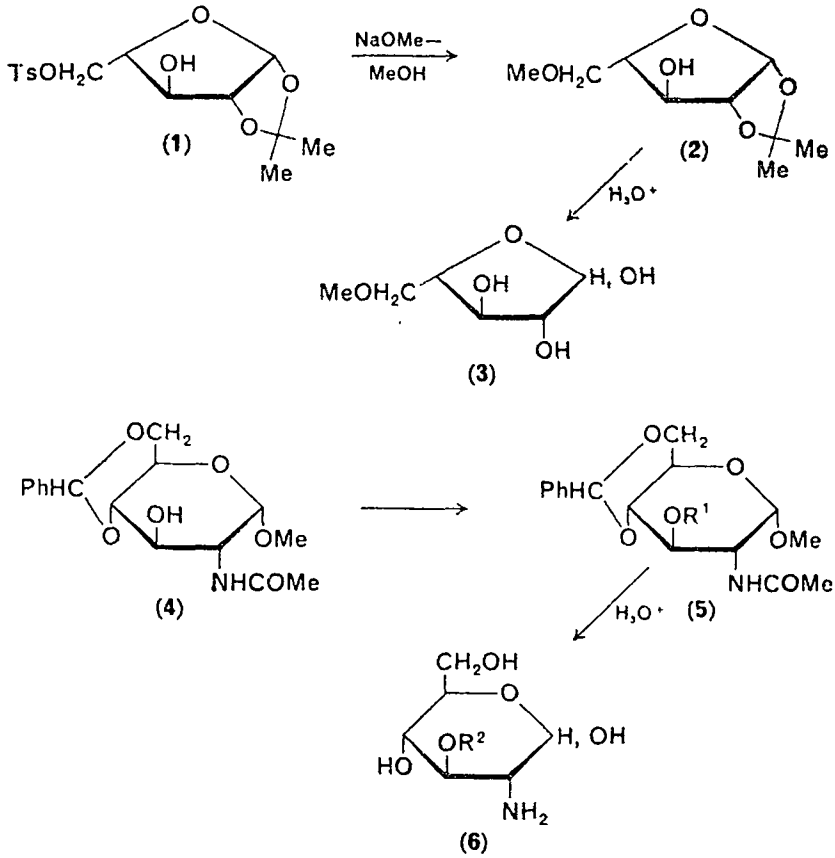
Partial, selective methylation is possible if a two-phase system is used to remove the partially methylated product effectively from the methylating agent[5].

Equation (2) may be considered in the form:

$$MeO^- + RX \longrightarrow MeOR + X^- \qquad (3)$$

Thus the nucleophilic displacement of, e.g., primary sulphonate esters by methoxide ion may be used to prepare methyl ethers, as illustrated by a preparation of 5-*O*-methyl-L-arabinose (**3**)[6].

Recently, the methylation of alkoxide ions with alkyl halides (equation 2) has been extended to carbohydrate chemistry[7, 8]. In the presence of sodium hydride in aprotic solvents, oxygen anions of sugars are formed and react with halides to produce ethers. The 3-*O*-lactyl ether (**6**) of 2-amino-2-deoxy-D-glucose (muramic acid) which is an important constituent of bacterial cell walls, was first synthesized by such a process; the sodium salt of the 3-hydroxyl group was prepared in dioxan solution and reacted with ethyl α-iodopropionate[9].



$R^1 = CH_3CH(CO_2Et)$; $R^2 = CH_3CH(CO_2H)$

This approach may be compared to a much older, less frequently used, method of generating the alkoxide ion. Reaction of a carbohydrate with sodium in liquid ammonia, followed by treatment with methyl iodide in an inert solvent, afforded methyl ethers[10].

However, owing to the lower stability of such alkoxide ions compared to their aromatic analogues, the most common approach to the methylation of carbohydrates has been to follow equation (1). Treatment of an aqueous solution of the substance with alkali and dimethyl sulphate[11], or dissolution in methyl iodide in the presence of silver oxide[12], was the commonly used method for methylating carbohydrates for many years. Dipolar, aprotic solvents such as *N,N*-dimethylformamide[13] or dimethyl sulphoxide give more rapid reaction, and replacement of the silver oxide with barium oxide or barium hydroxide is often efficacious[14]. The complete polymethylation

of a carbohydrate may be a long and tedious process involving many repetitions; it may be greatly facilitated by the use of aprotic solvents with metallic oxides or sodium hydroxide.

Methylation of polyols containing protecting groups poses certain problems, e.g., esters are not stable to strong, alkaline conditions, and acyl migration frequently occurs even under the mildly basic conditions of the Purdie method[15].

(ii) Phenols are readily methylated by diazomethane. Alcohols do not usually react with this reagent, although the more acidic anomeric hydroxyl group adjacent to the electron-withdrawing acetamido group in 2-acetamido-2-deoxy-D-glucose has been methylated by it[16]. Acid catalysts, however, such as boron trifluoride or fluoroboric acid[17], convert diazomethane to a sufficiently reactive species to methylate alcohols. A possible advantage of this method in sugar chemistry is that in the small number of examples reported so far migration of ester groups has not occurred during the process of methylation[18].

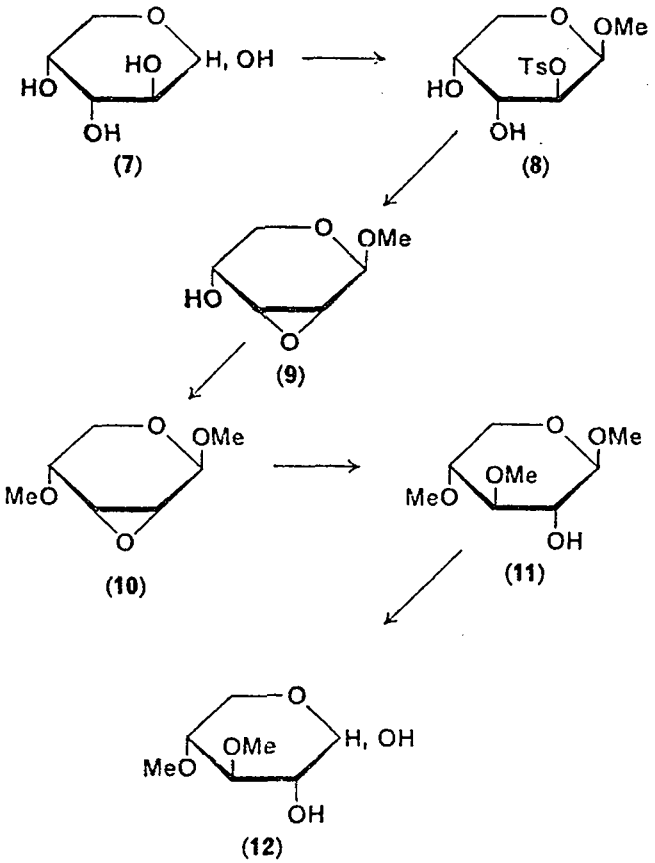
(iii) Ring-opening reactions. An industrial process for the production of glycol monoethers employs the reaction of ethylene oxide with alcohols in the presence of catalysts. Epoxides are attacked by alkoxide ions (see section IV.A).

(6)

This reaction is illustrated by the conversion of D-arabinose (**7**) via its 2-*O*-*p*-toluenesulphonate (**8**) and the 2,3-anhydro-D-ribopyranoside (**9**) to 3,4-di-*O*-methyl-D-xylose (**12**) (equation 7)[19].

2. Reactions

Methyl ethers are very stable compounds which are unaffected by most reaction conditions, although the OMe group may provide anchimeric assistance in displacement reactions[20]; their removal requires strongly acidic media. This necessity for vigorous, acid conditions for regeneration of the hydroxyl group is more often a grave disadvantage in carbohydrate chemistry than it is, for example, in the preparation of aromatic derivatives. Since the anomeric hydroxyl group of sugars is often protected as a glycoside, or other acid-labile derivative, the conditions used for the removal of the ethers must be such that other acid-labile bonds are not broken. Boron trichloride and boron tribromide are very powerful



(7)

demethylating agents which can be used under very mild conditions[21]. Cleavage of methyl ethers by oxidation with anhydrous chromium trioxide in acetic acid to the corresponding formates, followed by alkaline hydrolysis, regenerates the alcohols in 50–60% yield[22].

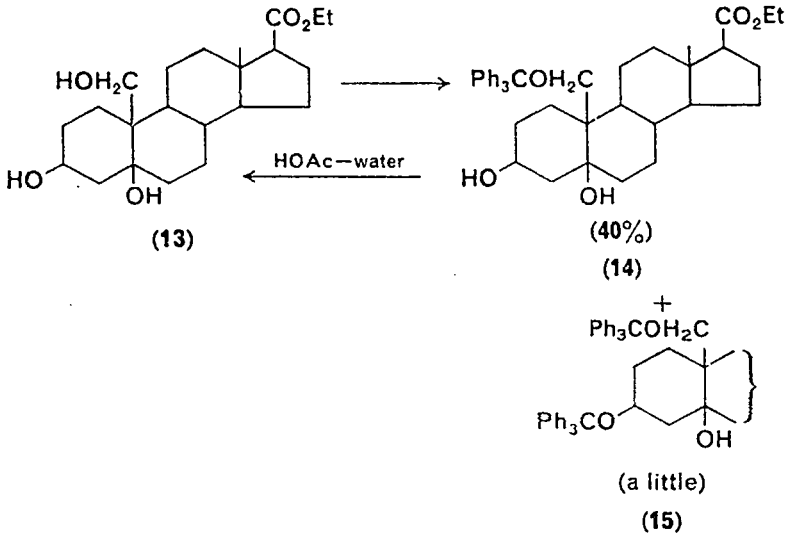
Methylation was the method used classically for the determination of the ring structure of monosaccharides, and has found frequent application in the linkage analysis of polysaccharides. The free hydroxyl groups in a polysaccharide are protected by methylation and the polymethyl ether is hydrolysed to monosaccharide fragments. The free hydroxyl groups in these units correspond to the points of linkage which were not previously available for methylation.

Isopropyl ethers are more readily hydrolysed than methyl ethers and have found some use in the flavone field[23]. *Benzyl ethers*[24] afford the advantage that they can be cleaved selectively by hydrogenolysis

and the use of benzyl bromide with silver oxide in *N,N*-dimethylformamide results in benzylation without deacetylation[25]. *Allyl ethers* may be prepared and converted to prop-1- enyl ethers (by the action of potassium *t*-butoxide in dimethyl sulphoxide) which are subsequently cleaved by mild acid hydrolysis[26].

B. Trityl Ethers

Triphenylchloromethane (trityl chloride) in pyridine solution reacts selectively with primary or unhindered secondary alcoholic groups[27]. The trityl group can be removed under mildly acidic conditions or by catalytic hydrogenolysis. The following is an example, among many, of the utilization of trityl ethers in steroid chemistry[28].



The trityl ether linkage was stable to acetylating and deacetylating conditions, and oxidation of **14** with *N*-bromoacetamide gave the 3-ketone without removal of the ether. Chromium trioxide in acetic acid, however, oxidized the 3-hydroxyl group with concomitant cleavage of the ether linkage. Trityl ethers do not appear to have been used for the protection of phenols. They have found frequent use in carbohydrate chemistry[29].

C. Trimethylsilyl Ethers

The advantage of the trimethylsilyl protecting group is its ready introduction by rapid, high-yield reactions, and its selective removal under mildly acidic conditions. Phenols react with trimethylsilyl chloride[30], while less reactive alcohols[31] and carbohydrates[32] react

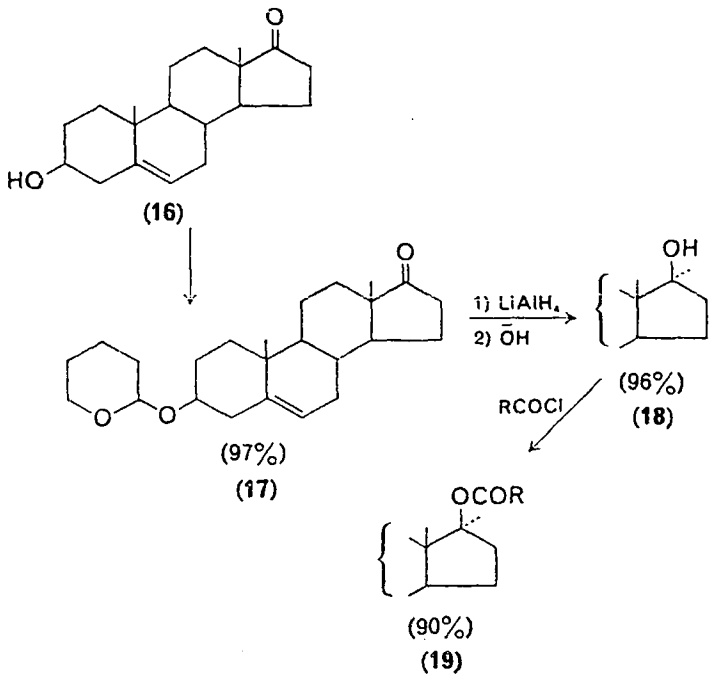
with trimethylsilyl chloride and hexamethyldisilazane in pyridine solution. The 6-*O*-ether linkage in methyl 2,3,4,6-tetra-*O*-trimethylsilyl-α-D-glucopyranoside can be selectively methanolysed to regenerate the 6-hydroxyl group[33], thus providing a method of preparing 6-*O*-substituted derivatives of methyl-α-D-glucopyranoside in addition to that utilizing the 6-*O*-trityl ether[29].

The volatility of these ethers has led to their widespread use in the gas–liquid chromatographic separation and identification of carbohydrates[32].

D. Tetrahydropyranyl Ethers

The extremely useful tetrahydropyranyl (THP) ethers are prepared by the reaction of a hydroxyl group with 2,3-dihydropyran in the presence of an acid catalyst[34–37]. They have found frequent use for the protection of steroid alcohols, but limited use with aromatic compounds[35]. A disadvantage of this method lies in the accompanying formation of an additional asymmetric centre, but this is usually not an insurmountable objection. Equation (9) is an illustration from the steroid field[38].

The ether was removed quantitatively from **19** by refluxing with



(9)

ethanol containing a little hydrogen chloride. Tetrahydropyranyl ethers can also be cleaved by dilute, aqueous acids at room temperature. The selective removal of a THP-group in the presence of an isopropylidene group has been achieved[39].

E. Glycosides of Sugars[40, 41]

In the common ring form, the aldehydic or ketonic function present in sugars is converted to an extremely reactive hydroxyl group. The most widely employed method (although not the only one) for the protection of such a group is by the formation of glycosides. Such glycosides are, frequently, stable to weak or anhydrous acids and to alkalies, but are hydrolysed by aqueous solutions of strong acids. The synthesis of glycosides is complicated by the necessity for stereoselective control in conformity with the desired ring form (pyranoid or furanoid) and anomeric configuration (α or β). In general, reducing sugars are converted to glycosides by treatment with an alcohol or phenol in the presence of an acid catalyst. Alternatively, a reactive saccharide derivative can be prepared. In the presence of an acid acceptor, the substituent at $C_{(1)}$ is expelled and the carbonium ion formed reacts with the nucleophilic oxygen of the hydroxyl group of the reagent; in other cases a solvolytic reaction may be involved.

1. From reducing sugars

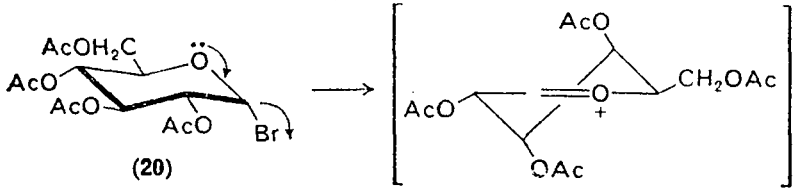
The sugar is treated with a dilute solution of hydrogen chloride in a liquid aliphatic alcohol[42]. Cation exchange resins may conveniently replace the mineral acid[43], and the use of benzyl alcohol affords the extremely useful benzyl glucosides. When the reaction conditions are such that equilibrium has been attained, the preponderant product will have the most stable conformation with the least number of nonbonded interactions, and its anomeric configuration and ring size will vary, accordingly, with the sugar converted. A number of methods have been employed to follow the course and separate the products of such reactions, the most sensitive being that of gas–liquid chromatography[44].

2. From O-acylglycosyl halides

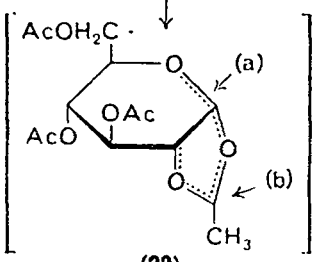
The original 'Koenigs–Knorr reaction' consisted in treating a fully acetylated glycosyl halide with an alcohol, often dissolved in an inert, dry solvent in the presence of either silver carbonate or silver oxide ('acid acceptor'[40]). Later modifications included the addition of iodine, or silver perchlorate[45], to speed the reaction and 'drierite'

(anhydrous calcium sulphate) to maintain rigorously anhydrous conditions. The replacement of silver salts by mercuric salts, especially mercuric cyanide[46, 47], often leads to higher yields.

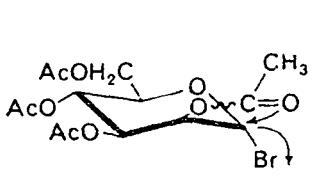
It is generally considered that a carbonium ion is produced at the anomeric carbon atom of the sugar[48, 49], presumably stabilized by the participation of other groups, such as the ring oxygen or the 2-acetoxy group when suitably orientated stereochemically. A typical example of the anchimeric assistance of the 2-acetoxy group is afforded by the glycosidation of tetra-*O*-acetyl-α-D-gluco-pyranosyl bromide (**20**) or the corresponding derivative of D-mannose (**23**).



(20) (21)



(22) (10)



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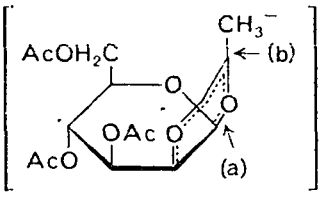

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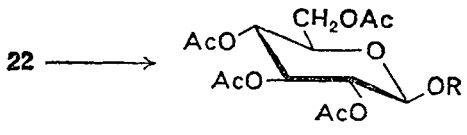
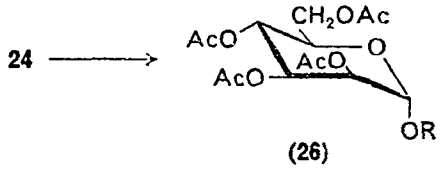


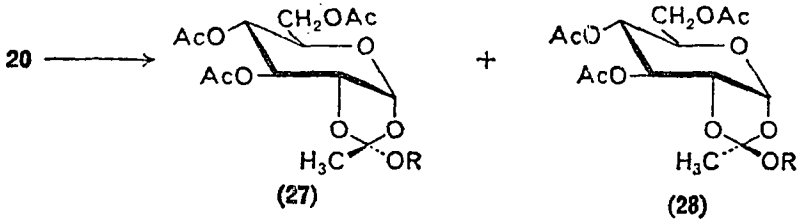
(25) (12)

If the nucleophilic attack by the oxygen of the alcohol occurs as indicated by (a), a β-D-glycopyranoside (**25**) or α-D-mannopyranoside (**26**) is formed, as illustrated.



(26) (13)

If, however, attack (b) occurs, orthoesters are produced, e.g.,



(27) (28) (14)

Aromatic glycosides can also be prepared by heating a melt of the polyacetate in the presence of an acid catalyst such as *p*-toluenesulphonic acid or zinc chloride[50]. Occasionally, aliphatic glycosides have been prepared by a rather similar method[51].

3. Additional methods

Glycosides have also been prepared from 1,2-epoxides (e.g., Brigl's anhydride)[52], by solvolysis reactions from glycosyl fluorides[53], and recently from 1,2-*ortho*-acetates[54] and 1,2-unsaturated sugars[54a].

III. ESTERS

A. With Organic Acids

Unhindered hydroxyl groups are generally esterified under mild conditions; the reactions are often more facile than those employed in the preparation of ethers and excellent yields are usually obtained. Organic esters are stable to acids, but in contrast to ethers, they are cleaved by alkalies or by catalytic transesterification reactions. They are also stable to acylating conditions, to various oxidative processes, to catalytic hydrogenolysis (if not aromatic) and to the conditions of the Koenigs–Knorr reaction for the preparation of glycosides and disaccharides.

The selectivity of ester-formation and hydrolysis is governed by both steric and electronic factors and is more evident when bulkier acyl groups, such as benzoyl or succinoyl, are used. Secondary and

tertiary alcohols are less readily acylated than are primary alcohols. Phenols are less reactive than secondary alcohols, but aryl esters are saponified more rapidly than alkyl esters owing to the resonance-stabilization of the phenoxide ion produced.

Strongly acid catalysts must be avoided during the esterification of derivatives with acid-labile functions such as glycosides, acetals or anhydrides. On the other hand, acid-catalysed acetylation (acetolysis) may be used to cleave an acid-labile function with simultaneous esterification, e.g., the acetolysis of 1,6-anhydrohexopyranoses gives the fully esterified hexose, while the acetolysis of polysaccharides affords mixtures of oligosaccharide polyacetates, the identity of which provides information on the types of interglycosidic linkages in the original polysaccharides[55].

1. Formates and trihaloacetates

Formates and trihaloacetates can be prepared from even very hindered hydroxyl groups, such as that at $C_{(11)}$ in steroids and they are saponified rapidly under mildly basic conditions[56]. Tri-*O*-acetyl-2-trichloroacetyl-β-D-glucopyranosyl chloride has been prepared by the action of phosphorus pentachloride on penta-*O*-acetyl-β-D-glucopyranose. The trichloroacetyl group may be selectively removed by controlled ammonolysis to give 3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl chloride[57].

2. Acetates

Acetates are the most commonly used esters for the protection of hydroxyl groups, and can be prepared in high yield from the hydroxyl function using acetyl chloride or acetic anhydride with a variety of catalysts such as pyridine, sodium acetate, zinc chloride, perchloric acid or *p*-toluenesulphonic acid. They have also been prepared by ester-interchange reactions, e.g., with ethyl acetate in the presence of an acid catalyst[58], when the less reactive phenolic hydroxyl is unaffected. Isopropenyl acetate, which converts ketones into enol acetates, can be used to acetylate less reactive hydroxyl groups such as 11β-hydroxyl of steroids[59]. Apart from their alkaline-lability, acetates are cleaved reductively by lithium aluminium hydride.

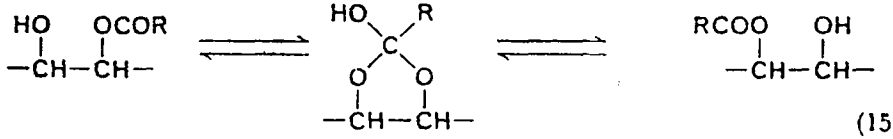
3. Benzoates

Benzoates show similar properties to acetates, with rather more selectivity owing to the bulkier group involved. They are usually

prepared by the action of benzoyl chloride in pyridine on the compound.

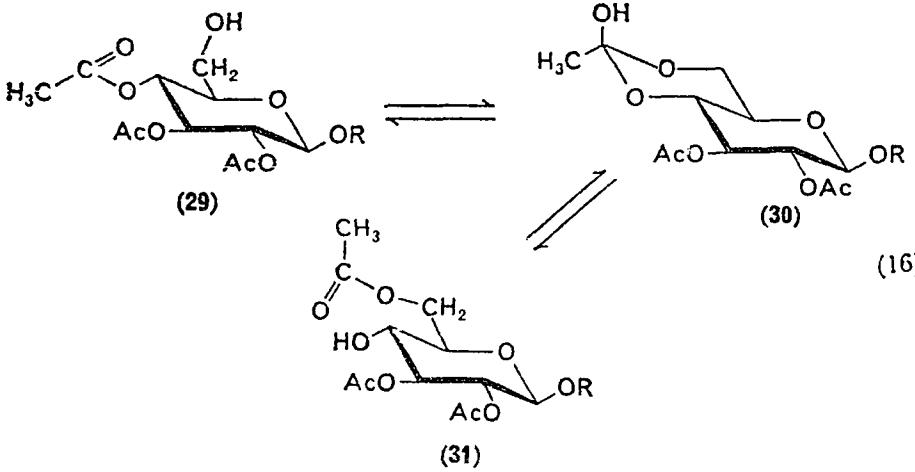
4. Ester migration

The utility of esters of organic acids for the protection of hydroxyl groups in polyols is limited by the ability of ester groups to migrate from one hydroxyl to another without concomitant deacylation. Accordingly, reactions on polyols, in which some of the hydroxyl groups are protected as esters, especially in alkaline media (e.g., during ether formation), may not be clear-cut owing to the intervention of such migrations. Examples of this phenomenon were first noted with partially acetylated glyceryl esters[60–62], and many examples are now known in the carbohydrate[63] and inositol[64] fields. The rearrangements are believed to occur intramolecularly via cyclic orthoacid intermediates and thermodynamic equilibrium is attained.



(15)

There is a strong tendency for the ester migration to proceed from secondary alcohols to less-hindered, unprotected, primary alcoholic groups in the same molecule, as illustrated by the preparation of methyl 2,3,6-tri-*O*-acetyl-*β*-D-glucopyranoside (**31**) from the 2,3,4-tri-*O*-acetate (**29**)[65]. Benzoyl groups migrate less readily than acetyl

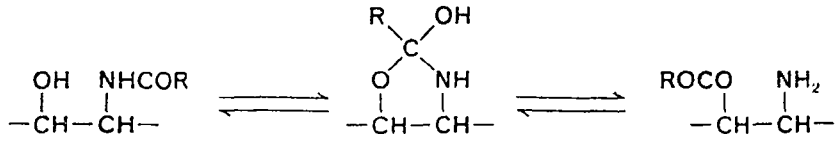


(16)

groups owing to the greater loss in resonance energy involved in formation of the orthoester intermediate. However, examples are

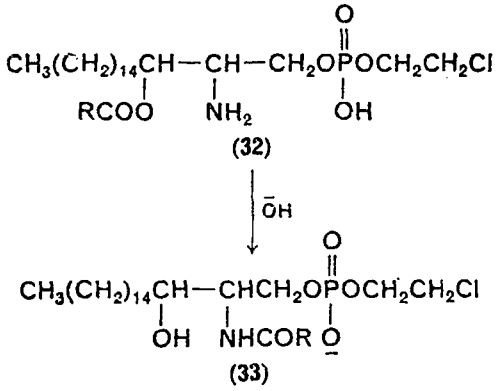
known of such benzoyl migrations[66, 67]. Acyl migrations under neutral[68] and acidic[69, 70] conditions have also been reported.

Ester groups vicinal to amino groups undergo an even more facile O→N acyl migration under neutral or mildly alkaline conditions, thereby producing hydroxyamides from 1,2-aminoesters. Reversal of this process requires strong acids, and the rate of the ensuing N→O acyl migration is critically affected by the stereochemistry of the molecule[71].



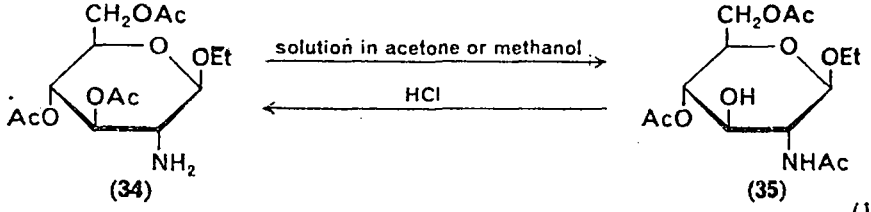
(17)

An example from the chemistry of lipids was provided during a synthesis of dihydrosphingomyelin[72]:



(18)

A typical example from carbohydrate chemistry is the following[73]:



(19)

5. Sulphonate esters

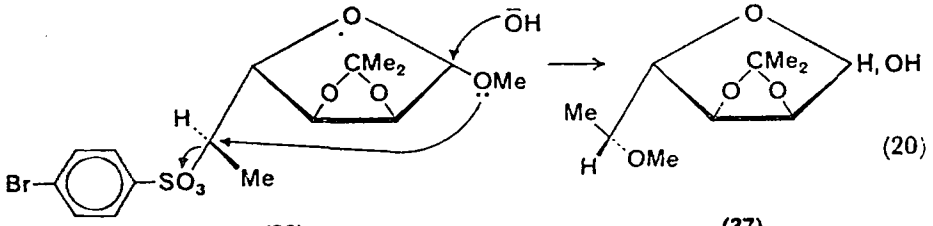
The most frequently encountered sulphonate esters are *p*-toluenesulphonates (tosylates) and methanesulphonates (mesylates), prepared by the reaction of an alcohol or a phenol with the sulphonyl

chloride in the presence of base (sodium hydroxide or pyridine)[74]. Prolonged reaction at elevated temperatures in the presence of pyridinium chloride may lead to the displacement of primary sulphonate by chloride ion[75]. The anomeric hydroxyl group in sugars is usually converted to a glycosyl chloride by a sulphonyl chloride in the presence of pyridine[76].

Sulphonates are exceedingly stable to acid hydrolysis. Arylsulphonates have high thermal stability and it is possible to oxidize the methyl groups of *m*- and *p*-cresol benzenesulphonates by selenium dioxide at 200° to aldehydes without affecting the sulphonate ester group[77].

a. Removal of sulphonate groups. (i) Sulphonates are often stable in mildly basic media, e.g., during methylations using silver oxide.

(ii) Isolated sulphonate esters, in molecules which do not afford the possibility of participation reactions, are saponified by boiling, aqueous alkali, with retention of configuration. Many reactions have been reported in carbohydrate chemistry in which the removal of sulphonate groups is facilitated by anchimeric assistance[74], including ring contractions[78]. A glycosidic methoxyl group may even participate in such desulphonoxylations, as in the alkaline conversion of methyl 2,3-*O*-isopropylidene-5-*O*-*p*-bromobenzenesulphonyl-6-deoxy-β-L-allofuranoside (**36**) to 6-deoxy-2,3-*O*-isopropylidene-5-*O*-methyl-D-talofuranose (**37**) in 81% yield[79].

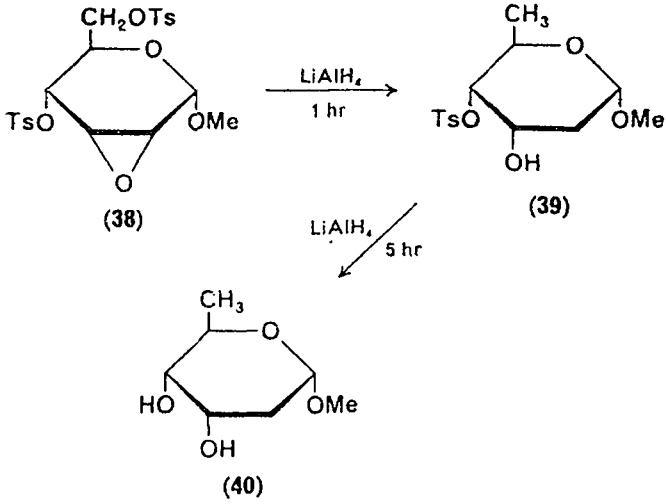


(20)

(iii) Reductive desulphonylation, using, typically, 2–4% sodium amalgam or Raney-nickel, has been used extensively for cleaving tosylates, although the reaction may be complicated by the intervention of anhydride formation in the mildly basic conditions employed if facilitated by the stereochemical configuration of the molecule[74].

Reduction of primary sulphonates with lithium aluminium hydride usually results in desulphonoxylation and the production of the ω-deoxy derivative. This reaction is the basis of a widely used synthesis of ω-deoxy sugars. Iodide ion also replaces primary tosylates by iodides which can be reduced by lithium aluminium hydride,

thus affording the deoxy sugar from the tosylate by a two-stage process. Secondary sulphonates are removed by, predominantly, O–S bond fission, giving the alcohol[74]. Since this is a slower reaction, it is often possible to remove selectively a primary in the presence of a secondary tosylate (equation 21)[80].



(21)

A sulphonyloxy group *trans* to a vicinal acylamido group may be removed with participation of the amide nitrogen and formation of an epimine (aziridine) derivative[81].

(iv) Sulphonate esters undergo typical S_N2-type displacement reactions, accompanied by C–O bond fission and inversion of configuration of the carbon atom bearing the original ester, with a variety of nucleophilic reagents:

$$\bar{X} \longrightarrow R^1\!-\!O\!-\!SO_2R^2 \longrightarrow R^1X + R^2SO_2O^- \qquad (22)$$

The reactivity of the sulphonate group in such reactions, and the product, are critically dependent upon the type, and stereochemistry, of the original sulphonate ester. Primary sulphonates are the most reactive, while sulphonates adjacent to the anomeric group in glycosides (i.e., 2-*O*-sulphonyl-aldopyranosides and the 1-*O*-sulphonates in 1-*O*-sulphonyl-2-ketosides) are extremely unreactive[74]. Replacement of secondary sulphonates in sugars usually requires a high-boiling, aprotic solvent and favourable stereochemical and electronic factors[82–83]. The configurational changes accompanying

the anchimerically-assisted displacement of sulphonate esters have been studied extensively (for a review see Reference 84).

Mesyl esters of equatorial secondary hydroxyl groups in pyranose rings and of a secondary hydroxyl group in a furanose ring were converted to ethers by reaction with sodium methoxide or ethoxide in dry dimethyl sulphoxide. The reactions proceeded with retention of configuration, attributed to a reaction mechanism involving an initial, slow, nucleophilic attack by alkoxide ion on sulphur in the mesyl ester, followed by a rapid competition between the liberated carbohydrate oxide anion and the excess alkoxide for the alkyl methylate produced[85].

6. Tiglates[86]

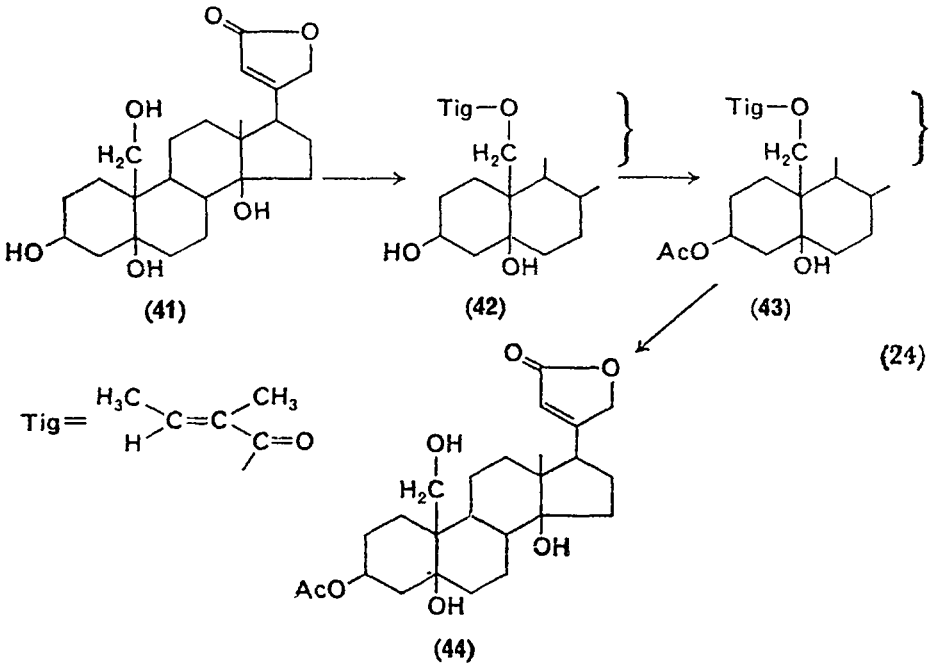
In a search for a selective blocking group for the hydroxyl function which could be removed under mildly basic conditions without affecting other ester groups in the molecule, the use of tiglate esters was introduced into the steroid field. Primary hydroxyl groups can be selectively acylated with tigloyl chloride (*cis*-2-methyl-Δ^2-butenoyl chloride) in pyridine. The resulting tiglates can be cleaved by oxidation with osmium tetroxide–periodic acid to the extremely alkali-labile pyruvic esters:

(23)

Strophanthidol 3-acetate (44) was synthesized by the sequence as shown at the top of p. 1019.

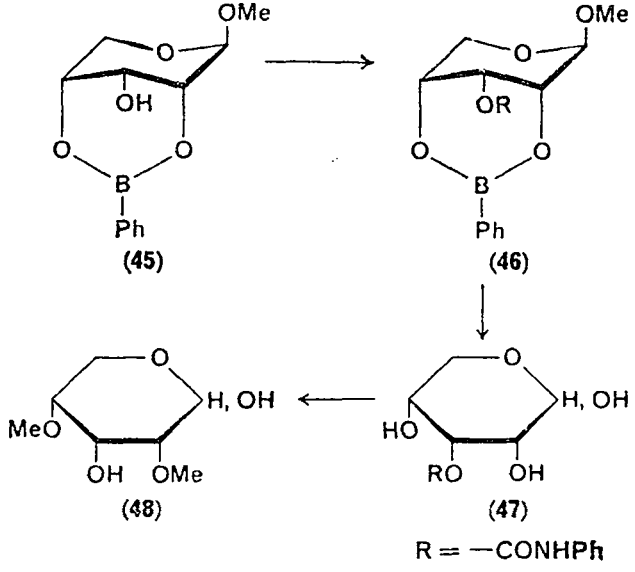
7. Phenylcarbamates[87]

Phenyl isocyanate reacts quantitatively with the hydroxyl groups of carbohydrates in either pyridine or neutral solvents such as benzene. No acetyl migration accompanies the esterification, and the phenylcarbamates are stable to acids. The alkali-lability of the esters is diminished by *N*-methylation, which occurs on treatment with methyl iodide and silver oxide in *N*,*N*-dimethylformamide solution. The *N*-methylphenylcarbamoyl group is removed smoothly by reduction with lithium aluminium hydride. An attempt to utilize phenylcarbamate esters as selective hydroxyl-blocking groups for the preparation of methyl ethers was vitiated by the discovery that the phenylcarbamate group may migrate under the basic conditions employed for the methylation of carbohydrates. However, a successful synthesis of 2,4-di-*O*-methyl-D-ribose employed a phenylcarbamate



(24)

protective group[88]. Methyl β-D-ribopyranoside 2,4-phenylboronate (**45**) gave the 3-*O*-phenylcarbamate (**46**), from which the cyclic boronate ester was removed by treatment with propan-1,3-diol.



(25)

Methylation, and subsequent removal of the carbamate and methyl glycoside gave the required 2,4-di-*O*-methyl ether (**48**).

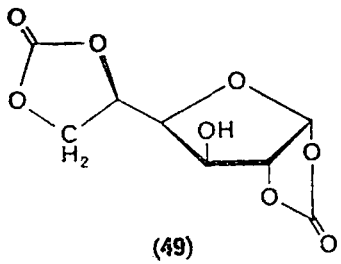
The lack of phenylcarbamate migration in **47** may be attributed to an unsuitable stereochemical configuration precluding the formation of the intermediate cyclic product presumably implicated in any possible ester migration from $C_{(3)}$ to either $C_{(2)}$ or $C_{(4)}$.

8. Carbalkoxy esters

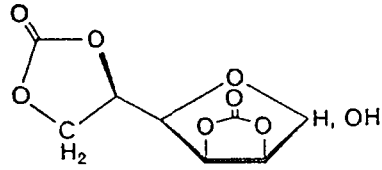
Carbomethoxy derivatives of phenols were prepared by the reaction of methyl chloroformate with a solution of the phenol in aqueous alkali, or by the addition of methyl chloroformate and dimethylamine to a solution of the phenol in benzene[89]. Reaction of ethyl chloroformate and pyridine with reactive hydroxyl groups affords carbethoxy esters[90]. The advantage of such carbalkoxy esters lies in their selectivity of formation and ease of removal[91].

9. Carbonates

Cyclic carbonates have found little use in the simultaneous protection of two hydroxyl functions in phenols and steroids, but have been frequently employed in carbohydrate chemistry[92]. They are readily prepared by the reaction of polyols with phosgene in pyridine solution, or with chloroformic esters in aqueous alkali. Alternatively, cyclic carbonates may be conveniently prepared by transesterification of a diaryl carbonate or a cyclic aryl carbonate with a polyol at 100–150° in a suitable solvent in the presence of an alkaline catalyst[93]. As esters, they are relatively stable to acids but are removed by mild alkalies. The ring formation enables the simultaneous protection of two hydroxyl groups and, also, the preparation of otherwise not easily accessible derivatives, e.g., of furanoid sugars. The 5-membered carbonate ring fused to a 5-membered furanoid sugar is more stable than a 5-membered ring fused to a 6-membered pyranose ring system. D-Glucose affords the 1,2:5,6-dicarbonate (**49**)



(**49**)



(**50**)

and D-mannose the 2,3:5,6-dicarbonate (**50**), the vicinal *cis*-orientated hydroxyl groups reacting preferentially[94].

α-D-Ribofuranosyl phosphate, and its 5-*C*-phosphate, have been prepared from methyl 5-*O*-benzyl-D-ribofuranoside 2,3-carbonate by avoidance of neighbouring group participation in reactions at the anomeric carbon atom[95]. Carbonate esters of furanosyl halides may be prepared by the reaction of sugar carbonates with thionyl chloride, or hydrogen bromide in acetic acid[96].

D-Glucitol, D-mannitol and DL-galactitol give the 1,2:3,4:5,6-tricarbonates[97], the first two polyols reacting, at room temperature, in their preferred zig-zag conformation, in which the vicinal hydroxyl groups are suitably orientated for ring formation, whereas galactitol requires heat to facilitate an unfavourable conformational change to enable formation of the 3,4-carbonate.

10. Thiocarbonates[98]

Thiocarbonates may be prepared according to the general reaction

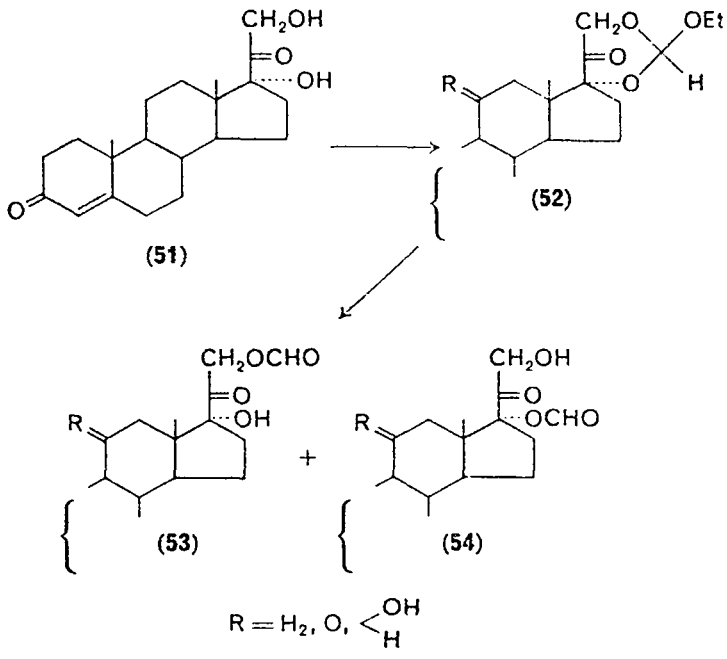
$$R^2OH + ClCSR^1 \longrightarrow R^2OCSR^1 + HCl \qquad (26)$$

The (benzylthio) carbonyl group is stable to concentrated hydrochloric acid, and consequently 3-*O*-[(benzylthio) carbonyl]-β-D-glucopyranose can be prepared from the acid-labile 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose. Subsequent acylation affords 2,4,6-tri-*O*-esters, and the protecting thiocarbonate can be selectively removed by oxidation with peracetic acid.

11. Orthoesters

Unlike the esters considered previously, the cyclic orthoesters are stable to basic conditions but are readily hydrolysed by acids. The formation of orthoesters affords the possibility of two stereoisomers at the particular carbon atom involved, the selective formation of which can sometimes be controlled. For example, reaction of the steroid **51** with ethyl orthoformate gave the more dextrorotary isomer of **52** when pyridinium hydrochloride was used as catalyst, while *p*-toluenesulphonic acid catalysed the formation of the other epimer[99].

The 16α,17α-orthoester (**56**) was prepared from **55** and ethyl orthoformate using perchloric acid as catalyst (equation 28).



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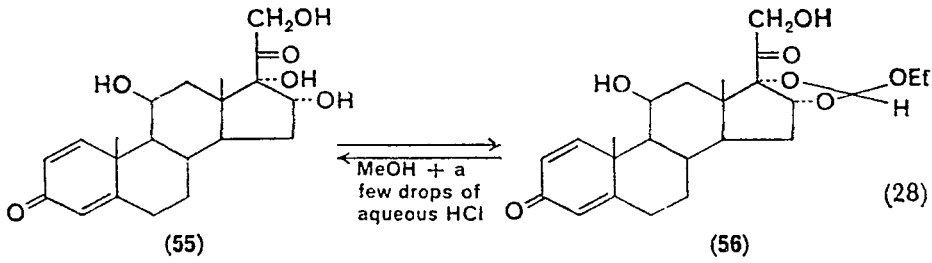
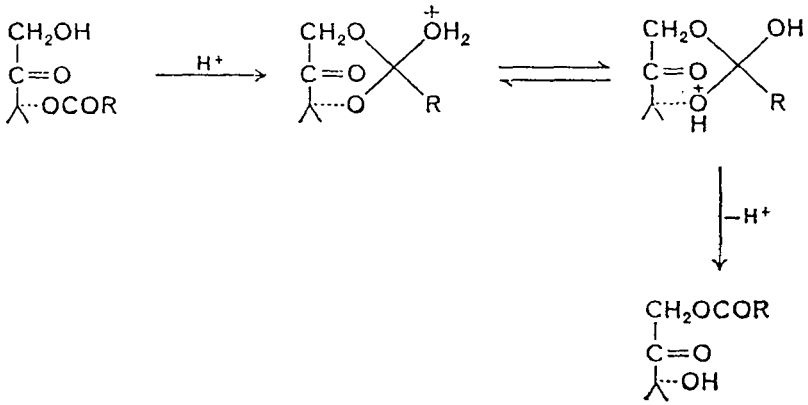


(28)

The 17α,21-orthoesters were invoked as an explanation of the acyl migration observed when corticosteroid 17α-monoesters are refluxed with benzene in the presence of *p*-toluenesulphonic acid, 21-monoesters being isolated in quantitative yield (compare equation (15), section III.A.4).

The intermediate in equation (29) is, in fact, the protonated orthoacid rather than the orthoester.

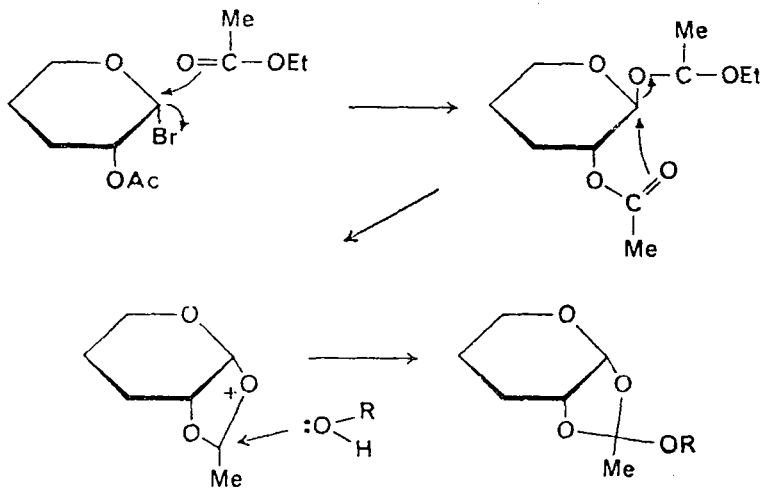
The most common carbohydrate orthoesters are 1,2-cyclic compounds formed by reaction of glycosyl halides with alcohols in the presence of hydrogen halide acceptors[100] (equation 14). Although they are more readily obtained from sugars having the *trans* relationship of the halide at $C_{(1)}$ and the acyl group at $C_{(2)}$, the use of hindered bases enables the preparation of 1,2-cyclic orthoesters from



(29)

cis-2-*O*-acyl-1-halo-derivatives[101]. Nevertheless, a prior anomerization of the α-halide to the less stable β-halide, thus producing the required *trans* relationship, probably occurs, catalysed by halide ion.

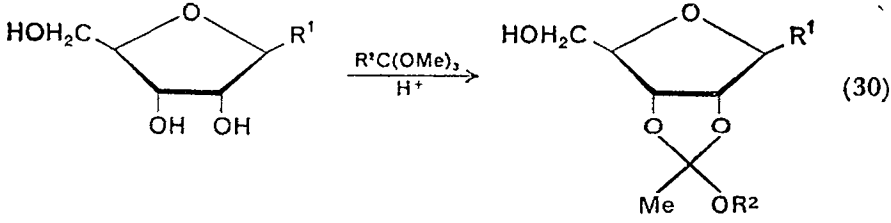
Another method of preparing 1,2-orthoesters from *cis*-acylglycosyl halides in ethyl acetate solution, with lead carbonate and drierite, presumably involves a double inversion at $C_{(1)}$ with participation of the solvent[54].



1,2-orthoesters can be used for the preparation of glycosides and disaccharides (see section II.A.3).

Cyclic orthoesters can be prepared from vicinal *cis* diols by acid-catalysed exchange with a trimethyl orthoester. In this way, ribonucleosides were converted to the corresponding 2′,3′-orthoformates,

orthoacetates and orthobenzoates[102]. Hydrolysis of the orthoesters with very dilute acid afforded a mixture of the 2- and 3-*O*-esters, thus giving an approach to the preparation of monoesters of vicinal diols.



(57) (58) (30)

B. Esters of Inorganic Acids

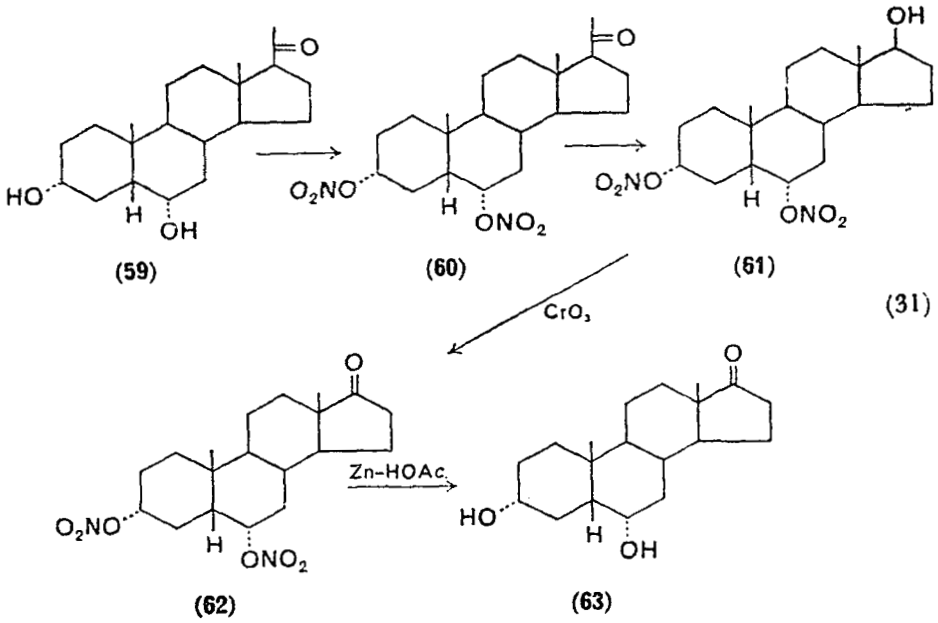
1. Nitrate esters

Nitric acid–acetic anhydride mixtures esterify alcohols rapidly, and the nitrates formed are generally stable to mild acids and mild alkalies. They are unaffected by chromium trioxide–acetic acid, Wolf–Kishner reduction, lead tetracetate and peracids, silver oxide–methyl iodide, acetylation and acetalation conditions. Although reasonably stable to acids, acetolysis, using 10% sulphuric acid in acetic anhydride, replaces nitrates by acetates. Vigorously alkaline conditions, e.g., ethanolic potassium hydroxide, give N–O and C–O bond fission, leading to ketones which are further degraded under the alkaline conditions[103]. The best method of denitration is by use of reducing agents, e.g., iron or zinc dust in boiling acetic acid, aqueous, alcoholic sodium sulphide, lithium aluminium hydride, hydrazine or catalytic hydrogenolysis[103]. Sodium nitrite removes certain secondary nitrates selectively, e.g., methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2,3-dinitrate gives the 3-nitrate ester[104]. The use of the nonparticipating nitrate at $C_{(2)}$ of an aldopyranosyl chloride enabled the preparation of an α-linked disaccharide, isomaltose[105], and the derived trisaccharide panose[106]. The protecting nitrate group was removed from the products by hydrogenolysis in the presence of a palladium–charcoal catalyst. Nitrate esters were utilized as protecting groups in the conversion of pregnandiol (3α,6α)-20-one (**59**) to 17α-methyl-testosterone (**63**)[107].

2. Sulphates

Sulphate esters have been used for the protection of phenols[108]. Although many sulphate esters of carbohydrates have been syn-

thesized because of their intrinsic interest as natural materials or degradation products of naturally occurring polymers[109], they have

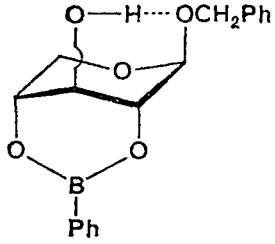


found little utility as protecting groups. Migration of sulphate ester groups, presumably via cyclic intermediates, has been reported[110].

3. Borates and phenylboronates

Sugar and alditol borates are known only in solution, but their formation is readily followed by the changes in optical rotation and conductivity observed when polyols are dissolved in boric acid or borate solutions[111, 112]. Borate complexes have been employed as protecting groups for the synthesis of a number of carbohydrate derivatives, such as 2,6-di-*O*-benzoyl-D-glucose[113] and 3,6-di-*O*-methyl-D-glucose[114]. The corresponding phenylboronates are more stable esters which are decomposed, however, by water or alcohols. They are prepared from polyols by reaction with phenylboronic acid under dehydrating conditions[115]. Sugar alcohols react much more rapidly than do monosaccharides. Cyclic phenylboronate formation enables the simultaneous protection of two hydroxyl groups in a molecule which sometimes cannot similarly be protected by any other reagent (see also section III.7). For example, methyl-β-D-ribopyranoside affords the 2,4-phenylboronate (**46**) in 90%

yield, and this is a useful precursor of 3-*O*-acyl esters of D-ribose[87]. The six-membered boronate rings are generally more stable than their five-membered counterparts; in the case of the ribopyranoside (**46**), this is explained as due to the coordination of $O_{(3)}$ to boron. Benzyl-β-D-xylopyranoside 2,4-phenylboronate (**64**) is more reactive than the α-anomer in Koenigs–Knorr reactions[116]. This has been explained as being due to the intramolecular hydrogen bonding of the free hydroxyl group, thereby enhancing the nucleophilic character of the oxygen (but contrast an opposite effect of hydrogen bonding on the methylation of phenols in section V).



(**64**)

Selective methylation of phenolic or enolic hydroxyl groups in flavones or flavonols is possible after protecting other hydroxyl groups as borate complexes[117].

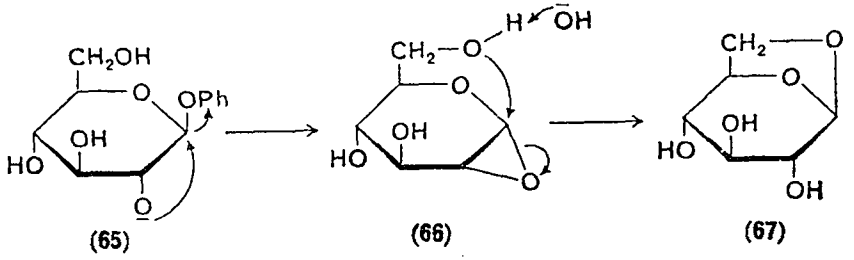
IV. MISCELLANEOUS HETEROCYCLIC RINGS

A. Oxides

Epoxides and cyclic anhydrides[118–120] can be prepared by reactions involving the intermolecular displacement of a 'good leaving-group' by a neighbouring nucleophilic oxygen atom, usually in the presence of base:

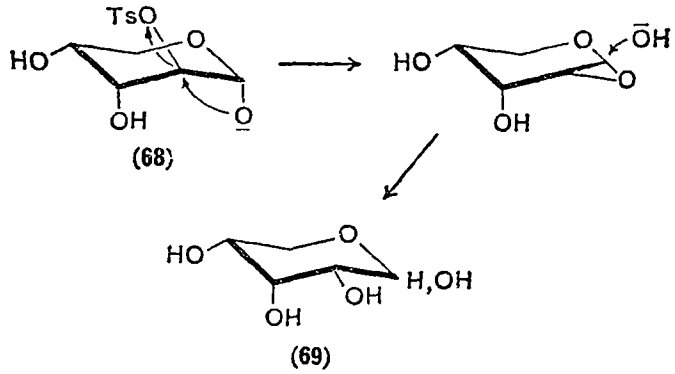
Phenyl β-D-glucoside (**65**), for example, is thus converted by alkali to 1,6-anhydro-β-D-glucose (**67**)[118].

The acid- or base-catalysed hydrolysis of epoxides and cyclic anhydrides replaces the ring with a diol. The ease of formation and hydrolysis of these rings, and the configuration of the products, depend upon stereochemical factors. For example, by cyclization



(32)

and subsequent hydrolysis, a tosylate (**68**) of D-arabinose is converted to D-ribose (**69**) via an epoxide intermediate[121]:

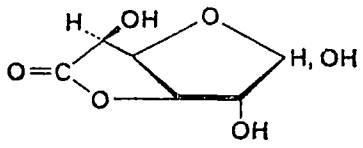


(33)

Epoxide migrations when neighbouring hydroxyl groups are suitably disposed sterically further complicate the results of such cyclization, ring-opening sequences[119]. The acid hydrolysis of epoxides and anhydrides requires conditions which hydrolyse simultaneously other acid-labile groups such as acetals and glycosides, while the base-catalysed hydrolyses remove esters. From the above, it is obvious that such cyclization reactions generally do not offer suitable means of protection of hydroxyl groups in polyols. However, 1,6-anhydrosugars have been employed in the synthesis of a number of disaccharides, inducing cellobiose and lactose[122].

B. Lactones

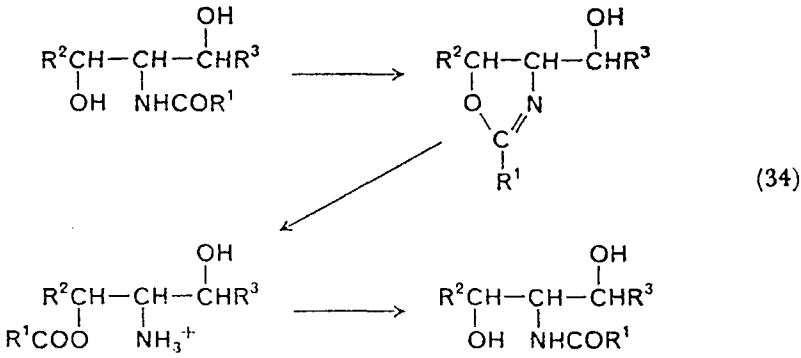
Occasionally, lactone formation has been utilized for the simultaneous protection of hydroxyl and carboxyl functions. The lactone (**70**) of D-glucuronic acid, for example, forms a convenient starting material for the preparation of many derivatives[123–125], while the lactone(**41**) was utilized for the preparation of the steroid derivative **44** (equation 24).



(70)

C. Oxazolines[126]

Syntheses of derivatives of 2-amino 1,3-diols have been achieved by simultaneous protection of one hydroxyl and the amino group as a heterocyclic ring, leaving the other group free for reaction[127, 128] (equation 34).



(34)

The oxazoline ring is stabilized when R^1 is an electron-attracting group such as dichloroacetyl or aryl. Mildly acid conditions open the ring to an aminoester which undergoes acyl migration to an amidoalcohol in basic media. The process of ring-closure to an oxazoline may involve inversion of configuration of the carbon atom bearing the hydroxyl function involved in the cyclization, while the acid-catalysed ring-opening and O→N acyl migration reactions proceed with preservation of configuration[129, 130]. Ethers[131], glycosides and disaccharides[132] of amino sugars have been prepared from oxazoline derivatives.

V. CYCLIC ACETALS[133, 134]

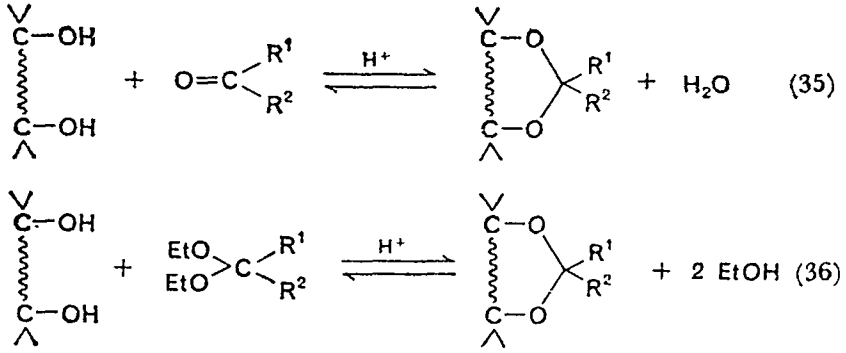
A. Preparation

Two contiguous hydroxyl groups may be condensed with aldehydic or ketonic reagents to give cyclic derivatives, generally by acid-catalysed reactions (see equation 35).

Acetal-exchange reactions, e.g., using 2,2-diethoxypropane, may also afford acetals (see equation 36).

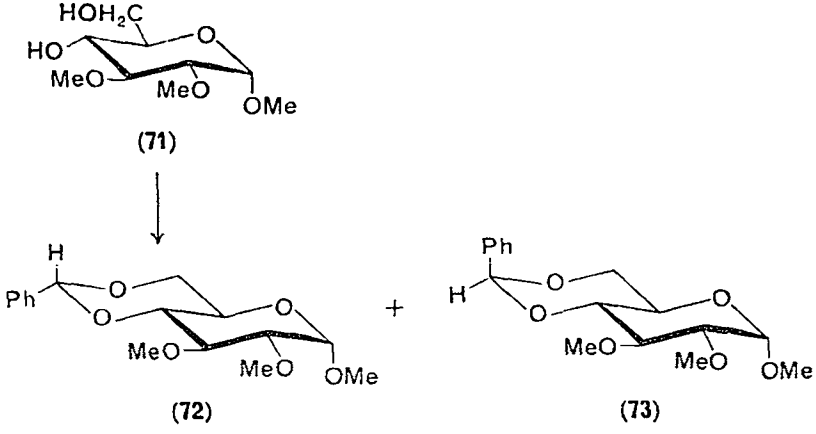
In the general reactions depicted in equations (35) and (36) equilibria are attained; the actual product will be governed by energy considerations, and, in general, the acetal with the preferred conformation of lowest energy will be formed.

A variety of acid-catalysts have been employed, often with the



addition of dehydrating agents to remove the water formed (equation 35) and thus to shift the equilibrium to the side of acetal formation. Various acid-type dehydrating agents, such as phosphorous pentoxide, sulphuric acid, zinc chloride and cupric sulphate, are useful activators[134]. Sometimes, acetals can be prepared in neutral media in the presence of a strong, neutral desiccant, e.g., calcium carbide[135]. The water formed may be removed by means of azeotropic distillation[136, 137].

When the groups R^1 and R^2 are different, an additional asymmetric centre may be introduced into the product. The acid-catalysed equilibrium generally produces the isomer with the more



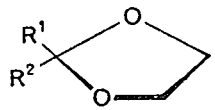
stable structure. However, in alkaline media, a mixture of diastereoisomers can be prepared and separated. Equilibration of each of these compounds under acid conditions produces the more stable isomer[138].

Reaction of methyl 2,3-di-*O*-methyl α-D-glucopyranoside (**71**) with benzylidene bromide and potassium *t*-butoxide afforded both isomers of the acetal with *equatorial* **72** and *axial* **73** phenyl groups, which could be separated. The thermodynamically less stable isomer **73** was converted to **72** by treatment with acid reagents.

In reactions producing five-membered acetal rings, the difference in stability between the diastereomers is larger and it is thus possible to isolate two separate acetals even under acid-catalysed conditions of condensation. The absolute configurations of the diastereomeric acetals have been determined by n.m.r. spectroscopy, the chemical shift of the acetal-proton depending upon its *exo* **72** or *endo* **73** configuration with respect to the bicyclic ring system[139].

Acetals are stable to many reagents and reaction conditions, including metalation, alkaline saponification, esterification and deesterification, oxidation and reduction, and thus provide useful protection of hydroxyl functions. They are generally stable to Koenigs–Knorr conditions and there are indications that the presence of an acetal ring increases the nucleophilicity of the oxygen of an adjacent hydroxyl group, thus facilitating the condensation of this hydroxyl with acylglycosyl halides in the Koenigs–Knorr reaction[140, 141].

Acetals of phenols have rarely been prepared, although the isopropylidene derivative of catechol is known; it is unusual in being extremely stable to acids[142]. Various empirical rules have been proposed for the prediction of the type of ring formed preferentially (size and configuration) in polyhydroxyl compounds[132]. Ketones usually tend to produce five-membered acetal (1,3-dioxolane) rings (**74**) rather than six-membered (1,3-dioxane) rings (**75**), possibly owing to the fact that one of the alkyl groups must necessarily occupy an axial position on the six-membered ring.



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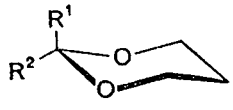
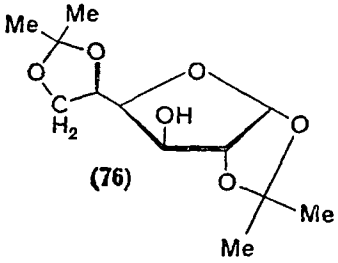


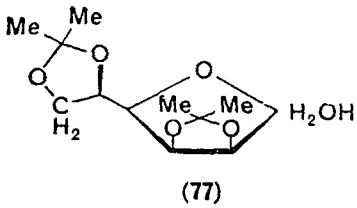
(75)

Erythro- or *cis*-diols react preferentially with acetone in the presence of acids. Whenever possible a furanose ring is formed, probably

due to the lower strain encountered in two fused five-membered rings as compared with the fusion of a five- with six-membered ring. Thus, D-glucose gives 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**76**)[143], while D-mannose gives the 2,3:5,6-diacetal (**77**)[144] (compare section III.A.9).



(**76**)

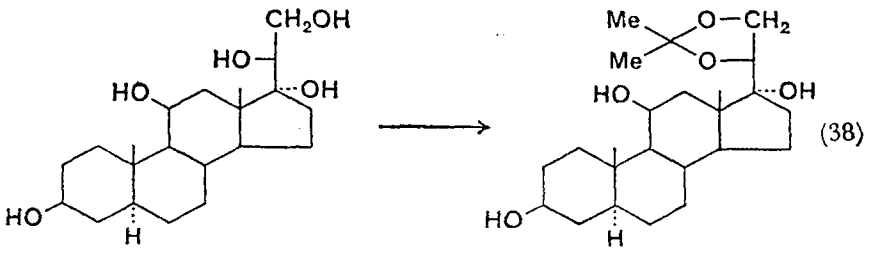


(**77**)

Glucosides, which do not have vicinal *cis* hydroxyl groups, do not form isopropylidene derivatives except under forcing conditions[145], while the pyranosides derived from mannose and lyxose readily give the 2,3-acetals. Similarly, the pyranosides derived from arabinose, galactose and altrose afford 3,4-acetals with acetone.

Tri-*O*-isopropylidene derivatives of inositols in which one of the five-membered acetal rings is *trans*-fused to the six-membered cyclohexane ring, can also be produced[146]. The third acetal (derived from contiguous *trans*-hydroxyl groups) is introduced more slowly and hydrolysed more readily. Such a *trans*-cyclization occurs only with cyclitol derivatives which already contain two acetal rings, and has been explained as being due to distortion of the cyclohexane ring by the two acetal groups previously attached; this distortion facilitates the closer approach of the two *trans*-hydroxyl groups to each other.

The sterol **78** reacted with acetone in the presence of zinc chloride to afford a five-membered acetal **79** which was stable to acetylation



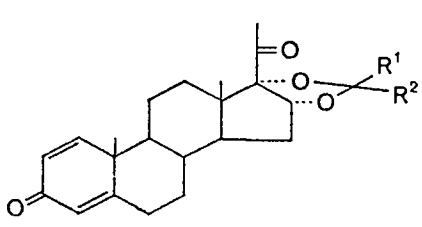
(**78**) (**79**) (38)

and tosylation of the 3-β-hydroxyl group, and was hydrolysed by 50% aqueous acetic acid[147].

Acetone condenses with two vicinal hydroxyl groups of glycerol, leaving the third (primary) hydroxyl group free, thus affording a facile synthesis of 1-acyl glycerides[148]. Benzaldehyde, on the other hand, gives 1,3-benzylidene-glycerol[149]. The secondary hydroxyl group can be converted to the benzyl ether. After removal of the benzylidene protecting group by mild, acid hydrolysis, acylation, followed by catalytic hydrogenolysis, affords 1,3-diacyl glycerides. Alternatively, acylation of 1,3-benzylidene-glycerol followed by selective acid hydrolysis of the acetal group affords 2-acyl glycerides. Owing to the facile acyl migrations of ester groups in derivatives of glycerol, it is preferable to cleave the acetal by a two-stage process: glycerol 1,3-diborate is first prepared by treatment of the acetal with boric acid in triethyl borate at temperatures above 100°; the isolated borate ester is then decomposed by the addition of water, without accompanying acyl migration.

The 16α,17α-acetals of the general structure **80** were prepared from the ketone or aldehyde using catalytic amounts of aqueous (70%) perchloric acid as catalyst[150].

The bis-methylenedioxy *spiro* ring system in **82**, prepared from hydrocortisone **81**, was stable to alkaline, reducing and acylating conditions[151].



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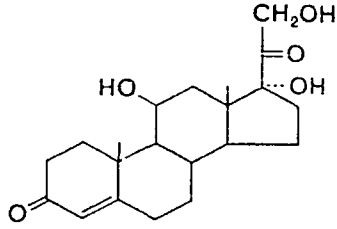

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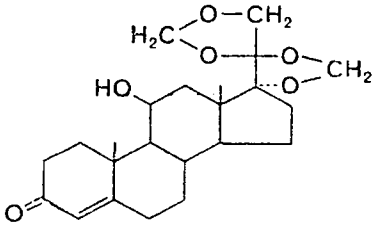
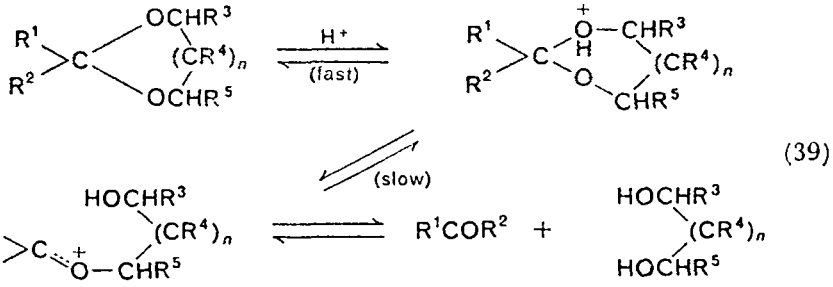


(82)

B. Cleavage of Acetals

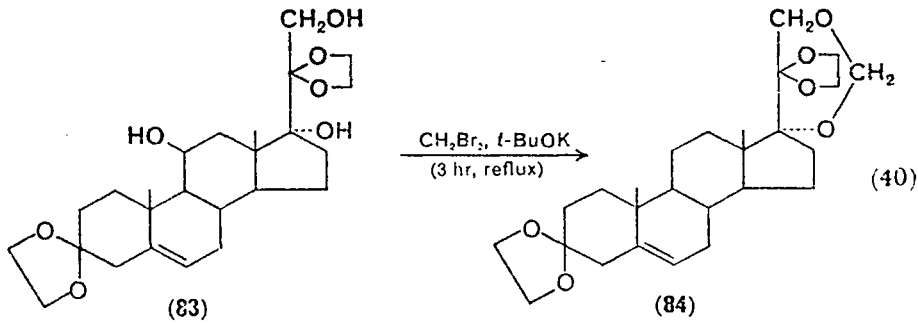
Acetals are usually hydrolysed by dilute, aqueous acid, their stability being controlled, inter alia, by the nature of R^1 and R^2 (equation 39)[152].



(39)

The general order of ease of acid hydrolysis of acetals is *p*-methoxybenzylidene > benzylidene > isopropylidene > ethylidene > methylene[153]. The methylene acetals are extremely stable to hydrolytic conditions, but can be degraded smoothly by acetolysis.

The 17α,21-methylene acetal in compound **84** was stable to all attempts of hydrolysis[154].

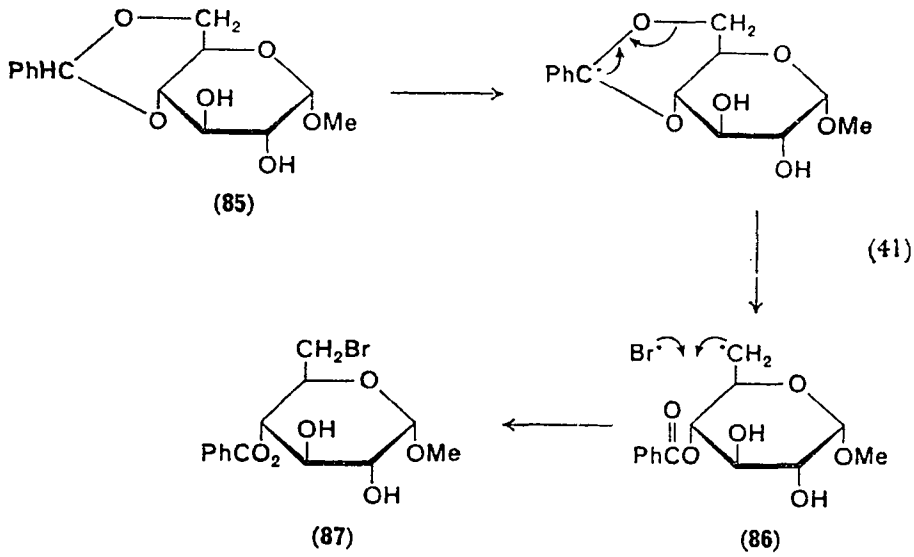


(83) (84)

(40)

Acetal rings have also been cleaved by boron trichloride[155], bromine in ether[156], and aqueous trifluoroacetic acid[157]. A novel reaction of 4,6-*O*-benzylidene acetals of hexopyranosides is the oxidation by *N*-bromosuccinimide under free radical conditions to produce 6-bromo-4-benzoates in good yield[158] (equation 41).

The differential stability of acetals towards acids has been exploited for the selective removal of acetals in the presence of one another. Since the exocyclic acetonides are more readily hydrolysed than those fused to a sugar ring, it is possible, for example, to hydrolyse 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**76**) to the



(41)

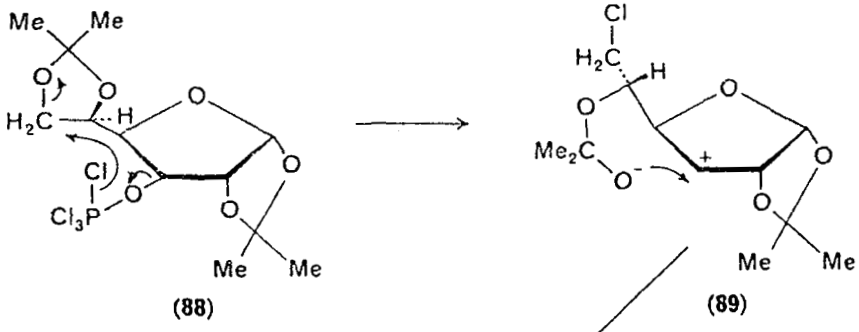
1,2-acetal. Similarly, 2:3,5:6-di-*O*-isopropylidene-D-mannofuranose (**77**) affords the 2,3-acetal upon partial, acid, hydrolysis[159].

The benzylidene residue in 1,4-anhydro-3,5-*O*-benzylidene-6-chloro-6-deoxy-D-glucitol is removed during steam distillation to give 1,4,3:6-dianhydro-D-glucitol as the major product, and 1,4-anhydro-6-chloro-6-deoxy-D-glucitol as the minor product[160]. As it was suspected that the acidity of the water due to dissolved carbon dioxide (pH 5·5) might have been sufficient to hydrolyse the acetal, excess potassium hydroxide was added during the steam distillation, but, again, the benzylidene group was removed. This is a rare case of an alkali-labile acetal. Benzylidene acetals, owing to the aromatic substituent, are also removed by catalytic hydrogenolysis.

Migration of acetal functions is rare, but the formation of 1,6-di-*O*-benzoyl-2,3:4,5-di-*O*-isopropylidene-D-galactitol from the more strained 2,3:5,6-di-*O*-isopropylidene-D-galactitol by treatment with benzoyl chloride in pyridine at elevated temperatures has been attributed to this effect[68]. Reaction of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**76**) with phosphorus pentachloride gave 6-chloro-6-deoxy-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose (**90**), as a result of a S_Ni mechanism of chlorination[161].

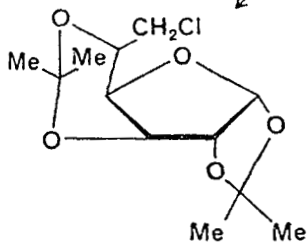
An isolated hydroxyl group adjacent to a thiol has been protected by cyclization to a hemithioketal, enabling selective reaction of the 3-hydroxyl group (equation 43). The thioketal could be cleaved by

dilute acids, Raney-nickel and acidic or basic solvolysis in the presence of mercuric salts[162].

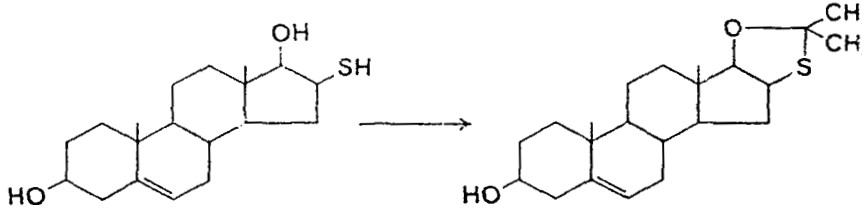


(88) (89)

(42)



(90)



(91) (92)

(43)

Compound **92** was produced by refluxing the steroid **91** with acetone for 8 hours in the presence of *p*-toluenesulphonic acid. Alternatively, hemithioketals can be prepared by treating the thioalcohol with a ketone for 20 hours at room temperature in the presence of zinc chloride and sodium sulphate.

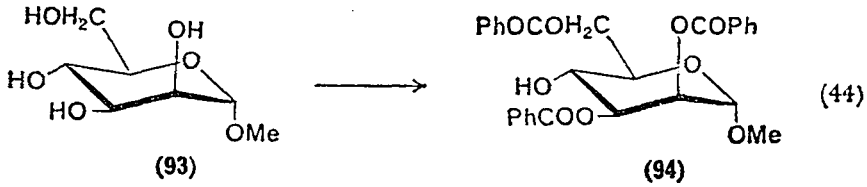
VI. SELECTIVE REACTIVITY OF HYDROXYL GROUPS

As pointed out several times previously, steric and electronic factors influence the reactivity of hydroxyl groups towards a variety of reagents and it is often possible to exploit their effects to enable the

protection of specific hydroxyl groups in polyols. The bulky triphenylchloromethane reacts preferentially under mild conditions with primary alcoholic groups (see section II.C). Primary, and unhindered secondary, alcoholic groups in steroids are often acylated while the more hindered secondary (and tertiary) alcoholic groups do not react: there are differences in the rates of hydrolysis of the esters formed[163].

In hexopyranosides, the primary hydroxyl group is the most reactive in base-catalysed esterification and etherification reactions[164]. Conformational effects appear to have great influence on the reactivity of secondary alcoholic groups. The 4-hydroxyl in the more stable (C1) conformation of D-galactopyranosides (*axial*) is the least reactive to acylating conditions[165]. Its lower reactivity was also utilized for the preparation of 3-*O*-glycosyl derivatives (disaccharides) of D-galactose[166] and 2-acetamido-2-deoxy-D-galactose[167] starting from a protected glycoside in which both the 3- and 4-hydroxyl groups were free.

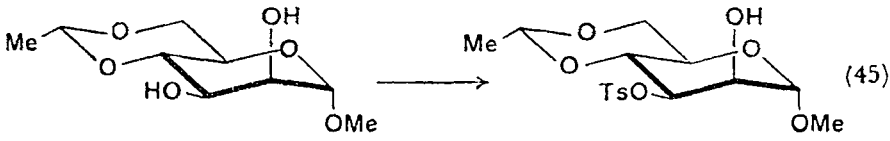
The intervention of influences other than those due to *axial* or *equatorial* conformations is illustrated in the selective acylation of methyl α-D-mannopyranoside (**93**) to methyl 2,3,6-tri-*O*-benzoyl-α-D-mannopyranoside (**94**)[165].



(93) (94) (44)

The *axial* 2-hydroxyl group is esterified preferentially to the *equatorial* 4-hydroxyl group. The large $C_{(5)}$-substituent decreased the reactivity of the 4-hydroxyl group which is also less than might be expected in glucopyranosides where this hydroxyl group is equatorially orientated in the stable (C1) conformation. Furthermore, there is enhanced reactivity of the 2-hydroxyl group in methyl α-D-hexopyranosides[168], attributed to the formation of an intramolecular hydrogen bond to the 1-methoxyl group[169]. This enhanced reactivity is apparently lacking in the β-anomers of D-glucose and D-galactose in which hydrogen-bond formation to the oxygen at $C_{(1)}$ may be expected not to be favoured on stereochemical grounds[170]. Hydrogen bonding, on the other hand, does not readily explain the enhanced reactivity of the $C_{(2)}$ oxygen in α-D-mannopyranosides unless it is

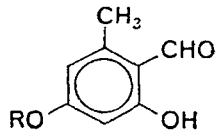
postulated that there is hydrogen bonding to the carbonyl oxygen of the benzoyloxy group introduced at $C_{(3)}$ or to the ring oxygen. However, treatment of methyl 4,6-*O*-ethylidene-α-D-mannopyranoside (**95**) with 1 mole of *p*-toluenesulphonyl chloride gives reaction predominantly with the 3-hydroxyl group, the axial hydroxyl at $C_{(2}$ remaining free[171] (equation 45).



(95) (96) (45)

In this case, hydrogen bonding to the oxygen of the acetal ring may be invoked to explain the enhanced reactivity of the 3-hydroxyl group, as well as the more ready accessibility of the equatorial, rather than the axial, hydroxyl group.

It may be noted, in contrast, that the *lower* reactivity of an alcoholic group adjacent to an aldehydic function in a phenol was attributed to hydrogen bonding to the oxygen of the aldehyde[172]. Orcyl aldehyde (**97**; R = H) was methylated selectively to everninic aldehyde (**97**; R = CH_3).



(97)

The primary hydroxyl groups of DL-galactitol are extremely reactive and may be esterified preferentially by treatment with 50% acetic acid at 80°[173].

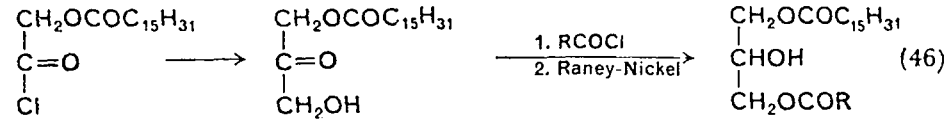
Equatorial hydroxyl groups in cyclitols are tosylated in preference to *axial* hydroxyl groups[146].

Advantage may be taken of the selective reactivity of amines and alcohols in various media to enable the preparation of N-acylamino alcohols or amino esters. In general, in acid media the protonated amine is stable to acylation while in aqueous alkaline media the amine is acylated and alcoholic groups are unaffected. Thus, the perchloric acid-catalysed acetylation of alcohols is rapid and selective[174], and, on the other hand, there are many examples known of the *N*-acylation of amino alcohols, hydroxyamino acids and amino

sugars in aqueous or aqueous alcoholic media in the presence of alkali. Similarly, the choice of reaction conditions enables the selective *N*- or *O*-sulphonation of amino alcohols[175].

VII. INDIRECT PROTECTION BY CONVERSION TO KETONIC DERIVATIVES

It is possible in some cases to oxidize selectively a desired hydroxyl group in a polyol to a ketone: the ketonic group can be protected by specific reagents, if necessary, leaving the other hydroxyl groups free for further reaction. The original hydroxyl group is then regenerated by reduction of the ketone. A process analogous to the above scheme was employed in a synthesis of 1,3-diacyl glycerides[176]:



(98) (99) (100) (46)

Oxidations of secondary alcohols to ketones have been performed by a variety of chemical reagents and also by several microorganisms.

A. Chemical Oxidations

Air or oxygen, in the presence of rare metal catalysts, e.g., platinic oxide or palladium, oxidize preferentially primary or more reactive secondary alcoholic groups[177, 178]. Manganese dioxide oxidizes allylic, as opposed to saturated, alcohols[179].

A large number of different chemical reagents have been developed for the nonspecific oxidation of hydroxyl groups in polyols (cf Reference 180 and loc. cit.). These reagents suffer from the disadvantage that all other hydroxyl groups in the molecule, apart from those required to be oxidized, must be previously protected.

B. Biochemical Oxidations

Various strains of Acetobacter oxidize certain secondary alcoholic groups in polyols to ketones[173]. The groups oxidized are determined by their configuration; the original rules suggested for the prediction of the products of such oxidation reactions[181] have been variously modified[182]. Induced enzymes have been isolated from *Pseudomonas*

testosteroni which oxidize the 3-, or the 3- and 17-hydroxyl groups in steroids[183].

D-Galactose oxidase is unusual in that it oxidizes the primary hydroxyl group of D-galactose to an aldehyde[184].

Sucrose is oxidized by *Agrobacterium tumefaciens* in the glucopyranose ring[185] to '3 keto-sucrose' while lactose and maltose are oxidized in the nonreducing moiety[186].

Reduction of the ketone to regenerate the alcoholic function is complicated by the possible production of two diastereoisomers. Consequently, recovery of a compound with the alcoholic group having its original stereochemistry may not always be feasible, or its overall yield may be low. On the other hand, the sequence >CHOH → >C=O → >CHOH may be of value in converting a secondary alcohol to its less easily accessible diastereoisomer[187].

VIII. CONCLUDING REMARKS

We have attempted to summarize and evaluate the more common methods available for the protection of hydroxyl groups in various classes of organic compounds. The main types of protecting agents used have been classified and more recent advances especially stressed. The influence of electronic and stereochemical factors upon the reactions have been discussed. The large number and diversity of such protecting groups (of which we have dealt with only a portion) are a reflection of the necessity for different approaches for various purposes, rendering the preparation of a universal protecting agent an impossibility.

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The Chemistry of The Hydroxyl Group
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CHAPTER 19

The mass spectra of hydroxyl compounds

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I. INTRODUCTION

Many hydroxyl compounds are thermally unstable and/or involatile, which makes them less than ideal substances for mass spectrometry. Nevertheless, not only are they now routinely characterized by their mass spectra, but they have also provided some of the impetus for the development of new techniques of ion formation and analysis. Their study has helped initiate and maintain an interest in the relationship between stereochemistry and ionic fragmentation and OH compounds have provided important test cases for the quasi-equilibrium theory of mass spectra. The fact that so many compounds of natural origin possess one or more hydroxyl groups and the well-known advantages of mass spectrometry for the analysis of small amounts of such materials has stimulated interest in the mass spectra of hydroxyl compounds and of the numerous derivatives used as protecting groups for this functionality. Skeletal rearrangements involving the hydroxyl group and the energetics and structures of ions

involved in some fragmentations of hydroxyl compounds have also been the subject of significant investigations.

This review is addressed both to the organic chemist who might use mass spectrometry in dealing with known or unknown hydroxyl compounds and to the mass spectroscopist whose interest lies in the mechanisms, kinetics and energetics of fragmentation. To this end principles and interpretations are emphasized and although references to spectral data for various types of hydroxyl compounds are given, some structural problems might be best solved by *ab initio* consideration of the mass spectrometric characteristics of hydroxyl compounds. Especial attention has been given to relating the established body of data on this subject to the newer concepts emerging from a more rigorous physical approach to organic mass spectrometry. Literature coverage extends through 1968. The nomenclature used to indicate metastable transitions, the position of the bond broken and whether cleavage is homolytic or heterolytic is that of Budzikiewicz, Djerassi and Williams[1].

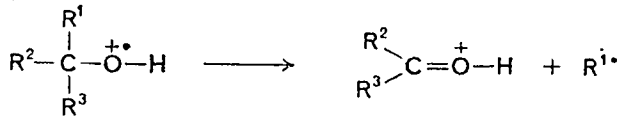
II. GENERAL CHARACTERISTICS OF THE MASS SPECTRA OF OH COMPOUNDS

The results discussed in this section are, for the most part, well established and are covered in several recent compendia on mass spectrometry[2–4]. For these reasons the treatment is as brief as possible, consistent with the relevance of these results to the succeeding discussion and with the desirability of a unified treatment of the whole subject.

Early work on hydroxyl compounds was hampered by their involatility and their tendency to undergo thermal dehydration and decomposition. These difficulties have been largely overcome. For instance, by inserting the sample directly into the ion source, which may be cooled to operate at ca 60°, involatile and/or unstable substances give reproducible electron impact spectra. Alternatively, a stable volatile derivative of the hydroxyl compound may be employed (section VII) or some method of ion formation other than electron impact may be used (section VIII). With the improvements noted above, electron impact is suitable for most mono- and even for many poly-hydroxy compounds and unless otherwise stated all the spectra discussed were obtained by this method.

Perhaps the most characteristic fragmentation of aliphatic alcohols is simple cleavage of an α-bond with loss of a radical, illustrated

below. The long-recognized importance of product ion stability explains this cleavage in the charge localized form (**1**) of the molecular



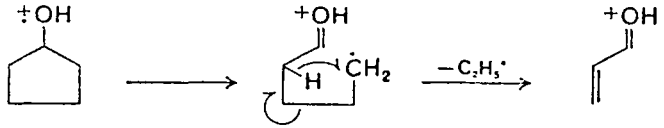
(**1**) R^1, R^2, R^3 = alkyl, substituted alkyl, or H

ion. The formation of stable fragments by valency expansion at oxygen is a unifying feature underlining a good deal of the mass spectrometry of OH compounds. The results of a systematic study[5] on a variety of primary, secondary and tertiary aliphatic alcohols allow these generalizations: (i) alkyl radicals are more readily lost than hydrogen, (ii) α-cleavage is most important in tertiary and least important in primary alcohols and (iii) larger primary radicals are more readily lost than smaller. While these observations are readily rationalized in terms of the stabilities of the ionic and neutral products, some of the difficulties in assessing relative rates of fragmentations by comparing 70 eV spectra are apparent from the results[5] for 2-methyl-3-heptanol which can lose either a primary butyl or a secondary propyl radical by α-cleavage. The former gives the more abundant product ion, but further loss of water from $(M - i\text{-}Pr)^+$ gives the base peak in the spectrum. It seems from this result that the nature of the radical lost is more important than its size. Unfortunately, the early studies on alcohols[5–7] could not make use of the direct insertion technique and the importance of low energy spectra was not then fully recognized. Recently there has been interest in the factors controlling the relative rates of radical loss upon electron impact. Especially notable are the observed lower activation energies for loss of the smaller *n*-alkyl radicals from phenyl alkanes[8], acetals[9] and ketones[10] in spite of the greater abundance of the ions formed by loss of the larger radicals in 70 eV spectra. It is not known if alcohols also show this behaviour and there is a need for detailed investigation of radical loss from simple alcohols*.

In the more complex OH compounds commonly encountered, α-cleavage is still a notable feature, although other groups in the

* *Added in proof.* In a recent study [J. Kossanyi, J. P. Morizur, B. Furth, J. Wieman, A. M. Duffield and C. Djerassi, *Org. Mass Spectrom.*, **1**, 777 (1968)] it was found that the larger alkyl group was lost preferentially from aliphatic 1,2-glycols at both high and low electron beam energies. This paper also contains data on α-cleavage, dehydration and hydrogen transfer processes in 1,2-glycols which supplement the present discussion.

molecule may enhance or retard particular α-cleavages. Thus in 1,2-glycols, cleavage of the bond between the hydroxylated carbons is particularly favoured[11], while in aryl-substituted hydroxyl compounds (excluding phenols in which α-cleavage cannot occur) the benzylic bond and that α to the hydroxyl may be coincident, as in 2-phenylethanol derivatives[12]. These compounds, in contrast to benzyl alcohol derivatives[13], give abundant ions by loss of $HOCH_2^{\bullet}$ or its derivatives (loss of $HOCH_2^{\bullet}$ from benzyl alcohol is a multi-step process[13]). In cyclic alcohols too, α-cleavage is very important although some other cleavage is also necessary to give fragment ions. The major fragment ion in the spectrum of cyclopentanol (**2**), for example, arises as shown[14].



(2)

The ability of the OH group to direct fragmentation in competition with other groups in multi-functional compounds has been the subject of some discussion. Although such a concept necessarily has qualitative significance only, the suggestion has been made that OH is a poorer directing group than the amino group[3] but is better than the enone function in steroids[15]. Even in the absence of other groups, fragmentation by α-cleavage to the OH functionality can sometimes be negligible. In the fatty alcohols, for instance, ease of loss of water greatly outweighs α-cleavage and most fragment ions arise by loss of olefin molecules or alkyl radicals from the $(M\text{-}H_2O)^+$ ion, while chain branching can provide additional sites for simple cleavages unrelated to the presence of the heteroatom. Long chain alcohols have been of interest because of their occurrence in such natural products as waxes and lipids and details of their mass spectra are available[16]. α-Cleavage with charge retention by the hydrocarbon fragment is normally a minor process but may be important when a particularly stable ion can be formed. Also of minor importance, are cleavages of the β, γ, δ, . . . bonds since neither the ionic nor the neutral fragments are expected to possess any special stability, although the possibility has been raised[3, 4] that the formation of a cyclic oxonium product may account for the slightly enhanced tendency for δ-cleavage.

In addition to α-cleavage, a second fragmentation which is char-

acteristic of hydroxyl compounds of most types is the loss of water from the molecular ion. Although the problem of thermal dehydration has largely been overcome, it is not always easy, even in compounds for which electron impact dehydration is confirmed by the presence of an appropriate metastable peak, to establish that the thermal process is not also operative. The tendency for the molecular ion (ionized on oxygen) to increase its valency explains the transfer of hydrogen to oxygen while the associated elimination of a neutral molecule is energetically favourable. It is now well established that loss of water occurs as a 1,4-elimination in acyclic compounds[17, 18] and as a 1,4- or 1,3-process in cyclic compounds[19–21] but details of the stereochemistry of these processes is an area of active interest (section V).

The striking similarities[2, 4] between the spectra of alcohols and 1-olefins poses a question concerning the structure of the $(M\text{-}H_2O)^+$ species formed from alcohols. Carbon–carbon bond formation may occur to give the corresponding ionized cycloalkane or H migration may accompany dehydration, so yielding the molecular ion of an olefin[17, 18]. Meyerson and Leitch[18] have suggested from the variation with electron beam energy of the label distribution in fragment ions formed from the $(M\text{-}H_2O)^+$ ion of *n*-hexanol, that this ion represents a mixture of structures. They also note that the distinction between a cyclic and an olefinic $(M\text{-}H_2O)^+$ structure can be expected to be blurred by the tendency for the former to isomerize. There is indeed evidence that at least some of the fragmenting forms of cycloalkane molecular ions have open chain structures[22]. Moreover, the various isomeric alkenes are difficult to distinguish by mass spectrometry and their spectra closely resemble those of the cycloalkanes[22].

In polyhydroxy compounds loss of water frequently involves H from a second O–H rather than a C–H bond. This is even true of some 1,2-glycols[11b] although there is evidence in some acyclic glycols that the more usual larger transition states are preferred[23]. Cyclohexane polyols have been studied by three groups[24]. Several mechanisms of dehydration operate and the occurrence of a variety of skeletal and hydrogen rearrangements has also been reported[24]. The importance of the loss of water from cyclic alcohols is partly due to the fact that the major competitive process, α-cleavage, frequently cannot give fragment ions directly. Among the simple monocyclic alcohols, cyclohexanol and cycloheptanol lose water most readily, a fact which Natalis suggests is related to their ability to take up an axial or pseudoaxial configuration[25]. The elimination of water

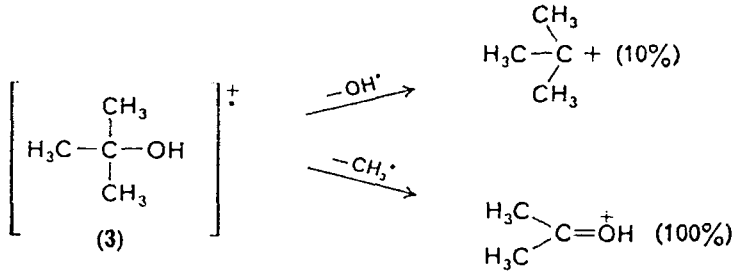
from acyclic alcohols is relatively more important in the primary than in the secondary and tertiary series[5], since in the latter cases the high frequency factor (*vide infra*) α-cleavage process gives more stable product ions. Electron impact induced dehydration of phenols is of no importance.

Because of the above possibilities for formation of stable fragment ions, and because of the limited effectiveness of charge stabilization in the molecular ions of OH compounds (with the notable exception of phenols), it is not surprising that alcohols are characterized by low abundance molecular ions (and phenols by abundant molecular ions). In a high molecular weight alcohol the molecular ion will frequently not be detectable and this is an important reason for the widespread use of alcohol derivatives for mass spectroscopy (section VII). The problem may also be overcome by employing field ionization (section VIII) or by introducing a group of low ionization potential into the molecule—see next section.

Hydroxyl compounds also fragment by a variety of other characteristic routes, some of which will be mentioned here. Several types of hydrogen rearrangement have been identified in the spectra of alcohols, notably those resulting in formation of $CH_3—\overset{+}{O}H_2$ (*m/e* 33) and H_3O^+ (*m/e* 19)[2–4, 26]. These rather complex processes involve, once again, the formation of trivalent oxonium ions, although it has been noted[2] that the stability of the radical which is lost may provide much of the driving force for reaction. Some deuterium labelling has been performed[27] to establish the origin of the transferred hydrogens, but no specific site seems to be implicated —this probably means that hydrogen scrambling in the alkyl chain is fast relative to the rearrangement (compare section III). Several hydrogen rearrangements which occur in particular cyclic and aromatic alcohols are discussed in section IV. Further fragmentation of ions formed by dehydration and α-cleavage accounts for many abundant ions in alcohol mass spectra. For instance, the $(M-46)^+$ ion, previously suggested[3] to arise by concerted loss of H_2O and C_2H_4 via a six-membered transition state, must, from metastable peak data[2], be formed at least in part by ethylene loss from the $(M-H_2O)^+$ ion.

Two simple fragmentations not yet considered are loss of $OH^\bullet$ and loss of $H^\bullet$ from the OH group. The latter process can be dismissed immediately since it involves the formation of a monovalent oxygen ion; the $(M-1)^+$ ions observed[5] in secondary and primary

alcohols must therefore be due to α-cleavage. The loss of OH• is of some importance in cyclic and acyclic tertiary alcohols and in the latter compounds it may give a more abundant ion than does loss of H_2O. In *t*-butanol (3) both the increased stability of the *t*-butyl



cation and the limitation of dehydration to 1,2-processes combine to make OH• elimination important relative to loss of water. α-Cleavage nevertheless remains the dominant process. OH• elimination is not observed in phenols and even in benzyl alcohol[13], where the extremely stable $C_7H_7^+$ ion results, it is not a major process.

Some comments on phenols can usefully be made here since their behaviour provides exceptions to many of the above generalizations (they give abundant molecular ions, and do not undergo α-cleavage or dehydration). Their most significant fragmentation is loss of CO, presumably following keto-enol tautomerism and possibly giving a cyclic product ion[2–4]. Loss of CHO• is also a major process and it has been suggested[4] that the stability of the ionic product, perhaps the cyclopentadiene cation, relative to the stability of the $(M\text{-}CO)^+$ ion may account for the importance of the process in spite of the relative instability of the radical eliminated. The hydrogen lost as CHO• may come from the hydroxyl group alone, but if so, labelling shows[28] that hydrogen scrambling must occur prior to fragmentation. Substituted phenols show spectra which can differ considerably from that of phenol itself since ring expansion (alkyl substituents), proximity effects and fragmentation through the substituent can be involved.

III. THEORETICAL BASES FOR THE BEHAVIOUR OF OH COMPOUNDS UPON ELECTRON IMPACT

With the data of section II as a backdrop, it will now be useful to examine more closely some of the concepts used so far. The developing physical approach[29, 30] (as opposed to the empirical approach)

to the mass spectra of organic compounds is, for several reasons, particularly appropriate to OH compounds. First, the two major fragmentation processes in alcohols, α-cleavage and dehydration, are representative of high and low frequency factor processes. Secondly, a great deal of deuterium- and ^{13}C-labelling of OH compounds has been done and, thirdly, theoretical calculations of electron impact spectra from quasi-equilibrium theory[31] (QET) are available. Finally, methods of ion formation other than electron impact have been quite widely used. The importance of each of these four features will be obvious later in this section. Two additional desiderata for application of the physical approach are spectral data taken at low electron beam energies and adequate ionization and appearance potential (IP and AP) data on typical compounds. Currently, the available data for OH compounds are limited in both these respects.

Before dealing with ion structures and energies, it is reasonable to consider only the kinetics of fragmentation and to draw some conclusions on how relative abundances of product ions vary with conditions used in obtaining spectra. The QET [31], used here as a basis for discussion of rate processes, has unquestioned value in explaining, at least qualitatively, the mass spectra of organic compounds. Mass spectra arise from the unimolecular fragmentations of molecular and fragment ions. These processes are normally competitive and each has a rate which depends on the nature and internal energy (E) of the species reacting and the potential surface over which it moves (the surface defines the activation energy, E_a, while the relationship between the reactant and the transition state geometries can be expressed as a 'frequency factor', ν). A given decomposition has a rate constant k, which is most simply expressed[31a, b] as $k = \nu[(E - E_a)/E]^{S-1}$ where S is the number of effective harmonic oscillators in the decomposing ion.

There is considerable evidence, both from theoretical calculations[32] and from low eV studies[29, 33], that the frequency factor for a typical simple cleavage is high and approaches the bond vibrational frequency, while that for a rearrangement is low. (The validity of this statement is not limited to unimolecular ionic reactions[34].) The second basic parameter controlling rates, the activation energy, is normally lowered when bond breaking is accompanied by bond making, a situation which obtains during hydrogen and skeletal rearrangements and results in their having low activation energies which may (partly at least) offset their low frequency factors[35]. The

combination of low E_a and ν, typical of rearrangements, results in a much slower rise of k with E than is found for simple fragmentations.

Since it is low energy ions which undergo metastable decompositions, the frequent observation of metastable loss of water from alcohols and the usual absence of metastable peaks corresponding to α-cleavage, implies that the former process has the lower activation energy*. Appearance potential data for *n*-propanol[32a, 35] confirm this. In alcohols, α-cleavages are expected to have high frequency factors while loss of water should have a low frequency factor. Theoretical results[32a] agree with this assignment. The preceding factors account for the dominance of α-cleavage over hydration in most acyclic alcohols run at 70 eV since, as E increases, k tends to ν. They also suggest that the elimination of water should become relatively more important in ions of low energy. What little low eV work has been done on alcohols is in agreement with this expectation[25, 37]. Finally, since activation energies reflect product (ion and neutral) stabilities it is not surprising that in primary alcohols, where the stability of the α-cleavage ionic product is at a minimum, dehydration competes more successfully than it does in secondary and tertiary alcohols[5].

Another important consequence of the QET postulates and the effects of E_a and ν on reaction rates is that hydrogen scrambling, a low E_a/low ν process, will be most extensive in ions of long lifetime (i.e. low internal energy)[29]. Hence a rapid process such as α-cleavage can hardly be accompanied by hydrogen randomization though this may be extensive or complete during slower fragmentations. This conclusion can be discussed with reference to the spectra of some labelled acyclic alcohols. Dehydration of *n*-hexanol for instance, while almost completely specific, does involve to a small extent (ca 10%) the loss of a hydrogen atom originating at some site other than C_4 [17, 18]. While it has been recognized that this may be a consequence of partial H/D scrambling[17], apparently the expectation that scrambling should be more extensive in metastable ions and in daughter ions at low eV has not been tested. In agreement with expectation are the observations (i) that simple α-cleavage in *n*-butanol occurs without scrambling, while formation of the secondary $C_3H_5^+$ and $C_3H_3^+$ ions is accompanied by considerable H/D exchange [27a] and (ii) that loss of water from even-electron fragment

* Although not a rearrangement, bond breaking and making are probably synchronous during α-cleavage of alcohols and this must lower the activation energy for this process somewhat.

ions is often far less specific than from molecular ions[17, 38]. 3-Phenyl-1-propanol provides a good example of the increase in scrambling within a molecular ion on increasing the ion lifetime. Nibbering and de Boer[39] showed that hydrogen exchange involving the hydroxyl group, the two *ortho* hydrogen atoms and the γ-methylene group must occur in this compound but their results show that in fragment ions this exchange is incomplete. Their metastable ion data, which include identical metastable peak profiles for the γ-d_2 and the *ortho*-d_2 compounds at low eV, indicate *complete* scrambling under these conditions.

The ideas advanced above also have obvious relevance to the abundance of the molecular ions of hydroxyl compounds. Frequently, even in the absence of such non-mass spectrometric factors as thermal dehydration, molecular ions are not distinguishable. In theory, molecular ion abundances can be increased by collecting ions sooner or by transferring less energy to the ion upon formation. The former method is limited by various practical considerations (accelerating voltage, source residence time) though both factors operate to produce the abundant molecular ions which characterize field ionization spectra (section VIII). A unique and potentially valuable method[40] of increasing the molecular ion abundance depends on the introduction of a group of low IP into the molecule, so increasing the fraction of molecular ions with insufficient energy to undergo *any* fragmentation at a fast enough rate ($>10^5$) so that appreciable decomposition occurs in the short interval (typically 30 μsec) the molecular ion spends in the mass spectrometer. This method cannot be applied if there are important fragmentations which require vibrational energy only (as distinct from a particular charged or radical site) but it has been successful in providing a molecular ion of measurable abundance in a disaccharide which otherwise gave no fragments in the molecular ion region[41].

Another aspect of the kinetics of mass spectrometric processes, and one of great mechanistic interest, concerns the evaluation of substituent effects on rate data[42]. Since only a limited amount of work has been done outside of aromatic systems, these remarks are limited to aromatics and particular interest focuses on phenols. In many series of compounds correlations between rates of fragmentation (more specifically, fragment and parent ion abundances) and Hammett σ values exist—at the time of writing, however, there is considerable discussion[29, 30, 43] on the reasons for these correlations and the conclusions they permit. In particular, the variety of factors

influencing rate data and the difficulties in separating individual contributions have been emphasized[29, 43a]. An OH substituent on an aromatic nucleus causes a considerable reduction in the ionization potential (phenol and benzene have IP's of 8·50 eV and 9·25 eV respectively[44]) and may therefore considerably increase the molecular relative to the fragment ion abundance by increasing the fraction of molecular ions with insufficient energy to fragment. The electron-donating ability of the *p*-OH substituent (recognized in its σ value[45] of $-0{\cdot}37$) will also frequently have a major effect on activation energy and hence on the fragmentation rate.

Finally in this consideration of kinetics, some discussion of the validity of the QET as specifically applied to alcohols is called for. Detailed calculations of electron impact and photoionization spectra of simple alcohols have been attempted by several workers[32a, 32b], and although there has been some disagreement on the relative importances of some processes, adequate agreement with measured spectra is reported (serious errors introduced by using too large a value for the number of harmonic oscillators are corrected in the revised QET [31b]). Features of the calculated results and ancillary measurements include (i) the much lower energy requirement for 1,3-dehydration (PrOH) than for 1,2-dehydration (*i*-PrOH) and the consequent greater importance of dehydration in the former compound, (ii) the relatively low energy requirement for α-cleavage, (iii) the high energy requirement for $OH^{\bullet}$ loss, (iv) and the low frequency factors for loss of CH_4 and H_2O.

A novel test of QET, as applied to simple alcohols, has been carried out by Lindholm and collaborators[46]. By charge exchange using atomic ions of different recombination energies, molecular ions of particular internal energies could be formed. The resulting spectra, averaged over the assumed molecular ion energy distributions for electron impact, gave calculated spectra which agreed well with measured electron impact spectra and satisfactorily with spectra calculated using the QET. The possibility of fragmentation from isolated electronic states is particularly important in simple molecules and metastable and appearance potential data indicate that such a process apparently occurs in ethanol (loss of $OH^{\bullet}$ has a high AP and yet it gives a metastable ion[47]). Fragmentation from separate electronic states is, however, readily incorporated into the QET.

A major aspect of the physical approach to mass spectrometry concerns ion structures. In treating this topic it is first necessary to discuss the primary processes undergone by OH compounds upon

electron impact and the structures of the resulting molecular ions. The ionization potential of an aliphatic alcohol is the energy required to remove the least strongly bound electron—one of the lone pair electrons on oxygen—a process which requires some 10 eV [44]. To quote Al-Joboury and Turner[48], 'there is no doubt that the first ionization potential of . . . aliphatic alcohols . . . measures the energy required to remove an electron from a 2*p*-orbital practically confined to the oxygen atom'. When an alcohol is bombarded with 70 eV electrons the possibility of an electron transferring all its energy to the alcohol is remote (ionization cross-sections vary inversely with the energy of the state which is formed[49]). Nevertheless, the amount of energy transferred averages ca 15 eV [50] (5 eV in excess of the first ionization potential) which is sufficient to remove at random any of the bonding or lone pair electrons in the primary ionization process. It is a postulate of the QET that the resulting molecular ions have time, prior to fragmentation, to interconvert electronic and vibrational energy by crossing of potential energy surfaces and for vibrational excess energy to be statistically distributed through all the bonds of the ion. It has become accepted practice to visualize the molecular ion as that species in which the low-lying electronic levels are occupied (frequently a species in which the charge may be considered as localized on a heteroatom or multiple bond) and to consider fragments as arising from decomposition of this ion[51]. While a complete theoretical justification of this simplified picture is not possible it has been shown that the charge localization concept is not inconsistent with QET [43a]. Moreover, its practical usefulness as a means of interpreting and predicting fragmentations in many compounds, including OH compounds, is very well established.

While the methods for establishing ion structures in mass spectrometry necessarily differ from those applicable in solution chemistry, there have been rapid recent advances[29] in the use of techniques which give structural information, and one can look forward to the accumulation of logically consistent bodies of data on individual ions (which, perhaps, is all that 'structure' means). The structurally relevant data include ionic heats of formation, modes of formation and fragmentation (in particular quantitative metastable/parent/daughter ion abundance ratios), kinetic energy release in metastable fragmentations, and substituent effects on fragmentation rates. In the remainder of this section applications of these methods to the solution of problems involving OH compounds are illustrated.

One such problem, already mentioned in section II, concerns the structure of the $(M\text{-}H_2O)^+$ ion from alcohols and whether or not it is identical with the molecular ion of the corresponding olefin. (In general, it is easier to provide evidence that two ions do or do not have the same structure than it is to argue for a particular structure.) Several studies[52] on terpenols and the corresponding terpenes have noted the presence of many common metastable ions (similarities involve shape as well as position) and these results point strongly to identical $(M\text{-}H_2O)^+$ and olefin molecular ion structures. It may be noted that the terpene alcohols provide a particularly difficult problem of ion structure which has been discussed in some detail[52a]. Similarities in metastable and daughter ion profiles point to complex skeletal reorganizations which give common molecular ions in these compounds[52a].

The use of data from energetics in establishing ion structures requires care, since structurally identical ions may be formed with different amounts of internal energy at their appearance potentials, and hence behave differently. For instance, the $C_6H_6O^+$ ion formed by a McLafferty rearrangement from a series of alkyl phenyl ethers has a heat of formation which is considerably greater than that of the phenol molecular ion[53]. While this may mean that the two ions are structurally distinct[53] it need not, since the fragment ion may be formed at its appearance potential with considerable excess energy[29]*. A consideration of the fragmentations undergone by the $C_6H_6O^+$ ion should be valuable. In particular, in several related cases including the tropolone/phenol pair[54], ions formed by fragmentation showed greater daughter and metastable ion abundances relative to parent ions than did the isomeric molecular ions, which is consistent with common structures but higher average internal energies in the fragment ions (as might be expected). The phenol/phenetole pair examined in this way[54], showed the opposite behaviour, but this result is still not inconsistent with formation of structurally identical ions since the amount of internal energy carried off by the neutral fragment depends on its number of degrees of freedom (see below) and with the loss of relatively large neutral fragments from high energy ions this effect could offset the effect of the threshold excess energy.

A complex ion structure problem, which has been tackled by energetics and by metastable and labelling studies, concerns the

* *Added in proof.* Recent evidence (F. W. McLafferty and L. J. Schiff, *Org. Mass Spectrom.*, **2**, 757 (1969)) points to structurally identical ions.

$C_2H_5O^+$ ions formed from primary and secondary alcohols and other compounds. A primary structural and/or energy division is established between those $C_2H_5O^+$ ions which fragment to give H_3O^+ ions accompanied by a 'metastable peak' and those which do not[55]. This distinction is reinforced by the fact that the latter also fail to release kinetic energy[56] in eliminating CH_4 (narrow metastable peaks are observed). The H_3O^+ ions which are formed from $C_2H_5O^+$ ions in a variety of compounds have similar energies (ΔH_f 160 $\pm$ 5 kcal/mole) and deuterium labelling results imply a symmetrical, therefore protonated ethylene oxide, structure for their $C_2H_5O^+$ precursors[57]. Recent ^{13}C-labelling results, however, show a more complicated situation with apparently two distinct $C_2H_5O^+$ ions fragmenting to give H_3O^+ [58]. The use of the relative abundances of two metastable transitions to characterize the fragmenting ion(s) indicated varying proportions of the protonated ethylene oxide ($C_2H_5O^+$) structure or a single structure with different internal energies depending upon its source[55].

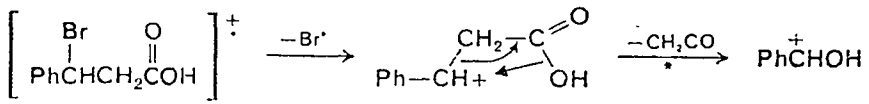
Even a cursory treatment of some ion structure problems shows the great importance of metastable peaks in mass spectra. They have, of course, long been valuable in establishing fragmentation sequences but now their shapes, abundances and positions have taken on new importance as indicators both of molecular and ionic structures. The useful correlation between metastable ion abundance and the occurrence of bond forming reactions[29, 33, 59] has been mentioned. The kinetic energy released during a metastable transition can be calculated from its width[56] and structural distinctions are possible on this basis, for example, *m*- and *p*-nitrophenols lose NO with release of 0·0 and 0·74 eV respectively[60]. In a series of secondary alcohols[61], the relative metastable to parent ion abundances for the reactions $C_2H_5O^+ \rightarrow H_3O^+$ and $C_2H_5O^+ \rightarrow CH_3O^+$ are inversely proportional to the number of degrees of freedom in the secondary alcohol. This result points to the uptake of internal energy by the alcohol which is independent of its size and dependent only on the OH function, while subsequent common ion formation occurs with loss of a fraction of the total internal energy which is proportional to the size of the neutral fragment lost. These results agree with the QET postulate of equilibration of vibrational energy and are also of some interest from the point of view of the charge localization approximation. A final observation concerning metastable ions in OH compounds was the recent discovery of an anomolous metastable ion in methanol[62]. This compound has recently been the subject of

a searching investigation[63] and the reader is referred to the original article for details of the thermochemical, kinetic and ion structural information obtained.

IV. SKELETAL AND HYDROGEN REARRANGEMENTS[35]

The notable tendency of the molecular ions of alcohols to form a third bond to oxygen can be indulged by means of skeletal rearrangement or by the simple cleavages and hydrogen migrations already noted in section II. Other properties of the OH group, including its ability to migrate as a nucleophile and the possibility of its displacement as a radical, also allow skeletal rearrangement.

Limiting the discussion to skeletal rearrangements which directly involve the OH group in the bond breaking and making sequences which constitute rearrangements, three types can be distinguished. They are (i) OH migration, (ii) OH displacement and (iii) formation of new bonds to the hydroxyl oxygen. Migration of a nucleophilic group in both odd- and even-electron ions with concomitant loss of a radical or a neutral molecule is a well-documented process[35]. OH compares well with other nucleophiles as a migrating group[64], and provided a suitable positive site is available and a stable neutral molecule is eliminated, the reaction can give abundant fragment ions. The base peak in the spectrum of **4**, for example, arises by the rearrangement shown[64]. The detailed mechanisms of



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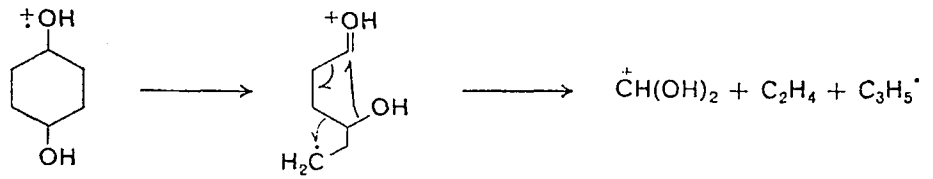
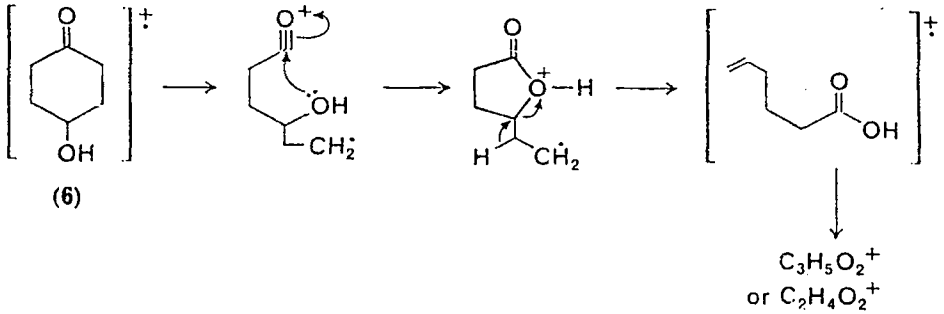
the corresponding processes in odd-electron ions are less clear[35]. A possible representation[24a] of one such rearrangement in the cyclohexane diol **5** is illustrated. Here and in the OH migrations which



(5)

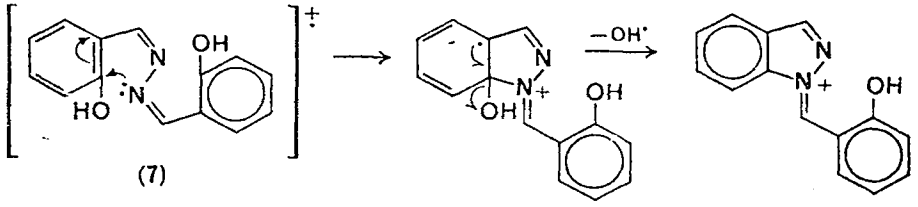
occur in sugars[65, 66] and in acyclic polyols[67] the importance of forming stable products is paramount. The OH group in aryl ketoximes

can migrate to give the corresponding phenol molecular ion[68] and OH migration to the metal atom is known in substituted ferrocenes[69]. A final and rather complex example of OH migration is the carefully studied[70] molecular ion isomerization which occurs in hydroxycyclohexanones (e.g., **6**) and related compounds.



(6)

Skeletal rearrangements which involve the displacement of OH• from an aromatic ring may be considered within a general rearrangement type which includes various intramolecular aromatic substitutions[35]. It is of particular interest that the loss of OH• from **7**

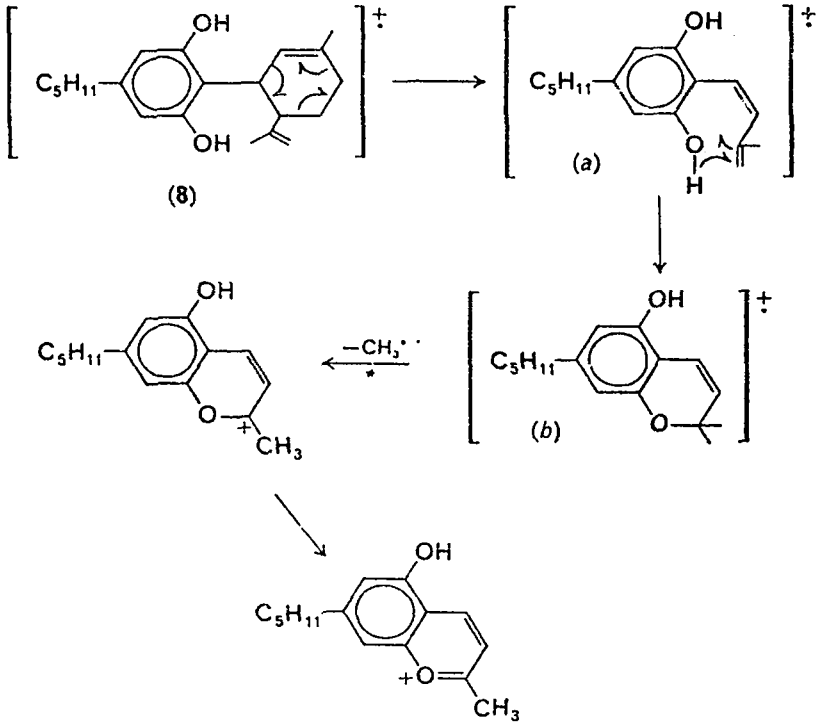


(7)

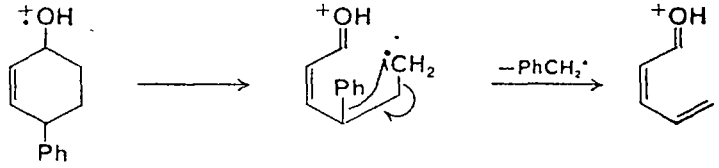
proceeds more slowly than the loss of many other radicals[71], reflecting the strength of the C–O bond in phenols and the relative instability of OH•.

Examples of the formation of a new bond to the oxygen of an OH group occur in phenolic compounds. The hashish constituent **8** shows an abundant ion corresponding to the loss of a methyl radical from the retro Diels–Alder product (*a*) and this is best accounted for by the rearrangement $a \rightarrow b$ which converts a vinylic to an allylic methyl group[72]. Deuterium labelling data are consistent with the mechanism shown. A variety of C–O bond forming reactions have also been noted in 1-hydroxynaphthalenes containing acetyl or benzoyl groups at $C_{(8)}$ [73].

Turning to skeletal rearrangements in which the OH group is not itself involved in the bond breaking/bond making sequence, just a few points will be made. First, the OH group can have an important



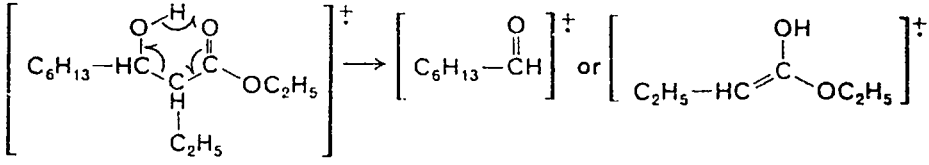
charge-stabilizing role in radical-induced migrations and so contribute considerably to the driving force for rearrangement, as in the example illustrated[74]:



Secondly, ring expansion processes which primarily involve the carbon skeleton, may occur prior to or during fragmentation of the molecular ions of OH compounds and will considerably affect their spectra. However, in spite of intensive investigation of ring expansion in benzyl alcohol[13c, 75] and related compounds[12a, 39] including the use of energetic data and labelling studies, it has not been decisively established under what conditions and to what extent ring expansion occurs.

While skeletal rearrangements are of moderate importance in

OH compounds themselves, some of their derivatives, especially the trimethylsilyl ethers, display a variety of very important rearrangement reactions. Several examples and further discussion can be found elsewhere[35]. One of the reasons for the moderate extent to which skeletal rearrangements occur in OH compounds is the fact that hydrogen rearrangement is often able to compete successfully. Examples of hydrogen and double hydrogen migration in hydroxyl compounds are numerous and they may be divided into two types. Firstly, those involving migration of a hydrogen atom to the OH group and second, those in which the hydroxyl hydrogen atom migrates to some other position. The former type has been discussed in some detail by Natalis[26], especially as regards the $CH_3—\overset{+}{O}H_2$ and H_3O^+ ions. Studies by the same author[25] on the low energy spectra of alcohols reveal the increased importance of hydrogen rearrangements under these conditions. The loss of water, of course, involves hydrogen migration to oxygen although the new bond is formed in the neutral and not in the ion. In simple monofunctional OH compounds only the first type of hydrogen transfer, including that involved in dehydration, is energetically accessible in view of the tendency to maintain oxygen in the uncharged bivalent or charged trivalent state. In more complex molecules, however, the hydrogen of the OH group can rearrange with concomitant formation of a C=O bond. This rearrangement apparently involves a six-membered transition state in the molecular ion of compound



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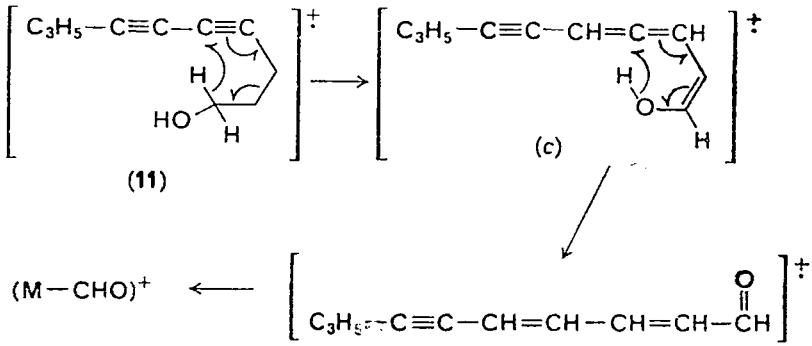
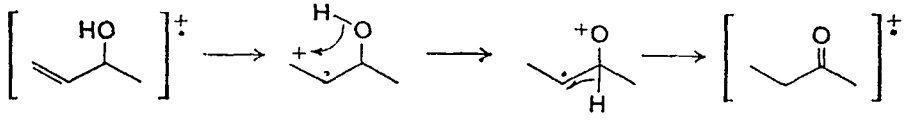


(11)

10 [76] and in the rearranged form (*c*) of the molecular ion of the polyacetylene **11** [77]. Both rearrangements are formally of the McLafferty type and numerous analogous processes have been suggested[78].

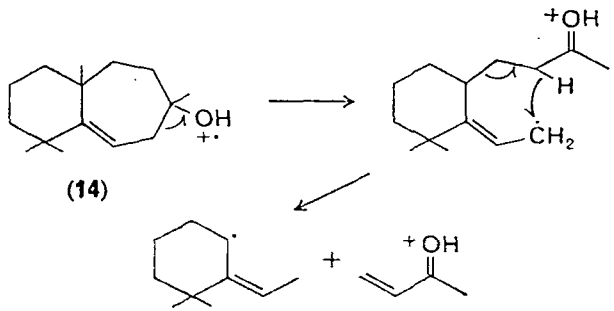
Hydrogen migration from the OH group, presumably by ketonization[3], must also occur prior to the decarbonylation of phenols. (Decarbonylation may involve recyclization[35] in which case a skeletal rearrangement is also involved.) A notable instance of hydrogen migration from the OH group is to be found in α,β-unsaturated alcohols which apparently undergo a double hydrogen rearrangement upon electron impact to give the corresponding ketone molecular ions (e.g., **12**→**13**)[37, 79]. The rearrangement has



(12) **(13)**

been investigated by deuterium labelling[37, 79] which supports the mechanism shown, although many fragment ions arising from the ketonic form of the molecular ion show some randomization of the label. This is not surprising since, given time, hydrogen randomization in alkyl ketones is known to occur[80] (indeed, it could even involve a mechanism which includes the above reaction and its reverse reaction). Unfortunately, in neither study of allyl alcohols[37, 79] are low eV spectra of the deuterated compounds recorded nor are hydrogen scrambling processes considered in detail.

Just as with skeletal rearrangements, some hydrogen migrations in OH compounds depend upon, but do not directly involve, the OH group. An instructive case which occurs in the sesquiterpenol widdrol (**14**), has been confirmed by high resolution and deuterium labelling[78a]. Other examples are to be found in the fragmentations



(14)

of simple cyclic alcohols[39, 81] as already illustrated in section II. Finally, a good example of the complexity of hydrogen rearrangements possible in OH compounds is provided by the spectra of some terpenols and their deuterated derivatives[82].

V. STEREOCHEMISTRY AND THE ELIMINATION OF WATER

It has already been noted that loss of water from acyclic alcohols occurs preferentially as a 1,4-elimination and has a relatively low frequency factor. A low activation energy for a mass spectrometric elimination often requires concerted bond formation and cleavage and hence a cyclic transition state[35]. This explains the 1,4-elimination mechanism, while the low frequency factor arises from the low probability of the acyclic molecular ion taking up a cyclic conformation in which interaction between OH and the $C_{(4)}H$ can occur. In cyclic molecular ions (which may or may not result from ionization of cyclic alcohols, the possibility of ring opening constituting a notable complication in the use of mass spectroscopy for stereochemical assignments) much of the conformational choice open to acyclics is lost. Among the (few) conformations open to a particular stereoisomer the orientation of OH relative to suitable H atoms may allow several modes of dehydration each with varying energy requirements. These modes and their energy requirements will generally differ in epimers and may allow stereochemical assignments by mass spectrometry. Generally only the most rapid mode of dehydration for a particular epimer will be of interest*.

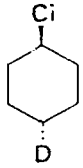
In a concise and valuable review on stereoisomeric effects in mass spectrometry, Meyerson and Weitkamp[83] point out several advantages in using ions of low internal energy (formed by using low energy electrons and low source temperatures or by photoionization) to distinguish stereoisomers. These are (i) interconversion of epimers is minimized, (ii) processes other than that of lowest energy are relatively less important and (iii) further decomposition of the diagnostic primary fragment ions is reduced. Maximum differences

* In a stereoisomer in which H and OH can take up an optimum relationship, the activation energy for dehydration will approximate that found in acyclic alcohols but the frequency factor may be much higher. Dehydration should therefore be correspondingly more important and the k versus E curve should resemble that for a simple cleavage. A variable eV experiment might help to distinguish the basically different rate characteristics expected for dehydrations of cyclic and acyclic alcohols.

in rates of fragmentation of epimers therefore result. Considerable efforts have been made to reduce source temperatures in this type of study, but less attention has been given to low energy experiments. It is worth noting that, when deuterium labelling is used to establish the mechanism of a dehydration the process may, at low eV, appear less specific than it actually is due to hydrogen/deuterium scrambling in the ions of longer lifetime[29]. On the other hand, at higher beam energies other modes of dehydration might well obscure the mechanism of the process of interest.

Because of the constraints imposed by cyclic systems both 1,4- and 1,3-dehydrations are commonly observed (on the other hand when labelling data suggests a 1,2-elimination a thermal process should be suspected). Almost all the relevant mass spectrometric-stereochemical studies on water elimination from alcohols deal with cyclohexane derivatives and their major features have been discussed by Meyerson and Weitkamp[83]. In essence, (i) the relative thermochemical stabilities of the isomers are not of major importance as was originally thought[84], rather (ii) the orientation of H and OH are critical and only an axial OH can normally approach a hydrogen atom (that at $C_{(3)}$ in the chair and at $C_{(4)}$ in the boat conformation) closely enough to allow dehydration. (iii) The question of the structure of the $(M\text{-}H_2O)^+$ ion(s) has not been resolved, although Meyerson and Weitkamp note that C–C bond formation[19, 85] during 1,4-elimination is not the only reasonable possibility, and (iv) the degree of substitution at $C_{(3)}$ and $C_{(4)}$ is important, it having been shown[20] that the normally dominant 1,4-process can be less important than the 1,3-elimination if $C_{(3)}$ is made tertiary and $C_{(4)}$ secondary.

In an important study Green and Schwab[21] were able to separate the contributions of cyclic and acyclic molecular ions to the $(M\text{-}H_2O)^+$ ion of cyclohexanol. In agreement with previous findings they showed that 1,4-dehydration is considerably more important than 1,3-dehydration, and they also found this to be true of the loss of HCl from cyclohexyl chloride. They then studied the 1,4-processes



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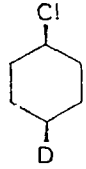

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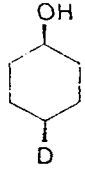


(17)

in detail, using the specifically deuterated compounds **15–17**. Compound **15** did not lose DCl while loss of DCl from **16** accounted for the total contribution of the 1,4-process. This stereospecific *cis*-elimination was also observed in cyclohexanol although the importance of α-cleavage in alcohols led to some contribution (~40%) from dehydration of the acyclic molecular ion[21]. The results of this paper are of interest for the information they provide on *ion structures* as well as for their stereochemical importance.

Following the pioneering communication of Biemann and Seibl[84] on the use of mass spectral elimination reactions as indicators of stereochemistry, the work of the Russian school of Zaretskii, Wulfson and collaborators[86] has been among the most significant in this field, and in treating a variety of steroidal systems these authors have given the solution of real stereochemical problems due weight. They use $(M\text{-}H_2O)^+/M^+$ abundances as a measure of the rate of dehydration but the value of this parameter in assigning stereochemistry in the absence of the spectra of both epimers[87] has perhaps been overstated, and has drawn some criticism[15]. When both isomers are available, however, the axial OH compound is readily distinguished. The $(M\text{-}H_2O)^+/M^+$ abundance ratio for epimeric axial and equatorial OH compounds can differ[19] by a factor of 100 although values of 1 to 20 are more common (the greater abundance ratio belonging to the axial OH epimer). Frequently the observed differences outweigh the inaccuracies inherent in the use of the abundance ratio as a measure of the rate of dehydration*.

In addition to the Russian workers a number of other groups[15,88–91] have also investigated sterols, although in several of these studies undue weight has apparently been given to the nature of the ring fusions as opposed to the axial or equatorial orientation of the hydroxyl group. By investigating the dehydration of the even-electron $(M\text{-}CH_3)^+$ ion in some sterols[90] thermal effects could be excluded and again the importance of the relative orientation of the OH group was confirmed. The terpenols are another group of natural products the stereochemistry of which has been investigated by mass spectrometry. Useful results, in accord with the more rapid loss of the axial hydroxyl as water, have been obtained[52b, 82, 92].

In summary this approach to stereochemistry appears to have considerable potential and with more extensive use of milder conditions, especially photoionization, differences between stereo-

* The limitations of relative ion abundances as measures of fragmentation rates have been discussed elsewhere[54, 83].

isomers more pronounced than those which are now usual should be obtained routinely.

VI. COMPOUNDS OF NATURAL ORIGIN

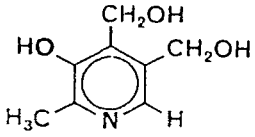
Terpenes, steroids, saccharides, alkaloids, vitamins, natural colouring matters, drug metabolites and many other natural compounds frequently contain OH groups. In many instances the OH moiety is directly attached to a ring, sometimes an aromatic ring.

Mass spectrometry is of course well established as a structural tool in this field, although in some of the above classes of compound the OH group is hardly significant in determining the fragmentation pattern while in others, such as sugars, it is usually derivatized prior to mass spectroscopy. Below, the spectra of specific compounds and examples of structural determination are discussed. Since so much work has been done, the choice of material for discussion is somewhat arbitrary although emphasis is given to cases where the mass spectra were studied in depth, for instance, by exact mass measurements, labelling techniques and the use of metastable transitions. For a general discussion of the elucidation of structure by mass spectrometry, Spiteller's chapter[93] is notable.

Several vitamins containing OH groups have been the objects of recent mass spectrometric studies. DeJongh and co-workers have made detailed studies[94, 95] on the B_6 group including their metabolites, analogues and derivatives, and have used deuterium labelling and exact mass measurements to substantiate fragmentation mechanisms. As is typical of heteroaromatics the molecular ions are intense and even in pyridoxol (**18**) which has three OH groups, the molecular ion is the base peak[94]. In this compound, which is fairly typical of the group, a few major fragment ions dominate the spectrum. They are due to elimination of small neutral molecules, often formed as a result of interactions between substituents. This makes mass spectrometry an ideal method for distinguishing the various compounds of the B_6 group even at the microgram levels which are encountered in metabolic studies. The similarities between the observed fragmentations and those occurring in simple benzene derivatives have been emphasized[94, 95].

The trimethylsilyl derivatives of the B_6 group have been investigated by Vetter and co-workers[96] who have also studied both the TMS derivatives and the free vitamins of the A and K groups[97, 98]. The unsaturated side chain is responsible for the abundant molecular

ion in all-*trans* vitamin A (**19**) and its isomers, although, with the exception of a large fragment ion formed by cleavage alpha to the OH group in *retro* vitamin A* (**20**), the fragment ions of both **19** and **20** are of limited value in structural recognition. Vitamins of the K



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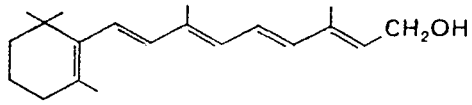

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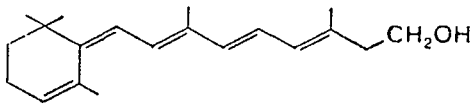


(20)

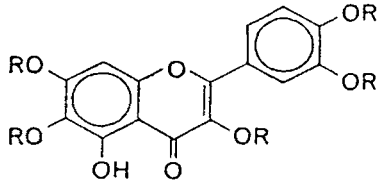
group were most conveniently analysed as the TMS derivatives of the corresponding quinols[98].

Vitamin B_1, a quaternary ammonium compound, decomposes thermally in the ion source but the spectra of the decomposition products can be used to deduce their structures and that of the vitamin[99]. The same procedure can be applied to analogues of the vitamin[99]. The spectra of a variety of ring-open tertiary amine derivatives of thiamine have been recorded[100].

An enormous variety of oxygenated aromatic compounds, including phenolics, occur in nature; mass spectrometry is useful in their structural determination and the spectra of the underivatized compounds display abundant molecular ions. Frequently, however, the OH group is not of primary importance in the fragmentation sequence. This is apparent from a study of some oxygenated naphthoquinones[101] in which fragmentation is directed by the keto group. Even loss of CO from the phenolic moiety is not important, the only notable features attributable to the OH group being hydrogen migration during formation of the benzoyl ion[101]. Similar remarks apply to the spectra of naturally occurring acridones, which also undergo a characteristic hydrogen rearrangement from the OH group[102], and to the naphthaquinone pigments found in sea urchins[103]. These latter compounds often contain acetyl in addition to hydroxyl substituents and fragmentation occurs preferentially

* The bond alpha to the OH group is also vinylic to a double bond in all-*trans* vitamin A (**19**) but it is allylic in *retro* vitamin A (**20**). The variation in the ease of α-cleavage follows.

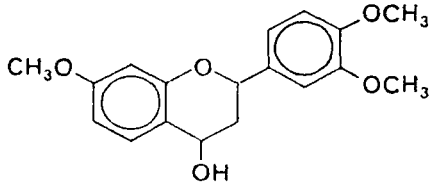
through the former. In none of the above compounds[101–103] is dehydration of the molecular ion of much significance, although it does give rise to fairly abundant fragment ions in those quercetagetin derivatives (**21**) which contain *ortho* OH and OCH_3 groups[104].



R = H, CH_3 or C_2H_5

(21)

The mechanism of this dehydration has not been established. In addition to the study of Bowie and Cameron[104] several others[105–107] have also dealt with the mass spectra of flavonoid compounds. These compounds may carry OH substituents on aromatic and/or alicyclic rings and in some compounds, for example the 3,4-diols studied by Drewes[105], dehydration may be significant. An attempt[81] to relate the rate of dehydration to the stereochemistry of these diols failed, perhaps because steps were not taken to lower the internal energies of the molecular ions. Dehydration yielded abundant fragment ions in the 4-hydroxy series—compound **22** showed a 60% relative abundance $(M-18)^+$ ion and a 3% molecular ion—in marked contrast to the 3-hydroxy compounds where **23**, for example,



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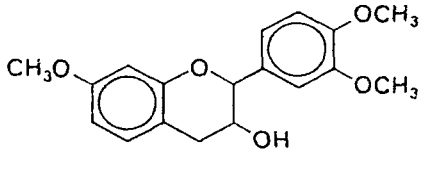
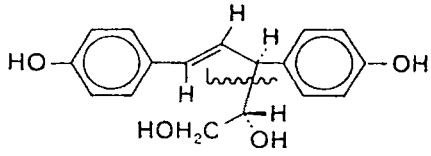


(23)

displayed a 0·6% $(M-18)^+$ ion and a 49% molecular ion[105]. Although not specifically commented upon by the author[105], this striking and structurally diagnostic difference is obviously related to the possibility of abstraction of a tertiary hydrogen atom in the 1,3-dehydration of **22**, while in **23** either an aromatic hydrogen must be lost or a 1,2-elimination must occur and neither is likely. The results of Pelter and co-workers[107] are in accord with the above observations on the elimination of water, although these workers supposed that dehydration of the 3,4-diols involves only the two hydroxyl groups. The passivity of the phenolic hydroxyl groups in initiating fragmentations is also evident from their results[107].

A series of compounds isolated from conifer resins also carry both phenolic and alcoholic hydroxyl groups and they include, for instance, the glycol **24** [108]. The only fragmentations of significance in **24** are cleavage alpha to the secondary alcohol, assisted by the fact



(24)

that this is also a benzylic and an allylic bond, and those processes involving further decomposition of this ion. In spite of having four OH groups, the molecular ion is easily recognizable.

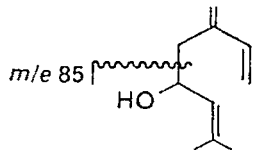
Recent typical investigations of other phenolic natural products have covered hashish constituents[72, 109] benzofuran and xanthone derivatives from lichens[110], aphid pigments[111], and the tetrahydroprotoberbine alkaloids[112]. The retro Diels–Alder reaction is of major importance in these fused ring systems but the mass spectra give no direct indication of the presence of the OH groups (however, derivatization and the consequent change in M^+ allows easy determination of the number of phenolic hydroxyl groups). Although many classes of alkaloids contain hydroxyl groups, their mass spectra have been adequately discussed elsewhere[113].

The advances in technique which now permit the study of the mass spectra of relatively unstable compounds obtained from complex mixtures in small amounts are worthy of emphasis. For instance, the spectra of some polyhydroxy lipid constituents of low molecular weight have been measured at 40–55° by the direct insertion technique[23]. Structural studies on the polyacetylenes, including those containing alcoholic substituents, have also benefited from the application of mass spectrometry[77]. The combined gas chromatography–mass spectrometry technique has found especially wide application in studies of this type.

Extensive reference has already been made (section V) to one aspect of the mass spectra of sterols—the loss of water. Fragmentation of these compounds may be initiated by cleavage alpha to the OH group. This is especially notable for $C_{(17)}$-hydroxyl substituents[89] but is important for hydroxyl substituents at other positions in rings C and D [87, 114, 115] and it may allow determination of the position of the substituent. Further details on other aspects of the much-studied

mass spectra of sterols may be found in the references listed by the above authors[86–91, 114, 115] or an earlier review[116] may be consulted.

The final group of natural products to be discussed here are the terpenols. Of considerable interest are the monoterpene sex attractants studied by Silverstein and Rodin[117]. Compound **25**, for instance,



(25)

showed a molecular ion and $(M\text{-}H_2O)^+$ and $(M\text{-}H_2O\text{–}CH_3)^+$ fragment ions, in addition to the base peak at *m/e* 85 formed by cleavage of the doubly activated bond indicated. The g.l.c./m.s. method of separation and structural elucidation is virtually the only practicable method for compounds such as the phenomes in view of the complex mixtures, small quantities and high volatilities encountered. Several studies have been made on monoterpenols from other sources[52, 82]. Isomerization of the molecular ion and/or the $(M\text{-}H_2O)^+$ ion in these compounds can lead to difficulties in distinguishing structural isomers. However, the polar OH group considerably influences the fragmentation and makes for far more unique spectra than are obtained from the parent terpenes. Consequently secondary and tertiary alcohols are often easily distinguished from each other, while isomeric secondary (or tertiary) terpenols are sometimes distinguishable. The aromatic alcohols are naturally particularly easy to characterize[52b]. Several investigators have studied sesquiterpenols[78a], pentacyclic triterpenols[118, 119] and steroidal triterpenols[120].

VII. DERIVATIVES OF OH COMPOUNDS

Because of the difficulties which have been encountered in obtaining spectra of hydroxyl and polyhydroxyl compounds a great deal of attention has been given to the spectra of their derivatives. In this section the trimethylsilyl ethers and acetates, together with several other derivatives on which less work has been done, are discussed. The analogies between the behaviour of the derivatives and that of the parent hydroxyl compounds is emphasized. Especially interesting are processes corresponding to the three major characteristics

(α-cleavage, the elimination of water and OH migration) of the parent OH compounds. Other aspects of the spectra of the derivatives which are important in structural elucidation are also noted.

The TMS derivatives of alcohols are easily prepared[121], stable and volatile. Although the molecular ion may be absent, especially in the polyol derivatives, the $(M\text{-}CH_3)^+$ ion is very characteristic and can be used for molecular weight determination. Two other features, which in certain circumstances are disadvantageous, are the sharp increase in molecular weight on derivatization and the propensity of these derivatives to undergo skeletal rearrangements, some of which may be difficult to predict. In addition to the loss of $CH_3^{\bullet}$, α-cleavage can also lead to C–C bond fission in TMS ethers. This process gives low abundance fragment ions in the lower acyclic compounds[122] and much more abundant ions in the derivatives of long chain hydroxyesters[123–125] where it allows determination of the position of the oxygen substituent. α-Cleavage is also one of the more notable features of the spectra of the parent long chain hydroxyl esters[125–127]. The position(s) of the double bond(s) in long chain olefins may be determined from the pronounced tendency for α-cleavage between the oxygenated carbon atoms of the TMS derivatives of the corresponding glycols[125].

It has been reported[128] that one mode of fragmentation of disaccharides is direct cleavage of the glycosidic bond, a process which is in competition with the α-cleavage modes leading to ring opening and to the $(M\text{-}CH_3)^+$ ion. Mass spectrometry has considerable potential value in structural studies on oligosaccharides. The TMS derivative of an antibiotic tetrasaccharide[129] gave a good spectrum which included a barely distinguishable molecular ion (*m/e* 1401) and a more abundant $(M\text{-}CH_3)^+$ ion. Major fragmentation again occurred at the weak glycosidic bonds[129]. The TMS derivatives of diglycerides derived from phospholipids are suitable compounds for structural determination by mass spectrometry[130]. Monoglycerides have also been investigated as their TMS derivatives[131].

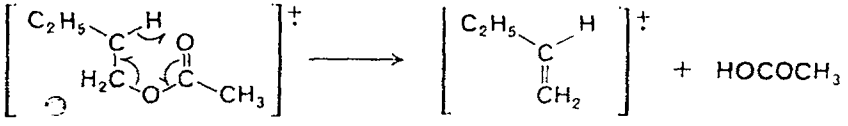
The elimination of trimethylsilanol, which corresponds to the loss of water from alcohols, is an important aspect of the behaviour, upon electron impact, of TMS ethers, especially those of high molecular weight. For example, the spectrum of the TMS ether of the antibiotic filipin[132] is dominated in the high mass region by fragments 90 mass units apart. Successive losses of trimethylsilanol from the $(M\text{-}CH_3)^+$ ion are observed in disaccharide derivatives[128] and the same molecule is lost from the molecular and fragment ions

of hydroxyester[125] and sugar lactone[133] derivatives. Investigations on the mechanism of loss of trimethylsilanol do not yet permit firm conclusions and are hampered by the fact that the simple acyclic trimethylsilyl ethers do not undergo this process[122]. Dickman and Djerassi[134], using TMS derivatives of deuterium labelled sterols, found that the mechanism apparently is not analogous to that found for loss of water from the corresponding alcohol, 40% being lost by a 1,2-elimination and at least some of the remainder by a 1,3-process. Although the site of hydrogen abstraction was not investigated, the loss of trimethylsilanol from glycol derivatives increases in relative importance as the electron beam energy is decreased[135], an observation in accord with the anticipated low frequency factor for this process.

The skeletal rearrangements occurring in trimethylsilyl ethers have been the subject of considerable study and have been discussed collectively[35]. They are far less pronounced in the derivatives of simple acyclic alcohols[122] than in those of simple diols[135], in which one TMS group can provide a positively charged migration terminus while the other can act as the migrating group. In polyfunctional trimethylsilyl compounds complex rearrangements occur[96, 122, 123, 125]. It is also noteworthy that migration of the intact trimethylsilyloxyl group to a carbonium ion or other positively charged site is a reaction of considerable importance in sugar derivatives[66, 128] and this behaviour parallels known rearrangements of the hydroxyl group. The transfer of a trimethylsilyl group from a distan site to a carbonyl function is a notable phenomenon in the mass spectral behaviour of TMS derivatives of hydroxy esters[123, 136]. Exactly analogous hydrogen transfers via many-membered cyclic transition states occur in the parent hydroxyl compounds, the similarities extending to the ensuing fragmentations of the rearranged molecular ions[123, 137], one of these subsequent processes being the elimination of a $CH_3OH/CH_3OSi(CH_3)_3$ group.

Parallels are also exhibited between the behaviour of the acetates and the parent hydroxyl compounds. In addition to fragmentations characteristic of the ester group, both the elimination of acetic acid and migration of the acetoxy group take place. The acetates have been employed in attempts to make stereochemical assignments by the method used for alcohols (discussed in section V). Loss of acetic acid from some steroids has been found[138] to be much more pronounced when the acetate is axial than when it is equatorial, while in other investigations differences in rate were not significant[85]. A

complication not encountered in the dehydration of alcohols, is that loss of acetic acid takes place by two competitive mechanisms[17, 82, 85] involving hydrogen transfer to one or other of the oxygen atoms of the acetate. These alternative processes are illustrated for *n*-butylacetate (**26**); possible ion structures are also shown but these are by



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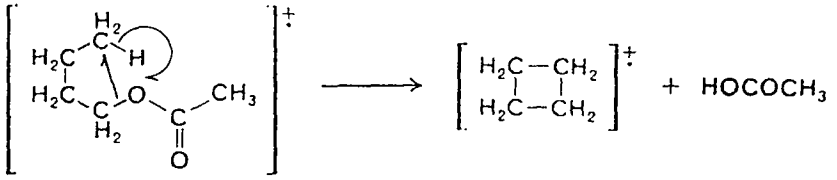


(26)

no means established. The former process is frequently the more important while the latter can involve a 1,3- as well as a 1,4-elimination[85]. Because of the complexity of the M^+-$HOCOCH_3$ reaction it cannot yet form the basis for stereochemical correlations and the observation made by several authors[139, 140] that acetic acid elimination is more pronounced than is the loss of water from the corresponding alcohol can have but limited significance. The occurrence of acetoxyl migrations to carbonium ion centres[66, 67, 141] and the usefulness of acetates as derivatives which allow structural studies on such natural products as glucosides[142] and disaccharides[143] merits attention.

Among the many other OH derivatives which have been studied by mass spectrometry, the methoxyl[66] and isopropylidene[143] substituents have been useful in the investigation of carbohydrates. For the investigation of sugars there is no one derivative of preference—the characteristics of TMS ethers and acetates have already been discussed, while methoxyl derivatives also have advantages, including their low molecular weights and the absence of prominent rearrangements other than methoxyl migration to a carbonium ion centre; isopropylidene derivatives are of interest for the information they can yield on stereochemistry[143].

Stereospecific elimination of methanol from a number of methylated cyclic diols and triols has been briefly reported[144]. The usefulness of a substituent containing an aromatic ring in increasing the

molecular ion abundance is the reason for recent interest in triphenylmethyl ethers[145] and *o*-aminobenzoates[146] as alcohol derivatives. Boronates may have some future as derivatives of diols for mass spectrometric investigation[147].

VIII. NEW TECHNIQUES FOR ION FORMATION AND ANALYSIS

The fact that electron impact (EI) is a less than ideal method for the ionization of alcohols has led to considerable interest in alternative methods. One of these alternatives is photoionization (PI) which has been referred to above and will be commented on briefly here. PI has the considerable advantage over EI that ionization is effected in the absence of a hot metal filament and, furthermore, the energy imparted to the ion commonly corresponds to that supplied by low energy electron beams. These advantages emphasize its potential for stereochemical studies but only a little work of this type has been reported[19]. Overall PI and EI differ relatively little in the processes which they initiate and in the energies, and hence in the relative rates of decomposition of the ionic species they produce.

Radically different kinetics and/or reactions are involved in field ionization (FI), negative ion spectroscopy (NI or EA*), and in ion-molecule reactions. Ionization prior to ion-molecule reactions may be produced by many methods, including PI, EI and FI, and the techniques used to study these reactions may also vary considerably. The types of ion-molecule reactions undergone by alcohols are directly related to the properties of the OH group and they will be indicated briefly before FI and EA spectra are dealt with.

Charge exchange between an ionized atomic or molecular projectile and a neutral molecule was the method of ionization used by Lindholm and his group in their studies[46a, b] on ion-molecule reactions in alcohols. Reactions between the projectile and a neutral molecule or between ionized and un-ionized molecules result in new ionic species which are readily detected after being accelerated and separated according to their masses. Futrell and his colleagues[148, 149] employed a conventional electron impact ion source in their study of ion-molecule reactions in alcohols. They followed the effect of such parameters as source pressure on the yields of particular ion-molecule reaction products. The new technique of ion cyclotron

* From the German 'ElektronenAnlagerung'. This is the most interesting of the several processes whereby negative ions are formed.

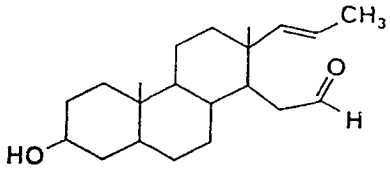
resonance[150] can also employ electron impact as the method of ionization but the use of ion resonance allows the reactions of particular ions to be followed with amazing specificity. The ion-molecule reactions occurring in methanol have been studied in great detail by this method[151]. Whatever the experimental approach, the large cross-section for proton transfer reactions is the most characteristic feature of ion-molecule processes in alcohols. This tendency to form protonated alcohols is in accord with the basic drive for the alcohol molecular ion to form a third bond to oxygen (section II). Aggregates such as $(ROH)_n \cdot ROH_2^+$ are also formed[151, 152]. Among many others the following proton and hydride transfers are typical:

$$CH_2OH^+ + CH_3OH \longrightarrow CH_2O + CH_3OH_2^+ \text{ [148, 151]}$$
$$CH_3CHOH^+ + CH_3CH_2OH \longrightarrow CH_3CHO + CH_3CH_2OH_2^+ \text{ [148]}$$
$$CH_3^+ + CH_3OH \longrightarrow CH_4 + CH_2OH^+ \text{ [153]}$$

References to other studies on ion-molecule reactions are made by the authors cited above[46b, 149, 151] and many aspects of the technique have been reviewed[154]. The use of tandem mass spectrometers[149] increases the power of the conventional ion source studies but the future should see the dominance of ion cyclotron resonance.

Negatively charged ions are formed upon electron impact[155] but have not taken on a significance remotely comparable to that of the corresponding positive ions. This is largely due to lower ion yields (by a 10^{-3} to 10^{-4} factor) but even when spectra are obtained they frequently show no ions in the molecular ion region and difficulties are experienced in the theoretical interpretation of the spectra because of the many types of processes involved. This last fact is of considerable practical importance since under different conditions varying contributions to the observed spectra are made by three major processes[155]; (i) resonance capture of an electron, $AB + e \rightarrow AB^{\cdot -}$, (ii) dissociative resonance capture, $AB + e \rightarrow A^- + B^{\cdot}$ and (iii) ion pair formation, $AB + e \rightarrow A^- + B^+ + e$. Alcohols are one of the few classes of compound in which negative ion spectrometry has been useful, the stability of the alkoxyl anion often resulting in an easily observable $(M\text{-}H)^-$ ion. Probably all three of the above processes contribute to the $(M\text{-}H)^-$ observed[156,157] using 'normal' mass spectrometric conditions, i.e. 70 eV and $\sim 10^{-6}$ mm source pressure (the slow electrons necessary for resonance capture are generated during positive ion formation). In order to increase the cross-section for electron capture (EA) and so obtain more useful and less complex spectra, von Ardenne and co-workers[158] have introduced the use of a gas discharge source in which the slow

electrons required for resonance capture are readily formed by ionization of argon which is present at a much greater concentration (10^{-2} mm) than is the sample (10^{-6} mm). Using this method, negative molecular ions are recorded for many more classes of compound but sensitivity remains low and instrumental modifications are necessary. Another disadvantage of the EA technique and indeed of most negative ion experiments, is the frequent occurrence of ion-molecule reactions which create new difficulties in recognizing molecular ions. Nevertheless alcohols and even some polyhydroxyl compounds[159] do give molecular ions and/or $(M-H)^-$ ions using von Ardenne's approach, which has consequently found some use in the solution of structural problems. For example, the observation of the $(M-H)^-$ ion (base peak) at m/e 317 was of value in deducing the structure of compound **27** [160].



(27)

Field ionization[161] differs radically from other methods of ionization and because of the characteristics described below it is rapidly increasing in importance, especially as a complementary technique to EI. The kinetics involved in FI spectra are complex since ions are formed by a variety of processes which include[162] (i) molecular ion formation by tunnelling of an electron through the potential barrier of the molecule which is lowered by the strong field, (ii) formation of a molecular ion in an excited state above its dissociation limit, (iii) various field-assisted fragmentations of the molecular ion, including a statistical process involving energy fluctuation in the ion but with the dissociation energy lowered by the field, (iv) statistical processes in a zero field region which correspond to the fragmentation mechanisms operative in electron impact spectra. Furthermore, adsorbed molecules, as opposed to gaseous molecules, may be ionized by field desorption[163]. In spite of this complexity, two features[164] characterize FI mass spectrometry: (i) low excitation energies are involved and consequently molecular ions are abundant and fragment ions very weak indeed, and (ii) the acceleration given ions by the field means that ions are examined sooner than usual in EI and PI spectra, consequently metastable ions are formed after

10^{-8}–10^{-6} sec (whereas in other methods 10^{-6}–10^{-5} sec elapse) and they are very intense. On the other hand fragment ions must be formed within 10^{-14}–10^{-12} sec if they are not to be recorded as 'fast' metastable ions, and this is why their abundances are comparable to or even lower than those of the various types of metastable ions.

The formation of abundant molecular ions is an obvious advantage of FI for the study of alcohols. This fact in addition to full use of the 'fast' and normal metastable ions, allows terpenols to be characterized readily[165]. Especially important is the fact that rearrangements and multi-step fragmentations are easily distinguished from simple bond cleavages since the slower rearrangement (and multi-step) processes give intense metastable peaks but low abundance daughter ions and vice versa[166]. Another striking application of FI was that of Brunnée and colleagues[167] who obtained spectra on some very unstable compounds including diacetone alcohol and several diols. The illustrations in their paper should be consulted to appreciate the remarkable improvement of FI spectra over EI spectra in these cases. As expected, the major daughter ions in the FI spectra of alcohols include those formed by α-cleavage[166, 167], while the $(M\text{-}H_2O)^+$ ion tends to occur as an abundant metastable ion[166, 168]. Among the disadvantages of field ionization are poor reproducibility[161], the occurrence of gas-phase ion-molecule reactions, particularly proton transfer in alcohols, and the formation of a condensed phase which can lead to ion clusters such as $(CH_3OH)_nCH_3OH^{+\cdot}$ [161a]. The above features, together with more detail, are to be found in a study of aliphatic alcohols by Beckey and Schulze[168] and in a Russian study[169] of methanol, ethanol and their labelled derivatives.

Added in proof: Recent work in several areas covered by this review has been intensive; very little can be referenced here. Brown and colleagues[170] have obtained evidence for a concerted 6-centre dehydration accompanied, in the same molecular ion, by a stepwise 7-centre dehydration. Reversible hydrogen transfer to the ionized hydroxyl group is associated with the latter process. Green[171] has continued his detailed inquiries into the stereochemistry of mass spectral elimination reactions using the dehydration of alcohols as a model system. Ionization efficiency curves have been used[172] in an approach to the stereochemistry of sterols. Evidence has been obtained for the occurrence of the hydroxylated cyclopropane ion in the spectrum of *t*-butanol[173]. Neighbouring group participations

have been discovered in the mass spectra of some azulylethanols and their derivatives[174]. There has been a continuing interest in keto–enol tautomerism and in the fragmentation of enols[175, 176]. Finally, the determination of the mass spectra of some tri-, tetra- and pentasaccharide derivatives[177], illustrates the continuing extension of the technique in applications involving hydroxylated natural products.

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The Chemistry of The Hydroxyl Group
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CHAPTER 20

Hydroxide–alkoxide ion equilibria and their influence on chemical reactions

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I. INTRODUCTION

When an alkali is added to a mixture of water and an alcohol ROH, two anion bases, the hydroxide and alkoxide ions, are present at equilibrium:

$$OH^- + ROH \rightleftharpoons RO^- + H_2O \qquad (1)$$

Since this equilibrium reaction is a proton transfer, the equilibrium is usually attained instantaneously[1].

These equilibria have been neglected in many studies, especially those dealing with reaction kinetics and syntheses in which aqueous alcohols containing alkali have frequently been employed as media. There are many reasons for this neglect. For example, the (apparent) rate constants based on the measurement of the decrease in the total concentration of alkali in these media do not drift with time more than in pure solvents and excellent Arrhenius plots are usually obtained although the rate constants are usually greatly influenced by equilibrium reaction (1). Alkoxide ions often react much faster than the hydroxide ion (see section VI), and thus practically only one product may be formed. Also, only one of the two concurrent reactions may lead to a new product as is the case in certain ester hydrolyses. In all these cases, however, the rate constants are apparent quantities influenced by equilibrium reaction (1) and differ from the true rate constants.

On the other hand, the properties of hydroxide and alkoxide ions are very similar. For example, they are all strong bases, and titration of their mixtures with an acid gives the sum of their concentrations. Both kinds of lyate ion influence also other measurements, as, for example, e.m.f. and conductometric measurements. The standard potentials and equivalent conductivities vary with solvent composition and are not known and must be estimated in some way if they are to be used to determine the equilibrium constants of reaction (1). Only in the case of acidic alcohols such as 2,2,2-trifluoroethanol are accurate determinations of the position of equilibrium reaction (1) possible at present. The kinetic method to be described below has one advantage over other methods; the ratios of the products of substitution reactions give direct information about the simultaneous existence of different lyate ions.

The purpose of the present article is to discuss the magnitudes of the equilibrium constants and to clarify what effects equilibrium reaction (1) has on the products, rate constants and other data of chemical reactions, and also to discuss the relative reactivities of hydroxide and alkoxide ions. This last problem is closely connected with the determination of the equilibrium constants of reaction (1). Attention will be mainly centred on the equilibria between methoxide and hydroxide and between ethoxide and hydroxide ions.

II. DIRECT EVIDENCE FOR THE EXISTENCE OF HYDROXIDE–ALKOXIDE EQUILIBRIA

The existence of these equilibria in aqueous methanol and aqueous ethanol is seen in many ways:

(i) A solution of sodium hydroxide in an alcohol has the properties of a solution of the corresponding sodium alkoxide in the alcohol and substitution reactions in both solutions lead to the introduction of an alkoxy group; the rate constants of the reactions are usually the same in the former and in the latter solution. (It is somewhat misleading, as is sometimes done, to speak of 'alcoholic sodium hydroxide'.)

(ii) Addition of sodium alkoxide to water leads to its conversion to the hydroxide.

(iii) Substitution reactions in solutions of alkali in aqueous alcohols lead to the formation of mixtures of hydroxy and alkoxy compounds, and the influence of the lyate ion equilibrium reaction (1) is seen on inspection of the reaction products (this was done for the first time by Lobry de Bruyn and Steger[2]). For substitution reactions, a product composition quantity B'_{ha} can be defined (see section IV.A.3), which is a constant at low alcohol contents when the solvent composition is varied, and this constancy can be explained only in terms of equilibrium reaction (1).

(iv) The conductances of sodium hydroxide and sodium alkoxide are nearly equal in an aqueous alcohol[3, 4], which indicates that the conducting ions are the same in both cases.

(v) Rate constants for the disappearance of total alkali in substitution reactions increase when small amounts of water are added to methanol and decrease when small amounts of water are added to ethanol; this discrepancy disappears when the respective equilibria (reaction 1) are taken into consideration (see section IV.A.1).

III. EXPRESSIONS FOR THE EQUILIBRIUM CONSTANTS

A. Hydroxide–Alkoxide Equilibria

The thermodynamic equilibrium constant for reaction (1) is given by

$$K^0_{ha} = \frac{a_{H_2O}a_{RO^-}}{a_{ROH}a_{OH^-}} = \frac{a_{H_2O}[RO^-]f_{RO^-}}{a_{ROH}[OH^-]f_{OH^-}} \tag{2}$$

where the subscript 'h' refers to the hydroxide ion, on the left in equation (1), and the subscript 'a' refers to the alkoxide ion, a_{H_2O} and a_{ROH} are the activities of water and alcohol with respect to the pure liquids as standard states, and the (degenerate[5]) activity coefficients f_{RO^-} and f_{OH^-} are unity in infinitely dilute solutions in pure water. The terms in square brackets in expression (2) denote molar concentrations. In methanol–water and in ethanol–water mixtures subscripts m and e, respectively, may replace the subscript a.

If, as a first approximation, we take f_{RO^-} and f_{OH^-} to vary similarly with solvent composition, we can use instead of equation (2) the expression

$$\tilde{K}_{ha} = \frac{a_{H_2O}[RO^-]}{a_{ROH}[OH^-]} \tag{3}$$

However, the activity coefficients of the lyate ions seem not to vary similarly with solvent composition and thus K_{ha} can vary considerably when the solvent is varied[4].

A third type of expression that at present seems to be the most useful in practical work (see section V.D) is

$$K'_{ha} = \frac{[H_2O][RO^-]}{[ROH][OH^-]} = \frac{x_{H_2O}[RO^-]}{x_{ROH}[OH^-]} \tag{4}$$

where x_{H_2O} and x_{ROH} are the mole fractions of water and alcohol, respectively.

B. Acid Dissociation Constants of Alcohols

The determination of the acid dissociation constant of an alcohol in water means, in principle, that the equilibrium constant of reaction (1) in this solvent has been determined. In water we have the autoprotolysis reaction

$$ROH + H_2O \rightleftharpoons RO^- + H_3O^+ \tag{5}$$

and thus we can write for dilute aqueous solutions of the alcohol

$$K_a = \frac{[RO^-][H_3O^+]}{[ROH]} \tag{6}$$

and therefore

$$K_a = \frac{K'_{ha} K_w}{[H_2O]} \tag{7}$$

where K_w is the ionic product of water. In equation (6) the concentration of water has been set equal to unity and the standard state for each of the other species (also for ROH) is a hypothetical one molar concentration with unit activity coefficient. The pK_a of water is hence $-\log K_w/[H_2O] = 15{\cdot}74$ (at 25°) (Table 3).

Inspection of equations (4) and (6) reveals that K'_{ha} is the ratio of the acid dissociation constant of the alcohol to that of water in an aqueous solvent of low alcohol content (K^0_{ha} is the ratio in any solvent[4]).

IV. HYDROXIDE–ALKOXIDE EQUILIBRIA IN REACTION KINETICS

A. Substitution Reactions

Many papers have been published where results concerning substitution reactions in alkaline aqueous alcohols are presented[2, 6–28]. Some of these have been discussed previously by the writer[14].

1. Reaction rates

Let us take a simple example, the simultaneous alkaline hydrolysis and alcoholysis of methyl iodide in an aqueous alcohol[14]:

$$MeI + OH^- \longrightarrow MeOH + I^- \tag{8}$$

$$MeI + RO^- \longrightarrow MeOR + I^- \tag{9}$$

The rates of product formation are:

$$\frac{d[MeOH]}{dt} = k^0_h[MeI][OH^-] = k^0_h\frac{[OH^-]}{[alkali]}[MeI][alkali] \tag{10}$$

$$\frac{d[MeOR]}{dt} = k^0_a[MeI][RO^-] = k^0_a\frac{[RO^-]}{[alkali]}[MeI][alkali] \tag{11}$$

where $[alkali] = [OH^-] + [RO^-]$. The expressions

$$k_h = k^0_h\frac{[OH^-]}{[alkali]} = k^0_h s_h \tag{12}$$

and

$$k_a = k^0_a\frac{[RO^-]}{[alkali]} = k^0_a s_a \tag{13}$$

remain constant as the reaction proceeds because of the rapid establishment of equilibrium (reaction 1) (on the assumption, however, that the true rate constants k^0_h and k^0_a remain constant and that

the reaction is not capable of altering the ratio $[H_2O]/[ROH]$ to an appreciable extent, i.e., the concentrations of the reacting species are low). The constants k_h and k_a are apparent rate constants as they contain the 'base fractions' $s_h = [OH^-]/[\text{alkali}]$ and $s_a = [RO^-]/[\text{alkali}]$.

If we add the rate equations (10) and (11), we see that the total rate of product formation, i.e., total rate of disappearance of alkali or methyl iodide is

$$-\frac{d[\text{alkali}]}{dt} = -\frac{d[\text{MeI}]}{dt} = (k_a + k_h)[\text{MeI}][\text{alkali}]$$
$$= k[\text{MeI}][\text{alkali}] \quad (14)$$

and thus
$$k = k_a + k_h \quad (15)$$

is the apparent rate constant of second order calculated from the consumption of methyl iodide or total alkali. It shows good constancy although it is an apparent quantity and relates to both the hydroxylation and alkoxylation reactions.

If we divide equation (10) by equation (11), we get

$$\frac{d[\text{MeOH}]}{d[\text{MeOR}]} = \frac{k_h}{k_a} = \frac{k_h^0[OH^-]}{k_a^0[RO^-]} = \frac{k_h^0[H_2O]}{k_a^0[ROH]K'_{ha}} \quad (16)$$

i.e., the products are formed in constant ratio. Thus

$$\frac{[\text{MeOH}]}{[\text{MeOR}]} = \frac{k_h}{k_a} \quad (17)$$

(see also References 2, 14, 29, 30). If we know the product ratios (in this case from gas-chromatographic analyses) and the rate constants for the disappearance of the total alkali (from titrations with acid), we can evaluate the values of k_a and k_h by expressions (15) and (17)[14]. This is a procedure of formal kinetics only and does not involve any extraneous assumptions. However, if we wish to evaluate k_h^0 and k_a^0, we need an estimate of K'_{ha}.

The above discussion is, of course, applicable to all alkaline solvolysis reactions in alcohol–water mixtures and usually also to other reactions that lead to different hydrolysis and alcoholysis products.

Experimental (apparent) values of the rate constants are plotted together with estimated values of the 'true' rate constants in Figures 1 and 2. It will be seen that the value of the apparent composite constant k decreases on adding water to ethanol and increases on adding water to methanol. This behaviour was first observed by

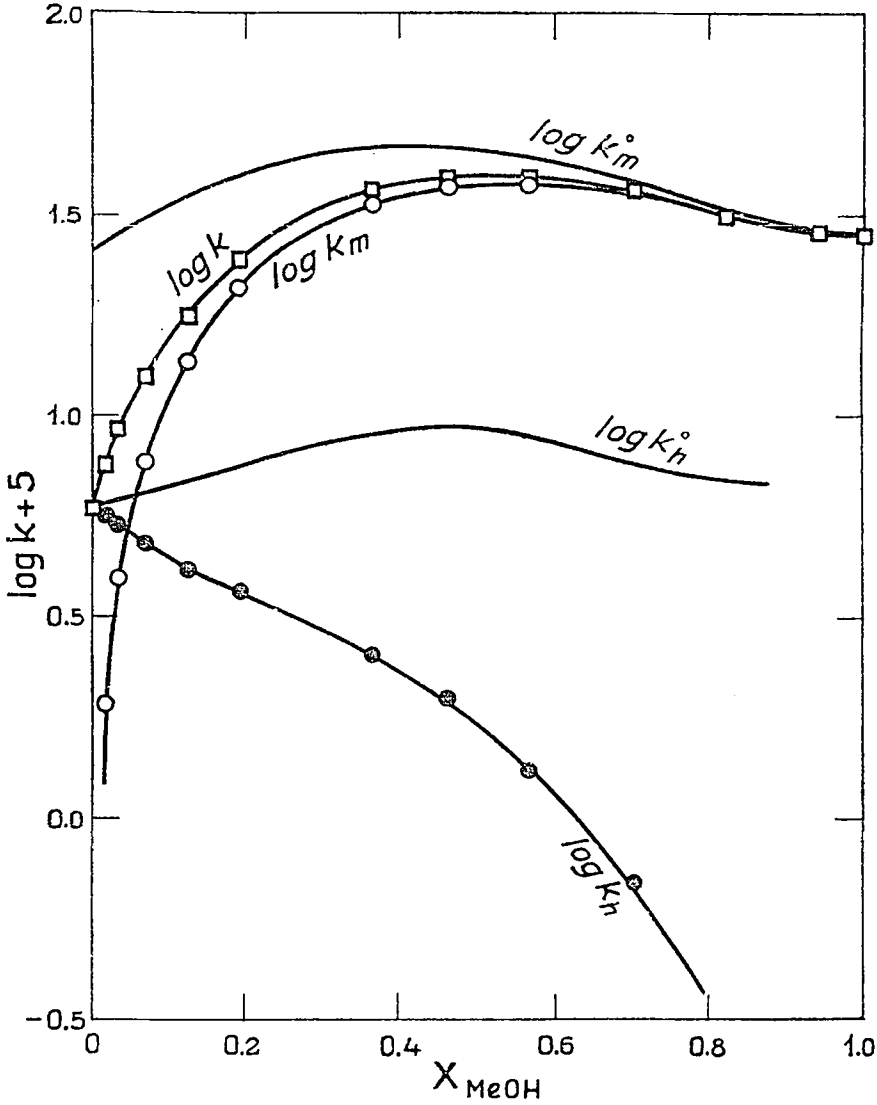

FIGURE 1. Plots of logarithms of the rate constants of methyl iodide against solvent composition in alkaline methanol–water mixtures at 25° [14]. The 'true' constants k_h^0 and k_m^0 were calculated assuming that $K'_{hm} = 4{\cdot}5$. X denotes the mole fraction.

Lobry de Bruyn and Steger[2] and is typical of S_N2 and S_NAr reactions[14, 18]. The difference between aqueous methanol and aqueous ethanol is only apparent[30, 10, 11, 14], and disappears when the estimated values of the true rate constants are plotted. The values of k_m^0 and k_e^0 initially increase on adding water to alcohol, which is

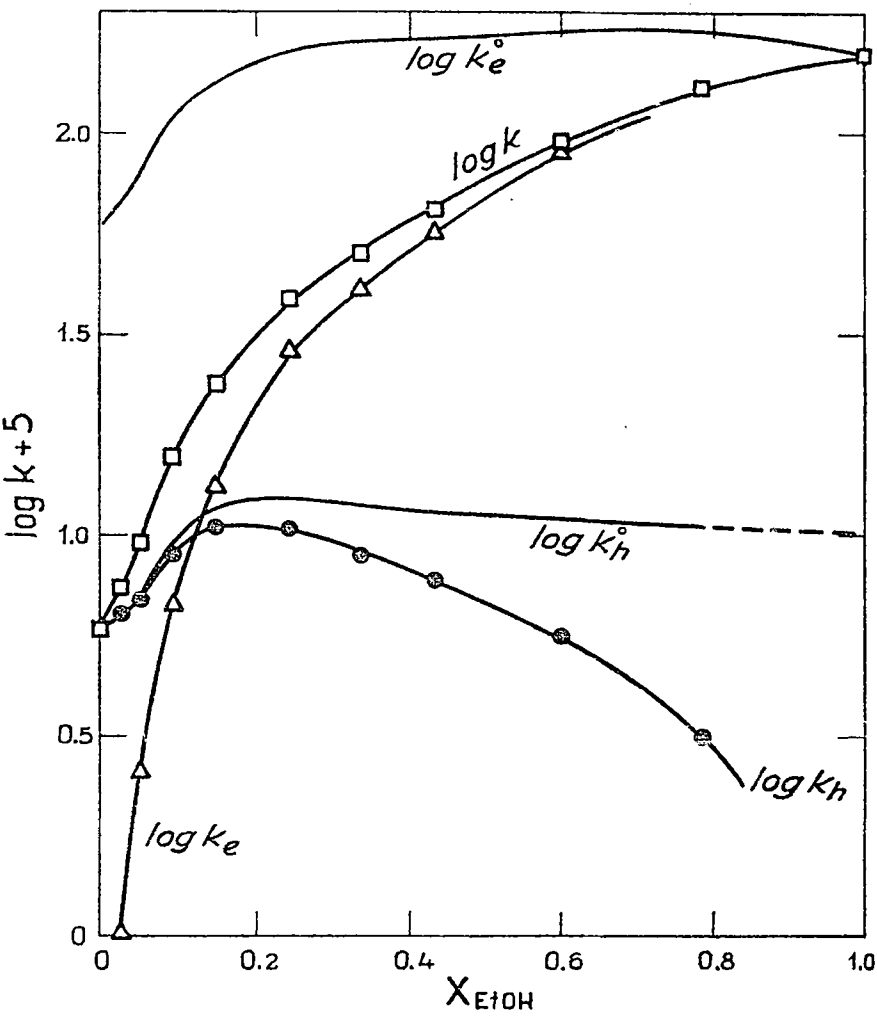

FIGURE 2. Logarithms of the rate constants of the reactions of methyl iodide in alkaline ethanol–water mixtures at 25° [14]. The 'true' constants k_h^0 and k_e^0 were calculated assuming that $K'_{he} = 0{\cdot}65$. X denotes the mole fraction.

contrary to predictions based on the Hughes–Ingold theory of solvent action[31].

It may be mentioned that Riklis[7] has reported that the rate constant of alkaline solvolysis of 1-chloro-2-nitrobenzene decreases on adding water to methanol, but this finding has proved to be erroneous[8, 11].

2. Thermodynamic functions of activation

Excellent Arrhenius plots are usually obtained when $\log k_h$ or $\log k_a$ is plotted against $1/T$. These plots give values of the energies of activation, E_h and E_a, and of the frequency factors, A_h and A_a, respectively. As the rate constants are apparent quantities, so also, of course, are the derived quantities. The true energies of activation (i.e., those not influenced by equilibrium reaction (1)) are denoted by E_h^0 and E_a^0 and the true frequency factors by A_h^0 and A_a^0.

a. Energies of activation. It can be shown[32, 14, 33] that the apparent and true energies of activation are related by the equations

$$E_h = E_h^0 - s_a \Delta H_{ha} \tag{18}$$

$$E_a = E_a^0 + s_h \Delta H_{ha} \tag{19}$$

where ΔH_{ha} is the heat of the equilibrium reaction (1). The base fractions s_h and s_a (equations 12 and 13) vary from zero to unity when going from one pure solvent to the other. Thus the differences between the true and apparent energies of activation vary linearly as the base fractions and do not exceed ΔH_{ha} in magnitude. As ΔH_{ha} is negative (see section V.D), E_h increases relative to E_h^0 with decreasing water content and E_a decreases relative to E_a^0 with decreasing alcohol content.

b. Frequency factors. We have the following relationships[32, 14] between the apparent and true frequency factors:

$$\ln A_h = \ln A_h^0 + \ln s_h - \frac{s_a \Delta H_{ha}}{RT} \tag{20}$$

$$\ln A_a = \ln A_a^0 + \ln s_a + \frac{s_h \Delta H_{ha}}{RT} \tag{21}$$

As ΔH_{ha} is negative, the plot of $\ln A_h$ against solvent composition passes through a maximum[32, 14] (provided A_h^0 does not vary too much with solvent composition) and tends to $-\infty$ at very low water contents where s_h approaches zero. Similarly, $\ln A_a$ tends to $-\infty$ at low alcohol contents but there are no maxima[14].

c. Linearity of apparent Arrhenius plots. The deviations of the apparent Arrhenius plots from linearity are usually extremely small. On the assumption that the true energies of activation and ΔH_{ha} do not vary with temperature, we obtain[14]

$$\frac{d^2 \ln k_h}{d(1/T)^2} = -\frac{1}{R}\frac{dE_h}{d(1/T)} = -\frac{s_h s_a \Delta H_{ha}^2}{R^2} = \frac{d^2 \ln k_a}{d(1/T)^2} \tag{22}$$

which is a maximum when $s_h = s_a = 1/2$. As ΔH_{ha} is only a few kilocalories, the measurements must be extended over a wide temperature range (of the order of 100 degrees) to establish a curvature due to the hydroxide–alkoxide equilibrium (and this demonstration may be impossible even then because of the natural curvature of plots of the true rate constants k_h^0 and k_a^0).

Also the apparent composite rate constants $k = k_h + k_a$ usually yield linear Arrhenius plots.

3. Reaction products

We can gather the known concentrations in equation (16) together and, taking also equation (17) into consideration, obtain an expression which is here denoted by B'_{ha}[14, 19]:

$$B'_{ha} = \frac{[MeOR][H_2O]}{[MeOH][ROH]} = \frac{k_a^0}{k_h^0} K'_{ha} \qquad (23)$$

The product composition quantity B'_{ha} can thus be computed if the solvent composition and the ratio of the reaction products are known. For reactions of other substrates, the concentrations [MeOR] and [MeOH] in B'_{ha} must, of course, be replaced by the concentrations of the respective products of alkoxylation and hydroxylation.

Values of B'_{ha} remain usually relatively constant as the solvent concentration ratio $[H_2O]/[ROH]$ is varied. If we assume that k_h^0 and k_a^0 vary similarly with solvent composition, this constancy indicates a relatively good constancy of K'_{ha} (cf also Table 2, section V.B).

The quantities B'_{ha} are valuable in many ways:

(i) As B'_{ha} varies relatively little with solvent composition, product ratios at different alcohol contents can easily be compared if the values of B'_{ha} have been computed.

(ii) As the values of B'_{ha} are derived from the product ratios, the rate constants need not be known (the reactions may, for example, be too fast to permit accurate rate measurements as in the reactions of picryl fluoride[20]).

(iii) If the values of B'_{ha} for the reactions of a substrate in aqueous mixtures of various alcohols are extrapolated to pure water, the values of k_a^0 are obtained from expression (23) provided the values of K'_{ha} and the value of k_h^0 are known[19, 20]. Thus the reactivities of several alkoxide ions can be compared in the same solvent, even when the reactions are very fast[20, 34, 35].

(iv) Values of the slope α in the Brønsted relations $\log k_a^0 = \alpha p K_a$

$+\beta$ are obtained from plots of $\log B'_{ha}$ against pK_a (Figure 5, section VI) without any rate constant determinations.

(v) From equation (23) we obtain[14]

$$\frac{d \ln B'_{ha}}{d(1/T)} = \frac{1}{R}(E_a^0 - E_h^0 + \Delta H_{ha}) = \frac{1}{R}(E_h - E_a) = \text{constant} \quad (24)$$

Thus the plot of $\log B'_{ha}$ against $1/T$ should be (and usually is) linear. Such plots give information about differences in the energies of activation[14].

A quantity analogous to B'_{ha} can be defined for S_N2 and S_NAr solvolysis reactions in alcohol–water mixtures which also lead to two different products. For solvolyses of picryl fluoride this quantity varies with solvent composition in the same way as B'_{ha} for alkaline solvolyses[20]. It may be mentioned in this connection that Grunwald and Winstein[36] have proposed the use of the 80% ethanol–water mixture as a reference solvent for reactivity correlations. Their method should be used only for compounds that solvolyse by a rate-determining ionization, and not for compounds which solvolyse by a bimolecular mechanism.

B. Alkaline Ester Hydrolyses

Aqueous alcohols have been very popular media in studies of the alkaline hydrolysis of esters[29, 32–34, 37–58]. The hydroxide–alkoxide equilibria have been taken into consideration in some papers[29, 33, 38–40, 41–47, 52]. The papers of Selman[38, 39] must be mentioned as they contain an early clear demonstration of the influence of the equilibrium reactions (1).

The formal treatment of these reactions is in many respects similar to that of the substitution reactions since the reactions lead to two products, an ester (transesterification) and an alcohol:

$$R^1CO_2R^2 + R^3O^- \rightleftharpoons R^1CO_2R^3 + R^2O^- \quad (25)$$

$$R^1CO_2R^2 + OH^- \longrightarrow R^1CO_2^- + R^2OH \quad (26)$$

The reversibility of the transesterification is an additional complicating factor. In the case of methyl acetate in aqueous methanol and ethyl acetate in aqueous ethanol, the products of the alcoholysis reactions are the initial reactants.

Only the reaction with hydroxide ion leads to consumption of alkali; the alcoholysis reaction must be followed by other means (e.g., by using ^{14}C as tracer as done by Bender and Glasson[47]).

If k'_h and k''_h are the apparent rate constants of the reactions of

two different esters with hydroxide ion in the *same* alcohol–water mixture, then (cf equation 12)

$$\frac{k'_h}{k''_h} = \frac{k^{0'}_h}{k^{0''}_h} \tag{27}$$

Hence, if no transesterification leading to a new ester occurs or if the transesterification is slow and can be neglected, the measured rates of disappearance of alkali give directly the true ratio $k^{0'}_h/k^{0''}_h$. When, for example, ethyl formate and ethyl acetate react in an alkaline aqueous ethanol, equation (27) gives directly the ratio of the true rate constants of the reactions with hydroxide ion in the solvent employed[43].

If the transesterification reaction gives an ester different from that initially present, the new compound will react with the hydroxide ion at a different rate. If the new compound is rapidly formed, the measured rate constant will vary with time as two esters are simultaneously present or the measured rate of hydrolysis may be that of the new ester.

Thus, when the rate constants of the reactions of different esters in an aqueous alcohol are compared, the absence of complications due to the transesterification reactions must be confirmed. This is not often done. However, one should bear in mind that the alcoholysis reaction is usually faster than the hydrolysis reaction (see section VI).

The most detailed study of the alkaline hydrolysis reactions of an ester (ethyl acetate) in alcohol–water mixtures is that of Tommila, Koivisto and co-workers[32]. These writers discussed also the influence of the hydroxide–alkoxide equilibria on the reactions and found maxima due to these equilibria in the plots of log A_h against solvent composition.

Solvent effects other than those caused by the lyate ion equilibrium are usually quite prominent in ester hydrolysis reactions and may completely mask the influence of the equilibrium[14, 32], i.e., k^0_h and rate constants derived from the disappearance of alkali may vary with solvent in a roughly similar way. The same is true for the Arrhenius parameters, at least for the reactions in aqueous mixtures of alcohols less acidic than methanol[14].

C. Eliminations and Other Reactions that Lead to Only One Product

In reactions where only one product is formed in the presence of hydroxide and alkoxide ions, the anionic bases usually attack a hydrogen atom and their relative reactivities might be expected to

parallel the thermodynamic basicities more closely than the nucleophilicities of the bases[59, 60]. As the products are the same, regardless of the base that effects the reaction, it is very difficult or impossible to devise an experimental method to measure the individual rate constants of the reactions with hydroxide and alkoxide ions[59]. Thus only overall rate constants are obtained, and if the reactivities of various substrates are to be compared, it is best to avoid using aqueous alcohols as solvents. Also, since the nucleophiles must have basic properties to be effective, it is not possible to study the influence of solvent on the reactions of non-basic reference anions[59] (cf section V.C).

Buckley, England and McLennan[59] studied the *E*2 elimination of hydrogen bromide from *β*-phenylethyl bromide and ethylene dibromide, and also the *E*1*cB*-like elimination reactions of chloroform and ethylene chlorohydrin in alkaline aqueous methanol and ethanol. According to Winstein and Lucas[61], the initial proton transfer is from oxygen rather than from carbon in the latter reactions and the reactions are intramolecular displacement reactions:

$$CH_2ClCH_2OH + B^- \rightleftharpoons CH_2ClCH_2O^- + BH \qquad (28)$$

$$CH_2ClCH_2O^- \longrightarrow \underset{\diagdown\,\diagup}{CH_2CH_2}\;\underset{O}{} + Cl^- \qquad (29)$$

where B^- is either a hydroxide or an alkoxide ion. These reactions have been extensively studied in aqueous alcohols also by Warner and co-workers[62–64]. The decomposition of diacetone alcohol by alkali is also of the *E*1*cB* type[65]. This reaction in aqueous alcohols has been studied by Åkerlöf[66].

The rate constants of *E*2 elimination reactions often increase when water is added to methanol and decrease when water is added to ethanol[59]. However, it has been found[67] that the reaction of DDT is slower in alkaline 95% methanol–water than in alkaline non-aqueous methanol.

Reactions that also lead to only one product are those of nitroparaffins with bases[68]. The reaction velocity is determined by the rate of transfer of a proton from the α-carbon atom of the nitroparaffin to the base to give the anion of the aci-form as the product:

$$RCH_2NO_2 + B^- \longrightarrow RCH{=}\overset{+}{N}\begin{matrix}O^-\\ O^-\end{matrix} + BH \qquad (30)$$

Jones and co-workers[68] estimated the variation of the hydroxide–methoxide equilibrium constant (K_{hm}) with solvent composition

from studies of neutralization of nitroethane and they presented the results in graphical form.

V. EVALUATION OF HYDROXIDE–ALKOXIDE EQUILIBRIUM CONSTANTS

Methods that have been employed by different workers to study the hydroxide–alkoxide equilibria are solubility measurements[69, 70], conductivity measurements[3, 70, 71], cryoscopic measurements[70], qualitative i.r.-spectroscopic measurements[72], thermodynamic distillations[73], e.m.f. measurements[74, 75], measurements with indicators[4, 76–78] and reaction kinetic measurements[10, 11, 14, 17–22, 25, 27, 28, 42, 45, 68]. Since these methods have been reviewed elsewhere by the present writer[14], only the most important features will be considered. The main emphasis will be on methanol–water and ethanol–water mixtures. It may be noted that it is always necessary to make certain assumptions concerning the constancy or variation with solvent composition of some properties in these determinations.

A. Electrochemical Methods

Koskikallio[75] measured the e.m.f. of the cell

$$H_2 \mid MOCH_3, MCl \mid AgCl, Ag,$$

where M = Li, Na or *K* (a cell without any liquid junction potentials) employing methanol–water mixtures as solvents. He derived the equation

$$K_{exp} = K_1'\left(1 + \frac{a_{MeOH}}{a_{H_2O}} K_{lun}\right) \tag{31}$$

where K_{exp} is the (measured) apparent ionic product in the methanol–water mixtures:

$$K_{exp} = ([H_3O^+] + [CH_3OH_2^+])([OH^-] + [MeO^-]) \tag{32}$$
$$\approx [H_3O^+]([OH^-] + [MeO^-])$$

and K_1' is the ionic product of water in these mixtures. As the variation of the values of K_1' with solvent composition is not known, Koskikallio assumed that at low methanol contents K_1' varies in the same way as the dissociation constant of acetic acid and obtained the value 7·7 for the equilibrium constant in aqueous methanol (at 25°). If, in addition, the dissociation constants of propionic, butyric and benzoic acids are employed, the constants plotted in Figure 3 are obtained[14] – mole fractions instead of activities were employed when

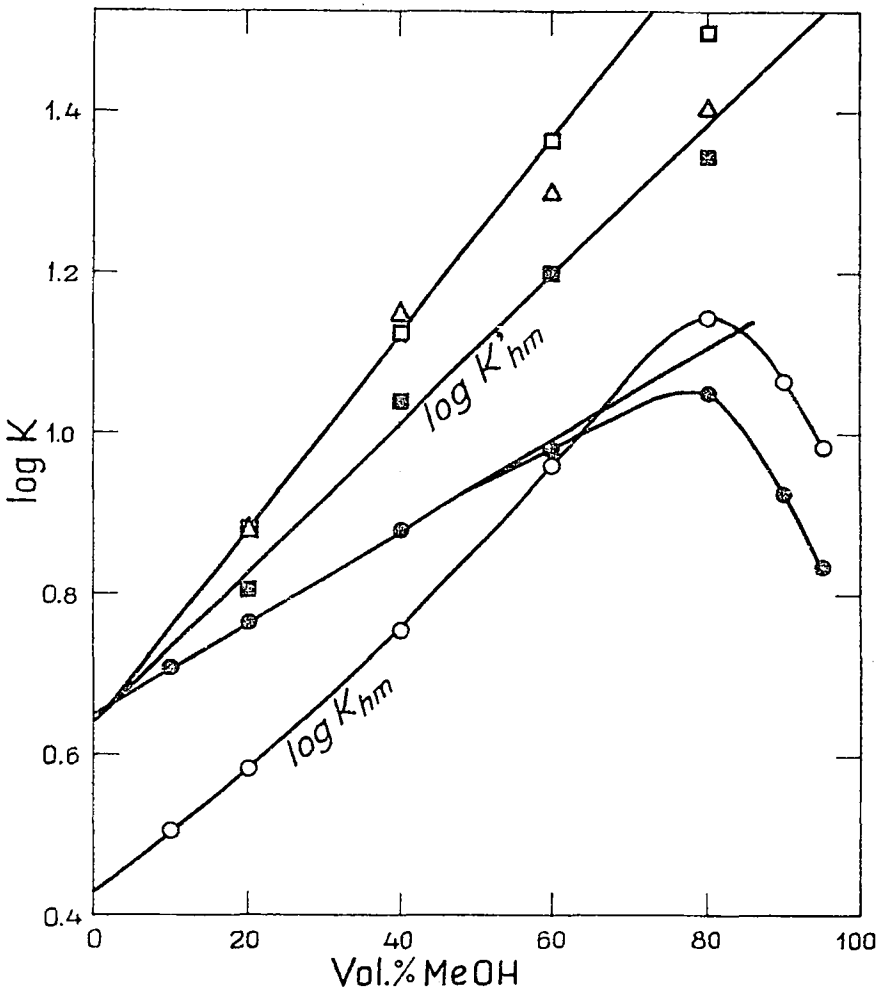

FIGURE 3. Values of log K'_{hm} and K_{hm} in methanol–water mixtures as computed by the method of Koskikallio[75]. The ionic product of water was assumed to vary as the dissociation constant of acetic acid (○ and ●), propionic acid (▣), butyric acid (△) and benzoic acid (□).

computing the values of K'_{hm} from equation (31). The plots of log K'_{hm} pass through a common point, where $K'_{hm} = 4{\cdot}5$ and $K_{hm} = 2{\cdot}7$, in pure water (at 25°).

Ballinger and Long[71] determined values of pK_a for several alcohols in water at 25° (see also Table 3) by a conductometric method. Since the equilibrium reaction (1) leads to the replacement of hydroxide ion with an equivalent conductivity of about 190 by an alkoxide ion with an equivalent conductivity around 30, the change

in conductivity is large[71]. This method works well with the acidic alcohols. However, in the case of methanol and ethanol, considerable amounts of the alcohol must be added to water before sufficient changes in conductivity occur, and the solvent is then no longer pure water. With methanol the necessary viscosity correction amounts to over 80% of the observed conductivity effect[71]. As a consequence, the ionization constants found for methanol and ethanol are much less accurate than those obtained for more acidic alcohols. The values obtained for methanol are $K_{hm} = 1{\cdot}04$, $K'_{hm} = 1{\cdot}6$, and those obtained for ethanol are $K_{he} = 0{\cdot}2$ and $K'_{he} = 0{\cdot}7$ at 25° [14, 71].

B. Indicator Methods

Hine and Hine[76] determined spectrophotometrically the acidities of various hydroxylic compounds in 2-propanol employing 4-nitrodiphenylamine as indicator. They reported values of the equilibrium constants $K_e = [RO^-]/[ROH][2\text{-}PrO^-]$ relating to the equilibria $ROH + 2\text{-}PrO^- \rightleftharpoons 2\text{-}PrOH + RO^-$. Values of K'_{ha} referring to 2-propanol as solvent at 27° that were computed from the values of K_e are given in Table 1.

TABLE 1. Values of K'_{ha} for some alcohols in 2-propanol at 27° [14, 76].

Alcohol	K'_{ha}
2-Propanol	0·063
1-Propanol	ca 0·4
2-Methyl-1-propanol	ca 0·4
1-Butanol	ca 0·5
Ethanol	0·79
Water	1·00
Allyl alcohol	2·3
Benzyl alcohol	3·2
Methanol	3·3
1,2-Ethanediol	36
1,2,3-Propanetriol	146

Caldin and Long[4] studied spectrophotometrically the hydroxide–ethoxide equilibrium in water–ethanol mixtures containing from 12·6 to 47·0 wt% water. They employed trinitrotoluene as an indicator. If BH denotes the indicator, the following equilibria also prevail in these mixtures:

$$BH + EtO^- \rightleftharpoons B^- + EtOH \quad (33)$$

$$BH + OH^- \rightleftharpoons B^- + H_2O \quad (34)$$

The ratio of the corresponding equilibrium constants is equal to the equilibrium constant of the hydroxide–ethoxide reaction. It was assumed that the equilibrium constant of reaction (33) has the same value in aqueous ethanol as in pure ethanol.

Values of K_{he} reported by Caldin and Long for the hydroxide–ethoxide equilibrium in ethanol–water and values of K'_{he} computed by the present author[14] from these are given in Table 2. It is seen

TABLE 2. Values of K_{he} and K'_{he} for aqueous ethanol at 25° based on data of Caldin and Long[4, 14].

Wt% water	K_{he}	K'_{he}
0·0	(2·0)	—
12·6	1·0	0·54
24·2	0·91	0·70
28·8	0·71	0·63
38·8	0·37	0·44
47·0	0·32	0·47
100·0	(0·2)	—
	Mean	0·56

that K_{he} varies systematically (the plot of K_{he} against the reciprocal of the dielectric constant is almost linear[4]), but K'_{he} varies little and irregularly about an average value of 0·56. This constancy may be purely fortuitous, although it may also be noted that some kinetic data yield values of better constancy for B'_{ha} (equation 23) or K'_{ha} than for the corresponding quantities that relate to solvent activities instead of concentrations.

C. Reaction Kinetic Method

It is easy to show that[14]

$$K'_{ha} = \frac{[H_2O](k_h^0 - k_h)}{[ROH]k_h} \tag{35}$$

and that

$$K'_{ha} = \frac{[H_2O]k_a}{[ROH](k_a^0 - k_a)} \tag{36}$$

If either k_h^0 or k_a^0 in an alcohol–water mixture is known, K'_{ha} can be calculated from one of these equations. Usually neither value is

known and the value of the constant in pure water or alcohol must be used instead, or the variation of k_h^0 or of k_a^0 with solvent composition must be estimated in some way. For the determination of K'_{ha}, it is best to use reactions for which k_h^0 and k_a^0 vary as little as possible with solvent; S_N2 and S_NAr substitutions are useful reactions. Ester hydrolyses and ionic reactions have also been used, but the true rate constants of these reactions usually vary greatly with solvent composition and this fact may partly explain why widely differing results have been obtained by the kinetic method.

The following values of K'_{hm} have been derived[14] from data for S_N2 or S_NAr reactions with hydroxide ion in aqueous methanol at 25° on the assumption that k_h^0 is constant: $K'_{hm} = 2{\cdot}5$ (from the reaction of methyl iodide) and 4·1 (from the reaction of 2,4-dinitroanisole). The following values were derived for K'_{he} in aqueous ethanol at 25° from the reactions with ethoxide ion[14, 18]: 0·79 (methyl iodide), 0·69 (1,2-dinitrobenzene), 0·91 (1,4-dinitrobenzene), 0·9 (1-chloro- and 1-bromo-2,4-dinitrobenzene) and 0·58 (1-fluoro-2,4-dinitrobenzene). No visible colour formation occurred due to the Meisenheimer reaction (in the reactions of the aromatic compounds)[cf 21]. Some workers[10, 68] have reported their results in graphical form.

The next step to refine the kinetic method is to estimate the variation of the true rate constants with solvent composition. One way to do this is to use suitable reference reactions[10, 11, 17, 70]. It is assumed that k_a^0 varies with solvent in the same manner as the rate constants of related reactions with a nucleophile which is not involved in a lyate ion equilibrium. It is seen in Figure 4 that the slopes of curves 1–3 are initially similar at low water contents; the nucleophiles in these reactions are practically completely in the form of naphthoxide or thiophenoxide ions. On the other hand, curves 4–8 have nearly equal negative slopes. If it is assumed that the values of k_e^0 for the latter reactions vary similarly as those for the reactions with naphthoxide and thiophenoxide ions (curve 9 in Figure 4), the value 0·66 is obtained for K'_{he} at 25° [17].

The kinetic method would be expected to give the most accurate results when K'_{ha} has a very low or a very high value. As an example of the former type, we may mention the hydroxide–2-propoxide equilibrium. The value of k_a (or k) usually falls much more rapidly on adding water to 2-propanol than on adding water to ethanol, and thus the variation of k_a^0 with solvent composition influences the value of K'_{ha} less in the former case. Data for reactions of

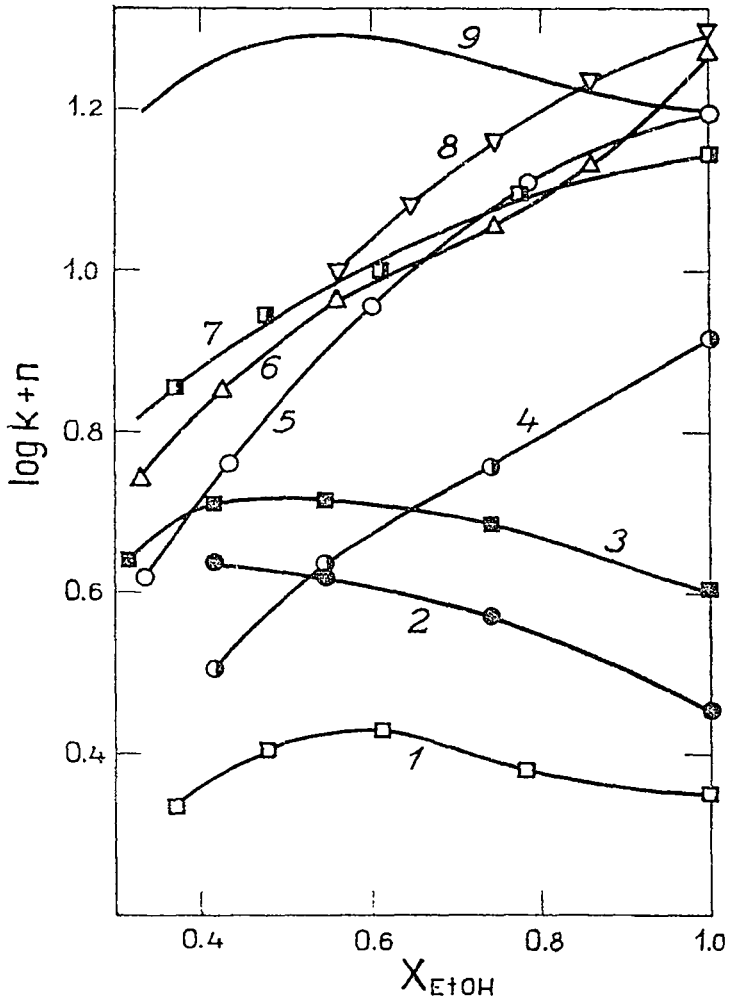

FIGURE 4. Apparent rate constants (k_a or k) in ethanol–water mixtures[17]. X denotes the mole fraction.

1. EtI + β-naphthoxide ion at 50°, $n = 2{\cdot}8$ [79].
2. 2,4-Dinitrochlorobenzene + $C_6H_5S^-$ at 0°, $n = -1$ [10].
3. MeI + $C_6H_5S^-$ at 0°, $n = 1$ [10].
4. 2,4-Dinitrochlorobenzene + (EtO^- + OH^-) at 25°, $n = 2$ [10].
5. MeI + EtO^- at 25°, $n = 4$ [14].
6. 1,2-Dinitrobenzene + EtO^- at 25°, $n = 5$ [15].
7. EtI + (EtO^- + OH^-) at 25°, $n = 4$ [2].
8. 1,4-Dinitrobenzene + EtO^- at 25°, $n = 4$ [15].
9. Plot of log k_e^0 for reaction 5 (see text).

1-fluoro-2,4-dinitrobenzene in aqueous 2-propanol lead to the value 0·043 for K'_{ha} at 25° [18], at a mole fraction of 2-propanol of 0·5.

On the other hand, addition of small amounts of acidic alcohols

TABLE 3. Values of pK_a and K'_{ha} (equation 4) for some alcohols and phenols at 25°.

ROH	pK_a	K'_{ha}	ΔH_{ha}	Ref.
2-Methyl-2-propanol	$\geqslant$19	$\leqslant 5\cdot10^{-4}$	—	19, 83
2-Butanol	17·6	0·01	—	19
2-Propanol	17·1	0·043	−3·3	19, 83
2-Methyl-1-propanol	16·1	0·4	—	19
1-Propanol	16·1	0·4	—	19
1-Butanol	16·1	0·4	—	19
Ethanol	15·93	0·65	−3·5	14
Water	15·74	(1)	(0)	
Allyl alcohol	15·52	1·7	—	71
Benzyl alcohol	15·4	2	—	19
Methanol	15·09	4·5	−3·5	14
2-Phenoxyethanol	15·1	4	—	19
1,3-Propanediol	15·1	4	—	19
1,4-Butanediol	15·1	4	—	19
1,2-Ethanediol	15·1 (14·8[a])	4(9[a])	—	71
1,2-Propanediol	14·9	7	—	19
2-Methoxyethanol	14·8	9	—	71
1,2,3-Propanetriol	14·40	22	—	71
2-Chloroethanol	14·31	27	—	71
Pentaerythritol	14·10	44	—	71
2-Propyn-1-ol	13·55	155	—	71
D-Mannitol	13·29	282	—	84, 19
2,2,3,3-Tetrafluoro-1-propanol	12·74	1000	—	71
2,2,2-Trifluoroethanol	12·39	2200	−5·49	71
2,2,2-Trichloroethanol	12·25	3120	—	71
1-Phenyl-2,2,2-trifluoro-ethanol	11·90[b]	6900	—	85
Phenol	9·97	594,000	−8·35	86
1,1,1,3,3,3-Hexafluoro-2-propanol	9·3	$2\cdot8\cdot10^{6}$	—	87, 88
4-Nitrophenol	7·15	$3\cdot9\cdot10^{8}$	—	89
Perfluoro-2-methyl-2-propanol	5·4	$2\cdot2\cdot10^{10}$	—	88
2,4-Dinitrophenol	4·02	$5\cdot2\cdot10^{11}$	—	90
Picric acid	0·33	$2\cdot6\cdot10^{15}$	—	91

[a] As computed from the dissociation constant given in Reference 71.

[b] See Reference 85 for the acidities of other trifluoromethyl carbinols and the corresponding ketone hydrates.

such as 2,2,2-trifluoroethanol to water, results in a rapid decrease in hydroxide ion concentration and consequently the apparent rate constant k_h of the hydroxide reaction decreases. Thus accurate values of the equilibrium constants are obtained (Table 3). However, in these cases the constants can be evaluated more easily by other methods such as conductometry.

If K'_{ha} is measured at several temperatures, an estimate is obtained for the heat of the equilibrium reaction (1), ΔH_{ha}. The estimates of ΔH_{ha} for aqueous methanol and ethanol obtained from data for several reactions are all close to −3·5 kcal/mole [14]. Values of this magnitude have been derived for proton transfer reactions of similar type from n.m.r. data[1]. The value of ΔH_{ha} decreases (its absolute value increases) with decreasing pK_a of the alcohol (see Table 3).

It has been found[22] that pressures up to 2500 atm influence the hydroxide–methoxide equilibrium only slightly.

D. Values of Hydroxide–Alkoxide Equilibrium Constants for Various Alcohols and Phenols

Values of pK_a and K'_{ha} for several alcohols and phenols are given in Table 3. To facilitate the use of these data in studies of reactivity correlations, compounds of very low and very marked acidity have been included. The values reported for methanol and ethanol are the 'best values' chosen on the basis of the discussion in the preceding sections.

The values of K'_{ha} for the acidic compounds were obtained from the pK_a values using the relationship $\log K'_{ha} = 15{\cdot}74 - pK_a$ and are thus to be considered relatively accurate. They refer to water as solvent. The values of K'_{ha} for the less acidic alcohols are more or less accurate estimates by the aid of which kinetic data for various reactions in aqueous alcohols can be explained and also optimum conditions sought for syntheses. It is the opinion of the writer that it is at present unnecessary to introduce activities of water and alcohols and to use the solvent-dependent values of K_{ha} instead of the values of K'_{ha}, as the latter vary only slightly with solvent composition. One numerical value of K'_{ha} serves to define the hydroxide–alkoxide equilibria in mixtures of an alcohol with water (at constant temperature) with as high an accuracy as is attainable at present.

The value of K'_{ha} for 2-methyl-2-propanol (*t*-butyl alcohol) is very low. Thus, even small amounts of water in this alcohol effect hydrolysis of the alkoxide. Reactions with 2-methyl-2-propoxide must therefore be carried out under strictly anhydrous conditions.

If $K'_{ha} = 1$, the alcohol in question is as strong an acid as water, and the respective base fraction of the alkoxide, s_a (and also k_a on the assumption of constancy of k_a^0), decreases linearly with increasing mole fraction of water. This seems to be approximately the case in aqueous ethanol; in aqueous methanol the equilibrium favours the methoxide ion to some extent. However, many substrates seem to react only with an alkoxide ion because this is usually more reactive than the hydroxide ion (see section VI). Examples are the reactions of 1-fluoro-2,4-dinitrobenzene in alcohol–water mixtures. The reaction of this compound in water that contains only 0·5% methanol leads to an equimolar ratio of 2,4-dinitroanisole and 2,4-dinitrophenol at 0° [22]. Considerable amounts of water in alcohols can thus be tolerated in syntheses of many alkoxy-substituted compounds (provided that the reaction mixture is not heated too much so that the alkoxyl group is replaced by a hydroxyl group).

Sodium or potassium methoxide and ethoxide have sometimes been used to dry the respective alcohols, but, in view of the position of equilibrium reaction (1) in these alcohols, this is a very inefficient method[4]. The efficacy of magnesium alkoxides for this purpose is due to the insolubility of magnesium hydroxide in alcohols. Thus hydroxide ions formed by equilibrium reaction (1) are removed from solution, and as the equilibrium is disturbed, more water reacts with alkoxide and water is progressively removed[4]. The equilibrium can be disturbed also by adding an ester to the solution as only the hydroxide reaction consumes alkali[46].

The hydroxide–phenoxide equilibrium lies almost entirely on the side of the phenoxide ion. If an alcohol–water mixture contains alkali and phenol, the alkoxide–phenoxide equilibrium must also be taken into consideration. At least in the case of the less acidic alcohols these equilibria lie very far on the side of the phenoxide ion. However, the alkoxide ion may react so much faster than the phenoxide ion with some substrates that the alkoxide reaction must also be taken into consideration[80].

In solutions of alkali in mixtures of water and highly halogenated alcohols, the equilibrium favours the halogenoalkoxide ion to a marked degree. In the case of the chlorinated aliphatic alcohols, the hydrolysis of the alkoxide ions must also be considered (e.g., the reaction of 2-chloroethanol with alkali gives ethylene oxide). The fluoroalkoxides hydrolyse much more slowly and their solutions may usually be considered stable[63]. Since trifluoroethanol is relatively acidic, solutions of phenoxides in trifluoroethanol contain appreciable

amounts of trifluoroethoxide ion[81]:

$$PhO^- + CF_3CH_2OH \rightleftharpoons PhOH + CF_3CH_2O^- \quad (37)$$

It may be noted in this connection that the presence of amines or other basic compounds in an aqueous alcohol may lead to considerable amounts of hydroxide and alkoxide ions in equilibrium with each other, and this can result in undesirable side reactions[13, 82].

In alkaline mixtures of two alcohols, two alkoxide ions are in equilibrium. Rough estimates of the equilibrium constants can be derived from the data in Table 3. As estimated from the rate constants for the alkaline transetherification reactions of 2,4-dinitrophenyl alkyl ethers in binary mixtures of alcohols at 25°, the equilibrium constant for the methoxide–ethoxide equilibrium

$$MeO^- + EtOH \rightleftharpoons MeOH + EtO^- \quad (38)$$

is about 0·23, that for the methoxide–1-propoxide equilibrium about 0·20, and for the ethoxide–1-propoxide equilibrium 1·0, in mixtures of the respective alcohols[14]. These constants do not vary with temperature, and hence the heats ΔH of the alkoxide conversion reactions are practically zero[14].

Table 4 gives values of K'_{hm} and K'_{he} at several temperatures. As

TABLE 4. Values of K'_{hm} (MeOH–H_2O) and K'_{he} (EtOH–H_2O) at different temperatures[14]. The values were computed assuming $\Delta H_{hm} = \Delta H_{he} = -3{\cdot}5$ kcal/mole.

Temp °C	0°	15°	25°	40°	50°	75°	100°
K'_{hm}	7·7	5·5	4·5	3·4	2·8	1·9	1·4
K'_{he}	1·1	0·80	0·65	0·49	0·41	0·28	0·20

the values of ΔH_{ha} are negative, all hydroxide–alkoxide equilibria shift in favour of the hydroxide ion with rising temperature.

VI. RELATIVE REACTIVITIES OF HYDROXIDE AND ALKOXIDE IONS

A problem closely connected with the positions of the hydroxide–alkoxide equilibria is the question of the relative reactivities of the ions. Once the value of K'_{ha} in a solvent mixture is known, the individual true rate constants can be evaluated as discussed above and the reactivities of the two ions compared (at least in substitution reactions), and vice versa, given the relative reactivities, the value of

K'_{ha} is easily found. If we wish to compare the reactivities of several lyate ions derived from hydroxylic solvents, the problem is complicated by the fact that the individual (true) rate constants must relate to a common solvent before comparisons are meaningful. Before the reactivities of more than two lyate ions can be compared, the rate constant values must usually be extrapolated to a common solvent.

The estimated reactivities of methoxide, ethoxide and phenoxide ions with various compounds are compared with the reactivities of hydroxide ion in Table 5. The reactivity ratios given here are those

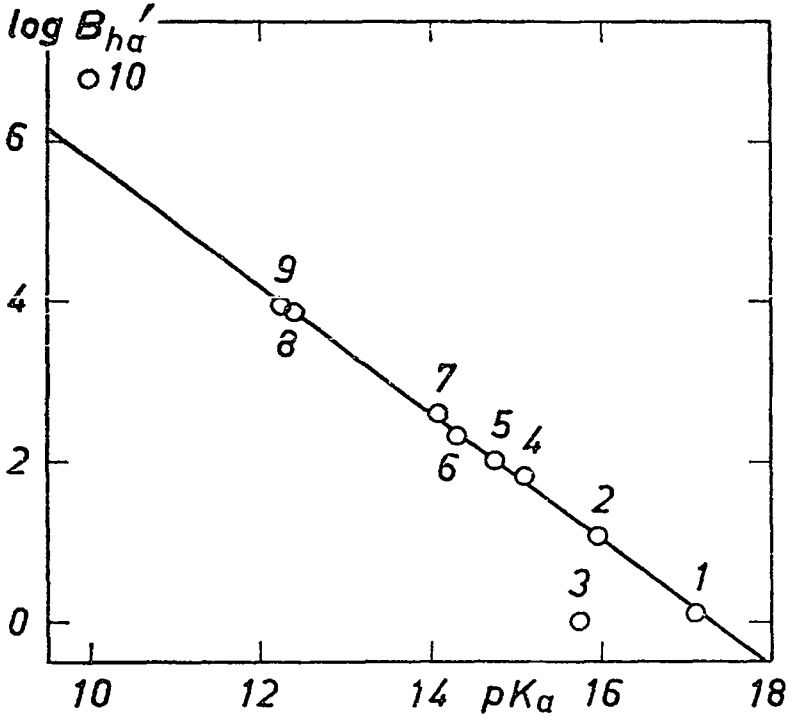

FIGURE 5. Plot of log B'_{ha} against the pK_a of the alcohol at 25°, taken from ref. 20. The numbers refer to the following compounds: 1, 2-propanol; 2, ethanol; 3, water; 4, methanol; 5, 1,2-ethanediol; 6, 2-chloroethanol; 7, pentaerythritol; 8, 2,2,2-trifluoroethanol; 9, 2,2,2-trichloroethanol; 10, phenol.

reported in the original papers, and it is to be noted that somewhat different values of K'_{ha} have been used by different authors in the calculation of the ratios.

It will be seen that the reactivities of hydroxide ion with many substrates are surprisingly low when compared with those of the

TABLE 5. Comparison of estimated reactivities of methoxide, ethoxide, phenoxide and hydroxide ions. The original papers should be consulted for the values of the hydroxide–alkoxide equilibrium constants employed in the calculations.

Substrate	$\frac{k_m^0}{k_h^0}$	$\frac{k_o^0}{k_h^0}$	$\frac{k_{ph}^0}{k_h^0}$	T, °C	Solvent	Ref.
Methyl iodide	3·0	3·7	—	35·2	Dioxan	12
Methyl iodide	0·22	0·15	—	25	Dimethyl sulphoxide	92
2,4-Dinitrochloro-benzene	33	—	11	25·2	60% Aq. dioxan	96
2,4-Dinitrochloro-benzene	20	—	—	25	Aq. MeOH	12
2,4-Dinitrofluorobenzene	46	63	4	25	Water	19
1,2-Dinitrobenzene	38	—	—	25	Aq. MeOH[a]	14
1,2-Dinitrobenzene	—	40	—	25	Aq. EtOH[a]	14
1,4-Dinitrobenzene	185	—	—	25	Aq. MeOH[a]	14
1,4-Dinitrobenzene	—	200	—	25	Aq. EtOH[a]	14
Picryl fluoride[b]	15	18	10	25	Water	20
Picryl chloride[b]	⩾1	—	—	20	Aq. MeOH[c]	25
2-Fluoro-5-nitropyridine	49	65	—	25	Water	24
2-Fluoro-3-nitropyridine	22	28	—	25	Water	24
Methyl iodide	5	—	—	25	Aq. MeOH[d]	14
Methyl iodide	—	12	—	25	Aq. EtOH[e]	14
Sodium bromoacetate	1	—	—	52·4	MeOH	14
1-Bromobutane	11	13	—	25–27	Mixtures[f]	26
Benzyl bromide	12	14	—	25–27	Mixtures[f]	26
Ethylene oxide	8	17	—	0–2	Mixtures[f]	26
Phenyl acetate	—	—	0·020	25	Water	47
Acetyl-L-phenylalanine esters	1·6	4·2	—	25	Water	47
4-Nitrophenyl acetate	450	170	—	25	Aq. alcohols[g]	34
4-Nitrophenyl acetate	—	—	0·019	30	28·5% Aq.EtOH	95,47
Acetic anhydride	7	16	1·1	25	Water	35
Dimethylmaleic anhydride	23	—	—	25	Water	35
Nitroethane (neutralization)	—	>100	—	25	Water	68

[a] Mole fraction of the alcohol 0·5.
[b] Alkaline alcoholysis of these compounds leads to coloured Meisenheimer compounds; no visible colour formation occurs with the hydroxide ion at the low concentrations employed[21].
[c] From 1·5 to 15·6 wt% methanol in the solvent.
[d] From 5·9 to 60·2 wt% methanol in the solvent.
[e] From 5·9 to 79·4 wt% ethanol in the solvent.
[f] About equimolar mixtures of the solvent components.
[g] At low alcohol contents.

methoxide and ethoxide ions[96]. With some substrates the last two ions may react several hundred times faster than hydroxide ion[14].

The situation is more favourable to the hydroxide ion in dipolar aprotic solvents such as dimethyl sulphoxide. The inherently very marked reactivity of the hydroxide ion is greatly suppressed due to solvation in alcohols and other protic solvents[92, 93].

The low nucleophilic reactivity of the hydroxide ion explains some puzzling phenomena, including the Schotten–Baumann reactions, where an acid chloride reacts preferentially with the amine or alcohol being acylated and not with the aqueous alkali present in large excess[96, 97].

When the two concurrent reactions lead to different products, the reactivities of hydroxide and alkoxide ions are most easily compared, as shown in section IV.A.3, by determining product ratios and values of B'_{ha}. In that section it was also mentioned that the slope of the plot of log B'_{ha} against the pK_a of the alcohol is related to that of the linear Brønsted plot ($\log k_a^0 = \alpha pK_a + \beta$). Such a plot for reactions of picryl fluoride is shown in Figure 5 (page 1110).

The abnormally low reactivity of the hydroxide ion is seen also on inspection of Figure 5. Also the point for phenol does not lie on the line; phenols often yield a plot different from that found for alkoxides[21, 80].

The reactivities of several alkoxides and phenoxides in reactions with aromatic nitro compounds in a common solvent have been studied by the above method[19, 21]. A comparison of the reactivities of alkoxides and phenoxides with their leaving abilities is now possible[21, 94].

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