The Chemistry of the Carbonyl Group
Edited by Saul Patai

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The editor dedicates this volume, with humble thanks, to

Mr. Donald Ross

who uses the resources of surgery and science and above these his understanding and humanity in order to aid, to restore, and to heal

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Foreword

This book is the second in a series of treatises dealing with the chemistry of functional groups. As in the first volume (*The Chemistry of Alkenes*, 1964), this present volume again attempts to encompass all facets of a functional group and to give up-to-date descriptions of the nature of the carbonyl group, of the main pathways leading to its formation, and of its main modes of reaction. Special topics, such as the biochemistry and the photochemistry of the carbonyl group and the chemistry of thiocarbonyl compounds, are treated in separate chapters.

The authors of the chapters were asked to concentrate their efforts on a critical discussion of their subjects, emphasizing recent advances and new developments, and addressing themselves mainly to post-graduate students and research workers. Material appearing in modern textbooks or reviewed satisfactorily in easily available sources was to be covered briefly and only then if it was considered to be necessary for the balance of the presentation. Nevertheless, each author was asked to treat his subject monographically and a certain amount of overlap between the chapters was accepted in order to preserve their structural unity and to spare the reader from too frequent recourse to different chapters of the book.

Two of the chapters promised for the book failed to materialize on time ('Equilibrium additions to carbonyl groups' and 'Syntheses and uses of isotopically labelled carbonyl compounds'). The policy previously established for the series was followed again and the volume is presented on schedule, the editor and publisher preferring relative incompleteness to obsolescence.

For the guidance and trust of Dr. Arnold Weissberger, my mentor and friend, I continue to stand indebted. Most of my editorial work on this volume was carried out in a period of hardship and calamity: the shared strength and understanding of my wife made completion of my task possible. I also wish to thank the staff of the publisher's editorial office in London for their exceptional patience, helpfulness, and efficiency.

Jerusalem, November 1965 SAUL PATAI

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The Chemistry of the Carbonyl Group
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CHAPTER 1

General and theoretical aspects of the carbonyl group

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I. INTRODUCTION

In this chapter we shall deal with the physicochemical properties and the theoretical treatment of carbonyl compounds. In the carbonyl group, a very characteristic functional group of organic chemistry, the bonds between the carbon and the oxygen atoms are made up of σ and π types. The oxygen atom bears two lone-pair electrons; one lone-pair orbital is mainly of type $2s$, but the other lone-pair orbital is of type $2p$ and its axis is directed perpendicularly to the direction of the π orbitals. The main physicochemical properties of carbonyl compounds are controlled by this electronic structure and also by the geometrical position of the carbonyl bond. In an aldehyde the functional group is necessarily located at a terminal position in the molecule; in a ketone the group may be located in another part of the molecule but the oxygen atom is still bound only to one carbon. We will see in section II that the physicochemical properties of carbonyl compounds are very homogeneous in the case of aldehydes, and also in the case of those ketones where the carbonyl group is not connected with another functional group. As the $2p$ lone pair has its orbital directed in a direction perpendicular to that of the π bond, the lone-pair electrons cannot be conjugated with the π system, and the properties of this lone pair are relatively constant. The properties connected with the π electrons of the carbonyl bond are also fairly constant, this bond being usually very slightly delocalized. With pyridine or analogous compounds, there are two unsaturated atoms in the vicinity of the nitrogen atom and the heteroatom lone pair has a certain amount of s character which may vary from one compound to another. Hence, the explanation of the physicochemical properties is much less simple in these cases.

In section III the different possible theoretical treatments of carbonyl compounds are given for the ground state and for some excited states; the theoretical treatment of some radicals derived from carbonyl compounds is also outlined. In order not to repeat the definitions of the essential concepts of quantum chemistry, section III is based on the chapter written by Coulson and Stewart in the first volume of this series*. The notation of these authors is kept as far as possible, and many references are given in section III to equations used by them (referred to, in parentheses, as C.S. followed by the section number). However, the complete theoretical treatment of the

* C. A. Coulson and E. T. Stewart in *The Chemistry of Alkenes* (Ed. S. Patai), Interscience Publishers, London, 1964, pp. 1–147.

carbon–carbon double bond is not necessary for the understanding of the present chapter on carbonyl compounds.

II. PHYSICOCHEMICAL PICTURE OF THE CARBONYL GROUP

A. Physical Properties and Polarity

1. Length of the C=O bond

The length of the C=O bond in aldehydes, ketones, acids, and esters is about 1·20 Å according to the most recent determinations, particularly those by electron diffraction and by microwave spectroscopy. Inorganic molecules containing the carbonyl group, such as carbon monoxide, carbon dioxide, or the carbonate ion, have bond lengths clearly different from 1·20 Å (see Table 1). Walsh[1] proposed to correlate the length of the carbonyl bond with its polarity: the length of a bond increases as its polarity decreases. This would explain the fact that the carbon–oxygen distance is larger in acetaldehyde than in formaldehyde by taking into account the direction of the inductive effect of the CH_3 group. For the same reason, the length of the carbonyl bond in acetyl fluoride is less than 1·20 Å (1·181 Å) and smaller than in acetyl chloride (1·192 Å). The C=O distance (1·166 Å) in phosgene shows that the polarity of the carbonyl bond in this molecule is much smaller than in formaldehyde.

It is well known and has been borne out by the theoretical work of Mulligan[2] and of Peters[3] that the polarity of the carbonyl bond in carbon dioxide is small. The experimental determination of the dipole moment of carbon monoxide has given a very small value (μ = 0·1 D) with the polarity $C^- — O^+$ [4]. In fact the direction of this polarity has recently been discussed critically[5]. The very small value of the dipole moment, i.e. the very small polarity, is in agreement with the very small value of the bond length (1·128 Å).

The conjugation of the carbonyl bond with a double or a triple carbon–carbon bond or with the C≡N bond has only a small influence on the C=O distance; thus the length of the carbonyl bond is the same in propynal as in acetaldehyde (1·215 Å). A value of the same order of magnitude (1·222 Å) is given by a recent x-ray structure determination of *p*-benzoquinone[6]. The same situation exists for conjugated double and triple carbon–carbon bonds[7], the constancy of the C=C and the C≡C bond length at about 1·335 Å and 1·206 Å, respectively, being well established[8].

It is clear that the hybridization is not simple sp^2 when the bond directions of the carbon linked to the oxygen are considered. For example, in the planar ground state of the HCHO molecule, the $\widehat{HCH}$ angle is 116°31′[9] and in acetaldehyde the $\widehat{CCO}$ angle is 123°55′[10] instead of 120° for a simple sp^2 hybridization. We will see (section III.E) that this fact does not affect the results of *ab initio* calculations such as those made on formaldehyde by Goodfriend and coworkers[11], since these calculations do not rely on hybridization.

The data on the bond lengths used in this discussion are collected in Table 1.

TABLE 1. C=O bond lengths.

Compound	Length (Å)	Method[a]	Ref.
CO	1·1282	spect.	1
	1·1308	m.w.	2
CO_2	1·1632	spect.	3
C_3O_2	1·16	e.d.	4
COS	1·1637	m.w.	5
$COCl_2$	1·166	m.w.	6
COF_2	1·174	m.w.	7
CH_3COF	1·181	m.w.	8
CH_3COCl	1·192	m.w.	9
$HCOOCH_3$	1·200	m.w.	10
HCOOH	1·202	m.w.	11
HCHO	1·2078	m.w.	12
CH_3CHO	1·216	m.w.	13
	1·208	e.d.	14
$CH{\equiv}CCHO$	1·215	m.w.	15, 16
CH_3COCH_3	1·22	e.d.	17
$CH_2{=}CHCHO$	1·22	m.w.	18
CHOCHO	1·20	spect.	19
p-Benzoquinone	1·222	x.r.	20
CH_3COCN	1·226	m.w.	21
CO_3^{2-}	1·264 1·346	x.r.	22
$HCOOCH_3$ (CO)	1·334	m.w.	10
CH_3OH	1·427	m.w.	23, 24

[a] Abbreviations are as follows:

spect. = spectroscopy
m.w. = microwave spectroscopy
e.d. = electron diffraction
x.r. = x-ray structure determination

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2. Bond energies

Glockler[12] determined carbon–oxygen bond energies for the most important molecules containing this bond. From the values shown in Table 2, it can be seen that strong carbon–oxygen bonds have

TABLE 2. Carbonyl bond energies.

Compound		Bond energy (kcal/mole)
CO		257·3
CO_2		192·1
$CH_2{=}C{=}O$		184·8
HCHO	C=O	160·0
	O···H	5·0
CH_3COCH_3	C=O	160·0
	O···H	3·1
HCOOH	C=O	160·0
	C—O	106·0
$HCOOCH_3$	C=O	160·0
	C—O	106·0
CH_3OH	C—O	81·2

relatively short lengths. The bond in carbon monoxide has the highest carbon–oxygen bond energy (257·3 kcal), which strongly supports the interpretation of a carbon monoxide electronic structure with a triple bond between carbon and oxygen.

The behavior of formaldehyde was found unusual, and Glockler assumed this to be due to the presence of an intramolecular hydrogen bonding. The hydrogen-bonding energy was estimated as 5·0 kcal/mole. The same situation is found in other aldehydes and in carboxylic acids; the existence of an intramolecular hydrogen bonding of about the same energy is thought to exist between protons and the oxygen atom of the carbonyl group in the aldehyde and carboxyl groups[12].

3. Dipole moments

Dipole moments are usually determined by studying the dielectric constant of solutions and by measurement of the Stark effect on microwave transitions[13]. The dipole moment, as obtained experimentally, is a number that does not specify direction. One of the very rare determinations of direction has been recently discussed critically[4,5]. With suitable assumptions, the total dipole moment of a molecule can be dissected into component bond moments which are assumed to be relatively constant properties of the σ bonds of the molecules. This procedure is only of empirical utility; it ignores the lone-pair electrons and the polarization induced by neighboring dipoles. This last effect can change the ionic character of a bond and sometimes even the geometry of the molecule.

For compounds containing π-bond networks it has been convenient to separate the total dipole moment into a σ moment and a π moment. We will see later (section III.E) that such a procedure is not theoretically justifiable.

The dipole moments of some carbonyl compounds are collected in Table 3. The very small bond polarity of carbon monoxide and of carbon oxysulfide is in agreement with remarks by Walsh[1]. The influence of the inductive effect of the methyl group is very clear if we compare the dipole moment of acetone (2·9 D) with those of acetaldehyde (2·68 D) and of formaldehyde (2·339 D); adjacent methyl groups increase the polarity of the carbonyl bond. On the contrary, chlorine atoms decrease the polarity as seen from comparison of the dipole moment of phosgene (1·19 D) with that of formaldehyde (2·339 D). This is also very clear in the cases of acetyl

TABLE 3. Dipole moments of some carbonyl compounds.

Compound		Dipole moment (D)	Method[a]	Ref.
CO		0·112	m.w.	1
		0·13	comp.	2
COS		0·7124	m.w.	3
$COCl_2$		1·109	d.	4
HCOF		2·02	m.w.	5
HCHO		2·339	m.w.	6
HCOOH		1·415	m.w.	5, 6, 20
CH_3OH		1·69	m.w.	7
ClCOCOCl		0·92	d.	8
$H_2C{=}C{=}O$		1·387	m.w.	9
$(COOH)_2$		2·63	d.	10
CH_3CHO		2·68	m.	11
CH_3COBr		2·45	d.	12
CH_3COCl		2·47	d.	12
CH_2ClCHO		1·99	d.	13
CH_3COCH_3		2·90	m.w.	14
$H_2C{=}CHCHO$	*s-cis*	2·6	m.w.	15
	s-trans	3·11	m.w.	15
$HC{\equiv}CCHO$		2·46	m.w.	16
C_6H_5CHO		2·724	r.t.	17
$C_6H_5COCH_3$		2·97	d.	18
Cyclohexanone		3·08	comp.	2
$CH_3(CH_2)_5CHO$		2·58	d.	19

[a] Abbreviations are as follows:
m.w. = Stark effect on microwave spectra
comp. = computation from the experimental values obtained by different methods
d. = dielectric-constant method
r.t. = relaxation-time method

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chloride and of chloroacetaldehyde, where the inductive effect of the methyl group is completely cancelled.

The conjugation of the carbonyl bond with a double or a triple carbon–carbon bond has only a very small influence on the C=O moment as in the case of bond lengths: for example, propynal has a dipole moment of 2·46 D.

One might expect that to a first approximation the moment of an aromatic compound and that of the corresponding aliphatic compound would be nearly the same; but because of the greater polarizability of the phenyl group in the near neighborhood of a dipolar group, the moment of an aromatic compound should be slightly larger. In fact this is roughly true in the case of a *meta*-directing group (such as —CHO or —COR) but not in the case of an *ortho–para*-directing group. In any case it seems that the influence of the mesomeric effect is very small; it must be responsible for the very small difference between the dipole moment of benzaldehyde (2·72 D) and that of the corresponding aliphatic aldehyde, n-heptaldehyde (2·61 D).

4. Ionization potentials

Ionization potentials can be determined either by extrapolation of the Rydberg series in the vacuum ultraviolet spectra of the

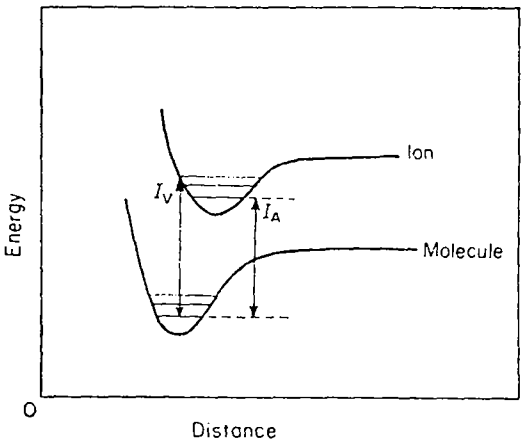

FIGURE 1. Vertical and adiabatic ionization potentials.

molecules, or from the appearance potentials of the ions in a mass spectrometer (electron-impact method), or by studying the photoionization efficiency curves[14]. The first of these methods yields the

energy difference between the ground states of the ion and of the molecule, both of these states being at the zeroth vibrational level; this spectroscopic value is an adiabatic ionization potential. In the second method the transition is considered to be so fast that the nuclei do not effectively change their positions during the transition. The ion is at a vibrational level frequently above that of the zeroth level; thus the electron-impact method is supposed to yield the vertical ionization potential. The relation between these two ionization potentials in the case of a diatomic molecule is indicated in Figure 1. The vertical ionization potentials (I_V) are equal or greater in magnitude than adiabatic potentials (I_A). In fact the identification of electron-impact appearance potentials with vertical ionization potentials has been doubted by Morrison[15]. It was recently shown, by photoionization and by using a mass spectrometer to collect the product cations, that it is possible to obtain values for the two potentials I_V and I_A[16]. Both of these values for different ketones are given in Table 4. For the same molecule they differ by some hundredths of an electron volt.

TABLE 4. Ionization potentials of some carbonyl compounds.

Molecule	Ionization potential (ev)	Method	Ref.
CO	14·013	spect.	1
	14·01	impact	2
	14·01	photoion.	3
	14·11	impact	4
CO_2	13·88	impact	5
	13·788	spect.	6
COS	11·23	spect.	7
C_3O_2	10·8	impact	8
HCHO	10·87	photoion.	2
	10·85	impact	9
	10·87	impact	10
	10·88	spect.	11
CH_3CHO	10·25	impact	12
	10·25	photoioniz.	13
	10·228	spect.	14
CH_3CH_2CHO	10·14	impact	12
$CH_2{=}CHCHO$	10·10	photoioniz.	2
	10·14	impact	9
$CH_3CH{=}CHCHO$	9·81	impact	10
$CH_3CH_2CH_2CHO$	10·14	impact	10

(*Table continued*)

TABLE 4—*continued*

Molecule	Ionization potential (ev)	Method	Ref.
H_3C \ CHCHO / H_3C	9·81	impact	15
HCO·	9·88	impact	15
CH_3CO·	7·08	photoioniz.	16
	8·08	impact	15
$CH_2{=}C{=}O$	9·607	spect.	17
	9·60	photoioniz.	18
CH_3COCH_3	9·69	photoioniz.	3, 18
	9·68	photoioniz.	16
	9·89	impact	10
	9·92	impact	19
CH_3COCH_3, enol form	8·2	photoioniz.	16
$CH_3COCH_2CH_3$	9·58	impact	20
	$I_V = 9{\cdot}51$; $I_N = 9{\cdot}48$	photoioniz.	16
$CH_3COCH_2CH_2CH_3$	$I_V = 9{\cdot}41$; $I_A = 9{\cdot}37$	photoioniz.	16
CH_3OH	10·85	photoioniz.	3
	10·9	impact	21
HCOOH	11·05	photoioniz.	3
CH_3COCl	11·02	spect.	22
$COCl_2$	11·78	photoioniz.	23
	11·77	impact	24
$HCOOCH_3$	11·14	impact	25
	10·92	impact	20
CH_3OCH_3	10·00	photoioniz.	3, 18
	10·13	impact	26

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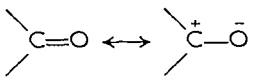
The values of the first ionization potentials of some molecules containing the carbonyl group are collected in Table 4. It is easy to see that the inductive effect has a much stronger influence on the ionization potential than on the bond length. For example, acetaldehyde has an ionization potential (10·25 ev) greater than propanal (10·14 ev) and the very strong inductive effect of chlorine is shown by the difference between the ionization potentials of acetyl chloride (11·02 ev) and of phosgene (11·78 ev). The effect of a conjugated double bond is also clearer in this case; thus acrolein has a smaller potential (10·10 ev) than has formaldehyde (10·87 ev). In this molecule the first ionization process (10·8 ev) is almost certainly the removal of a nonbonding electron[17]. According to a suggestion of Sugden and Price[18], the second ionization process (11·8 ev) corresponds to the removal of a π electron and the third one (13·1 ev) to the removal of a σ electron from the carbonyl bond. These facts had been corroborated by the *ab initio* calculations[11,19] on this molecule.

Many years ago, Walsh[1] showed that it is possible to correlate the length of the carbonyl bond of a molecule with its first ionization potential: the bond length increases with a decrease of the ionization potential. A relation of this sort is to be expected because a decrease of the ionization potential means an increase of the negative charge on the oxygen atom, and this in turn means an increase of bond length, probably because of increased single-bond character according to the resonance description of the carbonyl bond.



5. Vibration spectra

We will consider here only the carbonyl stretching vibration which is typical of infrared spectra. Since in the majority of cases the Raman and infrared bands occur near the same frequencies, we will discuss only the infrared spectra[20]. All compounds containing a carbonyl

group show a very strong band in the region 1650–1850 cm^{-1} (Table 5). The region where this vibration appears is very narrow for a series of similar compounds. For example, most aromatic aldehydes have a stretching vibration in the region 1670–1750 cm^{-1}. Furthermore, it is generally possible to identify a carbonyl group by a vibration located in this region. Indeed, there are only a few other groups (C=C, aromatic, >NH and —OH) having a characteristic vibration frequency in the carbonyl region, but with the exception of the —C—NH group the carbonyl bands are much stronger.

An analysis of the carbonyl stretching frequencies in various types of carbonyl compounds suggests that the observed band position results from the interplay of several factors among which the following are clearly important: (*a*) the physical state of the compound; (*b*) the inductive effect; (*c*) electronic and mass effects of neighboring substituents; (*d*) ring strain and vibrational coupling between neighboring carbonyl groups; (*e*) hydrogen bonding; (*f*) enolization; and (*g*) solvent effects. Before studying the variation of the carbonyl group frequency with the environment of this group in the molecule, it is necessary to point out that the physical state of a compound has a rather important effect on the frequency value. For many compounds the highest value is for the gaseous state, with lower ones for the liquid or solid state. The values corresponding to the solutions are intermediate between these two limits; for example, cyclohexanone in the vapor phase absorbs at 1742 cm^{-1} and in the liquid phase at 1717 cm^{-1}. The frequency variations seem to be mainly due to variations in bond type or to variations in molecular geometry. We will see in the following section that it is possible to calculate the force constant K, which in the case of an isolated diatomic vibrator is linked to the vibration frequency ν by

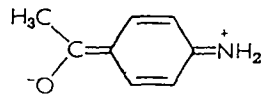
$$\nu = \frac{1}{2\pi}\left(\frac{K}{\mu}\right)^{\frac{1}{2}}$$

where μ is the reduced mass of the system. The force constant varies with the molecular electronic distribution; these variations are usually interpreted as resulting from inductive and mesomeric effects.

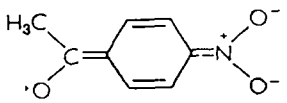
Groups with a strong electron-attracting inductive effect decrease the negative charge on the oxygen and the vibration frequency increases by comparison to that of the normal ketones. For example, acetone absorbs at 1738 cm^{-1} in the vapor phase whereas acetyl chloride absorbs at 1822 cm^{-1}. The electron-repelling inductive effect of the ethyl group is larger than that of the methyl group; its

result is an increase in the negative charge on oxygen, and this effect is responsible for the shift in stretching vibration from 1689 cm^{-1} for acetone to 1694 cm^{-1} for propiophenone. Other effects can add their influence to that of the inductive effect; these include variation of the force constant of adjacent bonds or the action of an electrostatic field created by a neighboring electronic cloud. The first effect is responsible for the acid fluoride frequency being higher by approximately 50 cm^{-1} than the frequencies of acid chlorides and acid bromides[21]. The second effect causes the rotation isomers of α-chlorocarbonyl compounds to have a different stretching vibration: the compound with the shortest chlorine–oxygen distance has the highest frequency[22]. By this repulsive electrostatic interaction, both the dipole moment and the stretching vibration of α-halogenated aldehydes and ketones can be explained[23].

The mesomeric effect occurs when the carbon–oxygen double bond is conjugated either with another double bond or with a lone pair of electrons. Usually in this case the carbonyl bond is more polarized, the force constant is smaller, and the stretching bands are shifted towards lower frequencies; for example, the carbonyl stretching frequency shifts from 1739 cm^{-1} in acetone to 1724 cm^{-1} in acrolein. Similarly for propynal, where conjugation is possible in the direction of the $2p_x$ orbitals and in the direction of the $2p_y$ orbitals, the vibration frequency is located at 1697 cm^{-1}. The stretching bands of ketones conjugated with two double bonds and of quinones are shifted towards frequencies under 1700 cm^{-1}. Benzoquinone shows a triplet at the frequencies 1689 cm^{-1}, 1683 cm^{-1}, and 1667 cm^{-1}. This charge displacement on the oxygen can be transmitted through a benzene ring; for example, substituents like the *p*-amino group which force electrons into the benzene ring to stabilize the quinoid structure



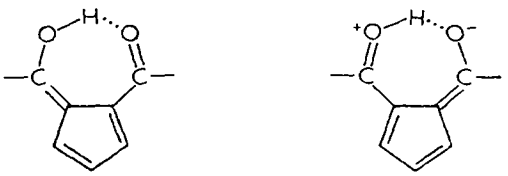
will reduce the double-bond character of the carbonyl bond and lower the frequency[24]. The nitro group which attracts electrons from the benzene ring to stabilize the structure



will reduce the polarity of the carbonyl bond and increase the frequency. The stretching frequencies are 1677 cm^{-1} in *p*-amino-acetophenone, 1689 cm^{-1} in acetophenone, and 1700 cm^{-1} in *p*-nitroacetophenone. The charge displacement on the oxygen is impossible when the carbonyl group is conjugated with another carbonyl group. Experimentally the carbonyl groups conjugated with other carbonyl groups show a stretching vibration frequency comparable to those of isolated carbonyl groups; for example, glyoxal absorbs at 1730 cm^{-1}.

All these effects can be seen on other molecules containing a non-ketonic carbonyl group. The inductive effect of the residues CH_3, CH_2CH_3, $CH_2CH_2CH_3$, and Cl is very clear from the stretching vibration frequencies of ethyl acetate (1745 cm^{-1}), ethyl propionate (1741 cm^{-1}), ethyl butanoate (1739 cm^{-1}), and ethyl chloroformate (1782 cm^{-1}). The stretching vibration frequency of ethyl benzoate (1725 cm^{-1}) shows the mesomeric effect of the aromatic ring[25].

A mesomeric effect can also occur in molecules with hydrogen bonding, as in the case of ketones with conjugated bonds and with a hydrogen bond, i.e. a contributing structure becomes important, in which a negative charge appears on the carbonyl oxygen and a positive charge on the atom carrying the hydrogen atom of the hydrogen bond. Due to hydrogen bonding the charge displacement is again increased. For instance, in 6-hydroxyfulvenes with the carbonyl in position 1 the carbonyl vibration frequency appears at 1635 cm^{-1}[26]. The influence of the geometry of the molecule is



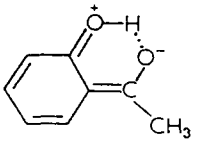
particularly clear in the case of cyclic ketones. The carbonyl group of cyclohexanone has a vibration frequency (1717 cm^{-1} in solution) very close to that of acetone (1715 cm^{-1}); but this frequency increases as the ring angle decreases in the smaller ketones. It will be seen in the next section that this change of geometry increases the coupling between the C=O and the adjacent C—C vibrators (section III.C).

Jones and coworkers[24] noticed that if the ν_{max} of the carbonyl stretching band is plotted against the Hammett reactivity constant,

the linearity of this relationship seems to show that the same combination of factors is responsible for both the shift in carbonyl stretching frequency and the reactivity. This is probably the resultant of the mesomeric and inductive effects. Similarly, the carbonyl stretching band intensity in substituted ketones can be correlated with the inductive properties of the attached group[27]. For the halogenated derivatives of acetic acid[28] and for some esters[25], the intensity decreases when the substituents are more electronegative. For conjugated ketones it was pointed out[29] that a linear relationship exists between the intensity and the resonance energy.

There is also the mass effect of the α-substituents to be considered. In series of related compounds the mass effect is small; for example, diethyl ketone has a moderately intense band at 1720 cm^{-1} in carbon tetrachloride solution whereas in the fully deuterated compound the band maximum is displaced to 1714 cm^{-1}[30]. The deuterium atoms in the methylene group are mainly responsible for this displacement, since $CH_3CD_2COCD_2CH_3$ also absorbs at 1714 cm^{-1} and $CD_3CH_2COCH_2CD_3$ at 1720 cm^{-1}.

If partial enolization should occur in a single saturated ketone, it would be expected to cause a fall in the carbonyl band intensity and the appearance of O—H and C=C stretching bands. A new carbonyl band might also appear as a consequence of hydrogen bonding between the ketonic and enolic species. For example, when an *ortho*-hydroxyl group is introduced into acetophenone, the carbonyl frequency is shifted from 1687 to 1635 cm^{-1}[31]. Conjugated chelation seems to be responsible for this shift to a shorter wavelength, due to the contribution of a resonance form such as



The last effects to be considered are the solvent effects. Some workers[32] have associated frequency shifts with changes in the dielectric constant of the medium. Bellamy and Williams showed that the frequency shifts all follow a common pattern and seem to be produced by local association effects[33]. They plotted the relative variation of frequency $\Delta\nu/\nu \times 10^3$ for a given ketone against the same quantity for acetophenone and they found no break or change in slope of any of the obtained lines on passing from a proton-donating solvent such as pyrrole to a nondonor such as ether. The

TABLE 5. Stretching vibrations of carbonyl compounds.

Molecule	Stretching vibration $\nu_{C=O}$ (cm^{-1})	
	Vapor phase	Solution
CH_3COF	1869 (1, 2)	
CH_3COCl	1822 (1, 3)	
CH_3COBr	1821 (1)	
CH_3CHO	1743 (4)	
$(CH_3)_2CO$	1738 (2), 1736 (5)	1715 (6)
CH_3COCN	1740 (7)	
HCHO	1744 (8)	
C_6H_5CHO		1710 (6)
Cyclohexanone	1742 (2)	1717 (2, 9)
Cyclopentanone		1746, 1728 (10)
Cyclobutanone	1816 (11)	
$HCOOC_2H_5$		1733 (12)
CH_3COOCH_3	1770 (2)	
$CH_3COOC_2H_5$		1745 (12)
$ClCOOC_2H_5$		1782 (12)
$C_6H_5COOC_2H_5$		1725 (12)
$CH_3CH_2COOC_2H_5$		1741 (12)
$CH_3CH_2CH_2COOC_2H_5$		1739 (12)
$C_6H_5COCH_3$	1709 (2)	1689 (13)
$C_6H_5COCH_2CH_3$		1694 (13)
COBrF		1874 (14)
COClF		1868 (1, 15)
COF_2		1928 (1)
$COCl_2$		1827 (1)
HCOCHO	1730 (16)	
$CH_2{=}CHCHO$	1724 (16)	
$CH{\equiv}CCHO$	1697 (17)	
p-Benzoquinone	1689, 1683, 1667 (18, 19)	
p-Aminoacetophenone		1677 (20)
p-Methylacetophenone		1687 (20)
p-Fluoroacetophenone		1692 (20)
p-Nitroacetophenone		1700 (20)

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individual sensitivities to solvent effects vary widely; for example, the observed slopes for some ketones are as follows:

benzophenone	1·12	cyclohexanone	0·74
acetone	1·08	diisopropyl ketone	0·96
acetophenone	1·00		

These values do not parallel the variations of the stretching vibration frequencies nor of the ionization potentials. Probably there are two factors: the proton affinity of the carbonyl group and the geometry of the molecule. The theoretical treatment by Buckingham[34] and the experimental results on *s-cis* and *s-trans* unsaturated ketones[35] seem to corroborate this interpretation.

B. *Ultraviolet Spectra*

In this section we will discuss the ultraviolet spectra of carbonyl compounds, but have excluded steroid spectra, as many books can be consulted on this subject[36,37].

Simple carbonyl compounds present several regions of absorption below the Rydberg bands in the ultraviolet region. The first band is located near 4000 Å and corresponds to a very weak absorption ($\varepsilon_{max} \simeq 10^{-3}$); the second band near 3000 Å corresponds to a weak absorption ($\varepsilon_{max} \simeq 10$). The third and the fourth bands of moderate to strong intensity lie near 1800 Å; the fifth band, which corresponds to a very strong intensity, is at shorter wavelength (about 1600 Å).

As we will see, the first two bands correspond to a transition from an oxygen $2p$ lone-pair orbital to the carbonyl antibonding π orbital. We will study them together. Either the third band or the fourth one (both of which are located in the far ultraviolet and do not show a strong absorption and are therefore not well known) corresponds to

a transition of an oxygen $2p$ lone-pair electron to the carbonyl antibonding σ orbital. The fifth band is better known and it corresponds to a transition from a π electron to the antibonding π^* orbital.

We will discuss first the main characteristics of $n \rightarrow \pi^*$ transitions (Tables 6 and 7). Since the n–π^* bands are near the visible part of the spectrum, they were the first ones to be studied.

TABLE 6. Singlet–singlet $n \rightarrow \pi^*$ transitions.

Compound	Transition (Å)		Phase	Ref.
HCHO	3538		vapor	1, 2
CH_3CHO	3390		vapor	3, 4
$CH_2{=}CHCHO$	3860		vapor	5
$CH_2{=}C(CH_3)CHO$	3350	$\varepsilon = 25$	cyclohexane	6
$CH{\equiv}CCHO$	3821		vapor	7
$CH_3C{\equiv}CCHO$	3756	$\varepsilon = 91$	vapor	8
C_6H_5CHO	3909	$\varepsilon = 10$	n-hexane	9
CH_3COCH_3	2750	$\varepsilon = 22$	cyclohexane	10
$CH_3CH{=}CHCOCH{=}CHCH_3$	3360	$\varepsilon = 55$	ethanol	11
Cyclopentanone	2780	$\varepsilon = 18$	methanol	12
Cyclohexanone	2820	$\varepsilon = 15$	methanol	12
Cycloheptanone	2838	$\varepsilon = 20$	methanol	12
$C_6H_5COCH_3$	3628	$\varepsilon = 78$	n-hexane	9
$C_6H_5COC_6H_5$	3787	$\varepsilon = 33{\cdot}7$	n-hexane	9
$(CHO)_2$	4550	$\varepsilon = 18$	vapor	13
$(COCH_3)_2$	4484	$\varepsilon = 21{\cdot}4$	n-heptane	14
CH_3COCl	2400	$\varepsilon = 34$	n-heptane	6, 15
$(COCl)_2$	3553		cyclohexane	6, 16
CH_3COBr	2500	$\varepsilon = 95$	cyclohexane	6
p-Benzoquinone	4958		vapor	17
HCOOH	2173		vapor	18
$CH_3COOC_2H_5$	2070	$\varepsilon = 70$	petroleum ether	19

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TABLE 7. Singlet–triplet $n\rightarrow\pi^*$ transitions.

Compound	Transition (Å)		Phase	Ref.
HCHO	3968·2		vapor	1, 2
$CH_2{=}CHCHO$	4059		vapor	3, 4
$CH{\equiv}CCHO$	4145		vapor	3
C_6H_5CHO	3969	$\varepsilon = 0{\cdot}1$	n-hexane	5
$C_6H_5COCH_3$	3885	$\varepsilon = 0{\cdot}03$	n-hexane	5, 6
$C_6H_5COC_6H_5$	4121	$\varepsilon = 0{\cdot}03$	n-hexane	5, 6
CHOCHO	5117		vapor	7, 8
$CH_3COCOCH_3$	4897		crystal	9
	5279·3	$\varepsilon = 12$	crystal	10
p-Benzoquinone	5352·7	$\varepsilon = 19{\cdot}6$	vapor	11

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I. $n\rightarrow\pi^*$ transitions

After the pioneering work of Burawoy[38], Mulliken and McMurry[39,40] gave a theoretical interpretation and Kasha[41] and McConnell[42] developed criteria for characterizing $n\rightarrow\pi^*$ transitions.

If we compare the spectrum of formaldehyde with that of its hydrocarbon analog, ethylene, we can see that ethylene presents a strong absorption in the far ultraviolet; this absorption begins at 1750 Å and there is a maximum at 1620 Å but there is no absorption near 3500 Å[43]. To observe a long wavelength $n\rightarrow\pi^*$ band it is necessary that a lone-pair electron should be on a heteroatom, e.g. on O or N, conjugated with at least one other atom. The existence of an electron lone pair can be demonstrated by the fact that the

n–π^* bands can disappear in acid media by protonation of the lone pair[44].

It is now well accepted that the first band around 4000 Å is due to an $n \rightarrow \pi^*$ transition, where the ground state is a singlet (all the electrons are paired) and the excited state is a triplet (two unpaired electrons). Some of these bands have been recently studied again[45], and the position of the O—O band determined by phosphorescence[46,47]. Many experiments have established that phosphorescence is due to a triplet state[48]. The intensity of this first band is always very small, since these bands involve two states of different multiplicity and are therefore 'forbidden'. The polarization of the phosphorescence spectrum indicates that the lowest triplet state is an (n, π^*) state[47]. The separation of the two n–π^* bands is rather small; for example, 1765 cm^{-1} for benzaldehyde or 1820 cm^{-1} for acetophenone[46].

The first intense absorption band of ethylene occurs at about 1680 Å (59,400 cm^{-1})[43] and the first triplet state has been located at 2700 Å (37,000 cm^{-1})[49]; the triplet–singlet separation is about 22,400 cm^{-1}. A small triplet–singlet separation will be a necessary but not a sufficient characteristic of an $n \rightarrow \pi^*$ transition.

If the carbonyl bond is conjugated with a double bond or with a conjugated system, both the singlet–singlet and the singlet–triplet $n \rightarrow \pi^*$ transitions will shift to longer wavelengths (red shift); for instance, the shift is of 91 Å for the singlet–triplet transition and of 322 Å for the singlet–singlet transition on going from formaldehyde to acrolein[50–52]. In the case of several conjugated bonds the shift of the π–π^* band can be so large that the n–π^* band will be seen only as a shoulder of the π–π^* band or will even disappear[53]. The π–π^* shift is due to the lowering of the π^* orbital, but also to the raising of the π orbital. Because of this, the π–π^* shift is larger than the n–π^* shift (375 Å instead of 322 Å on going from formaldehyde to acrolein).

In contrast to the effect of a double bond an alkyl group replacing an aldehyde hydrogen shifts the carbonyl $n \rightarrow \pi^*$ transition to shorter wavelengths. This is very clear in the series formaldehyde (λ_{max} = 3538 Å)[51], acetaldehyde (λ_{max} = 3390 Å)[54], and acetone (λ_{max} = 2750 Å)[55]. As stated by Nagakura[56], the $n \rightarrow \pi^*$ transition involves transfer of negative charge from the oxygen to the carbon atom; the substituent groups that donate charge to the carbonyl carbon raise the energy of the antibonding π orbital, causing a blue shift of the $n \rightarrow \pi^*$ transition of carbonyl compounds. This effect is

still the same in the replacement of H by CH_3 in a conjugated aldehyde. The $n \rightarrow \pi^*$ transition is shifted toward the blue and the carbonyl stretching frequency decreases on going from propargyl aldehyde to tetrolaldehyde[57,58]. This systematic slight blue shift is also obvious in the series formed by propionaldehyde, acetone, and diethyl ketone when the measurements are carried out under the same conditions for these three compounds[59]. It must be noted that these n–π^* bands have a very low intensity and that their wavelengths depend very much on the solvent. The values are usually rather scattered in the literature and, if possible, they must be compared for exactly the same experimental conditions. It has been found also that the $n \rightarrow \pi^*$ transition in various carboxyl spectra is blue-shifted by alkyl substitution in a much more pronounced fashion[59].

Substitution of the aldehydic hydrogen by a group such as OH, NH_2, or Cl gives a hypsochromic effect (shift to shorter wavelengths) relative to acetaldehyde. These groups are more electronegative than carbon; and the lone-pair electrons on the carbonyl oxygen are held more firmly than they would be in the absence of an inductive effect. The result is a lowering of the n level and a hypsochromic effect on going from CH_3CHO (λ_{max} = 3390 Å)[54] to, e.g., CH_3COCl (λ_{max} = 2400 Å)[60].

Cookson[61,62] has analyzed the effect of polar substituents on the n–π^* band of saturated cyclic ketones. In the cyclohexanone series axial α-halogen or oxygen substituents shift the carbonyl n–π^* band by some 40–300 Å to *longer* wavelengths, whereas equatorial substituents shift the absorption to *shorter* wavelengths. The intensity increase is larger in the case of the axial substituent than in the equatorial case. The interaction between a carbonyl group and an equatorial substituent seems to be similar to that between the carbonyl group and the chlorine in acetyl chloride, since it gives similar changes. In the case of an axial substituent it is probably a charge-transfer interaction which produces the bathochromic shift to longer wavelengths.

The solvent effect on the position of the n–π^* band has been known for many years. There is a large blue shift on going from a nonpolar solvent to a polar one, which is a general property of the n–π^* bands[41,42]. It is particularly evident on going from a hydrocarbon to a hydroxylic solvent and, as has been shown in the case of the infrared spectra, the shift is probably due to the formation of hydrogen bonds rather than to a dielectric effect. In fact a simple relationship exists between solvent-induced frequency shifts of the

n–π^* absorption band and that of the infrared carbonyl band[63]. The order of the increase in the n–π^* band frequency is that of the decrease in the carbonyl frequency with the exception of acetone. As the solvent shift in the vibrational spectra can only be a measure of the solute–solvent interaction in the electronic ground state, the existence of a linear relationship between n–π^* and carbonyl band shifts suggests that the solute–solvent interaction in the excited state does not contribute very much to the blue shift of the n–π^* absorption. As has been shown recently on formaldehyde[64] and on propionaldehyde[65], the dipole moment of an aldehyde decreases on going from the ground state to the excited state, showing that the formation of hydrogen bonds in the excited state is unlikely, since the lone pair on oxygen is no longer available for the formation of hydrogen bonds. The results relating to benzophenone are collected in Table 8. Brealey and Kasha[66] demonstrated that, in the case of pyridazine, a major cause of the n–π^* blue shift is the formation of hydrogen-bonded solvates at the heteroatom lone pair of the molecule.

TABLE 8. Solvent effects on benzophenone spectra[63].

Solvent	n–π^* absorption of benzophenone (cm^{-1})	Carbonyl vibration band of benzophenone (cm^{-1})
n-Hexane	28,810	1673
Dioxane	29,230	1667
Chloroform	29,670	1662
Ethyl alcohol	30,020	1657

The qualitative classification proposed by McConnell[42] can be replaced by a semiquantitative classification by using Kosower's Z constants which were introduced in the study of the 1-alkylpyridinium iodide spectra[67]. The charge-transfer spectra of these iodides show a striking shift in the position of the bands with a change in the polarity of the solvent in which the light absorption is measured. The transition energies for this salt in a given solvent are called Z values[68]. Usually the $n \rightarrow \pi^*$ transitions vary linearly[69] with the solvent polarity standard Z. For example, in the case of cycloalkanones $(\overbrace{CH_2)_{n-1}C}{=}O$ with $n = 5$ or 6, the $n \rightarrow \pi^*$ transitions vary in a linear fashion with the polarity of the solvent as measured by Z; if $n = 7$, 8, 9, and 10, reasonably good correlations are

obtained with the same parameter. Cyclopentadecanone ($n = 15$) gives a poorer correlation and hence it is concluded that the nonpolar portion of the molecule is folded. This correlation can be explained in the case of polar molecules and polar solvents by saying that the ground state is stabilized by interaction of the molecule dipole with the solvent dipole[70]. Since the molecule dipole changes very fast (in about 10^{-15} sec), the excited state is destabilized, because the solvent molecules are organized for a dipole moment which is not present. The solvent dipole reorientation would need a time greater than 10^{-13} sec. The assumption that the packing of the solvent molecules is very different in the ground state and in the excited state is also proved by the fact that there is no solvent shift in emission[71].

Experimental results about the intensity of the n–π^* bands give much information: they suggest, for example, that the most important of these excitations has a charge-transfer character[72]. The progressive replacement of the hydrogen atoms of formaldehyde by methyl groups doubles and then quadruples the extinction coefficient. The $n \rightarrow \pi^*$ transitions are characterized, even if symmetry allowed, by oscillator strengths[71] of the order of magnitude of 10^{-2} with molar absorption coefficients in the range 300 to 2000. As we will see in section III.B, even if these bands are allowed by the total symmetry of the molecule, they are always forbidden by local symmetry. The major part of the absorption intensity of formaldehyde n–π^* band is found experimentally to be polarized in the plane of the molecule but in a direction perpendicular to the carbonyl bond[51]. It was stated[73] that the bands with this polarization arise from the mixing of the forbidden $n \rightarrow \pi^*$ transition with a high-energy allowed transition induced by the out-of-plane bending vibration. In formaldehyde the weaker bands of the $n \rightarrow \pi^*$ transitions have transition moments parallel to the carbonyl bond, which have been ascribed to an electronic interaction with rotation about the carbonyl axis[73] or to a magnetic dipole transition[74]. The weak O—O band of the 3500 Å system belongs to this weak system. An entirely similar band of this system has been recently analyzed[75] and it has been shown that the only solution is a magnetic transition moment parallel to the carbon–oxygen bond.

More important intensity changes result from the substitution of unsaturated groups or atoms bearing lone-pair electrons at the carbonyl group or at neighboring positions along a saturated chain. We will see later that this enhancement of intensity is particularly clear in the case of some diketones. A similar intensification can also

happen in the case of some sterically hindered α,β-unsaturated ketones or in β,γ-unsaturated ketones. It was shown[61,76,77] that a necessary condition for such an intensity variation is the non-coplanarity of the ethylenic and carbonyl double bonds. These intense carbonyl n–π^* bands are associated with very large optical rotatory dispersions[72,78]. The normal carbonyl transition is forbidden for electric dipole absorption, which means that

$$\int \psi_2^* \mathbf{P} \psi_1 \mathrm{d}\tau = 0$$

where ψ_1 and ψ_2 are the wave functions of the two electronic states and $\mathbf{P}$ the electric dipole operator. This carbonyl transition is magnetic-dipole allowed, which means that

$$\int \psi_2^* \mathbf{M} \psi_1 \mathrm{d}\tau \neq 0$$

where $\mathbf{M}$ is the magnetic dipole operator. The operator $\mathbf{M}$ has the same symmetry properties as a rotation and the operator $\mathbf{P}$ transforms as a translation. When, for some geometrical reason, one makes the $n \rightarrow \pi^*$ transition allowed for electric dipole absorption also, as in the asymmetric β,γ-unsaturated ketones, then one has just the condition for high optical rotation. An electron-donating substituent which, as we have seen above, enhances the 3000 Å absorption intensity of an asymmetric ketone, also frequently enhances the rotatory power of the molecule[79,80].

The rotatory dispersion is more frequently used than the rotatory power, and this technique recently found many applications in the stereochemistry of ketones. The rotation of the plane of linearly polarized light in transparent spectral regions is the dispersion phenomenon connected with the differential absorption of left- and right-handed circularly polarized light. The light is elliptically polarized since the left- and right-handed components are no longer equal in intensity. This last effect is called circular dichroism and the Cotton effect is the combination of circular dichroism with an optical rotatory effect. In such a case the rotatory dispersion curve, if studied close to an absorption band, becomes anomalous and shows a positive or a negative Cotton effect (Figure 2). The rotational strength of a transition may be obtained from the observed magnitude of the anomaly in the optical rotatory curve at the frequency of the corresponding absorption[72].

Recent study of the saturated ketones have led to two empirical rules, the 'axial haloketone rule' and the 'octant rule'. The sub-

stitution of an axial halogen next to the carbonyl group in cyclohexanone leads to shifts in the spectra of these compounds as we have seen above, resulting in a corresponding shift in the rotatory dispersion peaks. Equatorial substituents (Cl, Br, OH, OAc) have little effect on the shape of the dispersion curve. An axial substituent can increase the amplitude of the dispersion and the introduction of an axial Cl, Br, or I next to the keto group may change the sign of the Cotton effect. In this case the sign of the Cotton effect may be predicted by the 'axial haloketone rule' and if it is known that the substituent is axial, then its location may be determined[81]. The 'octant rule' relates the sign of the rotatory power of an optically active ketone in the 3000 Å region to the stereochemical disposition

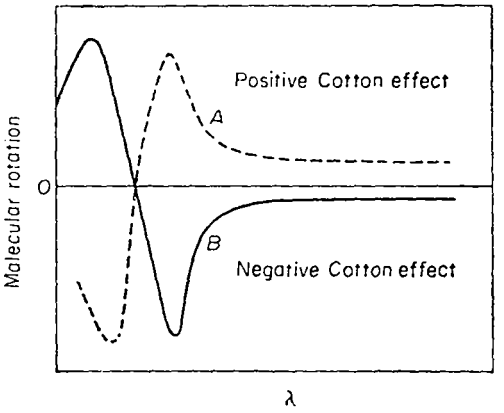

FIGURE 2. Rotary dispersion curve for ketones.

of the atoms creating the dissymmetry of the molecule[82,83]. A fluorine atom induces a rotatory power of opposite sign to that given by a corresponding alkyl or unsaturated group[80-82]. Since the enhancement of the n–π^* band intensity is due to charge transfer, the effect of fluorine is due to its strong electron-attractive nature[84]. It has been shown that the octant rule cannot be applied to α,β-unsaturated ketones[85]. Many applications of rotatory dispersion and circular dichroism to ketones have appeared in the last few years[86-88]. It seems that in the case of carbonyl compounds, the circular dichroism yields information slightly more precise and easier to understand than that obtained by rotatory dispersion[86].

In the last ten years the study of the n–π^* absorption bands has offered much information about the properties of the excited states. The first and the most thoroughly studied case was the n–π^* excited

state of formaldehyde[50,51,64,88]. The $^1A_1 \rightarrow {}^3A_2$ transition (3600–4000 Å) is forbidden by change of spin multiplicity and is extremely weak ($f = 10^{-6}$)[89]. The $^1A_1 \rightarrow {}^1A_2$ transition is forbidden by the electronic selection rules, and the absorption intensity of the band system 3500–2500 Å is low ($f = 2{\cdot}4 \times 10^{-4}$). Walsh[90] predicted that the equilibrium configuration for the first excited singlet of formaldehyde must be one in which the carbonyl bond intersects the CH_2 plane at a small angle. Brand proved this by the complete analysis of the absorption and emission spectra[51]. The carbonyl stretching frequency in the excited state is equal to about 1180 cm^{-1} and in the ground state to 1745 cm^{-1}, which indicates that the carbonyl bond distance changes considerably in the excited state. A rotational analysis of the ultraviolet bands has been carried out and the parameters of the pyramidal excited state determined by this analysis are: C—H = 1·09 Å, C—O = 1·32 Å, $\widehat{HCN} = 120°$; the out-of-plane angle (between the H_2C plane and the extended C—O axis) is about 27°. The vibrational analysis of the singlet–triplet band, $^1A_1 \rightarrow {}^3A_2$, is similar to that of the singlet[91]. The barrier to inversion is higher and the carbonyl bond is shorter than in the A_2 singlet state.

Other examples of nonplanar excited states have been found by the analysis of the n–π^* carbonyl bands. In the excited state of acetaldehyde[92] the carbonyl bond increases in length, as it does in formaldehyde (0·1 Å). In glyoxal[93] and in acrolein[94] the changes are small; probably the angles $\widehat{CCO}$ and $\widehat{CCC}$ are increased by about 3°. In propionaldehyde[95] the carbonyl bond length increases by about 0·11 Å; it is not completely clear if the excited state is planar or pyramidal; but if it is pyramidal, the out-of-plane angle is unlikely to exceed 4°.

By measuring the Stark splittings of some rotational lines, it has been possible to determine the dipole moment of the n–π^* states of formaldehyde[64] and of propionaldehyde[65]: the value is 1·48 ± 0·07 D for the former and 0·92 ± 0·02 D for the latter.

In α-diketones there are two $2p$ lone-pair orbitals, n_1 and n_2. If there is no overlap between them, then there are two degenerate molecular orbitals available for the four lone-pair electrons. In the overlap case one of these orbitals corresponds to the symmetric combination of n_1 and n_2 and the other one to the antisymmetric combination; the first one has the lower energy. In the same way the π^* orbitals of each carbonyl group can combine with each other and give two different molecular orbitals. It can happen that the n

orbitals do not differ in energy by more than 100 cm^{-1}. The spectrum of glyoxal contains three bands in the long wavelength region[96]: the first band corresponds to a singlet–triplet transition and is located at 19,544 cm^{-1}. Magnetic rotation spectra corresponding to the singlet–triplet transition in formaldehyde and in glyoxal corroborates the assignment of the triplet states of these molecules[97]. The second band corresponds to a singlet–singlet transition and is symmetry allowed and polarized at right angles to the molecular plane[93]. The third band, forbidden by symmetry, has a very low intensity and is almost degenerate with the first one[96]. In biacetyl the situation is about the same: the first singlet–singlet and singlet–triplet transitions are located at 22,873 cm^{-1} and 20,421 cm^{-1}, respectively, in the crystal[98] and at 22,300 cm^{-1} and 19,800 cm^{-1} in solution[99]. In more complicated compounds with carbonyl groups not orthogonal to each other[100,101], two different n–π^* bands appear because there are two different n orbitals and two different π^* orbitals. The transitions between the two symmetric or the two antisymmetric orbitals are the only ones allowed.

Biacetyl phosphoresces in the gas, liquid, and solid phases, but this is a very rare case, since in solution the long lifetime of the triplet which is the excited state responsible for phosphorescence makes it highly susceptible to quenching before it radiates. In fluorescence the excited state responsible is the singlet state and biacetyl fluorescence may be sensitized by a number of other substances[102,103]. It has been observed that the ratio of phosphorescence increases with the time of irradiation for aqueous solutions of biacetyl, and reaction of the excited biacetyl with oxygen in the solvent has been assumed[104]. Biacetyl is often used in triplet transfer experiments in liquids[105,106]. By quenching the fluorescence of naphthalene, benzene, and twelve of its alkyl derivatives by biacetyl, it was possible to determine the lifetimes of the excited donors[107].

The promotion of an n-orbital electron to a π-antibonding orbital leaves one electron in the n orbital; the n–π^* excited state may have a radical-like behavior. For example, unsaturated carbonyl compounds are well known for their rearrangement on irradiation[88,108]. It seems likely that the mechanism of rearrangement involves a radiationless transition[109]; this transition leads to the final stable product. The reduction of ketones upon irradiation in different alcohols involves hydrogen abstraction from the alcohol by the triplet n–π^* state of the ketone[110,111] and the reactive properties of excited ketones are similar to those of alkoxy radicals[112]. The

carbonyl n–π^* state is also necessary for the photochemical cycloaddition of ketones to olefins[113]. Many other examples show that the photochemistry arising from the n–π^* excited states requires radical-like intermediates for its interpretation.

2. $\pi \rightarrow \pi^*$ transitions

As can be seen in Table 9, the transition located at about 1500 Å in simple carbonyl compounds exhibits a very strong absorption ($\varepsilon_{max} \sim 20{,}000$). This band has the intensity and the polarization required of a $\pi \rightarrow \pi^*$ transition and the variations of this band position under the influence of an electron-donating substituent or by conjugation with an unsaturated group corroborate this assignment[74]. In a recent study of carbonyl and carboxyl compounds[59] the polarization of these π–π^* bands has been found in the plane of the bonds of the carbon linked to the carbonyl oxygen and parallel to the carbonyl bond.

TABLE 9. Singlet $\pi \rightarrow \pi^*$ transitions.

Compound	Transition (Å)		Phase	Ref.
HCHO	1554	$\varepsilon = 23{,}500$	vapor	1
CH_3CHO	1650		vapor	2, 3
$H_2C{=}CHCHO$	1935	$\varepsilon = 16{,}000$	vapor	4
	2070	$\varepsilon = 11{,}200$	ethanol	5
$HC{\equiv}CCHO$	2120	$\varepsilon = 14{,}600$	isooctane	6
$CH_3C{\equiv}CCHO$	2113	$\varepsilon = 10{,}000$	vapor	7
$CH_3CH{=}CHCHO$	2180	$\varepsilon = 17{,}900$	ethanol	5
$(CH_3)_2C{=}CHCHO$	2355	$\varepsilon = 11{,}900$	ethanol	5
$(CH_3)_2C{=}C(CH_3)CHO$	2450	$\varepsilon = 13{,}000$	ethanol	5
C_6H_5CHO	2480	$\varepsilon = 12{,}700$	vapor	8
CH_3COCH_3	1880	$\varepsilon = 900$	vapor	3
$CH_2{=}CHCOCH_3$	2190	$\varepsilon = 3600$	ethanol	9
$(CH_3)_2C{=}CHCOCH_3$	2490	$\varepsilon = 2490$	ethanol	9
$CH_3CH{=}CHCOCH{=}CHCH_3$	2510	$\varepsilon = 15{,}500$	ethanol	10
$HC{\equiv}CCOCH_3$	2150	$\varepsilon = 5000$	ethanol	11
$C_6H_5COC_6H_5$	2600		ethanol	12
HCOOH	1492		vapor	13

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An electron-donating substituent shifts the absorption to longer wavelengths, owing to resonance interaction between the π-electron system and the substituent. This displacement is clear in the series formaldehyde (λ_{max} = 1560 Å), acetaldehyde (λ_{max} = 1650 Å), and acetone (λ_{max} = 1880 Å). The differentiation between homologs is possible for alkan-2-ones (C_3 to C_6), alkanals (C_2 to C_6), and cycloalkanones (C_5 to C_8)[114]. There is also a bathochromic progression in the series acrolein, crotonaldehyde, β-methylcrotonaldehyde, and 2,3-dimethylbut-2-enal. This effect is general since there is also a bathochromic shift on going from propargyl aldehyde to tetrolaldehyde. A group with a $2p\pi$ lone pair causes a shift in the opposite direction: for instance, formaldehyde absorbs at 1554 Å and formic acid at 1492 Å[59]. The effect is more pronounced with an oxygen atom than with a nitrogen atom; going from methylformamide to methylformate causes a blue shift (from 1724 Å to around 1538 Å)[59].

The conjugation of a double bond with a carbonyl group leads to intense absorption ($\varepsilon_{max} \simeq 15{,}000$) and to an important red shift (Table 9); this band corresponds to the transfer of a π electron from a π-molecular orbital to a π^*-molecular orbital and has a charge-transfer character (see section III.C). In fact this charge-transfer band exists also in the spectra of β,γ-unsaturated ketones in the region of 2200 Å[77,115]. The prediction of the maxima of the π–π^* bands of α,β-unsaturated ketones can be made by Woodward's rules or by extension and modification of these rules[36,116].

A main difference between the n–π^* and the π–π^* bands consists in the solvent effect. On going from a nonpolar solvent to a polar solvent, the π–π^* bands shift to longer wavelengths. For instance, bicyclo[4.4.0]dec-6-en-8-one absorbs at 2290 Å in cyclohexane and at 2455 Å in water and the absorption intensity decreases (ε_{max} = 16,500 in cyclohexane and 15,100 in water)[117]. The interaction with the solvent stabilizes the ground and excited states in a different way and induces the red shift of the $\pi \rightarrow \pi^*$ transition.

3. Other transitions

Usually the assignment of the first band on the blue side of the spectrum after the n–π^* bands is n–σ^* (promotion of a nonbonding electron to an antibonding σ orbital). The corresponding intensity is moderate to strong ($\varepsilon_{max} \simeq 10^3$). This band can shift as a result of substitution; for example, the hyperconjugative effect of a cyclopropane ring on the carbon atom α to a carbonyl group causes a red shift of the n–σ^* band[118]. This assignment has recently been critically discussed[59] and an $n' \rightarrow \pi^*$ assignment (promotion of an electron from the second lone pair to the π^* orbital) has been proposed. The polarization is found to be out-of-plane and this fact is not compatible with an $n \rightarrow \sigma^*$ transition. If the lone-pair n' was a pure $2s$ one, such an assignment would be impossible, owing to the very large promotion energy. However, it is not impossible that this lone pair has a strong $2p$ character.

There is a second (but little investigated) band in this part of the spectrum, which is narrow and sharp and does not change from one carbonyl compound to the other. This band, polarized in the plane of the bonds of the carbon linked to the carbonyl oxygen and perpendicular to the C—O bond, is probably the beginning of a Rydberg series $n \rightarrow 3s$[119]. Bands of this type can be considered as well as n–σ^* bands[90,120].

III. THEORETICAL APPROACH TO MOLECULES WITH CARBONYL BONDS

A. *Molecular-orbital and Valence-bond Descriptions of Carbonyl Bonds*

A complete study of the electronic structure of a given molecule means in principle the calculation of the total molecular wave function. In the case where the nuclei are assumed to be fixed in space (cf. C.S., III.C) this total wave function depends upon the space and spin coordinates of all the electrons of the molecule. This function must satisfy the Schrödinger equation, but even an approximate solution of the Schrödinger equation is practically impossible for the compounds in which chemists are usually interested. Despite the development of automatic computing techniques, it is still only possible to build up complete approximate electronic wave functions for molecules with a very small number of nuclei. Among carbonyl compounds this has only been done for formaldehyde[11,19]. To get information on the electronic structure of more complex molecules,

one takes advantage of the fact that the most accessible physicochemical properties outline the behavior of the electrons that can be ascribed to the characteristic chemical groups of the molecule; then the problem is simplified by building up an electronic wave function limited to these particular electrons. Such a description is more easy if the molecule contains well individualized bonds or lone pairs. This is precisely the case of molecules containing the carbonyl group, since most of their properties are due either to the carbon–oxygen double bond or to the oxygen lone pairs.

In saturated aldehydes and ketones, $R^1R^2C{=}O$, the electrons can be grouped into three categories: the first one includes the inner electrons of the different atoms (1*s* electrons of carbons and oxygen) that can be omitted in the study of the usual physical and chemical properties; the second one includes the electrons of the C—H and C—C bonds of the groups R^1 and R^2 and the electrons of the C—C bonds between the groups R^1 and R^2 and the C=O grouping; the third one includes the electrons of the carbonyl group itself. The building up of a wave function limited to the carbonyl group requires assumptions about the electronic distribution in the rest of the molecule. As the localization of the bonds is very strong in such compounds, one can assume that one pair of electrons corresponds to each C—C or C—H and that these electrons can be described by a two-center wave function including the two nuclei being considered. Though it is not usually necessary to specify the form of these bond wave functions, they can be considered as the solutions of a two-electron problem; this problem may be treated by the usual methods of quantum chemistry. To form these bond functions, the valence atomic orbitals of the different atoms (1*s* orbital of hydrogens, 2*s*, $2p_x$, $2p_y$ and $2p_z$ orbitals of carbons) are used, and the atoms are taken in a hybridization state appropriate to the molecular geometry (cf. C.S., VIII.C). Four tetrahedral hybrid orbitals (te_1, te_2, te_3, te_4) point towards the next nuclei from each saturated carbon. The carbonyl group carbon itself is placed in a trigonal hybridization state, since it is a double-bond carbon with three bond angles of about 120°; thus this atom has three coplanar hybrid orbitals (tr_1, tr_2, tr_3) at its disposal and one pure $2p_x$ orbital perpendicular to the plane yOz of the three hybrids. This situation allows it to form three σ bonds and one π bond with the adjacent atoms (Figure 3). The first two hybrid orbitals are used for binding the saturated residues R^1 and R^2, and the carbonyl carbon therefore gives one axial symmetry orbital (tr_3) and one π orbital to the carbonyl system; each of

these last two orbitals brings one electron to the carbonyl system. It is not necessary here to specify the oxygen hybridization because it is not determined by geometrical considerations, there being no other atom than carbon in the oxygen neighborhood; this hybridization depends upon the variational process used to calculate the total energy of the molecule (cf. C.S., VIII.G). Besides, the oxygen hybridization is probably not an important factor in the nature of the carbonyl bond. Every hybridization process indeed involves an energy loss at the atomic level and this loss must be balanced by the actual formation of chemical bonds; but the carbonyl group oxygen always retains two lone pairs that are unable to make ordinary chemical bonds and the energy loss cannot be recovered by these bondings.

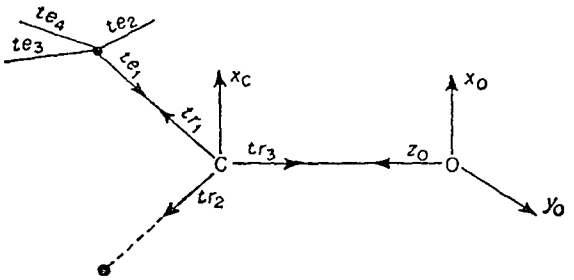


FIGURE 3. Electronic structure of a saturated carbonyl compound.

The electron configurations of a saturated aldehyde or ketone in the ground state N will be written, with the notation of Figure 3,

$$N: \ldots (te_1 tr_1)^2 (s_O)^2 (z_O tr_3)^2 (x_O x_C)^2 (y_O)^2$$

where $(te_1 tr_1)^2$ describes one pair of electrons making the σ bond joining the carbonyl group to the residue R^1, $(z_O tr_3)^2$ and $(x_O x_C)^2$ two pairs of electrons, one of type σ, the other of type π involved in the formation of the carbon–oxygen double bond, $(s_O)^2$ and $(y_O)^2$ the two lone pairs of the oxygen atom, one of character s, the other of character p but located in the plane of the carbonyl bonds[40,121].

If the carbonyl group is bound to unsaturated atoms (as in the conjugated aldehydes and ketones, in quinones, and also in the compounds where R^1 together with the carbonyl group forms a function of acid, ester, or amide type), the electrons of the carbonyl and the electrons of the radicals R^1 and R^2 must be considered as a single system of delocalized electrons[40]. The carbons of such a conjugated chain must be put in the trigonal hybridization state so as to be able

to make a system of coplanar orbitals; this σ system allows a maximum π-electron delocalization and then a maximum stability of the molecule if other steric factors are not involved (Figure 4).

Thus, the electron configuration of the conjugated aldehyde $H(CH{=}CH)_nCHO$ can be written in the following shortened form

$$N{:}\ldots(tr_{R^1}tr_1)^2(s_O)^2(z_Otr_3)^2(x'_{R^1}x_{R^1})^{2n}(x_Ox_C)^2(y_O)^2$$

where the electrons of the σ bonds of R^1 are assigned to localized bond wave functions, but where the π electron system described by $(x'_{R^1}x_{R^1})^{2n}(x_Ox_C)^2$ must be considered as a whole.

The compounds with two conjugated carbonyl functions as the α-diketones or the quinones have a similar electron configuration with a $2s$ lone pair and a $2p_y$ lone pair for each oxygen.

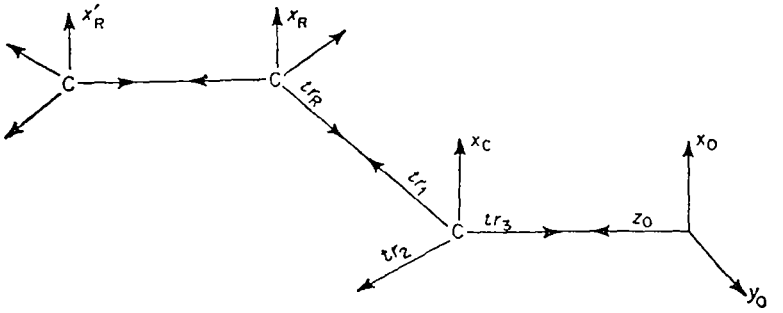


FIGURE 4. Electronic structure of a conjugated carbonyl compound.

With the exception of formaldehyde, the theoretical work carried out until now is only concerned with the outermost electrons of aldehydes and ketones. The number of electrons considered in the carbonyl group itself depends upon the level of approximation used by the authors in order to analyze the properties in which they are interested. The carbonyl bond is very often treated only as a two-electron problem where the two electrons taken in consideration are the $2p_z$ electrons of the double bond; this is particularly the case in studies of the conjugation of the C=O double bond with other C=C or C=O double bonds or with heteroatoms containing lone pairs (amide-group nitrogen, carboxyl-group oxygen). Later, it was found advantageous to include the two $2p_y$ electrons of oxygen in the π-electron system, in order to be able to study the properties connected with the presence of the n lone pair on oxygen[122,123]. All these works consider the carbonyl bond σ electrons, which were

placed in the orbitals tr_3 and z_O in Figures 3 and 4, as making a 'frozen core', i.e. an electron cloud whose shape is known *ab initio*. The σ–π electron interaction in the carbonyl group was studied in the case of formaldehyde and treated as a problem with two centers, carbon and oxygen, and with six electrons, two σ and two π electrons for the carbonyl bond and the two electrons of the n lone pair of oxygen[124].

We will only discuss the descriptions of aldehydes and ketones with the π electrons and the n lone pairs of the carbonyl group, because these descriptions are sufficient to explain the usual physicochemical properties of these compounds. However, as we will see for formaldehyde, the σ and π electrons of these molecules are not independent-particle systems; even a small modification in the distribution of π electrons can strongly vary the distribution of σ electrons and, conversely, a modification of the σ distribution can also vary the π distribution very much.

If the principles of the molecular-orbital method are applied to building up the total wave function Ψ of the electrons of aldehydes and ketones, an individual wave function χ_i, called the molecular orbital, and an individual energy e_i can be assigned to each electron. The orbitals must be such that the total energy of the system be minimum (cf. C.S., VII.A, B). The set of molecular orbitals necessary for the description of the molecule is given by linear combinations of a basis set of atomic orbitals; these linear combinations must have appropriate symmetry properties. In the present case the molecular orbitals χ_i are linear combinations of $2p_x$ orbitals based on the m unsaturated atoms (carbons, oxygens) which form the conjugated chain; and we have

$$\chi_i = \sum_{p=1}^{m} c_{p\,i}\psi_p$$

If the molecule contains a number of π electrons equal to $2l$ ($l = n + 1$ for the previously considered conjugated aldehydes), the simplest way of making up the wave function describing the system in its ground state is to place two electrons of opposite spins in the l molecular orbitals χ_i, ordered according to increasing energy. Since m independent linear combinations can be made up with m functions of the basis set ψ_p the $(m - l)$ molecular orbitals not used in the ground-state wave function are still available; they can be used to describe excited states or to improve the wave function obtained for

the ground state by a configuration interaction treatment (cf. C.S., VI.F). In the configurational representation we have discussed so far, the coefficients c_{pi} of the occupied orbitals χ_i are determined by the variational calculation on the energy itself, but the numerical values of these coefficients depend upon the more or less elaborate form of theory used. In the semiempirical form of the molecular-orbital method, the energies e_i of the occupied orbitals χ_i and the corresponding coefficients c_{pi} are the first l eigenvalues and eigenvectors of a hamiltonian matrix $\mathbf{H}$; the elements of $\mathbf{H}$ are typical of the different atoms and the nondiagonal elements typical of the different bonds of the molecule.

The elements of $\mathbf{H}$ are usually written in the following form

$$\mathbf{H}_{pp} = \alpha + h_p\beta$$
$$\mathbf{H}_{pq} = k_{pq}\beta$$

where α and β respectively represent the diagonal and nondiagonal elements relative to an isolated bond taken as a standard[125,126]. The coulomb parameter h_p for the atom p is supposed greater when the orbital electronegativity of the atom p (for a $2p_x$ orbital) is higher in absolute value; according to valence-state tables[127], the electronegativities of carbon and oxygen atoms involved in a conjugated system are respectively equal to 6·0 ev and 10 ev so that oxygen is characterized by a positive h_O parameter. To evaluate the exchange parameter k_{CO} relative to the carbonyl bond, it is impossible to rely on the corresponding values of the overlap integrals; this criterion cannot be applied in the case of such a strong heteropolar bond as C=O[128]. If we assume that the exchange integral β represents approximatively the energy difference between a single bond and a double bond[129], we can write

$$k_{CO} = \frac{\beta_{CO}}{\beta_{CC}} = \frac{E_{C-O} - E_{C=O}}{E_{C-C} - E_{C=C}}$$

and this leads to a value of k higher than 1.

Since the first work on carbonyl compounds[130], in which h_O and k_{CO} were taken equal to +2, slightly different parameters have frequently been used. However, the results obtained by different authors do not differ essentially; they simply illustrate the fact that the carbonyl oxygen attracts the electrons to it ($h_O > 0$) and that the carbon–oxygen double bond is more strongly set in a conjugated system than the carbon–carbon double bond. This last point is in

agreement with the usual ideas. In addition to its empirical character this purely parametric molecular-orbital method presents more important deficiencies in the case of molecules with heteroatoms such as oxygen or nitrogen than it does in the case of hydrocarbons. It is not easy to modify the carbonyl-bond parameters in a systematic way in terms of the electronic structure variations of the π system in going from one compound to another. It is also not possible to improve the description of the molecule by adding electrons of a different type to the π electrons, as the n lone pair of the oxygen atoms, for example. As a matter of fact, the atomic orbitals $2p_x$ cannot combine with orbitals of a different symmetry, such as the orbitals of type $2p_y$ or σ, and the electrons are distributed among completely independent systems. To study such problems, the hamiltonian and the wave function effectively used must be specified and this fact introduces at the very beginning electron-repulsion terms that are very difficult to take into account in a completely empirical method. The carbonyl group has been studied non-empirically as a two-electron problem[131-133], and recently as a four-[122,123,134] and a six-electron[124] problem. Works on this subject are numerous, but a detailed discussion is more interesting for the sake of comparison of the approximations used than for the knowledge of the carbonyl bond itself.

If we consider only the π electrons of the conjugated chain and the oxygen n lone pair of a carbonyl compound, the wave function Ψ describing the electronic configuration of the ground state is an antisymmetrized product of molecular orbitals; this product can be written in the following form (cf. C.S., V.C)

$$\Psi = (N!)^{-\frac{1}{2}} \det \{\ldots \chi_l(N-3)\alpha(N-3)\, \chi_l(N-2)\beta(N-2)\, \chi_n(N-1)\alpha(N-1)\, \chi_n(N)\beta(N)\}$$

where N is the total number of electrons included in the calculation ($N = 2l + 2$) and χ_l and χ_n are the highest molecular orbitals occupied by the π electrons and by the oxygen lone pair respectively. The hamiltonian corresponding to the wave function Ψ is

$$\mathcal{H} = \sum_{\nu=1}^{N} \mathbf{H}^{\text{core}}(\nu) + \sum_{\mu<\nu}^{N} \frac{e^2}{r_{\mu\nu}}$$

where the operator $\mathbf{H}^{\text{core}}$ describes the electron motion in the field of the molecule stripped of the N electrons considered. If the principles of the self-consistent field theory are applied to the molecular-orbital theory[135], it is found that the coefficients c_{pi} are the eigenvectors of a

matrix equation. The full matrix **H** of this new system includes two terms: the first one corresponds to the operator $\mathbf{H}^{core}$ and has the same structure as in the semiempirical method, but with a slightly different physical meaning; the second one corresponds to the electrostatic repulsion terms of the molecular hamiltonian and depends upon the N-electron distribution among the different atoms. The electrons occupying molecular orbitals of different symmetry (π electrons and n lone pairs) interact through the second term of **H**, although the atomic orbitals of different symmetry do not combine with each other.

This by now classical method was applied by several authors to conjugated aldehydes and ketones, quinones, and other similar compounds[136-138]. It is difficult to compare these calculations, because different approximations are used to compute the electronic integrals included in the expression of the matrix elements $\mathbf{H}_{pq}$; however the general electronic structure description is the same in these different calculations and corroborates the results of the semiempirical method. Here, we only give the molecular orbitals obtained for the isolated carbonyl bond in a self-consistent treatment where the overlap of the carbon and oxygen $2p_x$ orbitals was included for the computations of the electronic integrals and of the orbital energies e_i[139]. The one-center electron repulsion integrals were estimated from spectroscopic data on the carbon and oxygen atoms and the two-center repulsion integrals were accordingly adjusted. The numerical values used for the coulomb energy of two electrons belonging to carbon or to oxygen are 9·87 ev and 13·66 ev respectively, and 12·19 ev for the interaction energy of one π and one n electron of oxygen. The core integrals α_C and α_O, which are the diagonal matrix elements of the operator $\mathbf{H}^{core}$, were determined by the usual processes using the ionization energies W^A_{2p} of the atoms A considered in the appropriate valence state; the core integral β_{CO} was written

$$\beta_{CO} = \tfrac{1}{2}S_{CO}(\chi_C + \chi_O) + \varepsilon_{CO}$$

where the corrective term ε_{CO} was estimated equal to -3.05 ev[140]. The molecular orbitals corresponding to the atomic-orbital basis used are given in Table 10. The n lone-pair orbital is χ_n and is completely localized on oxygen and χ_{π^*} is an additional orbital of type π and unoccupied in the ground state. According to a well-known property of the self-consistent field methods, the energy e_i of an occupied molecular orbital χ_i represents the energy quantity necessary to remove one electron from this orbital.

In a π-electron problem the expression for e_i contains one or several constants W^{A}_{2p} representing the energy of an isolated electron in a potential reduced to that created by the atom A in the molecule. These constants are known for the free atom in the appropriate valence state, but the values inferred from the atomic valence state tables are too large in absolute value by comparison with the molecular ionization potentials[137]. It is not necessary to know the constants W^{A}_{2p} in order to compute the molecular energies; it is sufficient to fix their relative position in an arbitrary energy scale using the free atom valence-state table for a basis (see Table 10). As has been seen in section II, the ionization potential, which is observed to be about 10 ev in unconjugated aldehydes and ketones, corresponds to the removal of an oxygen lone-pair electron.

TABLE 10. Molecular orbitals for π and n electrons of the carbonyl group.

Molecular orbitals	Orbital energies* (ev)
$\chi_{\pi^*} = 0{\cdot}905\psi_C(2p_z) - 0{\cdot}667\psi_O(2p_z)$	$e_{\pi^*} = \frac{1}{2}(W^C_z + W^O_z) + 14{\cdot}42$
$\chi_n = \psi_O(2p_y)$	$e_n = W^O_y + 1{\cdot}41$
$\chi_\pi = 0{\cdot}481\psi_C(2p_z) + 0{\cdot}779\psi_O(2p_z)$	$e_\pi = \frac{1}{2}(W^C_z + W^O_z) - 0{\cdot}63$

* $W^C_z = E(C, sppp) - E(C^+, spp)$ $W^O_z = E(O, s^2p^2pp) - E(O^+, s^2p^2p)$
$= W^C_z - 5{\cdot}67$ ev
$W^O_y = E(O, s^2p^2pp) - E(O^+, sppp)$ $= W^C_z - 3{\cdot}21$ ev

The values of Table 10 are in agreement with this interpretation and, in addition, they suggest that the ionization potential of the carbon–oxygen double-bond π electrons is equal to about 12·5 ev; in formaldehyde the experimental value of the second ionization potential which is usually assigned to the removal of a π electron, is 11.8 ev[18]. The shape of the π molecular orbital is the same as in the semiempirical method: the occupied orbital χ_π is polarized in the direction $C^+—O^-$, whereas the antibonding orbital χ_{π^*} is polarized in the opposite direction. Later we shall discuss this point several times.

Up to this point the ground state of the carbonyl bond was represented by a wave function formed only by the molecular orbital χ_π and the lone-pair orbital χ_n. With the additional orbital χ_{π^*}, some 'excited' configurations can be made up, which form with the fundamental configuration

$$\Psi_1 = (4!)^{-\frac{1}{2}} \det\{\chi_\pi(1)\alpha(1)\ \chi_\pi(2)\beta(2)\ \chi_n(3)\alpha(3)\ \chi_n(4)\beta(4)\}$$

a set of orthonormal functions, all with the same basis functions ψ. In order that a set of functions Ψ_i could represent the different stationary states of a system, it is necessary for the matrix of elements $\int \Psi_i^* \mathcal{H} \Psi_j d\tau$ to be diagonal, since it defines the possible energies of the system. In general the electronic configurations made up with a given basis of atomic orbitals do not verify this condition and thus it is possible to improve the description of the molecule by replacing the functions Ψ_i by linear combinations of the form

$$\Phi_t = \sum_i d_{it} \Psi_i$$

where the coefficients d_{it} of every Φ_t are the eigenvectors of the previous energy matrix. By this configuration interaction a limited set of wave functions Φ_t is obtained, for which the new energy matrix is diagonal.

The nine possible configurations for the carbonyl group considered as a four electron problem are gathered in Table 11. There are three excited configurations combining with the ground configuration Ψ_1. The three excited singlets of the same symmetry are Ψ_2, Ψ_3, and Ψ_5. With the electronic integrals used in this calculation, the carbonyl-group ground state appears as almost entirely made up of the lowest energy configuration Ψ_1.

The interest of this configuration-interaction calculation lies in using it as an intermediate for studying the carbonyl group by the valence-bond method. It is well known that the molecular-orbital method with configuration interaction and the valence-bond method with ionic structures are completely equivalent representations for an homopolar two-center problem such as the two $1s$ electrons of the hydrogen molecule or the two π electrons of ethylene. This can be extended to any molecular system, providing that the same basis of atomic orbitals and the same electronic integrals are used in both methods and providing that on one hand all the configurations and on the other hand all the ionic structures are taken into consideration. The equivalence of both methods is due to the fact that the set of configurations Ψ_i and the set of structures Ω_j are linked by a linear transformation T leading to the same eigenvalue problem[123]. In the present case the carbonyl-group wave function in the valence-bond method has the form

$$\Phi'_t = \sum_j d'_{jt} \Omega_j$$

where the Ω_j are the valence structures of Table 12.

TABLE 11. Configurations for the carbonyl group.

	Singlet configurations[a]	Symmetry[b]	Weight[c]	Triplet configurations[a]
Ψ_1	$\uparrow\downarrow$ / $\uparrow\downarrow$	A_1	0·988	
Ψ_2	$\uparrow\downarrow$ / $\uparrow\downarrow$	A_1	0·000	
Ψ_3	$\uparrow\downarrow$ / $\uparrow\downarrow$	A_1	0·011	
Ψ_4	$\downarrow\ \uparrow$ / $\uparrow\ \downarrow$ / $\uparrow\downarrow$ $-$ $\downarrow\ \uparrow$ / $\uparrow\downarrow$	A_2	0	Ψ'_4 $\downarrow\ \uparrow$ / $\uparrow\ \downarrow$ / $\uparrow\downarrow$ $+$ $\downarrow\ \uparrow$ / $\uparrow\downarrow$
Ψ_5	$\downarrow\ \uparrow$ / $\uparrow\downarrow$ / $\uparrow$ $-$ $\uparrow\ \downarrow$ / $\downarrow$	A_1	0·000	Ψ'_5 $\downarrow\ \uparrow$ / $\uparrow\downarrow$ / $\uparrow$ $+$ $\uparrow\ \downarrow$ / $\downarrow$
Ψ_6	$\uparrow\downarrow$ / $\downarrow$ $-$ $\uparrow\ \downarrow$ / $\uparrow$	A_2	0	Ψ'_6 $\uparrow\downarrow$ / $\downarrow$ $+$ $\uparrow\ \downarrow$ / $\uparrow$

[a] The upper arrows denote electrons with the spin function α and the lower ones electrons with the spin functions β.
[b] Symmetry species for the C_{2v} group.
[c] Normalized weights for the ground state.

By using the matrix transformation T, the ground configuration Ψ_1 is found to be a linear combination of Ω_j including only the normal covalent structure Ω_1 and the two opposite ionic structures Ω_2 and Ω_3; the same result is found for the configurations Ψ_3 and Ψ_5.

TABLE 12. Valence-bond structures for the carbonyl group.

	Singlet structures[a]	Symmetry	Weight[b]		Triplet structures[a]
Ω_1	$\dot{C}{=}\dot{O}$ (yy)	A_1	0·540	Ω_1'	$\dot{C}\cdots\dot{O}$ (yy)
Ω_2	$C^+{-}\ddot{O}^-$ (yy)	A_1	0·404		
Ω_3	$\ddot{C}^-{-}O^+$ (yy)	A_1	0·056		
Ω_4	$\ddot{C}^-{=}\dot{O}^+$ (y)	A_2	0	Ω_4'	$\ddot{C}^-\cdots O^+$ (y)
Ω_5	$\ddot{C}^-{-}\ddot{O}^+$	A_1	0·000		
Ω_6	$\dot{C}{=}\ddot{O}$ (y)	A_2	0	Ω_6'	$\dot{C}\cdots\ddot{O}$ (y)

[a] Straight lines between atoms denote singlet valence-bond wave functions of Heitler–London type (covalent structures); dotted lines denote the corresponding triplet functions.
A bold dot indicates an electron in a $2p_x$ atomic orbital; a small *y* indicates one in a $2p_y$ orbital (Zimmerman's notation, *Advan. Photochem.*, **1**, 183 (1963)).
[b] Normalized weights for the ground state, including the contributions of transitional structures.

The structure Ω_5, which has the same symmetry, is an ionic structure in which one electron of the oxygen lone pair is transferred toward the carbon $2p_x$ orbital and the other toward the oxygen $2p_x$ orbital. It is completely equivalent to the configuration Ψ_2 involving the excitation of the lone pair and does not make any appreciable contribution to the ground state configuration. The carbonyl bond can be represented by the superposition of the covalent and ionic structures C=O, $C^+{-}O^-$, and $C^-{-}O^+$, even if the lone pair is included in the calculation. The normal covalent structure contributes to the carbonyl bond with a weight of slightly more than 50%, but the actual charge on the oxygen atom is only about one-third *e* because the structure $C^-{-}O^+$ also contributes.

If the carbonyl-group dipole moment is computed and if the overlap moment due to the different sizes of the carbon and oxygen $2p_x$ orbitals is taken in account, a value of 2·23 D is obtained; this value corresponds to a charge transfer of 0·38*e* on to the oxygen. The same calculation carried out for the ground configuration Ψ_1 yields 2·38 D or a charge of 0·41*e*. Smaller values were obtained with

different approximations by several authors[133,134,141]. As has been seen in section II.A, the dipole moment of aldehydes and ketones is close to 2·5 D. This total moment includes not only the contribution of π electrons but also that of σ localized bond electrons and that of oxygen lone-pair electrons. In the works on unsaturated molecules the dipole moment of a compound is usually evaluated by vector addition of the calculated π moment and of the empirical σ bond moments; the value for the C—O σ bond is 1·1 D[142]. However, the σ-bond polarity of the carbonyl group is usually considered as negligible and the hybridization moment of the oxygen lone pairs is considered as the only important contribution coming from the localized electrons. This lone-pair contribution is estimated to equal about 1·5 D[133,134,141].

Even if the splitting of a dipole moment into several components is justified from an experimental point of view, it can be dangerous to add experimentally determined moments to a theoretical moment obtained in a π-electron problem; these former moments are only used to palliate the deficiencies of the theory. We will see in discussing the electronic structure of formaldehyde (section III.E) that such a practice for the carbonyl compounds seems rather dubious.

B. Excited States

The electronic spectrum of a molecule is formed by the set of stationary states satisfying the Schrödinger equation of the electronic system under consideration. Therefore the electronic transitions do not correspond to the jump of electrons from a level to another, but to the jump of the electronic system as a whole from one possible state to another under the influence of an external factor. In order to visualize the different excited states, however, it is convenient to adopt an independent particle model as in the atomic case; in such a model it is possible to define individual wave functions and individual electronic levels. All the electrons of a molecule are described by orthogonal molecular orbitals which are completely delocalized; these orbitals reflect the symmetry properties of the molecule. Thus it is not possible to keep wholly the concept of σ electrons localized on particular bonds; but the total wave function so defined can be submitted to linear transformations restoring the optimum localization degree. The ground state of the system is obtained by filling the orbitals in the natural order of their energies; the excited states are obtained by leaving vacant some of these orbitals occupied in the ground state and by filling higher energy orbitals.

As an atomic orbital occupied by an electron of given spin is characterized by four quantum numbers (n, l, m_l, m_s), four indices (η, λ, μ, σ) would have to be assigned to every molecular orbital of a given electronic configuration. The last index, σ, would specify the nature of the spin function, α or β, associated with the electron, the second and the third ones, λ and μ, would characterize the symmetry properties of the considered orbital, and finally the first index, η, would simply be a number used to distinguish orbitals of the same symmetry. But since for one energy level it is possible to place two electrons of opposite spins in a space orbital χ, it is useless to specify the index σ if the orbital χ is doubly occupied and it is superfluous if the orbital χ is occupied by one electron, because the value of σ can be determined from the total spin of the system. Likewise it is useless to specify the index μ in the case of a nondegenerate level, since the index μ is connected to the degree of degeneracy of a level e; in the case of a degenerate level it is superfluous, because the level e is associated with a family of orbitals χ_μ transforming into each other by the symmetry operations. For instance, the molecular orbitals of the two equivalent groups of π electrons in linear molecules as CO_2 or C_2H_2 differ from each other only by the factor $\exp(\pm i\phi)$ and form the basis vectors of a representation of dimension two in the group $D_{\infty h}$ or $C_{\infty v}$ (representation Π). Thus the nature of the occupied levels can be specified by the symbol $(\eta\lambda)^n$ where n is the number of electrons placed in a given level e of multiplicity m ($n \leqslant 2m$). The complete spectroscopic notation[143] identifies the index λ with the symbol of the irreducible representation to which the orbitals χ belong in the symmetry group of the whole molecule. Thus the geometry of formaldehyde (see section II.A), at least for the ground state, has the symmetry elements of the group C_{2v}; the wave function Ψ of the system of sixteen electrons is totally symmetrical and belongs to the representation A_1 of C_{2v} but the individual electrons have for wave functions orbitals χ of species A_1, B_1, or B_2. These molecular orbitals χ are characterized by taking the corresponding lower-case letter a_1, b_1 or b_2. The totally symmetrical molecular orbitals a_1 are occupied by electrons usually assigned to the bonds of the formaldehyde skeleton. The molecular orbitals b_2 are also symmetrical with respect to the molecular plane but they are antisymmetrical with respect to the perpendicular plane containing the C—O axis; they represent the hyperconjugation of the CH_2 group with the n lone pair of oxygen and the highest orbital ($2b_2$) is mainly formed by the $2p_y$ orbital of oxygen. The molecular orbitals

b_1 are antisymmetrical with respect to the molecular plane and the π electrons of the carbonyl bond are placed in them. If the inner $1s$ electrons of carbon and oxygen are neglected, the ground state of formaldehyde may be written

$$\ldots\ (1a_1)^2\ (2a_1)^2\ (1b_2)^2\ (3a_1)^2\ (1b_1)^2\ (2b_2)^2 \qquad {}^1A_1$$

The first excited states of the molecules are obtained by completing the set of molecular orbitals of the ground state with molecular orbitals of higher energy, which are made up with the same atomic orbitals, and among which the outer electrons of the molecule can be distributed. In the unsaturated hydrocarbons these transitions which do not entail any change of the principal quantum number of the basic atomic orbitals involve the highest bonding and the lowest antibonding molecular orbitals of the π electrons. The carbonyl compounds have both π electrons and lone-pair electrons and the $2p_y$ lone pair of the heteroatom has higher energy than the π electrons; one can anticipate transitions where one of the oxygen $2p_y$ electrons is shifted toward one of the antibonding molecular orbitals (σ or π) of the carbonyl group. If we disregard the possibility of geometrical deformation at this point, the lowest excited states of formaldehyde are the triplets and the singlets obtained after these three types of excitation

$$\ldots\ (1a_1)^2\ (2a_1)^2\ (1b_2)^2\ (3a_1)^2\ (1b_1)^2\ (2b_2)\ \ (2b_1) \qquad {}^{1,3}A_2$$
$$\ldots\ (1a_1)^2\ (2a_1)^2\ (1b_2)^2\ (3a_1)^2\ (1b_1)^2\ (2b_2)\ \ (4a_1) \qquad {}^{1,3}B_2$$
$$\ldots\ (1a_1)^2\ (2a_1)^2\ (1b_2)^2\ (3a_1)^2\ (1b_1)\ \ (2b_2)^2\ (2b_1) \qquad {}^{1,3}A_1$$

where $(2b_1)$ and $(4a_1)$ are π and σ orbitals with a node between carbon and oxygen. As we will see later, the transitions to these excited states can be identified in carbonyl-compound spectra, even if the molecule does not possess the same symmetry elements as formaldehyde (see also section II.B). The possibility of a Rydberg transition in which one of the oxygen $2p_y$ electrons is excited to a Rydberg orbital similar to a $3s$ orbital of the oxygen atom cannot be left out; but it is not easy to distinguish by experiments as well as by theory between a state such as

$$\ldots\ (1a_1)^2\ (2a_1)^2\ (1b_2)^2\ (3a_1)^2\ (1b_1)^2\ (2b_1)\ (3s_0)$$

and the A_1 state formed by the antibonding σ orbital of the carbonyl bond[90,120].

In the former description we have a configurational model where

the wave function is given by the product of the molecular orbitals occupied in each state, but no restrictive relation between the molecular orbitals of the different excited states has been assumed. If we now suppose that the initial and final states considered are described by molecular orbitals belonging to the same set of orthonormal monoelectronic functions, in order to define completely the problem from a theoretical point of view, it is enough to quote the molecular orbitals whose number of electrons change during the transition. Instead of keeping the group theory terms (implying that the molecular geometry is known), the molecular orbitals are described by the symbols n, π, π^*, σ, σ^*; these symbols represent the lone-pair orbital of the heteroatom, and the highest occupied and the lowest unoccupied π or σ orbitals, respectively. In these conditions the notations for the first transitions of formaldehyde are

$2b_2$–$2b_1$	or	n–π^*	singlet and triplet
$2b_2$–$4a_1$	or	n–σ^*	singlet and triplet
$1b_1$–$2b_1$	or	π–π^*	singlet and triplet

In the experimentally important transitions involving the lone pairs[41,44,144] it is now usual, particularly in photochemistry, to designate the different transitions and the corresponding chemical processes by the symbols n–π^* and n–σ^*. The recommended spectroscopic notations are N–Q for the lone-pair transitions, called also N–A in the first case (n–π^*) and N–B in the second case ($n\rightarrow\sigma^*$), and N–V for the $\pi\rightarrow\pi^*$ transitions[143].

If the possible changes of geometry are not taken in account, the transition intensity from the ground state to the different excited singlet states is given by the selection rules of the symmetry group to which the molecule belongs. For the C_{2v} group, the $n\rightarrow\pi^*$ transition is forbidden, the $n\rightarrow\sigma^*$ transition is allowed and polarized in the molecular plane in the direction of an axis perpendicular to the C=O bond, and the $\pi\rightarrow\pi^*$ transition is allowed and polarized in the C=O direction. Instead of considering the total molecular symmetry, which is not the same for all carbonyl compounds and can vary with the excitation, it would be more convenient to connect the electronic transition characteristics to the shape of the concerned molecular orbitals (Figure 5). Thus the local symmetry of the carbonyl group can be used, and this is indeed the most useful factor for the identification of transitions[74,144]. In an $n\rightarrow\pi^*$ or $n\rightarrow\sigma^*$ transition, the electron is almost entirely localized on the oxygen atom at the starting point; the only appreciable contribution to the transition moment comes

from the oxygen-atom orbitals appearing in the initial and final molecular orbitals. According to the atomic selection rules, the transition is allowed if there is a change in the quantum number l of the oxygen atomic orbitals in the transition. For an n lone pair localized on a pure $2p_y$ orbital, the final molecular orbital must have an s component on the oxygen atom. This is possible in the case of the σ^* orbital but not in the case of the π^* orbital. However, it can

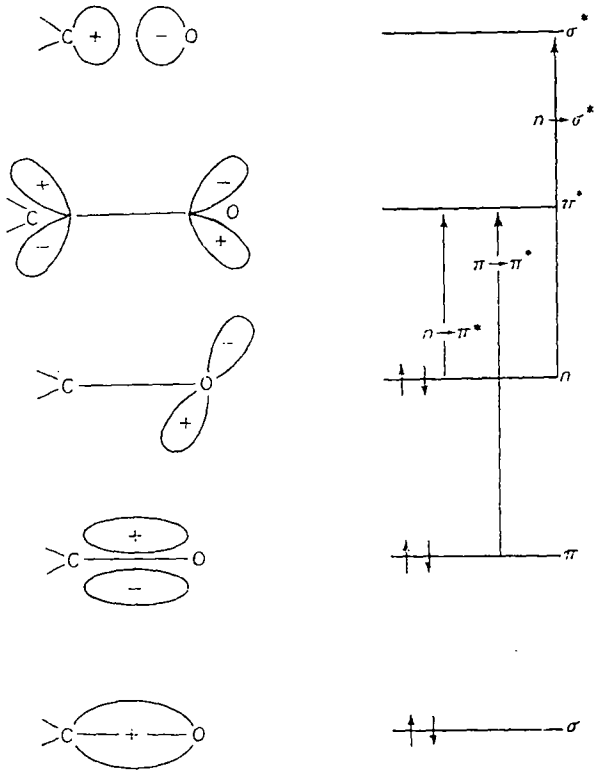


FIGURE 5. Molecular orbitals in a carbonyl bond.

happen that the n lone pair forms a single molecular orbital with some atomic orbitals whose transition moment with double-bond $2p_x$ orbitals is not equal to zero. This can occur for instance under the effect of geometric distortions caused by the substituents R of the carbonyl group. Such a transition is not forbidden at the level of the carbonyl group, except in the cases of absolute prohibition enforced by the symmetry group to which the whole molecule belongs. If we are not considering this last case, the transition moment is different

from zero, but as the molecular orbitals have very different shape the electronic transition intensity remains low.

To emphasize the influence of the local conditions on the n electron transition intensity, the excited states corresponding to an $n\rightarrow\pi^*$ or $n\rightarrow\sigma^*$ transition allowed by the local symmetry of the carbonyl group are sometimes assigned the symbol W (W for allowed) and those corresponding to a locally forbidden transition are assigned the symbol U (U for unallowed). Thus the $n\rightarrow\pi^*$ transition from the ground state A_1 to the first singlet state A_2 of formaldehyde is called $^1U\leftarrow{}^1A_1$, and the $n\rightarrow\sigma^*$ transition from the ground state to the first singlet state B_2 is called $^1W\leftarrow{}^1A_1$. In the case of triplet upper states the transitions are called $^3U\leftarrow{}^1A_1$ and $^3W\leftarrow{}^1A_1$[144].

As it has been pointed out before (section II.B), the transitions of the n electrons of oxygen atom are the ones observed at the longest wavelengths in the spectrum of molecules containing a carbonyl group: the $n\rightarrow\pi^*$ transition is responsible for the region of low intensity at the long wavelengths and the $n\rightarrow\sigma^*$ transition is responsible for the region of higher absorption at the end of the ordinary ultraviolet spectrum. The $\pi\rightarrow\pi^*$ transition involving the excitation of the carbon–oxygen double bond is located in the far ultraviolet; the intensity is not determined any more by the characteristics of the atomic orbitals but by the shapes of the bonding and antibonding molecular orbitals describing the states of the π electrons of the carbonyl bond.

When an ethylenic grouping and the carbonyl group are conugated, the energy levels of the n and σ^* localized orbitals do not vary much but the same conjugation shifts the levels of the electrons assigned to the π and π^* orbitals closer to each other. The result is that the $\pi\rightarrow\pi^*$ transition is shifted very clearly toward the red and is located very close to the $n\rightarrow\pi^*$ transition, whereas the $n\rightarrow\sigma^*$ transition remains in the same spectral region[145]. We will discuss only the $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ transitions that are of most importance in photochemistry.

We have seen in section III.A that the system formed by the two $2p_x$ orbitals of the carbon–oxygen double bond and the $2p_y$ orbital of the oxygen atom gives four configurations of symmetry A_1 and two configurations of symmetry A_2 for the possible singlet states of the carbonyl group considered as a four-electron problem. It gives also one configuration of symmetry A_1 and two configurations of symmetry A_2 for the triplet states (see Table 11). If a single configuration is only taken to represent the excited states of the system, the

wave function of the first excited state of symmetry A_2 will be given by

$$^{1,3}\Psi_4 = 2^{-\frac{1}{2}}(4!)^{-\frac{1}{2}}[\det\{\chi_\pi(1)\alpha(1)\ \chi_\pi(2)\beta(2)\ \chi_n(3)\alpha(3)\ \chi_{\pi^*}(4)\beta(4)\} \pm \det\{\chi_\pi(1)\alpha(1)\ \chi_\pi(2)\beta(2)\ \chi_n(3)\beta(3)\ \chi_{\pi^*}(4)\alpha(4)\}]$$

with the negative sign for the singlet state and the positive sign for the triplet state. In the same way the wave function of the lowest excited state of symmetry A_1 will be

$$^{1,3}\Psi_5 = 2^{-\frac{1}{2}}(4!)^{-\frac{1}{2}}[\det\{\chi_\pi(1)\alpha(1)\ \chi_n(2)\alpha(2)\ \chi_n(3)\beta(3)\ \chi_{\pi^*}(4)\beta(4)\} \pm \det\{\chi_\pi(1)\beta(1)\ \chi_n(2)\alpha(2)\ \chi_n(3)\beta(3)\ \chi_{\pi^*}(4)\alpha(4)\}]$$

By keeping the carbon–oxygen internuclear distance and the electronic integrals of the ground state to compute the excited states, the first triplet and singlet A_2 states are found 4·03 and 4·51 ev higher than the ground state, while the region of low intensity assigned to the $n\rightarrow\pi^*$ transition is located at about 2900 Å (4·3 ev) in the absorption spectra of saturated ketones. The first excited triplet state of symmetry A_1 is 5·20 ev above the ground state and the corresponding singlet is at 8·49 ev; these results are in good agreement with the position of the region of high absorption which arises from the $\pi\rightarrow\pi^*$ transition in the far ultraviolet. It is interesting to note the very different order of magnitude of the singlet–triplet separation in the two types of transition. The small value obtained for the $n\rightarrow\pi^*$ transition comes from the very different shapes of the molecular orbitals involved in the excitation and more precisely it is due to the fact that the n and π^* orbitals are formed by atomic orbitals pointing in perpendicular directions. In such a case the variation of energy due to the change of the total spin of the two electrons occupying the n orbital before the transition (twice the exchange integral $K_{n\pi^*}$) is necessarily small[74,146]. On the contrary, the singlet–triplet separation obtained for the $\pi\rightarrow\pi^*$ transition is rather important, since the molecular orbitals point in the same direction; its value is near to that observed for ethylene, 3·0 ev[49].

In quantum methods where the two-electron interaction integrals are approximated by values obtained from atomic spectroscopy, the energy of the excited states in the two equivalent treatments, i.e. configuration interaction and valence bond, is not very different from the values obtained by a simple configurational representation (Table 13). The $n\rightarrow\pi^*$ transition is now equal to 3·99 ev for the triplet and 4·22 ev for the singlet and thus the separation $^3A_2$–$^1A_2$ is reduced to 0·2 ev. The transition $\pi\rightarrow\pi^*$ does not vary much: 5·46 ev for the triplet, 8·41 ev for the singlet or a $^3A_1$–$^1A_1$ separation

of about 3 ev. On the other hand, the description of the excited states is slightly different, particularly for the polarity of the singlet and triplet states deriving from the same configuration (Table 14). In the excited state A_2, the carbonyl group must be considered as formed by a three-electron π bond, essentially covalent, and one n electron localized on the oxygen atom; a mixed ionic–covalent structure such as $\ddot{C}^- = \underset{y}{\dot{O}}^+$ shifts the charges in an opposite direction to the polarity of the ground state; and this shift is more important for the triplet

TABLE 13. Excited states of the carbonyl group.

	Configurations[a]		Structures[b]		Energies[c]
		Weight		Weight	(ev)
Ground state	see Table 11		see Table 12		−0·18
$^3A_2$	Ψ'_4	0·974	Ω'_4	0·179	3·82
	Ψ'_6	0·026	Ω'_6	0·821	
$^1A_2$	Ψ_4	0·951	Ω_4	0·135	4·05
	Ψ_6	0·049	Ω_6	0·865	
$^3A_1$	Ψ_5	1	Ω'_1	1	5·29
$^1A_1$	Ψ_1	0·001	Ω_1	0·201	8·23
	Ψ_2	0·006	Ω_2	0·523	
	Ψ_3	0·030	Ω_3	0·269	
	Ψ_5	0·963	Ω_5	0·006	

[a] Notations in Table 11.
[b] Notations in Table 12.
[c] With respect to the energy of the ground configuration.

state than for the singlet state. This nature of a three-electron bond is in harmony with the decrease of the carbonyl bond strength constant: $6{\cdot}29 \times 10^5$ dyn/cm instead of $11{\cdot}72 \times 10^5$ [147] and in harmony with the smaller value of the dipole moment in the $^1A_2$ excited state of formaldehyde (1·48 D) than in the ground state (2·34 D) [64]. But owing to the influence of the σ electrons on these physical properties, it would be very difficult to compare these experimental data with numerical values obtained in a treatment limited to the n and π electrons.

In the first excited state A_1 of the same symmetry as the ground

state, an important difference between the triplet and the singlet is established. The electron system of the carbonyl group in the triplet state $^3A_1$ is almost neutral, for it is described by one structure of covalent type $\dot{C}{=}\dot{O}$ (yy). On the other hand in the singlet excited state $^1A_1$ this electron system has a polarity similar to that of the ground state $^1A_1$; this polarity is only slightly reduced owing to the smaller importance of the structure $C^+—\ddot{O}^-$ (yy).

TABLE 14. Charge distribution in excited states of the carbonyl group.

	Self-consistent field method		Configuration-interaction or valence-bond method	
	Net charges	Dipole moment in D	Net charges	Dipole moment in D[a]
Ground state	$C^+—O^-$ $\pm 0{\cdot}41$	2·38	$C^+—O^-$ $\pm 0{\cdot}38$	2·23
$^3A_2$	$C^-—O^+$ $\mp 0{\cdot}31$	1·78	$C^-—O^+$ $\mp 0{\cdot}17$	0·98
$^1A_2$	$C^-—O^+$ $\mp 0{\cdot}31$	1·78	$C^-—O^+$ $\mp 0{\cdot}13$	0·73
$^3A_1$	$C^-—O^+$ $\mp 0{\cdot}01$	0·06	$C^-—O^+$ $\mp 0{\cdot}01$	0·06
$^1A_1$	$C^-—O^+$ $\mp 0{\cdot}01$	0·06	$C^+—O^-$ $\pm 0{\cdot}24$	1·37

[a] Found by taking the same internuclear distance (CO = 1·21 Å) for the ground state and all excited states.

There is no difference between the singlet and the triplet states in the simple configurational representation of the self-consistent field (SCF) method, because the function Ψ_5 assigns equal weights to the former two ionic structures whatever may be the molecular orbital coefficients; hence for the calculation of the charges there is just a contribution of the only covalent structure $\dot{C}{=}\dot{O}$ (yy). Although the function Ψ_5 gives a reasonable value for the transition energy $^1A_1$–$^1A_1$, it gives a rather bad description of the first excited state $^1A_1$. It seems to us that this result must be kept in mind for the

theoretical interpretation of the photochemical reactions involving the $\pi \rightarrow \pi^*$ transition.

C. Electronic Structures of Conjugated Carbonyl Compounds

The interaction between a carbonyl group and an unsaturated residue R directly attached to it is usually considered as an interaction of donor–acceptor type involving the π electrons of the molecule. The group R acts as the electron donor and the carbonyl bond as the electron acceptor in consequence of the electron delocalization. If R does not possess heteroatoms having lone pairs conjugated with the carbonyl bond, the acceptor character of the carbonyl grouping can be entirely attributed to the larger electronegativity of the oxygen atom; for there would be no intramolecular charge transfers according to the semiempirical molecular-orbital method (at least in absence of odd conjugated cycles) if all the atoms could be characterized by the same coulomb parameter α. We will only discuss here the cases where R is a system of conjugated double bonds or an aromatic ring, disregarding the case where R forms a single functional group with the carbonyl bond. When a conjugated residue R is fixed to a carbon–oxygen double bond, some physicochemical properties undergo significant changes. Thus from formaldehyde to acrolein the ionization potential decreases by 0·63 ev and the carbonyl stretching vibration by 44 cm^{-1}, whereas the dipole moment increases by 0·77 D[148].

All these properties are explained by showing an increase of the carbonyl-bond polarity as a result of conjugation. Indeed the ionization of one oxygen n electron depends upon the electrostatic repulsion between the lone pair and the π-electron cloud and is made easier by a π-charge accumulation on the oxygen. In the same way the decrease of the carbonyl stretching vibration is explained in resonance language by an enlarged contribution of ionic structures, e.g.

$$C{=}C{-}C{=}O \longleftrightarrow \overset{+}{C}{-}C{=}C{-}\overset{-}{O}$$

Such a purely descriptive explanation does not say anything about the nature or the magnitude of the observed physical effects. By taking as an example the variations of the carbonyl stretching vibration in carbonyl compounds, we would like to emphasize the necessity of analyzing the molecular properties in terms of physical quantities effectively related to them in the frame of the approximate method taken for the calculation.

In the theory of normal vibrational modes the vibration frequencies of a polyatomic molecule are given by

$$\nu_j = \frac{1}{2\pi} (\lambda_j)^{\frac{1}{2}}$$

where the λ_j are the eigenvalues of the Wilson **FG** matrix. The matrices **F** and **G** represent the potential energy and the kinetic energy of the molecule vibrating in the normal coordinate system and respectively depend upon the restoring and coupling forces between the different oscillators and on the reciprocal of the mass of these oscillators. In principle any stretching vibration depends upon the set of force and coupling constants and on the set of masses of the atoms forming the molecule. However, it is sometimes possible to simplify the problem as, e.g. in the cases of the C=O or N—O bonds.

The study of the infrared and Raman spectra of compounds of type $R^1R^2C{=}O$ suggests that the characteristic frequency of the carbonyl group located around 1700 cm^{-1} represents to a first approximation the vibration of a system of reduced mass μ under the effect of a simple restoring force proportional to the force constant of the carbonyl bond

$$(\mathbf{FG})_{CO} = \frac{K}{\mu} = \lambda$$

where λ is the only term of the **FG** matrix in this case; and we have

$$\nu = \frac{1}{2\pi}\left(\frac{K}{\mu}\right)^{\frac{1}{2}}$$

Furthermore, for a given type of bond (e.g. in aldehydes, ketones, or esters) ν does not depend much upon the masses of substituents, so that the reduced mass μ can be considered as an effective constant. Under these conditions the variations of the carbonyl frequency in a series of related compounds must be assigned to electronic perturbations having an effect on the force constant K of the carbonyl bond; then we will have

$$\nu = \nu_0\left(\frac{K}{K_0}\right)^{\frac{1}{2}}$$

where K and K_0 are the force constants of the compound studied and of a reference compound, and ν and ν_0 the corresponding frequencies. As a matter of fact, the carbonyl vibration is not completely independent of the rest of the molecule, but the contribution of the

different couplings to the observed frequency can be calculated by a perturbation procedure providing that the force constant K_{CO}[149] is given. In practice it can be more than enough to estimate the effect of the couplings in comparison with a pattern whose structural parameters are fixed. If the carbonyl vibration of the saturated ketones (ν = 1706 cm^{-1}) is taken as a standard, the effect of the vibroperturbations $\Delta\nu$ is found to be an increase or a decrease of the carbonyl frequency depending upon the case considered (Table 15).

The importance of the vibrational perturbations is illustrated by the typical example of the saturated cycloalkanones, e.g. cyclobutanone. In this compound the abnormally high value of the

TABLE 15. Effect of the vibroperturbations $\Delta\nu$[149].

Compounds	$\Delta\nu$ (cm^{-1})	$\nu_{C=O}$ (cm^{-1})	$k_{C=O}$ (10^5 dyn/cm)
Saturated ketones	0	1705–1725	10·0–10·3
Conjugated ketones	+11	1650–1700	9·0–9·8
Cyclobutanone	+46	1775	10·3
Aldehydes	−17	1720–1740	10·6–10·9
o-Quinones	*sym-* +61 *asym-* −26	1660–1690	9·7–10·1
p-Quinones	−10	1660–1690	9·5–9·9

carbonyl frequency is mainly due to the coupling of the C=O group with the adjacent C—C bonds. This perturbation is a decreasing function of the angle (OC)$\widehat{CC}$ and an almost purely mechanical explanation must be given for the decrease of the carbonyl frequency in the higher cyclanones. In a general way the vibrational effects come mainly from the coupling between the motions of the carbonyl group and those of the surrounding atoms. This fact explains that the carbonyl bond might be considered as an apparently isolated oscillator and that it is possible to ascribe the carbonyl frequency changes to variations of the force constant $K_{C=O}$ of an electronic nature, provided one remains within a homogeneous series of compounds.

The resonance theory, in a qualitative way, explains the lowering of the force constant $K_{C=O}$ in the conjugated aldehydes and ketones by the decrease of the double bond character and by the resulting

charge increase on oxygen[150]. In the molecular-orbital method without overlap, the corresponding quantities are

$$p_{CO} = 2 \sum_{i}^{occ} c_{1i}c_{2i} \qquad q_O = 2 \sum_{i}^{occ} c_{1i}^2$$

where the summation is taken over the squares or over the products of the coefficients relative to the orbitals of oxygen (c_{1i}) or of the adjacent carbon (c_{2i}) in the occupied molecular orbitals.

The analysis of the problem in the frame of the semiempirical molecular-orbital method shows that the force constant $K_{C=O}$ does not depend upon the oxygen charge q_O (in π electrons), but first of all depends upon the carbonyl mobile bond order p_{CO}[151,152]. In fact the complete expression of the force constant K_{ab} of a conjugated bond between two atoms A and B contains two terms

$$K_{ab} = [K_s(1 - p_{ab}) + K_d p_{ab}] + \left[\frac{K_s K_d(s - d)}{K_s(1 - p_{ab}) + K_d p_{ab}}\right]^2 \times \frac{\pi_{ab,ab}}{2}$$

where p_{ab} and $\pi_{ab,ab}$ are the π-bond order and the autopolarizability of the considered bond, and s and K_s, d and K_d constants representing the length and the force constant of a purely single bond ($p_{ab} = 0$) and of a purely double bond ($p_{ab} = 1$) between the atoms A and B[153]. The bond order p_{ab} and the autopolarizability $\pi_{ab,ab}$ are half the first derivative and half the second derivative of the total energy of the π electrons with respect to the exchange integral β_{ab}, respectively; as K_{ab} is the second derivative of the energy with respect to the equilibrium distance between atoms A and B, they both appear in the expression of the force constants. However, in the particular case of the carbonyl bond the second term brings a negative contribution not exceeding 4% of the total force constant; since the bond order p_{CO} remains close to its maximum value, owing to the fact that the carbonyl bonds are not very delocalized, consequently the autopolarizability π_{CO} remains very small[128]. If the self-consistent field method is used to determine the molecular orbitals, the theoretical expression of the force constants keeps the same structure as in the semiempirical method: the first term is a function of the bond order and plays a leading part for the very localized bonds[138]. But it must be noted that this first term in addition includes a function of the electron repulsion integrals representing long-range forces.

The theoretical data obtained by the molecular-orbital method for a series of conjugated aldehydes and ketones are given in Table 16 with $K_{CO} = 10{\cdot}7 \times 10^5$ dyn/cm for the isolated carbonyl group-

ing[149]. Figure 6 shows that there exists a rather good linear relationship between the experimental infrared frequencies ν_{CO} and the square root of theoretical force constants in agreement with the approximation of the independent C=O oscillator; but it must be noticed that the straight line representing ketones is lower than that of aldehydes and particularly that the point for formaldehyde is far from the aldehyde line. This shift must be ascribed to the electronic effect of the alkyl groups on the constant K_{CO}, because that is the same in the force constants assigned to the saturated compounds

TABLE 16. Theoretical force constants K_{CO} for conjugated carbonyl compounds.

Compound	q_O	p_{CO}	$-\pi_{CO}/\beta$	K_{CO}
(1) Carbonyl group	1·287[a]	0·958[a]	0·048[b]	10·37[b]
(2) Glyoxal	1·266	0·937	0·044	10·25
(3) Benzaldehyde	1·317	0·905	0·076	10·00
(4) Acrolein	1·323	0·895	0·085	9·93
(5) Benzophenone	1·346	0·857	0·105	9·66
(6) Perinaphthenone	1·384	0·820	0·146	9·35
(7) Cyclopentadienone	1·214	0·895	0·063	9·97
(8) Fluorenone	1·308	0·871	0·092	9·77
(9) 1,2;7,8-Dibenzofluorenone	1·300	0·869	0·097	9·75
(10) Tropone	1·459	0·779	0·172	9·03
(11) 4,5-Benzotropone	1·424	0·799	0·157	9·19
(12) 2,3;6,7-Dibenzotropone	1·376	0·834	0·128	9·47
(13) *o*-Benzoquinone	1·283	0·879	0·090	9·82
(14) *p*-Benzoquinone	1·307	0·856	0·104	9·66

[a] Parameters for carbonyl groups: $\alpha_O = \alpha + 1{\cdot}2\beta$, $\beta_{CO} = 2\beta$.
[b] Calculated with $\beta = 3 \times 10^{12}$ erg and the constants of ref. 149,

$s = 1{\cdot}43$ Å $\quad K_s = 5 \times 10^5$ dyn/cm
$d = 1{\cdot}22$ Å $\quad K_d = 10{\cdot}7 \times 10^5$ dyn/cm

themselves: the analysis of the vibration spectrum with a rather simple potential function leads to a value of $10{\cdot}2 \times 10^5$ dyn/cm for the unconjugated ketones[154], against $11{\cdot}72 \times 10^5$ for formaldehyde[147]. On the whole, the carbonyl frequency decreases when the size of the conjugated system increases, except for tropones and some series of quinones (not discussed here)[128,154]. The calculation gives only an account of the essential properties of the cyclic conjugated ketones: a very low carbonyl frequency is associated with a large polarity in the cycloheptatrienones (tropones) and a very high frequency and a lowered polarity with cyclopentadienones (fluorenones)[155]; but the numerical agreement with experiment is much less

good than in the usual compounds. The abnormally high value of ν_{CO} in fluorenone must be compared with the frequency increase by a vibrational effect that we found previously in the saturated homologs (cyclopentanone). But another explanation must be found for the augmentation of tropone frequencies (influence of electron repulsion terms, of the σ skeleton, etc.) because the vibrational perturbations in cyclohexanone and cycloheptanone create an effect in the

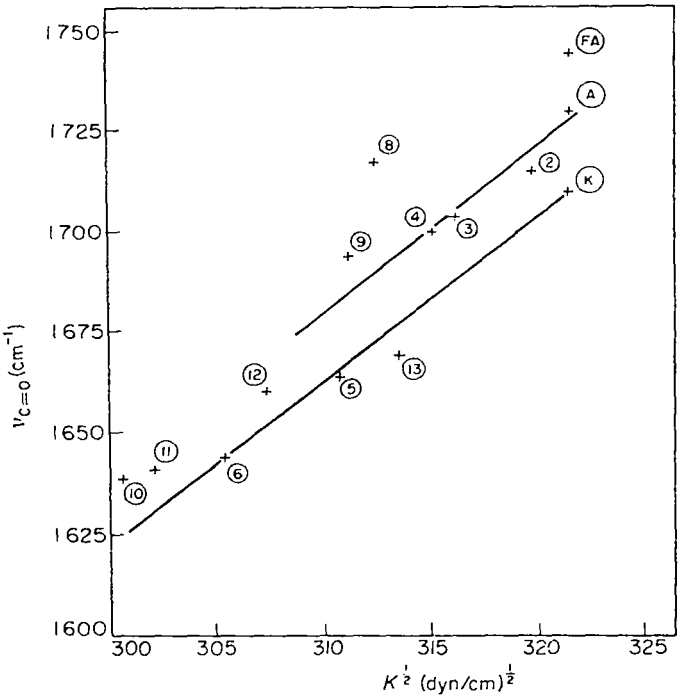


FIGURE 6. Experimental infrared frequencies *versus* force constants. (Numbers refer to compounds in Table 16; FA = formaldehyde, A = aldehydes, K = ketones.)

opposite direction. The theory is also deficient in the case of fluorenones; a variation of ν_{CO} is observed on going from fluorenone to dibenzofluorenone[155], but the calculated force constant remains almost unchanged, because the addition of distant benzene rings is almost without effect on the bond order of the carbonyl in the middle of the molecule. Similar facts have been reported for quinones[156] and the agreement with experiment was improved by modifying the exchange integrals in function of the interatomic

distances[157]. It is tempting to ascribe these variations to the long-range forces completely neglected in the usual molecular-orbital method.

It is hardly possible to apply the nonempirical methods of quantum chemistry to conjugated aldehydes and ketones, even if only the π electron systems are considered. By using the configurational approximation of the self-consistent field theory it has been possible to improve the calculation of π-electron molecular orbitals, but only with very drastic simplifications in the estimation of the electron repulsion terms[137,138]. The problem of the conjugation of the carbonyl group with an unsaturated residue R (C=C double bond or a heteroatom with a lone pair) was tackled by a simplified configuration-interaction method where the choice of the important

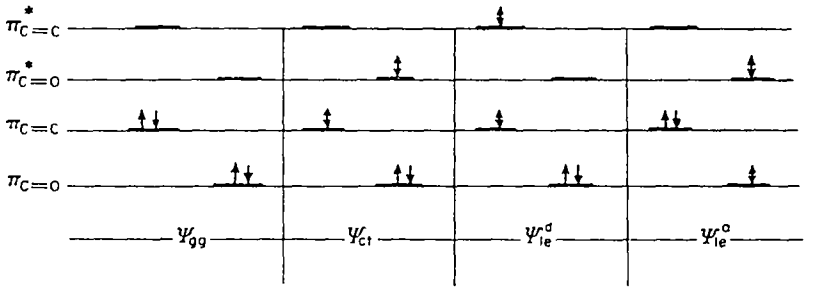


FIGURE 7. Electron configurations for acrolein. A double arrow means that the unpaired electrons have unspecified coupled spins, i.e. $2^{-\frac{1}{2}}(\alpha\beta - \beta\alpha)$ for singlet states.

configurations is made according to the physical nature of the problem as in the valence-bond method[158]. The theoretical treatment is based upon the composite system formalism[159,160] and uses the fact that the system C=C—C=O can be separated into one electron-donor group, the C=C double bond, and one electron-acceptor, the carbonyl group. The total wave function Φ of the π electrons of acrolein is represented by the superposition of the four configurations of Figure 7. Each configuration is the antisymmetrized product of the molecular orbitals occupied by the four electrons of the system, the spin degeneracy of the excited configurations being taken into account. The ground configuration Ψ_{gg} is simply the juxtaposition of the ground configurations of the two bonds. The charge transfer configuration Ψ_{ct} indicates the donor character of the C=C double bond and the acceptor character of the carbonyl. The locally excited

configurations Ψ_{le}^{d} or Ψ_{le}^{a} correspond to an electron excitation inside the donor group C=C or inside the acceptor group C=O. If the energy of the ground configuration Ψ_{gg} is taken as the zero point, the diagonal elements of the energy matrix constructed from the function Ψ can be approximated by the energy variation necessary to reach the physical state to which the excited configurations correspond. Thus the energy of the locally excited configurations is represented by the energy of the first absorption band $\pi-\pi^*$ of ethylene and of formaldehyde: 7·6 ev for Ψ_{le}^{d} and 7·9 ev for Ψ_{le}^{a}. The energy of the charge transfer configuration Ψ_{ct} will have an expression of the form

$$E_{ct} = I_d - A_a - C_e = 6{\cdot}4 \text{ ev}$$

where I_d is the donor ionization potential (10·5 ev for ethylene), A_a is the acceptor electroaffinity (assumed as being equal to $-1{\cdot}2$ ev

TABLE 17. π states of acrolein.

	Normalized weight of each singlet configuration			
	Ground state	First excited state	Second excited state	Third excited state
Ψ_{gg}	0·954	0·038	0·001	0·008
Ψ_{ct}	0·045	0·656	0·016	0·280
Ψ_{le}^{d}	0·0007	0·235	0·410	0·360
Ψ_{le}^{a}	0·0003	0·071	0·573	0·352
ΔE^a	0	6·23	8·10	8·81
Exp[b]		6·32	8·35 and 8·46	

[a] Excitation energies in ev according to ref. 158.
[b] $\pi \rightarrow \pi^*$ transitions according to ref. 145.

for the carbonyl group) and C_e is a sum representing the coulomb attraction energy between the groupings $(C{=}C)^+$ and $(C{=}O)^-$. The last term depends upon the polarity of the molecular orbitals χ_π and χ_{π^*} used for describing the isolated C=O grouping and was calculated equal to 5·3 ev[158]. The off-diagonal elements of the energy matrix must be theoretically estimated with the formulas of the composite-molecule method; they depend upon the molecular-orbital coefficients of the two parts and on the value assigned to the exchange integral β of the C—C bond joining them ($\beta_{C-C} = 1{\cdot}7$ ev). Table 17 gives the results obtained with these parameters for acrolein.

The previous model ascribes an extremely clear physical meaning to the configuration-interaction wave functions. The acrolein ground state is essentially constituted by the juxtaposition of the ground states of the C=C and C=O groups with a small contribution from an intramolecular charge-transfer complex $(C{=}C)^{+}(C{=}O)^{-}$.

This description, which is similar to that of the classical intermolecular charge-transfer complex, gives a very simple picture of the polarity variations of the C=O grouping by conjugation: the structure of charge-transfer type brings a contribution to the dipole moment increasing the component along the carbonyl bond axis, but at the same time creating a component in the perpendicular direction; the last point is due to the fact that the molecule is bent. A Stark-effect study actually showed that acrolein possesses a dipole moment of 3·06 D in the C—O direction (compared to 2·3 D for formaldehyde) and of 0·54 D in the perpendicular direction[161]. The excited states describe only the excitation processes involving the π electrons. The structure of charge-transfer type dominates in the first excited state, the locally excited configuration of the carbonyl group in the second excited state; the third excited state is a mixture of these structures. The calculated excitation energies ΔE (Table 17) are in good agreement with the position of the $\pi \rightarrow \pi^*$ transition in the acrolein absorption spectrum[145]. Thus the first $\pi \rightarrow \pi^*$ transition can be considered as an intramolecular charge-transfer band; this band, located at 1935 Å in acrolein, shifts toward the visible region while the donor ionization potential decreases, e.g. if the carbon–carbon double bond of acrolein is replaced by a longer conjugated chain. The assignment of the two absorption bands found at 1480 Å and at 1460 Å is more dubious; the former corresponds in this interpretation to a blue shift of the formaldehyde $\pi \rightarrow \pi^*$ transition located at 1560 Å. The interpretations to which this simplified configuration-interaction method leads are often taken too literally. However, the results obtained must not cause the limits set by the semiempirical character of the process to be forgotten.

D. Radical Ions Derived from Aldehydes and Ketones

The electronic structure of positive and negative ions derived from molecules containing only unsaturated carbon and hydrogen atoms are very similar, particularly in the case of alternant systems[125,126], i.e. conjugated and aromatic hydrocarbons without odd-membered rings. In these compounds the levels where it is easiest to capture or

remove an electron are those of π electrons. Thus the positive ions obtained by the action of sulfuric acid on an aromatic hydrocarbon are described by a wave function with one π electron less in the highest occupied molecular orbital than for the neutral molecule, while the negative ions obtained with alkali metals will have one electron in the first antibonding orbital of the π electron system. The energy of the highest occupied orbital and that of the lowest free orbital of an alternant hydrocarbon are quantities of opposite sign of the form

$$e_i = \alpha \pm m_i\beta$$

according to the semiempirical Hückel molecular-orbital method; furthermore, the electron density that these two orbitals produce on each carbon when they are occupied by one electron is the same, so that the distribution of the positive charges coincides with that of the negative charges for two ions of opposite sign derived from an alternant hydrocarbon. These characteristics have been used to explain the rather similar physicochemical properties of the two categories of ions such as parallelism of polarographic oxidation and reduction potentials[162], similarity of the absorption spectra in the visible region[163], and hyperfine structure of the electronic paramagnetic resonance spectra[164]. No analogy of this kind is possible in the case of positive and negative ions derived from molecules containing atoms with lone-pair electrons such as the carbonyl compounds.

As the n electrons of a heteroatom are usually the easiest ones to remove, the positive ions will have a positive charge localized on the $2p_y$ orbital of the heteroatom. The negative ions will be formed by fixation of an electron in the first antibonding molecular orbital χ_{π^*} of the π electron system, and the resulting negative charge will be delocalized on all the atoms of the conjugated chain; this is the case in ketyl radicals obtained by reduction of aldehydes and ketones.

The positive ions of the carbonyl compounds are mainly known by their appearance potential from the neutral molecules. We saw in section II.A that the ionization potential and the polarity of the carbonyl bond vary in opposite direction under the effect of a substituent X on the carbonyl group. The variations of the ionization potential of the lone pair are often explained by saying that the electric charge at the oxygen atom creates a more or less important electronic repulsion on the lone-pair electrons. In the case of con-

jugated aldehydes and ketones a correlation between the ionization potential of the molecule and the oxygen charge q_O created by the π-electron system can also be established. In the frame of a classical electrostatic interpretation such a process completely neglects the coulomb interactions of the lone-pair electrons with the other atoms of the molecule and leads to rather disappointing results when the molecule contains several heteroatoms of different nature[165,166]. By the self-consistent field method it is possible with some approximations to establish a simple formula, giving a much more satisfying expression, and to calculate the ionization potential of the lone pair belonging to a heteroatom involved in a conjugated system. According to Koopmans' theorem, the ionization potential of an electron occupying a molecular orbital χ_i is equal to the opposite of the energy e_i of the considered orbital so that

$$e_i = I_i + J_{ii} + \sum_{j \neq i} (2J_{ij} - K_{ij})$$

where the summation is over the occupied orbitals in the closed-shell ground state of the neutral molecule. For an n electron localized on a heteroatom, this expression is written

$$e_n = I_n + J_{nn} + \sum_j (2J_{nj} - K_{nj})$$

where the summation is over the molecular orbitals χ_j occupied by the π electrons. The term I_n can be split in two parts: the first one I'_n depicting the contribution of the heteroatom itself, the second one I''_n summing up the contribution from the other atoms to the nuclear attraction potential acting on the n electron. The quantity $(I'_n + J_{nn})$ is the energy necessary to remove one electron from the heteroatom assumed isolated and can be considered as a constant W_n in a series of related molecules. The quantity $(I''_n + \sum_j 2J_{nj})$ represents the coulomb interaction energy between an n electron and the distribution of local charges appearing in the regions where the π electron density does not exactly balance the nuclear charges. To the first approximation, we can write

$$I''_n + \sum_j 2J_{nj} = \sum_r (q_r - 1)(nn; x_r x_r)$$

where q_r is the total π electron charge of every atom carrying one π electron to the system, and $(nn; x_r x_r)$ the integral giving the value of the coulomb repulsion energy for two electrons, one described by the ψ_n orbital of the heteroatom and the other one by a $2p_x$ orbital

centered at the atom r. As was seen in section III.B, the exchange terms K_{nj} are small and can be neglected in a comparative study. With these approximations the ionization potential of an n electron of the oxygen lone pair $(2p_y)^2$ is written

$$P_n = -W_n + \sum_r (1 - q_r)(nn; x_r x_r)$$

where W_n is a negative specific constant and $(1 - q_r)$ is the net charge in π electrons of the atom r[165,166]. The preceding summation is over all the atoms r of the conjugated system, including the heteroatom itself; as the coulomb repulsion integrals decrease when the distance between the atomic orbital increases, the largest term in this expression comes in general from the negative charge q_O at the heteroatom and we can write

$$P_n = -W_n + (1 - q_O)(nn; x_O x_O) + \cdots$$

But as coulomb repulsion forces are long-range forces, the other terms are never negligible. Although the presence of a large negative charge on the heteroatom lowers the ionization potential of the lone pair, an absolute significance must not be ascribed to such correlations which are often noticed in homogeneous series of molecules, such as carbonyl compounds.

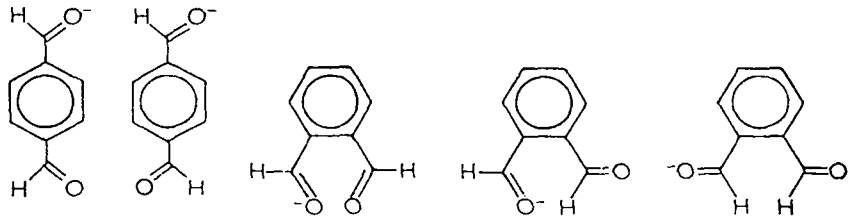
The negative ions of ketones form stable ketyl radicals, which have been known for a long time. They are obtained by the reduction of ketones with alkali, alkaline- and rare-earth metals in ether as solvent; but they are in equilibrium with paramagnetic species formed by ketyl radicals associated with positive metal ions. Thus the ketyls obtained by sodium give a dimer with two Na^+ ions and they are transformed into the diamagnetic pinacolate if, instead of ether, benzene is used as solvent[167]. The electroreduction at high pH of aldehydes and ketones also leads to ketyl radicals; the polarographic half-wave potential $\varepsilon_{\frac{1}{2}}$ is determined by the electroaffinity of the reduced molecule and varies in a parallel direction to the energy of the lowest free orbital of the π electron system in conjugated aldehydes and ketones[168]. As the energy of the oxygen lone-pair electrons is less sensitive to structural modifications than the energy of the free orbital, a correlation is found between the polarographic reduction potential and the energy of $n \rightarrow \pi^*$ transition of ketones[169,170]. As a matter of fact, the electronic structure of the ketyl grouping looks very much like that of the carbonyl grouping in the A_2 excited state: the C—O bond in the negative ions of aldehydes and ketones can be

described as a three-electron π bond and can be represented by two resonance structures similar to the structures Ω_4 and Ω_6 of the carbonyl group:

$$\ddot{C}^{-}=\dot{O}_{yy} \longleftrightarrow \dot{C}=\ddot{O}_{yy}^{-}$$

The situation is the same for the N—O bond in nitroxide radicals R^1R^2—NO, which are neutral molecules isoelectronic with the ketyls and have similar properties[171,172].

The study of the hyperfine structure of electronic paramagnetic resonance spectra of the ketyl radicals gives informations on the importance of the conjugation of the ketyl group with an unsaturated residue R. In the ions derived from benzaldehyde or from its *para*-substituted derivatives XC_6H_4CHO, the hyperfine coupling constants of two *ortho* or *meta* protons are different[173–175]. The rotation of the ketyl group around the axis C—C is hindered, since there is no symmetry axis passing by the C—X bond. The result is that the benzaldehyde anions with cyano or nitro substituents and the aromatic dialdehyde anions exist as several rotamer forms whose presence is detected by the analysis of the corresponding electronic paramagnetic spectrum. Thus the terephthalaldehyde anion is a mixture of both *cis* and *trans* planar conformations, where the *trans* form is more stable. In contrast there is only one conformation for the phthalaldehyde anion and this is the unsymmetrical *meso* rotamer; the large relative stability of the *meso* rotamer may be due to an intramolecular hydrogen bond[176]:



The hyperfine coupling constants a^X of a free radical are determined by the electron spin density ρ^X that the molecule shows at the nucleus X responsible for the coupling. If the wave function of the electron system is represented by a series of molecular orbitals doubly and singly occupied, the spin density at any point can be considered identical to the probability of finding the unpaired electron at this point. In the case of conjugated free radicals the unpaired electron belongs to a π-molecular orbital formed by atomic $2p_x$ orbitals whose

nodal plane coincides with the molecular plane; thus it does not bring any contribution to the spin density ρ^H on the protons located in this plane. But the hyperfine coupling constants a^H for the protons of the conjugated system are not equal to zero, because the interaction of the unpaired electron with the electrons of the C—H bonds creates an *s*-character spin density on the protons[177]. To explain this effect, either the preceding independent particle model must be improved by a σ–π configuration interaction mechanism, or the notion of orbitals occupied by two electrons of opposite spins must be abandoned and replaced by a model using different space orbitals for different electron-spin values[178,179]. To the first approximation, the coupling constants a^H are proportional to the spin density ρ_π^C brought by the unpaired electron to the neighborhood of the carbon of the C—H bonds; the following expression is used

$$a^H = Q\rho_\pi^C$$

and the value of the constant Q is determined by using the experimental value for a^H in the case of a compound whose spin density ρ_π^C is known without ambiguity (for methyl radical $\rho_\pi^C = 1{\cdot}0, a^H = -23{\cdot}0$ oe). In the LCAO–MO approximation without overlap, the spin density ρ_r on an atom r, which is part of a conjugated system, is identical to the partial charge brought to the atom r by the molecular orbital χ_m of the unpaired π electron:

$$\rho_r = c_{rm}^2$$

Therefore the spin densities of the usual molecular-orbital method are inevitably positive, or equal to zero if the unpaired electron wave function becomes zero on the atom r. But the analysis of the paramagnetic resonance spectra of aromatic free radicals, such as benzyl or triphenylmethyl radicals, shows that spin densities of some atoms actually are negative. To interpret this fact, a spin polarization effect must be introduced in the π-electron system itself, either by carrying out a configuration-interaction calculation or by using different molecular orbitals for different spins[177]. To the first approximation, the spin densities of the classical method can be corrected simply by taking the spin-polarization effect into account by a perturbation procedure[180]. In such a case we have

$$(\rho_r)_{pert} = c_{rm}^2 - \lambda \sum_s \pi_{rs} c_{sm}^2$$

where λ is an adjustable semiempirical parameter and π_{rs} is the mutual polarizability of atoms r and s.

Under its parametrical form, the molecular-orbital method gives an appropriate distribution of the spin densities in the aromatic ketyls, provided that the usual set of integrals for the carbonyl group is completed by additional parameters destroying the equivalence of the two *ortho*- and *meta*-positions of benzaldehyde. Two processes have been used: in the first one the coulomb integral α_C for the *ortho*-carbon, which is nearer to the carbonyl group, is supposed modified by the proximity of oxygen; in the second one the exchange integral β_{OC} between this carbon and the oxygen is supposed to take an appreciable value[176].

The order of the carbon atoms of the ring according to the relative value of the spin densities is not the same in the two cases, but the assignment of the coupling constants a^H observed for the ring

TABLE 18. Spin densities in conjugated ketyl radicals.

Compound	Calculated spin densities[a]		Experimental[b]
	ρ	ρ_{Port}	ρ_{exp}
Benzaldehyde	0·2773	0·3129	0·3589
4-Cyanobenzaldehyde	0·2122	0·2361	0·2346
Terephthalaldehyde (*trans*)	0·1456	0·1590	0·1641
Terephthalaldehyde (*cis*)	0·1467	0·1602	0·1607
4-Nitrobenzaldehyde	0·0697	0·0730	0·0578

[a] Parameters of ref. 174 with $\lambda = 1{\cdot}2\,\beta$.
[b] $\rho_{exp} = a^H/Q$ with $Q = -23{\cdot}7$ oe.

protons has not been determined experimentally and it is impossible to determine the best process empirically. In Table 18 we only give the spin density of the carbonyl carbon, calculated with the assumption of a modification of the integral α_C[174], and the value of the ratio a^H/Q deduced from the hyperfine coupling constant of the aldehyde proton, the assignment of which is certain. From a qualitative point of view, the effects observed with monosubstituted benzaldehydes are consistent with the calculation indications, except for the two terephthalaldehyde rotamers which are reversed. It happens that the relative positions of the two rotamers is better explained by the introduction of a nonzero exchange integral β_{OC} than by a modification of the coulomb integral α_C[176]; but the observed effect is probably too fine to be explained by such an oversimplified theory. To use less arbitrary processes such as the self-consistent field method or the configuration-interaction method,

which have been applied to some ketyl radicals[180] is much more advisable.

E. An Example of a Complete Quantum-mechanical Calculation: the Ground State of Formaldehyde

The methods of quantum chemistry (molecular-orbital, valence-bond, and other methods) are only processes for finding an approximate solution of the Schrödinger equation. Their development can take on a semiempirical or a purely mathematical aspect: in a semiempirical treatment some theoretical factors are identified with experimental quantities and numerically replaced by them; in a purely mathematical treatment the wave function used for the calculation of the physicochemical observables calls for the fundamental constants of physics only. The introduction of semiempirical elements into a theory simplifies the mathematical formalism and usually makes the comparison with experiment easier but at the same time it spoils the deductive character of the predictions made. In contrast the results obtained by the *ab initio* methods originate from theoretical principles but depend closely upon the degree of approximation that the chosen wave functions represent for the Schrödinger equation; besides, it is impossible to carry a nonempirical calculation to the very end without taking into account all the electrons and this restricts the application of such methods to small molecules.

Two *ab initio* calculations devoted to the formaldehyde ground state were published in 1960[11,19]. Both of these works have been carried out by the self-consistent field method in the LCAO approximation. All the electrons of the molecule, including those of the K shells of carbon and oxygen, have been included in a single system of sixteen electrons. The total electronic wave function Ψ is represented by a Slater determinant made up by eight molecular orbitals χ_i occupied by two electrons of opposite spins. The atomic-orbital basis used in the development of the molecular orbitals is formed by simple Slater functions ψ_p namely by functions whose radial part is the product of a power of r by an exponential $e^{-\zeta_p r}$ containing an appropriate exponent ζ_p. A choice of more complicated atomic orbitals would have increased the already very large number of atomic integrals which must be determined before the beginning of the so-called variational calculation. The electronic energy of the system has only been computed for the equilibrium geometrical configuration as it is given by experiment.

We describe only one of these calculations[11] in full detail. The assumed geometrical structure is the result of an analysis of the molecular microwave spectrum[181]. In its ground state formaldehyde is planar and belongs to the symmetry group C_{2v}; the internuclear distances are r C—H = 1·12 Å and r C—O = 1·21 Å and the angle $\widehat{HCH}$ is equal to 118°. The carbon atom is placed at the center of a cartesian coordinate system; the Oz axis coincides with the C—O bond and points towards the oxygen atom and the Ox axis is placed in the molecular plane (Figure 8). The basis of atomic orbitals includes the $1s$ orbitals of the two hydrogen atoms and the $1s$ and $2s$ orbitals as well as the three $2p$ orbitals of both carbon and oxygen, i.e. a total of twelve orbitals. With these functions it is possible to build up twelve molecular orbitals which can be classified according

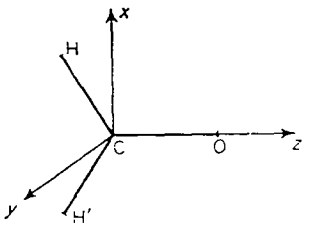


FIGURE 8. Geometrical structure of formaldehyde. In this figure the axes Ox and Oy are the same as in the original work[11]. The choice of axes is different in the previous sections.

to their transformations under the action of the symmetry-group operations. In seven of these molecular orbitals appear, on one hand, the s and $2p_z$ orbitals of carbon and oxygen and, on the other hand, the normalized combination $(1s_H + 1s_{H'})/N_+$ of the $1s$ orbitals of the two hydrogens. These functions belong to the A_1 representation of the group C_{2v}; this means that they remain unchanged by symmetry operations transforming the molecule into itself as, for instance, a 180° rotation about the Oz axis. Three of these molecular orbitals are built up with the combination $(1s_H - 1s_{H'})/N_-$ of the two hydrogens and with the $2p_x$ orbitals of carbon and oxygen; they belong to the B_1 representation (the functions are antisymmetric with respect to the vertical plane passing by the carbonyl bond). The last two molecular orbitals contain only the $2p_y$ orbitals of carbon and oxygen; they belong to the B_2 representation (the functions are antisymmetric with respect to the molecular plane). To describe the ground state of the molecule, it is found that five molecular orbitals

of type A_1, two of type B_1, and one of type B_2 must be used. The B_1 molecular orbitals can be seen as depicting the hyperconjugation of n lone-pair electrons of oxygen with the hydrogens linked to carbon; the molecular orbitals B_2 correspond to the π electrons of the carbonyl bond.

The molecular orbitals of formaldehyde can be written in the general form

$$\chi_i(\Gamma) = \sum_p c_{ip}\psi_p(\Gamma)$$

where the summation is only over the atomic orbitals occurring in the molecular orbital of type Γ. According to LCAO–SCF theory, the energies e_i of these orbitals are the solutions of the equation

$$\det | \mathbf{L} - e\mathbf{S} | = 0$$

where $\mathbf{S}$ is the overlap matrix and $\mathbf{L}$ is the matrix associated with Fock's operator

$$\mathbf{F} = \mathbf{H} + \sum_i^{occ} (2\mathbf{J}_i - \mathbf{K}_i)$$

with respect to the basis ψ_p[182]. The operator $\mathbf{F}$ contains an operator $\mathbf{H}$ representing the kinetic and potential energy of one electron in the field of the nuclei and a sum of coulomb operators $\mathbf{J}_i$ and exchange operators $\mathbf{K}_i$ operating only on the occupied molecular orbitals; this last sum forms the average potential by which the SCF theory represents the interaction of the electrons of the system. Due to the fact that the operator $\mathbf{F}$ contains the molecular orbitals to be determined, the computation of the molecular orbitals is an iterative process: with the eigenvectors C_i of the previous eigenvalue equation the matrix elements of the following iteration are determined. A total of twenty iterations has been necessary to obtain a good coincidence between the matrix elements of two successive iterations.

If the atomic orbital coefficients in the different molecular orbitals are considered (Table 19), it is noticed that each of the orbitals χ_1 and χ_2 represent one electron pair almost entirely localized on the K shell of carbon or oxygen atom. It is also established that the highest occupied orbital χ_8 contains a very strong contribution of $2p_x$ orbital of oxygen and that, consequently, the oxygen n lone pair is almost entirely localized on the heteroatom; this last result is in agreement with those of the less elaborated calculations of section III.A. The structure of the orbital χ_7 representing the electrons of the carbonyl bond is more astonishing; contrary to the usual descriptions, this

TABLE 19. Atomic orbital coefficients in the molecular orbitals of formaldehyde [11].

	$\chi_1(A_1)$	$\chi_2(A_1)$	$\chi_3(A_1)$	$\chi_4(B_1)$	$\chi_5(A_1)$	$\chi_6(A_1)$	$\chi_7(B_2)$	$\chi_8(B_1)$
$\frac{1s_H + 1s_{H'}}{N_+}$	−0·018	−0·001	−0·150		−0·167	0·647		
$(1s)_C$	−0·001	1·000	−0·037		0·025	−0·035		
$(2s)_C$	−0·002	0·019	0·372		−0·697	−0·375		
$(2p_z)_C$	−0·042	0·006	−0·013		0·312	−0·336		
$(1s)_O$	1·003	−0·001	−0·026		0·011	0·024		
$(2s)_O$	0·037	−0·008	0·807		0·448	0·447		
$(2p_z)_O$	−0·017	0·001	−0·207		0·243	0·592		
$\frac{1s_H - 1s_{H'}}{N_-}$				0·430				−0·368
$(2p_x)_C$				0·489				−0·270
$(2p_x)_O$				0·433				0·905
$(2p_y)_C$							0·655	
$(2p_y)_O$							0·626	
ε_i (ev)	−562·88	−309·14	−38·73	−22·10	−21·94	−19·25	−15·08	−11·53

orbital has a homopolar nature with a slight polarity $C^-—O^+$. According to Koopmans' theorem, the energy of the orbital ε_8 gives the value of the first ionization potential of formaldehyde as 11·53 ev; this value is in rather good agreement with the experimental value (10·8 ev). The second ionization potential given by the energy of the orbital χ_7 (15·08 ev) is too high in comparison with the experimental value (11·8 ev). However, these results corroborate the assignment of the first two ionization potentials of formaldehyde to the removal of an oxygen *n* lone-pair electron and to that of a double bond π electron [17].

The distribution of the electrons among the different atoms as can be inferred from the molecular-orbital coefficients seems to indicate that charge transfer from the hydrogens towards carbon and oxygen occurs. If the electron density at the atom A is identified with the gross atomic population

$$q_A = 2 \sum_{i}^{occ} \sum_{r} [c_{ir}^2 + \sum_{s \neq r} c_{is} c_{ir} S_{rs}]$$

where *r* and *s* range through the different atomic orbitals ψ_r centered in *A*, and *i* ranges through the different occupied molecular orbitals, then the following charges are found:

$$\underset{1\cdot80}{H_2}—\underset{6\cdot10}{C}—\underset{8\cdot10}{O}$$

But the calculated dipole moment has its positive end pointed towards the oxygen atom and is equal to 0·62 D. This result is not in agreement with the experimental dipole moment (2·34 D) with its direction (which has not been determined by experiment) probably pointing in the opposite way.

As atomic populations are defined to characterize the different atoms, overlap populations can be defined to characterize the bonds[183]. The overlap population between two atoms A and B is given by

$$p_{AB} = 2 \sum_{i} \sum_{r=1}^{m} \sum_{s=1}^{n} c_{ir} c_{is} S_{rs}$$

where S_{rs} is the overlap integral between an orbital ψ_r belonging to the atom A and an orbital ψ_s belonging to the atom B. The

TABLE 20. Energy data on formaldehyde[11].

	Computed (atomic units)	Experimental (atomic units)
Total electronic energy	−114·705	
Repulsion of nuclei	31·114	
Total molecular energy	−113·591	−114·550
Energy of separated atoms	−113·151	−113·964
Dissociation energy	0·440	0·586

summations on r and s are taken on all the orbitals ψ_r and ψ_s centered at the atoms A and B, respectively, and the summation on i is taken on all the occupied molecular orbitals χ_i. The population analysis shows that the orbitals χ_1 and χ_2 are nonbonding orbitals (electrons from the K shell of carbon and oxygen); it shows also that the orbitals χ_3, χ_4, χ_5, χ_6, and χ_7 are bonding and that the oxygen lone pair orbital χ_8 is slightly antibonding. It is established also that the orbital $(2s)_O$, built up by orthogonalizing the $2s$ nodeless function of oxygen with the $1s$ orbital, is mixed with orbitals of the same symmetry; thus it cannot be identified with the wave function of a lone pair of character s and localized on the heteroatom.

The energy values of Table 20 are very close to the results obtained in the other *ab initio* calculation of the formaldehyde ground state[19]; for instance, the value found for the total molecular energy was −113·534 a.u. However the dipole moment which is much more sensitive to the details of the wave function is rather different (1·1 D);

nevertheless the structure of the molecular orbital assigned to the π electrons of the carbon–oxygen double bond is the same. It is well known that the completely delocalized molecular orbitals of the self-consistent field method can be transformed into localized orbitals; with these new orbitals it is possible to find the usual ideas of the valence theory again: e.g. two-electron bond, lone pair, etc.[184]. The molecular orbitals of the first calculation described here were subjected to such a treatment[3,185]. To obtain this representation, in general one is obliged to remove the imperfections of the localization process used and this alters the observables to a slight extent. After such a transformation the electronic structure of formaldehyde can be described as follows: the oxygen atom bears two lone pairs, one of pure p character, the other of s character slightly changed by a $2p_{zO}$ orbital contribution; the carbon atom disposes of three σ orbitals in an approximately sp^2 hybridization state, two of these σ orbitals forming the C—H bonds with the hydrogen $1s$ orbitals and the third

TABLE 21. Charge distribution in formaldehyde[185].

	q_H	q_C	q_O
σ charges in C—H	+0·15	−0·15	
σ charges in C—O		+0·17	−0·17
π charges in C—C		−0·03	+0·03

one forming a σ bond with the oxygen $2p_z$ orbital. This description corresponds to the charge distribution of Table 21 and gives a dipole moment of 2·6 D in rather good agreement with the experimental value.

A rather astonishing fact appears from the consideration of the σ and π charge distributions between the two atoms of the carbonyl group: oxygen, which as a rule is more electronegative than carbon, effectively draws the σ electrons to itself but repels the π electrons towards the carbon and, on the whole, remains negatively charged. This result is not an isolated one; it occurs also in molecules containing nitrogen as a heteroatom, e.g. in hydrocyanic acid[185] and in pyridine[186]. The origin of this peculiarity is immediately seen by scrutinizing the structure of the matrix elements of the LCAO–SCF method: the σ-charge accumulation on the heteroatom alters the electron repulsion terms relative to the π orbitals so strongly that the heteroatom becomes less electronegative than carbon for the π

electrons. It would be interesting to know whether similar phenomena occur in most unsaturated heterocyclic molecules: if this were the case, it would mean either that the usual theories must be replaced by a theory introducing the σ electrons or that the present self-consistent field method in LCAO approximation must be discarded as leading to results which are physically meaningless.

IV. ACKNOWLEDGMENTS

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The Chemistry of the Carbonyl Group
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CHAPTER 2

Carbonyl-forming oxidations

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I. INTRODUCTION

Carbonyl compounds are produced by the oxidation of a wide variety of organic compounds, the most important of which are hydrocarbons and alcohols. In order to limit the scope of this chapter only these starting materials will, in general, be considered here.

The required oxidation may be effected by a number of established reagents such as dichromate, permanganate, selenium dioxide, ozone and various inorganic and organic peroxides. In many ways, however, the most attractive oxidant is molecular oxygen, the use of which sometimes leads to good yields and which has the advantages of ready availability and low cost. It is not surprising then that the use of this oxidant forms the basis of several industrial processes in which the starting compound may be present either in the liquid or vapour states. Thus useful amounts of carbonyl compounds may be formed both from uncatalysed and catalysed liquid-phase oxidation and from homogeneous and heterogeneous gaseous oxidation processes. Gas-phase reactions are particularly attractive commercially, particularly if the desired product(s) can be separated without condensation of the total organic reactor effluent, since a recycling

process may then be used to increase the yield without the necessity of revaporizing the initial organic compound.

In much of the earlier work, particularly that on the gaseous oxidation of organic compounds, the absence of suitable analytical methods for estimating the small quantities of products involved in laboratory-scale experiments made it impossible to obtain reliable data for the formation of individual carbonyl-containing products. Determinations could often be made only of total aldehydes or in some cases of formaldehyde and higher aldehydes. Only comparatively recently too did workers in this field become conscious of the necessity to estimate ketones. However, the development of chromatographic and spectroscopic methods of analysis has now made it quite easy to determine reliably all the individual aldehydes and ketones which may be formed as intermediates during oxidation processes. In the same way most of the mechanisms proposed by earlier workers for the production of such compounds had little experimental support, but in recent years the use of isotopic tracer methods has enabled more definite conclusions to be reached regarding the nature of the reactions leading to the formation of carbonyl compounds. Valuable confirmatory evidence has also been provided in some cases by direct studies of other related reactions.

In the present chapter carbonyl-forming oxidations will be described which involve both molecular oxygen and other specific oxidants, although it is the intention to lay rather special emphasis on the uses and wide applicability of the former reagent. The various reactions concerned will be classified according to the different main classes of organic starting material which may be used for the oxidative production of carbonyl compounds.

II. OXIDATION OF ALKANES AND CYCLOALKANES

A. Reactions Involving Molecular Oxygen

1. Gas-phase reactions

a. *Oxidation in the absence of catalysts.* i. Alkanes. The sole parent alkane giving only one carbonyl compound is methane, which produces small amounts of formaldehyde as an intermediate product on slow oxidation. Bone and Gardner[1] first detected this compound during the induction period preceding methane oxidation at about 400°c, the yield at the end of the induction period being about 0·2%. Slotin and Style[2] showed that the yield of formaldehyde at 430°c

passes through a well-defined maximum and then decreases again, presumably owing to further oxidation of this product. Egerton, Minkoff and Salooja [3] found that the largest amounts of formaldehyde were formed in $2\ CH_4 + 1\ O_2$ mixtures and that the maximum yields decreased as the temperature was increased from 460 to 500°c (Table 1). The maximum concentration of the aldehyde formed at 510°c is formed at the time of the maximum rate and is said [4,5] to be given by the relationship (1).

$$[HCHO]_{max} \approx 10^{-3}[CH_4] \qquad (1)$$

TABLE 1. Maximum yields of formaldehyde formed during the oxidation of methane[3].

Temperature (°c)	Pressure (mm)	% Formaldehyde in products from		
		$2\ CH_4 + O_2$	$CH_4 + O_2$	$CH_4 + 2\ O_2$
460	350	0·40	0·39	0·33
460	300	–	–	0·31
460	250	0·40	0·39	0·30
460	200	–	–	0·29
460	100	0·40	0·37	0·27
480	350	0·37	0·38	0·31
480	250	0·37	0·37	0·29
480	150	0·38	0·38	–
500	350	–	0·35	0·30
500	300	–	0·35	0·29
500	250	–	0·33	0·28
500	200	–	0·35	0·27
500	150	–	0·34	0·25
500	100	–	0·35	0·24

There is little doubt that formaldehyde is produced during the non-catalytic gaseous oxidation of methane as a result of the direct reaction of methyl radicals with oxygen. Below about 200°c, such interaction gives rise by a third-order process [6–8] to methylperoxy radicals, the principal fate of which is to decompose bimolecularly yielding some formaldehyde (equation 2). There is, however, con-

$$CH_3O_2 + CH_3O_2^{\cdot} \longrightarrow CH_3OH + HCHO + O_2 \qquad (2)$$

siderable uncertainty as to whether methylperoxy radicals are in fact formed at the relatively high temperatures at which methane and

oxygen react thermally, although they have apparently been detected by mass spectroscopy at temperatures as high as 1000°c[9]. In general it seems more likely that, at temperatures of the order of 500°c, the main reaction leading to formaldehyde is (3), for which there is abundant evidence from flash photolysis[10].

$$CH_3^{\cdot} + O_2 \longrightarrow HCHO + {}^{\cdot}OH \qquad (3)$$

The slow oxidation of ethane generally also yields formaldehyde as well as smaller amounts of acetaldehyde. Bone and Hill[11] found that at an oxidation temperature of 313°c, the maximum yields of formaldehyde were about 1% and those of acetaldehyde were about 0·3%. The use of high pressures (and consequently lower temperatures) increases the amounts of acetaldehyde and decreases those of formaldehyde in the products[12]. Knox and Norrish[13] showed that acetaldehyde was a product of ethane oxidation only at temperatures below 360°c, and Knox and Wells[14] found that at 300–320°c formaldehyde was a very abundant early product, the initial yield of which (based on ethane consumed) was in some cases as high as 60%. The observation that the extent of acetaldehyde formation (unlike that of formaldehyde) depended upon the oxygen pressure prompted the suggestion that both aldehydes were formed by the decomposition of intermediate ethylperoxy radicals[15,16], the production of formaldehyde taking place by the straightforward reaction (4) and that of acetaldehyde by the process (5) involving a six-membered ring in the transition state.

$$CH_3CH_2OO^{\cdot} \longrightarrow CH_3O^{\cdot} + HCHO \qquad (4)$$

$$CH_3CH_2OO^{\cdot} + O_2 \longrightarrow CH_3CHO + {}^{\cdot}OH + O_2 \qquad (5)$$

Most early investigators of the gaseous oxidation of propane came to the conclusion that both formaldehyde and higher aldehydes were intermediate reaction products[17–21]. Newitt and Thornes[22] showed that at 300°c the formation of higher aldehydes precedes that of formaldehyde, and Newitt and Schmidt[23] found that acetone was also a product of the reaction at high pressures. The amount of aldehydes which can be isolated generally decreases with increasing temperature[24,25]. Knox and Norrish[26] first showed that the higher aldehydes found by earlier workers consisted of both propionaldehyde and acetaldehyde; under cool-flame conditions the relative amounts of aldehydes detected were 1 part C_2H_5CHO:40 parts CH_3CHO:60 parts HCHO.

Although the formation of carbonyl compounds has generally been

assumed to occur as the result of various modes of breakdown of propylperoxy radicals[19,27], e.g. reaction (6), recent work[28,29] has

$$CH_3CH(OO^{\bullet})CH_3 \longrightarrow CH_3\dot{C}HOOCH_3 \longrightarrow CH_3CHO + CH_3O^{\bullet} \qquad (6)$$

shown that even at low temperatures (300–360°c) the principal primary product is propylene and that the carbonyl (and other oxygenated organic) products are formed mainly by the further oxidation of the olefin.

Some useful information regarding the mechanism of formation of the carbonyl products has been obtained from isotopic tracer studies. Thus Byrko, Kryuglakova and Lukovnikov[30] showed by radioassay of the formaldehyde formed by oxidation of 2-^{14}C-propane that 77% of this compound arose from the methyl groups of the initial hydrocarbon. Ferguson and Yokley[31] have studied the cool-flame oxidation of 2-^{13}C-propane and shown that the products formed from an equimolar propane + oxygen mixture at 318°c contained all three aldehydes as well as acetone. The isotopic composition of the aldehydes indicated that propionaldehyde and acetaldehyde were formed intact from the parent hydrocarbon molecule, while formaldehyde was of mixed origin, being produced principally from the terminal positions. The results also showed somewhat surprisingly that about 20% of the acetone formed must have been produced by the complete breakdown and reassembly of the carbon chain.

The oxidation of n-butane is probably in most respects analogous to that of propane but there is little detailed information available regarding the carbonyl compounds produced during the reaction. Apart from aldehydes[17], however, acetone[32,33] and 1-butanal-3-one[34] are reported to be formed. The use of isotopic tracer methods has shown that the rate of formation of aldehydes during the oxidation of n-butane at 250°c is considerably greater than the rate of disappearance of butylhydroperoxide[35]; this implies that a substantial proportion of the carbonyl products is formed by routes not involving intermediate formation of a hydroperoxide. Measurement of the activities of the aldehydes formed during the cool-flame combustion of 1-^{14}C-n-butane[36] shows that, whereas the formaldehyde is derived approximately equally from each carbon atom, the carbonyl group of the acetaldehyde is derived entirely from $C_{(2)}$ and $C_{(3)}$. In other experiments[37,38] determinations have been made by addition of 1% of 1-^{14}C-acetaldehyde of the separate rates of formation and destruction of this compound in the cool flame of n-butane.

Batten, Gardner and Ridge[39] found that higher aldehydes and formaldehyde were formed during the oxidation of isobutane and that their concentrations passed through pronounced maxima (corresponding to a total aldehyde yield of about 5%) at the maximum rate of pressure rise; the concentration of acetone, in contrast, rose continuously with time, there being about 3% in the final products formed at 291°c (Figure 1). Bose[40] first detected small amounts of

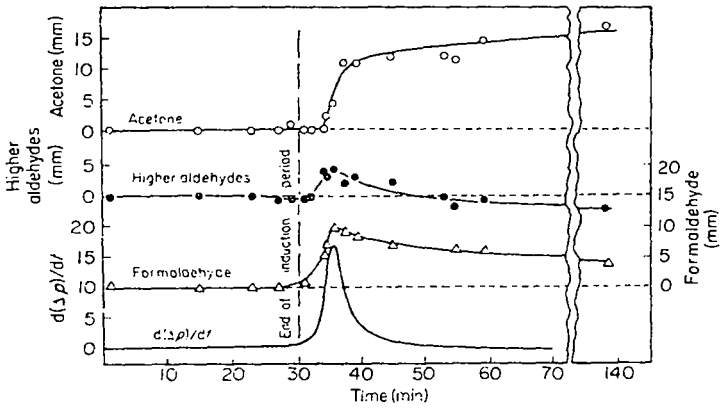


FIGURE 1. The formation of carbonyl products (and acids) during the gaseous oxidation of isobutane. Temperature = 291°c, isobutane pressure = 80 mm, oxygen pressure = 350 mm. [Reproduced, by permission, from ref. 39.]

methyl ethyl ketone as well as acetone and suggested that this compound was formed by reaction (7).

$$CH_3COCH_3 \xrightarrow{-H} CH_3\dot{C}OCH_2 \xrightarrow{+CH_3} CH_3COCH_2CH_3 \qquad (7)$$

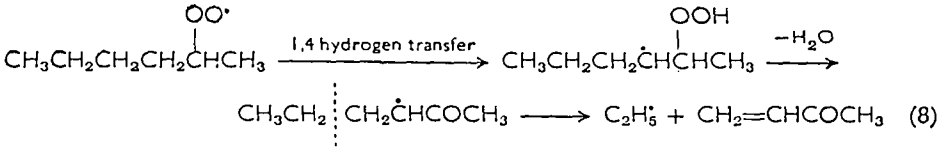
More recent work[41] has confirmed that both ketones are formed during the oxidation of isobutane and has shown that, although acetone predominates (by a factor of 20) in the products of slow combustion, methyl ethyl ketone is the principal ketonic product (by a factor of 27) under cool-flame conditions. Addition of 1,3-^{14}C-acetone to reacting isobutane + oxygen mixtures has established that none of the methyl ethyl ketone formed in the cool-flame region and only about 25% of that formed during slow combustion arises from further reactions of acetone. The formation of methyl ethyl ketone almost certainly involves predominantly isomerization and subsequent decomposition of *t*-butylperoxy radicals. The occurrence of such intramolecular rearrangement (particularly during the

induction period) has also been suggested by Zeelenberg and Bickel[42], who have detected isobutyraldehyde and methacrolein (as well as lower aldehydes) among the products of the slow oxidation of isobutane at about 300°c.

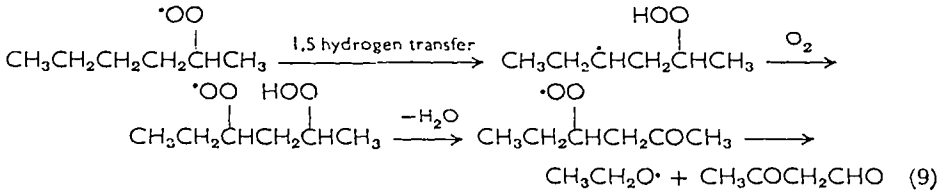
Although aldehydic products have long been known to be formed during the slow oxidation of n-pentane[43], it is only quite recently that Sandler and coworkers[44,45] have definitely identified such compounds. Determinations have been made of the amounts of n-butyraldehyde, propionaldehyde, acetaldehyde, formaldehyde, acrolein and acetone formed at different temperatures and from different n-pentane + oxygen mixtures. Such products are generally believed to arise by the decomposition (sometimes involving also intramolecular rearrangement) of alkylperoxy radicals or of the corresponding alkylhydroperoxides. The apparent absence of n-valeraldehyde suggests that such decomposition generally involves the fission of a C—C bond simultaneously with O—O homolysis. The formation of the β-diketone, 2,4-pentanedione, from n-pentane has also been reported[34]. Studies of the combustion of 1-^{14}C-, 2-^{14}C- and 3-^{14}C-n-pentane have shown that $C_{(2)}$ (rather than $C_{(1)}$) is the major source of formaldehyde[46].

Very little work has been carried out with branched-chain pentanes but a recent study[47] of the oxidation of isopentane has shown that the carbonyl products include acetaldehyde, acetone and methyl ethyl ketone, the formation of which can be accounted for in terms of reactions of amylperoxy radicals other than those involving the intermediate production of the corresponding monohydroperoxides. Oxidation of neopentane at 260°c[48] yields some acetone as well as acetaldehyde, isobutyraldehyde and pivaldehyde; these (and other oxygenated) products appear to be formed by a mechanism involving various modes of intramolecular rearrangement of intermediate alkylperoxy radicals.

Both formaldehyde and higher aldehydes have been found among the oxidation products of n-hexane at quite low temperatures[49], although at higher temperatures only formaldehyde can be detected. Bailey and Norrish[50] have found a complete series of homologous aldehydes (from C_1 to C_6) in the cool-flame products of n-hexane, and Kyryacos, Menapace and Boord[51] have shown that, in addition, acetone, methyl ethyl ketone and methyl vinyl ketone may be formed by oxidation of this hydrocarbon. The formation of such compounds almost certainly involves isomerization of the initially formed 2-hexylperoxy radicals, e.g. reactions (8). Similar rearrangements are



probably responsible for the formation of unsaturated aldehydes[52] and β-dicarbonyl compounds[53], e.g. reactions (9).

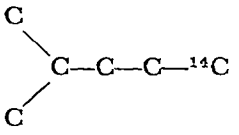
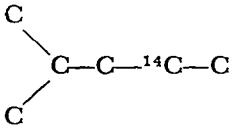
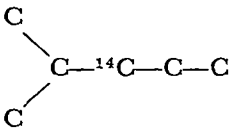
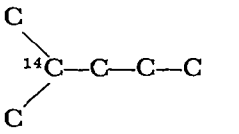


A variety of carbonyl compounds has been obtained by oxidation of n-hexane and higher alkanes in the presence of a 'rain' of inert solid particles[53a]. The principal action of the solid is apparently to conduct away the heat of reaction and so establish conditions more favourable for the preservation of thermally unstable intermediate products.

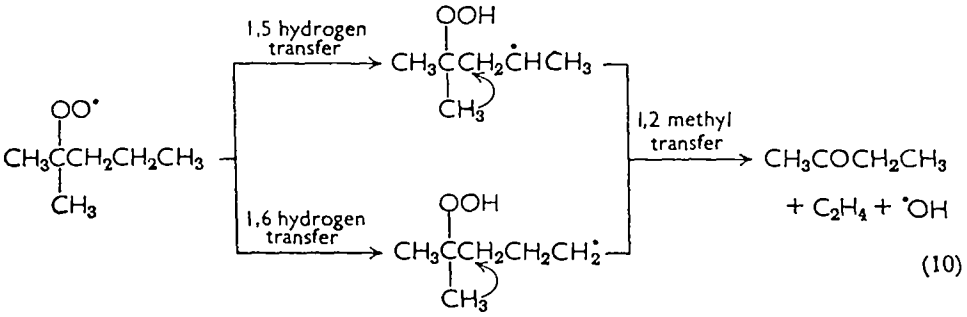
The oxidation of 2-methylpentane yields appreciable amounts of ketones[54] and the principal source of these compounds (acetone, methyl ethyl ketone and methyl n-propyl ketone) has recently been elucidated by separation and degradation of the ketones formed from various specifically ^{14}C-labelled hydrocarbons[55]. The activities of the various compounds (Table 2) show that the carbonyl group of each ketone is always derived from the 2-position of the hydrocarbon, and it is clear that the acetone and methyl n-propyl ketone arise from decomposition of the radical n-$C_3H_7(CH_3)_2CO\cdot$. The formation of methyl ethyl ketone, the yield of which (based on hydrocarbon consumed) is about 13%, is more difficult to explain. The specific activities of samples of this compound formed from 2-^{14}C-, 3-^{14}C-, 4-^{14}C- and 5-^{14}C-2-methylpentanes show, however, that the four carbon atoms from which the ketone is formed have the arrangement C—C(C)—C in the fuel. An intramolecular rearrangement producing a straight four-carbon chain must therefore be involved and almost certainly occurs in the n-$C_3H_7(CH_3)_2COO\cdot$ radical (reactions 10).

A similar rearrangement probably takes place during the oxidation of another isomeric hexane, 2,3-dimethylbutane[56]. Here the products contain (in addition to acetone, methyl ethyl ketone, methyl isopropyl

TABLE 2. Relative activities of ketones formed from ^{14}C-labelled 2-methylpentanes[55].

Labelled hydrocarbon	Activity of carbonyl products (relative to hydrocarbon = 100)	
	Acetone	Methyl ethyl ketone
	1	2
	3	3
	3	102
	106	97

ketone and acetaldehyde) appreciable quantities of pinacolone (3,3-dimethyl-2-butanone). The most likely route involves the stages shown in reaction (11). It is of interest, however, that pinacolone is not formed from 2,2-dimethylbutane[56,57] although the two compounds have the same carbon skeleton. Probably the absence of tertiary or secondary CH groups in the α-position makes it impossible



(10)

$$(CH_3)_2\overset{OO^\bullet}{\overset{|}{C}}CH(CH_3)_2 \xrightarrow{1,4\ \text{hydrogen transfer}} (CH_3)_2\overset{OOH}{\overset{|}{C}}\dot{C}(CH_3)_2 \xrightarrow{1,2\ \text{methyl transfer}} CH_3COC(CH_3)_3 + {}^\bullet OH \quad (11)$$

for the radical $(CH_3)_3CCH(OO^\bullet)CH_3$ to stabilize itself by internal hydrogen abstraction. Without this stabilization, the peroxy radical suffers extensive C—C bond fission and no stable C_6 oxygenated products can be formed from it.

Although several studies have been made of the gaseous oxidation of n-heptane, the most detailed information about the nature of the carbonyl products is provided by the work of Garner and his colleagues. Thus Garner and Petty[58] showed that an appreciable proportion of the aldehydes and ketones formed by oxidation of the hydrocarbon are of relatively high molecular weight; formaldehyde is not produced by stepwise degradation of higher aldehydes and carboxylic acids are not formed by further oxidation of the corresponding aldehydes. Garner, Long and Temple[59] found all the homologous aldehydes from acetaldehyde to n-valeraldehyde among the products but were unable to identify the various ketones also present. Cartlidge and Tipper[60] detected all aldehydes up to caproaldehyde but concluded that the lower molecular weight compounds predominated; they also found some β-dicarbonyl products during the oxidation of n-heptane at about 300°c.

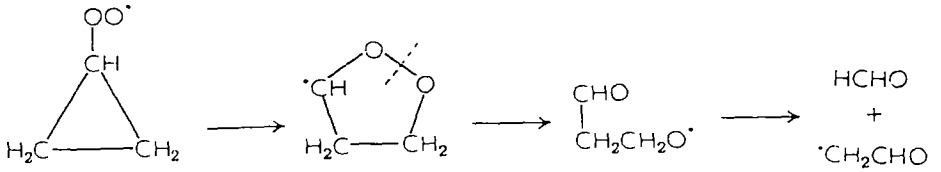
It is fairly firmly established therefore that carbonyl compounds are formed during the uncatalysed gaseous oxidation of alkanes by two main routes: (*i*) the decomposition of hydroperoxides giving—via alkoxy radicals—carbonyl compounds whose skeletons bear a direct relation to that of the fuel[61], e.g. reaction (12), and (*ii*) the

$$R^1R^2R^3COOH \xrightarrow{-OH} R^1R^2R^3CO^\bullet \xrightarrow{-R} R^1R^2C{=}O + R^2R^3C{=}O + R^3R^1C{=}O \quad (12)$$

isomerization, decomposition and oxidation of alkylperoxy radicals leading to rearranged carbonyl compounds and dicarbonyls[62], e.g. reaction (13).

$$\begin{array}{l} R^1R^2\overset{OO^\bullet}{\overset{|}{C}}CH_2CH_2R^3 \xrightarrow{1,5\ \text{hydrogen transfer}} R^1R^2\overset{OOH}{\overset{|}{C}}CH_2\dot{C}HR^3 \xrightarrow[\text{and decomposition}]{1,2\ R^2\ \text{transfer}} R^1COCH_2R^2 \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \Big\downarrow O_2\ \text{then RH} \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad OOH\ OOH \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad | \quad | \\ R^1R^2CCH_2CHR^3 \longrightarrow R^1COCH_2COR^3 \end{array} \quad (13)$$

ii. Cycloalkanes. The gaseous oxidation of the simplest cycloalkane, cyclopropane, like that of methane, gives rise to only one carbonyl compound, formaldehyde, the concentration of which rises to a well-defined maximum at the maximum rate of pressure increase[63]. This compound is believed to be formed by the rearrangement and ring-splitting of cyclopropylperoxy radicals (reactions 14).



(14)

·CH_2CHO is probably further oxidized via ·$OOCH_2CHO$ to formaldehyde, carbon monoxide and OH·. The oxidation of cyclopentane yields both higher aldehydes (mainly acetaldehyde) and formaldehyde, the formation of which appears to involve the interaction of cyclopentylperoxy radicals with oxygen[64]. The corresponding reaction of cyclohexane can, at appropriate temperatures and under otherwise suitable conditions, give quite high yields of aldehydes (e.g. 1·4 mole per mole of cyclohexane consumed) and carbonyl products identified include formaldehyde, acetaldehyde, acrolein, n-valeraldehyde and cyclohexanone[65]. Other workers[66] have also detected propionaldehyde and have shown that the comparatively small amounts of ketones contain acetone, methyl ethyl ketone and methyl n-propyl ketone; the apparent absence of appreciable quantities of cyclic ketones was taken as evidence of the early breaking of the ring, probably at the cyclohexylperoxy radical stage. The presence of β-dicarbonyl compounds among the products of cyclohexane oxidation has also been reported[34].

A number of studies has also been made of the gaseous oxidation of alkyl-substituted cycloalkanes. Burgoyne and Silk[67] showed that aldehydes (including formaldehyde) and ketones are formed during partial oxidation of methylcyclopentane, and Allen and Long[68] have found that acetaldehyde is the principal carbonyl product formed from this hydrocarbon. Garner, Long and Temple[59] have made quite a detailed study of the carbonyl compounds formed during oxidation of methylcyclohexane. The results in Table 3 show that the products include formaldehyde, acetaldehyde (the predominant aldehyde), propionaldehyde and (at higher temperatures) n-butyr-

TABLE 3. The formation of carbonyl products during the gaseous oxidation of methylcyclohexane[59].

Products	Moles per mole of hydrocarbon introduced	
	330°c	380°c
Aldehydes		
Formaldehyde	0·058	0·052
Acetaldehyde	0·256	0·221
Propionaldehyde	0·050	0·033
n-Butyraldehyde	nil	0·007
Total aldehydes	0·364	0·313
Ketones	0·084	0·064

aldehyde; ketones (which are on the whole found in comparatively small quantities) include acetone, methyl ethyl ketone, methyl isopropyl ketone and di-n-propyl ketone as well as traces of the cyclic compounds 2-, 3- and 4-methylcyclohexanone.

b. Oxidation in the presence of homogeneous catalysts. The compounds which have been most widely used for the promotion of gaseous oxidation reactions are simple oxygen-containing species such as ozone and nitrogen oxides (NO and/or NO_2), and halogen compounds such as hydrogen bromide and chlorine.

Early work showed that alkanes are oxidized by ozonized oxygen at temperatures as low as 100°c[69-71]. The ratio of the oxygen in the products to that in the consumed ozone was found to be less than unity at the lower temperatures investigated but to exceed unity (showing that true catalysis of a reaction involving oxygen occurs) as the temperature was raised.

The only work giving detailed information about the reaction products is that of Schubert and Pease[72], who studied the reaction of oxygen containing about 3% ozone with C_3 and C_4 alkanes at 30°c. With propane, acetone is a major product and with isobutane about one-third of the consumed ozone is converted into acetone and the remainder to *t*-butyl alcohol. The kinetic relationships and product distribution were shown to be consistent with a mechanism involving the initial reaction (15), the resulting alkoxy radical either breaking

$$RH + O_3 \longrightarrow RO^{\cdot} + HO_2^{\cdot} \qquad (15)$$

down to yield a carbonyl compound or abstracting hydrogen to give an alcohol (reaction 16). The formation, predominantly, of carbonyl

$$\text{ROH} \xleftarrow{+\text{RH}} \text{RO}\cdot \longrightarrow \text{Carbonyl compound} \qquad (16)$$

compounds from straight-chain alkanes and of alcohols from branched-chain alkanes is consistent with the known modes of decomposition of the derived alkoxy radicals[73]. It should perhaps be pointed out that, according to this mechanism, ozone acts solely as an initiator and does not apparently take part in the propagation

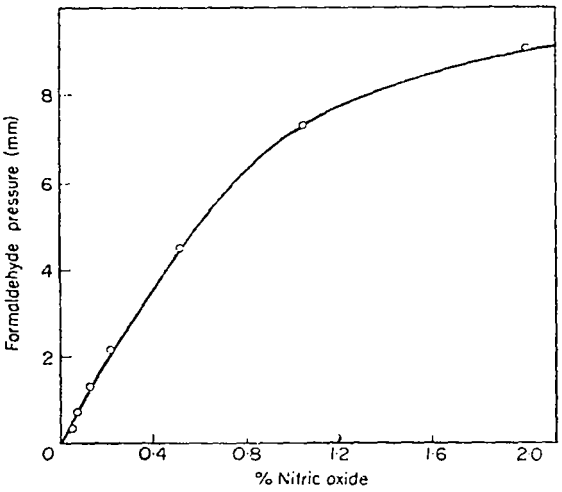


FIGURE 2. The formation of formaldehyde during the NO-catalysed oxidation of methane. Temperature = 650°c, contact time = 0·1 sec, $CH_4:O_2:N_2$ = 9:1:10. [Reproduced, by permission, from ref. 81.]

steps; nevertheless its action is catalytic in the sense that it results in the production of species which are not normally formed in the early stages of reaction and its presence does therefore modify the nature and distribution of the reaction products.

Nitrogen oxides have long been known to have a powerful promoting effect on the oxidation of alkanes and early work showed that the yields of formaldehyde obtained by oxidation of methane were much higher in the presence of these additives (up to 5%) than in the uncatalysed reaction[74–76]. Later work has confirmed this finding[77–79] and in particular has elucidated the optimum conditions for obtaining high yields of formaldehyde[80,81] (Figure 2). In studies of the NO-catalysed oxidation of methane in a flow

system at 600–900°c, it was shown that the use of a boric acid-coated vessel (instead of a glass vessel) greatly improved the reproducibility, lowered the minimum reaction temperature by about 70°c and caused a three-fold increase in the yield of formaldehyde. Indeed with a mixture containing 1 part CH_4, 2 parts air and not more than 1 mole NO per 10 moles HCHO formed, a reactor temperature of 700°c and a contact time of 1 sec, the yield of formaldehyde (based on methane consumed) was about 70%[82].

Several studies have also been made of the NO-catalysed oxidation of propane[83–85]. In general it appears that the catalysis is most pronounced at 300°c but the products were much the same as those from the uncatalysed reaction[83].

Although halogen compounds have a generally inhibiting influence on hydrocarbon + oxygen flame reactions, hydrogen bromide and (to a smaller extent) chlorine are powerful promoters of the slow oxidation of hydrocarbons[86]. HBr-catalysed oxidations are in fact characterized by high specificity of attack on the hydrocarbon and lead to products which are not formed in appreciable quantities in the uncatalysed oxidation. It is chiefly those alkanes which contain CH_2 groups that yield large amounts of carbonyl compounds (although only disappointingly low yields of cyclic ketones could be obtained from cycloalkanes). Thus a mixture containing 2 parts of propane, 2 parts of oxygen and 1 part of hydrogen bromide gives a 75% yield of acetone at 190°c. In the same way n-butane gives a 75% yield of methyl ethyl ketone (together with small amounts of diacetyl), and 2,2,-dimethylbutane gives a 50% yield of pinacolone (methyl *t*-butyl ketone). The mechanism of HBr-catalysed oxidation is thought to involve the stages shown in Scheme 1, and reaction thus

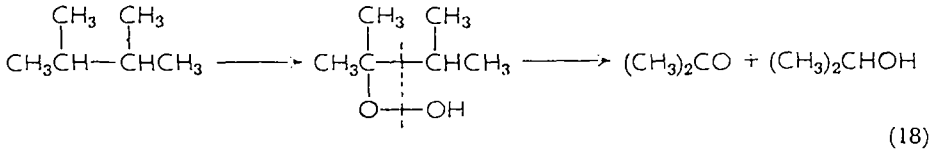
$$\begin{aligned} HBr + O_2 &\longrightarrow Br^{\bullet} + HO_2^{\bullet} \\ RH + Br^{\bullet} &\longrightarrow HBr + R^{\bullet} \\ R^{\bullet} + O_2 &\longrightarrow RO_2^{\bullet} \\ RO_2^{\bullet} + HBr &\longrightarrow ROOH + Br^{\bullet} \end{aligned}$$

SCHEME 1.

results initially in the formation of large amounts of the hydroperoxide ROOH. When RH is a branched-chain alkane, the resulting hydroperoxide is usually fairly stable (e.g. *t*-butyl hydroperoxide obtained from isobutane) whereas, if RH is a straight-chain alkane, extensive decomposition takes place (equation 17) mainly to yield the

$$R^1R^2CHOOH \longrightarrow R^1R^2C{=}O + H_2O \qquad (17)$$

corresponding carbonyl compound. (In this way ethane gives acetaldehyde which is, however, rapidly and completely further oxidized to acetic acid.) Small yields of ketones are nevertheless also formed from branched-chain compounds owing to some decomposition of the initially formed hydroperoxide; thus traces of acetone are formed from isopentane and considerable quantities of this compound are produced during oxidation of 2,3-dimethylbutane (reaction 18).



(18)

The HBr-catalysed oxidation of propane has been very fully studied by Russian workers[87–89]. An equimolar mixture of propane and oxygen containing 3–20% of hydrogen bromide reacts at 200°c to give acetone as the main product, although the yield rarely exceeds 50%. This work shows that there is a well-defined limit to the amount of this compound which can be formed since its presence inhibits further reaction.

Although chlorine is a less effective promoter than hydrogen bromide, its use does enable much more extensive oxidation of hydrocarbons to take place at lower temperatures. In particular the addition of this compound to methane + oxygen mixtures causes a considerable increase in the yields of formaldehyde obtained[78,90]. In the same way chlorine increases the amount of aldehydes formed during the oxidation of propane although the presence of too much halogen causes complete combustion of the hydrocarbon[91].

c. Gaseous oxidation in the presence of heterogeneous catalysts. The heterogeneous catalytic oxidation of alkanes produces, according to the nature of the catalyst and the reaction conditions used, several types of carbonyl compound including saturated and unsaturated aldehydes and ketones. The first step in such oxidation is, however, usually dehydrogenation of the alkane to the corresponding alkene, which is then followed by the oxidation of the alkene. The oxidation of alkanes will therefore be dealt with in the discussion of the heterogeneous catalytic oxidation of alkenes.

The one important exception, where a carbonyl compound is formed without the intermediate production of an alkene, is the oxidation of methane, which can under appropriate conditions give

quite high yields of formaldehyde. A wide variety of catalysts has been tested[92–94] but the two most efficient compounds for this purpose are probably barium chloride[95,96] and cupric oxide[97–99]; the optimum temperature range for this conversion is 500–600°c. Good yields of formaldehyde are also claimed to be obtained by the passage of mixtures of methane and ozonized air over a barium oxide catalyst at 100°c[100]. In most instances the catalytic oxidation of cycloalkanes probably follows a similar route to that with higher alkanes and may lead, as a result first of dehydrogenation and then of C—C bond cleavage, to the formation of saturated and unsaturated aldehydes. Thus cyclohexane, when oxidized over a tin vanadate catalyst, yields considerable amounts of acetaldehyde and acrolein, which are indeed the predominant products of the reaction at about 400°c[100a]. In other cases, however, there is no evidence for dehydrogenation as the first step; methylcyclohexane, for example, can be oxidized over a silver oxide catalyst at 400–500°c to give principally methylcyclohexanone[100b].

2. Liquid-phase reactions

a. General. The liquid-phase oxidation of alkanes and cycloalkanes by molecular oxygen in non-polar media takes place by a mechanism which is in some respects quite similar to that of the corresponding gas-phase reaction at low temperatures. However, in the liquid phase, hydroperoxides are undoubtedly the normal primary products and can often be isolated in high yield. Carbonyl compounds are formed only as a result of the further reaction of hydroperoxides or of their radical precursors. Thus hydroperoxides may decompose to give a carbonyl compound and an alcohol (equation 19) and certain alkylperoxy radicals may disproportionate

$$R^1R^2R^3COOH \longrightarrow R^1COR^2 + R^3OH \qquad (19)$$

with the resulting formation of equivalent quantities of a carbonyl compound and an alcohol and also regeneration of oxygen (equation 20).

$$2\,R^1R^2CHOO\cdot \longrightarrow R^1COR^2 + R^1CH(OH)R^2 + O_2 \qquad (20)$$

In most cases where carbonyl compounds have been detected among the products of the liquid-phase oxidation of alkanes and cycloalkanes, the amounts formed are relatively small and the mechanism of production is unspecific. Thus ketones are detected (together with hydroperoxides) in the oxidation of n-decane[101,102] but the formation of 1-, 2-, 3- and 4-decanol on reduction with

lithium aluminium hydride shows that there is random attack by oxygen at the different CH_2 groups in the original hydrocarbon (Table 4). Similar results are found with n-heptane[103] where, how-

TABLE 4. Relative amounts of ketones formed during the liquid-phase oxidation of n-decane at 145°c[101].

Ketone	% of total ketones formed
2-Decanone	25
3-Decanone	22
4-Decanone	25
5-Decanone	28

ever, under appropriate conditions (150°c and 33 atm pressure) ketones resulting from oxidative C—C bond fission are formed as major products[104]. It has been shown that temperature is probably one of the most important factors controlling the decomposition of hydroperoxides (and hence the yield of ketones) formed during the oxidation of C_{10} to C_{12} straight-chain alkanes[105]. Methyl ethyl ketone is quite an important product of the oxidation of liquefied n-butane at 145°c and 50 atm pressure[106]; acetaldehyde and acetone are also formed during the oxidation of this alkane[107]. In certain cases β-dicarbonyl compounds have been detected among the products of autoxidation of alkanes (e.g. 2,6-dimethylheptane)[108]. The formation of such compounds is consistent with a mechanism involving intramolecular isomerization of the initially formed alkylperoxy radical followed by addition of further oxygen to form another peroxy radical and perhaps eventually a dihydroperoxide, either of which species may subsequently decompose with the production of a dicarbonyl compound.

The liquid-phase oxidation of cycloalkanes also leads to cyclic ketones in suitable circumstances. Thus the oxidation of cyclohexane at 155°c and 9 atm pressure results in the formation of cyclohexanone (and cyclohexanol)[109]; cyclododecanone is produced in 96% yield (via the intermediate corresponding hydroperoxide) when oxygen is passed through cyclododecane at 150°c for 2–3 h[110,111].

b. The role of catalysts. The function of a catalyst in the liquid-phase oxidation of saturated hydrocarbons is usually two-fold. Firstly it may increase the rate of incorporation of oxygen during the primary chain cycle producing hydroperoxide; thus, for example,

the rate of formation of hydroperoxide will be high in the presence of a substance, SH, which is itself a good hydrogen donor for reaction (21). Secondly, however, it may affect the stability of the

$$RO_2^{\bullet} + SH \longrightarrow ROOH + S^{\bullet} \qquad (21)$$

initially formed hydroperoxide and influence the course of its decomposition. Peroxides can decompose by several routes depending upon the nature of the catalyst present but in cases where the favoured mode of decomposition produces carbonyl compounds the catalyst increases the yields of such compounds. Thus metal-catalysed decomposition leads to the species $RO^{\bullet}$, RO^-, $RO_2^{\bullet}$, RO_2^+, H^+ and OH^- [112]. The usual fate of the free radicals $RO^{\bullet}$ and $RO_2^{\bullet}$ is electron acceptance from metal ions to give RO^- and RO_2^-. If R is a tertiary alkyl group, however, decomposition to carbonyl compounds is the predominant fate of $RO^{\bullet}$ and $RO_2^{\bullet}$. If the redox potential of the metal ion couple is appropriate, pairs of reactions such as (22a) and (22b) combine to give the overall change of

$$M^{n+} + ROOH \longrightarrow M^{(n+1)+} + RO^{\bullet} + OH^- \qquad (22a)$$

$$M^{(n+1)+} + ROOH \longrightarrow M^{n+} + RO_2^{\bullet} + H^+ \qquad (22b)$$

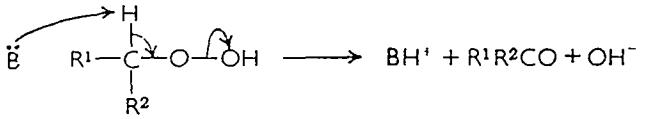
equation (23) and thus lead to extensive production of ketones if R

$$2\,ROOH \xrightarrow{M^{n+}} RO^{\bullet} + RO_2^{\bullet} + OH^- + H^+ \qquad (23)$$

is a tertiary alkyl group. The solvent too will influence the rate of formation of $RO^{\bullet}$ from ROOH as a result of the reaction (24) and

$$ROOH + SH \longrightarrow S^{\bullet} + RO^{\bullet} + H_2O \qquad (24)$$

will affect also the fate of $RO^{\bullet}$, hydrogen-donating solvents tending to favour production of alcohols, ROH, rather than carbonyl compounds. Base-catalysed decomposition of peroxides occurs by three different elimination reactions, one of which produces specifically the carbonyl compound R^1R^2CO from the peroxide R^1R^2CHOOH (i.e. from the initial alkane $R^1CH_2R^2$) (equation 25).



$$\longrightarrow BH^+ + R^1R^2CO + OH^- \qquad (25)$$

The metal-catalysed autoxidation of cycloalkanes to ketones has been investigated industrially; cobalt naphthenate, for example, catalyses the oxidation of cyclooctane at 120°c giving cyclooctanone,

1-cyclooctanol-4-one and 1-cyclooctanol-5-one as well as cyclooctanol[112a].

Boric acid is a useful catalyst for the autoxidation of higher alkanes, although mixtures of isomeric ketones are formed as products. At 165°c the oxidation of n-hexadecane with 4% oxygen in nitrogen in the presence of boric acid produces all the possible hexadecanones as well as some diones and triones[112b]. Under similar conditions, over 50% yields of ketones (together with alcohols and acids) are produced by the oxidation of C_{16} to C_{18} alkane fractions[112c]. The reaction probably follows the route (26).

$$R^1CH_2R^2 \xrightarrow{-H} R^1\dot{C}HR^2 \xrightarrow{+O_2} R^1\dot{C}H(OO\cdot)R^2 \longrightarrow R^1\dot{C}(OOH)R^2 \longrightarrow R^1R^2CO + \cdot OH \quad (26)$$

B. Reactions Involving Other Oxidants

1. Gas-phase reactions

Several studies have been made of the gas-phase reaction of alkanes with oxygen atoms, but little information is available regarding the products. However, small amounts of formaldehyde and acetaldehyde are formed from methane[113] and ethane[114] respectively.

Nitrous oxide also reacts with alkanes to give low yields of carbonyl compounds. With methane, reaction takes place only above about 700°c where some decomposition of nitrous oxide to oxygen atoms is probably taking place[115]. Reaction appears to involve the stages (27a) and (27b) followed by the direct interaction of the resulting

$$CH_4 + O \longrightarrow CH_3^{\cdot} + \cdot OH \quad (27a)$$
$$\cdot OH + CH_4 \longrightarrow CH_3^{\cdot} + H_2O \quad (27b)$$

methyl radicals with unchanged nitrous oxide (reaction 28). The formaldehyde produced is, however, rapidly oxidized further.

$$CH_3^{\cdot} + N_2O \longrightarrow CH_3O\cdot + N_2 \quad (28)$$
$$\downarrow$$
$$HCHO + H\cdot$$

With ethane, reaction occurs at about 550°c (where nitrous oxide is stable) and probably involves direct interaction of ethyl radicals, formed by pyrolysis of the alkane, with nitrous oxide[116]. The

reaction (29) can be shown, however, to have a high activation

$$C_2H_5^{\cdot} + N_2O \longrightarrow C_2H_5O^{\cdot} + N_2$$
$$\downarrow$$
$$CH_3^{\cdot} + HCHO \qquad (29)$$

energy (31 kcal/mole) and thus to be slow, so that the yields of aldehydes are always low[117]. A similar mechanism operates for higher alkanes[118], the small amounts of carbonyl products presumably arising from breakdown of alkoxy radicals formed by reaction (30).

$$R^{\cdot} + N_2O \longrightarrow RO^{\cdot} + N_2 \qquad (30)$$

2. Liquid-phase reactions

Methyl and methylene groups in saturated hydrocarbons can, under appropriate experimental conditions, be oxidized to —CHO and >CO respectively by several reagents (e.g. chromates and permanganates), although, if a tertiary CH group is also present, attack generally occurs preferentially at this latter position leading to the formation of a tertiary alcohol. Although a considerable amount of work has been done on the liquid-phase oxidation to carbonyl compounds of hydrocarbons containing one or more aromatic rings (this is discussed in section IV), very little information exists regarding the oxidation of alkanes and cycloalkanes.

One reagent, however, which converts such hydrocarbons into carbonyl compounds is chromium trioxide in acetic anhydride (or glacial acetic acid). Thus 2,2,4-trimethylpentane is oxidized to acetone and 4,4-dimethyl-2-pentanone[119], and in the same way 2,3-dimethylbutane can be oxidized to acetone and 3-methyl-2-butanone, 2,2-dimethylbutane to 3,3-dimethyl-2-butanone, and methylcyclohexane to cyclohexanone, 2-methylcyclohexanone and other unidentified ketones[120]. Measurements of the rate of oxidation by chromium trioxide of a number of saturated hydrocarbons enable approximate assessments to be made of the relative reactivity of >CH, $>CH_2$ and $—CH_3$ groups towards oxidative attack[121]. A methyl group is shown to be attacked about 10^3 times slower than a (tertiary) CH group, although in alkanes having a CH_3 group adjacent to a tertiary centre the methyl group is attacked preferentially.

Fuming nitric acid at ambient temperatures converts n-octane into 2-octanone, probably via octane-2-nitrate[121a].

III. OXIDATION OF ALKENES, CYCLOALKENES AND ALKYNES

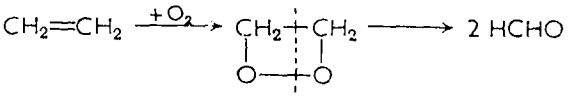
A. Reactions Involving Molecular Oxygen

1. Gas-phase reactions

a. Homogeneous oxidation. The gaseous oxidation of unsaturated hydrocarbons has been considerably less fully studied than that of the corresponding saturated compounds. In general, however, the reactions of alkenes and alkynes would be expected to be rather more complex, for the presence of a multiple bond in the initial organic compound makes possible not only addition of oxygen to this bond but also the production of resonance-stabilized radicals as a result of abstraction of hydrogen.

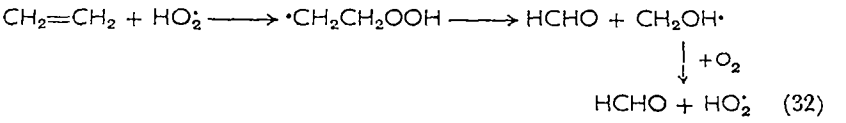
It is generally agreed that aldehydes are formed as early intermediate products of the gaseous oxidation of ethylene. Bone and Wheeler[122] found that formaldehyde was the most prominent carbonyl product and that its formation preceded that of carbon oxides and water. Blair and Wheeler[123,124] showed that acetaldehyde could also be a major product under appropriate conditions and claimed a yield of 50% in one experiment. Most later workers agree that formaldehyde is generally formed in rather larger amounts than acetaldehyde[125–129] but the production of acetaldehyde appears to be favoured by the use of high pressures[127,129]. Lenher[125] detected glyoxal as well as formaldehyde when ethylene was oxidized at 360–400°c but could not find acetaldehyde or glycollaldehyde under these conditions; above 400°c and with low contact times, however, acetaldehyde was present among the products although it was clearly formed *after* formaldehyde. Harding and Norrish[130] compared the oxidation of ethylene with that of formaldehyde under similar conditions and showed that the rate of oxidation of ethylene is closely dependent on the growth of formaldehyde, which has the required properties of a degenerate chain-branching agent. During the oxidation of ethylene the formaldehyde concentration reaches a maximum value at the same time as the rate of reaction and artificial addition of the aldehyde reduces or eliminates the preceding induction period. Knox and Wells[129] have recently shown that, in the initial stages of the oxidation of pure ethylene at 362°c, over 80% of the alkene consumed is converted into formaldehyde. Although the formation of this compound is most simply accounted

for by a mechanism involving the production and subsequent breakdown of a four-membered cyclic peroxide (reaction 31), it is



(31)

concluded that other features of the oxidation are more consistent with a series of radical reactions such as (32).



(32)

In some respects the behaviour of ethylene is not entirely characteristic of unsaturated hydrocarbons since full olefinic properties are not developed until the molecule contains a CH_2 group adjacent to the double bond. The simplest compound in which this is the case is, of course, propylene, the oxidation mechanism for which differs appreciably from that for ethylene. Lenher[125,131], who studied the oxidation of propylene around 300°c, claimed to have found small amounts of propionaldehyde, acetaldehyde and formaldehyde among the products. In most later work, however, only total aldehydes and formaldehyde (and thus, by difference, higher aldehydes) have been determined; there seems to be little doubt that acetaldehyde is an important constituent of the higher aldehydes[132–134] but the exact nature of other compounds present has not always been elucidated. Newitt and Mene[127] studied the oxidation of propylene at temperatures from 215 to 260°c and at pressures up to 20 atm. Only total aldehydes were systematically determined and their concentration appeared to increase with the proportion of propylene in the initial gas mixture; it was concluded that between one-third and one-half of the aldehydes was formaldehyde. Burgoyne and Cox[128] studied the reaction at somewhat higher temperatures (400–600°c) in a flow system and found small amounts of formaldehyde, even less acetaldehyde, and no other carbonyl compound. When a steel reaction vessel was substituted for a Pyrex glass vessel, scarcely any aldehydes were formed except at elevated pressures. Mulcahy and Ridge[135] made a special study of the reactions taking place during the induction period preceding propylene oxidation at 290°c. The concentration of formaldehyde becomes appreciable half-way through the induction period and then rises continuously; in contrast the amounts of

higher aldehydes remain very small until near the end of the induction period and then increase rapidly. The length of the induction period appears to depend upon the rate of production of both higher aldehydes and formaldehyde but it is believed that degenerate chain-branching is caused mainly by the higher aldehydes. This conclusion is supported by the work of Mullen and Skirrow[136], who showed not only that formaldehyde is formed in smaller quantities than higher aldehydes (Table 5) but also that the former compound is not nearly as effective an additive as acetaldehyde in eliminating the induction period; these workers also found acrolein among the intermediate oxidation products but concluded that its concentration was generally only about 10% of that of

TABLE 5. The formation of formaldehyde and acetaldehyde during the gaseous oxidation of propylene at 340°C[136]. Propylene pressure, 50 mm; oxygen pressure, 70 mm.

Stage of reaction	HCHO (10^{-4} mole)	CH_3CHO (10^{-4} mole)
End of induction period	0·03	0·22
Pressure change = 7 mm	0·08	0·34
Pressure change = 11 mm	0·12	0·23
End of reaction	0·08	0·13

acetaldehyde. It was suggested that the most probable mechanism for the formation of acetaldehyde which would explain its observed invariable predominance over formaldehyde, is one involving the stages (33).

$$CH_3CH{=}CH_2 \xrightarrow{+R} CH_3\dot{C}HCH_2R \xrightarrow{+O_2} CH_3\overset{OO\cdot}{\overset{|}{C}}HCH_2R \xrightarrow{+H} CH_3\overset{OOH}{\overset{|}{C}}HCH_2R \longrightarrow CH_3CHO + R\dot{C}H_2 + {\cdot}OH \tag{33}$$

Some light has also been thrown on the mechanism of formation of carbonyl products during the oxidation of propylene by the use of isotopic tracer techniques. Lukovnikov and Neiman[137], studying the oxidation of 2-^{14}C-propylene, showed that all the acrolein and acetaldehyde formed are labelled but that practically none of the

formaldehyde is. ^{14}C-labelled azomethane has been used as an additive during the gaseous oxidation of propylene[138], and the resulting ^{14}C-methyl radicals were found to react to give labelled formaldehyde, so that methyl radicals are probably the precursors of this product in the uncatalysed oxidation of propylene. Addition of about 1% of 1-^{14}C-acetaldehyde has made it possible to determine the separate rates of formation and destruction of this carbonyl compound during the gaseous oxidation of propylene[139]. Both rates are found to be exceptionally high under cool-flame conditions and the observed values for the rate of formation of acetaldehyde agree well with those calculated from the oxidation mechanism postulated by Shtern and Polyak[140,141].

Comparatively little work has been done on higher monoolefins. An early study of the oxidation of 2-butene at temperatures from 400 to 500°c showed the presence among the products of considerable amounts of acetaldehyde together with a little glyoxal or glycollaldehyde[142]. Dobrinskaya and Neiman[143] investigated the oxidation of this same alkene at 300–400°c and, using polarographic methods of analysis, detected crotonaldehyde among the products. Blundell and Skirrow[144] determined total aldehydes formed from 2-butene under comparable conditions and identified formaldehyde, acetaldehyde and acrolein (but no crotonaldehyde); formaldehyde accounted for about half the total aldehydes. It was shown that acetaldehyde was much more effective than formaldehyde in eliminating the induction period and was therefore probably the main compound responsible for degenerate chain-branching. It was suggested that acetaldehyde was formed largely by decomposition of an intermediate hydroperoxide (reactions 34). Considerable amounts of

$$\mathrm{CH_3CH{=}CHCH_3} \xrightarrow{-H} \mathrm{CH_3CH{=}C\dot{H}CH_2} \rightleftharpoons \mathrm{CH_3\dot{C}HCH{=}CH_2} \xrightarrow{+O_2}$$

$$\mathrm{CH_3CH(OO\cdot)CH{=}CH_2} \xrightarrow{+H} \mathrm{CH_3CH(OOH)CH{=}CH_2} \longrightarrow \mathrm{CH_3CHO + C_2H_3^{\cdot} + {\cdot}OH} \quad (34)$$

acetone are obtained from 2-butene when this hydrocarbon is oxidized in the presence of a fine dispersion of solid particles which helps to maintain isothermal conditions[145]; in the same way quite large quantities of formaldehyde and propionaldehyde (as well as small amounts of various ketones) are obtained from 1-butene. The homogeneous oxidation of isobutene has been studied by Skirrow and Williams[146], who have shown that the early formation of carbonyl products (acetone and formaldehyde, in equal quantities,

and isobutyraldehyde) can be accounted for by assuming the simultaneous occurrence of the two overall reactions (35a) and (35b).

$$(CH_3)_2C{=}CH_2 + O_2 \longrightarrow (CH_3)_2CO + HCHO \qquad (35a)$$

$$(CH_3)_2C{=}CH_2 + \tfrac{1}{2}O_2 \longrightarrow (CH_3)_2CHCHO \qquad (35b)$$

The gaseous oxidation of 2-methyl-2-butene has been extensively studied by Cullis, Fish and Turner[147,148]. The kinetic and analytical data for the oxidation of this alkene (mainly around 250°c)[147] suggest that two mechanisms operate concurrently, viz. hydrogen

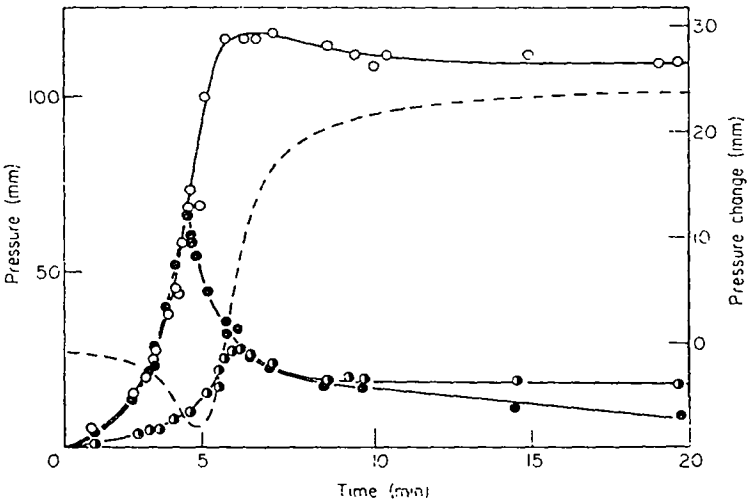
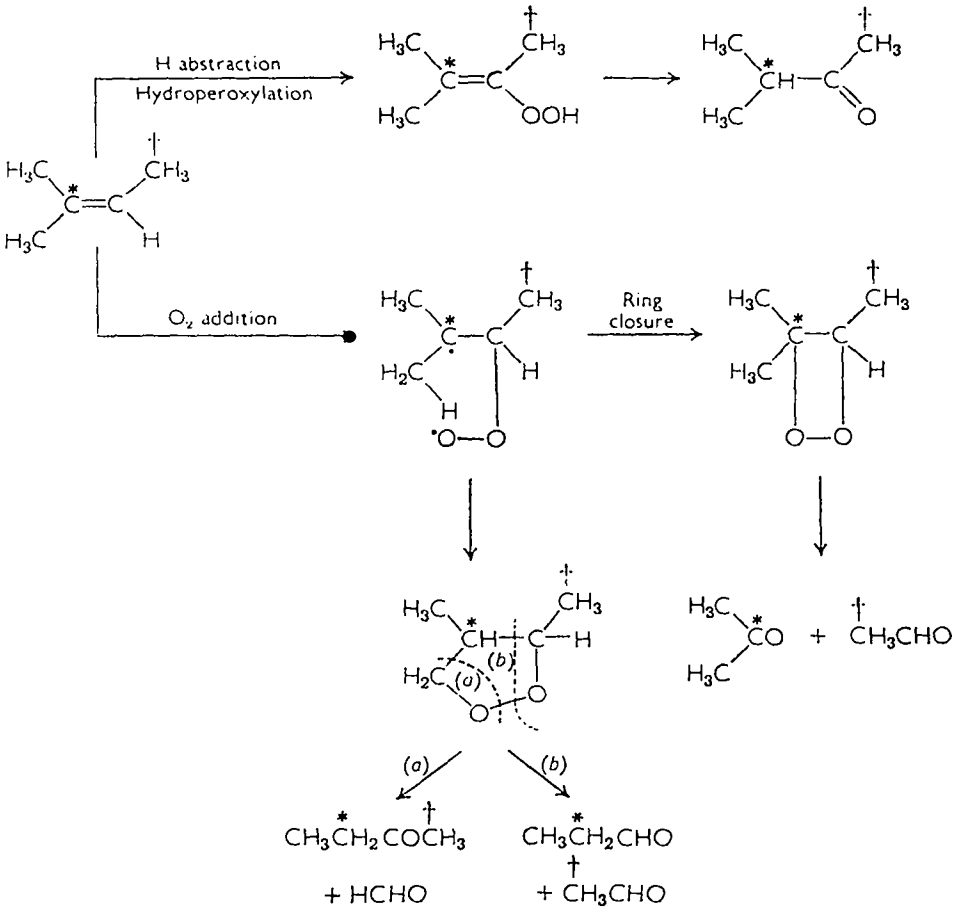


FIGURE 3. The formation of the major carbonyl products during the gaseous oxidation of 2-methyl-2-butene. Temperature = 265°c, alkene pressure = 200 mm, oxygen pressure = 200 mm. ○ = acetone, ● = acetaldehyde, ◑ = methyl isopropyl ketone; – – – – = pressure change. [Reproduced, by permission, from ref. 147.]

abstraction followed by hydroperoxylation (leading to methyl isopropyl ketone) and oxygen addition at the double bond forming in turn a biradical and a cyclic peroxide (which is the precursor of acetone and acetaldehyde). The pattern of formation of the three major carbonyl products is shown in Figure 3. The correctness of this conclusion is confirmed by determination of the specific activities of, and sites of carbon-14 in, the major carbonyl products (acetone, acetaldehyde and methyl isopropyl ketone) and the minor carbonyl

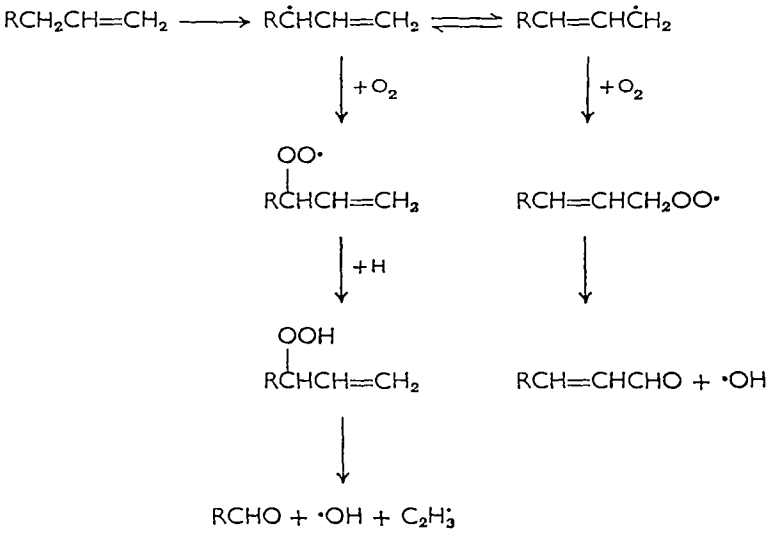
products (methyl ethyl ketone and propionaldehyde) formed by oxidation of 2-^{14}C- and 4-^{14}C-2-methyl-2-butenes[148]. The probable course of the oxidation is shown in Scheme 2[149].



SCHEME 2.

Analysis of the oxidation products of 1-hexene at 263°c suggests the presence of small amounts of both saturated and unsaturated aldehydes[150]. Formaldehyde accounts for about half the total aldehydes produced but the analytical results indicate the formation of an appreciable quantity of aldehydes containing three or more carbon atoms. The aldehydes appear to be formed by breakdown both of initially formed hydroperoxides and of the precursor peroxy

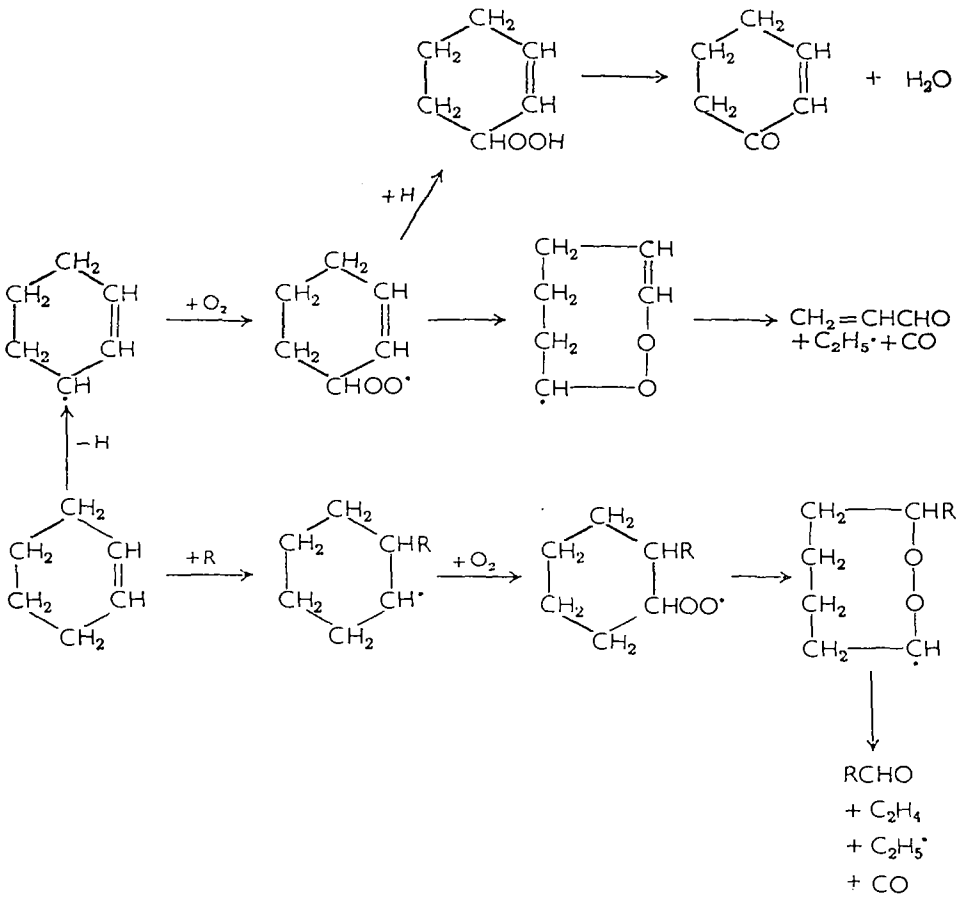
radicals, the production of which, as with 2-butene, probably involves some isomerization of the original alkene radical (Scheme 3).



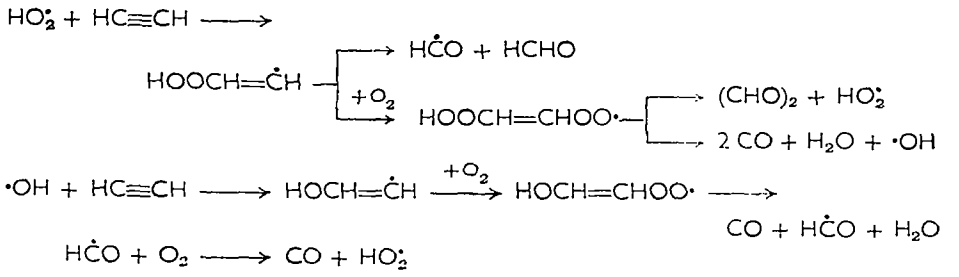
SCHEME 3.

One alkene which is especially resistant to oxidation is 2,2,4-trimethyl-1-pentene[151]. This compound yields no carbonyl products below 400°c but increasing amounts of such compounds (especially formaldehyde) are formed up to temperatures of about 660°c.

The gaseous oxidation of unsaturated hydrocarbons other than acyclic monoolefins has received very little attention. The oxidation of cyclohexene at about 240°c leads to the formation of several carbonyl compounds including formaldehyde, acetaldehyde, acrolein, acetone and 1-cyclohexen-3-one[152]. Several mechanisms may be postulated to account for the observed products, e.g. Scheme 4. A study of the gaseous oxidation of butadiene[153] has shown that formaldehyde, acrolein and glyoxal are produced. Both glyoxal and formaldehyde are products of the gaseous oxidation of acetylene at 250–300°c[154,155]. Although it has frequently been assumed that the reaction proceeds almost entirely via the intermediate formation of glyoxal[154–158], it seems more likely that the formation of both carbonyl compounds takes place by what are essentially side-reactions and that the oxidation involves mainly attack of acetylene by HO_2 and ·OH radicals (Scheme 5)[159].



Scheme 4.



Scheme 5.

Almost no systematic work has been done on homogeneous catalysis of the oxidation of unsaturated hydrocarbons. The oxidation of isobutene catalysed by hydrogen bromide has been studied at

temperatures from 100 to 200°c but only at the higher temperatures can appreciable amounts of carbonyl compounds (mainly acetone and methacrolein) be detected[160]. The oxidation of 1-pentene is catalysed by ozone and leads to the formation of some n-butyraldehyde, probably via an intermediate ozonide[161]. Nitrogen oxides are good catalysts for the gaseous oxidation of acetylene and the yields of glyoxal found under these conditions can be as high as 50% (based on the acetylene consumed)[162]. Glyoxal is also the principal product of the direct reaction between nitrogen dioxide and acetylene[163] and the catalysed oxidation probably involves the overall reaction (36) followed by reoxidation of the nitric oxide to nitrogen dioxide.

$$C_2H_2 + 2\,NO_2 \longrightarrow (CHO)_2 + 2\,NO \qquad (36)$$

b. Oxidation in the presence of heterogeneous catalysts. Considerable attention has recently been paid to the oxidation of alkenes to unsaturated carbonyl compounds; industrially important reactions

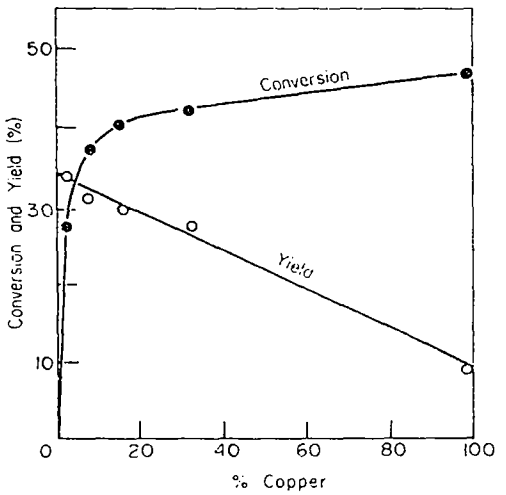


FIGURE 4. The effect of copper content on the oxidation of isobutene to methacrolein over a supported copper oxide catalyst. Temperature = 400°c, isobutene: oxygen = 1:1. [Reproduced, by permission, from ref. 168.]

of this kind include the conversions of propylene into acrolein and of isobutene into methacrolein. Quite a wide variety of catalysts enable such reactions to take place selectively. Thus, for example, the passage of nitrogen or steam containing 2–10% propylene and

2–15% oxygen over a mixed tin–antimony oxide catalyst at 300–500°c gives an 83% yield of acrolein at 48% conversion[164,165]; other catalysts for this reaction include copper oxide[166,167], bismuth phosphomolybdate, cobalt manganates ($CoMn_2O_4$ and Co_2MnO_4) and hexamolybdenum (or hexatungsten) tellurate. Copper oxide catalysts are particularly effective in converting isobutene into methacrolein, the conversion obtainable rising sharply with the percentage of copper in the catalyst until this reaches 10%; further increase in copper content has the disadvantage of reducing the selectivity of the oxidation (Figure 4)[168].

Some valuable information about the mechanism of such conversions is provided by isotopic tracer studies. Thus oxidation of 1-^{13}C-propylene over a mixed bismuth–phosphorus–molybdenum oxide catalyst yields equal amounts of $^{13}CH_2{=}CHCHO$ and $CH_2{=}CH^{13}CHO$[169]. Although at 250°c a high proportion of the recovered alkene had isomerized to 3-^{13}C-propylene, at 450°c it was largely unchanged. The isomerization taking place during the formation of acrolein is thus not connected with the prior isomerization of the alkene and shows that the oxidation of propylene takes place through a symmetrical intermediate. In order to determine whether this is the allyl radical, $CH_2{=}CH\dot{C}H_2$, or the isopropyl radical, $CH_3\dot{C}HCH_3$, experiments were carried out with a catalyst surface which had been treated with D_2O at 450°c. Under these conditions the route via allyl should give no deuteroacrolein while that via isopropyl should give 50% of the deuteratcd product. In fact 95% of the acrolein formed was undeuterated, thus supporting strongly the allyl route. There are several other systems where the use of tracer techniques can throw light on the oxidation mechanism[170–173].

Unless special precautions are taken, most oxidations involving relatively large alkene molecules are not so clear-cut and result in the formation of a variety of carbonyl (and other) products; in general, high yields of any single species arc not obtained.

Thus the oxidation of the isomeric butencs over vanadium pentoxide yields formaldehyde and acetaldehydc as the principal carbonyl products[174] and 2,4,4-trimethyl-1- and -2-pentenes, when oxidized over cupric oxidc, give some methacrolein as well as C_8 unsaturated aldehydes[175]. During the oxidation of α-pinene over vanadium pentoxide, formaldehyde is produced in large quantities particularly at high pinene:oxygen ratios[176]. The yield of this product approaches 65% under favourable conditions although the

main interest of the process is clearly the production of maleic anhydride (maximum yield 29%). Under essentially similar conditions, Rafikov and Suvorov[177] have observed the formation of benzaldehyde, *p*-isopropylbenzaldehyde and *p*-tolyl methyl ketone in addition to formaldehyde.

Detailed studies have recently been made of the oxidation of pentenes over vanadium pentoxide at about 300°c[178,179]. The reaction produces saturated carbonyl compounds both corresponding to the original olefin skeleton and resulting from scission of the alkene, as well as small amounts of α,β-unsaturated carbonyl products. Since the pentenes all tend to isomerize (both by transfer of hydrogen and, to a lesser extent, transfer of methyl) on the catalyst, oxidation tends to give a spectrum of products characteristic not only of the starting pentene but also of its isomers. Fundamental studies of the kinetics of the reactions concerned[178,179] and of the physicochemical properties of the catalyst[180] enable the formation of each type of carbonyl product to be tentatively associated with the reaction of given species among the variety of possible adsorbed forms of alkene and oxygen. For example, during the oxidation of 2-methyl-2-butene[178], the adsorbed alkene is oxidized by V^{5+} to two cations, $(CH_3)_2\overset{+}{C}CHCH_{3(ads)}$ and $(CH_3)_2C\overset{+}{C}HCH_{3(ads)}$, each of which reacts with the O^{2-} ions of the catalyst to give an adsorbed anion which is in turn the precursor of a given carbonyl scission product. Thus the former cation leads to the formation of acetone (reaction 37) and the latter to the formation of acetaldehyde (reaction 38).

$$(CH_3)_2\overset{+}{C}-\underset{(ads)}{CHCH_3} + O^{2-} \longrightarrow (CH_3)_2\overset{O^-}{C}-\underset{(ads)}{CHCH_3} \longrightarrow (CH_3)_2C{=}O \qquad (37)$$

$$(CH_3)_2C-\overset{+}{C}HCH_3 + O^{2-} \longrightarrow (CH_3)_2C-\overset{-O}{C}HCH_3 \longrightarrow CH_3CHO \qquad (38)$$

Either of the organic oxyanions involved can give also 2-methyl-2,3-epoxybutane (by losing an electron to the surface and then cyclizing) which can in turn isomerize on the surface to 3-methyl-2-butanone. Such conclusions may eventually make it possible to explain why different heterogeneous catalysts cause the conversion of the same alkene into a carbonyl product or into a diene. Thus, for example, 2-butene is oxidized predominantly to methyl vinyl ketone

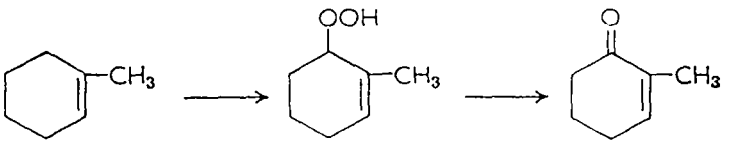
over cuprous oxide on silicon carbide[181] but suffers oxidative dehydrogenation to butadiene on bismuth molybdate[172]. Similar explanations may be advanced to account for the fact that the same catalyst is effective in the conversion of closely related alkenes into widely different products, e.g. bismuth molybdate[172] produces acrolein from propylene and methacrolein from isobutene but converts n-butenes and n-pentenes into dienes.

2. Liquid-phase reactions

a. General. The reaction of alkenes and cycloalkenes in the liquid phase with gaseous oxygen is in some ways similar to the corresponding homogeneous oxidation of such compounds in the gas phase; mechanisms involving initially both hydrogen abstraction and addition of oxygen to double bonds can undoubtedly operate.

With acyclic non-conjugated dienes and cycloalkenes, the hydroperoxylation mechanism predominates and generally leads to high yields of α,β-unsaturated hydroperoxides as primary products. Such compounds vary considerably in their stability and in their modes of breakdown but, in some cases, ketones, formed apparently by decomposition of hydroperoxides, are found among the products.

Mechanisms of ketone production have been discussed by Farmer and his coworkers[182,183]. Thus 1-methylcyclohexen-6-one and 1,2-dimethylcyclohexen-3-one have been found among the products of the liquid-phase oxidation of 1-methylcyclohexene[184] and 1,2-dimethylcyclohexene[185] respectively, these carbonyl compounds being assumed to be formed by dehydration of the initially formed hydroperoxide, e.g. reaction (39). Farmer and Sundralingham[182]



(39)

were, however, unable to obtain cyclic ketones from the uncatalysed oxidation of cyclohexenes although they point out that such compounds are formed in the presence of suitable catalysts.

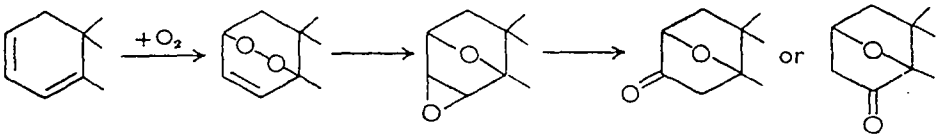
As hydrogen abstraction from the initial hydrocarbon becomes less easy, however, there is a well-defined decrease in the yield of hydroperoxide[186]. Particularly striking is the reduction in yield which takes place on introduction of a methyl group at the double

bond. Olefins with a trisubstituted double bond give very small amounts of hydroperoxide and are oxidized in the liquid phase only with concurrent loss of unsaturation and formation of carbonyl compounds of relatively low molecular weight.

Such behaviour might be explained in principle on the basis of the very early suggestion[187] that the primary oxidation products of alkenes are four-membered ring cyclic peroxides (moloxides) which subsequently break down by simultaneous O—O and C—C bond fission, e.g. reaction (40). In some cases direct addition of oxygen to

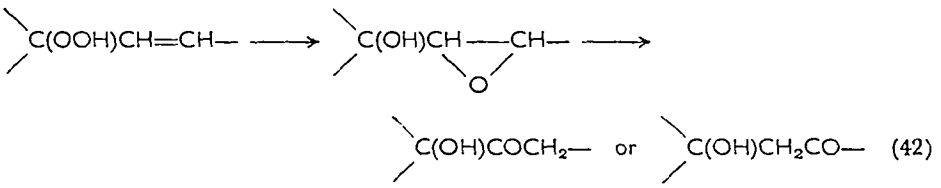
$$R^1R^2C{=}CR^3R^4 + O_2 \longrightarrow R^1R^2C(-O-O-)CR^3R^4 \longrightarrow R^1R^2CO + R^3R^4CO \quad (40)$$

an unsaturated hydrocarbon can indeed occur but this reaction takes place mainly with conjugated (1,3-) dienes of cyclic structure[188] where the initial step is transannular addition of oxygen followed by formation of an epoxide which subsequently rearranges to yield carbonyl products[189], e.g. reactions (41). There appears, however, to



(41)

be little evidence to indicate that the analogous sequence (42) takes



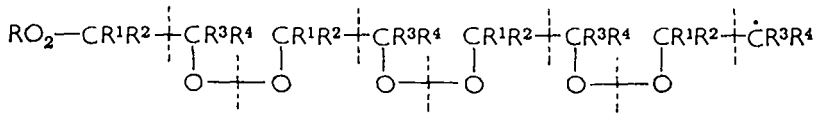
(42)

place with unconjugated alkenes, although certain workers have claimed that enolizable α-ketols are formed during autoxidation of unsaturated compounds[190].

In other cases where the nature of the carbonyl products appears to indicate direct addition of oxygen to a double bond, more recent work has shown that a copolymerization mechanism is in operation, in which a peroxy monoradical adds to the alkene, e.g. equation (43),

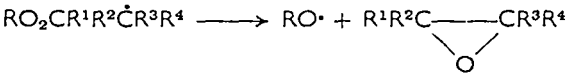
$$RO_2^{\cdot} + R^1R^2C{=}CR^3R^4 \longrightarrow RO_2{-}CR^1R^2{-}\dot{C}R^3R^4 \quad (43)$$

followed by alternate addition of oxygen and alkene to yield a structure **1** which breaks down as shown to yield mainly the carbonyl



(**1**)

products R^1R^2CO and R^3R^4CO. This type of mechanism has been substantiated, for example, for the thermally initiated and the α,α'-azobisisobutyronitrile-initiated oxidation of 2,4,4-trimethyl-1-pentene in which ketones are major products[191]. During such copolymerization, the end groups also react, e.g. equation (44), giving the



(44)

epoxide of the original alkene which may then rearrange to give the isomeric carbonyl compounds $R^1R^2R^3CCOR^4$ and $R^1COCR^2R^3R^4$. This behaviour is found with hexenes[192], as well as with 2-methyl-1-nonene and 2,4,4-trimethyl-1-pentene[193], the oxidations of which produce high yields of ketones.

Mechanisms which are in all respects analogous to those outlined for alkenes operate with their simple derivatives such as olefinic acids and esters, and lead in suitable circumstances to products containing carbonyl groups.

b. The role of catalysts. The products obtained from the liquid-phase oxidation of alkenes vary considerably with the nature of the catalyst used, the principal effect of which is to change the rate and mode of decomposition of initially-formed hydroperoxides. Thus, for example, Willstätter and Sonnenfeld[194,195] obtained 1-cyclohexanol-2-one by oxidation of cyclohexene in the presence of osmium, and Cook[196] found that ferrous phthalocyanine catalyses the production of 1-methylcyclohexen-6-one from 1-methylcyclohexene. Other metal catalysts cause the formation of ketones during the oxidation of α- and β-pinene[197–199].

The mechanism of action of transition metal ion catalysts is probably generally similar to that operative during the liquid-phase oxidation of alkanes. Thus Bawn, Pennington and Tipper[200] have shown that the primary hydroperoxide formed from 2-methyl-2-

butene reacts with cobalt ions in accordance with equations (44) and

$$ROOH + Co^{2+} \longrightarrow RO\cdot + OH^- + Co^{3+} \quad (44a)$$

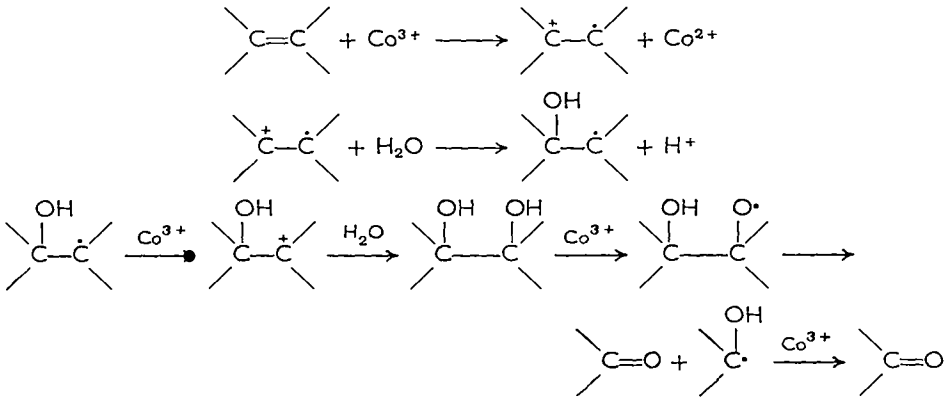
$$ROOH + Co^{3+} \longrightarrow RO_2\cdot + Co^{2+} + H^+ \quad (44b)$$

thus leads to the formation of the aldehyde $(CH_3)_2C{=}CHCHO$ as one of the main decomposition products.

In order to elucidate the catalytic effect of transition metal ions in autoxidation processes, studies have been made of the reaction of cobaltic ions in the absence of oxygen with several alkenes (2-methyl-2-butene, 2-pentene, 1-hexene, 1-heptene, 1-octene, 2-ethyl-1-butene and isoprene)[201]. Analysis shows that the alkenes suffer oxidative disruption at the double bond to give saturated carbonyl compounds, e.g. reaction (45). The aldehydes so formed rapidly react further to

$$(CH_3)_2C{=}CHCH_3 \xrightarrow{Co^{3+}} (CH_3)_2CO + CH_3CHO \quad (45)$$

give acids, but the ketones are relatively stable. The mechanism of the reaction probably involves the initial formation of a radical ion which leads to carbonyl compounds by several alternate hydrolysis and electron-transfer steps (Scheme 6).



SCHEME 6.

Several other metal ions, e.g. Pd^{2+}, readily form complexes with alkenes and the formation of such compounds alters profoundly the rate and course of their oxidations. One especially interesting example of the catalysed oxidation of alkenes is the conversion of ethylene into acetaldehyde in the presence of palladous chloride, a reaction which now forms the basis of a large-scale process for the preparation of acetaldehyde[202]. The essential overall stages are a reaction, via a π-bonded metal–alkene complex, between ethylene

and palladous chloride (equation 46) followed by the reconversion of

$$C_2H_4 + PdCl_2 + H_2O \longrightarrow CH_3CHO + Pd + 2\,HCl \qquad (46)$$

the resulting palladium metal into palladous chloride by oxygen in the presence of hydrochloric acid (equation 47). The mechanism of

$$Pd + \tfrac{1}{2}O_2 + 2\,HCl \longrightarrow PdCl_2 + H_2O \qquad (47)$$

the reaction has been fully studied by Smidt and his coworkers[203] who have shown that the two main steps are formation of a complex (equation 48) and the subsequent reaction of this with water to

$$[PdCl_2(OH)(H_2O)]^- + C_2H_4 \longrightarrow [PdCl_2(OH)C_2H_4]^- + H_2O \qquad (48)$$

form acetaldehyde. Other olefins such as propylene, 2-butene and isobutene also react to give high yields of carbonyl products. Warhaftig, Moiseev and Sirkin[204] have studied the oxidation of cyclohexene to cyclohexanone in the presence of the same catalyst.

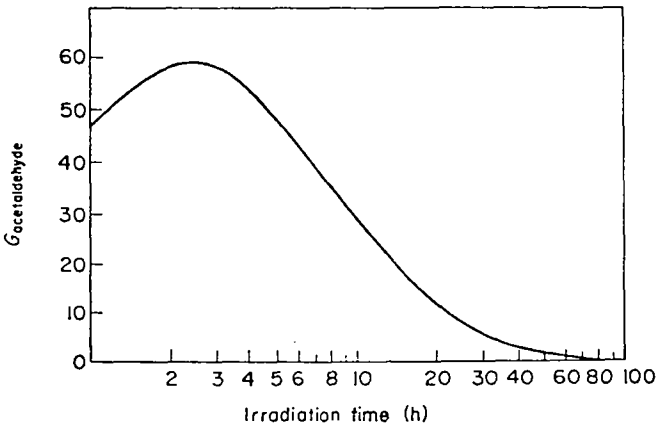


FIGURE 5. The formation of acetaldehyde during the radiation-induced oxidation of ethylene in aqueous solution. Temperature $\approx$ 20°c, total gas pressure = 8 atm, ethylene: oxygen = 1:1. [Reproduced, by permission, from ref. 205.]

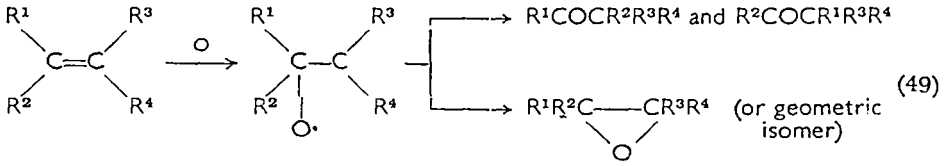
Finally, the oxidation of olefins to carbonyl compounds can be brought about by the use of γ-radiation. Aqueous solutions of ethylene and oxygen were first irradiated by Henley and coworkers[205,206] who obtained acetaldehyde in very high yield (Figure 5) suggesting the occurrence of a chain reaction. More recent work[207,208] has, however, failed to confirm the existence of chains and one study has

shown that several other carbonyl compounds, such as formaldehyde and glycollaldehyde, are also formed in small yields.

B. Reactions Involving Other Oxidants

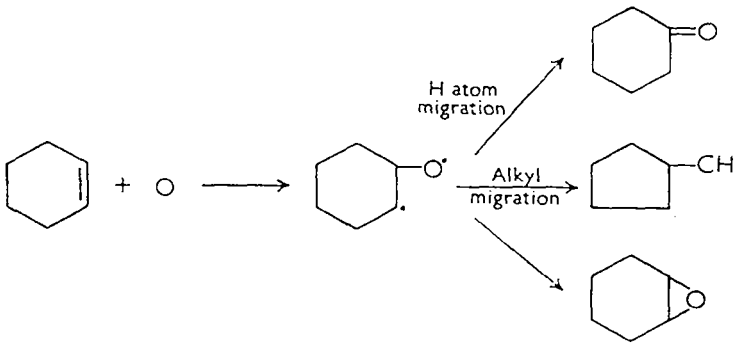
1. Gas-phase reactions

a. Oxygen atoms. The reaction of oxygen atoms with alkenes in the gas-phase has been fully studied, mainly by Cvetanovic and his coworkers. In most work in which special attention was paid to the nature of the reaction products, oxygen atoms were generated by the mercury-photosensitized decomposition of nitrous oxide. The reaction of oxygen atoms with ethylene[209] gives several carbonyl products including acetaldehyde, propionaldehyde and n-butyraldehyde as well as traces of formaldehyde. The behaviour of a number of higher alkenes (propylene, 2-butene, isobutene, 2-pentene and 2,3-dimethyl-2-butene) has also been investigated[210]. In all cases carbonyl compounds are major products; the first step appears to be addition of an oxygen atom to one end of the C=C bond, this taking place with unsymmetrical alkenes predominantly at the less substituted carbon atom. The resulting biradical then undergoes degradation to the ground state forming either the corresponding epoxide or, as a result of 1,2-migration of either a hydrogen atom or an alkyl radical, carbonyl compounds (reactions 49). Butadiene reacts by 1,2-addition



(49)

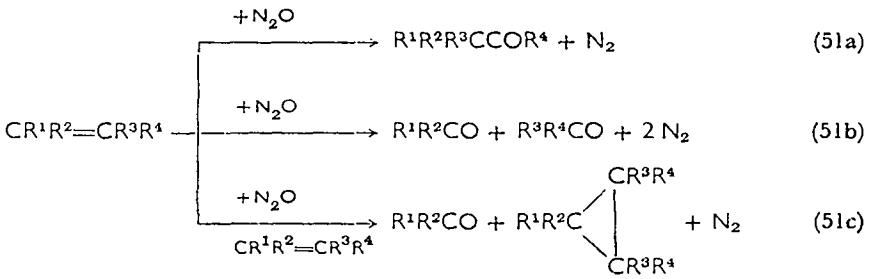
only, giving 3-butenal[211], and acetylene gives ketene[212]. Studies



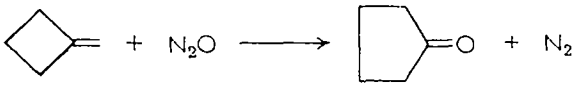
(50)

have also been made of the reactions of 1-butene and isobutene[213] and of 2-pentene[214] with oxygen atoms produced by the photolysis of nitrogen dioxide at 3660 Å; again several carbonyl products are formed. With cycloalkenes, the formation of carbonyl compounds is particularly striking since the migration of one of the alkyl groups must involve a change in ring size. Thus the reaction of oxygen atoms with cyclohexene[210], for example, yields an aldehyde and a ketone as well as an epoxide (reactions 50).

b. Nitrogen oxides. At 200–400°c and pressures up to 2000 atm, nitrous oxide readily reacts with alkenes in three different ways, all of which produce carbonyl compounds as major products (equations 51)[215, 216]. Ethylene and monosubstituted and 1,2-disubstituted



ethylenes react mainly by reaction (51a) but, in many cases, (51b) and (51c) also occur. 1,1-Disubstituted ethylenes, except methylenecyclobutane which gives cyclopentanone as the only identifiable product (equation 52), react exclusively by reaction (51c). Alkynes are converted into ketenes[217].



(52)

A kinetic study has been made of the reaction of ethylene with nitrous oxide at about 600°c[218]. Acetaldehyde is the primary product formed under these conditions (equation 53), but the yields obtained

$$N_2O + C_2H_4 \longrightarrow CH_3CHO + N_2 \qquad (53)$$

are very low since the aldehyde rapidly breaks down at the temperatures concerned.

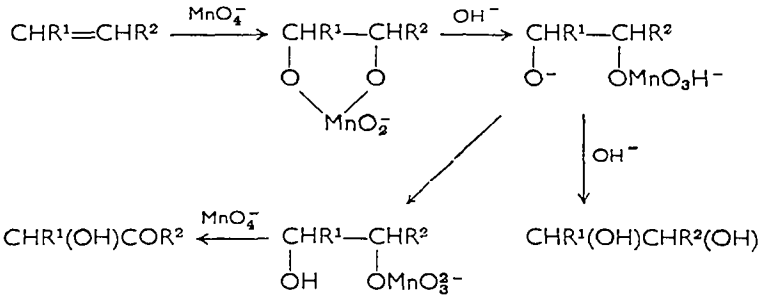
No carbonyl products are reported to be formed by the gaseous

reaction of ethylene with nitrogen peroxide[219], but, as already stated, quite large yields of glyoxal are formed from acetylene[163].

2. Liquid-phase reactions

In the liquid phase relatively few reagents oxidize alkenes and cycloalkenes to carbonyl compounds as primary products. The action of ozone on unsaturated compounds first produces an ozonide which may in certain circumstances break down to yield carbonyl cleavage compounds, which have been detected spectroscopically among the products of ozonization of various olefins and olefinic esters[220]. 'Abnormal' ozonolysis, of olefins with double bonds attached to unsaturated groups, gives epoxides which readily rearrange to carbonyl compounds with the original alkene skeleton[221].

Although under normal conditions alkaline permanganate oxidizes alkenes to diols, the reaction tends, if the hydroxyl ion concentration is low enough, to produce instead α-hydroxy ketones[222]. These latter compounds are not produced by further oxidation of diols and it seems likely that a common intermediate exists for the production of both diols and hydroxy ketones[223]. A possible reaction path is shown in Scheme 7. In some cases, e.g. bicyclo[2.2.1]-2-heptene, reaction leads to cleavage to a dialdehyde[223].



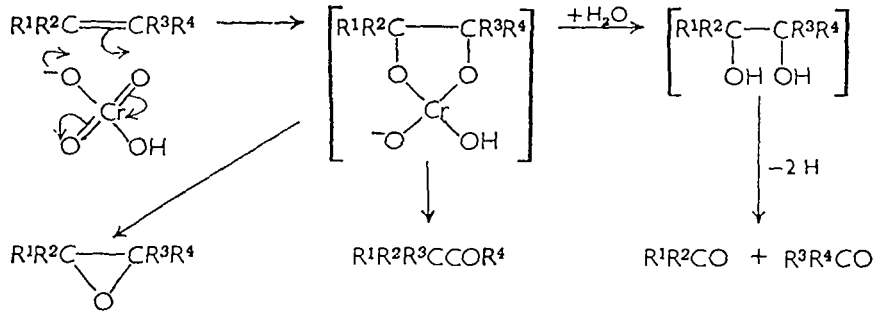
SCHEME 7.

Chromic acid generally converts alkenes into either epoxides or glycols but in some cases carbonyl products may be formed as products of subsequent cleavage of the glycols[224]. One case in which rearrangement rather than cleavage occurs and the ketone produced has the same number of carbon atoms at the original alkene is 2,3-dimethyl-2-butene which is converted by chromic acid into 3,3-dimethyl-2-butanone (reaction 54)[225]; somewhat similar behaviour

$$(CH_3)_2C{=}C(CH_3)_2 \longrightarrow (CH_3)_3CCOCH_3 \qquad (54)$$

is found in the oxidation of 2,2,4,6,6-pentamethyl-3-heptene by chromic acid, where, in addition to the normal carbonyl cleavage product (2,2-dimethyl-4-pentanone), another ketone, viz. 4-hydroxy-2,2,4,6,6-pentamethyl-3-heptanone, is found in small quantities[226].

Kinetic, analytical and spectral data on the oxidation of alkenes by chromic acid are consistent with oxidation by addition of chromate ion to the double bond as the rate-determining step, as illustrated by Scheme 8[227]. Oxidation of conjugated dienes to unsaturated diones

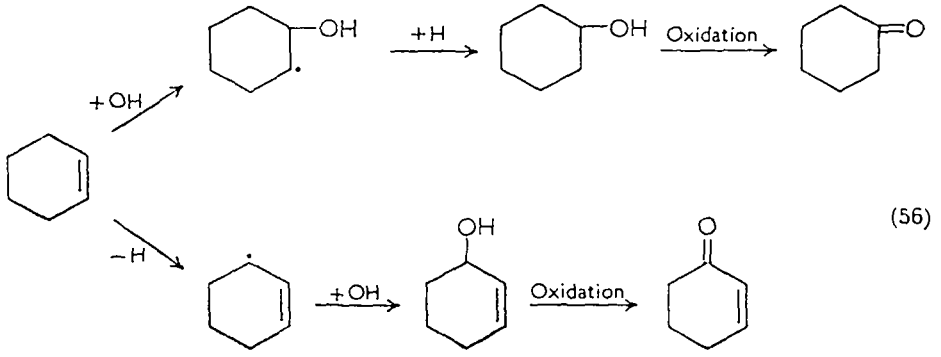


Scheme 8.

(reaction 55) may take place by an analogous route.

$$R^1CH{=}CHCH{=}CHR^2 \longrightarrow R^1COCH{=}CHCOR^2 \qquad (55)$$

One reagent which will oxidize cycloalkenes to cyclic ketones is pernitrous acid. Thus cyclohexene is converted into cyclohexanone and 1-cyclohexen-3-one[228]; the mechanism shown in reactions (56) is suggested.



(56)

IV. OXIDATION OF AROMATIC HYDROCARBONS

A. Reactions Involving Molecular Oxygen

1. Gas-phase reactions

a. Homogeneous oxidation. Relatively few studies have been made of the homogeneous oxidation of aromatic hydrocarbons in the gas phase and in only a small proportion of these has any attempt been made to analyse the reaction products. Formaldehyde is the only carbonyl compound which has been detected among the intermediate oxidation products of benzene[229-231] and the yields reported are

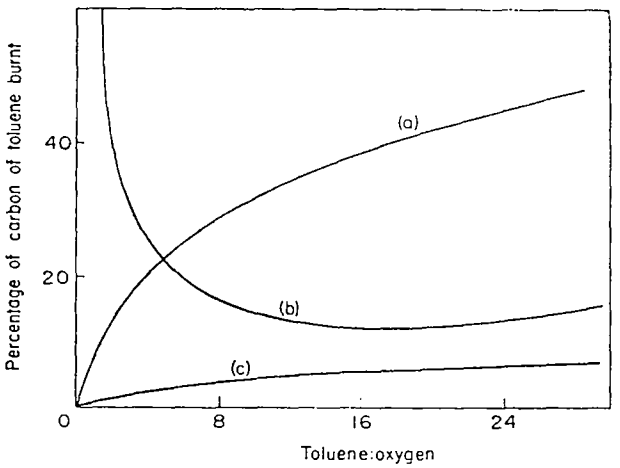


FIGURE 6. The formation of (a) benzaldehyde, (b) benzoic acid and (c) benzyl alcohol during the gaseous oxidation of toluene. Total pressure = 20 atm. [Reproduced, by permission, from ref. 229.]

very small. In general appreciable amounts of aromatic carbonyl compounds are produced only when oxidation takes place preferentially at a side-chain or when some other non-aromatic part of the molecule is being oxidized. Benzaldehyde is formed from toluene[229,230] and the yields of this compound are increased by the use of high pressures and low temperatures[229]; another important factor is the toluene: oxygen ratio[229], a large excess of the hydrocarbon enabling yields of benzaldehyde as high as 40% to be obtained apparently at the expense of other intermediate oxygenated products (Figure 6). The isolation of quite large amounts of benzaldehyde from oxidation of toluene has also been reported by Kroger and Bigoraski[232]. With higher monoalkylbenzenes, side-chain oxidation appears to take

place largely, if not exclusively, at the α-position; thus acetophenone and benzaldehyde are formed from ethylbenzene[229,230,233] and propiophenone and benzaldehyde from n-propylbenzene[230]. The yields of both aromatic aldehydes and ketones may, in appropriate circumstances, be as high as 10%. In all cases traces of formaldehyde are also formed, probably as a result of direct oxidation of the aromatic nucleus. Indeed in the oxidation of *p*-xylene at about 500°c[234] formaldehyde is the only carbonyl product which can be detected and it has been shown that this compound, the concentration of which runs closely parallel to the reaction rate (Figure 7), is

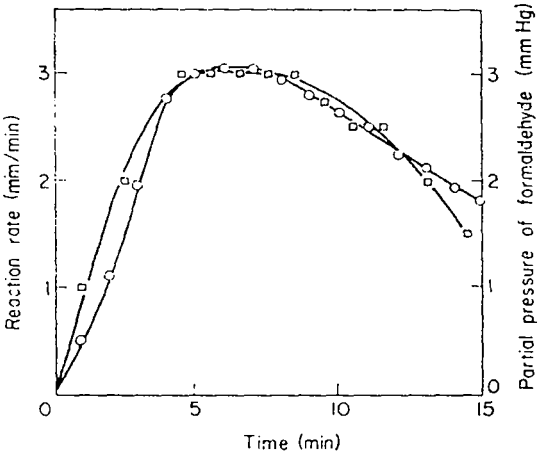
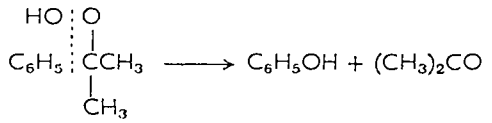


FIGURE 7. The formation of formaldehyde during the gaseous oxidation of *p*-xylene. Temperature = 460°c, total pressure = 200 mm, *p*-xylene:oxygen = 1:2·5. ○ = formaldehyde, □ = reaction rate. [Reproduced, by permission, from ref. 234.]

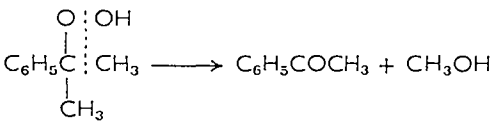
almost certainly the species responsible for degenerate chain-branching. Formaldehyde also is the principal intermediate product of the oxidation of toluene under similar conditions, although small amounts of benzaldehyde can also be detected[235]. On the other hand, *o*-tolualdehyde is found in appreciable quantities during the oxidation of *o*-xylene in a flow system at 650°c and is believed to be the principal chain-branching intermediate in this reaction[236]. Quite good yields of the normally expected carbonyl products can be obtained by oxidation of both toluene and ethylbenzene in the presence of a dispersion of inert solid particles[237].

Although the oxidation of aromatic hydrocarbons, like that of aliphatic compounds, is powerfully catalysed by hydrogen bromide,

reactions involving aromatics are much less clear-cut and the resulting product distributions are in consequence very complex. It is reported that no carbonyl compounds are obtained from toluene[238] although the normal reaction temperature for this hydrocarbon is lowered to about 200°c. However, more recent work[239] has shown that quite high yields of benzaldehyde (but no formaldehyde) are obtained by the HBr-catalysed oxidation of this compound. The major carbonyl product formed from ethylbenzene is acetophenone but the yields of this compound are generally only around 10%[238]. Both acetone and acetophenone are obtained by HBr-catalysed oxidation of cumene at 195°c[238] and it is believed that the initially formed hydroperoxide can break down in two ways (equations 57), the first shown reaction predominating.



(57a)



(57b)

b. Oxidation in the presence of heterogeneous catalysts. In the presence of suitable heterogeneous catalysts, aromatic hydrocarbons such as benzene and naphthalene, which contain no reactive side-chains, are almost invariably oxidized mainly to quinones and acid anhydrides, although small amounts of phenols may be formed as intermediates. Hydrocarbons with a saturated or unsaturated side-chain may, however, be converted into aromatic carbonyl compounds and under appropriate conditions the yields of such products may be quite high. Thus the oxidation of toluene leads to benzaldehyde and the use of high temperatures, short contact times and mild catalysts favours the formation of this compound[240]. Benzaldehyde is the primary product with molybdenum trioxide as catalyst at temperatures of 450–530°c and the oxides of tungsten, zirconium and tantalum also give high yields of this carbonyl compound[240]. Other workers have reported quite high yields of benzaldehyde (up to 60%) with both molybdate[241–245] and vanadate[243,244,246–249] catalysts.

The heterogeneous catalytic oxidation of *o*-xylene has also been quite fully studied. The production of *o*-tolualdehyde (in preference to phthalic anhydride) is favoured by use of high xylene:oxygen

ratios and of catalysts such as zirconium, molybdenum and tungsten oxides[250]. The formation of considerable amounts of *o*-tolualdehyde has also been observed during the oxidation of *o*-xylene over vanadium pentoxide[251], although other workers[252,253] have found only phthalic and maleic anhydrides as products with this catalyst. Rafikov and Suvorov[254] have found *p*-methylacetophenone and *p*-isopropylbenzaldehyde, and Okada and Fushisaki[255] have detected the latter aldehyde, among the products of the V_2O_5-catalysed oxidation of *p*-cymene. Good yields of benzaldehyde are obtained by oxidation of 1,2-diphenylethane in the presence of manganese dioxide at about 200°C[256].

2. Liquid-phase reactions

The primary product of the liquid-phase oxidation of aromatic hydrocarbons is, generally speaking, a hydroperoxide, although variable amounts of carbonyl compounds are frequently formed also, partly as a result of the spontaneous or metal-catalysed decomposition of intermediate peroxides. Carbonyl-containing products appear to be produced from aromatic hydrocarbons containing no side-chain, such as *cis*-decalin[257], but reasonably high yields of specific aldehydes and ketones are usually obtained only by oxidation of aromatic compounds containing a reactive side-chain.

Thus acetophenone is obtained (as well as α-phenylethylhydroperoxide) during the liquid-phase oxidation of ethylbenzene at 60°C[258]. This ketone is probably formed, not by the decomposition of the peroxide, but as a result of the termination reaction (58) which appears to take place by a mechanism involving a cyclic transition state[259].

$$2\,C_6H_5CH(OO\cdot)CH_3 \longrightarrow C_6H_5COCH_3 + C_6H_5CH(OH)CH_3 + O_2 \qquad (58)$$

The oxidation of cumene readily gives high yields of α-cumylhydroperoxide[260] but this intermediate product breaks down fairly cleanly under acid conditions to give mainly acetone and phenol (as well as small amounts of methanol and acetophenone) (compare equations 57). Indeed this reaction now constitutes an important industrial process for the manufacture of phenol in which acetone is formed as a coproduct[261]. The uptake of oxygen by cumene, which is normally very slow, is accelerated by the use of an alkaline oil-in-water emulsion[262]. It has been shown that the nature of the emulsifying agent[263], the presence of metal ions[264] and the pressure of oxygen[265]

all affect the rates both of oxygen uptake by cumene and of decomposition of the resulting cumylhydroperoxide. The oxidation of cumene is also catalysed by lead dioxide and various other metal oxides[266] and such additives accelerate not only formation of the initial hydroperoxide but also its decomposition to acetophenone. Detailed studies of the amounts of ketonic products (acetone and acetophenone) formed under different experimental conditions have yielded a considerable amount of information regarding the kinetics of cumene oxidation[267].

A termination reaction analogous to that operative with ethylbenzene cannot take place with cumene owing to the absence of hydrogen on the α-carbon atom in the cumylperoxy radical. However, some acetophenone is probably formed as a result of the reactions (59) and (60)[268], although the work of Antonovskii

$$2\ C_6H_5C(OO\cdot)(CH_3)_2 \longrightarrow 2\ C_6H_5\overset{O\cdot}{\overset{|}{C}}(CH_3)_2 + O_2 \qquad (59)$$

$$C_6H_5\overset{O\cdot}{\overset{|}{C}}(CH_3)_2 \longrightarrow C_6H_5COCH_3 + CH_3^{\cdot} \qquad (60)$$

and Makalets[269] suggests that at least some of this ketone arises from unimolecular breakdown of cumylperoxy radicals (equation 61).

$$C_6H_5C(OO\cdot)(CH_3)_2 \longrightarrow C_6H_5COCH_3 + CH_3O\cdot \qquad (61)$$

s-Butylbenzene reacts analogously to cumene giving methyl ethyl ketone as the main carbonyl product (reaction 62)[270]. The use of

$$C_6H_5CH(CH_3)(C_2H_5) \xrightarrow{+O_2} C_6H_5C(OOH)(CH_3)(C_2H_5) \longrightarrow C_6H_5OH + CH_3COC_2H_5 \qquad (62)$$

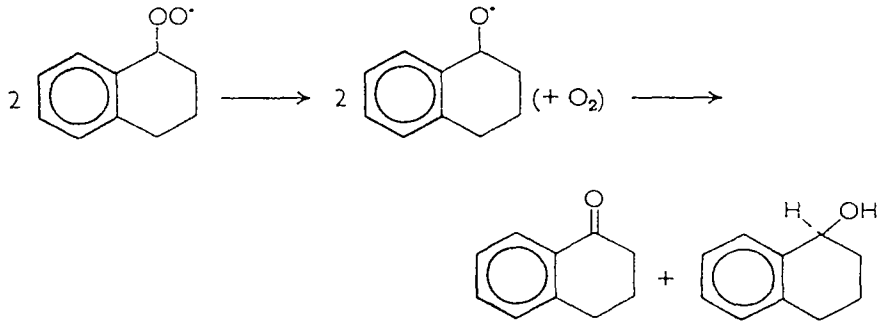
an alkaline oil-in-water emulsion again improves the rate of oxygen uptake by the hydrocarbon[271].

p-Cymene may be oxidized mainly to the peroxide $CH_3C_6H_4C(OOH)(CH_3)_2$ with smaller amounts of the isomeric compound $CH_2(OOH)C_6H_4CH(CH_3)_2$[272]. The principal carbonyl product is *p*-methylacetophenone which appears to be formed mainly if not entirely by the termination reaction (63)[273]. Tetralin also very

$$2\ CH_3C_6H_4C(OO\cdot)(CH_3)_2 \longrightarrow CH_3C_6H_4C(OOH)(CH_3)_2 + CH_3C_6H_4COCH_3 + HCHO \qquad (63)$$

readily reacts with oxygen to form α-tetralylhydroperoxide in high yield[274,275] and this compound is exceptionally stable in the absence of catalysts. In the presence of suitable additives, however, the

hydroperoxide breaks down to give principally α-tetralone (and α-tetralol) as well as much smaller quantities of 4-(*o*-hydroxyphenyl)-butyraldehyde; these carbonyl compounds are thus found among the products of oxidation of tetralin under conditions where the initial hydroperoxide is unstable[276]. The breakdown of α-tetralylhydroperoxide has been shown to be weakly catalysed by alkalis[275] and by ferrous ions[274] but to occur rapidly in the presence of iron pentacarbonyl[277] or iron phthalocyanine[278]. Kinetic studies of tetralin oxidation[279] have proved however that some α-tetralone also arises from the termination reaction (64).



(64)

Aromatic hydrocarbons containing only methyl substituents are generally much more resistant to attack than compounds in which CH_2 or CH groups are present. Thus *p*-methylbenzylhydroperoxide is formed only very slowly and in small amounts during the liquid-phase oxidation of *p*-xylene around 100°c[280]. Even under more vigorous conditions (130°c and use of large amounts of di-*t*-butyl peroxide as catalyst), only very low yields (about 0·5%) of the peroxide are obtained; the recombination of *p*-methylbenzyl radicals apparently prevents the propagation of long chains[281]. Both *p*-methylbenzaldehyde and acetone are formed as by-products during the reaction and quite high yields (up to 40%) of *p*-tolualdehyde are formed as a result of the acid-catalysed decomposition of *p*-methylbenzylhydroperoxide (equation 65).

$$CH_3C_6H_4CH_2OOH \longrightarrow CH_3C_6H_4CHO + H_2O \qquad (65)$$

Aromatic hydrocarbons with unsaturated side-chains react quite differently with oxygen. Medvedev and Zeitlin[282] found that benzaldehyde and formaldehyde are effectively the sole products of the reaction of oxygen with bulk styrene at 80°c. These aldehydes

were also found as minor products (together with a polymeric styrene peroxide) during the emulsion polymerization of styrene in the presence of oxygen at 50°C[283]. Very detailed kinetic studies of the oxidation of styrene[284–286] have established that the reaction involves two principal processes, formation of a polyperoxide (styrene–oxygen copolymer) and its cleavage to yield equimolar

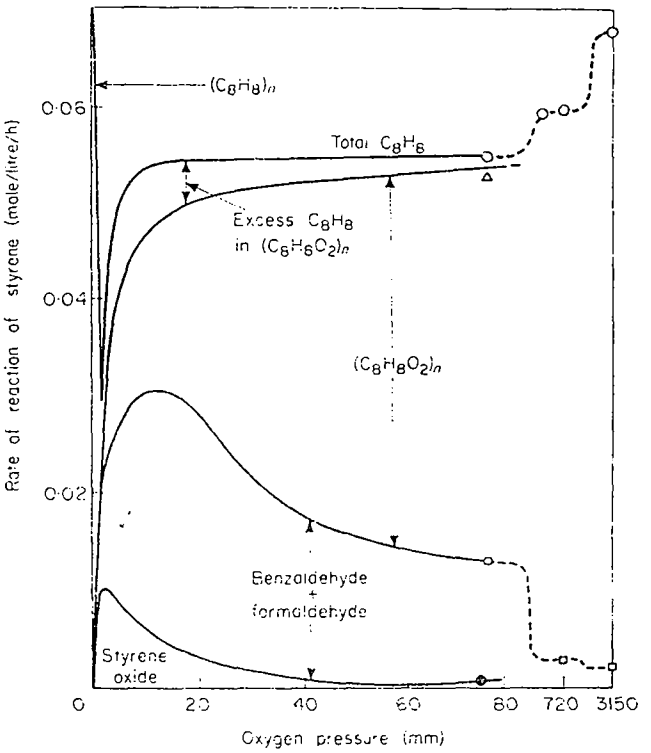
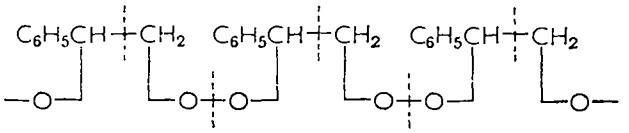


FIGURE 8. The formation of products during the oxidation of styrene at 50°C in the presence of 0·01 M α,α′-azobisisobutyronitrile. [Reproduced, by permission, from ref. 286.]

quantities of benzaldehyde and formaldehyde. Competition between these two processes depends upon the temperature and even more markedly on the oxygen pressure[284,286], the aldehyde yield passing through a well-defined maximum as the available oxygen is increased (Figure 8). The formation of the two aldehydes can be shown as resulting from the rupture of C—C and O—O bonds in the polyperoxide **2**. A second much less important mode of decomposition of styrene peroxide can yield α-hydroxyacetophenone and phenyl-

glyoxal[285]. Behaviour generally analogous to that observed with styrene is found with α-methylstyrene[287]; the predominant carbonyl products here are acetophenone and formaldehyde, the yields of which are markedly dependent on oxygen pressure. The reaction of indene with oxygen also follows a broadly similar course[288].



(2)

B. Reactions Involving Other Oxidants

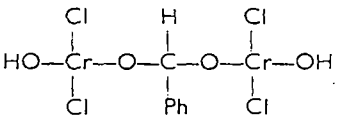
The only two types of oxidizing agent which have been used to any extent for the oxidation of aromatic hydrocarbons to carbonyl compounds are chromic acid (and related chromium compounds) and permanganate. Both oxidants are, under appropriate conditions, general reagents for the conversion of CH_2 and CH_3 groups to $>C{=}O$ and —CHO respectively but the vulnerability of such groups to oxidative attack is usually considerably increased by the proximity of one or more aromatic rings.

Most of the work with chromic acid has been carried out with hydrocarbons containing tertiary C—H groups, in which case the corresponding tertiary alcohol is the main product. Slack and Waters[289,290] have, however, studied the oxidation of various aromatic hydrocarbons, particularly diphenylmethane, by chromium trioxide in glacial acetic acid, and have shown that the main product is benzophenone, which is very slowly oxidized further to benzoic acid. It is suggested that the initial attack of the hydrocarbon involves abstraction of a hydrogen atom to yield a free radical $Ph_2\dot{C}H$[289], and that transient complexes of tetravalent and hexavalent chromium may be formed as intermediates[290]. Wiberg and Evans[291] have also studied the oxidation of diphenylmethane and conclude that reaction takes place with the formation of a hexavalent chromium ester followed by solvolysis with Cr—O bond cleavage.

Chromyl chloride too has long been recognized as an effective oxidant for the methyl groups in toluene and its analogues. The overall reaction may be represented as in (66), the chromyl chloride

$$C_6H_5CH_3 \longrightarrow (C_6H_5CH_3{\cdot}2CrO_2Cl_2) \xrightarrow{+H_2O} C_6H_5CHO \qquad (66)$$

being reduced, on hydrolysis of the adduct, to a mixture containing 1 mole of chromic acid and 2 moles of a chromic salt. The initial complex formed, a dark brown solid insoluble in organic solvents, probably has the structure shown in **3**, since magnetic susceptibility



(3)

measurements have shown that the chromium atoms are tetravalent and spectroscopic evidence has established the presence of hydroxyl groups[291a]. In the case of higher alkylbenzenes, mixtures of products are formed, the reagent attacking methylene groups to produce ketones as well as methyl groups to give aldehydes. Ethylbenzene is converted into acetophenone and phenylacetaldehyde, and isopropylbenzene into acetophenone (by methyl group displacement) and 2-phenylpropionaldehyde, approximately equal amounts of ketone and aldehyde being produced in each case. Studies of the Étard reaction using n-propylbenzene as reactant[291b] have shown that methyl benzyl ketone is produced in higher yield than ethyl phenyl ketone, despite the fact that the latter arises from the reactive benzylic position. It appears that oxidation proceeds initially at the benzylic position but that rearrangement occurs. Thus the oxidation of 2,2-dideutero-1-phenylpropane gave methyl benzyl ketone with 60% of deuterium in the position α to the ring. The total yield of ketones is less than 50% since chlorination takes place as a side-reaction. Similarly, tetralin is converted into α- and β-indanone, although the yields are very low and a large amount of polymer is formed[291a].

Despite the very wide use of permanganate as an oxidizing agent, its reactions with hydrocarbons have been little studied. Oxidation of toluene by potassium permanganate in aqueous acetic acid solution[292] involves primarily attack on the methyl group (as well as some disruption of the aromatic ring); reaction probably proceeds through the well-defined stages (67) since appreciable quantities of

$$C_6H_5CH_3 \longrightarrow C_6H_5CH_2OH \longrightarrow C_6H_5CHO \longrightarrow C_6H_5COOH \qquad (67)$$

benzaldehyde can be isolated from the products. The three isomeric tolualdehydes can also be obtained by oxidation of the corresponding xylenes[293]. With ethylbenzene, attack takes place principally at the α-position and acetophenone can be formed in about 50% yield[294],

although this compound is slowly oxidized further to benzoic acid. n-Propylbenzene yields propiophenone[295], which is rapidly oxidized further to benzoic and acetic acids, and cumene gives acetophenone[295], which is slowly converted into benzoic acid and carbon dioxide. The nature of the species responsible for oxidation appears to depend on whether the group adjacent to the aromatic ring is primary, secondary or tertiary. In general, susceptibility to direct attack by MnO_4^- ions and overall reactivity both decrease in the order CH > CH_2 > CH_3. Thus with ethylbenzene and the propylbenzenes the permanganate ion plays a large part in the reaction but with toluene and the xylenes the Mn^{3+} ion appears to be the most important oxidizing entity.

V. OXIDATION OF ALCOHOLS

A. Reactions Involving Molecular Oxygen

1. Gas-phase reactions

a. Homogeneous oxidation. The presence of formaldehyde among the products of the homogeneous gaseous oxidation of methyl alcohol was first observed by Newitt and Szego[296], who studied the reaction at high pressures and around 250°c. It had earlier been shown that formaldehyde, which is formed during the high-pressure oxidation of methane[297], probably arises from further oxidation of methyl alcohol. Bone and Gardner[1], who later investigated the oxidation of methyl alcohol at subatmospheric pressures, found that a maximum yield of formaldehyde of about 3% was obtained from a 2 CH_3OH + O_2 mixture at 390°c. The production of formaldehyde during the homogeneous oxidation of methyl alcohol has also been investigated by Loos and Polyakov[298] and by Enikolopyan and Belgovskii[299]. The kinetics of the reaction and the pattern of product formation were fully studied by Bell and Tipper[300]. It was shown that, in the early stages of reaction, the conversion of methyl alcohol into formaldehyde could be as high as 25%. The concentration of formaldehyde passes through a maximum at the time of the maximum rate and this maximum concentration is independent of oxygen pressure and directly proportional to the pressure of methyl alcohol. The formation of hydrogen peroxide simultaneously with formaldehyde suggests that the primary chain involves the reactions (68),

$$HO_2^{\bullet} + CH_3OH \longrightarrow H_2O_2 + \dot{C}H_2OH \qquad (68a)$$

$$\dot{C}H_2OH + O_2 \longrightarrow HCHO + HO_2^{\bullet} \qquad (68b)$$

further oxidation of the formaldehyde being responsible for degenerate chain-branching. The extent of conversion of methyl alcohol into formaldehyde is dependent on the nature of the surface[301], being higher, for example, in a boric acid-coated vessel than in one coated with potassium chloride (Figure 9). A 37% yield of formaldehyde has been reported during the oxidation of methyl alcohol at 370°c in a silver-coated vessel[299].

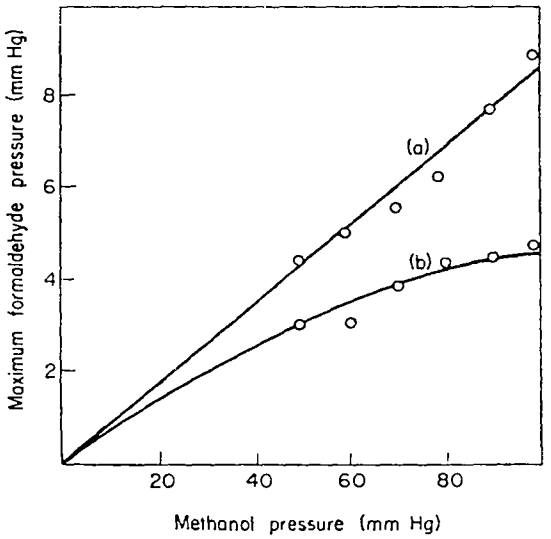


FIGURE 9. The influence of the surface on the maximum pressure of formaldehyde formed during the gaseous oxidation of methyl alcohol. Oxygen pressure = 100 mm. (a) B_2O_3-coated vessel (404°c); (b) KCl-coated vessel (466°c). [Reproduced, by permission, from ref. 301.]

Although several studies have been made of the combustion of higher aliphatic alcohols, only in relatively few cases has analysis of reaction products been carried out. Newitt and Szego[296] detected small amounts of acetaldehyde and formaldehyde among the products of the oxidation of ethyl alcohol at high pressures. A detailed analytical investigation has also been made of the products of the oxidation of ethyl alcohol at subatmospheric pressures and at temperatures from 270 to 370°c[302-4]. It was shown that during an initial induction period the alcohol may be converted quantitatively into acetaldehyde until a critical concentration of this intermediate (corresponding to about 4% of the alcohol initially present) has accumulated. The pressure then begins to rise autocatalytically, and

formaldehyde (and other oxygenated organic products) become detectable. Since hydrogen peroxide is the only product, other than acetaldehyde, formed during the induction period, a primary chain involving $HO_2^{\cdot}$ and $CH_3\dot{C}H(OH)$ radicals and formally analogous to but more clear-cut than that postulated for the oxidation of methyl alcohol appears to operate. The initially formed acetaldehyde is subsequently oxidized in a branching-chain cycle and this process leads, through the formation of $CH_3^{\cdot}$ radicals, to formaldehyde and the other C_1 products observed.

Oxidation of n-propyl alcohol can be carried out at somewhat lower temperatures[305] but the yields of aldehydes (propionaldehyde and acetaldehyde) are not as large as those obtained from ethyl alcohol. With n-butyl alcohol and isobutyl alcohol[306], the yields of the corresponding aldehydes at small conversions are of the order of 80–90% at temperatures from 300 to 400°c and in mixtures containing both a deficit and an excess of oxygen. The yields fall off quite rapidly, however, if reaction is allowed to proceed further.

With secondary alcohols, the greater stability of ketones as compared with aldehydes facilitates the isolation of considerably larger amounts of these products. Thus, under optimum conditions, 100% yields of acetone (and hydrogen peroxide) can be obtained from isopropyl alcohol at conversions of up to 40%[305,307], but the nature of the surface of the reaction vessel appears to play quite an important part in the reaction[308]. Although, during the early stages, effectively the only process in operation is the linear chain cycle (69), other

$$(CH_3)_2CHOH + HO_2^{\cdot} \longrightarrow (CH_3)_2\dot{C}OH + H_2O_2 \qquad (69a)$$

$$(CH_3)_2COH + O_2 \longrightarrow (CH_3)_2CO + HO_2^{\cdot} \qquad (69b)$$

reactions subsequently occur. For example, thermal decomposition of the initial 'alcohol radical' probably leads to acetaldehyde (equation 70) and the methyl radicals formed concurrently may be

$$(CH_3)_2\dot{C}OH \longrightarrow CH_3CHO + CH_3^{\cdot} \qquad (70)$$

oxidized partly to formaldehyde. Glyoxal is another minor carbonyl product[309].

Yields of acetone and hydrogen peroxide during the homogeneous gaseous oxidation of isopropyl alcohol are high enough for commercial development of the reaction to have been investigated. Thus the reaction with air of isopropyl alcohol at 300–350°c leads after 4–8 min to a 40% yield of hydrogen peroxide and an even higher

yield of acetone[310], although surface reactions lead to some decomposition of the former product. Pretreatment of the reaction tube with 10–15% aqueous hydrogen peroxide has enabled a 6·8% peroxide yield at 38·5% conversion to be obtained by reaction at 320°c of 2 parts of isopropyl alcohol with 1·3 parts of atmospheric oxygen in a flow system[311].

Very high yields of methyl ethyl ketone (and hydrogen peroxide) can be obtained by the gaseous oxidation of *s*-butyl alcohol[306,312], even at quite high conversions (Table 6).

TABLE 6. The formation of methyl ethyl ketone during the gaseous oxidation of *s*-butyl alcohol[312].

Alcohol pressure (mm)	Oxygen pressure (mm)	Temperature (°c)	% alcohol consumed	% conversion of alcohol to ketone
40	60	295	8·7	89
40	60	295	25	70
40	60	295	50	59
40	200	295	10	88
40	200	295	25	81
40	200	295	50	65
40	60	400	11·2	95
40	60	400	25	75
40	60	400	50	55
40	60	400	75	40

Only one study appears to have been made of the slow combustion of a tertiary alcohol. Thus, with *t*-butyl alcohol[306], the principal carbon-containing product is acetone. Here due to the absence of α-C—H bonds there can be no overall reaction analogous to that occurring with primary and secondary alcohols. Initial attack of this compound presumably involves abstraction of hydrogen from the OH group, followed by breakdown of the resulting *t*-butoxy radical (reaction 71). Small amounts of acetaldehyde and formaldehyde are also found among the products.

$$(CH_3)_3COH \xrightarrow{-H} (CH_3)_3CO\cdot \longrightarrow (CH_3)_2CO + CH_3\cdot \qquad (71)$$

Very little work has been carried out on the gaseous oxidation of alcohols in the presence of homogeneous catalysts. Nitrogen oxides lower considerably the oxidation temperature of methyl alcohol but do not appreciably affect the maximum yields of formaldehyde which

can be obtained[313]. The nature of the surface has a well-defined effect on the rate of the NO-catalysed reaction and on the amounts of formaldehyde which can be recovered, the largest amounts of this carbonyl product being obtained in a boric acid-coated vessel[314]. Hydrogen bromide also acts as a catalyst for the gaseous oxidation of methyl alcohol but the maximum pressure of formaldehyde formed is only about one-tenth of that obtained under similar conditions in the uncatalysed and NO-catalysed reactions (Table 7)[315].

TABLE 7. Comparison of the amounts of formaldehyde formed during the gaseous oxidation of methyl alcohol[315]. Methyl alcohol pressure 100 mm; oxygen pressure 75 mm.

	Uncatalysed reaction at 390°c	Reaction at 310°c catalysed by 2 mm NO	Reaction at 310°c catalysed by 15 mm HBr
Maximum formaldehyde pressure (mm)	8·5	8·0	0·7
Final formaldehyde pressure (mm)	1·5	7·2	0·2

b. Oxidation in the presence of heterogeneous catalysts. Primary and secondary alcohols are readily dehydrogenated over suitable catalysts in the absence of air or oxygen to form aldehydes and ketones respectively (section V.B.2). In many systems, however, yields of carbonyl products are considerably increased by the presence of oxygen, although the main function of the oxidant often appears to be a secondary one, not directly connected with the principal chemical change involved.

Both metals and metal oxides have been used as catalysts but the first detailed work on the oxidation of alcohols over metals was that of Thomas[316], who studied the reaction of methyl alcohol with air over copper, silver and gold catalysts. The yields of formaldehyde obtained over a silver catalyst may be as high as 95% but decrease as the oxygen:alcohol ratio is increased, excess oxygen causing the production of considerable amounts of oxides of carbon (Figure 10). Similar results were found with copper and gold catalysts, although these metals gave somewhat smaller amounts of formaldehyde.

The oxygen clearly plays an important part since the yields of formaldehyde obtained by dehydrogenation of methyl alcohol in the absence of oxygen are considerably lower than would be expected

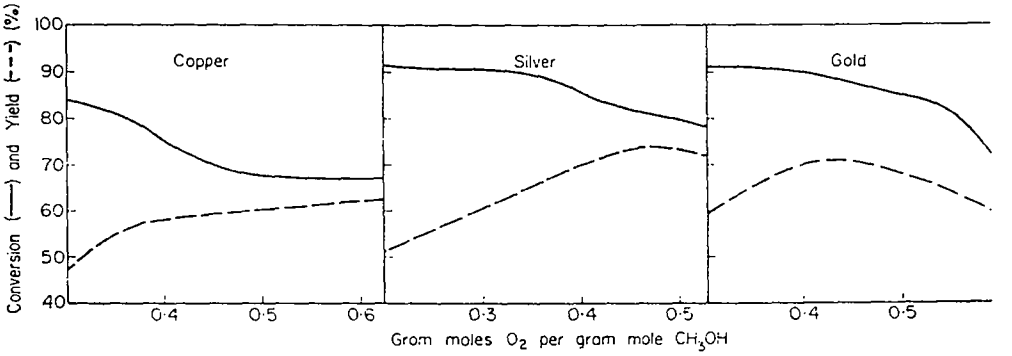


FIGURE 10. The influence of reactant-mixture composition on the conversions and yields for the oxidation of methyl alcohol to formaldehyde by air in the presence of metallic catalysts[316]. Flow rate of air ≈ 130 l/h.

from equilibrium considerations[317]. It seems to be generally agreed that the basic reactions (72) are taking place although there is some

$$CH_3OH \longrightarrow HCHO + H_2 \qquad (72a)$$

$$HCHO \longrightarrow CO + H_2 \qquad (72b)$$

disagreement as to whether the role of the oxygen is to maintain the necessary reaction temperature by oxidation of the hydrogen liberated[318] or to keep the catalyst active by oxidative destruction of catalyst poisons[316]. On the other hand, Vlodavets and Pshezhetskii[319], who also studied the reaction over a silver catalyst, concluded that oxygen plays a more direct part, adsorbed oxygen reacting with methyl alcohol from the gas phase and converting it into formaldehyde. Polyakov and coworkers believe that both dehydrogenation (at low oxygen concentrations) and oxidation (at high oxygen concentrations) occur over a silver catalyst[320], whereas dehydrogenation is effectively the only reaction over a platinum catalyst[321]. The yields of aldehyde formed by metal-catalysed oxidation of methyl alcohol are improved by the addition of large amounts of water vapour[322] or of small quantities of organic sulphur compounds[323], and by the use of cooling sprays[324]. This last technique has, for example, been applied to the oxidation of methyl alcohol at 500°c in a copper vessel containing a silver catalyst and results in a yield of 74% at 80% conversion[324].

Somewhat more recently, studies have been reported of the controlled oxidation of relatively lean methyl alcohol + oxygen mixtures

over metal oxide catalysts. With pure molybdenum oxide at about 400°c, 100% conversions of methyl alcohol into formaldehyde are obtained initially, but the catalyst becomes steadily less efficient with increasing use[325]. Better results are obtained with mixtures of molybdenum and iron oxides[325,326], although ferric oxide alone causes more or less complete oxidation of methyl alcohol to carbon dioxide and little or no formaldehyde can be isolated. Thus, for example, the use at 425°c of a catalyst consisting of 3 parts of ferrous oxide and 2 parts of molybdenum trioxide on silicon carbide as support, previously activated at 260°c, has produced a yield of formaldehyde of 87·2%[327]. At temperatures of 300–500°c with similar catalysts, 90% yields of formaldehyde at conversions exceeding 90% have been claimed[328]. Moreover, iron–molybdenum oxide catalysts, when spent, can be regenerated by treatment with solutions of molybdenum salts followed by reactivation[329]. Quite high conversions of methyl alcohol into formaldehyde can also be achieved by oxidation over other suitable molybdate[330,331] or vanadate[332,333] catalysts.

Several large-scale processes for the manufacture of formaldehyde have been described which involve the catalytic oxidation of methyl alcohol over both metal and metal oxide catalysts[334,335].

The oxidation of higher aliphatic alcohols to carbonyl compounds over heterogeneous catalysts has also been effected. Ethyl alcohol is converted into acetaldehyde by gaseous oxidation in the presence of vanadium pentoxide on iron or zinc[336], while catalysts consisting of mixtures of iron oxide with calcium carbonate bring about the rather unusual conversion of ethyl alcohol into acetone, although a variety of other products are also formed[337]. Iron–molybdenum oxide catalysts, similar to those used for the oxidation of methyl alcohol[327], catalyse the oxidations of n-butyl alcohol, ethylene glycol and glycollic acid to the corresponding aldehyde, dialdehyde and aldehyde acid respectively[338]. Isopropyl alcohol is oxidized to acetone by air at 240–340°c in the presence of a silver catalyst supported on pumice[339]. The overall activation energy of the reaction is 15 kcal/mole and a free-radical chain mechanism is involved[340].

The combined catalytic oxidation and dehydrogenation to carbonyl compounds of primary and secondary alcohols can be brought about by catalysts consisting of silver, which acts as an oxidation catalyst, mixed with an oxide of zinc, magnesium, beryllium, titanium or zirconium, which effects dehydrogenation. At temperatures below 580°c, methyl, ethyl, isopropyl and cyclohexyl

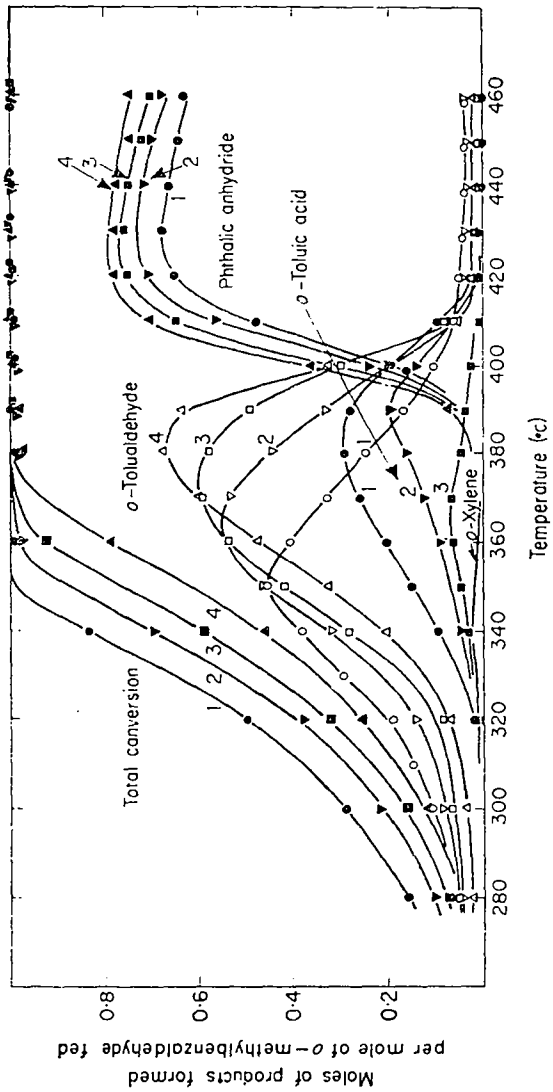


FIGURE 11. The influence of temperature on the formation of *o*-methylbenzaldehyde during the oxidation of *o*-methylbenzyl alcohol over a vanadium pentoxide catalyst. Average oxygen concentration = $9{\cdot}3 \times 10^{-3}$ g mole/l; contact time = 0·6 sec; initial concentration of *o*-methylbenzyl alcohol (10^{-4} g mole/l): (1) 0·62; (2) 0·93; (3) 1·24; (4) 1·86. [Reproduced, by permission, from ref. 342.]

alcohols are converted into the corresponding carbonyl compounds in yields of between 90 and 98%[341].

Some work has also been carried out on the heterogeneous catalytic oxidation of aryl-substituted alcohols, generally in connection with the corresponding reactions of the parent hydrocarbons. Thus, during studies of the controlled oxidation of toluene, the behaviour of benzyl alcohol over vanadate catalysts has been investigated; benzaldehyde was formed as an intermediate product[247,248]. In the same way the catalytic oxidation of *o*-methylbenzyl alcohol has been studied in an attempt to obtain a better understanding of the reactions of *o*-xylene[342]; the results show that the nature of the products depends markedly upon the temperature used but that around 400°c *o*-tolualdehyde is the principal species formed (Figure 11).

2. Liquid-phase reactions

Alcohols are not in general readily oxidized in the liquid phase by molecular oxygen and comparatively little work has been done in this field.

Heyns and Blazejewicz[343] have outlined a general procedure for the conversion of primary alcohols into aldehydes (and, in some cases, acids) and of secondary alcohols into ketones, which involves the use of molecular oxygen in conjunction with a platinum catalyst under mild conditions. The best conditions for selective oxidation vary with alcohol structure, but the method is of general applicability to a large number of alcohols (Table 8) and is particularly well suited to the preparation of long-chain aldehydes.

Methyl alcohol is converted into formaldehyde in 80% yield by the use of oxygen at 25°c in the presence of complexes formed from copper salts and amines[344]. The photosensitized oxidation of ethyl alcohol at ambient temperatures has been studied in some detail by Bolland and Cooper[345,346]. With low oxygen pressures and high concentrations of sensitizer (anthraquinone 2,6-disodium sulphonate), effectively the sole products are acetaldehyde and hydrogen peroxide; at high oxygen pressures and low sensitizer concentrations, the yields of aldehyde fall off and increasing amounts of acids are formed (Figure 12), these latter compounds arising apparently by direct oxidation of ethyl alcohol and not via the aldehyde. Since the quantum yield at temperatures up to 40°c is invariably unity, no chains are involved, indicating presumably that α-hydroxyethylperoxy radicals are formed initially but, instead of reacting with

TABLE 8. Yields of aldehydes and ketones formed by the reaction of molecular oxygen with primary and secondary alcohols in solution in the presence of a platinum catalyst[343].

Alcohol	Reaction time (h)	Temperature (°c)	Product	Yield (%)
1-Butanol	5	41	1-butanal	57
1-Pentanol	5	60	1-pentanal	51
1-Heptanol	1	60	1-heptanal	26
1-Dodecanol	0·25	60	1-dodecanal	77
Benzyl alcohol	1	60	benzaldehyde	78
2-Phenylethanol	1·5	60	2-phenylethanal	34
2-Propanol	0·5	17	acetone	91
2-Pentanol	1	17	2-pentanone	77
3-Pentanol	5·5	16	3-pentanone	71
2-Hexanol	6	17	2-hexanone	56
2-Octanol	96	20	2-octanone	80
Cyclopentanol	0·75	20	cyclopentanone	82
Cyclohexanol	1·5	20	cyclohexanone	92
Cycloheptanol	1	17	cycloheptanone	99
Diphenylmethanol	23	37	benzophenone	98

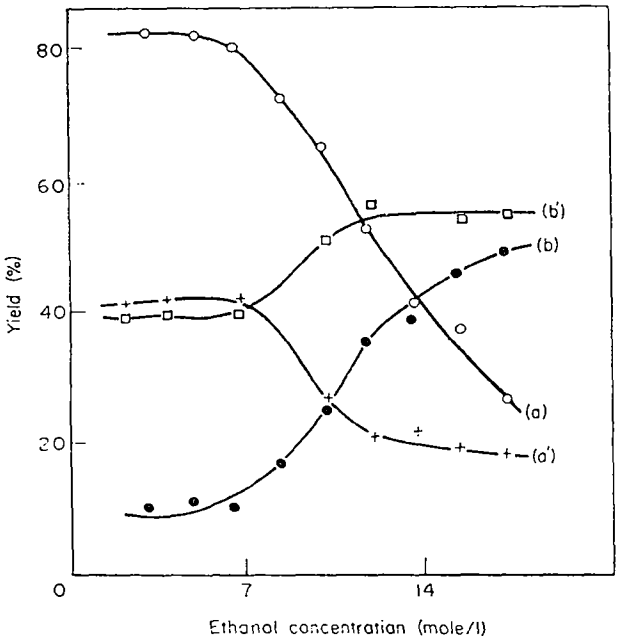


FIGURE 12. The formation of acetaldehyde and acetic acid during the photosensitized oxidation of ethyl alcohol. Oxygen pressure = 70 mm, $6{\cdot}6 \times 10^{-4}$ M anthraquinone: (a) acetaldehyde; (b) acetic acid. Oxygen pressure = 730 mm, $1{\cdot}7 \times 10^{-4}$ M anthraquinone: (a') acetaldehyde; (b') acetic acid. [Reproduced, by permission, from ref. 346.]

further ethyl alcohol to continue the chain, decompose to give acetaldehyde and $HO_2^{\cdot}$ radicals (equation 73). Comparative studies

$$CH_3\underset{\displaystyle OO^{\cdot}}{\underset{|}{C}}HOH \longrightarrow CH_3CHO + HO_2^{\cdot} \qquad (73)$$

have also been made of the gas-phase and liquid-phase oxidation of ethyl alcohol under similar experimental conditions[347]. In both cases acetaldehyde and hydrogen peroxide are the principal products. It is suggested, however, that in the gas phase α-hydroxyethylperoxy radicals break down unimolecularly, but in the liquid phase the corresponding hydroperoxide is formed as a result of hydrogen transfer and that this intermediate product then breaks down to give the two final molecular products directly (reactions 74).

$$\begin{array}{l} CH_3\underset{\displaystyle OO^{\cdot}}{\underset{|}{C}}HOH + CH_3CH_2OH \longrightarrow CH_3\underset{\displaystyle OOH}{\underset{|}{C}}HOH + CH_3\dot{C}HOH \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \downarrow \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad CH_3CHO + H_2O_2 \end{array} \qquad (74)$$

Under the influence of x-rays or bombardment by electrons, liquid ethyl alcohol suffers molecular dehydrogenation to give acetaldehyde as a major product, together with water, hydrogen, methane and carbon monoxide. If oxygen is dissolved in the alcohol, the yield of acetaldehyde increases by 50% due to the occurrence of additional radical reactions similar to those occurring in the photosensitized autoxidation[348].

Rottenberg and coworkers[349,350] have helped to elucidate the mechanism of autoxidation of alcohols by studying the platinum-catalysed oxidation of ethyl alcohol in the presence of water and labelling with ^{18}O either the water or the oxygen. The oxidation was allowed to proceed until acetic acid was formed and this was converted via barium acetate into carbon dioxide which was analysed by mass spectrometry. When the water was labelled, the barium acetate formed contained 70–80% of the ^{18}O but labelled gaseous oxygen led to a low level of incorporation of ^{18}O in the organic products. It is likely that the oxidation mechanism involves the hydrolysis of an intermediate product which may be a peroxide produced by an OH-radical chain reaction. Reversible dehydrogenation to acetaldehyde is, however, not the initial step.

Little work on the autoxidation of higher primary aliphatic alcohols has been reported. Irradiation of oxygen-containing aqueous

solutions of n-butyl alcohol by ^{60}Co γ-rays produces n-butyraldehyde and hydrogen peroxide in reasonable yield[351].

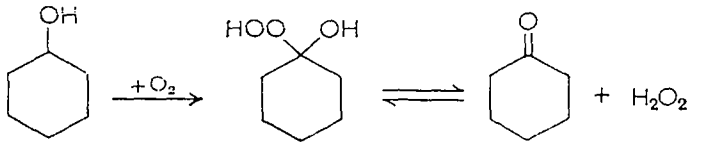
The liquid-phase oxidation of secondary alcohols, particularly of isopropyl alcohol, is the basis of methods of producing hydrogen peroxide and ketones on a commercially viable scale. Thus the uncatalysed reaction of liquid isopropyl alcohol with gaseous oxygen at 2·5 atm pressure and 70–160°c for 29 h produces acetone and hydrogen peroxide in 90% yield[352]. High yields of ketones and peroxide are also obtained from *s*-butyl alcohol, 4-methyl-2-pentanol, 2,3-butanediol and cyclohexanol. The amounts of the primary products which can be isolated may in certain cases be further improved by employing a variety of additives. Peroxides, for example, increase the yields of acetone obtainable from isopropyl alcohol to 93% and that of 4-methyl-2-pentanone from 4-methyl-2-pentanol to 74% (but produce only a 45% yield of methyl ethyl ketone from *s*-butyl alcohol), while the further addition of glacial acetic acid increases the yield of acetone obtained from isopropyl alcohol to 99%[353]. Salts of heavy metals and sequestering agents are also useful additives[354]. The process can be carried out to produce hydrogen peroxide continuously, the alcohol being regenerated by catalytic hydrogenation of the ketone formed.

The catalysed oxidation of secondary alcohols produces quite high yields of ketones. Isopropyl alcohol, containing 1% of titanium dioxide, is oxidized by molecular oxygen at 100°c and 2 atm pressure, under the influence of Hg radiation (3656 Å, 10^{-8} Einstein units/sec), to give, after 30 h, a 16% yield of acetone and a 10% yield of hydrogen peroxide[355]. Cyclohexanol, primary aliphatic alcohols, aromatic alcohols and hydroaromatic alcohols react similarly, producing the corresponding carbonyl compounds.

Although individual higher secondary alcohols have received little attention, the oxidation of commercially produced secondary alcohol fractions boiling between 125–170°c has been reported, the use at 165°c of 94% nitrogen and 6% oxygen as the oxidizing gas producing maximum yields of ketones of 64%[356].

Oxidation by molecular oxygen at pressures slightly higher than atmospheric of 2,4-pentanediol gives 2-pentanol-4-one and not 2,4-pentanedione[357]. In this respect the course of oxidation may be contrasted with that of alkanes (such as 2,4-dimethylpentane)[108]. It appears that the presence of an OH group in the β-position prevents intramolecular rearrangement of alkylperoxy radicals and hence formation of diones.

Some work has also been done on the liquid-phase oxidation of cyclopentanol and cyclohexanol[358,359]. The main products of the photosensitized oxidation around 100°C are the so-called cyclopentanone and cyclohexanone peroxides, although at sufficiently low concentrations only the cyclic ketones and hydrogen peroxide can be detected. Reaction probably takes place by a hydroperoxylation mechanism, the resulting hydroperoxide existing in equilibrium with its decomposition products, e.g. reaction (75). The autoxidation of



(75)

cyclohexanol has been studied kinetically by Denisov and coworkers[360,361]. Termolecular initiation (equation 76) is proposed;

$$2\,RH + O_2 \longrightarrow 2\,R^{\cdot} + H_2O_2 \qquad (76)$$

the resulting free-radical chains have lengths between 10^3 and 10^2 units and the overall activation energy of propagation is 7·7 kcal/mole. The intermediate peroxide is apparently consumed by a non-chain mechanism[362]. A complicating factor in the autoxidation is the reaction of the hydrogen peroxide formed with further cyclohexanol to increase the yield of cyclohexanone relative to that of hydrogen peroxide[363].

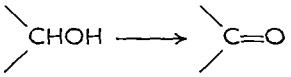
Secondary and tertiary aryl-substituted alcohols such as 1-phenyl-1-ethanol, 1-phenyl-1-propanol, 1-methyl-1-phenyl-1-ethanol, 2-methyl-1-phenyl-1-propanol and 1-phenyl-1-butanol are oxidized by molecular oxygen at about 100°C but give only small yields of ketones, extensive thermal dehydration taking place under these conditions[364]. Little recent work on aryl-substituted alcohols has been reported, although it has been established that at 25°C in the presence of copper–amine complexes, benzyl alcohol is converted by oxygen into benzaldehyde in 94% yield[344] and that a similar reaction occurs during γ-irradiation of benzyl alcohol in the presence of oxygen[351].

B. Reactions Involving Other Oxidants

1. Liquid-phase reactions

a. General. Primary and secondary alcohols are very readily oxidized to aldehydes and ketones, and indeed most oxidizing agents

will effect the relatively simple conversion (77). However, in only a



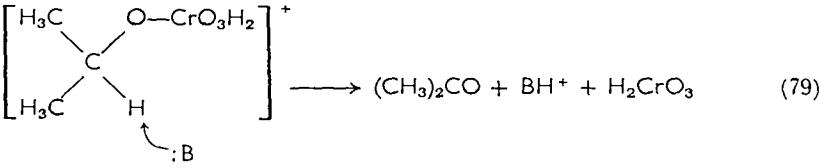
(77)

limited number of cases has the mechanism of this reaction been fully elucidated. Some of the principal mechanistic studies of the oxidation of alcohols by specific liquid-phase oxidants are considered below.

b. Chromates. The most detailed work with chromates has been carried out with secondary alcohols, and in particular with isopropyl alcohol. This last compound is readily oxidized quantitatively to acetone, and in aqueous solution the reaction is first-order with respect to acid chromate ion, $HCrO_4^-$, and to the alcohol and second-order with respect to hydrogen ions[365,366]. The compound $(CH_3)_2CDOH$ is oxidized at only about one-seventh of the rate of the undeuterated alcohol both in aqueous[367] and acetic acid[368] solution showing that the secondary hydrogen atom is involved in the rate-controlling step; a similar isotope effect is found with the tritium-substituted compound $(CH_3)_2CTOH$[369]. The reaction is retarded by manganous ions[370], and is catalysed by bases such as pyridine[371,372]. The oxidation in 87% aqueous acetic acid takes place 2500 times faster than in water[368] and under these conditions the reaction is first-order in acid chromate ion, alcohol and hydrogen ion, and is strongly inhibited by chloride ion. All the experimental findings can be explained on the basis of a mechanism involving the formation of an intermediate chromate ester (equation 78), the

$$(CH_3)_2CHOH + HCrO_4^- + 2\,H^+ \longrightarrow [(CH_3)_2CHOCrO_3H_2]^+ + H_2O \quad (78)$$

tetravalent chromium reacting with hexavalent chromium to form pentavalent chromium which oxidizes more isopropyl alcohol to acetone (equation 79). The intermediate ester, isopropyl chromate,



(79)

can be prepared and its decomposition is found to be catalysed by bases[373], showing that the mechanism is a reasonable one but not proving unequivocally that the oxidation of isopropyl alcohol by chromic acid proceeds via formation of this compound under normal

conditions. Nevertheless, the ester mechanism is generally accepted, although Roček and Krupicka[374-376] have suggested, following measurements of oxidation rate over a wide range of acidities, that the experimental results are more consistent with a rate-controlling step involving direct transfer as a hydride ion of a hydrogen atom from the alcohol to the oxidizing agent.

Oxidation of secondary alcohols in which one of the α-carbon atoms is fully substituted gives good yields of the corresponding ketones; at the same time, however, some C—C bond fission takes place and an aldehyde and a tertiary alcohol are formed. Thus, for example, 3,3-dimethyl-2-butanol, 3,3-dimethyl-2-pentanol and 2,4,4-trimethyl-3-hexanol are oxidized by chromic anhydride in aqueous acetic acid mainly to the corresponding ketones but a 6–7% yield of a tertiary alcohol is also obtained in each case[377], e.g. reactions (80).

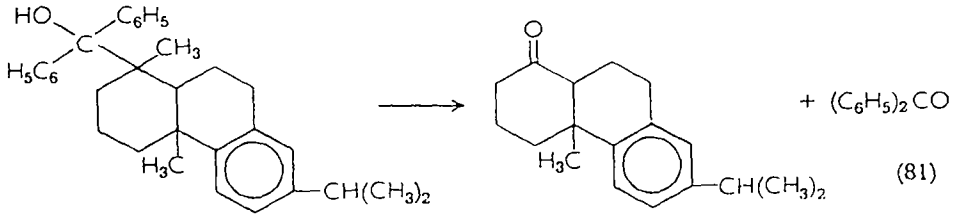
$$CH_3CH(OH)C(CH_3)_3 \begin{cases} \xrightarrow{\text{Direct oxidation}} CH_3COC(CH_3)_3 \\ \xrightarrow{\text{C—C bond fission}} CH_3CHO + (CH_3)_3COH \end{cases} \quad (80)$$

The general nature of this reaction has been demonstrated by the further work of Mosher and coworkers[378-380] and has been shown to occur with other oxidants as well as chromic acid[381]. Hampton, Leo and Westheimer[382] have shown that the extent of the cleavage reaction depends markedly on the experimental conditions. Thus, in the chromic acid oxidation of 2,2-dimethyl-1-phenyl-1-propanol, the yields of cleavage products (benzaldehyde and *t*-butyl alcohol) approach 60–70% in dilute solutions of chromic acid containing sodium acetate but fall to a low value in the presence of Mn^{2+} or Ce^{3+} ions or in concentrated solutions of chromic acid. The deuterated alcohol 1-deutero-2,2-dimethyl-1-phenyl-1-propanol is oxidized to the corresponding ketone, *t*-butyl alcohol and deutero-benzaldehyde. The yield of cleavage products is higher than with the ordinary alcohol and the rates of both oxidation and cleavage are only about one-tenth of those for the undeuterated compound. That the cleavage process is an ionic one is shown by carrying out the oxidation of 2,2-dimethyl-1-phenyl-1-propanol in ^{18}O-labelled water, when it was found that the labelled oxygen is present in the *t*-butyl alcohol[383,384]. Independent evidence of the formation of carbonium ions as intermediates has been obtained by Lansbury, Pattison and Diehl[385].

A considerable amount of work has also been done on the influence of steric factors and of molecular structure on the rate of conversion

of secondary alcohols to ketones by chromic acid. Vavon and co-workers[386,387] first showed that *cis*-2-alkylcyclohexanols are more readily oxidized than the corresponding *trans* isomers and since then conformational effects have been fully investigated[388–394]; both stereoelectronic accommodation and strain relief in the transition state appear to play an important part in determining rates of reaction. The effects of structure on reactivity have been investigated and discussed by Kuivila and Becker[395] and by Kwart and Francis[396].

The oxidation of tertiary alcohols by chromic acid usually leads to a complex mixture in which the yields of individual carbonyl compounds are low. There are one or two examples, however, where comparatively clean conversion into carbonyl products can be effected. Thus Zeiss[397] studied the oxidation of diphenyl-*t*-dehydroabietinol with chromic acid in glacial acetic acid and obtained at 80°c an approximately 70% yield of 12-methyl-1-oxo-7-isopropyl-1,2,3,4,9,10,11,12-octahydrophenanthrene together with benzophenone (reaction 81). The first step appears to be protonation of the

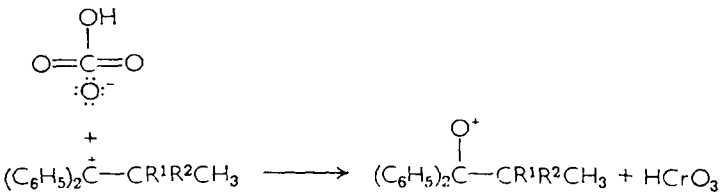


(81)

hydroxyl group, followed by loss of water to form a tertiary carbonium ion (reaction 82), which is stabilized by resonance contributions from the two phenyl groups. The resulting centre of low

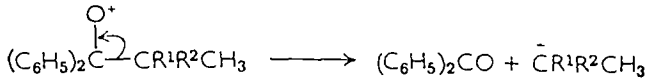
$$(C_6H_5)_2C(OH)CR^1R^2CH_3 \longrightarrow (C_6H_5)_2\overset{+}{C}—CR^1R^2CH_3 \qquad (82)$$

electron density is susceptible to nucleophilic attack by chromate ion (equation 83) and migration of the electrons of the C—C bond then



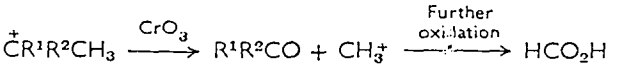
(83)

takes place (equation 84) followed by oxidation of the resulting



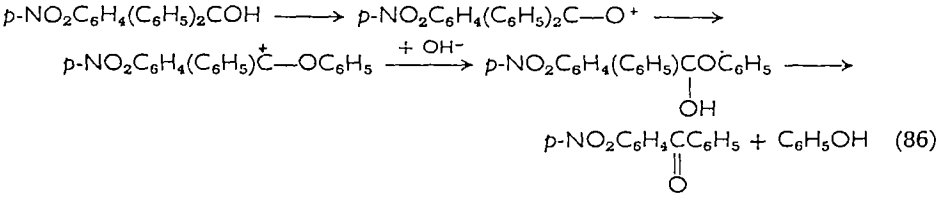
(84)

carbonium ion to give the principal ketonic product and further



(85)

oxidation products (reaction 85). In much the same way, (*p*-nitrophenyl)diphenylmethanol is converted into *p*-nitrobenzophenone (reactions 86)[398]. In this case migration of the phenyl group from carbon to oxygen is involved.



(86)

Chromic acid also oxidizes 1,2-glycols both in aqueous and acetic acid solution and the reaction is often accompanied by extensive C—C bond fission. Thus, formaldehyde can be obtained from ethylene glycol and glycerol, acetaldehyde from 2,3-butanediol, n-butyraldehyde from 4,5-octanediol and acetone from 2,3-dimethyl-2,3-butanediol[224]; reaction probably takes place via the intermediate formation of a cyclic chromium ester. On the other hand, with glycols containing a primary or secondary hydroxyl group, the action of chromic acid under appropriate conditions may (unlike that of most other glycol-cleaving oxidants) result in the formation of a hydroxyaldehyde or hydroxyketone rather than C—C bond fission[399,400]. Conformational effects are again clearly apparent in the chromic acid oxidation of glycols. Roček and Westheimer[401] have shown that chromic acid in aqueous solution oxidizes *cis*-1,2-dimethyl-1,2-cyclopentanediol to 2,6-heptanedione 17,000 times faster than the *trans* isomer. In 90% acetic acid the corresponding factor is 800. It appears that the *cis*-diol reacts rapidly and reversibly to form a cyclic ester with chromic acid and that the rate-determining step in the reaction is the decomposition of this ester with accompanying C—C bond cleavage. The *trans* isomer, on the other hand, appears to be oxidized via some non-cyclic intermediate.

Oppenauer and Oberrauch[402] have shown that *t*-butyl chromate is a useful specific reagent for the oxidation of primary and secondary alcohols in acetic acid solution. The reaction involves rapid transesterification with accompanying electron-pair displacement at the Cr atom, since, when ^{18}O-labelled *t*-butyl chromate is used, no ^{18}O is lost to the solvent on hydrolysis of the intermediate chromate ester.

c. Permanganate. Alkaline potassium permanganate readily oxidizes primary aliphatic alcohols and glycols even at room temperature[403] but carbonyl compounds, presumably owing to their rapid further oxidation[404], are not generally found among the products.

Oxidation of alcohols by acid permanganate does however lead to the formation of some carbonyl products. Thus the reactions of benzyl alcohol and of 1- and 2-phenylethanol, which have been investigated by Cullis and Ladbury[292,294], lead in each case to a carbonyl compound as the first identifiable product, although with benzyl alcohol considerable ring rupture occurs during the oxidation. Kinetically the reactions are initially of the first order with respect to each reactant. Stewart[405] has made quite a detailed study of the oxidation of benzhydrol by acid permanganate and has shown that the rate-determining step is the interaction between the benzhydrylate ion and the permanganate ion. A considerable isotope effect is observed when the α-hydrogen atom is replaced by deuterium. This finding and the absence of excess ^{18}O in the products when ^{18}O-labelled permanganate is used as the oxidizing agent suggest that reaction involves transfer of a hydride ion from a benzhydrylate ion to a permanganate ion. The oxidation to the corresponding carbonyl products of a number of partially fluorinated aromatic alcohols has also been studied by Stewart and van Linden[406,407]; again there is a large deuterium isotope effect and the kinetic results appear to be consistent with a hydride-ion transfer mechanism similar to that in operation in the oxidation of benzhydrol.

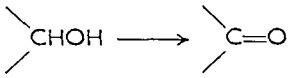
Acid permanganate can also be used for the oxidative cleavage of 1,2-glycols, leading to the formation of carbonyl products[224].

d. Transition metal ions. The oxidation of several alcohols by cobaltic ions has been studied by Hoare and Waters[408]. Cyclohexanol is converted into cyclohexanone, and *t*-butyl alcohol mainly into acetone. In both cases the rate of reaction varies inversely with the concentration of acid present. With cyclohexanol there is a small primary isotope effect, the undeuterated compound reacting about

1·7 times faster than 1-deuterocyclohexanol. In the oxidation of 3-pentanol, on the other hand, C—C bond fission predominates and the isotope effect is negligible[409].

The reaction of primary and secondary alcohols with pentavalent vanadium ions also results in the formation of the corresponding carbonyl compounds and has been studied mainly by Waters and coworkers. The first full kinetic study was of the oxidation of 2,3-dimethyl-2,3-butanediol[410] and this reaction, which leads to acetone as the principal carbonyl product, appears to involve the initial formation of a complex between VO_2H^{2+} ions and the alcohol. The oxidations of cyclohexanol and 1-deuterocyclohexanol in acid solution are of the first order with respect both to the oxidant and to the alcohol[411]. It appears that $[V(OH)_3]^{2+}$ is the active species in perchloric acid solution and $[VO(H_2O)SO_4]^+$ in sulphuric acid solution. Cyclohexanol forms complexes with both these ions and, since there is a kinetic isotope effect, C—H (or C—D) bond fission is involved in the rate-controlling step. 2-Phenylethanol and 2,2-dimethyl-1-phenyl-1-propanol both suffer C—C bond fission during oxidation, the former compound giving some benzaldehyde and the latter compound both benzaldehyde and 2,2-dimethyl-1-phenyl-1-propanone[412]. The oxidations of cyclohexanol and isopropyl alcohol by vanadium ions is catalysed by hydrogen bromide[413].

Acid solutions of pentavalent vanadium appear to oxidize glycols with the production of free radicals, and the accompanying colour changes show that labile glycol–vanadium complexes are formed[410]. Kinetic measurements on eight 1,2-glycols[414] show that mono- and ditertiary glycols are oxidized by C—C bond fission and that the oxidation of primary and secondary glycols involves the conversion (87). The kinetics of the oxidation of glycerol by pentavalent vanad-



(87)

ium are consistent with the formation of an initial complex which subsequently breaks down according to a first order kinetic law[415].

The oxidation of monohydric alcohols by ceric ions has been comparatively little studied. These ions will however cause oxidative cleavage of 1,2-glycols. Thus 2,3-butanediol may be oxidized to acetaldehyde, the reaction proceeding through the formation of a complex of ceric ions with the alcohol[416,417].

A kinetic study has been made of the oxidation of 2,3-dimethyl-2,3-butanediol (which is quantitatively converted into acetone) and

it has been shown that the reaction is of the first order with respect both to ceric ions and to the alcohol[418]. The rates of oxidation of a number of 1,2-glycols by ceric ions have been measured and compared with the corresponding reactions involving pentavalent vanadium and hexavalent chromium ions as oxidants[419].

The conversion of >CHOH groups into >C=O in selected compounds can also be effected by cupric salts[420–422].

e. Aluminium alkoxides. Very smooth oxidation of >CHOH to >CO can be brought about by the action of aluminium alkoxides (generally aluminium *t*-butoxide) in boiling acetone solution; this method has been used, for example, for the preparation of sterol ketones and of sex hormones[423]. Thus, cholesterol gives cholestenone in 94% yield, ergosterol gives ergostatrienone, dehydroandrosterol gives androstenedione and 17-methyl-5-androstene-3,17-diol gives methyltestosterone. No kinetic studies of oxidations involving aluminium alkoxides appear to have been made.

f. Non-metallic oxidants. Several investigations have been carried out of the kinetics of the oxidation of ethyl alcohol by bromine under conditions where acetaldehyde is one of the main reaction products[424]. Replacement of the hydrogen on the α-carbon atom by deuterium[425] or tritium[426] leads to a considerable reduction in oxidation rate suggesting that C—H bond fission is normally involved in the rate-determining step. Isotope effects are also found in the oxidation of isopropyl alcohol and 1-fluoro-2-propanol[427] where it can be shown that the kinetic results are consistent with a mechanism incorporating hydride transfer from carbon and proton transfer from oxygen. The kinetics of the oxidation of cyclohexanol and its derivatives to the corresponding cyclohexanones has been studied by Barker, Overend and Rees[428]; in acetic acid solution cyclohexanol is converted not into cyclohexanone but into the 2,6-dibromo derivative.

The oxidation of alcohols by peroxides has been studied by Kharasch and coworkers[429], who have shown that tertiary alcohols containing at least one aromatic group can be oxidized in acid solution by hydrogen peroxide or *t*-butyl hydroperoxide to a ketone and a phenol. Thus, for example, 1-methyl-1-phenylethanol is converted into acetone and phenol (reactions 88). Some typical yields of

$$C_6H_5(CH_3)_2COH \xrightarrow{+H_2O_2} (CH_3)_2CO + C_6H_5OH + H_2O \qquad (88)$$

$$C_6H_5(CH_3)_2COH \xrightarrow{+(CH_3)_3COOH} (CH_3)_2CO + C_6H_5OH + (CH_3)_3COH$$

ketones are given in Table 9. The oxidation of alcohols to carbonyl

TABLE 9. Yields of ketones formed by oxidation of tertiary alcohols with hydrogen peroxide in acetic acid solution[429].

Alcohol	Ketone	Yield (%)
Triphenylmethanol	benzophenone	93
o-Methoxyphenyldiphenylmethanol	benzophenone	75
	o-methoxybenzophenone	10
o-Methylphenyldiphenylmethanol	benzophenone	56
α-Naphthyldiphenylmethanol	benzophenone	70

compounds by persulphate has also been investigated by several workers. The conversion of methyl alcohol into formaldehyde[430] and the reactions of ethyl alcohol and allyl alcohol[431] were among the first processes of this type to be studied kinetically. Since that time the reaction between isopropyl alcohol and persulphate has been especially fully examined. It was originally suggested[432–434] that the first product is a complex which subsequently decomposes to give acetone and a bisulphate ion (reaction 89). However the absence of

$$(CH_3)_2CHOH + S_2O_8^{2-} \rightleftharpoons (CH_3)_2CHOOSO_3^- + SO_4^{2-}$$

$$\downarrow$$

$$(CH_3)_2CO + HSO_4^- + H^+ \qquad (89)$$

exchange between added sulphate (containing excess ^{35}S) and the persulphate ion makes such a mechanism unlikely and in consequence it is proposed that hydroxyl radicals are probably the active oxidizing species[435]. Several more recent studies[436–438] of the oxidation of isopropyl alcohol and other alcohols have thrown further light on the detailed reaction mechanism but it must be concluded that several points still remain to be clarified.

Dinitrogen tetroxide can be used to convert substituted benzyl alcohols into the corresponding aldehydes[439] and also to oxidize secondary alcohols containing one aromatic group to aryl alkyl ketones[440]; high yields are obtained in both cases (Table 10). In

TABLE 10. Yields of aromatic aldehydes and ketones formed by oxidation of the corresponding primary and secondary alcohols with dinitrogen tetroxide[439,440].

Aldehyde	Yield (%)	Ketone	Yield (%)
o-Tolualdehyde	95	Acetophenone	98
m-Tolualdehyde	98	Propiophenone	98
p-Tolualdehyde	98	Butyrophenone	98
o-Methoxybenzaldehyde	96	Valerophenone	96
p-Methoxybenzaldehyde	97	Octyl phenyl ketone	92
1-Naphthaldehyde	91	*o*-Methoxyacetophenone	90
		p-Methylacetophenone	95
		Benzophenone	89

contrast simple aliphatic alcohols are not readily oxidized by this reagent but instead react mainly to form the corresponding alkyl nitrites (equation 90). Methyl alcohol (as sodium methoxide) can,

$$ROH + N_2O_4 \longrightarrow RONO + HNO_3 \qquad (90)$$

however, be oxidized to formaldehyde (and formic acid) by nitrobenzene. A recent kinetic study of this reaction[442] has shown that it is second order with respect to the methoxide ion but there are many features (such as the retarding effects of oxygen and peroxides) which still require elucidation.

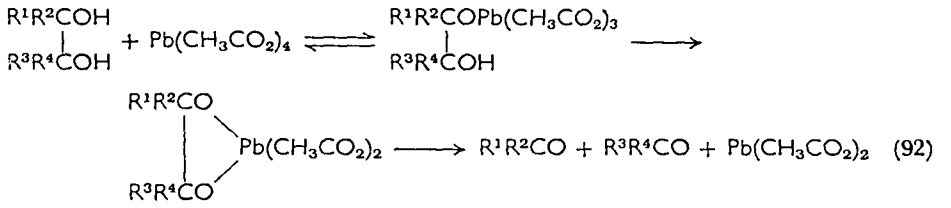
The oxidation of alcohols to carbonyl compounds can also be effected by carbonium ions. One important study is that of Bartlett and McCollum[443] who showed that the triphenylmethyl cation will abstract a hydride ion from n-propyl alcohol, isopropyl alcohol, isobutyl alcohol, *s*-butyl alcohol, 3-methyl-2-butanol and 3,3-dimethyl-2-butanol, but not from methyl alcohol. Further work on the reaction of carbonium ions with alcohols has recently been reported by Deno, Saines and Spangler[444].

g. Specific glycol-cleaving reagents. One of the most important reagents for the oxidative cleavage of 1,2-glycols to carbonyl products, e.g. reaction (91), is lead tetraacetate, the use of which

$$\begin{matrix} R^1CHOH \\ | \\ R^2R^3COH \end{matrix} \xrightarrow{+O} R^1CHO + R^2R^3CO \qquad (91)$$

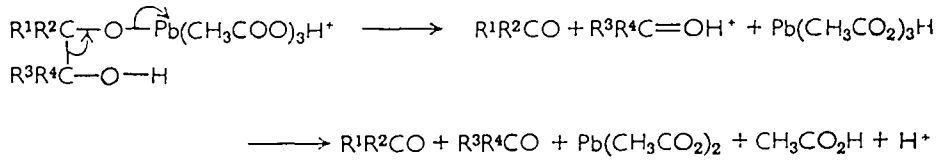
was first systematically investigated by Criegee and coworkers. In the first two of a series of papers[445,446] it was shown that the rate of oxidation varies tremendously with the nature of the solvent and

with the structure of the glycol, *cis* isomers being, in general, much more rapidly oxidized than the corresponding *trans* compounds. This latter finding and the fact that plumbic salts readily form esters with alcohols suggested that reaction proceeds through the formation of a cyclic intermediate which subsequently decomposes to give the reaction products, e.g. reactions (92).



The reaction is usually carried out in acetic acid solution but very careful work in this solvent[447] shows that the observed rate of reaction increases markedly with the concentration of water (and to a lesser extent, methyl alcohol) present in the acetic acid. The influence of structure and configuration of glycols on their reactivity towards lead tetracetate has been fully discussed following measurements of the rates of oxidation of a very large number of different glycols[448,449]; in many cases it can be shown that the relative rates of oxidation of *cis* and *trans* isomers can be correlated with the distance between the hydroxyl groups and indeed with large rings the *trans* compound sometimes reacts more rapidly than the *cis*[450]. The rates of oxidation by lead tetraacetate of the four diastereomeric 2,3-camphanediols[451] and of the four diastereomeric 3β,6,7-cholestanetriols[452] have been measured and compared, and the results support a cyclic ester mechanism, although it has been shown[453] that other routes may also be involved in certain systems.

Relatively few kinetic studies have been reported for the reactions of 1,2-glycols with lead tetraacetate. The kinetics of the oxidation of ethylene glycol in acetic acid solution have been investigated by Bell, Sturrock and Whitehead[454]. The reaction is of the first order with respect to each reactant and has an activation energy of about 21 kcal/mole and a steric factor of approximately unity. Kinetic studies of the behaviour of other glycols have been made by Cordner and Pausacker[455]. Oxidations of glycols by lead tetraacetate are catalysed both by acids[456] and by bases[449]; the associated mechanisms may be written as in reactions (93) for the acid-catalysed reaction, and as in (94) for the base-catalysed one. As an illustration of the difference between the two mechanisms, it may be mentioned that severely



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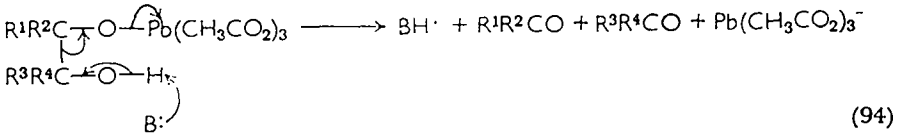
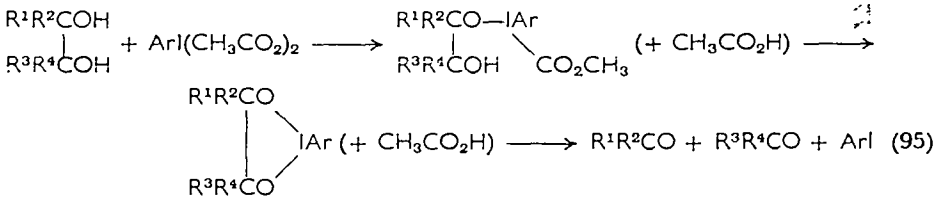


(94)

sterically hindered 1,2-glycols, which can be oxidized only with difficulty in acetic acid, may nevertheless be rapidly oxidized in pyridine[457] in which the steric requirements are evidently much less stringent.

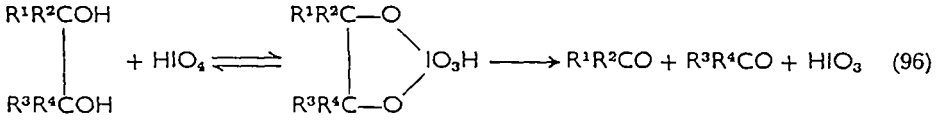
Aryl iodosoacetates form another class of oxidants which are similar to lead tetraacetate but cause somewhat less rapid oxidative cleavage of glycols[458]. Pausacker[459] has carried out kinetic investigations of the oxidation of isohydrobenzoin by several compounds of this type. All the kinetic and other evidence suggests that again the reaction involves the formation and subsequent breakdown of a cyclic intermediate (reactions 95). Periodic acid has also long been



(95)

known as a reagent for the oxidative cleavage of 1,2-glycols[460,461]. Criegee[462] showed that this oxidant behaves similarly to lead tetraacetate inasmuch as *cis* isomers are in general more readily oxidized than the corresponding *trans* compounds. Kinetic studies of the oxidation of ethylene glycol, 2,3-dimethyl-2,3-butanediol and *cis*- and *trans*-cyclohexanediols have been carried out by Price and coworkers[463,464]; the second-order velocity constants have been measured over a considerable range of pH values. Several other kinetic investigations of the oxidation by periodic acid of ethylene glycol[465–467] and other 1,2-glycols[466,468–470] have also been carried out and the results are, in all cases, consistent with a cyclic ester

mechanism of the general type (96), analogous to that in operation



with lead tetraacetate. Spectroscopic evidence has also been found for the cyclic intermediate[471] and, in addition, tracer experiments using ^{18}O have shown that the oxygen atom of the acetone formed by oxidations of 2,3-dimethyl-2,3-butanediol and of 2-methyl-1,2-propanediol comes from the diol in agreement with the view that this intermediate is formed by electrophilic attack of periodic acid on the glycol[472].

Other reagents which will convert 1,2-glycols into aldehydes and ketones in good yield include manganic pyrophosphate[403,473] and sodium bismuthate[474]. A cyclic intermediate mechanism is undoubtedly usually involved, although the work of Levesley, Waters and Wright[453] with manganic pyrophosphate has shown that reaction does not always proceed through the formation of a cyclic organometallic complex.

2. Gas–solid reactions

Primary and secondary alcohols generally undergo over suitable heterogeneous catalysts either dehydrogenation to aldehydes and ketones respectively or dehydration to alkenes. Dehydrogenation to yield carbonyl products is, however, usually the predominant process when metallic catalysts are used but can also be the principal fate of the alcohol with other catalysts. It has already been pointed out (section V.A.1.b) that the reaction of alcohols with oxygen over surface catalysts is in many cases essentially a dehydrogenation process in which oxygen is not involved in the principal stage but only in some secondary step. In this section only systems in which gaseous oxygen is not present will be considered.

The dehydrogenation of alcohols is an endothermic process and hence the position of equilibrium is progressively shifted in favour of the carbonyl products as the temperature is raised. In practice, however, reaction takes place fairly rapidly and is effectively complete at about 200°c.

Some of the earliest kinetic studies of the dehydrogenation of alcohols over a metal catalyst were carried out by Palmer and Constable. Copper was used as the catalyst and measurements were made of the rates of reaction of C_2 to C_5 saturated aliphatic

alcohols[475], cyclohexanol[475] and allyl alcohol[476]. It was shown that secondary alcohols are in general more reactive than primary compounds. Mechanisms were proposed involving the specific and strong adsorption of the >CHOH group on the catalyst, since the rates of dehydrogenation are largely independent of the alcohol pressure[477]. It was concluded that chemical reaction occurs only when the alcohol molecule is adsorbed over a characteristic array of copper atoms[478].

More recently, several studies have been made of the behaviour of a number of different alcohols over copper catalysts at 150–250°c[479]. The activation energy for dehydrogenation was found to be considerably smaller for secondary alcohols that for primary alcohols; the presence of a methyl group in the β-position in primary alcohols lowers the activation energy by about 3 kcal/mole but the introduction of such a group into secondary alcohols has little effect. According to the results of other investigations of dehydrogenation over copper catalysts[480], the activation energy is much the same for the reactions of primary and secondary aliphatic, alicyclic and aryl-substituted alcohols as shown by the following typical values: ethyl alcohol 12·8 kcal/mole, isopropyl alcohol 10·7 kcal/mole, cyclohexanol 11·1 kcal/mole, benzyl alcohol 12·3 kcal/mole. Further work has been carried out on the dehydrogenation both of ethyl alcohol and of several higher alcohols over copper, silver, gold, nickel, cobalt and iron[481,482]. On catalysts consisting of rhenium deposited on carbon[483], secondary aliphatic alcohols produce ketones but the aldehydes initially formed from primary alcohols react further to give esters and hydrocarbons. The activation energy for the dehydrogenation of a given secondary alcohol is lower by about 5 kcal/mole than that for the corresponding primary alcohol; in general activation energies increase by about 2 kcal/mole per carbon atom as a homologous series is ascended. It is of interest that, on a rhenium catalyst, 1,4-butanediol first loses hydrogen to produce 4-hydroxybutyraldehyde but this compound then reacts further to give γ-butyrolactone.

The kinetics of dehydrogenation of alcohols have also been studied on oxide catalysts. Results for the dehydrogenation at 150–200°c of a wide variety of alcohols[484–487] have established that C_2 to C_9 primary alcohols all react at approximately the same rate, whereas the rate of dehydrogenation of C_4 to C_8 secondary alcohols decreases as the molecular weight increases. In general straight-chain alcohols react faster than the corresponding branched-chain compounds.

Changes in rate are reflected by variations in activation energy and frequency factor. The activation energies for the conversion of primary alcohols (n-butyl alcohol, isobutyl alcohol and n-amyl alcohol) into aldehydes on catalysts consisting of zinc sulphide supported on pumice[488] are relatively high (about 22 kcal/mole).

A few studies have been made of the relative extents of dehydrogenation and dehydration of alcohols over a number of different metal oxide catalysts[489]. For ethyl alcohol, the dehydrogenation reaction has the lower activation energy and it has been shown that the balance between the two reactions depends to a large extent on the magnitudes of the respective frequency factors[490,491]. Other work on the decomposition of alcohols over alumina catalysts[492] has shown that reactions at the surface involve the formation and subsequent breakdown of aluminium alkoxides and that the balance between dehydrogenation and dehydration changes with temperature. Thus although at 300°c dibenzyl ether is the main compound formed from benzyl alcohol and only small amounts of benzaldehyde are produced, at 400°c the carbonyl compound becomes the principal reaction product (Table 11).

TABLE 11. The influence of temperature on the amount of benzaldehyde formed during the decomposition of benzyl alcohol over an alumina catalyst[492].

Temperature (°c)	Dibenzyl ether (mole %)	Benzaldehyde (mole %)
300	30·2	6·2
350	35·3	17·4
400	14·8	34·4

During the last thirty years, the catalytic dehydrogenation of alcohols has been increasingly used to produce carbonyl compounds on an industrial scale. A wide variety of catalysts has been employed, many of them based upon the copper–zinc system, but only a selection of results can be given here. A brass catalyst useful for the conversion of secondary alcohols into ketones was described many years ago[493]. Good yields of methyl ethyl ketone can be obtained by dehydrogenation of *s*-butyl alcohol over such a catalyst at 350°c and 15 atm pressure[494]. More recently a copper–zinc catalyst operating at 420°c in a process using two reactors in series has been used to convert ethyl

alcohol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol, *s*-butyl alcohol, 3-pentanol and cyclohexanol into the corresponding carbonyl compounds in yields approaching 100%[495]. Brass spelter catalysts also give good yields of ketones[496]. Alloys of copper (about 70%) with zinc containing less than 1% of iron and traces of aluminium or bismuth convert n-butyl alcohol into n-butyraldehyde in 98% yield at 400°c, producing also 0·2% crotonaldehyde, and effect similar conversions on other C_4 to C_9 primary alcohols, isopropyl alcohol and cyclohexanol[497]. Copper catalysts and zinc catalysts separately have also been widely used for the dehydrogenation of alcohols. Copper catalysts, prepared by precipitation from aqueous cupric nitrate with base and prereduction of the resulting cupric oxide with hydrogen, produce 91–95% of acetone from isopropyl alcohol at 325°c, giving 2,6-dimethyl-4-heptanone and 4-methyl-2-pentanone as by-products; in the same way *s*-butyl alcohol is converted into methyl ethyl ketone in 94–96% yield, with 5-methyl-3-heptanone as a by-product[498]. An active copper catalyst supported on silica gives 60–85% yields of ketones from secondary alcohols (e.g. 2-methylcyclohexanone from 2-methylcyclohexanol) at 240–340°c[499]. Catalysts containing copper together with an alkaline earth oxide, hydroxide or carbonate and an alkali metal compound also convert primary aliphatic alcohols into aldehydes in yields of 88–90%[500] and secondary aliphatic alcohols into ketones in yields greater than 90%[500,501]. The introduction of chromates into copper catalysts sometimes leads to increased selectivity at high conversions. For example, a copper oxide catalyst (40% on pumice as support) containing 0·5% of chromic oxide, used at 280–340°c, converts ethyl alcohol into acetaldehyde in 97·9% yield at 72% conversion and n-butyl alcohol into n-butyraldehyde in yields exceeding 90% at similar conversions[502,503]; the same catalyst at 260–70°c gives 99·4% of acetone from isopropyl alcohol at 88% conversion, and causes dehydrogenation of *s*-butyl alcohol to methyl ethyl ketone in similar yields[504,505]. Zinc oxide catalysts supported on α-alumina convert secondary alcohols into ketones[506,507]; introduction of chromic oxide has again improved yields[508].

Other solids which have been patented as catalysts for the dehydrogenation of alcohols include noble metal catalysts on non-acidic supports (platinum on carbon, for example)[509], neodymium oxide and samarium oxide[510], and the oxides of magnesium, calcium, beryllium and chromium supported on coke of low silica and ash contents and promoted and stabilized with the oxides of bismuth,

antimony, zirconium, thorium, cerium or vanadium in concentrations of about 6%[511].

Although the oxidation of methyl alcohol to formaldehyde has not been effected industrially by standard gas–solid techniques, passage of methyl alcohol through a lead oxide-lined stainless steel tube at temperatures exceeding 760°c produces formaldehyde in 48% yield[512].

VI. OXIDATION OF CARBONYL COMPOUNDS TO DI- AND TRICARBONYL COMPOUNDS

A. Reactions Involving Molecular Oxygen

The reactions of aldehydes with molecular oxygen, in both gaseous and liquid phases, fail to produce dicarbonyl compounds. During the oxidation of ketones, however, 1,2-dicarbonyl compounds are often formed in small yield. The oxidation of acetone in the gas phase, for example, gives glyoxal which is the major product of the reaction at 295°c of a $CH_3COCH_3 + 4\,O_2$ mixture, the yield after seven minutes being nearly 30% based on the acetone consumed[307]. The use of richer mixtures, however, reduces the amount of glyoxal which can be detected; at 284°c from a $2\,CH_3COCH_3 + O_2$ mixture, only 0·1% of glyoxal was produced even after 60 min reaction[513]. The formation of glyoxal possibly involves recombination of formyl radicals (equation 97).

$$2\cdot CHO \longrightarrow (CHO)_2 \qquad (97)$$

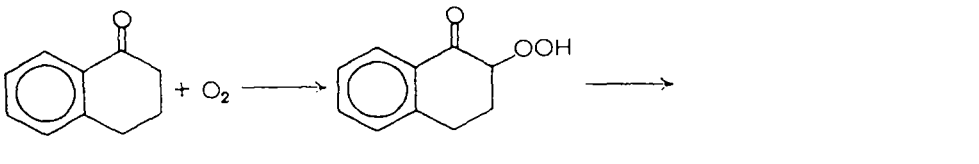
The formation from acetone of methylglyoxal (1-propanal-2-one), i.e. of the dicarbonyl compound directly derived from the acetone skeleton, has not been established either in the gas or the liquid phases. Methylglyoxal has been postulated as an intermediate product, however, of the photochemical liquid-phase oxidation of acetone[514], being formed by the reaction of oxygen with acetonyl radicals but rapidly oxidized further to acetic acid and carbon dioxide (reaction 98).

$$CH_3COCH_2^{\cdot} + O_2 \longrightarrow CH_3COCHO\ (+\cdot OH) \xrightarrow{O_2} CH_3CO_2H + CO_2 \qquad (98)$$

The autoxidation in the presence of 0·8% of nickel phthalocyanine as catalyst of higher aliphatic ketones leads, however, to considerable amounts of the corresponding 1,2-diones[515]. 2-Octanone, for example, produces at 130°c 1% of 2,3-octanedione after 100 h, and 4-heptanone

gives at 120°c 4% of 3,4-heptanedione after 75 h; in each case acids and alcohols are also produced.

The mechanism of such conversions may involve the formation of an α-hydroperoxy ketone, as is shown by the conversion of α-tetralone into tetrahydro-1,2-naphthalenedione. During the autoxidation of tetralin[276], α-tetralone is produced as a major product (section IV) and is itself autoxidized (within the tetralin–oxygen system) to an α-hydroperoxy ketone which breaks down to give, among the other products, tetrahydro-1,2-naphthalenedione and its enol tautomeride, β-naphthoquinol (reaction 99). Similarly, cyclohexanone gives 1,2-cyclohexanedione (reaction 100).



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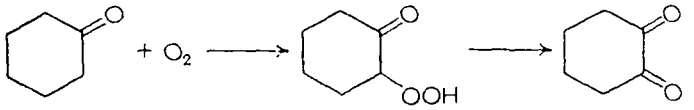


(100)

The conversion of 1,3-diones into metal chelates followed by the autoxidation at 100°c in diphenyl ether as solvent of these complexes produces 1,2,3-triones[516–518]. The rate of autoxidation depends both upon the structure of the organic ligand of the chelate (i.e. on the original dione) and upon the ability of the metal to undergo valency changes. Thus the dibenzoylmethane chelate of ferric iron reacts seven times faster than ferric acetylacetonate. On the other hand, the use of 3-phenylacetylacetone, 3-benzylacetylacetone or dipivaloylmethane renders the chelate inert, while variation of the metal gives the decreasing order of rates[516]

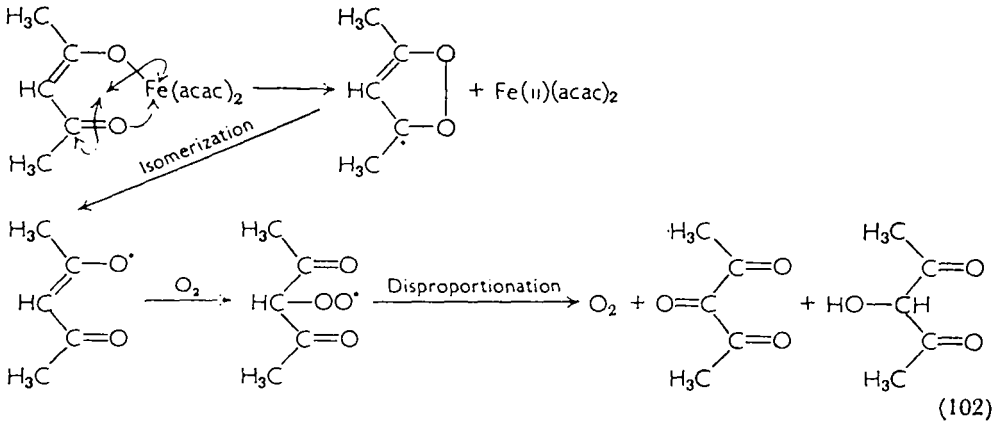
V(III) > Ce(IV) > Ni(II) > Mn(III) > Fe(III) > Co(II) > Co(III) > Th(IV).

It appears likely that the ligand of the chelate is not attacked directly by oxygen and that complex chain reactions characteristic of the

autoxidation of organic compounds do not participate. Moreover the reactions are inhibited by autoxidation initiators such as azo-bisisobutyronitrile and benzoyl peroxide but not by antioxidants such as phenol, hydroquinone and 2,4,6-tri-*t*-butylphenol. The autoxidation of ferric acetylacetonate, the chelate studied most extensively[518], follows the rate equation (101) and has an overall

$$\text{Rate} = k[\text{chelate}]^{0.5}[O_2]^{0.24} \qquad (101)$$

activation energy of 22 kcal/mole. The kinetic results suggest that the thermal decomposition of the chelate leads to rather stable radicals which rearrange to give other radicals which are readily oxidized with the accompanying production of 2,3,4-pentanetrione (reactions 102).



(102)

The trione formed is a powerful reducing agent and reacts further with oxygen to give diacetyl, water, carbon dioxide and acetic acid.

B. Reactions Involving Other Oxidants

1. Selenium dioxide

Selenium dioxide oxidizes compounds containing active methyl or methylene groups; in cases in which these groups are activated by carbonyl groups, 1,2-dicarbonyl compounds are formed (equation 103)[519]. Thus, simple aliphatic aldehydes are converted into glyoxals;

$$SeO_2 + R^1COCH_2R^2 \longrightarrow Se + R^1COCOR^2 + H_2O \qquad (103)$$

acetaldehyde in 75% aqueous acetic acid gives a 90% yield of glyoxal itself, propionaldehyde produces 30% of methylglyoxal, and n-butyraldehyde yields 40% of ethylglyoxal (1-butanal-2-one)[519,520]. Similarly, ketones give glyoxals or α-diketones, the former being

derived from attack on an α-methyl group and the latter from attack on an α-methylene group. Butanone, for example, gives both types of dicarbonyl product, forming 1-butanal-2-one in 17% yield and 2,3-butanedione in 1% yield[519,521-523]. Cyclic ketones[519,521] and aryl-substituted ketones[524] are similarly converted into diketones, cyclohexanone producing 1,2-cyclohexanedione in 35% yield and phenyl benzyl ketone (deoxybenzoin) giving 88% of benzil. It is of interest however that 2-methylcyclohexanone behaves anomalously[525], dehydrogenation as well as oxidation taking place and producing 3-methyl-3-cyclohexene-1,2-dione. The normal oxidation route is generally suffered by ketonic natural products although in certain cases dehydrogenation occurs in preference to oxidation. Cholestanone, for example, gives 30% of 2,3-cholestanedione[526] and camphor gives 95% of the corresponding 1,2-dione in acetic anhydride solution[527,528], although the yield is markedly dependent on the solvent. On the other hand, 3-benzylcamphor suffers dehydrogenation to 3-benzylidenecamphor in 95% yield[529].

Selenium dioxide will also oxidize to a carbonyl group a methylene group situated between two existing carbonyl groups, thus converting aliphatic (but not aromatic) 1,3-diones into 1,2,3-triones. Thus 2,4-pentanedione is oxidized in 29% yield to 2,3,4-pentanetrione but 1-phenyl-1,3-butanedione does not give the corresponding 1,2,3-trione[529]. 1,4-Diketones, such as 1,2-dibenzoylethane[530], are converted not into triones but into 2-ene-1,4-diones (reaction 104).

$$R^1COCH_2CH_2COR^2 \xrightarrow{SeO_2} R^1COCH{=}CHCOR^2 \qquad (104)$$

Although the scope of oxidations with selenium dioxide has been established for more than twenty-five years, it is only much more recently that any progress has been made towards the elucidation of the reaction mechanism. The oxidizing agent is itself prepared in aqueous solution and oxidation is normally carried out in hot acetic acid (although acetic anhydride, ethyl alcohol and toluene have also been used as solvents). It is likely that under these conditions the active species is undissociated selenious acid, H_2SeO_3, which is a weak acid ($k_1 = 2{\cdot}4 \times 10^{-3}$). Corey and Schaefer[531] have studied kinetically the oxidation of phenyl benzyl ketone and have shown that it will proceed by either an acid-catalysed or a base-catalysed path, both of which exhibit a large kinetic isotope effect when the methylenic hydrogens involved are replaced by deuterium. On the basis of such data, it has been proposed that the rate-determining step is the formation of an enol selenite ester directly from the ketone

(equations 105) by a process mechanistically related to enolization in which the electrophile–nucleophile pairs are $H_3SeO_3^+$ and $CH_3CO_2^-$ for the base-catalysed process. The enol selenite ester is believed to rearrange to an α-substituted divalent selenium ester which decomposes rapidly to the diketone and selenium (reactions 106). Further studies of the base-catalysed reaction[532] have substantiated this

$$PhCH_2COPh + H_3SeO_3^+ + H_2O \xrightarrow[\text{acid catalysed}]{\text{Slow}} PhCH{=}C(OSeO_2H)Ph + H_3O^+ + H_2O \quad (105a)$$

$$PhCH_2COPh + H_2SeO_3 + B \xrightarrow[\text{base catalysed}]{\text{Slow}} PhCH{=}C(OSeO_2H)Ph + BH^+ + OH^- \quad (105b)$$

$$PhCH{=}C(OSeO_2H)Ph \xrightarrow{\text{Fast}} PhCH(HOSeO)C(=O)Ph \xrightarrow{\text{Fast}} PhC(=O)C(=O)Ph + Se + H_2O \quad (106)$$

mechanism and clarified anomalous details. A similar mechanism involving enolization may account for the conversion of 1,4-diones to 2-ene-1,4-diones[533].

2. Nitrous acid

Nitrous acid, alkyl nitrites and organic nitroso compounds can similarly be used to convert α-methyl or α-methylenic carbonyl compounds into 1,2-dicarbonyl derivatives. The mode of action of these oxidants involves the formation of a condensation product, which may be a nitroso ketone $R^1COC(NO)HR^2$ or an oxime $R^1COC(=NOH)R^2$, and which is easily hydrolysed by acid to the diketone (reactions 107). Early work suggested that nitroso ketones

$$R^1COCH_2R^2 + HNO_2 \rightarrow \begin{cases} R^1COC(NO)HR^2 \\ R^1COC(=NOH)R^2 \end{cases} \xrightarrow{H^+} H_2NOH + R^1COCOR^2 \quad (107)$$

and oximes are formed by nitrosation of the enol form[534], perhaps by the nitrosonium ion (reactions 108), in a manner analogous to the

$$H_3O^+ + HNO_2 \longrightarrow 2\,H_2O + NO^+$$

$$NO^+ + R^1CH{=}C(OH)R^2 \longrightarrow R^1CH(NO)\overset{+}{C}(OH)R^2 \longrightarrow R^1CH(NO)C(=O)R^2 + H^+ \quad (108)$$

oxidation of ketones by a wide variety of other reagents. More recent studies[535] have shown, however, that unless enolization is strongly

catalysed by HNO_2 or by NO^+, the rate-determining step must involve, in the case of simple aliphatic ketones, the keto form. The step (109) or a similar reaction of HNO_2 itself are among the possible processes involved.

$$NO^+ + R^1CH_2COR^2 \longrightarrow R^1CH_2\overset{\displaystyle O-N=O}{\underset{\displaystyle R^2}{C^+}} \qquad (109)$$

1,3-Dicarbonyl compounds such as 2,4-pentanedione react with nitrous acid to form trinitroso compounds[536], but the isolation from such systems of tricarbonyl compounds has not been reported.

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The Chemistry of the Carbonyl Group
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CHAPTER 3

Formation of carbonyl groups in hydrolytic reactions

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I. INTRODUCTION

The reactions in which carbonyl groups are formed by hydrolysis consist of a variety of formally and mechanistically different transformations. For convenience, these reactions may be classified into

two main groups. In the first group two atoms or groups (e.g. halogens or alkoxyl groups) which are attached to the same saturated carbon atom are replaced by hydroxyl groups:

$$R_2CXY \longrightarrow R_2C(OH)_2 \longrightarrow R_2CO$$

A familiar example is the hydrolysis of benzal chloride, $PhCHCl_2$, to benzaldehyde. In the second group the site of attack is an unsaturated system and the reaction is accompanied either by a complete cleavage of the unsaturated linkage or its transformation into a single bond. The former case is illustrated by the hydrolysis of imines and their derivatives:

$$R_2C{=}NH + H_2O \longrightarrow R_2CO + NH_3$$

and the hydrolysis of olefins in the presence of suitable activating groups. The latter behavior is characteristic of ethylenic linkages in vinyl ethers and related compounds:

$$CH_2{=}CHOR + H_2O \longrightarrow CH_3CHO + ROH$$

In addition to these reactions there is a rather different class of transformations in which carbonyl groups are formed from certain intermediates by hydrolysis, viz. those involving organometallic compounds. These reactions are, however, beyond the scope of this chapter.

The utility of the reactions, when considered for synthetic purposes, will naturally depend upon the behavior of the parent compounds toward hydrolysis as well as on the methods available for their preparation. In this connection it should be noted that many of the hydrolysis reactions can be easily reversed to give the corresponding carbonyl derivatives. In fact there are several instances in which the reversal of the hydrolysis reaction is the best of available routes to the carbonyl derivative. In these cases the hydrolysis reaction often serves merely as an intermediate process in the isolation and purification of the carbonyl compound prepared by some other method. Nevertheless, the structural and mechanistic features of such reactions are of considerable interest in carbonyl-forming hydrolysis reactions in general, and therefore they will also be discussed briefly.

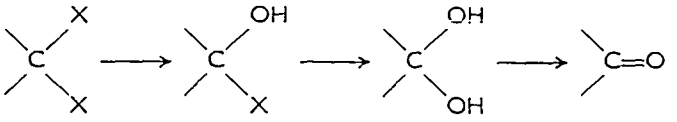
II. DISPLACEMENTS ON SATURATED SYSTEMS

A. α,α-Dihalides

1. General

The hydrolysis of α,α-dihalides to yield carbonyl compounds formally involves two successive displacements on the same carbon

atom, followed by loss of a water molecule from the aldehyde or ketone hydrate formed (equation 1). As the first displacement product cannot be generally isolated it must be very reactive in comparison to the dihalide and thus the first reaction determines the ease of the whole process. Actually, there are good reasons to doubt whether the overall reaction does involve at all a displacement of the second halogen atom rather than a direct decomposition of the hydroxyhalide (see section II.B).



(1)

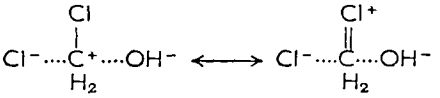
The susceptibility of α,α-dihalides toward hydrolysis is greatly influenced by the structure of the rest of the molecule. Thus, for example, dichlorodiphenylmethane hydrolyses to benzophenone at a rate comparable to the hydrolysis rate of acid chlorides[1,2], while drastic conditions are needed to produce formaldehyde from methylene chloride[3–6]. In comparison to the corresponding monohalides the relative ease of hydrolysis is, apart from the steric factors involved, governed by electronic effects, influencing the reaction in different directions. The second halogen atom attached to the reacting carbon atom will cause it to be more electronegative, reducing its ability to assume a partial positive charge in the transition state which leads to a heterolytic cleavage of the reacting carbon–halogen bond. On the other hand, the second halogen atom can share with the carbon atom the developing positive charge with $p\pi$ orbital overlap, thus accelerating the reaction. There may also be electronic repulsion between the second 'substituent' halogen atom and the oxygen atom of the attacking water molecule or hydroxyl ion in the transition state, or, in other terms, the p orbitals of these two atoms may have an antibonding overlap[7]. Which of these factors will predominate in a particular reaction will depend upon the structure of the rest of the dihalide molecule, as illustrated later in this section.

The most important practical application of the dihalide hydrolysis is in the preparation of aromatic aldehydes and ketones. This is due to the relative ease of hydrolysis as well as the fact that the corresponding dihalides are usually easily prepared, e.g. by side-chain chlorination of the respective aromatic hydrocarbons. Nevertheless, there are also numerous aliphatic carbonyl compounds which can be conveniently obtained by the hydrolysis method.

2. Aliphatic dihalides

Petrenko-Kritchenko and Opotsky[3] were the first to investigate systematically the relative reactivities of halogenated methanes toward solvolytic displacements, and since then a number of papers on this subject have been published[4-6,8-11]. The hydrolysis of methylene chloride is extremely slow; in water at 100°c the half-life of the first-order reaction is 330 h[5,6], which is about 250 times that of methyl chloride. The corresponding reactions with hydroxyl ion, which are first-order with respect to both reactants, show similar structural effects, the dihalide being about 150 times less reactive than the monohalide under the same conditions. A replacement of a hydrogen atom by fluorine in methyl chloride also retards the hydrolysis[11]. These results are wholly understood when it is assumed that these reaction rates are determined by nucleophilic displacements of the S_N2 type, as designated by Ingold, Hughes, and coworkers[12,13]*.

Methylene chloride has but little tendency to solvolyze via a carbonium ion mechanism and thus there is hardly any π-bond overlap in the transition state (equation 2). The absence of this



(2)

resonance effect is due to the weakness of carbon–chlorine double bonds in normal cases. Only in cases where this bond is a part of a conjugated system will this resonance effect come into act (see below). Therefore, the result of introducing the second chlorine atom into methyl chloride is to reduce the reactivity both by the negative substituent influencing the carbon atom and by electronic repulsion between this substituent and the attacking reagent, the 'neighboring bond overlap'[7]. In addition the influences of steric hindrance are in the same direction. The fact that chlorofluoromethane also hydrolyses less readily than chloromethane can be explained in a similar way, but an interesting observation is that the decrease of the rate is only about four-fold[11], irrespective of the higher electronegativity of fluorine. A possible explanation may be the less important influence of the neighboring bond overlap in the case of $2p$ orbitals than in higher p orbitals[7].

Whereas a number of technical applications of producing carbonyl

* An excellent critical survey of current views on the actual nature of different displacement mechanisms has been recently given by Streitwieser[14].

compounds by hydrolysis of the higher homologs of methylene dihalides may be found in the literature, e.g. the preparation of acetone from 2,2-dichloropropane[15], no comparative quantitative data seem to exist for these reactions. As in the hydrolysis of methylene dihalides, elevated temperatures are needed to achieve the reaction and the basicity of the solution must be kept low in order to avoid concurrent elimination of hydrogen halides. The chlorine atoms in symmetrical tetrachloroethane, $CHCl_2CHCl_2$, are even less reactive than those of methylene chloride. According to the method originally introduced by Ott[16] their displacement can, however, be effected by heating in fuming sulfuric acid with mercuric salts as catalysts. The glyoxal sulfate formed can then be easily transformed into glyoxal tetraethyl acetal or glyoxal tetraacetate[17], from which glyoxal is obtained by hydrolysis.

Schmerling[18] has prepared several higher aldehydes and ketones by the Prins condensation[19] of alkyl halides and monohaloolefins, and subsequent hydrolysis of the α,α-dihalides at elevated temperatures in the presence of magnesium oxide or sodium bicarbonate, e.g. equation (3). As the Prins condensation takes place most readily

$$(Me)_3CCl + CH_2{=}CHCl \xrightarrow{AlCl_3} (Me)_3CCH_2CHCl_2 \xrightarrow{H_2O} (Me)_3CCH_2CHO \quad (3)$$

with tertiary halides, this method is particularly useful for aldehydes and ketones with a tertiary carbon atom in the β-position to the carbonyl group. A similar synthesis has been described for chloromalonic dialdehyde[19], CHOCHClCHO, using chloroform and 1,2-dichloroethylene as the starting materials.

3. Aromatic dihalides

In aromatic compounds halogenated in a side-chain, hydrolysis does not show any essential differences from that of the aliphatic dihalides when the site of halogenation is not in conjugated position to the aromatic system. Interest is particularly attached, therefore, to cases where the halogen atoms are in the α-position to the aromatic ring, viz. to compounds of the general type:

$$Ar{-}CX_2{-}R \quad (X = \text{halogen, } R = H, \text{alkyl, aryl}) \quad (4)$$

It has been known for a long time that an aryl substitution in methylene dihalides enhances their reactivity. Hughes[20] was the first to offer an explanation in terms of electronic effects. He proposed the S_N1 mechanism for the hydrolysis of benzal chloride with

the rate-determining ionization as (5), the driving force of the

$$PhCHCl_2 \longrightarrow (PhCHCl)^+ + Cl^- \quad (5)$$

reaction being the resonance stabilization of the carbonium ion by the α-chlorine substituent (equation 6). In contrast to methylene

$$Ph—\overset{+}{C}H—Cl \longleftrightarrow Ph—CH=\overset{+}{C}l \quad (6)$$

dichloride, the stabilization is in this case relatively strong as the double-bonded structure is conjugated with the benzene ring and thus overcomes the influence of other electronic effects. As evidence, the work of Olivier and Weber[21] was cited, who found that benzal chloride hydrolyses faster than the corresponding monohalide, benzyl chloride, and the rate is not affected by moderately low concentrations of hydroxyl ion. Later studies on this and related reactions have confirmed and extended these conclusions[2,22-24].

The effect of α-halogen substitution on the solvolysis rates of benzyl halides has been extensively studied by Hine and coworkers[22-24]. Some of their results are recorded in Table 1. In the case of mixed halides like PhCHClBr, it is assumed that in the rate-determining displacement of the first halogen atom bromine will be displaced preferably to chlorine, and chlorine preferably to fluorine, in accordance with the observation generally made in nucleophilic displacement reactions of organic halides, independently of their mechanism. As another line of argument the authors point out that, for example, the displacement of bromine in PhCHClBr is activated by an α-chlorine atom, while that of chlorine is activated by an α-bromine atom, the former activation being more efficient. This is in accordance with the strength of the carbon–halogen π overlap, which decreases in the sequence F, Cl, Br, I[14]. The relative rates of Table 1 for the different chloro and bromo compounds can be explained in this way, when it is assumed that the benzyl halides react by a mechanism described formerly as involving simultaneous operation of both S_N1 and S_N2 mechanisms[20,cf.14], while the others by an S_N1 type of mechanism. The effect of fluorine is exceptional in that it should increase the reactivity of benzyl chloride even better than chlorine by the resonance effect, in a similar way as it does in the solvolysis of *p*-halo-substituted benzyl chlorides[25]. A probable explanation is[14,22] that the inductive effect of fluorine predominates in cases in which it is directly attached to the center of the reaction.

The solvolysis reactions of closely similar compounds, PhCXYMe (X = H, Cl, Br; Y = Cl, Br), have been investigated by Taylor[26]

TABLE 1. First-order rate coefficients for the hydrolysis of some benzyl halides and more halogenated derivatives[22-24].

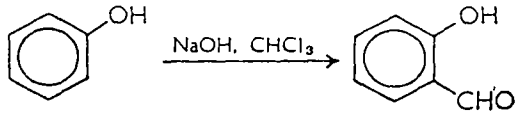
Compound	Conditions		10^6k (sec^{-1})
	% acetone/% water	°C	
$PhCH_2Cl$	50/50	30	0·372
$PhCH_2Br$	50/50	30	9·47
$PhCHCl_2$	50/50	30	3·69
$PhCHBr_2$	50/50	30	11·4
PhCHClBr	50/50	30	51·8
$PhCCl_3$	50/50	30	184
$PhCBr_3$	50/50	30	1880
$PhCCl_2Br$	50/50	30	3540
$PhCClBr_2$	50/50	30	3000
$PhCF_2Cl$	50/50	30	0·0698[a]
p-$MeOC_6H_4CH_2Cl$	83/17	36	49·5
p-$MeOC_6H_4CHCl_2$	83/17	36	1900

[a] Calculated from data at other temperatures.

and by Baddeley and Chadwick[27], the influence of the second halogen atom on the displacement of the first being in general conformity with the results discussed above.

A more extended conjugation than that of one benzene ring still favors the carbon–halogen π overlap, which is seen from the effect of a p-MeO substituent (Table 1) and, in particular, from the enhanced reactivity of dichlorodiphenylmethane[2,28], which is comparable with that of acid chlorides. The half-life at 0°C in a 75/25% acetone–water mixture is 26 min, which shows this compound hydrolyzes about six times faster than benzoyl chloride under the same conditions[29]. Similarly, β-dichloromethylstyrene, $PhCH{=}CHCHCl_2$, is readily hydrolyzed to cinnamic aldehyde even by cold water[30].

A rather different type of application of the dihalide hydrolysis to prepare aromatic carbonyl compounds is the reaction discovered by Reimer and Tiemann[31] for the preparation of salicylaldehyde and its analogs (equation 7). It is very probable that substituted benzal chlorides are involved as the reaction intermediates[32,33].

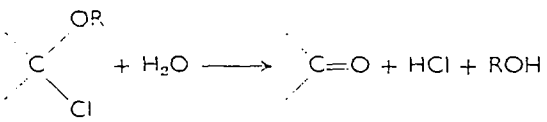


(7)

The increased reactivity effected by α-halogen atoms in benzal halides and their derivatives is in principle similar to that observed in such aliphatic systems in which the carbon–halogen bonds are conjugated to multiple bonds. Thus Vernon[34] found that allylene dichloride, $CH_2{=}CHCHCl_2$, hydrolyzed readily; in formic acid as solvent this compound was more reactive than the corresponding monohalide by a factor of about 60. Although more extensive comparative data on similar systems do not exist, it is evident from practical applications in preparing α,β-unsaturated aldehydes of the type $R^1R^2C{=}CR^3CHO$ from the corresponding dihalides[34–36] that the displacement of halogen atoms of these halides takes place very easily in comparison to the corresponding saturated halides.

B. α-Halo Ethers and Related Compounds

When one of the halogen atoms of α,α-dihalides is replaced by an alkoxyl group a very reactive class of compounds, α-halo ethers, is obtained (equation 8). For most α-halo ethers the reaction in water



(8)

solution is almost instantaneous and only rough estimates of its velocity can be made. Thus it has been estimated[37] that methyl chloromethyl ether hydrolyzes faster that n-propyl chloride by a factor of about 10^{13}. Another estimate is the following: the solvolysis rate of 2,3-dichloro-*p*-dioxane is much lower than that of chloromethyl ether, as measured in water and in a number of other solvents[38]. At 25°c, its solvolysis in water is faster than in ethanol by a factor of 20,000. If it is assumed, as a first approximation, that the solvent influence is similar in the case of chloromethyl ether, which is nearly true of several α-halo ethers in a variety of solvents[39], one can estimate from the rate of ethanolysis of chloromethyl ether[40] its hydrolysis rate. The rate coefficient thus obtained is of the order of 3000 sec^{-1} in water solution at 25°c. This may be contrasted with the value for methylene dichloride of 9×10^{-11} sec^{-1}, calculated from the corresponding data of Fells and Moelwyn-Hughes[5] for the same conditions.

The great reactivity of α-halo ethers can be derived from the same electronic effects that operate in benzal halides, viz. the resonance effects. However, the carbon–oxygen π overlap is much more

pronounced than that of carbon–halogen bond due to the relative strength of carbon–oxygen double bonds and thus comes into act without cooperation of additional unsaturated systems attached to the reaction center. The correctness of an early explanation given by Hughes and Ingold[41] has been confirmed by several lines of independent evidence[37–39] which indicate the solvolysis reactions of these compounds to proceed by an S_N1 mechanism, i.e. by a mechanism in which the nucleophilic participation of solvent molecules in the transition state is relatively small*. With stronger nucleophilic reagents, like hydroxyl ions, the participation is more pronounced, i.e. the mechanism will be closer to the S_N2 type of Ingold and Hughes. The resonance effect naturally enhances the reactivity also in the latter case, as actually found experimentally[37].

When the solvolysis of α-halo ethers takes place in solvents of low ionizing power, such as dioxane containing small amounts of water[42] or aliphatic alcohols[40], the reaction is much slower and is autocatalytically accelerated by the hydrogen halide formed. This acceleration is not due to proton catalysis as was proposed earlier[40,42] but is the result of a primary salt effect[39], which is especially strong in this type of media. Summers[43], who has given a comprehensive review on the methods of preparation of α-halo ethers and their synthetic uses in 1955, still used the former view when discussing solvolytic and certain other displacements of these compounds.

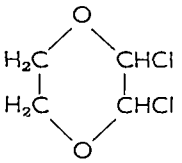
As the reactivity of α-halo ethers toward solvolysis is derived from the resonance effect discussed above it is evident that it is strongly affected by the polar character of substituent groups and their distance from the carbon–oxygen bond that will assume a partial double-bond character in the transition state. These effects are illustrated by the data of Table 2. The relatively low rate of *trans*-2,3-dichlorodioxane, which makes even its hydrolysis in water accessible to measurement (equation 9), can hardly be accounted for solely by the inductive effect of the second halogen atom; here the carbon–oxygen π overlap in the transition state is between orbitals of atoms of a nonplanar ring so that it probably involves steric hindrance[38]. The 2,3-dichlorodioxane obtained by direct chlorination of dioxane has *trans* chlorine atoms. Summerbell and Lunk[44] have prepared the

* The fast displacement of the second halogen atom in α,α-dihalides (section II.A) has probably a similar course; here the S_N1 type of mechanism leads directly to the protonated form of the carbonyl compound: $R_2C(OH)X \rightarrow R_2C{=}\overset{+}{O}H + X^-$. This is then followed by proton-distribution equilibrium between the carbonyl group and the solvent.

TABLE 2. Relative rates of solvolysis of α-halo ethers in ethanol solution at 25°c. For $MeOCH_2Cl$, taken as the standard, $k = 0{\cdot}150\ sec^{-1}$.

Compound	Relative rate	Ref.
$MeOCH_2Cl$	1	39, 40
$EtOCH_2Cl$	2·7[a]	39, 40
n-$PrOCH_2Cl$	2·8[a]	40
sec-$PrOCH_2Cl$	12[b]	40
$MeOCH_2Br$	46[b]	39
$ClCH_2OCH_2Cl$	0·00026	39
$ClCH_2CH_2OCH_2Cl$	0·17	45
$Cl_3CCH_2OCH_2Cl$	0·00085	46
MeOCH(Me)Cl	> 1000[b]	39
trans-2,3-Dichlorodioxane	0·000011	38

[a] Calculated from measurements at other temperatures.
[b] Estimated from relative rates in solvents containing dioxane.



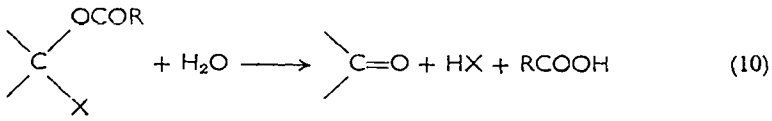
$$+ 2\,H_2O \longrightarrow CHOCHO + 2\,HCl + CH_2OHCH_2OH \qquad (9)$$

corresponding *cis* compound and found it to hydrolyze about 14 times faster than the *trans* compound. A possible explanation is that in the *cis* compound there is repulsion between the adjacent chlorine atoms (i.e. their *p* orbitals overlap to some extent, and this overlap is antibonding) which makes it less stable.

The studies of Hine and coworkers[23,24,47,48] on ethers containing more than one α-halogen atom attached to the same carbon atom are interesting when contrasted with the results obtained for benzal halides and related compounds (section II.A). The introduction of additional chlorine atoms into methyl chloromethyl ether reduces the rate of solvolysis, thus differing from the behavior of the aromatic polyhalides. The relative rates for $MeOCH_2Cl$, $MeOCHCl_2$, and $MeOCCl_3$ in 50% ethanol–diethyl ether solution at 0°c are 1, 0·0248, and 0·000380, respectively. The authors attribute this retardation to a greater stabilization of the reactants by contributing structures like $MeO^+{=}CHCl\ Cl^-$ rather than to the stabilization of the transition state by additional structures in which the positive charge is placed on a chlorine atom. The fact that there is no resonance stabilization by additional halogen atoms in this case is in general agreement with

the relative weakness of carbon–chlorine double bonds as compared to carbon–oxygen double bonds, which makes the structures with double-bonded chlorine insignificant. The results on corresponding fluorine compounds show similar features. Methyl fluoromethyl ether reacts within minutes in aqueous methanol, whereas methyl difluoromethyl ether is relatively stable under the same conditions.

The hydrolysis of α-haloalkyl esters, which can be considered as substituted α-halo ethers (equation 10), has been studied in detail by



(10)

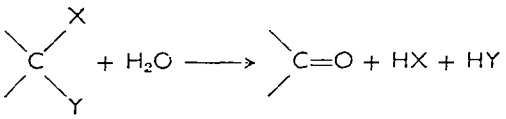
Euranto[49–51]. The reaction is rather complicated and it was shown that several concurrent mechanisms are involved, including neutral, acid- and base-catalyzed ester hydrolyses, and displacement of the halogen atom. The results of the latter reaction may be compared with those on α-halo ethers and it is found that the carbonyl group attached to the ether oxygen atom greatly reduces the solvolysis rate, in accordance with its polar character. The rate coefficient for the displacement of chlorine of chloromethyl acetate, CH_3COOCH_2Cl, in water solution is about 2×10^8 times smaller than the value estimated above for methyl chloromethyl ether. An α-alkyl substituent enhances the solvolysis rate similar to that of α-halo ethers (Table 2); α-chloroethyl acetate, $CH_3COOCHClCH_3$, solvolyzes in acetone–water solvent about 400 times faster than chloromethyl acetate. On the basis of this and other lines of evidence the author suggests that the former compound solvolyzes by S_N1 mechanism, whereas the latter displays a borderline case. The acid-catalyzed reaction shows all the features of a normal type of ester hydrolysis, $A_{AC}2$, and the reaction with hydroxyl ion those of the base-catalyzed ester hydrolysis mechanism $B_{AC}2$.

The sulfur analogs of α-halo ethers, viz. α-halo thioethers, also hydrolyze to carbonyl compounds, but are much less reactive[42,52]. This is understandable as, owing to the larger size of the *p* orbital of sulfur in comparison to oxygen, the π overlap is weaker in this case. From the close similarity of the *p* orbitals of carbon and nitrogen one may expect the nitrogen analogs, α-halo amines, to be even more reactive than the respective halo ethers. In fact α-halo amines have been shown to be exceptionally reactive[53–58], although no direct quantitative comparisons to the haloethers have been made.

The application of α-halo ethers to the preparation of carbonyl compounds and to other synthetic purposes has been reviewed by Summer[43].

C. Acetals, Ketals, Acetal Esters, etc.

Acetals and ketals are important intermediates in many syntheses of carbonyl compounds by virtue of their stability in neutral and alkaline solutions. Although the hydrolysis reactions of α,α-dihalides, α-halo ethers and acetals (or ketals) may be written in a similar formal way (equation 11), there are large differences between the



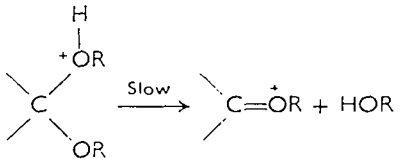
(X,Y = halogen, RO) (11)

three classes of compounds in their hydrolyses. The reactions of the first two classes of compounds involve both a displacement of a halogen atom in their rate-determining stages; the difference in reactivity is derived from the influence of the rest of the molecule, viz. from the different effects of α-halogen and α-alkoxyl substituents. On the other hand, in the hydrolyses of corresponding α-halo ethers and acetals (or ketals), the difference is in the groups that are displaced, the remnants of the molecules being the same. As a leaving group in a displacement reaction, the alkoxyl group is very unreactive in comparison to halogens, so that acetals are relatively stable. However, a protonated alkoxyl group is much more ready to act as a leaving group than an unprotonated one and therefore acetals can be hydrolyzed in acid media.

An idea of the susceptibility of protonated alkoxyl groups to displacement in acetal hydrolysis may be gained from the following estimate: the rate coefficient for the acid-catalyzed hydrolysis of formaldehyde dimethylacetal, $MeOCH_2OMe$, in dilute aqueous solutions of strong acids[59] at 25°C is $2{\cdot}50 \times 10^{-5}$ l/mole sec. As it is the protonated form of the compound that undergoes displacement, the above value includes both the rate coefficient for the displacement reaction and the equilibrium constant of the acid–base reaction between the acid medium and the substrate. Studies on the basicity of weak organic bases[60] show that the conjugate acids of aliphatic ethers have pK values of the order of -4, and therefore the above rate coefficient is to be multiplied by some four powers of ten to

obtain the rate coefficient (in sec^{-1}) for the hydrolytic displacement reaction of the conjugate acid of the acetal. A comparison with methyl chloromethyl ether (section II.B) shows then that a chlorine atom is more reactive than a protonated methoxyl group in these corresponding reactions by a factor of about 10^4.

The structural similarity of α-halo ethers and acetals suggests that their hydrolysis reactions are closely related mechanistically, except for the difference in the leaving groups involved. In fact there is a convincing body of evidence[61–63] supporting the original proposal of O'Gorman and Lucas[64], according to which these reactions involve as their rate-determining stages a cleavage of the carbon–oxygen bond of the protonated substrate (equation 12). Like the reaction of



(12)

α-halo ethers, this cleavage is facilitated by the carbon–oxygen π overlap in the transition state, which implies that the structural influences on both reactions should be similar. These conclusions are borne out by a large pattern of experimental results.

Kreevoy and Taft[65] have investigated in detail the effect of the carbonyl component on the rate of hydrolysis. Some of their results are given in Table 3. As the reaction mechanism implies that the

TABLE 3. Relative hydrolysis rates of diethyl acetals and ketals, $R^1R^2C(OEt)_2$, in 50·4% water–dioxane solution at 25°C[65].

R^1	R^2	Relative rate	R^1	R^2	Relative rate
H	H	1	H	$ClCH_2$	$2·08 \times 10^3$
H	Me	$6·00 \times 10^3$	H	Ph	$1·71 \times 10^5$
H	Et	$6·46 \times 10^3$	H	$PhCH{=}CH_2$	$3·70 \times 10^6$
H	*sec*-Pr	$3·97 \times 10^3$	Me	Me	$1·82 \times 10^7$
H	*tert*-Bu	$4·55 \times 10^3$	Me	$ClCH_2$	$2·08 \times 10^3$
H	$PhCH_2$	$2·11 \times 10^2$			

covalent participation of the solvent molecules in the transition state is small, the steric influences can be neglected as a first approximation. In fact the authors have shown that their data can be satisfactorily analyzed in terms of polar substituent constants, σ*, and hyperconjugative effects of hydrogen atoms that are in the α-position

to the reaction center in which the partial double bond is developing. More complicated situations arise in the cases of cyclic acetals and ketals[66,67]; here the progress toward the carbonium–oxonium ion geometry is more or less sterically restricted, depending upon the structure of the cyclic systems involved.

The influence of the alcohol component of acetals and ketals is a combined effect of different factors. Thus, for example, the relative hydrolysis rates of dimethyl acetal and diethyl acetal consist of changes in the group that is displaced in the rate-determining reaction as well as of changes in the rest of the molecule which remains intact in the rate-determining stage of the reaction. A differentiation of these effects has been made by analyzing the data on

TABLE 4. Structural effects in the hydrolysis of acetals of formaldehyde in water at 25°C[59]. Relative rates calculated for the individual cleavages, $R^1OCH_2{:}OR^2$.

(a) R^1 is varied

R^1	FCH_2CH_2	$ClCH_2CH_2$	$CH_3OCH_2CH_2$	Me	Et	*sec*-Pr
Relative rate	0·0801	0·0480	0·201	1	4·48	22·1

(b) R^2 is varied

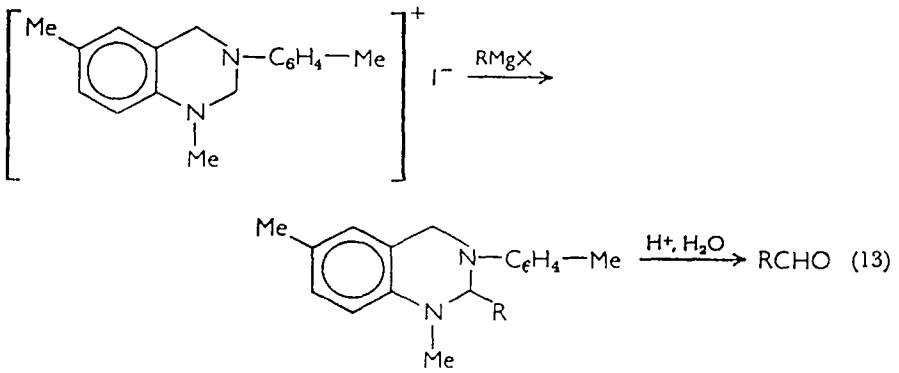
R^2	FCH_2CH_2	$ClCH_2CH_2$	$CH_3OCH_2CH_2$	Me	Et	*sec*-Pr
Relative rate	2·02	1·96	1·53	1	1·21	2·27

a large number of symmetrical and unsymmetrical acetals of formaldehyde[59], taking into account the concurrent cleavages involved. The validity of the results has been independently controlled by comparing calculated rate coefficients with those directly measured. Table 4 gives some of the results calculated for individual displacements. It is seen that the structural effects of substituents in the remnants of the molecule (Table 4a) are very similar to those observed in the solvolysis of α-halo ethers. The influence of the structure of the group that is displaced (Table 4b) is more complicated because a change in this group alters the basicity of the oxygen that is protonated as well as the polar character of the bond that is broken, these two factors acting in opposite directions.

Although the net influence of the structure of the leaving group on the hydrolysis of acetals seems to be relatively small, as in Table 4b, more pronounced effects become apparent when this group contains electronegative substituents close to the bond that is

broken. Acetal esters of the type $R_2C(OR)(OCOR)$, like methoxymethyl acetate, $MeCOOCH_2OMe$, hydrolyze in acid media faster than the corresponding dialkyl acetals by a factor of about 100[68,69] and, except for a few particular cases in which ester hydrolysis of a normal type is involved, the reactions take place by the same mechanism as the hydrolysis of acetals. The hydrolysis of these compounds occurs also in neutral solution[70] and shows the same structural behavior as the solvolysis of α-halo ethers and acetals. The influence of the leaving group, i.e. the acid component of the mixed acetal, is very significant and there is a correlation between the strength of the acid and the rate of hydrolysis. The alkaline hydrolysis of these compounds is relatively fast and presumably follows mainly the $B_{AC}2$ route of alkaline ester hydrolysis.

There seems to be no quantitative data on the reactivity of aminals to allow a comparison to their oxygen analogs, acetals, although it is known from synthetic applications that these compounds are usually readily converted into carbonyl compounds in acid solution. As the hydrolysis mechanisms are presumably the same, an inference may be drawn that the higher basicity of nitrogen and the resonance effect both favor the reaction, which is, however, opposed by the fact that a substituted amino group is less reactive as a leaving group than an alkoxyl group. As an example of many practical applications of the hydrolysis of aminals, the method of Fales[71] for the preparation of aldehydes may be cited. The method consists of a reaction between an aliphatic or aromatic Grignard reagent and the methiodide of 3,4-dihydro-6-methyl-3-*p*-tolylquinazoline (itself readily obtained by the reaction between *p*-toluidine, formaldehyde and formic acid), followed by acid hydrolysis of the aminal formed (equation 13).



(13)

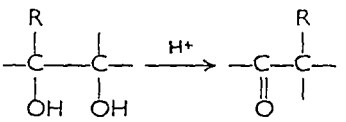
The sulfur analogs of acetals, mercaptals, are relatively stable even in acid solutions. If their hydrolysis mechanism is the same as that of acetals, as it has been suggested[72], this difference in reactivity can be accounted for by the same structural effects as those discussed above (section II.B) in connection with α-halo ethers and their sulfur analogs.

D. Hydrolyses Accompanied by Rearrangement

The common feature of the carbonyl-forming hydrolysis reactions discussed in the preceding sections is that two atoms or groups that are attached to the same saturated carbon atom will be replaced by carbonyl oxygen atom. There are, however, some instances in which the displaced groups are on the adjacent carbon atoms and therefore the formation of a carbonyl group by hydrolysis involves also a rearrangement. As an example, the reaction discovered by Eltekow[73], the formation of isobutyraldehyde from isobutylene dibromide on heating with water, may be cited (equation 14). Similar rearrangements have been observed in a number of other 1,2-dihalides[74,75].

$$Me_2CBrCH_2Br \xrightarrow{H_2O} Me_2CHCHO \qquad (14)$$

As these reactions display similar structural effects to the pinacol–pinacolone rearrangement (equation 15), the rearrangement of β-halohydrins, and the deamination of β-aminohydrins, it is very



(15)

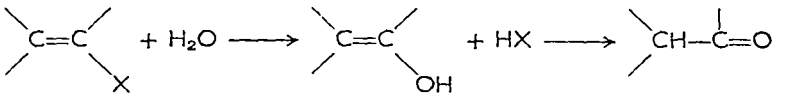
likely that the mechanisms are closely related. The current views concerning the mechanisms of these rearrangements have been discussed[76,77].

III. UNSATURATED SYSTEMS

A. Reactions Involving Ethylenic Linkages

1. Transformation to a single bond

The hydrolytic reactions to be dealt with in this section are of the general type (16). Formally, in these reactions an atom or a group



(16)

(X = halogen, alkoxyl group, etc.)

that is attached to an unsaturated carbon atom is displaced by a hydroxyl group, followed by a tautomerization of the enol form to aldo or keto form (assuming that it is the more stable). Whether a displacement of X actually occurs or not will depend upon the reaction mechanism and will be discussed below. The utility of the compounds of the vinyl type for the preparation of carbonyl compounds stems mainly from their relatively economical preparation from acetylene and its homologs.

It has been well known for a long time that a halogen atom attached directly to an unsaturated system is very unreactive toward nucleophilic displacement. This is the results of the resonance effect (i.e. the overlap between the halogen p orbital and the carbon–carbon π bond), which makes the halogen more positive and less susceptible to act as a leaving group in nucleophilic substitution. A comparative study of the reactivities of α-haloalkenes[79] illustrates this point clearly. There are, however, some particular instances in which the reaction occurs more readily, viz. cases in which a carbonyl double bond is in conjugated position to the ethylenic linkage. Thus, β-bromo-α-methylacrolein is easily converted by water into methylmalonic dialdehyde[80] (equation 17) and, similarly, 1-acyl-2-chloro-

$$CHBr{=}C(Me)CHO \longrightarrow CHOCH(Me)CHO \qquad (17)$$

ethylenes (themselves obtainable from the addition of acyl chlorides to acetylene) are readily transformed to 2-acylaldehydes[81] (equation 18).

$$RCOCH{=}CHCl \longrightarrow RCOCH_2CHO \qquad (18)$$

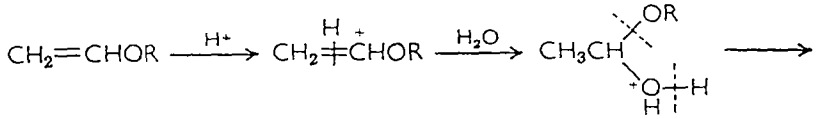
In contrast to α-haloalkenes, α-alkoxyalkenes and related compounds can be readily hydrolyzed in the presence of acid catalyst at a rate comparable to acetals, which makes them useful for several syntheses of carbonyl compounds. There are good reasons to believe that their hydrolysis does not involve a displacement of a protonated alkoxyl group, $R_2C{=}CR(\overset{+}{O}HR)$, but consists of another type of reaction discussed below. First, the basicity of the oxygen atom of these ethers is effectively reduced by resonance, which renders it more positive. Second, as pointed out above (section II.C), a chlorine atom is more effective as a leaving group in nucleophilic displacements than a protonated alkoxyl group. Both of these factors would make vinyl ethers even much less reactive than vinyl chloride toward solvolysis.

The kinetics of the acid-catalyzed hydrolysis of vinyl ethers have

been studied by Skrabal[82], who noted that ethyl vinyl ether hydrolyzes more rapidly than the corresponding saturated ether, diethyl ether, by a factor of about 10^{13}, other vinyl ethers displaying similar structural effects. The reaction mechanism has been discussed in connection with more recent studies. It has been suggested[83] that the protonated form of hemiacetal is first formed by an interaction of hydronium ion with both the ether oxygen atom and the β-carbon atom (equation 19), followed by a rapid decomposition of the

$$CH_2{=}CHOR + H_3O^+ \longrightarrow CH_3CH(OH)(\overset{+}{O}HR) \qquad (19)$$

hemiacetal to aldehyde. Although this reaction path may be correct in principle, it does not explain the nature of the hydronium ion attack and the reactivity of vinyl ethers. In a recent study[84] the reactions of ethyl, *sec*-propyl, and butyl vinyl ethers were followed in ^{18}O-labeled water and it was observed that no enrichment of ^{18}O resulted in the alcohol formed. This shows that the alkyl–oxygen bond remains intact during the reaction. The reaction mechanism proposed for this and a similar reaction, the hydrolysis of vinyl esters[85], was that involving a π-bond protonation (equation 20).



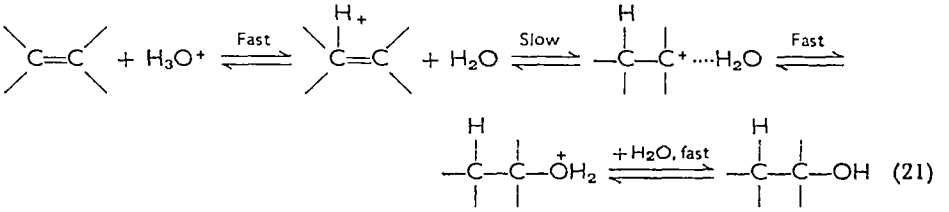
$$CH_3\overset{+}{C}HOH + ROH \longrightarrow CH_3CHO + H^+ + ROH \qquad (20)$$

The relative rates of these possible reactions steps and the structural effects were not discussed. As the decomposition of hemiacetals presumably proceeds by a mechanism similar to that of the dehydration of aldehyde hydrates[86], the last two steps are less probable, in particular, as an unprotonated alkoxyl group is assumed to act as a leaving group.

The structural effects are satisfactorily discussed in terms of the mechanism of the acid-catalyzed hydration of olefins*, investigated

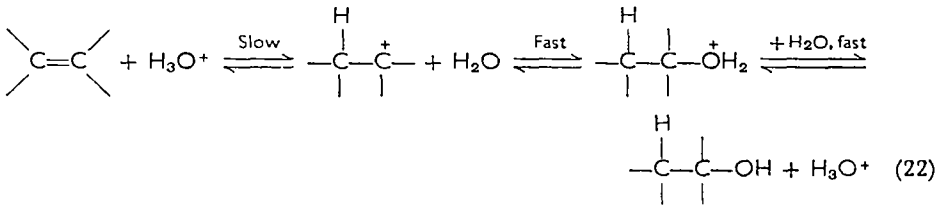
* *Note added in proof.* After this manuscript was submitted for publication, two kinetic investigations of vinyl ethers were published. Jones and Wood (*J. Chem. Soc.*, 5400 (1964)) studied the hydrolysis of a number of open-chained vinyl ethers in 80% dioxane–water mixture, and Fife (*J. Am. Chem. Soc.*, 1084 (1965)) made a kinetic study of a cyclic vinyl ether, 2-ethoxy-1-cyclopentene-1-carboxylic acid, in water solution. The conclusions drawn by these investigators were essentially identical with those arrived at here, although the lines of argumentation were different.

extensively by Taft and coworkers[87]. His results were consistent with two mechanistic schemes. The first involves a carbonium ion which is shielded by a water molecule, an 'encumbered' carbonium ion (equation 21). The other involves a solvated but in other respects



(21)

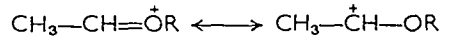
free carbonium ion (equation 22). While the information derived



(22)

from different independent sources was consistent with the both schemes, the former scheme involving a π complex and an 'encumbered' carbonium ion was proposed as the more probable.

If it is assumed that the hydrolysis of vinyl ethers occurs by a mechanism similar to that of the hydration of olefins, their hydrolysis rates are readily accounted for. The carbonium ion formed in the rate-determining stage, regardless of its detailed structure ('encumbered' or 'free'), is in this case greatly stabilized by the resonance (23), and in the transition state which leads to this ion,



(23)

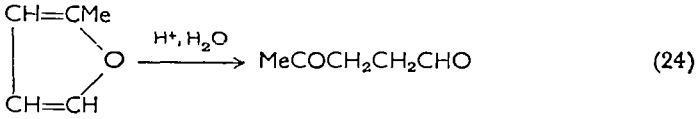
there will be a considerable overlap of the orbitals involved. Several facts may be presented in favor of this mechanism. First, the materially increased rates of hydrolysis of vinyl ethers when compared to olefins containing no α-alkoxyl substituents. Thus, the rate coefficient for the hydrolysis[82] of ethyl vinyl ether in dilute aqueous acid at 25°c is 5500 times the value calculated for the hydration of isobutylene from the data of Taft[88] corresponding to the same conditions. Second, the transition state of this mechanism would closely resemble that of the hydrolysis of acetals (cf. section II.C) as both yield ions that are of the same structure. This, apart from factors that relate to the parent compounds, should lead to comparable hydrolysis rates,

as actually observed[82]. Furthermore, both reactions should be similarly affected by similar structural changes in the reacting molecules. Although there is only a limited number of data to illustrate this point, it has been observed that *sec*-propyl vinyl ether hydrolyzes more readily than ethyl vinyl ether[82] (cf. Table 4a). Third, the entropies of activation for the hydration of olefins and the hydrolysis of vinyl ethers are of the same magnitude. The values for olefins are close to zero or negative by a few entropy units[88], and those for alkyl vinyl ethers are in the same range (-4 to 0) as calculated from the data of Skrabal[82].

Another piece of evidence in support of the above mechanism comes from a study of the hydrolysis of vinyl esters in acid solution. It was pointed out in connection with α-halo ethers (section II.B) that a replacement of the alkoxyl group by acyloxy group slows down the rate of solvolysis by some eight powers of ten. Similarly, in passing from ethyl vinyl ether to vinyl acetate, a decrease of roughly the same magnitude is expected in the rate of hydrolysis, assuming the olefin-hydration mechanism to be operative in both cases. The decrease actually observed is, however, only 20,000-fold[89]. This is readily understood because for vinyl acetate the reaction has another much easier route available, viz. the acid-catalyzed ester hydrolysis of the normal type $A_{AC}2$. The actual magnitude of the rate coefficient, which does not materially differ from that of ethyl acetate, as well as the value that can be calculated for the activation entropy, $-18{\cdot}7$ e.u., are in good agreement with this mechanism. Furthermore, an ester of the same polar character, phenyl acetate, hydrolyzes at a comparable rate[89], and in this case a mechanism similar to that of the hydration of olefins is completely ruled out.

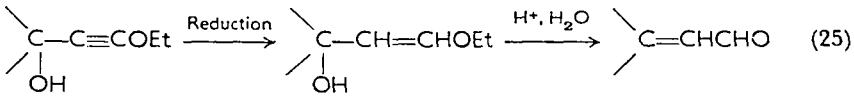
An essentially different mechanism has been recently proposed for the hydrolysis of vinyl acetate in connection with a study in ^{18}O-labeled water[85]. It was reported that only a negligible amount of ^{18}O was to be found in the acetic acid formed by the hydrolysis. This, of course, would completely invalidate the $A_{AC}2$ mechanism in this case. In other words this would imply that the rate of the normal acid-catalyzed acyl-oxygen fission reaction of esters would be greatly reduced when passing from ethyl acetate to vinyl acetate, so that another type of fission would become predominant. As the polar influence of substituents is rather small on this mechanism, and steric effects cannot cause any material differences in this case, the above result seems less acceptable. A reinvestigation of the reaction using the ^{18}O-tracer technique would seem desirable.

Some synthetic applications involving the use of α-unsaturated ethers and esters may be mentioned, in addition to the compounds obtainable from acetylene and its derivatives. α,γ-Dicarbonyl compounds are easily obtained from the hydrolysis of the substituted derivatives of furan and their nitrogen analogs[90–92], e.g. equation (24). Similar reactions of the pyran system, leading to α,δ-dicarbonyl compounds, have been described[93–95].



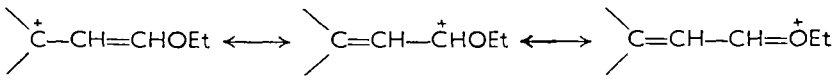
(24)

The preparation of α,β-unsaturated aldehydes through hydroxy-substituted vinyl ethers is of considerable practical and theoretical interest and has been recently reviewed by Arens[96], in connection with the synthetic use of ethynyl ethers. Ethoxy ethynyl carbinols can be easily reduced to the vinyl ethers, which hydrolyze fast in acid media to the unsaturated aldehydes (equation 25). In addition



(25)

to the hydrolysis of vinyl ethers, dehydration reactions are also involved. The mechanism of this transformation has not been studied in detail. One possibility is that the rate-determining stage involves the leaving of the hydroxyl group in its protonated form to give an ion of the structure

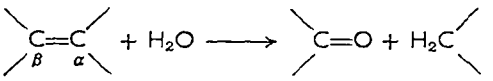


which is facilitated, even to a higher degree than the hydrolysis of unsubstituted vinyl ethers, by the resonance effect. The intermediate ion then rapidly reacts with the solvent, water, to yield the aldehyde, or alternatively the formation of the ion and its reaction with a water molecule is a concerted process in which the both changes occur essentially simultaneously.

2. Cleavage of ethylenic linkage by hydrolysis

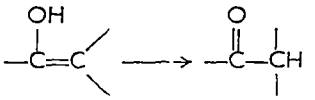
Although the carbon–carbon double bond of ordinary olefins cannot be broken by water, except under drastic conditions, there is

a number of cases in which the reaction (26) is activated by sub-



(26)

stituents, in particular, by strongly electron-attracting groups on the α-carbon atom. The very early examples are the hydrolyses of unsaturated nitro compounds[97–99]. Shemyakin and Shchukina[100] reviewed more recent results and emphasized the similarity of structural influences involved in reaction (26) and the corresponding tautomeric changes in the system



They also gave some qualitative rules about these structural effects.

Reaction (26) has recently been the subject of several kinetic investigations. Thus, Stewart[101] studied the base-catalyzed hydrolysis of vanillydinenitromethane and Crowell and Francis[102], in a similar study on piperonylidenenitromethane, demonstrated that a nitro alcohol is formed as the reaction intermediate. Patai and Rappoport[103] made extensive kinetic studies on the neutral and base-catalyzed hydrolyses of compounds of the general type ArCH=CXY (X, Y = cyano, ethoxycarbonyl, or carbamoyl group) and gave evidence that the rate-determining stage is an attack of a water molecule or a more nucleophilic catalyst on the carbon atom of the arylidene group. A detailed account on the hydrolytic reaction (26) may be found in a recent article by Patai and Rappoport[104].

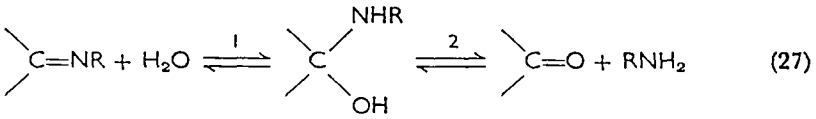
B. Reactions Involving Acetylenic Linkages

The hydration of acetylene and its derivatives to carbonyl compounds is a reaction of considerable practical interest, and a number of procedures involving the use of various catalysts have been patented (see, e.g., refs. 78 and 105, and references cited therein), which are, however, beyond the scope of this article. A relatively recent application is the hydration of acetylenes via hydroboration, which has been comprehensively reviewed by Zweifel and Brown[106]. In contrast to the hydration of olefins and related reactions, relatively little work has been thus far done on the mechanisms of these reactions and the structural effects involved.

C. Hydrolytic Cleavage of Carbon–Nitrogen Double Bond

1. General

The hydrolytic reactions in which a double-bonded nitrogen is replaced by carbonyl oxygen atom consist of a body of reactions that are of importance in the preparation, isolation, and purification of carbonyl compounds. The natural and easiest route for these replacements is via a carbinolamine intermediate (equation 27).



(27)

The hydrolyses of imines (R = H) and Schiff bases (R = alkyl, aryl) may be mentioned as examples, which are intermediate steps in many well-known carbonyl syntheses (e.g. the Gattermann, Vilsmeier, and Sandmeyer reactions; these and related reactions have been reviewed by Bayer[107]). When the group R is linked to the nitrogen atom through a heteroatom, oxygen or nitrogen, we have compounds like oximes, hydrazones, and semicarbazones, which are of particular use in the isolation and purification of carbonyl compounds rather than in their preparation itself. The reactions of the latter type of compounds will be dealt with in more detail in another chapter of this volume, but some references to them are needed in discussing the different factors involved in reactions like (27).

Any generalization concerning the influence of structure on these reactions is rendered difficult mainly because depending on conditions either of the two steps of (27) may be the slowest and thus rate determining. Independent of the latter, two general features are evident. First, regardless of the particular structure of the transition state it is obvious that its attainment involves a decrease of unsaturation and, therefore, substituents which contain unsaturated bonds conjugated to the carbon–nitrogen double bond of the nitrogen base will stabilize the starting material more than the transition state by resonance and retard the hydrolysis. Second, the reaction is strongly hindered by bulky substituents close to the central carbon atom.

2. Oximes and semicarbazones

The formation and hydrolysis of oximes and semicarbazones has been the subject of a number of classical investigations[108]. The

reactions were found to exhibit general acid catalysis and it was generally assumed that in the formation reaction the addition step is slow in comparison to the dehydration step (and similarly in the hydrolysis reaction, the deamination step is slower than the addition of water), i.e. the transition state of the reversible reaction (27) is that of step 2. The observation that the reactions showed pH optima (e.g. the formation of acetone semicarbazone was fastest at pH 4·6) was generally assumed to be the result of an interplay of two opposing effects, viz. that of general acid catalysis and the decrease in the concentration of the attacking free nitrogen base, the latter being gradually converted into its conjugate acid when the pH was lowered.

The oxime and semicarbazone reactions have been recently investigated by Jencks and coworkers[109–111], the results leading to conclusions differing from those earlier drawn. Independent evidence shows that the pH optima observed in these reactions are virtually due to transitions in the rate-determining stages with changing acidity of the reaction medium. As the carbinolamine intermediate lacks the ultraviolet and infrared absorption of the carbonyl group, it can be determined spectroscopically whether its formation is fast or slow in comparison to the overall rate of formation of oximes or semicarbazones (rate-determining dehydration step, or rate-determining addition step, respectively). The results show that at pH 7 the addition step is fast and in this region the overall rate increases with increasing acidity, the acid-catalyzed dehydration being now rate-determining. When the acidity is increased, the addition step becomes gradually slower (owing to the conversion of the nitrogen base into its conjugate acid), and at sufficiently high acidities it will determine the overall rate. This behavior is also illustrated by inductive effects of substituents, which are different on both sides of the pH optima. On the acid side, where the addition of the nitrogen base to the carbonyl group determines the overall rate, electron-withdrawing substituents increase and electron-donating substituents decrease the rate, as generally observed in carbonyl-addition reactions. The same substituents have, of course, an opposed influence on the rate of the dehydration step. When the latter is the slower as is the case in more alkaline solutions, the overall rate will be made up from the rate of this step and the equilibrium of the faster addition step, and one may expect that the net influence of polar substituents will be very slight, as is actually observed. Similar mechanistic conclusions apply of course to the reverse reaction, hydrolysis, because under

given conditions both reactions necessarily go through the same transition state.

3. Schiff bases

Early reports found in the literature on the relative stabilities of Schiff bases toward hydrolysis show many apparent discrepancies, the main source of error probably being in the different reaction conditions employed. The fact that a change in these conditions may change the nature of the rate-determining stage of the reaction and thus alter the influence of the structural factors involved has not been realized until recently. This pertains only to the factors that influence the stabilities of the possible transition states; as far as the stabilization of the parent Schiff base is concerned, it is easier to draw conclusions for each particular case. Thus, for example, the early observation[112] that the anil of cinnamic aldehyde, PhCH=CHCH=NPh, does not undergo hydrolysis even by boiling in aqueous acid can be explained by the resonance stabilization of the carbon–nitrogen double bond in this extended conjugated system.

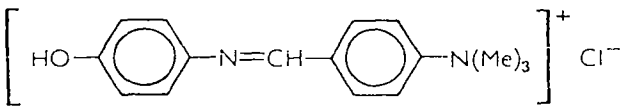
The first kinetic studies of the hydrolysis of Schiff bases were made relatively recently[113–115] using water–alcohol mixtures as solvent, and they consistently indicated that the reaction was subject to general acid catalysis. However, the conclusions drawn regarding the nature of the rate-determining stage were different. Willi[113,114] studied the hydrolysis of benzylideneaniline and proposed that step 1 of reaction (27), the addition of water to the Schiff base, is rate-determining at neutral pH, while Kastening[115] obtained evidence for an accumulation of the carbinolamine intermediate under the same conditions. As the rate of this reaction was too fast for conventional measurements at acidities below pH 5, the complete pH profile could not be ascertained.

In aqueous solution the hydrolysis of Schiff bases goes nearly to completion, which means that under these conditions the reverse reaction, the formation of a Schiff base, is slow in comparison to the forward reaction. Therefore the rate of the reverse reaction is much more amenable for a study over a wide pH range, excepting the unfavorable equilibrium. The disadvantage of the latter can, however, be avoided if the Schiff base formed is rapidly converted into another relatively stable compound. This is the principle of the method used by Cordes and Jencks[116]. They showed that the

Schiff-base formation is the rate-determining reaction in the aniline-catalyzed formation of semicarbazones in water solution. Semicarbazide therefore traps the Schiff base as soon as it is formed and carries the reaction nearly to completion.

On the basis of their results on benzylideneanilines, Cordes and Jencks suggested that the reaction undergoes a transition in its rate-determining stage with changing acidity, similar to that of oxime and semicarbazone reactions. This was supported by three lines of evidence. First, it was found that formation of Schiff bases exhibits a maximum in the pH–rate profile. This was not due to complications arising from general acid catalysis as the rate coefficients were corrected for these by extrapolating to zero buffer concentration. Second, the inductive effects of substituents showed different behavior on different sides of the pH optima. Third, the susceptibility of the reaction to general acid catalysis was different on the two sides of pH–rate maximum. When applied to the hydrolysis reaction it was concluded that in moderately acid solutions, step 2 of reaction (27), the deamination of the carbinolamine intermediate, becomes the slowest step of the overall reaction, while in approximately neutral solution the formation of the carbinolamine is the slowest.

Reeves[117] has made a similar study of the hydrolysis of a Schiff base (28) in the pH range 1·3 to 11·5 using flow techniques for the



(28)

most rapid rates. At pH 7·4 the reaction was followed both by the disappearance of the Schiff base (measured spectrophotometrically) and by the formation of *p*-aminophenol (measured polarographically). Both rates were equal and showed no accumulation of the intermediate carbinolamine at this pH, which is in accord with the above results of Cordes and Jencks. Furthermore, the same conclusion regarding the mechanism in moderately acid solutions could be drawn, viz. that in these solutions the decomposition of the carbinolamine becomes partially or wholly rate-determining.

4. Imines

Simple imines, $R_2C{=}NH$, in which the double bond is not stabilized by conjugation with other double bonds, tend to react through various routes (e.g. by polymerization) to give compounds

with single-bonded nitrogen. Therefore only 'stabilized' imines, in particular aromatic ones, are important as intermediates in the preparation of carbonyl compounds. In general the hydrolysis of aromatic aldimines, ArCH=NH, and that of alkyl aryl ketimines, RArC=NH, occurs easily in acid solution, excepting cases in which the reaction is sterically hindered by bulky substituents. Diaryl ketimines, Ar^1Ar^2C=NH, are more stabilized by conjugation, and due to this and other effects involved their hydrolysis may be rendered difficult in particular cases.

The most extensive data available on the effect of structure on the hydrolysis of imines are those of Culbertson and coworkers[118,119]. Most of their results are collected in Table 5, along with the

TABLE 5. The rates of hydrolysis of ketimine hydrochlorides, $RPhC{=}\overset{+}{N}H_2Cl^-$, in aqueous solution at 25°C[118-19].

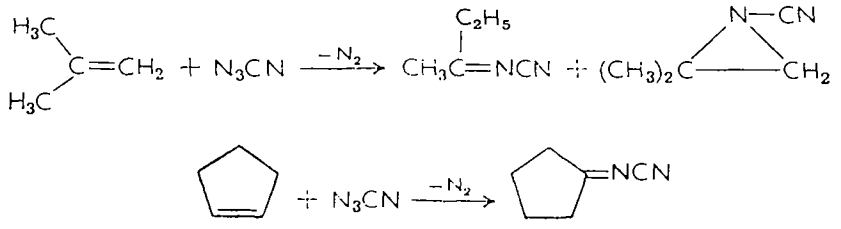
R	pK_{BH^+}	Half-life (min)
Phenyl	7·18	9·0
2-Methylphenyl	6·79	165
3-Methylphenyl	–	9·1
4-Methylphenyl	–	20·5
2-Chlorophenyl	5·59	23·9
3-Chlorophenyl	5·69	1·8
4-Chlorophenyl	–	5·4
2-Hydroxyphenyl	5·00	57·8
3-Hydroxyphenyl	7·08	5·5
4-Hydroxyphenyl	6·45	99
2-Methoxyphenyl	7·29	47
3-Methoxyphenyl	6·59	11
4-Methoxyphenyl	–	35
2,4-Dimethylphenyl	6·79	198
2,5-Dimethylphenyl	6·79	187
3,5-Dimethylphenyl	7·18	13·9
2,6-Dimethylphenyl	6·29	8670 (at 100°c)
2,4-Dihydroxyphenyl	5·00	1444
2,4-Dimethoxyphenyl	8·30	478
2,4,6-Trihydroxyphenyl	5·20	8450
2-Methylcyclohexyl	–	26
3-Methylcyclohexyl	–	0·36
4-Methylcyclohexyl	–	0·40
2,6-Dimethylcyclohexyl (*meso-trans* or *meso-cis*)	–	76,000 (at 100°c)
2,6-Dimethylcyclohexyl(racemic)	–	1750

respective pK values determined for the conjugate acids of the imines. Two general features are evident. First, relatively strong steric hindrance is effected by substituents located close to the central carbon atom. Second, the reaction is retarded by substituents in conjugated position to the nitrogen–carbon double bond (resonance effect), e.g. by hydroxyl and methoxyl groups in the *para* position. The possible imine–enamine tautomerism, suggested by Culbertson for the latter cases as an additional effect, would influence in the same direction.

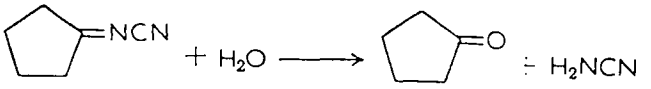
Although there seems to be a general conformity between expectations based on the above structural effects and the results observed experimentally, the question about the influence of the acidity of the reaction solution still remains unsettled. From the pK values of the conjugate acids of the imines, and from the initial concentration of the hydrochlorides used in these experiments (0·01 M), one can calculate that the initial acidity varied within the pH range 3·5 to 5·2 in the different experiments. In two cases only, viz. those of 2,4-dihydroxy- and 2,4-dimethoxy-substituted compounds, were experiments made with added hydrochloric acid (0·01 M). The rates of hydrolysis increased markedly by these additions, although it can be estimated from the results that the increase was not proportional to the hydronium ion concentration of the solution, the behavior in this acidity range being thus very similar to that of oximes, semicarbazones and Schiff bases.

5. Alkylidene cyanamides

An interesting new route to ketones from olefins, introduced by Marsh and Hermes[120], takes place via alkylidene cyanamides. Olefins react rapidly with cyanogen azide (itself prepared in almost quantitative yield from sodium azide and cyanogen chloride) to give alkylidene cyanamides and/or *N*-cyanoaziridines, e.g.



Alkylidene cyanamides are then readily hydrolyzed by aqueous acid to the corresponding ketones, e.g.

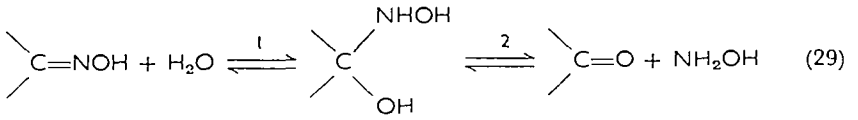


If the reactions prove to be generally applicable, they will certainly be of considerable significance for the synthesis of carbonyl compounds.

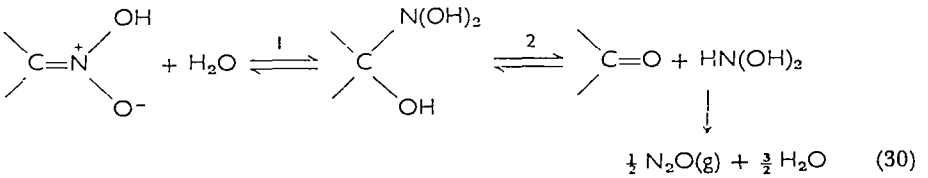
D. The Nef Reaction

The Nef reaction and its application to the synthesis of carbonyl compounds have recently been reviewed by Noland[121]. Therefore, only short additional comments will be made here, in particular to examine whether the more recent results on related reactions might be of use in explaining some of the structural and mechanistic features involved in this reaction.

The Nef reaction is the hydrolysis of the *aci* form of a nitro compound (to yield an aldehyde or a ketone), which occurs when a solution of a salt of the nitro compound is transferred into a moderately concentrated (usually over 10 M) solution of a strong acid. For the overall change which is taking place, one can write equations that are formally similar to those for the hydrolysis of oximes, semicarbazones or Schiff bases (omitting, for simplicity, the role of the catalyst acid), e.g. equations (29) and (30), although it must be emphasized that without more reliable arguments than the formal similarity no conclusions concerning the actual mechanism can be drawn.



(29)

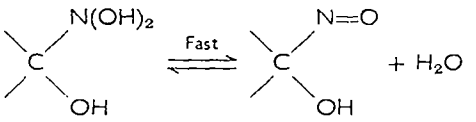


(30)

Van Tamelen and Thiede[122] have discussed the similarity of the above reactions and pointed out that the same structural factors that

retard the hydrolysis of oximes and semicarbazones, viz. steric hindrance and resonance effect arising from conjugation with the carbon–nitrogen double bond, seem to make the Nef reaction less favorable. On this basis they propose a mechanism for the Nef reaction which does not, however, account for the appearance of transient green or blue intermediates which seems to be an integral part of the reaction. Furthermore, the structural effects referred to relate primarily to the stability of the parent compound (cf. section III.C), the *aci* form of the nitro compound, and they would be in harmony with any mechanism that involved an attack on the central carbon atom.

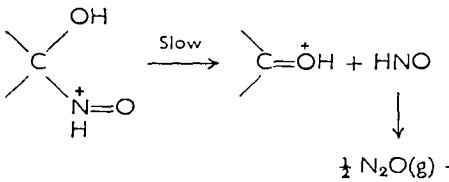
If equation (30) does describe the course of the Nef reaction, one might conclude from the recent results on the hydrolysis of oximes, semicarbazones and Schiff bases (section III.C) that, at the moderately high acidities at which the reaction occurs, the first reaction step would be fast in comparison to the second, thus leading to an accumulation of the intermediate. In this case, however, the intermediate would be relatively unstable and would decompose faster (equation 31) than pass directly to the products by step 2 of reaction



(31)

(30). Therefore, were the reaction in principle similar to that of oximes and semicarbazones, there should be an accumulation of the above nitroso alcohol intermediate. In fact there is independent evidence[121] that supports the presence of an intermediate of this type, which is presumably also responsible for the transient color observed.

An additional inference may be drawn. The rate-determining stage of the above mechanism would be an acid-catalyzed cleavage of the carbon–nitrogen bond of the nitroso alcohol to give a protonated carbonyl group (equation 32). This should be susceptible to similar polar influences of substituent groups than the hydrolysis of acetals and ketals (section II.C) substituted at the carbonyl com-



(32)

ponents, i.e. electronegative substituents should retard the reaction and vice versa. This naturally applies to cases in which this inductive effect is not masked by the other effects discussed above. The results on strongly fluorinated nitroalkanes and nitro alcohols[123] may be cited as examples. Thus, it has been observed that 3,3,4,4,5,5,5-heptafluoro-1-nitropentane does not undergo the Nef reaction.

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The Chemistry of the Carbonyl Group
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CHAPTER 4

Formation of aldehydes and ketones from carboxylic acids and their derivatives

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I. INTRODUCTION

The ready availability of many carboxylic acids makes them attractive as raw materials for the preparation of aldehydes and ketones. Most

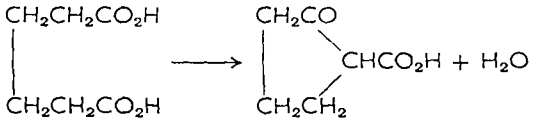
of such syntheses are carried out by way of amides, esters, or acid chlorides in which the carbonyl group is more vulnerable to nucleophilic attack than it is in carboxylate ions. The preparation of aldehydes from such acid derivatives requires hydrogenolysis. Conversion of acids into ketones (and aldehydes when formic acid is involved) corresponds to the loss of water and carbon dioxide from two molecules of acid. Nitriles, which are classified here as acid derivatives, are reduced to imines which yield aldehydes when hydrolyzed.

II. FROM ACIDS AND THEIR SALTS AND ANHYDRIDES BY PYROLYSIS

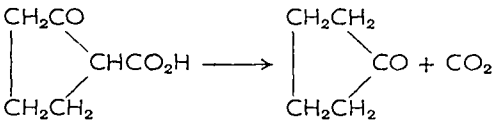
In general it may be said that ketones and aldehydes are more stable to heat than are acids and their salts and anhydrides. Pyrolysis of the latter, therefore, offers an attractive route to carbonyl compounds.

A. From Acids

Pyrolytic decarboxylation of β-keto acids is the last step in the acetoacetic ester synthesis of substituted acetones. The formation of ketones by pyrolysis of acids is believed to involve this step also. Pure adipic acid, for example, when heated in a quartz vessel at 300° gives cyclopentanone in nearly theoretical yields[1]. The transformation has been formulated as occurring in the two steps (1a) and (1b).

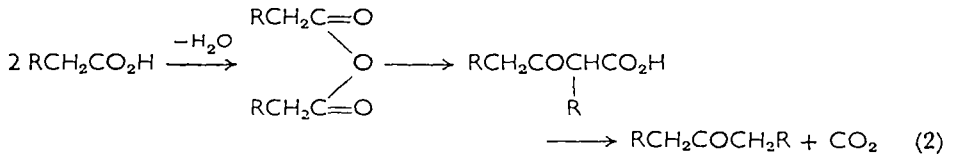


(1a)



(1b)

Evidence has been presented to support the hypothesis that ketones are formed from acids by way of anhydrides. The mechanism seems likely because the α-hydrogen atoms are more loosely held in anhydrides than in acids. Rearrangement of the anhydride to the β-keto acid would be followed by decarboxylation (equation 2)[2].



(2)

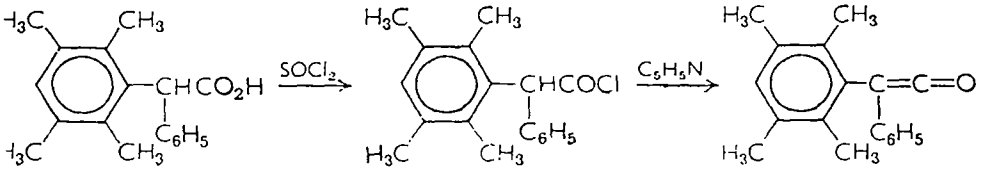
Postulation of the intermediate formation of β-keto acids is in accord with the observation that aliphatic acids without an α-hydrogen atom fail to give ketones. For the production of diaryl ketones from aromatic acids a different type of mechanism must be sought. One suggestion is that acylation of the aromatic ring occurs and is followed by decarboxylation of the resulting keto acid[1]. This mechanism might also explain the formation of aromatic aldehydes from aromatic acids and formic acid. The origin of formaldehyde in the distillation of formates seems to involve a complicated series of changes[3].

Apparently any compound containing the acetyl group gives ketene when pyrolyzed. Acetone and acetic acid are important examples. Ketenes have been made also by pyrolysis of disubstituted malonic anhydrides and certain mixed anhydrides, by dehalogenation of α-haloacyl halides, by pyrolysis of β-lactones, and by dehydrohalogenation of acid chlorides. According to the patent literature ketene is also produced by pyrolysis of acetic anhydride, vinyl esters, methyl acetate, and methyl propionate. These methods were reviewed by Hanford and Sauer in 1946[4].

One might expect to be able to make ketenes by dehydrochlorination of acid chlorides. Chlorides of suitably constituted acids do in fact lose hydrogen chloride when treated with tertiary amines but the ketenes are almost always obtained as dimers. When lauroyl chloride is treated with triethylamine, for example, decylketene dimer is produced (equation 3)[5]. Only when radicals such as mesityl

$$2\,C_{11}H_{23}COCl + 2\,(C_2H_5)_3N \longrightarrow C_{11}H_{23}COC(C_{10}H_{21})=C=O + 2\,(C_2H_5)_3N\cdot HCl \quad (3)$$

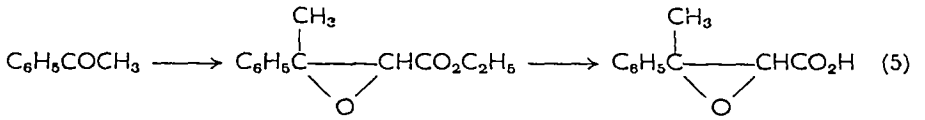
are present has the monomeric ketene been isolated. Durylphenylketene is obtained by treating durylphenylacetic acid with thionyl chloride in the presence of pyridine (equation 4). Evidently the acid chloride is formed and undergoes dehydrochlorination[6]. Presumably the failure of the ketene to dimerize is due to steric hindrance.



(4

Good directions have been worked out by Smith and Norton for making dimethylketene by the action of zinc on α-bromoisobutyryl bromide[7].

Glycidic acids lose carbon dioxide to form aldehydes or ketones[8,9]. An example is the production of hydratropaldehyde from acetophenone by way of ethyl methylphenylglycidate (equation 5). Hydrolysis of the ester gives the glycidic acid, which passes into the aldehyde by thermal decarboxylation (equation 6)[10].



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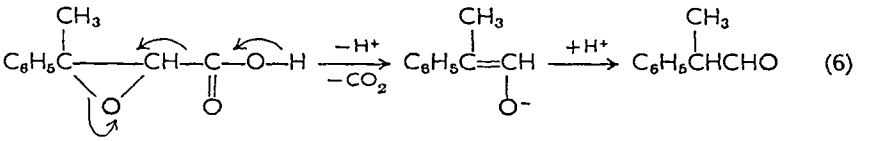
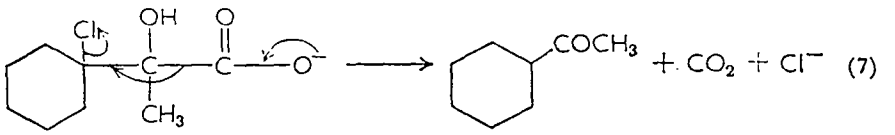


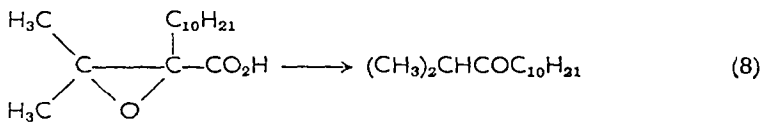
(6)

Another way of transforming glycidic acids into carbonyl compounds involves treatment with hydrogen chloride or hydrogen bromide to convert the epoxy acid into the corresponding α-hydroxy-β-halocarboxylic acid which, when treated with base, undergoes decomposition to give a carbonyl compound. An example is the formation of hexahydroacetophenone from cyclohexylmethylglycidic acid by way of the chlorohydrin. The breakdown of the anion shown



(7)

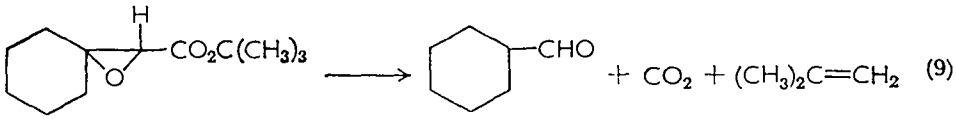
in (7) has been postulated[11]. Application of this method of decomposition to the glycidic acid from acetone and ethyl α-bromolaurate gives 2-methyl-3-tridecanone in 63% yield (equation 8)[12].



(8)

t-Butyl glycidates offer the advantage that they undergo decomposition directly, the *t*-butyl group being split off as isobutylene. In this way cyclohexanecarboxaldehyde is formed in 90% yield from

t-butyl α,β-epoxy-1-cyclohexylideneacetate (equation 9)[13]. The decomposition has been represented as in (10).



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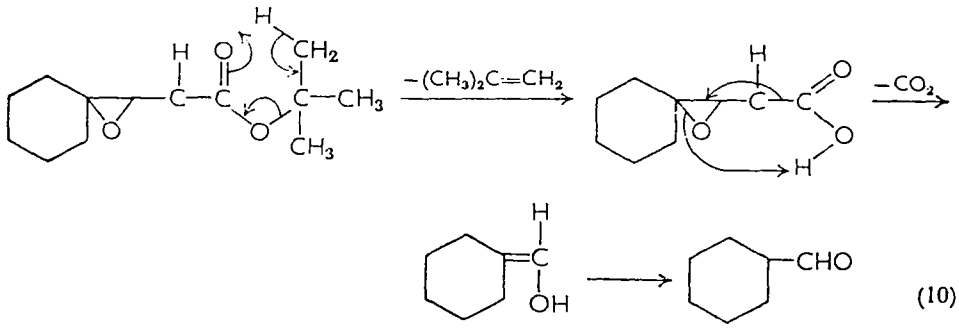


(10)

Glycidic esters are made by the Darzens condensation of carbonyl compounds with α-halo esters; the catalyst is a base such as sodium ethoxide or sodium amide[8].

B. From Salts

One of the oldest and most often cited methods of making carbonyl compounds is the pyrolytic decomposition of calcium, magnesium, and other salts of carboxylic acids. The procedure has not proved to be generally useful[14]. Sometimes it gives ketones in high yields, however; distillation of magnesium stearate, for example, produces stearone in 87% yield (equation 11)[15].

$$(C_{17}H_{35}CO_2)_2Mg \longrightarrow C_{17}H_{35}COC_{17}H_{35} + MgO + CO_2 \qquad (11)$$

Thermal decarboxylation of iron carboxylates has been shown to be an excellent method for the preparation of symmetrical straight-chain aliphatic ketones. When fatty acids are heated under reflux with iron powder, hydrogen is evolved and iron carboxylates are formed; heating converts them into ketones, ferrous oxide, and carbon dioxide. The decomposition is carried out in most cases at 250–300°. Under these conditions decanoic acid, for example, gives 10-nonadecanone in 96% yield[16].

Alkyl phenyl ketones are formed, generally in satisfactory yields,

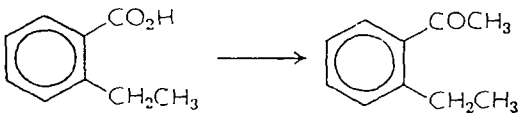
when this method is applied to mixtures of the iron salts of benzoic acid and an aliphatic acid[17].

In general better results are obtained by passing the acid or acids through a hot tube containing a catalyst such as manganese oxide or magnesium oxide. When acetic acid is passed through a hot tube containing manganous oxide, for example, acetone is produced in high yields. Only a small amount of the oxide is needed, presumably because manganous acetate is formed by the action of the acid on manganous oxide or carbonate.

Unsymmetrical ketones can be prepared satisfactorily if the low-molecular weight acid is used in large excess; acetic and phenylacetic acids form benzyl methyl ketone in 65% yield when passed over thorium oxide at 430–450°[18]. Similarly, ethyl phenylethyl ketone is produced from propionic and hydrocinnamic acids (equation 12)[18].

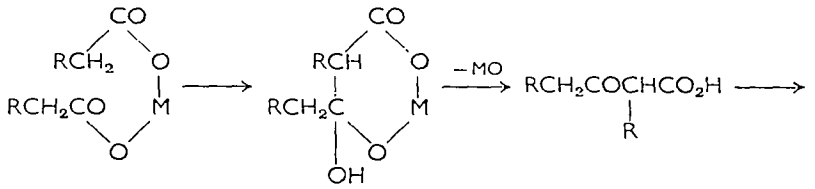
$$CH_3CH_2CO_2H + C_6H_5CH_2CH_2CO_2H \longrightarrow C_6H_5CH_2CH_2COCH_2CH_3 + CO_2 + H_2O \quad (12)$$

Aromatic acids may be used also: when a solution of *o*-ethylbenzoic acid in acetic acid is passed at 450° through a tube containing thorium oxide on pumice, *o*-ethylacetophenone is produced in 74% yield (equation 13)[19]. The reaction is bimolecular, taking place on the surface of the catalyst through the intermediate formation of the salt[20].



(13)

It seems possible that in the pyrolysis of salts of carboxylic acids an α-CH_2 group reacts with a carbonyl group in the aldol manner[21], as shown in equation (14).



$$RCH_2COCH_2R + CO_2 \quad (14)$$

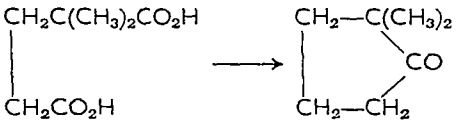
Comparison with other oxides and carbonates indicates that magnesium oxide is the most suitable for the commercial production of ketones such as stearone[22].

Mention should be made of Ruzicka and Brugger's classical synthesis of large-ring ketones by thermal decomposition of salts of dibasic acids[23]. By this method ketones with more than thirty ring-members have been made. Thorium oxide is a better catalyst than calcium or barium bases for the formation of large-ring cycloalkanones.

C. From Anhydrides

Anhydrides of monobasic aliphatic acids undergo thermal decomposition to yield ketones and carbon dioxide. The anhydride of n-butyric acid, for example, heated at 210° gives chiefly di-n-butyl ketone[2]. As has been mentioned, anhydrides may be produced as intermediates in the formation of ketones from acids.

Distillation of certain cyclic anhydrides gives the corresponding cycloalkanones. The anhydrides are formed conveniently by heating dicarboxylic acids with acetic anhydride. Only a little cycloheptanone is obtained in this way, and even with cyclopentanone and cyclohexanone the yields are not high. Alkyl substituents, especially the *gem*-dimethyl group, enhance the tendency of a chain to undergo cyclization. An example is the formation of 2,2-dimethylcyclopentanone from α,α-dimethyladipic acid (equation 15).



(15)

The facts have been summarized by the Blanc rule which states that, when adipic or pimelic acids are heated with acetic anhydride and the products are distilled (at about 300°), cycloalkanones are formed, whereas succinic and glutaric acids under similar conditions yield cyclic anhydrides. The rule has been used to determine the constitution of dibasic acids of the hydroaromatic series. Exceptions have been encountered with acids in which the two carboxyl groups are attached to different rings; such acids may form a seven-membered cyclic anhydride[24].

III. FROM ACID CHLORIDES

Acid chlorides, so important in the synthesis of aromatic ketones, serve also in the preparation of aldehydes.

A. Rosenmund Method

The Rosenmund method[25] was reviewed by Mosettig and Mozingo[26] a number of years ago, at which time it was considered to be perhaps the method of choice for converting acid chlorides into aldehydes. The acid chloride is subjected to hydrogenolysis in the presence of a catalyst such as palladium on barium sulfate (equation 16)[27]. The primary problem is to bring about hydrogenolysis without

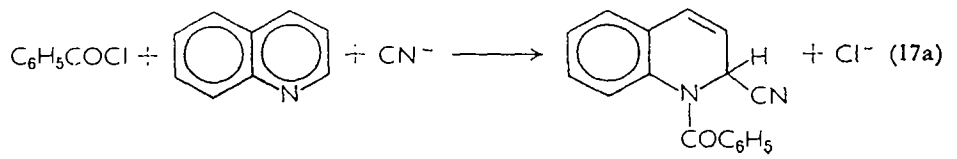
$$RCOCl + H_2 \xrightarrow{Pd/BaSO_4} RCHO + HCl \qquad (16)$$

subsequent hydrogenation of the aldehyde. One way of doing this is to operate at the lowest temperature at which reaction occurs as indicated by the evolution of hydrogen chloride. This procedure, although reported to give aldehydes in good yields[28], has not been used widely.

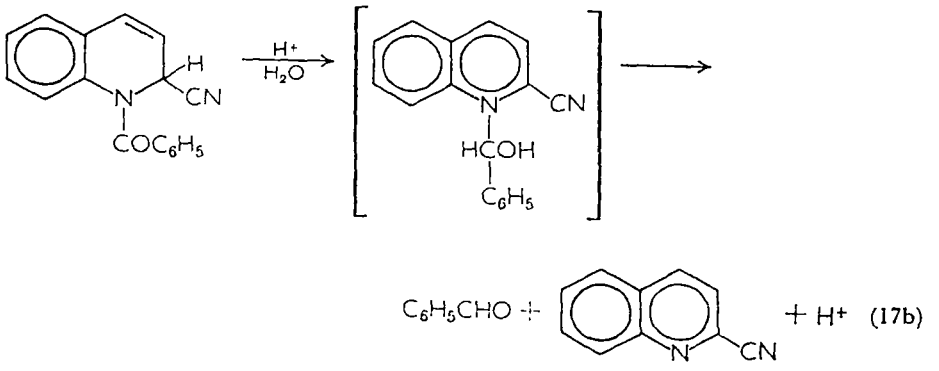
A much more common though not always reliable method is to introduce a regulator which acts as a catalyst 'poison'. The regulator of choice, called quinoline–sulfur, is made by heating a mixture of quinoline and sulfur[29]. By use of this regulator β-naphthaldehyde, for example, can be obtained from β-naphthoyl chloride in 81% yields. It is especially to be noted that the presence of nitro groups can be tolerated; *p*-nitrobenzoyl chloride gives *p*-nitrobenzaldehyde in high yield[30].

B. Reissert Method

It was discovered by Reissert that condensation of acid chlorides with quinoline in the presence of aqueous potassium cyanide yields 1-acyl-2-cyano-1,2-dihydroquinolines, which have come to be known as Reissert compounds. Of interest here is the acid-catalyzed decomposition of these compounds to form aldehydes. Benzoyl chloride, for example, gives benzaldehyde in high yield; the steps (17a) and (17b) have been proposed[31–33]. This method of making aldehydes was reviewed by Mosettig in 1955[34].



(17a)



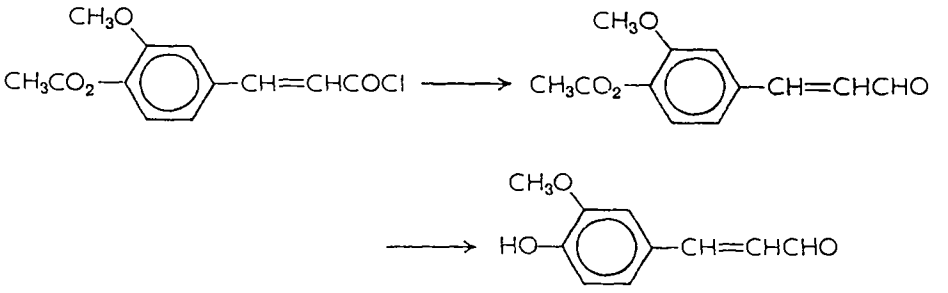
C. Metal Hydrides Method

One of the serious disadvantages of the Rosenmund method is the difficulty of poisoning the catalyst reproducibly. Also, some functional groups are sensitive to the hydrogenolysis conditions. These problems have been solved to a large degree by the use of complex metal hydrides. Some of these, notably the complex boron hydrides, reduce acid derivatives with difficulty[35]. Sodium borohydride ($NaBH_4$) when mixed with aluminum chloride in diglyme (the dimethyl ether of diethylene glycol), however, becomes such a strong reducing agent that, like lithium aluminum hydride[36–38], it generally carries the reduction to the alcohol stage*[39].

A milder reagent can be made by treating lithium aluminum hydride with *t*-butyl alcohol[40,41]. The product, lithium tri-*t*-butoxyaluminohydride—now available commercially[42]—reacts with acid chlorides at $-78°$ in dyglyme to give aldehydes. Many types of substituents can be tolerated, including some that are sensitive to reducing agents such as nitro, cyano, and carbethoxyl[43]. Coniferyl aldehyde, for example, has been prepared by the action of lithium tri-*t*-butoxyaluminohydride on acetylferuoyl chloride and hydrolysis of the acetylated aldehyde (equation 18). *p*-Coumaraldehyde has been made by a similar procedure[44,45].

Direct reduction of acids to aldehydes has been achieved in some instances with lithium aluminum hydride. Oxalic acid gives glyoxal in more than 50% yield. Salicylic and 2-hydroxy-3-naphthoic acids also give the corresponding aldehydes[46].

* Explosions have been reported in experiments involving lithium aluminum hydride (*Chem. Eng. News*, **31**, 2334 (1953); H. R. Watson, *Chem. Ind.* (*London*), 665 (1964)).



(18)

IV. FROM AMIDES

Amides react with metal hydrides under certain conditions to give aldehydes. As in the preparation of aldehydes and ketones from amides and Grignard reagents, hydrogen on the amide nitrogen atom destroys the reagent. For this reason primary and secondary amides are to be avoided.

A. McFadyen–Stevens Method

The McFadyen–Stevens reaction[47], previously reviewed by Mosettig[34], provides an indirect route for the reduction of an aromatic carboxylic acid to the corresponding aldehyde; the transformation takes place via the arylsulfonhydrazide, which decomposes when heated with solid sodium carbonate (equation 19).

$$Ar^1CONHNHSO_2Ar^2 \xrightarrow[\text{heat}]{Na_2CO_3} Ar^1CHO + N_2 + Ar^2SO_2H \qquad (19)$$

B. Sonn–Müller Method

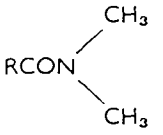
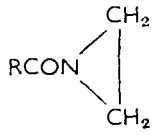
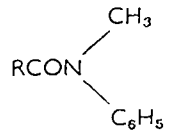
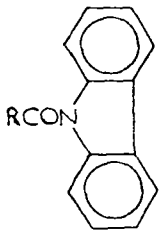
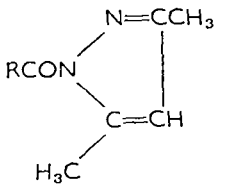
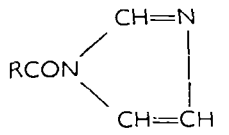
An acid anilide or toluide reacts with phosphorus pentachloride to give an imido chloride which can be reduced with stannous chloride to a Schiff base. Hydrolysis converts the base into an aldehyde. An example of this synthesis, known as the Sonn–Müller method[34], is the preparation of cinnamaldehyde from cinnamanilide (equation 20); the yield is 92%[48].

$$C_6H_5CH{=}CHCONHC_6H_5 \xrightarrow{PCl_5} C_6H_5CH{=}CHCCl{=}NC_6H_5 \xrightarrow{SnCl_2}$$
$$C_6H_5CH{=}CHCH{=}NC_6H_5 \xrightarrow{H_2O} C_6H_5CH{=}CHCHO \qquad (20)$$

C. Metal Hydrides Method

Hydrogenolysis of tertiary amides with lithium aluminum hydride furnishes a useful method of making aldehydes. In this and in many other ways the complex metal hydrides, notably lithium aluminum hydride, resemble Grignard reagents[49]. Table 1 lists the types of

TABLE 1.

Amides	Formula
N,*N*-Dimethylamides	
1-Acylaziridines	
N-Methylanilides	
N-Acylcarbazoles	
1-Acyl-3,5-dimethylpyrazoles	
Acylimidazolides	

amides that have proved to be most valuable. It is seen that the nitrogen atom of the amide group may hold alkyl or aryl groups or be a member of an aromatic heterocycle.

Lithium aluminum hydride in excess normally reduces tertiary amides to the corresponding tertiary amines. Success in stopping the reduction so as to get aldehydes has been achieved in two ways, one of which is to convert the reagent into alkoxy derivatives such as lithium diethoxyaluminohydride, made by treating it with ethanol or ethyl acetate (equation 21)[50]. The reagent may be prepared *in situ*

$$LiAlH_4 + 2\,C_2H_5OH \longrightarrow LiAlH_2(OC_2H_5)_2 + 2\,H_2 \qquad (21)$$

by bringing the reactants together in ether. An example is the conversion of *N*,*N*-dimethyl-*p*-chlorobenzamide into *p*-chlorobenzaldehyde (equation 22); the yield is 78%[50]. The method appears to be equally satisfactory in the aliphatic, alicyclic, and aromatic series.

$$p\text{-}ClC_6H_4CON(CH_3)_2 \xrightarrow{LiAlH_2(OC_2H_5)_2} p\text{-}ClC_6H_4CHO \qquad (22)$$

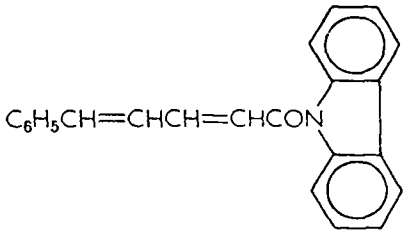
Later studies have shown that a mixture of lithium di- and triethoxyaluminohydrides can serve. By its use aldehydes of considerable variety have been made in yields of 60 to 90%[51].

The other and more common way of halting the action of lithium aluminum hydride is careful control of the amount used. Amides that give especially good results are 1-acylaziridines, which may be made *in situ*. Cyclopropanecarboxaldehyde can be prepared in 60% yield by this method (equation 23)[52].

(23)

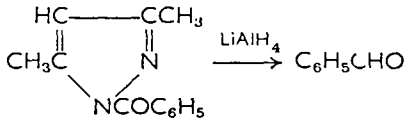
N-Benzoyl-*N*-methylanilines give aldehydes in good yields. The hydrogenolysis is effected in tetrahydrofuran with lithium aluminum hydride[46]. This method serves to produce dialdehydes also: *o*-phthalaldehyde and succindialdehyde are formed in 70 and 68% yields, respectively[53].

Acylcarbazoles, in which the amide nitrogen atom is joined to two aromatic rings, can likewise be converted into aldehydes. Outstanding is the synthesis of the unsaturated aldehydes, $C_6H_5(CH{=}CH)_nCHO$, from the corresponding *N*-acylcarbazoles[54]. Cinnamalacetylcarbazole, for example, gives the corresponding aldehyde in 72·9% yield (equation 24).



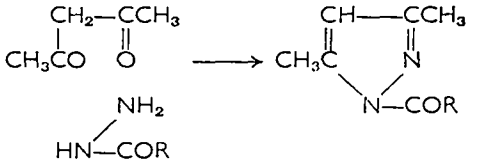
(24)

A similar route to aldehydes consists of hydrogenolysis of 1-acyl-3,5-dimethylpyrazoles with lithium aluminum hydride. Benzaldehyde, for example, has been made in this way (equation 25) in 96% yield[55]. This method has been applied with great success in the



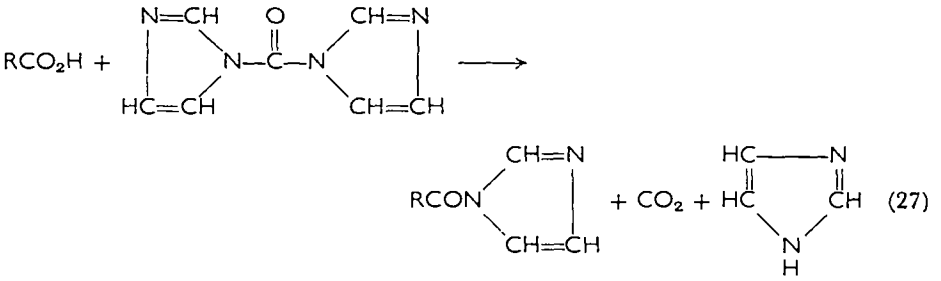
(25)

synthesis of arylacetaldehydes and dialdehydes[56]. The pyrazoles are readily made from the appropriate hydrazide and acetylacetone (equation 26).



(26)

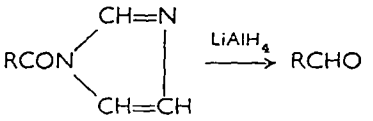
In the Staab method carboxylic acids are converted into aldehydes by way of the imidazolides, which are formed when the acids are allowed to react with *N*,*N*′-carbonyldiimidazole (equation 27)[57].



(27)

Reduction of the imidazolides with lithium aluminum hydride,

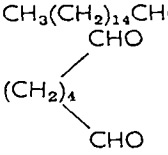
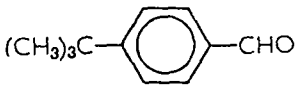
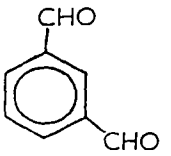
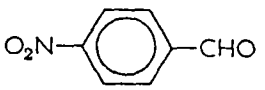
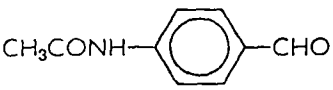
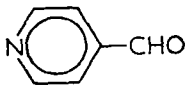
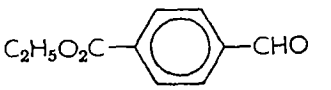
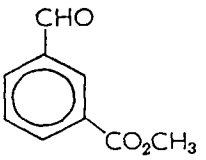
usually carried out in ether or tetrahydrofuran, gives aldehydes (equation 28) in moderate to good yields[58].



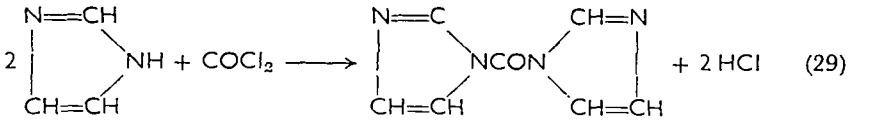
(28)

It is particularly advantageous that the reduction can be accomplished without isolation of the imidazolide. The acid and *N,N'*-carbonyldiimidazole, taken in equimolecular proportions, are allowed to react in ether or tetrahydrofuran, and lithium aluminum hydride is added immediately to the solution. The results given in Table 2 were obtained in this way.

TABLE 2. Aldehydes from imidazolides.

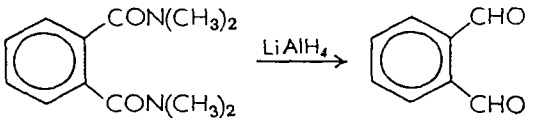
Aldehyde	Yield (%)	Aldehyde	Yield (%)
C_6H_5CHO	77·5	$CH_3(CH_2)_{14}CHO$	84
	79		65
	76		69·5
	87·5		53
	82		72
$C_6H_5CH{=}CHCHO$	69·5		51
$CH_3(CH_2)_2CHO$	60	$CH_3O_2C(CH_2)_4CHO$	71

N,N'-Carbonyldiimidazole, made from imidazole and phosgene (equation 29), is commercially available[59].



(29)

Many other tertiary amides have been tested. *N,N,N',N'*-tetramethyl-*o*-phthalamide gives the corresponding aldehyde in satisfactory yield (equation 30)[60]. The dipiperidide can also serve but gives the aldehyde in lower yields.



(30)

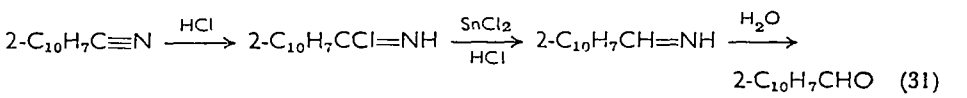
Benzaldehyde has been made from *N,N*-diethylbenzamide, *N*-benzoylpiperidine, *N*-benzoyl-1,2,3,4-tetrahydroquinoline, *N*-benzoylpyrrole, and *N*-benzoylindole[61].

V. FROM NITRILES

The first step in the conversion of nitriles into aldehydes is reduction to the corresponding imines, which are then hydrolyzed. Thus, at least in theory, this type of synthesis involves hydrolysis. However, since in practice the imines are not isolated it seems appropriate to discuss this method here.

A. Stephen Method

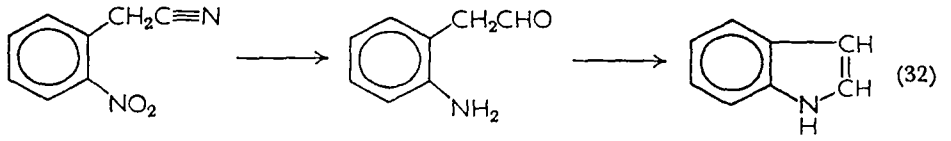
In the Stephen method[34] imido chlorides are reduced to aldimines by stannous chloride. Anhydrous stannous chloride is suspended in dry ether, and dry hydrogen chloride is passed in until the mixture forms two layers. The nitrile is added and hydrogen chloride is again passed in until the mixture is saturated. The double salt of the imine hydrochloride and stannic chloride is removed and hydrolyzed with boiling water. By this procedure 2-naphthonitrile, for example, gives 2-naphthaldehyde (equation 31) in 80% yield[62].



(31)

An interesting application of the method is the synthesis of indole

from *o*-nitrophenylacetonitrile (equation 32). Both the nitro and imido chloride groups are reduced[63].



(32)

B. Metal Hydrides Method

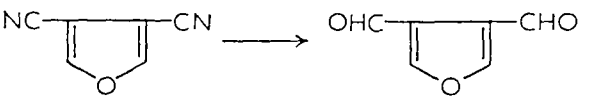
The use of lithium aluminum hydride in the preparation of aldehydes from nitriles, first reported by Friedman, was reviewed by Mosettig in 1955[34]. Since then other hydrides have been found to be more useful. Sodium triethoxyaluminohydride, formed from sodium hydride and aluminum ethoxide, is a good reducing agent for organic compounds that possess polar multiple bonds. Aromatic nitriles, for example, react to give aldehydes. Examples are shown in Table 3[64,65].

TABLE 3. Aldehydes from nitriles ($NaAl(OC_2H_5)_3H$ method).

Nitrile	Yield of aldehyde (%)
Benzonitrile	95
o-Tolunitrile	88
p-Chlorobenzonitrile	89
p-Methoxybenzonitrile	84
3-Cyanopyridine	81
1-Naphthonitrile	87
4,4′-Dicyanobiphenyl	70

The procedure is not satisfactory as a preparative method with aliphatic nitriles. Much better results have been obtained with lithium triethoxyaluminohydride. This reagent, prepared *in situ* from lithium aluminum hydride and ethanol or ethyl acetate, gives aliphatic aldehydes in yields of 70 to 80% and aromatic aldehydes in yields of 80 to 90%[66,67]. Examples are given in Table 4.

With this reagent 3,4-furandicarbonitrile gives 3,4-furandicarboxaldehyde (equation 33) in about 50% yield[68].

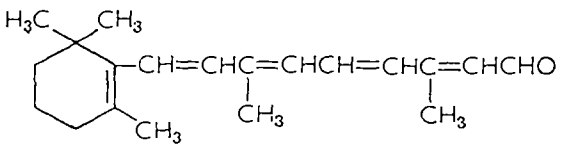


(33)

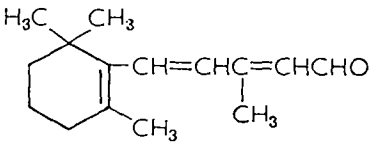
TABLE 4. Aldehydes from nitriles ($LiAl(OC_2H_5)_3H$ method).

Nitrile	Yield of aldehyde (%)
n-Butyronitrile	68
n-Capronitrile	69
Isobutyronitrile	81
Cyclopropanecarbonitrile	69
Cyclohexanecarbonitrile	76
Benzonitrile	96
o-Tolunitrile	87
1-Naphthonitrile	80
o-Chlorobenzonitrile	87
p-Chlorobenzonitrile	92
Cinnamonitrile	61

Sodium diisobutylaluminum hydride, readily available from sodium hydride and diisobutylaluminum hydride, also leads to the formation of aldehydes in high yields. This reagent has been used in the conversion of vitamin A nitrile into vitamin A aldehyde (**1**)[69].



(**1**)



(**2**)

In a similar manner the β-C_{15}-aldehyde (**2**) was made from the corresponding nitrile[70].

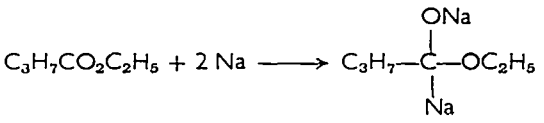
VI. FROM ESTERS

Of all the derivatives of acids, esters are probably the most readily available and easiest to handle. As a consequence much effort has been expended in trying to convert them into aldehydes and ketones.

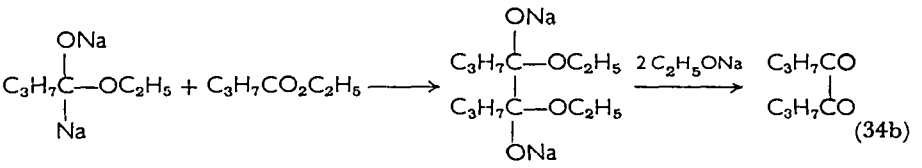
A. Acyloin Condensation

α-Hydroxy ketones or acyloins are formed by treating esters of aliphatic acids with sodium in aprotic solvents such as ether or toluene. The acyloin condensation, reviewed by McElvain in 1948[71], continues to be used especially as a route to large rings for which it is superior to all other methods[72].

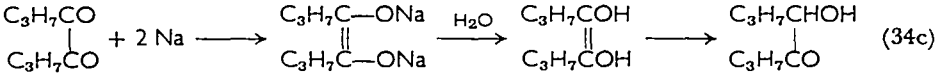
The condensation may proceed by way of a disodium derivative of the ester, which condenses with a second molecule of ester to give a diketone; the diketone is then reduced to the acyloin. For the synthesis of butyroin from ethyl n-butyrate[73] the steps (34a) to (34c)



(34a)



(34b)



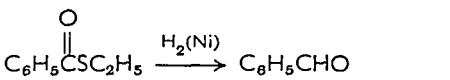
(34c)

would be involved. The yield is 70%. The method employs ether as solvent and is satisfactory for most simple esters. With higher esters, toluene or xylene as solvent gives much better results; these solvents have made possible the preparation of acyloins having from 12 to 36 carbon atoms. High dilution is not necessary and the yields are high.

The method is remarkably successful with the esters of long-chain dibasic acids; cyclic acyloins are formed in yields of 29 to 96%. Dimethyl sebacate, for example, gives sebacoin in 66% yield[74].

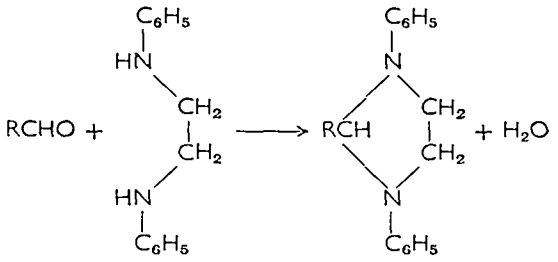
B. Desulfurization of Thiol Esters

Similar to the Rosenmund method is the hydrogenolysis of thiol esters over partially deactivated Raney nickel. The partial deactivation is accomplished by bringing the catalyst briefly in contact with boiling acetone. An example is the preparation of benzaldehyde from ethyl thiolbenzoate (equation 35)[75]. This method has been used successfully in the sugar[75] and steroid[76] fields.



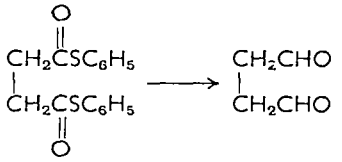
(35)

An improved procedure involves the use of 1,2-dianilinoethane, the aldehyde being isolated as the diphenyltetrahydroimidazole derivative (equation 36)[77].



(36)

Succinaldehyde has been made in 34% yield from diphenyl dithiolsuccinate (equation 37)[78].



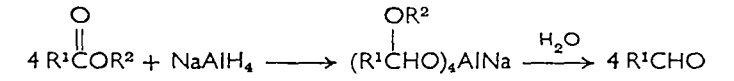
(37)

This method was reviewed by Mosettig in 1955[34] and by Pettit and van Tamelen in 1962[79].

C. Metal Hydrides Method

Lithium aluminum hydride generally reduces esters to alcohols. One exception is diethyl oxalate which gives glyoxal in more than 40% yield[60]. In tetrahydrofuran or pyridine (instead of ether) this reagent in a number of other cases gives aldehydes in fair yields.

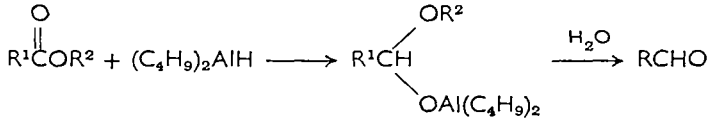
The reduction of esters to aldehydes is brought about more satisfactorily with sodium aluminum hydride; the steps involved are shown in equation (38)[80]. The reaction is carried out in tetra-



(38)

hydrofuran solution or in a tetrahydrofuran/pyridine mixture at low temperature (−65 to −45°). Reduction of esters of aromatic acids needs lower temperatures and longer times (5 to 7 h) and gives the aldehydes in yields somewhat lower than are obtained with aliphatic esters. Some results are shown in Table 5[80].

Diisobutylaluminum hydride (at about −70°) reduces aliphatic and aromatic esters to the corresponding aldehydes. The transformation proceeds as in (39)[81]. The reaction is carried out in



(39)

TABLE 5. Aldehydes from esters ($NaAlH_4$ method).

Ester	Yield of aldehyde (%)
Methyl n-butyrate	81
Methyl caproate	85
Ethyl nicotinate	81
Ethyl benzoate	48
Methyl *o*-chlorobenzoate	43
Dimethyl phthalate	52
Methyl cinnamate	46
Methyl hydrocinnamate	88

toluene, hexane and ether. Ethyl n-butyrate, for example, gives n-butyraldehyde in 88% yield.

Lithium tri-*t*-butoxyaluminohydride has been used successfully to reduce not only acid chlorides (see section III.C) but also phenyl esters to aldehydes[67].

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CHAPTER 5

Formation of ketones and aldehydes by acylation, formylation and some related processes

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I. INTRODUCTION

A. Preliminary Generalizations

In the most general terms there are three principal routes to aldehydes and ketones:

1. An organic compound may have one (or more) of its carbon atoms oxidized to a carbonyl group (Chapters 2, 3).

2. A compound which already contains a carbonyl group, but which is not an aldehyde or a ketone, may be modified until it is (Chapter 4).

3. An organic compound may have one (or more) carbonyl (or potential carbonyl) groups introduced into it.

This chapter, and Chapter 6, are concerned with route 3. This route always involves the formation of a new carbon–carbon bond. The reactions which introduce carbonyl groups directly are known as acylation and formylation. Acylation produces ketones by the introduction of a group RCO and formylation aldehydes by introducing a group CHO*. These two reactions are governed by similar principles and will be discussed together. In view of the existence of route 1 almost any reaction which extends the carbon skeleton of a compound may be said to have introduced a potential carbonyl group. For instance, the introduction of a benzyl group into benzene could be a step along a pathway to benzophenone. However, there exists a previously somewhat ill-defined set of reactions (mostly bearing familiar names—e.g. the Gattermann aldehyde synthesis) which, though not leading to the direct introduction of a carbonyl group, lead to intermediate compounds which are rather easily converted into aldehydes or ketones (often by oxidative hydrolysis). We shall deal with these reactions as well as with acylation and formylation. They involve the initial introduction either of a suitably

* The groups CHO and RCO may be called formyl and acyl, respectively. Other names are used less often.

substituted alkyl group (e.g. $-(R^1)C(Cl)OR^2$) or of a group like $-C(R)=NH$. Because of the particular nature of the entering group, some of these processes can only provide aldehydes but others may be used for both aldehyde and ketone synthesis.

B. Outline Reaction Mechanism

The breaking of chemical bonds involves either heterolysis or homolysis and the importance and exploitation of homolytic processes has, for some years now, been receiving increased attention. Nevertheless, the vast majority of those reactions coming under route 3 above, which have to date proved preparatively useful, involve heterolytic bond fissions only*. In this chapter an attempt is made to show how the various reactions may almost all be considered to be variations on a common heterolytic mechanism.

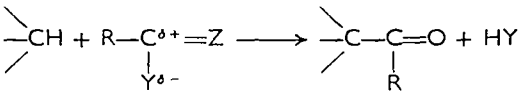
This mechanism involves an electrophilic attack by the carbonyl, or potential carbonyl, carbon atom of the reagent which provides this atom, on a carbon atom of the substrate; the substrate, therefore, always acts as a nucleophile. Any group split out of the substrate on forming the new carbon–carbon bond will need to possess some stability as a positive ion. This fact effectively limits the type of bond broken in substitution processes to carbon–hydrogen or carbon–metal. In cases of addition of the reagent a carbon–*carbon* multiple bond is attacked†. In short the substrate may always be considered as a hydrocarbon or a metal derivative of one, although, of course, it may contain non-hydrocarbon substituents which affect the reactivity of its hydrocarbon centres.

The reagent which introduces the carbonyl, or potential carbonyl, group may be given the very generalized form $R^1-\underset{\displaystyle Y}{\underset{|}{C}}=Z$. Here R^1 is aryl, alkyl or hydrogen, depending upon whether acylation or formylation is involved; C=Z is C=O, C=NH, $C(OR^2)_2$, CCl_2 or some similar unit readily converted into C=O; and Y is NH_2, OR^2, $OCOR^2$ or a group derived from the anion of an inorganic acid

* Of those to be discussed, probably only the Reimer–Tiemann reaction involves free radicals and even here these radicals are produced by successive heterolyses.

† Electrophilic attack by carbon on any other type of multiple bond (e.g. $>C=O$ or $-C\equiv N$) would not result in a new carbon–carbon bond (see, however, section II.F.4 for $>P=C<$ compounds. Phosphorus is sufficiently lacking in nucleophilicity for preferential attack to be at carbon).

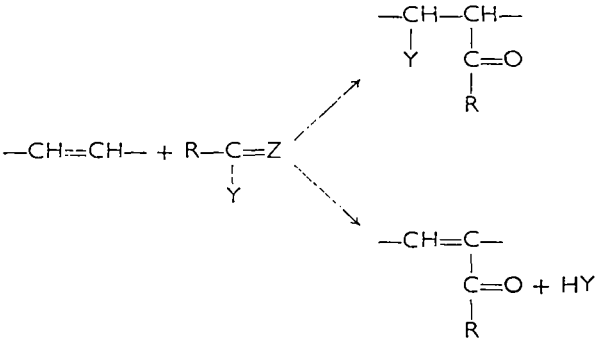
(e.g. Cl, ClO_4, BF_4, etc.). R^2 may be aryl, alkyl or hydrogen. The formation of the new carbonyl compound involves the severing of the C—Y bond of the reagent, and, when necessary, the conversion of C=Z into C=O (equation 1). As will be evident, these changes may be effected in a variety of ways. The facts summarized by (1) and the heterolytic nature of the reactions follow from considerations of the structure of the reactants and products and the nature of the effective catalysts. What does not follow from such information is the number and nature of the intermediate steps embraced by the stoichiometric equation (1), nor their relative importance in deter-



(1)

mining the overall speed of reaction. Sometimes other compounds are isolated (e.g. adducts between reagent and catalyst) and these lead to plausible postulations of particular intermediate steps, but kinetic analysis is really needed if guesswork is to be avoided. The study of changes in product yield with change in reactant structure under given conditions is a poor and unreliable substitute for proper kinetic analysis. Unfortunately, it is the best which is usually available in this particular field. Much mechanistic detail, therefore, still remains to be clarified.

If the substrate is unsaturated, two possibilities are open: addition (2) or substitution (3). The balance between these two processes will



(2)

(3)

be discussed when the individual reactions are dealt with. Not all the various apparently possible combinations of R, Y and Z have been tested—largely because of the instability or inaccessibility of some of these (e.g. $(HCO)_2O$). When the scattered data are assembled, however, a surprising number of permutations are found

to have been tried. Nevertheless, no systematic attack has been mounted, progress having been made by chance and through the testing of a series of inspired, though limited, analogies.

The formulation of the reagent as R—C=Z excludes the special
|
Y

category, containing the ketenes and carbon monoxide, for which either Y, or both R and Y, are absent. However, uncatalysed acylation at carbon by these reagents appears to be very rare and their successful catalysed reactions probably normally involve attack by species which may be considered to be derived from the general type R—C=Z. Carbon monoxide can behave differently and such cases
|
Y

will be emphasized.

C. Catalysis and Substituent Effects

Quite generally, because the reaction involves a nucleophilic role for a carbon atom of a hydrocarbon substrate and because such atoms are normally poor nucleophiles, significant reaction is usually only obtained in the presence of powerful catalysts. Catalysts function by increasing either the nucleophilicity of the substrate (basic catalysis) or the electrophilic character of the reagent (acidic catalysis). Because of the great importance of catalysis to the reactions considered, this aspect of them is often that which engages most attention. Moreover it is the necessity for powerful catalysts and the undesirable side-reactions caused by them which together set limits to the successful outcome of the various substrate–reagent combinations.

The general effects produced by substituents in the reactants follows from the outline mechanism given. Those substituents which under the given catalytic conditions render the substrate more nucleophilic and the attacking reagent more electrophilic will favour reaction—other complicating side-reactions being equal. Conversely, substituents which have the opposite effects on the reactants will discourage reaction. So far as the substrate is concerned, three broad groups are available: saturated hydrocarbons, unsaturated aliphatic hydrocarbons and aromatic hydrocarbons*. The carbon atoms of

* This ignores heterocyclic compounds. It is not possible to include a separate discussion of these within the limited confines of this chapter. However, they are often mentioned, and in any case, as far as their carbon atoms are concerned, the different classes of heterocycle often display behaviour in principle analogous to

saturated hydrocarbons are generally so lacking in nucleophilic character that reaction will only be possible if a suitable metal derivative or carbanion is first formed; this is in effect basic catalysis. Saturated hydrocarbons do yield desired products under acidic conditions but, as will be seen, this is due to preliminary reactions which first convert them into unsaturated compounds. Strictly speaking only unsaturated hydrocarbons undergo attack by R—C=Z under
|
Y
acidic conditions.

The following sections deal first with direct acylation and subsequently with indirect processes. The more important variations on R—C=Z which have been studied are covered and their applic-
|
Y
ability as reagents for the different groups of hydrocarbons outlined. The great volume of the available experimental data renders the treatment necessarily selective. It is hoped that it is not distorted. The lengths of the various sections roughly accord with the body of data they summarize. Throughout, the emphasis is on principles rather than on facts. As noted above, we hope to give some unity to the field by discussing the different reactions as variations on scheme (1). The close logical interrelationship and the frequent experimental similarity between the ketone and aldehyde syntheses is also stressed. Most of the reactions dealt with have been the subjects of recent lengthy reviews. These are used in the text as leading references.

II. DIRECT ACYLATION AND FORMYLATION OF HYDROCARBONS

In this context the reagent always has the form RCOY and is known as the acylating (or formylating) agent. By *direct* acylation we mean those processes in which the active reagent introduces the carbonyl group into the substrate in a single step, without this group losing its essential double-bond character. Typical of acylation and formylation

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that of one or other of the various types of homocycle. Frequently the heterocyclic atom is the most nucleophilic present and undergoes preferential acylation. When attack at carbon occurs it does so, in the great majority of cases, at the 2-position. Many heterocyclic compounds have the disadvantage of being rather liable to destruction by acid catalysts.

at carbon are the processes (4) and (5). If a solvent is used, a

$$(CH_3CO)_2O + RCH{=}CH_2 \xrightarrow{ZnCl_2} RCH{=}CHCOCH_3 + CH_3CO_2H \qquad (4)$$

$$HCOF + C_6H_6 \xrightarrow{BF_3} HCOC_6H_5 + HF \qquad (5)$$

compound more inert to acylation than the substrate must, of course, be chosen. The solvent must also permit the catalyst to function. These conditions normally mean that hydroxylic substances must be avoided.

A. Factors Affecting the Reactivity of RCOY

1. The leaving group Y

The following is a rough order of reactivity:

$$R^1CONR^2_2 < R^1CO_2R^2 < R^1COOCOR^2 < RCOHal < RCO_2SO_3H < RCOOClO_3 \sim RCO^+BF_4^-$$

Thus uncatalysed acylation by amides or esters is almost invariably so slow as to be impracticable, whereas the predominantly ionic acyl perchlorates and tetrafluoroborates are powerful reagents. The latter species are of the type often formed from milder reagents under acid catalysis (see below). When R (or R^1) = H, so far as is known, the same order of reactivity obtains. However, in this case not all the reagents are readily accessible. A reasonable generalization[1] is that the power of an acylating agent RCOY increases with the strength of the acid HY. The origin of the parallelism is clear: the separation of the anion Y^- is involved in both phenomena. In RCOY the carbonyl group is always polarized, some net positive charge being located on the carbon atom. Groups Y which attract electrons and possess some stability as Y^- will enhance this positive charge, promote cleavage into RCO^+ and Y^-, and thus aid reaction. Groups which repel electrons and provide anions of little stability will have the opposite effect. Examination of the rough reactivity series shows it to be consistent with the usual qualitative assignments of polar effects to groups[2].

The same generalization applies for subtler variations in the leaving group, achieved within a given type of reagent. Thus phenyl or cyanomethyl esters are more reactive than methyl derivatives and acyl bromides more reactive than the corresponding chlorides*. These minor differences may, however, be overridden under the

* N.B. The acid strengths of the hydrogen halides are in the order HI > HBr > HCl > HF.

influence of acid catalysts when other factors enter, in particular the ability of the leaving group to coordinate with the catalyst.

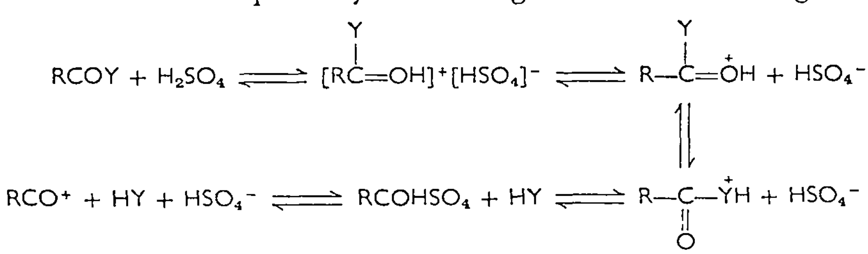
2. The group R (or R^1)

In formylation no variation in R is, of course, possible. For acylation, the effects on reactivity of changes in R are not as straightforward as for changes in Y. Substituents which, by provision of electrons, favour the departure of Y^- and stabilize the acylium ion have the effect of reducing the charge on the carbonyl carbon atom in both the acylium ion and the polarized reagent. Electron-withdrawing substituents increase this charge but hinder ionization. A balance of factors is therefore involved and the effect of changes in R will be expected to vary with the reaction concerned. This point is expanded below, where the consequences of the steric requirements are also discussed. R is represented in the literature by an enormous range of structures[3]. Ions like Me_3CCO^+ tend to lose carbon monoxide and so can lead to alkylation rather than to acylation[4].

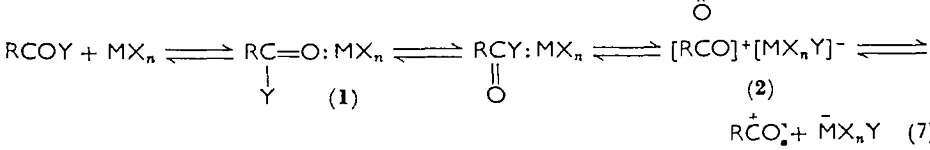
B. Acidic Catalysis

Acids may be divided into two sorts: Brønsted acids and Lewis acids. Among the latter, those of the metal halide type are the most important in the present contexts and are represented generally as MX_n. Acidic catalysis of the acylation of hydrocarbons normally involves anhydrous conditions.

As noted in section I.C, the essential function of the acid catalyst is to increase the electrophilic character of the carbonyl carbon atom of the reagent. In some cases the catalyst also has other subsidiary functions which affect the course of the reaction. These will be noted as the occasion arises. Among the ways in which the catalyst can increase the electrophilicity of the reagent are the following[5]:



(6)



(7)

In both equations (6) and (7) the relative positions of the different equilibria will depend upon RCOY, upon the acid, and upon the dielectric constant and solvating power of the medium. *Some* quantity of each species is, no doubt, always present and some species will clearly be better acylating agents than others. Systems which favour acylium-ion formation are generally the most useful. In solvents of low dielectric constant, few free ions will exist, and ion-paired and other particularly polar species (e.g. **1**) will often be self-associated in solution, especially at the high concentrations usually needed in preparative work[6]. In coordinating solvents yet other complexes involving the solvent will form. These points should be borne in mind throughout, for it is often convenient, and indeed desirable, to ignore such complexities when outlining in equations the essentials of particular reaction mechanisms.

Typical examples[5] of (6) are the behaviour of amides or esters in contact with sulphuric acid (equations 8 and 9). A familiar example of (7) is the behaviour of acyl halides with aluminium chloride (equation 10). Because of the complexity of the equilibria it is not

$$RCONH_2 + H_2SO_4 \rightleftharpoons RC(=\overset{+}{O}H)NH_2 + HSO_4^- \rightleftharpoons RC(=\overset{+}{N}H_3)OH + HSO_4^- \rightleftharpoons RCO^+ + NH_3 + HSO_4^- \quad (8)$$

$$R^1CO_2R^2 + H_2SO_4 \rightleftharpoons R^1C(=\overset{+}{O}H)OR^2 + HSO_4^- \rightleftharpoons R^1C(=O\overset{+}{H})OR^2 + HSO_4^- \rightleftharpoons R^1CO^+ + R^2OH + HSO_4^- \quad (9)$$

$$RCOCl + AlCl_3 \rightleftharpoons RC(=O{:}AlCl_3)Cl \rightleftharpoons [RCO^+][AlCl_4^-] \rightleftharpoons RCO^+ + AlCl_4^- \quad (10)$$

certain that even when other factors are equal the strongest acids will be the best catalysts. However, this is probably true in general and various qualitative comparisons[7] of catalytic activity, and hence of relative acidity, under different anhydrous conditions have been made—mainly with Lewis acids—about whose strengths few independent data exist[8]. The various orders of activity found as yet show little agreement in detail, though the aluminium halides, ferric halides and antimony pentachloride normally come near the head of the list, and zinc, mercuric and bismuth halides near its foot, with stannic chloride somewhere in the middle. In some cases[9] reagent and catalyst interact in a manner which, although providing a more

powerful acylating agent, leads to the destruction of the acid (e.g. equation (11)). Reactions which entail such phenomena are not strictly catalytic.

$$(RCO)_2O + AlCl_3 \longrightarrow RCOCl + RCOOAlCl_2 \qquad (11)$$

C. Basic Catalysis

The base serves to increase the nucleophilicity of the hydrocarbon. The type of basic catalyst appropriate depends upon the hydrocarbon; most are so little acidic that prior formation of a metal derivative (perhaps from the alkyl or aryl halide) is the extreme form of catalysis necessary. Only a few special reactions of this type will be dealt with in detail here. Others are discussed in a later chapter.

Aliphatic hydrocarbons with electron-attracting substituents (e.g. CN or CO) are often susceptible to attack by alkoxide, amide and similar ions (equation 12). The Claisen and related condensations are typical examples which employ this effect[10]. We shall deal with these reactions.

$$RCH_2CN + NH_2^- \rightleftharpoons R\bar{C}HCN + NH_3 \qquad (12)$$

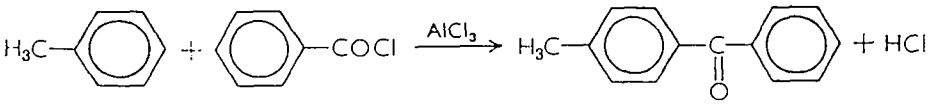
D. Substituent Effects on Substrate Reactivity

Under acidic catalysis the substrate is not directly involved with the catalyst, and therefore substituent effects are simple: electron-donating substituents will normally favour reaction. In basic catalysis, however, electron release will hinder carbanion formation, although it will activate this ion once formed. A balance of factors is therefore involved, similar to that obtaining for the structure of the acylating agent under acidic catalysis (section II.A.2 above).

E. Aromatic Hydrocarbons as Substrates

1. Acylation

a. Introduction and scope. Equation (13) typifies aromatic acylation. Substitution only is the rule in these reactions, which are, of course,



(13)

examples of electrophilic aromatic substitution. Basic catalysis takes the form of reaction between acylating agent and a metal derivative

of the hydrocarbon. These reactions are dealt with in another chapter and will be omitted here. To induce significant reaction in aromatic hydrocarbons not artificially activated in this way, an acylating agent at least as reactive as an acyl halide will usually be required and more normally one with significant acylium ion character. This means that if RCOY is not a compound like an acyl perchlorate or tetrafluoroborate*, then acidic catalysts will be required to transform it into such a species in the reaction mixture. Aromatics containing electron-withdrawing substituents are attacked with great difficulty[13] even by the most powerful reagents and this fact underlies the frequent use of nitrobenzene and of halobenzenes as solvents for the acylation of other aromatic compounds. It also means that the introduction of the first acyl group discourages the entry of a second, and disubstitution in the same ring is therefore rare[13]. Electron-repelling substituents which lead, of course[2], to predominant *ortho–para* direction, facilitate acylation (Table 1). Polysubstitution of this sort provides

TABLE 1. Relative rates of benzoylation of substituted benzene[a].

Substrate[c]	Relative rate[b]
Chlorobenzene	0·011
Benzene	1
Toluene	154
m-Xylene	3910
Mesitylene	125,000
Pentamethylbenzene	139,000

[a] H. C. Brown, B. A. Bolto and F. R. Jensen, *J. Org. Chem.*, **23**, 414 (1958); H. C. Brown and F. R. Jensen, *J. Am. Chem. Soc.*, **80**, 2296 (1958).
[b] Refers to total rate of substitution, i.e. at all positions.
[c] See also G. A. Olah and coworkers, *J. Am. Chem. Soc.*, **86**, 2198 (1964) for some more recent relative reactivities.

considerable enhancement of reactivity but reactive acylating agents are still apparently required[13]. Unfortunately, the available data are not sufficient to permit a decision on how far down the reactivity series (section II.A.1 above) it would be practicable to go with, for example, a compound such as 1,3,5-trimethoxybenzene. Many of the

* Such compounds are sometimes[11,12] formed metathetically prior to reaction, e.g. $RCOCl + AgClO_4 \rightarrow RCO^+ClO_4^- + AgCl$.

apparently uncatalysed[14,15a] reactions involving unsymmetrical anhydrides are probably catalysed by the free acid usually also present.

Reaction often fails with amines and phenols owing either to preferential *N*- or *O*-acylation or to interaction between substrate and catalyst, which removes the substrate from the reaction mixture or otherwise deactivates it[15b]. With phenols, however, acid–base interaction at the hydroxyl group sometimes protects this group and permits satisfactory nuclear acylation (cf. section III.B.3). Prior conversion of the phenol into the corresponding borate (**3**) is a recent, and successful, variation on this effect[16].

$(RC_6H_4O)_3B$
(**3**)

The acid-catalysed acylation of aromatic hydrocarbons, especially when the catalyst is a metal halide like aluminium chloride, is generally termed the Friedel–Crafts ketone synthesis after its discoverers[17]. It is the oldest and still one of the most widely used of the preparative methods discussed here. Friedel and Crafts themselves used mainly aluminium chloride but it is normally found convenient to include other similar Lewis acids and even strong Brønsted acids like hydrogen fluoride and sulphuric acid, which provide analogous effects, under the Friedel–Crafts umbrella[7]. The accumulated literature is of formidable proportions[13].

b. Reaction conditions. Reaction at room temperature is common. On some occasions the hydrocarbon acts as its own solvent, on others the catalyst (e.g. HF) serves, and on others still an inert solvent is required. Hydroxylic materials (especially water) must normally be excluded from the reaction mixtures for these both successfully compete for the acylating agent and may also deactivate the catalyst. Nitrobenzene, carbon disulphide, methylene and ethylene dichlorides, carbon tetrachloride and ether are, therefore, common solvents. It is best if the catalyst is soluble in the medium. Some Lewis acids (e.g. $AlCl_3$) are poorly soluble in most solvents. Nitrobenzene and ethers, which readily form coordination complexes with metal halides, are often used in such cases. Many recorded preparative reactions have been of an heterogeneous nature. Sometimes the catalyst will form a complex with one or more reactants which separates as a second phase, often highly coloured and of a very polar nature. On other occasions much catalyst is left undissolved and provides a solid surface. Under these heterogeneous conditions

it is by no means certain that the detailed reaction mechanism bears much resemblance to the mechanism of the same reaction were it to occur in a single homogeneous phase. This point is important to remember since most kinetic studies—the studies most valuable for the discovery of mechanistic detail—usually refer to simple homogeneous conditions. Some solvents (e.g. ethylene dichloride) fail to dissolve the catalyst but dissolve its complex with the acyl component. This is often convenient, for one of the best preparative procedures is to form a solution of this complex, to remove any excess of catalyst and then to add the substrate[18].

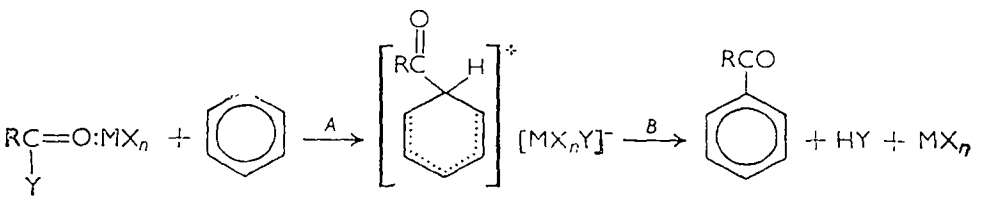
Apart from the varying degrees of heterogeneity attendant upon the use of different solvents, there are a number of other factors which complicate the mechanistic and even the preparative aspects of the Lewis acid catalysed syntheses[19]. Firstly, the product ketone frequently forms a complex with the metal halide and so removes some of this component from its effective sphere of action. This fact usually necessitates the use of roughly stoichiometric amounts of catalyst rather than 'catalytic' amounts. With weakly acidic catalysts (e.g. $ZnCl_2$) or at higher temperatures these complexes are not so prominent and smaller quantities of catalyst are adequate. Secondly, the actual value chosen for the molecular ratio of the catalyst to the acyl component—whether it be 0·5, 1·0 or 1·5, etc.—sometimes appears to affect the *position* of substitution. This is especially so for polycyclic hydrocarbons. Thirdly, some of the reactions are not strictly catalytic in that the catalyst is not regenerated, even in principle (section II.B above). Fourthly, the great reactivity of the most effective catalysts often leads to undesirable side-reactions and tar formation. These side-reactions include the isomerization of alkylated aromatics and the cleavage of alkoxide substituents to give phenolic products. It is, therefore, often advantageous to use a catalyst of only moderate activity. Finally, unless moisture is rigorously excluded, an unknown fraction of the catalyst will become hydrated or hydrolysed. In both cases Brønsted acids will result (e.g. H_2OBF_3 from BF_3, or HCl from $AlCl_3$). It is hardly surprising that irreproducibility has been a characteristic of the field.

c. Mechanism. Electrophilic aromatic substitution is one of the most thoroughly studied topics of organic chemistry and most aspects of some such substitutions (e.g. nitration) are understood in considerable detail[2,20]. For any given substitution, the features which normally receive most attention are (*a*) the nature of the active

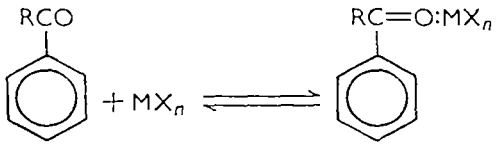
substituting agent (e.g. NO_2^+ in nitration), (*b*) the nature of the preliminary reactions which produce it, (*c*) the question of whether or not one of these preliminary reactions, or that of the substituting agent with the aromatic species, is the slow step of the whole sequence, and (*d*), if the latter, whether or not the expulsion of the proton is a significant feature of it.

The starting materials in Friedel–Crafts acylation are so diverse that a single type of solution to these questions is clearly very unlikely, though this is only slowly becoming realized[21,22]. Kinetic analyses are, of course, the best hope for answering such questions[23]. Several such studies have been made, and of the reactions discussed in this chapter direct aromatic acylation is by far the best documented from this viewpoint, the other reactions being virtually unexplored kinetically. The most thoroughly studied cases so far involve acyl (usually benzoyl) chlorides as reagents and an aluminium halide as catalyst[24]. The results show that a single molecule of the aromatic substrate is involved in the rate-determining step. From kinetic work with other systems[22,25] this appears a general result for Friedel–Crafts acylations. It implies that the substitution proper rather than the formation of the active acylating agent is the slow step in these processes. Unfortunately, the remainder of the kinetic data are compatible with either the oxonium ($RC(Cl)=O:AlCl_3$) or the acylium ($RCO^+AlCl_4^-$) type of species (section II.B above) as the active reagent. This particular ambiguity of the kinetic data often intrudes and is the major obstacle to the further elucidation of acylation mechanisms[25]. The kinetic studies[22a,24a] have, however, shown that attacking reagents with compositions like $(RCOCl)_2SnCl_4$ and $RCO^+Al_2Br_7^-$ may occur, as well as the various 1 : 1 adducts. If the reaction is represented simply and generally as in equations (14) to

$$MX_n + RCOY \rightleftharpoons RC(Y)=O:MX_n \quad \text{(or } RCO^+MX_nY^- \text{ etc.)} \quad \text{Fast} \qquad (14)$$



Slow (15)



Fast (16)

(16)*, then available data for substituent effects on the observed rates[22,24b] and studies with excess of acylating agent indicate that the reactions may be divided into two (extreme) types. With powerful catalysts like aluminium chloride and especially in the presence of non-coordinating solvents, the complex between catalyst and acyl component is essentially completely formed (i.e. the equilibrium (14) lies far to the right). Then step (15) controls substituent effects, and it is found that increasing electron withdrawal by R favours substitution (Table 2a). This implies that bond-forming processes by

TABLE 2. Effects of substituents in the acylating agent.

(a) In the aluminium chloride catalysed benzoylations of toluene with *p*-RC_6H_4COCl in chlorobenzene[a].

R	Relative rate[b]
$(CH_3)_3C$	0·18
CH_3	0·24
H	1·0
Cl	1·8
Br	1·9

(b) In the stannic chloride catalysed acetylations of β-naphthol with RCH_2COCl in carbon tetrachloride[c].

R	Relative rate[d]
C_2H_5	4·0
CH_3	1·6
H	1·0
Cl	< 0·03

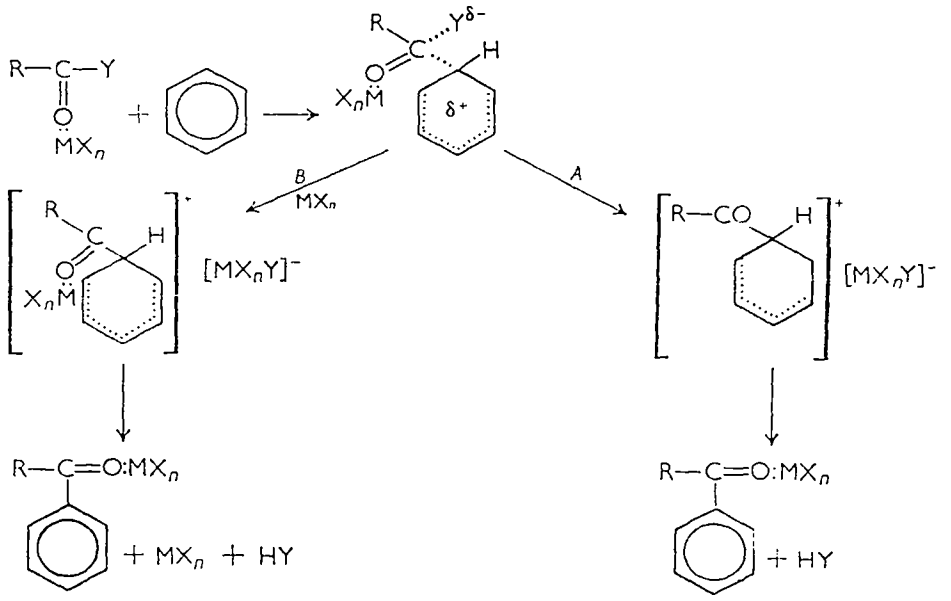
[a] P. J. Slootmackers, P. Roosen and J. Verhulst, *Bull. Soc. Chim. Belges*, 71, 446 (1962).
[b] Refers to total rate of substitution.
[c] D. P. N. Satchell, *J. Chem. Soc.*, 5404 (1961).
[d] Refers to acylation at oxygen and not at carbon. It is very probable but not certain that the order of efficiency of the different reagents will be the same for the more weakly nucleophilic carbon as for oxygen. This point requires checking.

* It is assumed, as is usual[20] in other aromatic substitutions, that during the slow step (15) the reactants pass through a configuration somewhat akin to a σ complex.

the acylating agent are here more important than the recession of Y^- (which will be made more difficult by electron withdrawal by R). When less powerful catalysts such as stannic chloride are involved, equilibrium (14) is probably *not* far to the right, and both steps (14) and (15) govern the overall substituent effect. In such cases it is found—at least when the substrate is oxygen rather than carbon (Table 2b)—that increasing electron release in R favours reaction, and electron withdrawal hinders it. This probably means that the dominant effect of R is on the position of the equilibrium (14) rather than on the rate of process (15), although a rate influencing departure of Y^- in (15) would lead to effects in the same direction. A kinetically significant departure of Y^- could, of course, only intrude if the reagent is the oxonium species. Work on the hydrogen isotope effect under various conditions[26] shows that phase *B* of step (15) can sometimes affect the rate.

We give below a résumé of the mechanistic features currently provoking particular interest.

1. While it is clear that an acylating agent carrying considerable charge on its carbonyl carbon atom is normally required, it is still debated whether the species (section II.B above) $RC(=\overset{+}{O}H)Y$, $RC(=\overset{+}{Y}H)O$, $RC(=O:MX_n)Y$, $RC(-Y:MX_n)O$, $[RCO]^+[MX_nY]^-$ and RCO^+ can all be active on occasions, whether the activity of some species usually predominates or whether, in fact, only RCO^+ (or $[RCO]^+[MX_nY]^-$) is ever involved. In recent reviews Gore[13] and Jensen[25] reach very different conclusions. Species such as $R{-}C(=\overset{+}{O}H)Y$ and $RC(=O:MX_n)Y$ are, in fact, not attractive because the facilitation of the removal of the leaving group Y requires either a shift in the position of the catalyst (equation 17, path *A*) or the involvement of a second molecule of this substance (equation 17, path *B*). No such problem arises when species like $[RC(=O)YH]^+$ are considered but, as



(17)

noted above, the involvement of two molecules of catalyst has sometimes been observed and may be indicative of the incursion of oxonium structures in these cases.

The essential problem in deciding between oxonium and acylium participation generally is to arrive at a reliable estimate of the inherent relative electrophilicities of these two species in particular cases. If it could be demonstrated that they were normally of roughly comparable reactivity, then, since spectroscopic data[27] show that one or other of the forms often greatly predominates in a reaction mixture, this form could be definitely identified as the species primarily responsible for reaction under these conditions. Such a demonstration would lead to the acceptance of acylation by both types of complex: sometimes one, sometimes the other, sometimes both together. Only if acylium-ion complexes are shown to be far more electrophilic than the corresponding oxonium complexes need the reservations about small undetectable amounts of $[RCO]^+[MX_nY]^-$ being responsible, in spite of the molecular predominance of $RC(=O{:}MX_n)Y$ (or vice versa) be retained in our arguments.

The fact that the *para*-substituted product is usually formed in

great excess over the *ortho* derivative is sometimes used as an argument in favour of the oxonium complex as the normally operative species, this species being supposedly bulkier than the acylium ion. These arguments and similar ones[13] based on the observed variations of the ratio of α- to β-substituted products in the naphthalene series are, however, groundless for they ignore the fact that the acylium ions must commonly participate in an ion-paired form which may, with its attendent solvation shell, be quite as bulky as the solvated oxonium species.

2. The complexity of the problem of comparing catalytic efficiencies is becoming more clearly realized[28]. The relative activities of different catalytic systems, even within a given context of solvent and reaction, are still very inadequately known. Few generalizations appear possible (section II.B above). Certain catalysts seem especially good for some classes of reaction. Thus Brønsted acids have found greatest use in intramolecular acylation. In meaningful quantitative comparisons of catalytic activity it is, of course, necessary for the kinetic form and mechanism of the reaction to be the same for all the catalysts compared. For Lewis acids this is a severe restriction and comparisons have usually, therefore, to be limited to sequences of MX_n in which n is the same. Progress in this important aspect of Friedel–Crafts systems awaits more thorough quantitative studies of Lewis acid–base interactions[8].

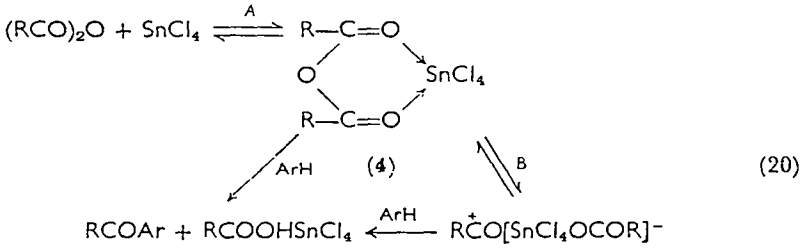
3. While in the past acyl halides have been the commonest reagents in both preparative and kinetic studies, other sources of the acyl group have currently begun to receive attention[11,22b] It is often assumed that carboxylic anhydrides, esters and acids are effective because they first undergo reaction with the catalyst (assumed to be a metal halide) to give the acyl halide as in equations (18) and (19).

$$(RCO)_2O + 3\,AlCl_3 \longrightarrow 2\,RCOClAlCl_3 + AlOCl \qquad (18)$$

$$RCO_2H + 2\,AlCl_3 \longrightarrow RCOClAlCl_3 + AlOCl + HCl \qquad (19)$$

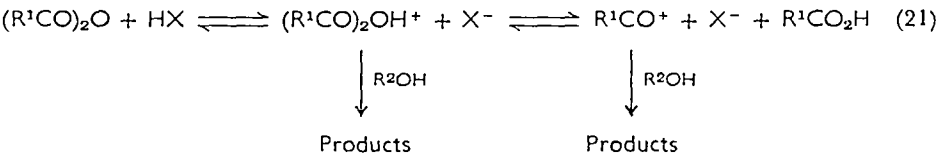
With powerful and easily solvolysed Lewis acids (e.g. $AlCl_3$, $TiCl_4$) these processes are probably important[9], though neither the detailed reaction scheme nor the kinetic form has been rigidly established in any case so far. With weaker Lewis acids (e.g. $ZnCl_2$, $SnCl_4$) the evidence[21,22b,29] points to the absence of such processes and to the direct participation of complexes between (say) the anhydride and metal halide (equation 20). It is quite incorrect to discuss Friedel–Crafts acylation as if it always involved acyl halide at some stage,

though this is occasionally done. Equilibria like *A* and *B* in (20) tend to lie to the left, so that in the absence of steric effects electron release by R favours reaction (see above).



(20)

Carboxylic acids and metal halides very often form complex Brønsted dual acids (e.g. $H_2SnCl_4(OCOR)_2$) of great strength and it is doubtless these acids which are responsible for the catalysis in such systems. Catalysis of aromatic acylation by Brønsted acids generally is presumably much along the lines of their catalysis of acylation in hydroxylic media[1] (e.g. equation 21). This point is



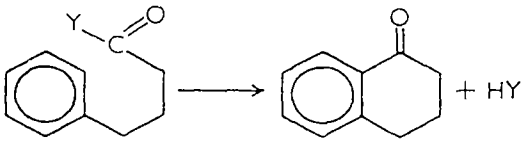
(21)

particularly relevant to the increasing use of mixed anhydrides based on trifluoroacetic acid[14]. In such systems any free trifluoroacetic acid will be expected to play an important role. Since most preparative Friedel–Crafts syntheses do not exclude water rigorously, there is certain to be some Brønsted acid available (e.g. H_2OBF_3, H_2OSnCl_4, etc.) from the start of such acylations. As reaction proceeds more becomes available owing to the elimination of HY (equation 1). The reactions of acyl halides are little susceptible to catalysis by Brønsted acids (because the leaving group, Hal^-, does not easily accept a proton) and the build up of available Brønsted acid would be expected to make little difference to their reactions, as found[24]. Anhydrides, esters and carboxylic acids are, however, susceptible to Brønsted acid catalysis and it may well be that the species $RCOOHMX_n$ and $ROHMX_n$ formed during acylations with them play an important role in the overall reaction. Detailed knowledge of the structures and ease of formation of the complexes which form between the various metal halides and the different types of acylating agent and also of those between metal halides and different

classes of Brønsted acid (HHal, ROH, RCOOH, etc.) is only just beginning to become available[27,30,31]. Without such knowledge, no proper understanding of the diversity of the Friedel–Crafts ketone synthesis is possible.

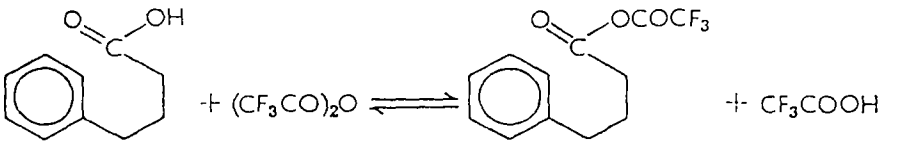
4. As already noted, in polycyclic systems in which more than one isomer may be formed (e.g. in naphthalene α- and β-acyl derivatives are produced) the solvent composition and the molecular ratio of catalyst to acyl component can affect the isomer distribution. A variety of interpretations appear possible[13,25] but the complexity of the phenomena makes the attempt to use the problem as a touchstone for the correctness of postulated mechanisms of acylation unconvincing. It seems very likely, however, that more than one acylating agent is operative in such systems. In very reactive aromatic compounds acylation is reversible, and this fact combined with different preparative recipes can lead to a variety of isomer distributions[13]. Independent studies of deacylation have also been made. Strong Brønsted acid catalysts are needed; the reaction is an electrophilic substitution by hydrogen.

d. Intramolecular acylation. Aromatic compounds containing an acyl group in a suitable position in a side-chain may undergo ring closure[32]. Five- and six-membered rings form most easily. There is



(22)

no reason to suppose that the essential mechanism of this process is different from that outlined above for intermolecular acylation. All the usual catalyst–acyl component combinations may be used, though catalysts of only moderate activity (e.g. $SnCl_4$) often seem particularly appropriate. The formation of a mixed anhydride with a halosubstituted acid (e.g. Y = CF_3COO) is often effective, though as noted above these reactions may be catalysed by free halosubstituted acid which is normally also present in the reaction mixture (equations 23, 24). The effectiveness of the mixtures of $AcOH/Ac_2O/ZnCl_2$ favoured by Johnson is probably due[33] to the similar series of reactions (25) to (28). The species **5** may be considered as a mixed anhydride of the powerful acid $H_2ZnCl_2(OCOCH_3)_2$.



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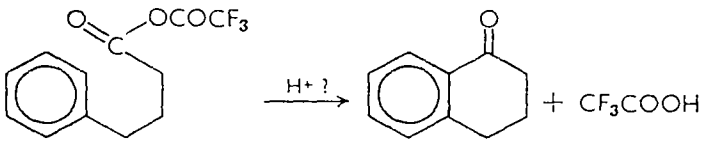

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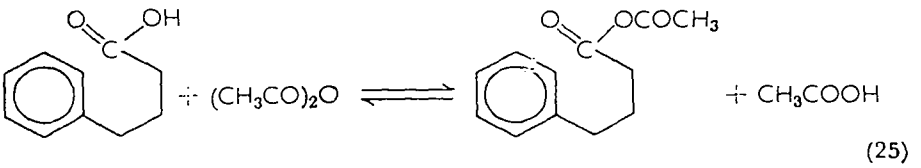
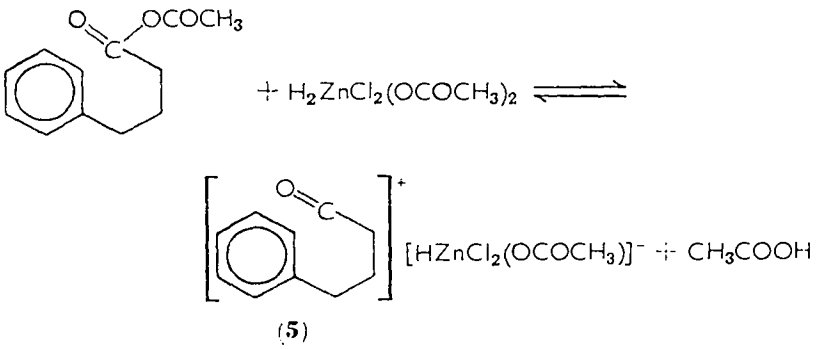


(25)

$$ZnCl_2 + 2\,CH_3COOH \rightleftharpoons H_2ZnCl_2(OCOCH_3)_2 \qquad (26)$$



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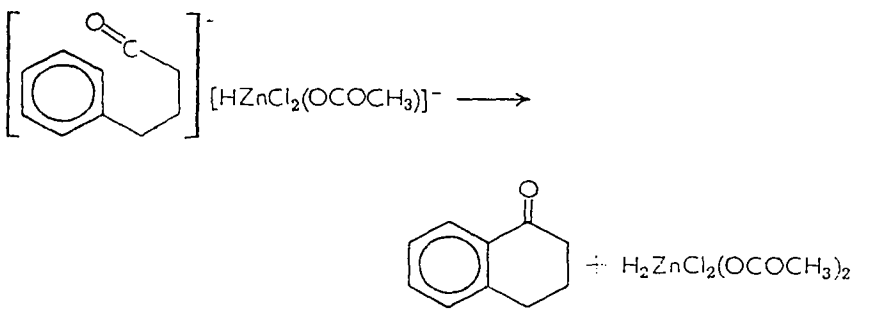
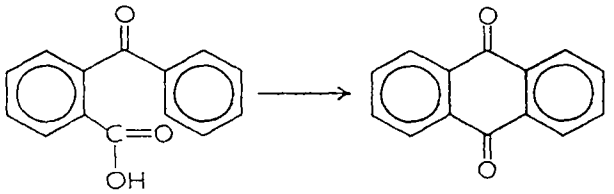
(5)



(28)

A notable feature of this topic is the widespread use of the carboxylic acid (Y = OH in equation 22) as reagent with catalysts such as hydrogen fluoride, sulphuric acid and particularly polyphosphoric acid[34], as well as in schemes like (23) and (25). Yields are good and products comparatively clean. Appreciable acylium-ion formation is likely in media of such high acidity and dielectric constant (cf. equation 6). It is curious that these methods have not found greater use in intermolecular acylation. Although there is little quantitative data on the point, it seems that the intramolecular reaction is easier to achieve than an equivalent intermolecular process. Thus *o*-benzoylbenzoic acids may be readily cyclized to anthraquinone (equation 29), whereas benzophenone itself is



(29)

resistant to acylation. This effect is doubtless due to the artificially enhanced collision number and to the favourable steric positioning involved in the intramolecular process.

Intramolecular acylation has many preparative ramifications and great potential—especially when judiciously coupled with appropriate Friedel–Crafts alkylation—for the synthesis of multi-ring systems[32b]. Although of great interest to the synthetic chemist, these topics involve no new principles and are omitted here.

2. Formylation

a. Introduction. In principle aromatic formylation is exactly analogous to aromatic acylation; and the general factors which govern its course and success are much the same (section II.E.1 above). Special limitations arise in practice in all formylations because of the instability of most formylating agents[35]. Thus the only formyl halide readily isolated is the fluoride; formic anhydride has not been obtained pure; formic acid and formic esters are notably unstable in the presence of acids. Nevertheless, satisfactory formylation can often be effected since transient formylating agents may be adequate for this purpose. Reaction normally involves acid catalysis; base-catalysed formylation of aromatics has apparently not been attempted.

b. Scope and reaction conditions. Gattermann and Koch[36] were the first to pursue the analogy with acylation. They bubbled an equimolecular mixture of hydrogen chloride and carbon monoxide into simple aromatics in the presence of aluminium chloride. The behaviour simulated that expected for formyl chloride. At atmospheric pressure much better results were obtained in the presence of cuprous chloride, which acts as a carbon monoxide carrier. At high pressures (40–90 atm), cuprous chloride may be dispensed with. Other variations have been tried[35]. Thus water may replace hydrogen chloride in the high pressure synthesis (though inevitably some hydrogen chloride will also form). Other catalysts may be used (e.g. $TiCl_4$, $AlBr_3$); $HF/CO/BF_3$ is another recent reagent combination. Temperatures between 20° and 40° are normal, since at higher temperatures the yields decline. The substrate usually acts as its own solvent, although other common inert solvents are also used. The cuprous chloride, metal halide and carbon monoxide form coloured complexes which partly dissolve in the liquid phase. All these $CO/MX_n/HY$ methods are known collectively as the Gattermann–Koch synthesis. Aromatic hydrocarbons more reactive than benzene form the most suitable substrates. As in acylation, phenols and amines usually present difficulties (see section II.E.1.a above), and with other substrates the side-reactions typical of Friedel–Crafts conditions often occur. Few applications to the heterocyclic field have been reported.

A recent analogous method makes use of the isolatable formyl fluoride in conjunction with boron trifluoride or similar catalysts[37,38]. In one procedure, employing a temperature below 0°, the substrate containing formyl fluoride is saturated with boron trifluoride. The powerful nature of the acid products (HF/BF_3) makes it desirable to remove these as soon as possible to avoid secondary complications.

Methods based on formic–carboxylic anhydrides, formic esters and formic acid itself have been little exploited[35]. Formic anhydride has not been isolated and unsymmetrical anhydrides (e.g. formic–acetic) are unstable in the presence of acids, yielding carbon monoxide[38]. They have proved poor formylating agents under Friedel–Crafts conditions. Factors affecting their direction of cleavage may also militate against success[39].

Formic acid, like other carboxylic acids[9], probably yields—though perhaps briefly—the corresponding formyl halide with suitable metal halides (equation 30). Such processes could result in formyla-

$$HCOOH + AlCl_3 \longrightarrow [HCOCl] + AlCl_2OH \qquad (30)$$

tion via the formyl halide. Poor yields are reported for the aluminium chloride system. It seems likely in view of the foregoing that use of metal fluorides would be more successful. With Brønsted acids, formic acid decomposes to carbon monoxide, perhaps[40] via CHO^+. In view of this, such systems deserve study as possible formylating agents. Alkyl, aryl and silicon formates also decompose to carbon monoxide in the presence of acids (e.g. $AlCl_3$), but probably without the intermediacy of CHO^+. They are poor formylating agents[35]. Recently, ethyl orthoformate ($HC(OEt)_3$), in conjunction with aluminium chloride, has proved a satisfactory reagent for the formylation of phenols[41]. This reaction, which is not a direct formylation, is discussed in section III.D.

c. Mechanism. We need only be concerned with the Gattermann–Koch and $HCOF/BF_3$ type systems. In these the active formylating agent is probably very similar. In liquid sulphur dioxide infrared spectral evidence[42] points to the existence of $H—C(=O):BF_3$ as the
F
predominant complex between formyl fluoride and boron trifluoride; very small amounts of the formylium complex $HCO^+BF_4^-$ are, of course, not excluded. Whether or not free formyl chloride is actually formed transiently under Gattermann–Koch conditions at high pressures is not yet clear; the point is somewhat academic since the overall process providing the formylating agent presumably approximates to (31). In the low pressure synthesis with cuprous chloride,

$$CO + HCl + AlCl_3 \longleftarrow HCO{:}AlCl_3 \rightleftharpoons HCO^+AlCl_4^- \qquad (31)$$
Cl

this compound appears to form a complex with the metal halide which can then retain carbon monoxide, perhaps[43] as in equations (32) to (34). In each case the formylating agent is doubtless essentially

$$CuCl + AlBr_3 \rightleftharpoons Cu^+AlBr_3Cl^- \qquad (32)$$

$$CO + Cu^+AlBr_3Cl^- \rightleftharpoons [CuCO]^+[AlBr_3Cl]^- \qquad (33)$$

$$HCl + [CuCO]^+[AlBr_3Cl]^- \rightleftharpoons CuCl + [HCO]^+[AlBr_3Cl]^- \qquad (34)$$

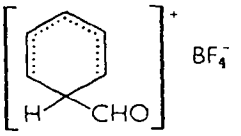
the same. (It should be remembered that all these equations must be oversimplifications, since the aluminium halides and hydrogen chloride/aluminium halide mixtures engage in separate equilibria with aromatics[44].) As for acylation, it is not possible to distinguish between the oxonium or the formylium complex as the responsible

entity (section II.E.1.c above). A rate-determining step like (35) is consistent with the one available kinetic study[43] and with the facts already outlined for acylation.

$$\begin{matrix} HCO{:}MX_n \\ | \\ Y \end{matrix} \quad \text{or} \quad [HCO]^+[MX_nY]^- + ArH \longrightarrow ArCHO{:}MX_n + HY \qquad (35)$$

Because *para*-substitution always greatly predominates over *ortho*-substitution, when both sites are available, it has been argued that the free formylium ion (of presumed low steric requirements) is unlikely to be the active reagent[35]. Significant concentrations of free HCO^+ are in any case very unlikely in most aromatic solvents. Similar arguments apply to Friedel–Crafts acylation: ion-paired or co-ordinated entities probably play the dominant roles in all these processes, except perhaps in solvents like nitrobenzene.

Two other aspects of these reactions warrant mention. First, at low temperatures it is possible[45] to prepare stable polar complexes between carbon monoxide, hydrogen fluoride, boron trifluoride and aromatic compounds. These so called σ complexes probably have the form



At ordinary temperatures these complexes decompose and therefore cannot be intermediates (in the technical sense) in the usual aldehyde synthesis, though this configuration can clearly be assumed at some stage. Secondly, the formation of aldehydes from carbon monoxide and aromatics is not significantly favoured thermodynamically: ΔG is small. It appears that the engagement of the product by the catalyst system is an important driving force in formylation[43]. Deformylation has also been studied, and proceeds at significant speeds at elevated temperatures, especially with reactive aromatic compounds. In the presence of proton acids it involves electrophilic substitution by hydrogen (discussed in a later chapter). The decomposition in the presence of Lewis acids appears more complex[43,46]. The tendency of aldehydes to decarbonylate in the presence of acids may account for the particularly strange order of Lewis acid catalytic activity found for the Gattermann–Koch reaction[43].

F. Olefins as Substrates

1. Acylation

a. Introduction. As with aromatic systems, basic catalysis normally involves formation of a metal derivative of the aliphatic substrate. This subject is largely treated in another chapter, though the special case of reactions involving carbon monoxide and metal carbonyls is discussed in section II.F.5 below. Under acidic catalysis the overall phenomena are also essentially the same as those associated with aromatic acylation but present some extra complications owing (*a*) to the possibility of addition (equation 36) as well as of substitution (equation 37), and (*b*) to the possibility of the mobility of the unsaturated linkage and its reduction in some systems. Thus not only

$$CH_3COCl + RCH{=}CH_2 \longrightarrow RCHClCH_2COCH_3 \quad (36)$$

$$\longrightarrow RCH{=}CHCOCH_3 + HCl \quad (37)$$

β- but also γ- and δ-haloketones are sometimes formed (equation 38); and β,γ- as well as α,β-unsaturated ketonic products may appear. Hydride transfers are involved in these processes (see below).

$$RCH_2CH{=}CH_2 + CH_3COCl \longrightarrow RCH_2CHCH_2COCH_3 + Cl^- \longrightarrow$$

$$R\overset{+}{C}HCH_2CH_2COCH_3 + Cl^- \longrightarrow \underset{\displaystyle Cl}{RCHCH_2CH_2COCH_3} \quad (38)$$

The extension of acid-catalysed acylation to unsubstituted aliphatic systems was attempted soon after the successes of Friedel and Crafts with aromatic compounds, but was not properly accomplished before the work of Kondakov[47] in 1892. The extension has proved an important synthetic tool, but the volume of work to date does not compare with that concerning aromatic systems[48].

In the presence of free-radical initiators, olefins possessing a terminal double bond add aldehydes, thus yielding saturated ketones[49]. These reactions have not yet achieved widespread preparative importance and are omitted here.

b. Scope and reaction conditions. In addition to the usual side-reactions encountered with Friedel–Crafts catalysts, the susceptibility of olefins to acid-catalysed polymerization makes the use of mild conditions particularly important. Kondakov used zinc chloride as catalyst, and both acyl chlorides and carboxylic anhydrides as sources of the acyl group. Other acylating agents have been rarely used except in

intramolecular variations, when carboxylic acids are successful[50]. Other catalysts have now been investigated. The reaction takes a superficially different course depending upon whether the acyl halide or anhydride is employed. With the former (equation 39) at tempera-

$$R^1COCl + R^2CH{=}CH_2 \longrightarrow R^2CHClCH_2COR^1 \xrightarrow{Heat} HCl + R^2CH{=}CHCOR^1 \quad (39)$$

$$(R^1CO)_2O + R^2CH{=}CH_2 \longrightarrow \left[R^2CH(OCOR^1)CH_2COR^1\right] \longrightarrow R^2CH{=}CHCOR^1 + R^1COOH \quad (40)$$

$$R^1COOCOCF_3 + R^2CH{=}CH_2 \longrightarrow R^2CH(OCOCF_3)CH_2COR^1 \longrightarrow R^2CH{=}CHCOR^1 + CF_3COOH \quad (41)$$

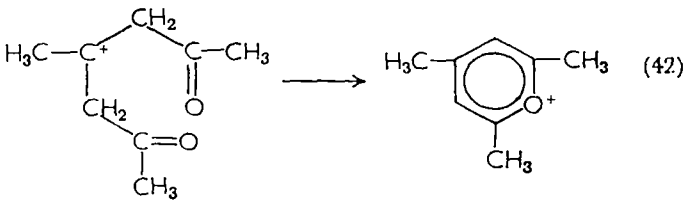
tures less than about 0°, the product is mainly the haloketone, which can be dehydrohalogenated by various procedures (e.g. by distillation or heating in the presence of bases). Actually, only β-halo ketones lose hydrogen halide readily and, because of the usual production of some other isomers, these syntheses rarely yield completely halogen-free products[48].

In the reaction of anhydrides (equation 40), in contrast, no addition product is usually isolated. However, it may be obtained in certain cases with anhydrides such as acetic–trifluoroacetic (equation 41) and, therefore, probably forms as a brief-lived intermediate in other examples also. The reaction with unsymmetrical anhydrides, prepared from the free acid and trifluoroacetic acid or anhydride, forms, in fact, the basis of an important recent modification of the process[14].

Reaction temperatures are usually kept fairly low to minimize side-reactions. Catalysed addition of the hydrogen chloride or

$$(CH_3)_2C{=}CH_2 \longrightarrow (CH_3)_2\overset{+}{C}{-}CH_2COCH_3 \longrightarrow H_3C{-}C(=CH_2){-}CH_2{-}C(=O){-}CH_3 \longrightarrow$$

(6)



(42)

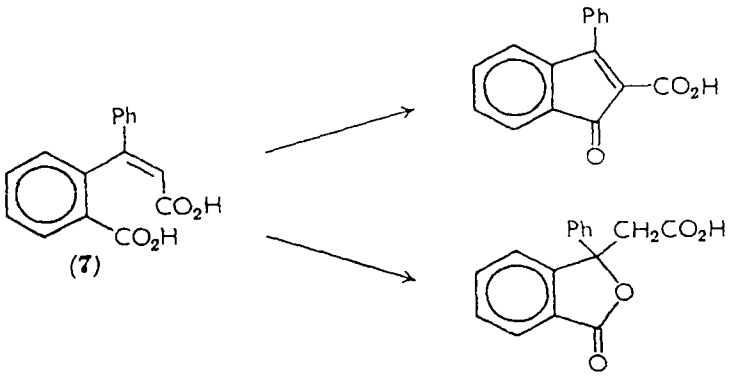
carboxylic acid products to the unreacted olefin is an important hazard of this sort. Carboxylic acids do not appear to act as acylating agents in these contexts but add to give esters. It is not certain how general this effect is, since (as noted above) in intramolecular versions of these acylations the free acid is often employed (see below).

The reaction is commonly carried out in excess of acyl halide or anhydride, though inert solvents are also used. Excess of acylating agent frequently leads to diacylation and subsequent pyrillium salt formation[51] (equation 42).

The catalyst is usually added last to keep polymerization of the olefin to a minimum. The most popular catalysts have been zinc chloride (mostly used with anhydrides), and aluminium and stannic chlorides (used with acyl halides). Of the latter, stannic chloride is generally more satisfactory, probably because of its relative mildness. Other catalysts have been tried sporadically. A variety of olefins have been studied and, as expected, electron-donating substituents facilitate reaction[48]. Because of the great variety of possible side-reactions in these aliphatic acylations, the yields are rarely quantitative and success depends upon a balance of factors not all, or even mostly, related to the efficiency of the actual acylation process. Hence yields are exceptionally poor guides to the intrinsic relative reactivities of the various reagents.

When a molecule contains both a double bond and a suitable acyl centre in appropriate relative positions, intramolecular acylation can be effected[32b,50]. As in other cyclizations, five- and six-membered rings are those most easily formed. The normal reagent-combinations have all been satisfactorily employed but, as in the analogous cyclizations involving aromatic compounds (section II.E.1.d), the use of the free acid (rather than anhydride or acyl halide) in conjunction with powerful Brønsted acid catalysts has recently become common. Polyphosphoric acid, introduced by Snyder and Werber[52], has proved a particularly effective catalyst. Between these cyclizations involving olefins and those involving aromatic compounds there is, however, an important difference: under acid catalysis, free carboxylic acids usually add to olefins to give esters rather than ketones (see above). In intramolecular reactions this effect often results in preferential lactone formation and poor yields of cyclic ketone[50]. The balance between lactonization and acylation appears to depend upon the catalyst and upon the degree of aromaticity of the olefin. Thus concentrated sulphuric acid, which leads primarily to lactones with straightforward olefinic acids but to good yields of

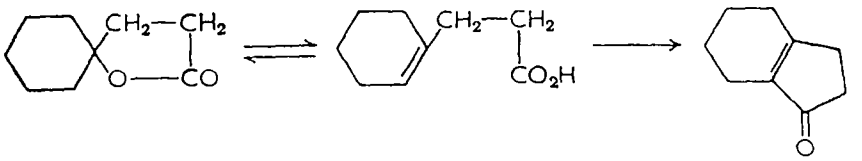
ketones with γ-arylalkanoic acids, provides[53] with **7** approximately equal amounts of lactone and ketone (equation 43).



(43)

It is clear that it is the susceptibility of the C=C bond to protonation which determines the susceptibility to lactonization. With olefinic acids the most desirable Brønsted acid catalysts are those which promote mixed anhydride or acylium ion formation at the carbonyl group (equation 6) with the minimum of protonation of the double bond. It appears that polyphosphoric acid and the $ZnCl_2$/AcOH/Ac_2O or $(CF_3CO)_2O/CF_3CO_2H$ combinations do this best[50].

Whereas these intramolecular acylations are essentially irreversible, the lactonizations are not, the suitable γ- and δ-lactones can, on occasion, be used as starting materials for the acylation (equation 44). The yields are poorer than with the free acids and it has been concluded[50], therefore, that the acylation does *not* normally proceed via



(44)

the lactone as intermediate. It would seem, however, that the lactone/ketone product ratio in any given case should depend upon the contact time.

c. Mechanism. As for aromatic compounds (section II.E.1.c), the essentials of the mechanism can be separated into two parts; (*a*) the formation of a sufficiently active acylating agent from the catalyst

and acyl compound, and (*b*) the attack of this species on the substrate and the subsequent behaviour of the intermediates thus formed.

It should be made clear at this point that the following descriptions are particularly conjectural, in view of the total absence of kinetic studies in this part of the field. However, so far as (*a*) is concerned, conclusions drawn from studies on aromatic acylation are clearly relevant.

A significant feature is that sometimes particularly basic (or nucleophilic) olefins may be acylated by acyl halides in the (apparent) absence of catalysts (though the process is usually slow)[54]. Since olefinic compounds are more reactive than aromatic compounds this is a reasonable result and, as expected, those acyl halides which are most able to form acylium ions (e.g. acyl iodides rather than chlorides, and aroyl halides rather than their aliphatic analogues) are the most effective in these uncatalysed processes.

The two usual reagent–catalyst combinations ($RCOHal/MX_n$ and $(RCO)_2O/ZnCl_2$) will provide the quasi-acylium species required for reaction with the olefin in different ways (section II.E.1.c). When acyl halide is used, complexes like **1** or **2** (equation 6) will participate, while with anhydrides, and in the absence of Brønsted acid catalysts, oxonium complexes like **4** (equation 20) will be involved, at least for zinc and stannic halides. In the additional (possibly adventitious) presence of free carboxylic acid or other Brønsted acids, strong dual acids will form (e.g. $H_2SnCl_4(OCOR)_2$) and these will probably be the effective catalyst when the reagent is the anhydride (equation 45). As noted under aromatic acylation (section II.E.1.d), this circumstance is especially relevant to the frequent use of the

$$(R^1CO)_2O + H_2SnCl_4(OCOR^2)_2 \rightleftharpoons [(R^1CO)_2OH]^+[HSnCl_4(OCOR^2)_2]^- \rightleftharpoons [R^1CO]^+[HSnCl_4(OCOR^2)_2]^- + R^1COOH \quad (45)$$

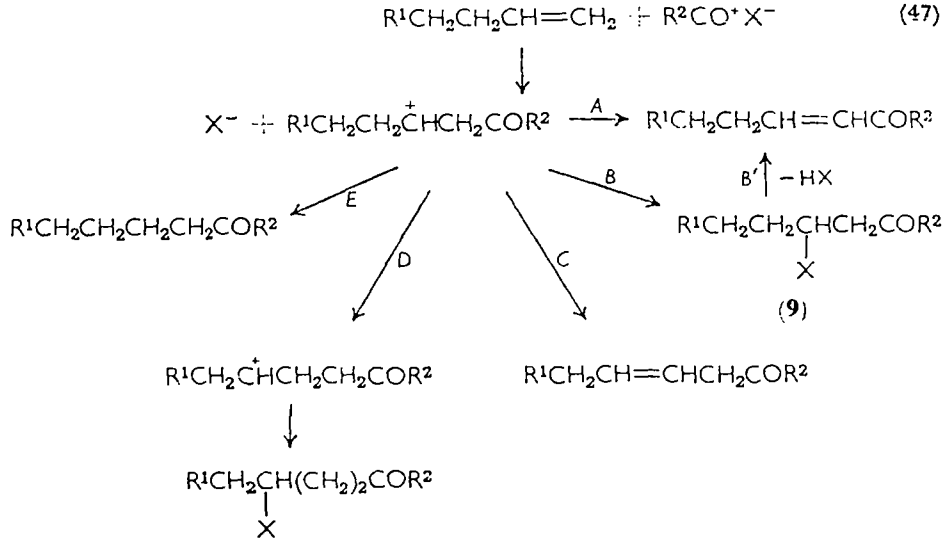
(**8**)

$$R^1COOH + H_2SnCl_4(OCOR^2)_2 \rightleftharpoons [R^1COOH_2]^+[HSnCl_4(OCOR^2)_2]^- \rightleftharpoons [R^1CO]^+[HSnCl_4(OCOR^2)_2]^- + H_2O \quad (46)$$

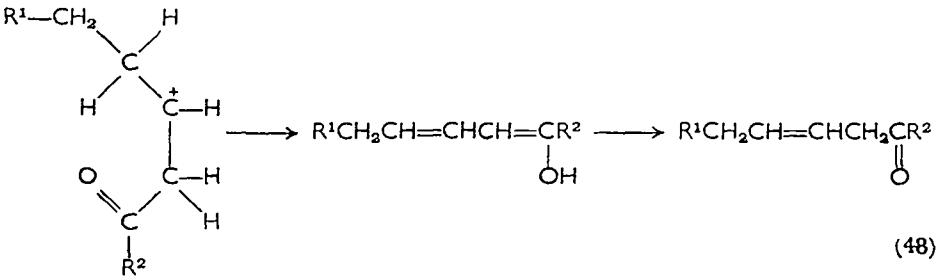
$Ac_2O/AcOH/ZnCl_2$ and $(CF_3CO)_2O/CF_3COOH$ recipes together with the free acid (RCOOH) in intramolecular acylation. Species **8** (cf. species **5**, equation 27) can be regarded as a mixed anhydride. Similar species no doubt exist in the sulphuric or phosphoric acid catalysed intramolecular acylations. (The apparent use of phosphoric oxide[55] is probably, in fact, the use of polyphosphoric acid, some water entering the apparatus.) Polyphosphoric acid will owe some of its effectiveness to its high dielectric constant,

which is favourable to acylium ion formation. As for the aromatic field, there seems no obvious reason why the free carboxylic acid should not be used more often as the reagent in intermolecular acylation.

In the second stage (b) of the reaction, the quasi-acylium entity attacks the olefinic substrate. The resulting carbonium-ion intermediate can suffer a number of fates, which have been outlined in the above discussion. These are now set out schematically in (47).



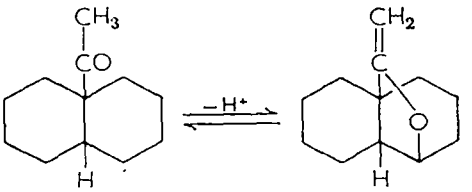
The relative importance of these various routes must vary with the actual system. The importance of *A*, which corresponds to a direct substitution, is not certain. *B* followed by *B′* is clearly one possible route to α,β-unsaturated ketones. The surprisingly frequent formation of the unconjugated β,γ-unsaturated ketones via *C* may be due to the opportunity present for a six-membered cyclic transition state leading to the corresponding dienol (equation 48). This is thought to be the route taken when diacylation leads to pyrillium salts[51b] (equation 42).



(48)

A possible reason why **9** is not found, in acylations by most anhydrides (see equation 40) is that the complexity of the anion X^- in these cases (see **8** in equation 45) discourages its formation. In procedures involving acyl halide or trifluoroacetic acid, X^- is Cl^- or $OCOCF_3^-$ and **9** can, therefore, form more easily.

Route *D* involves intramolecular hydride-ion transfer, a known process for aliphatic hydrocarbons[48], and *E* intermolecular hydride-ion transfer, also a known process. Route *E* is well covered by circumstantial evidence[56] and appears important when the solvent is a saturated hydrocarbon (e.g. cyclohexane). Hydride ion transfer assumes great importance in the acylation of saturated hydrocarbons (section II.G.1). It appears that in certain favourable cases species like **10** may lead to ether rather than ketone formation[57] (equation 49).



(49)

(**10**)

2. Formylation

Direct formylation of olefinic compounds under any conditions has rarely been achieved at a preparative level. Attempted Gattermann–Koch and similar procedures (section II.E.2 above) usually result mainly in carboxylic acid derivatives, together with small quantities of ketones[48]. It is thought[58] that aldehydes are probably *not* formed as intermediates (see section II.G.2 below). Even were they formed they would be difficult to isolate for aliphatic aldehydes and halo aldehydes are particularly unstable under acid conditions and, especially in the presence of Lewis acids, tend to rearrange to isomeric ketones[59]. Successful formylation of aliphatic compounds requires other than Friedel–Crafts conditions. They are described in sections II.F.5 and III.A.3 below.

3. Acylation of acetylenes

This topic has been little studied in comparison with olefin acylation[48]. The essential character of the acid-catalysed reaction is similar and the reagents used much the same, except that aluminium

chloride appears less disadvantageous where acetylenes are concerned. One important difference is that when acyl halides are employed, the initial product, a β-halovinyl ketone, is not easily dehydrohalogenated and normally is isolated as such (equation 50). These compounds prove useful intermediates in many syntheses, the β-halo atom possessing unusual reactivity.

$$RCOCl + CH{\equiv}CH \xrightarrow{AlCl_3} RCOCH{=}CHCl \qquad (50)$$

Reaction of acetylenes with a carboxylic acid and trifluoroacetic acid (or anhydride) provides a useful route to β-diketones[14] (equations 51, 52).

$$R^1COOH + (CF_3CO)_2O \rightleftharpoons R^1COOCOCF_3 + CF_3COOH \qquad (51)$$

$$R^1COOCOCF_3 + CH{\equiv}CR^2 \xrightarrow{CF_3COOH} R^1COCH{=}CR^2OCOCF_3 \xrightarrow{CH_3OH} R^1COCH{=}CR^2OH \longrightarrow R^1COCH_2COR^2 \qquad (52)$$

4. Acylation of alkylidenephosphoranes

Alkylidenephosphoranes (**11**) may be regarded as organophosphorus analogues of olefins. Recently[60a] they have been found to participate in superficially very similar reactions (equation 53) with the standard acylating agents RCOY to give intermediate β-ketoalkylphosphonium salts (**12**), which eliminate HY and yield stable β-ketoalkylidinephosphoranes (**13**). These compounds can, if

$$\underset{(11)}{Ph_3P{=}CHR^1} + R^2COY \longrightarrow \underset{(12)}{[Ph_3P^+CHR^1COR^2]Y^-} \xrightarrow{-HY} \underset{(13)}{Ph_3P{=}CR^1COR^2} \qquad (53)$$

$$Ph_3P{=}CR^1COR^2 \longrightarrow Ph_3P + R^1CH_2COR^2 \qquad (54)$$

desired, be reduced to the corresponding phosporus-free ketones (equation 54). Discussion of the mechanistic details of the reactions awaits further study. Acetylenic ketones may also be prepared[60b].

5. Acylation and formylation of olefins with carbon monoxide

a. Introduction. A variety of organic compounds, when heated under pressure with carbon monoxide, hydrogen and suitable transition metals or their compounds, undergo reactions leading to the introduction of the carbonyl group[61]. Depending upon the exact conditions of catalyst, solvent, temperature and acidity a variety of products, among which are ketones and aldehydes, may result from a particular substrate. The synthesis of ketones actually still constitutes only a minor feature of this field, such ketones as are formed

often being by-products from other main reactions. No routine ketone synthesis has yet appeared. Consequently ketone formation will not be emphasized here. The synthesis of saturated aliphatic aldehydes from olefins—sometimes termed the 'oxo process' and sometimes 'hydroformylation'—is, on the other hand, one of the major applications of this type of reaction, which grew originally out of the Fischer–Tropsch 'water-gas' process. Indeed, much of the early work in the field was performed in industrial laboratories, particularly by Reppe[62] in Germany.

The overall reaction is the addition of the elements of formaldehyde to an olefin (equation 55). The effective catalysts are metal carbonyls

$$RCH{=}CH_2 \xrightarrow[\text{catalyst}]{CO/H_2} RCH_2CH_2CHO \qquad (55)$$

and their derivatives. Understanding of the mechanisms of these, sometimes partially heterogeneous, processes is still far from complete, but facts are accumulating rapidly. As is shown in section II.F.5.c below, an outline scheme may be suggested.

b. Reaction conditions. Reaction is normally conducted either in the presence of an inert solvent (like benzene or ether) or with a supported catalyst. High pressures (200–300 atm) of carbon monoxide/hydrogen mixtures, and temperatures of about 100° are used. At higher temperatures ($> 150°$) the aldehyde is reduced to the corresponding alcohol[61]. The metal carbonyl catalyst can either be formed *in situ*, from the metal or its salts and carbon monoxide, or be added as such. Cobalt is the usual metal and can be added as the octacarbonyl. Other metals are occasionally used, for example rhodium and iridium, and under comparable conditions the sequence of efficiency appears to be[63] iridium < cobalt < rhodium. The *in situ* conversion process is rather slow and reactions employing this method tend to accelerate with time. It may be that the usual drastic conditions are unnecessary when the catalyst is added as the preformed metal carbonyl[61].

Both steric and electronic effects are detectable on variation of the olefin structure: the reaction rate is decreased by electron-withdrawing substituents and also by chain branching in simple olefinic hydrocarbons, when the aldehyde group tends to add to the less hindered side of the double bond[64]. Both molecular rearrangement and double-bond migration are often observed. A wide range of simple olefins has been studied[61]. Yields are often severely limited by condensation of the aldehyde products.

c. Mechanism. Most light has been thrown on the reaction mechanism by studies of the behaviour of metal carbonyls under conditions typical of hydroformylation. It has been observed[65] that under such conditions dicobalt octacarbonyl is rapidly converted into cobalt hydrocarbonyl (equation 56) and that this compound reacts with olefins absorbing carbon monoxide in the process (57). The rates of

$$Co_2(CO)_8 + H_2 \rightleftharpoons 2\,HCo(CO)_4 \tag{56}$$

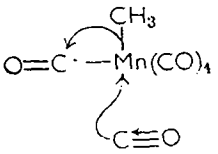
$$2\,HCo(CO)_4 + RCH{=}CH_2 + CO \longrightarrow RCH_2CH_2CHO + Co_2(CO)_8 \tag{57}$$

this process with different olefins at room temperature and pressure, parallel those of the hydroformylation of the same olefins under more extreme conditions[64a,65]. It has also been found that under normal hydroformylation conditions no hydrocarbonyl can be detected until all the olefin has been consumed[66a]. Since metal carbonyls appear to form in the usual reaction systems, even when the metal is added as the element or as its salt*, these results seem to implicate the hydrocarbonyl as an essential species in hydroformylation. The other successful catalysts besides cobalt—rhodium and iridium—also form hydrocarbonyls.

Indications of the finer details of reaction (57) come from work[67] with acyl and alkyl metal carbonyls. At high carbon monoxide pressures such compounds engage in equilibria like (58). Moreover,

$$CO + CH_3Mn(CO)_5 \rightleftharpoons CH_3COMn(CO)_5 \tag{58}$$

carbon-14 tracer studies show that this process is essentially an intramolecular rearrangement and that the entering or expelled carbonyl group is *not* that associated with the acyl group (59). It is to be noted that the forward step of (58) does not proceed with the



(59)

CF_3 group in place of CH_3. A variety of different metal alkyl carbonyls enter into such equilibria[68].

* The accelerating rates then observed (see section II.F.5.b above) can be accounted for by the increasing amounts of carbonyl being formed.

The above facts suggest the following four steps in the mechanism for hydroformylation[61]:

$$Co_2(CO)_8 + H_2 \longrightarrow 2\,HCo(CO)_4 \quad (60)$$

$$HCo(CO)_4 + RCH{=}CH_2 \longrightarrow RCH_2CH_2Co(CO)_4 \quad (61)$$

$$RCH_2CH_2Co(CO)_4 + CO \rightleftharpoons RCH_2CH_2COCo(CO)_4 \quad (62)$$

$$RCH_2CH_2COCo(CO)_4 + HCo(CO)_4 \longrightarrow R(CH_2)_2CHO + Co_2(CO)_8 \quad (63)$$

(14)

Such a scheme is compatible with the observed[69] first-order dependence of the rate of aldehyde production on the hydrogen and olefin concentrations in different pressure regions. At very high carbon monoxide pressures an inverse dependence on this substance is found and this may be due to a side-reaction which removes the octacarbonyl (equation 64). Reaction (61) is formally that of a metal

$$Co(CO)_8 + CO \longrightarrow Co(CO)_9 \quad (64)$$

hydride with the substrate, and a consideration of this and of scheme (59) shows that the carbonyl-substitution process can be thought of as particularly complicated variety of base-catalysed direct acylation in which the catalyst not only creates a potential carbanion but also provides the carbonyl carbon atom which attacks it. The unreactivity of the trifluorylmethyl derivatives emphasizes the normal electrophilic nature of the carbonylation processes.

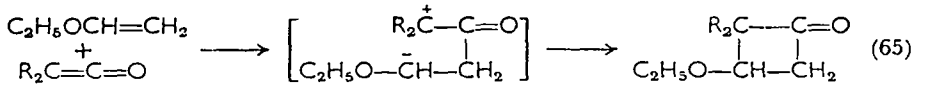
Steps like (63) have not received independent study. It has been suggested[66b] that in certain circumstances the alkylcarbonyl, rather than the hydrocarbonyl, may attack species **14** and so lead to the ketones sometimes observed.

The speculative nature of the foregoing remarks is emphasized. A topic now occupying much attention is the factors which underlie the structural changes in the olefin which often occur during hydroformylation. Current interest in the whole field is particularly intense.

6. Acylation of vinyl ethers with ketenes

Particularly nucleophilic olefins (e.g. vinyl ethers) are able to add ketenes in the apparent absence of catalysts, the product being a

cyclobutanone[70] (equation 65). This type of reaction seems restricted



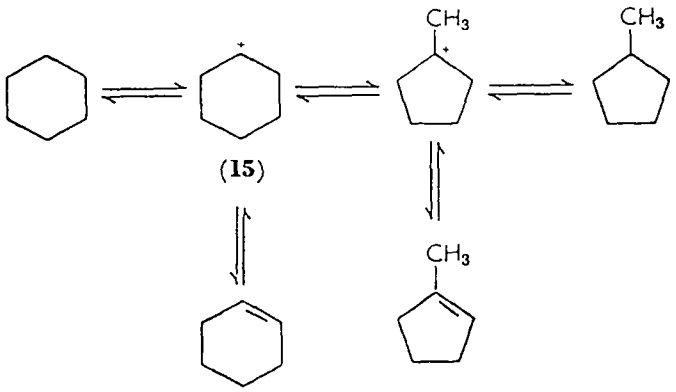
(65)

to a limited class of olefins. Its mechanism, although as yet little studied, appears straightforward. With acetylenic ethers, cyclobutenones are formed.

G. Unsubstituted Saturated Aliphatic Hydrocarbons as Substrates

1. Acylation

Saturated aliphatic hydrocarbons are particularly poor nucleophiles and uncatalysed acylation of them will, therefore, be very unusual. Basic catalysis, as in the other classes of compounds dealt with so far, involves formation of an organometal derivative (discussed in another chapter). The acid-catalysed reactions are complex[48]. There is rather little evidence (except perhaps for cyclopropane[71] which already shows some olefinic character) for a direct substitution mechanism, and reaction is considered to proceed via the olefin and along the lines discussed in section II.F above[48]. This requires the prior oxidation of the hydrocarbon. Olefin formation from alkanes in the presence of aluminium chloride and a suitable third substance is a known process and very probably involves hydride ion transfer. Related isomerizations can also occur and the overall scheme for cyclohexane has been reported by Nenitzescu (who has been associated with much of the work in this general field) to be as follows:



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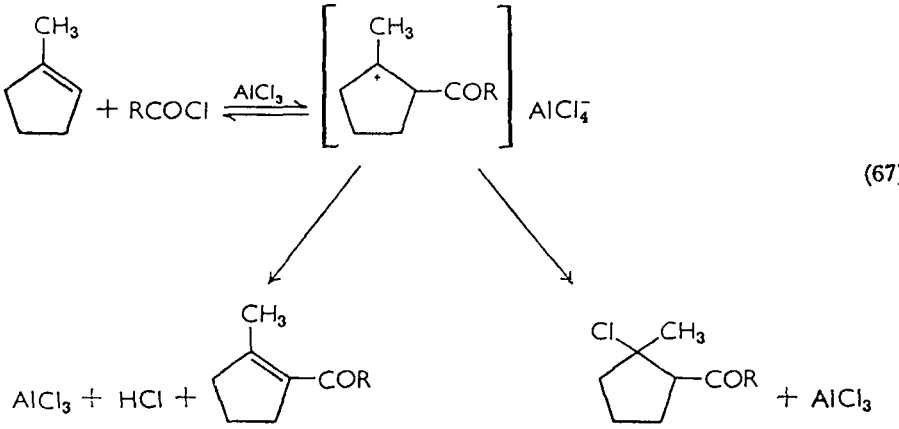


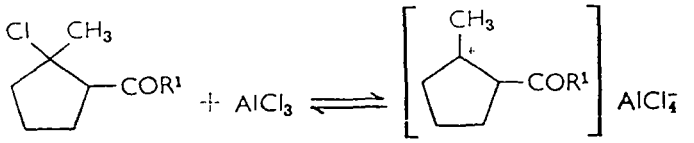
(67)

The species **15** (and similar entities) are probably formed by electrophilic attack by an acylium or a carbonium ion on hydrogen (equations 68, 69). Thus, strictly, acylation of saturated aliphatic compounds involves acylation of hydrogen—attack on carbon being too difficult. The resulting aldehyde (**16**) can on occasion be isolated,

$$R^1COCl + AlCl_3 \rightleftharpoons R^1CO^+AlCl_4^- \quad (68)$$

$$R^1CO^+AlCl_4^- + R^2H \longrightarrow [R^2]^+ + R^1CHO + AlCl_4^- \quad (69)$$

(**16**)



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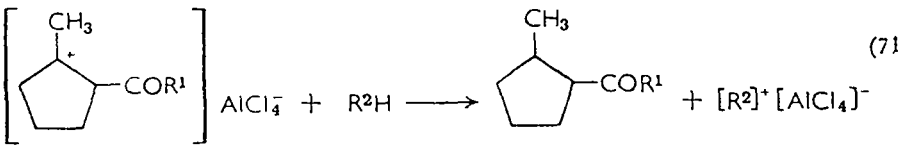


(71)

although it is thought that processes like (71) usually predominate as the products begin to build up, only traces of aldehyde then being formed. Schemes like the above undoubtedly approximate closely to the stoichiometrics of these reactions. The true details of the individual steps are, however, still very uncertain. Only powerful catalysts—such as aluminium chloride and antimony pentachloride—appear to promote these processes.

The amount of rearranged product in any given case depends

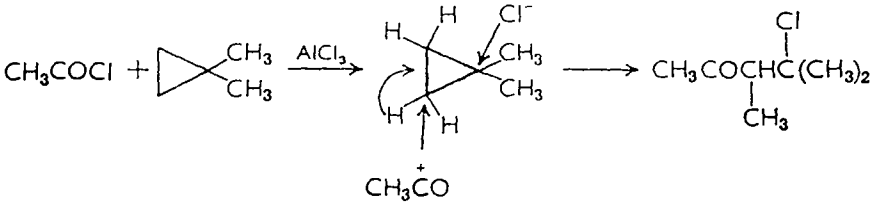
upon the starting material. With cyclohexane, no appreciable cyclohexyl derivatives are formed, the major products being derivatives of cyclopentane. As expected therefore, cyclopentanes do not rearrange. The stability of the intermediate carbonium ions is probably an important factor here, but the actual reasons can at present only be conjectured. The complexity of the systems has so far precluded systematic studies on substrate substituent effects[48].

With acyl halides, cyclopropanes yield not only the γ-halo ketone (**17**) expected from ring opening but also the β-haloisopropyl ketone (**18**), which is sometimes the major product[71]. Various tests are

$RCOCH_2CH_2CH_2Cl$ (**17**)

$RCOCHCH_2Cl$ with CH_3 (**18**)

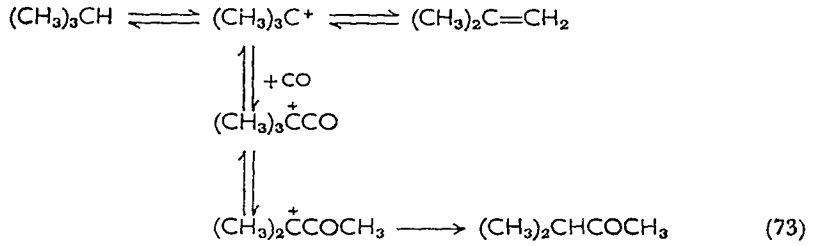
thought by Hart to leave a direct substitution (equation 72) as the most likely route to the latter.



(72)

2. Formylation

Attempted Gattermann–Koch reactions with saturated aliphatic hydrocarbons do not provide aldehydes but ketones, usually with skeletal rearrangement[48]. Although aliphatic aldehydes rearrange to ketones under the influence of aluminium chloride[59], the aldehydes which would be expected to form from the addition of CHO^+ to the intermediate olefins do not in fact rearrange to the observed ketone products and it is therefore considered that the ketones form directly under Gattermann–Koch conditions from carbonium ions and carbon monoxide[58] (equation 73). If this is so these reactions are the



(73)

only acylations discussed here in which the roles of substrate and reagent are reversed: nucleophilic attack by the carbonyl group on the substrate is involved. It is difficult, however, to understand why no direct aldehyde formation should occur.

Other formylating agents have not been studied in these contexts.

H. Substituted Saturated Aliphatic Compounds as Substrates

1. Acylation

a. Introduction. Rather few types of substituted compound have been studied, by far the most important being ketones, esters and nitriles. These compounds all carry electron-withdrawing substituents and these substituents render their α-hydrogen atoms 'active' or acidic. As a result the compounds form carbanions readily on contact with strong bases such as sodium ethoxide. They are the most susceptible of all types of organic compound to base-catalysed *C*-acylation, the prior formation of an organometallic derivative from the corresponding alkyl halide being unnecessary. We shall therefore discuss these base-catalysed reactions in this chapter[10].

The acid-catalysed acylation of ketones at an α-carbon atom has also been effected[10]. As with other acid-catalysed acylations at apparently saturated carbon atoms (section II.G.1 above), these reactions very probably involve the preliminary formation of an unsaturated centre.

b. Base-catalysed acylation. Scope and reaction conditions—The commonly used bases are sodium alkoxides, sodamide and sodium hydride; less often the very powerful triphenylmethylsodium is employed. The commonest acylating agent is an ester, although others are used in certain circumstances. The normal substrates are those listed in section H.1.a above. A very wide range of structures has been studied, especially for ketones and esters[10]. Typical acylations are shown in equations (74), (75) and (76). These reactions are generally

$$2\ CH_3CO_2C_2H_5 \xrightleftharpoons{NaOC_2H_5} CH_3COCH_2CO_2C_2H_5 + C_2H_5OH \qquad (74)$$

$$CH_3CO_2C_2H_5 + (CH_3)_2CO \xrightleftharpoons{NaOC_2H_5} CH_3COCH_2COCH_3 + C_2H_5OH \qquad (75)$$

$$CH_3CO_2C_2H_5 + RCH_2CN \xrightleftharpoons{NaOC_2H_5} RCH(CN)COCH_3 + C_2H_5OH \qquad (76)$$

termed Claisen condensations[72]; reaction (74) is, of course, the acetoacetic ester condensation. The products are β-diketones, β-keto esters, β-keto nitriles and related compounds. Reaction is often

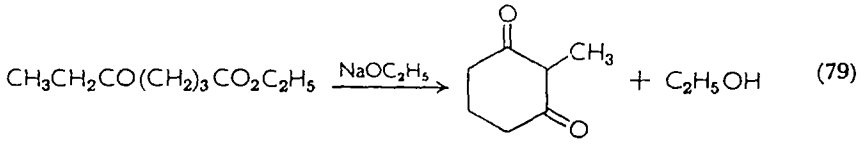
conducted in an excess of one reactant as solvent or in an inert medium like benzene or ether. The three essential components (substrate, acylating agent and catalyst) are mixed at ordinary temperatures and the product, a stronger acid than the original substrate, usually precipitates as its sodium salt. Were this not to occur these equilibria would often lie largely on the reactant side. When ethyl esters are used as acylating agents the forward process is often further aided by distilling out the ethanol as it is formed. Because catalyst is removed by the product, molecular proportions are necessary, and a two-fold excess is common. It is clear that side-reactions will frequently limit the yields. These are, however, often good. Self-condensation of the acylating agent, the substrate or the product, polysubstitution, and *O*- rather than, or as well as, *C*-acylation are all possibilities among others. The last two complications seem particularly important in variations which employ the acid chloride or anhydride with the preformed (i.e. free from alkoxide, etc.) sodium derivative of the substrate, e.g. equations (77) and (78). For these reasons the reaction with acyl halides and

$$2\,R^1COCl + NaCHR^2COR^3 \longrightarrow R^1COCR^2{=}CR^3OCOR^1 + HCl + NaCl \quad (77)$$

$$2\,R^1COCl + NaCH_2COR^2 \longrightarrow (R^1CO)_2CHCOR^2 + HCl + NaCl \quad (78)$$

anhydrides has proved of less preparative value than that with esters, except in special contexts (see below). Work on the factors which control the balance between *O*- and *C*-acylation is only just beginning[73,74].

With suitable keto esters, intramolecular acylations may be effected[10]. These produce normally five- or six-membered rings, the second keto group appearing endo- or exocyclic depending upon the original structure (equations 79, 80). When the substrate is a diester the cyclization is known as the Dieckmann reaction[75].



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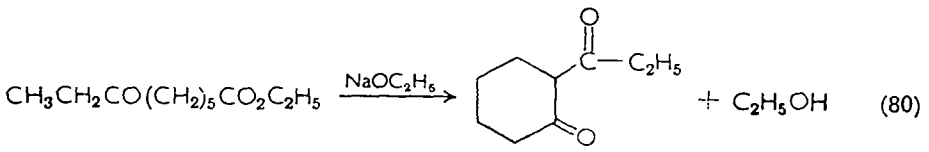
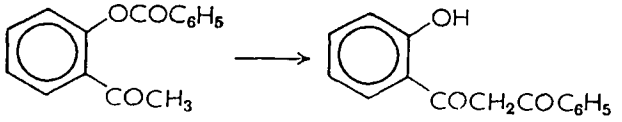


(80)

Other related intramolecular processes result in rearrangements[76] (equation 81). For these reactions mild catalysts like potassium



(81)

carbonate appear adequate. This circumstance is a further example of intramolecular effects requiring less forcing conditions than the corresponding intermolecular process (cf. section II.E.1.d above). The Kostanecki reaction is another intramolecular variation[77].

The ability of acyl halides and anhydrides to provide polyacylation at a single carbon atom is sometimes utilized when the intermediate polycarbonyl compound can be decomposed in a desired direction[78]. Thus acylation of suitable sodiomalonic esters provides a route to simple ketones (equation 82).

$$R^1COCl + [\bar{C}R^2(COOR^3)_2]Na^+ \longrightarrow R^1COCR^2(COOR^3)_2 + NaCl \xrightarrow{H_2O}$$
$$R^1COCR^2(COOH)_2 \longrightarrow R^1COCH_2R^2 \quad (82)$$

Very recently[79] aliphatic sulphoxides, sulphones and related compounds have been subjected to Claisen-like reactions. Their preformed carbanions react readily with esters. The acyl sulphoxides formed on hydrolysis can, if desired, be smoothly reduced to a sulphur-free ketone (equation 83).

$$R^1COOR^2 + 2\,CH_3SOCH_2^-Li^+ \longrightarrow [R^1COCHSOCH_3]^-Li^+ + Me_2SO + LiOR^2$$
$$\xrightarrow{H_3O^+} R^1COCH_2SOCH_3 \xrightarrow[H_2O]{Al/Ag} R^1COCH_3 \quad (83)$$

Mechanism—These base-catalysed acylations appear straightforward examples of equation (1), though appearances have not yet been supplemented by much kinetic evidence.

$$R^1CH_2COR^2 + NaOC_2H_5 \rightleftharpoons Na^+[R^1CHCOR^2]^- + C_2H_5OH \quad (84)$$

$$Na^+[R^1CHCOR^2]^- + R^3COOR^4 \rightleftharpoons R^1\underset{\displaystyle COR^3}{\underset{|}{C}}HCOR^2 + NaOR^4 \quad (85)$$

$$R^1\underset{\displaystyle COR^3}{\underset{|}{C}}HCOR^2 + NaOC_2H_5 \text{ (or } Na[OR^4]) \rightleftharpoons \left[R^1\underset{\displaystyle COR^3}{\underset{|}{C}}COR^2\right]^-Na^+ + C_2H_5OH \quad (86)$$

When sodium hydride or sodamide are used, (84) lies well to the right. These are forcing catalysts but are not always so experimentally convenient as sodium ethoxide. The slow step is probably

(85), since reaction seems favoured by electron withdrawal by R^3 or R^4: phenyl esters rather than ethyl esters are often advantageous[10]. In the substrate the more highly substituted the α-carbon atom the more difficult the reaction: methyl is usually substituted in preference to methylene. This effect parallels the relative stabilities and ease of formation of the respective carbanions and implies that the relative amounts of these species available are more important than their relative reactivities (cf. section II.D above). Steric factors may also intrude.

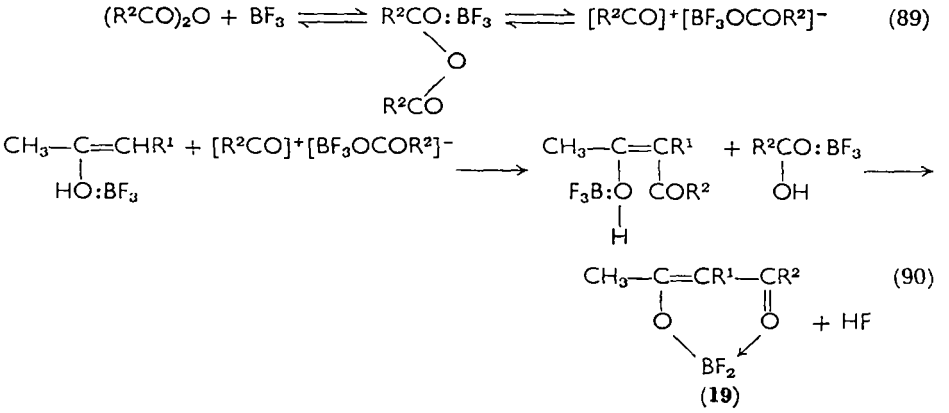
c. Acidic catalysis. Scope and reaction conditions—Rather little work exists in this context, except for the acylation of ketones by boron trifluoride/carboxylic anhydride mixtures[10]. (Recently aluminium chloride has also been used in similar reactions[80].) The mixture of substrate and anhydride is saturated with boron trifluoride at ordinary temperatures and the desired product (β-diketone) isolated after treatment with aqueous alkali (equation 87). The catalyst and product form a complex (decomposed by a base) which is possibly

$$(CH_3CO)_2O + CH_3COCH_3 \xrightarrow[2.\ Base]{1.\ BF_3} CH_3COCH_2COCH_3 + CH_3COOH \qquad (87)$$

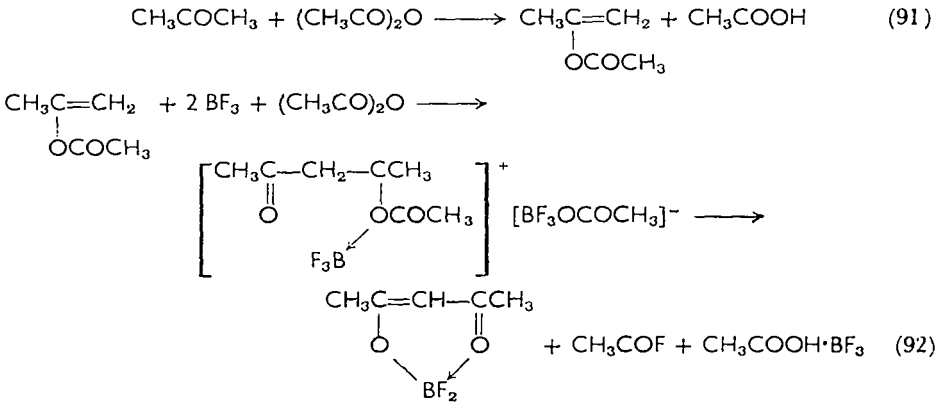
crucial to the preparative success of the reaction and is the reason for the apparent restriction to boron-like Lewis acid catalysts. Side-reactions include the catalysed self-condensation of the reactants. Yields normally, however, exceed 50%.

Mechanism—The currently proposed mechanism for these reactions must be considered to be based largely on guesswork and analogy. It is evident that the acylating agent probably does not attack a saturated carbon atom but that some kind of preliminary enolization occurs. In all real Lewis acid systems some Brønsted acid also exists (if only in traces) and this provides a rapid route to enolization (reaction 88). Electrophilic attack on the enol follows (90). Of the two possible enols from an unsymmetrical ketone, that to a methylene rather than to a methyl group provides the more nucleophilic carbon atom. This is probably why these acid-catalysed acylations yield predominantly methylene derivatives in such cases. This fact is useful since basic catalysis leads mostly to attack at the methyl group (see section II.H.1.b above). The product can often be

$$CH_3COCH_2R^1 + BF_3 + HF \rightleftharpoons CH_3{-}\underset{\displaystyle HO:BF_3}{\overset{|}{C}}{=}CHR^1 + HF \qquad (88)$$



isolated as the boron complex (**19**). This complex can also form from the *O*-acylated substrate (perhaps as in equations 91, 92) and this may be the reason why *O*-acylation does not prove a major complication in these reactions. Acyl fluorides have been isolated from the reaction mixtures.

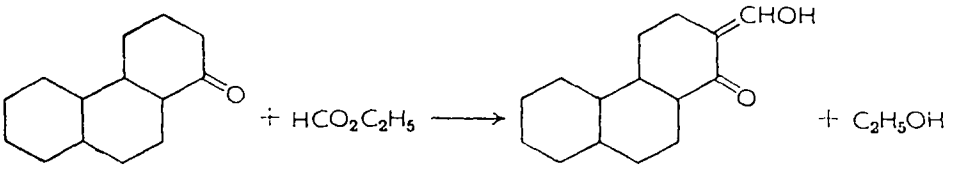


Some Brønsted acids (e.g. $HClO_4$) can also, in conjunction with anhydrides, effect the *C*-acylation of ketones. However, reaction is commonly accompanied by *O*-acylation[1], which is not surprising since it doubtless proceeds via the enol. As with basic catalysis (section II.H.1.b above), the factors which determine the balance between *O*- and *C*-acylation are little understood.

2. Formylation

Boron trifluoride-catalysed formylations, analogous to the acylations discussed above, have not been attempted. As noted in section II.E.2.b, formic anhydrides are unsatisfactory reagents.

A limited number of base-catalysed formylations have, however, been accomplished by reaction of formic esters with ketones and similar compounds[10,35]. The product, if formally a β-keto aldehyde, often exists mainly in the enolic form (equation 93). The reaction conditions used are similar to those described in section II.H.1. above for acylation.



(93)

Attempts to use formyl fluoride and sodium derivatives do not appear to have been yet made.

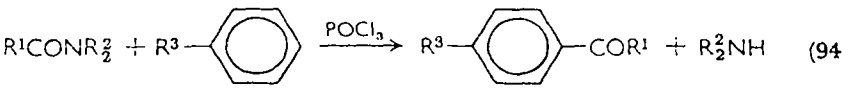
III. INDIRECT ACYLATION AND FORMYLATION OF HYDROCARBONS

The reactions coming under this heading differ from the direct acylation and formylation processes discussed earlier in that, while the carbonyl carbon atom is introduced in an electrophilic substitution by the reagent–catalyst combination as before, the carbonyl *oxygen* atom either is not, or alternatively when first introduced has little of its eventual double-bond character. The carbonyl unit is established during a subsequent step. Hence the carbonyl group is not introduced in a single process and for this reason these reactions are termed *indirect*. Strictly speaking they all involve an initial alkylation followed by some secondary process which is often oxidative hydrolysis. While all the reactions are examples of equation (1), the variations encountered in the structure of $RC(=Z)-Y$ are far greater than those involved in direct acylation. Moreover the exact reaction schemes are in several cases still matters for conjecture. For these reasons comprehensive generalizations about the effects of variations in R and Y cannot be made and the major subdivisions in this section, therefore, correspond to the types of reagent rather than to the types of substrate.

A. The Use of Carboxylic Acid Amides and Phosphorus Oxychloride

1. Introduction

This reaction may be used for both acylation (94) and formylation (95) depending upon whether a formamide or a higher amide is employed[81]. The reaction with formamides is usually called the Vilsmeier aldehyde synthesis[35,81].



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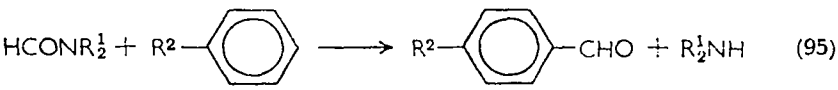


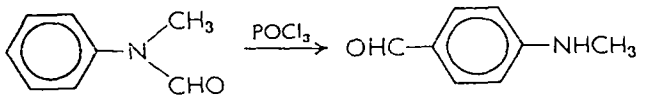
(95)

Because the reagent has the form RCOY, these processes lie nicely between the direct routes discussed in section II, which all employ reagents of this form, and the other indirect processes to follow, which do not. Direct acylation by amides has been very little studied[13]. The poorness of NR_2 as a leaving group means that very active substrates and powerful catalysts are normally necessary to provide reaction. With such powerful catalysts (e.g. $AlCl_3$) the amide is probably converted into the corresponding acyl halide, the true reagent being then not the amide at all. The secret of the success of Vilsmeier-type processes is that the catalyst–reagent complex is of such a nature that the role of the leaving group in the main substitution process is transferred from the NR_2 group to an oxygen atom (see section III.A.2.b below). A successful outcome is, however, still limited to cases involving rather reactive hydrocarbons. Nevertheless, because of the restricted nature of available direct formylations, the Vilsmeier method is of great importance and has received wide application in recent years[35,81]. It employs readily available starting materials and is also successful with compounds containing amino or hydroxyl groups—groups which usually lead to difficulties in direct Friedel–Crafts processes. It is in this latter context that the related acylations with phosphorus oxychloride have proved most valuable.

2. Aromatic hydrocarbons

a. Scope and reaction conditions. Unsubstituted amides and formamide itself have occasionally been employed as reagents but *N*-alkyl and

N-aryl derivatives are both more usual and more reactive. The commonest reagents for formylation are *N*-methylformanilide (used in the original work of Vilsmeier and Haack[82]) and dimethylformamide. Mild conditions (temperatures often below 40°) are usual, especially with formanilides, because of the chance of transformylation (equation 96). Most types of aromatic compound more

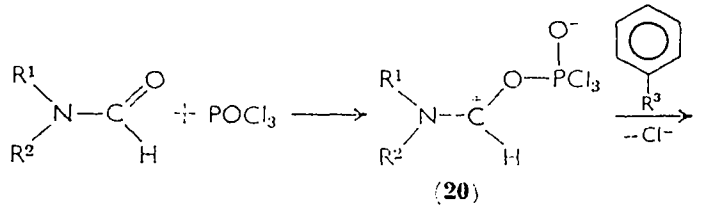


(96)

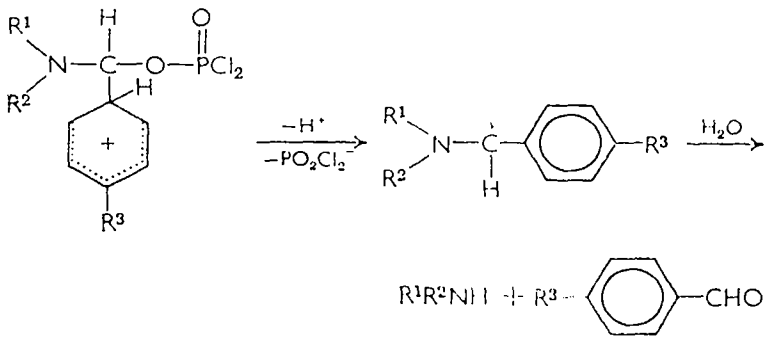
reactive than alkylbenzenes and -naphthalenes are satisfactory substrates. The reaction is also especially suitable for heterocyclic compounds (which are often destroyed by normal Friedel–Crafts catalysts).

Phosphorus oxychloride (or oxybromide) is the usual catalyst but phosgene and thionyl chloride have also been successfully employed with amides derived from secondary amines. A molecular equivalent of catalyst is required because it is not regenerated during the reaction. Strictly speaking, therefore, the reactions are not catalytic. Owing to the good solvent properties of formamides, an added solvent is often unnecessary. When required, most halogenated hydrocarbons are satisfactory.

b. Mechanism. The mechanism of these reactions is rather uncertain



(**20**)

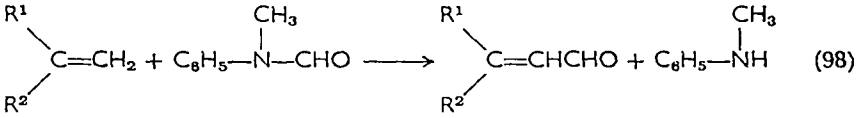


(97)

and current schemes are largely based on the reaction products, on the necessity for final hydrolysis, and on the analysis and spectroscopic characterization of various complexes like **20** isolated from the reaction mixtures. While isolated complexes are not *necessarily* reaction intermediates and while their exact structures are still debated, nevertheless most workers in the field are in apparent general agreement about the essentials of the reaction[35,81]. The particular scheme favoured by Zollinger[83] is (97). As noted previously, the reaction is essentially an electrophilic alkylation of the aromatic hydrocarbon. This accounts for the usual *ortho–para* orientation[81]. The finding that phosgene and thionyl chloride are only successful with some amides does not appear to have been satisfactorily explained.

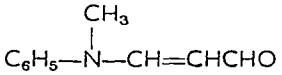
3. Olefinic hydrocarbons

a. Scope and reaction conditions. Few examples of acylation of olefins using amides and phosphorus oxychloride appear to exist[81]. This seems a promising field for exploration, since some most interesting formylations have been achieved[35,81]. Reaction usually takes place readily, simply on mixing the reagents, and the Vilsmeier method is one of the best routes to α,β-unsaturated aldehydes (equation 98).



(98)

If R^1 is aryl, R^2 may be hydrogen, an alkyl or a heterocyclic group. Unsaturated aldehydes may also be prepared by a modification of the usual reaction, devised by Jutz[84]. He employed vinylogues of the normal reagents, e.g. **21** and **22**. These compounds react readily with



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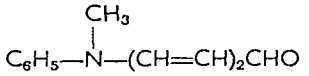
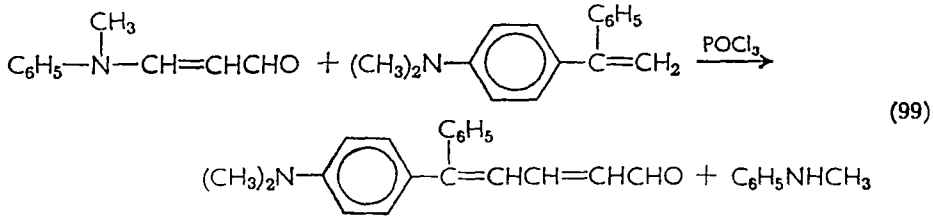


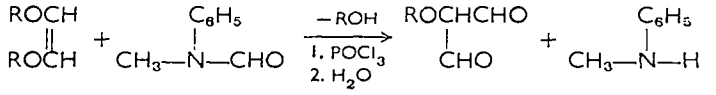
(22)

reactive aromatic substrates or with arylethylenes in chloroform (equation 99). Azulene also participates in these processes, which are

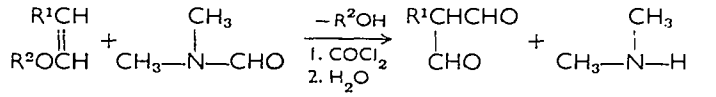


(99)

clearly effective because of the transmission of the positive charge along the conjugated system. Other[85] more involved reactions lead to the formation of dialdehydes from alkoxyethylenes (equations 100, 101).



(100)

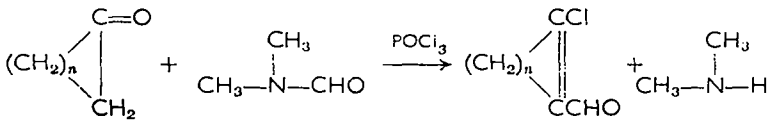


(101)

b. Mechanism. The mechanism of the more straightforward of these olefinic reactions is doubtless analogous to that outlined in section III.A.2.b above for aromatics. The more complex reactions (100, 101) obviously contain other species and other stages. It is evident, however, that cases of *addition* of the reagent to the double bond, analogous to the additions found with olefins in direct acylations (section II.F.1.a), would not be expected in the present context. All these processes warrant further study.

4. Saturated aliphatic hydrocarbons

Vilsmeier processes would not be expected to be effective for these substrates except for substituted compounds with very active α-hydrogen atoms. The processes (102) have been reported[86].



(102)

(n = 3–6)

B. The Use of Nitriles

1. Introduction

In this reaction a group —C(R^1)=NR^2 is introduced into a hydrocarbon. This group is subsequently hydrolysed to give a ketone or an aldehyde. The ketone synthesis, known generally as the Houben–Hoesch reaction[87], employs a nitrile (R^1CN) and catalysis by hydrogen chloride, often in the additional presence of zinc chloride or aluminium chloride. As will become evident in what follows, the group R^2 varies with the reaction conditions, one

variation being the scheme (103) in which a ketimine hydrochloride

$$RCN + HCl + ArH \xrightarrow{ZnCl_2} ArC(R)=NHHCl \xrightarrow{H_2O} ArCOR \qquad (103)$$

is formed. The corresponding aldehyde synthesis, which was the earlier of the two reactions to be devised and which clearly influenced Hoesch[87], is known as the Gattermann synthesis[35,88]. It employs hydrogen cyanide and hydrogen chloride, again often in the presence of aluminium chloride, zinc chloride or some other Lewis acid. Gattermann developed this synthesis because of the failure of the Gattermann–Koch reaction (section II.E.2.b) to formylate phenols. As with the Houben–Hoesch process, the intermediates have various compositions. One of the simplest is illustrated in equation (104).

$$HCN + HCl + ArH \xrightarrow{AlCl_3} ArCH=NHHCl \longrightarrow ArCHO \qquad (104)$$

2. Acylation of aromatic hydrocarbons

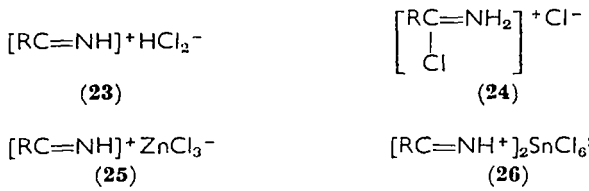
a. Scope and reaction conditions. The substituting agents in these reactions have normally been rather poor electrophiles and under such conditions only particularly reactive compounds are suitable substrates. Thus the applications of the reaction have been largely restricted to polyhydric phenols and their ethers, and to reactive heterocyclics such as pyrrole and furan[87]. However, it seems possible to achieve a gradation in the reactivity of the substituting agent. The mildest conditions employ nitrile and hydrogen chloride alone; added zinc chloride at ordinary temperatures, with ether as the solvent, provides a somewhat stronger reagent; ferric chloride, or especially aluminium chloride, in ether, or better, in an halogenated benzene solvent at temperatures of 50° and over, yields a potent reagent. With the latter recipes, even alkylbenzenes may be attacked in good yield, though aromatic compounds with electron-attracting substituents do not react significantly[87]. Hence the use of halobenzene solvents. The direction of substitution is, of course, normally *ortho–para*. Sometimes side-reactions occur when the most active position is blocked. In common with other acylations involving strongly acidic catalysts, aromatic amines are unsatisfactory substrates.

So far as the nitrile is concerned, electron-attracting substituents appear to favour reaction. This point is discussed more fully below. A wide variety of substituted nitriles may be used successfully and an excess of this component is often beneficial.

The intermediate products usually precipitate from solution and this facilitates their isolation and hydrolysis. The essential substitution occurs, however, under homogeneous conditions.

b. Mechanism. It may be fairly said that current ideas about the mechanism of this and of the related Gattermann synthesis are chaotic. A wealth of possible intermediates have been either discussed or suggested and it is a major difficulty to decide which of them are essential to the mechanism. Moreover, there is often disagreement about their proper composition[87]. No adequate kinetic data appear available. Of the two reactions, the present involving nitriles is probably the more straightforward. As with all acid-catalysed aromatic substitutions, the process may be divided into stages. In this case we have (*a*) the production of the substituting species from reagent and catalysts, (*b*) the substitution step and (*c*) the hydrolysis of the initial non-ketonic product. It is stage (*a*) which presents most difficulties.

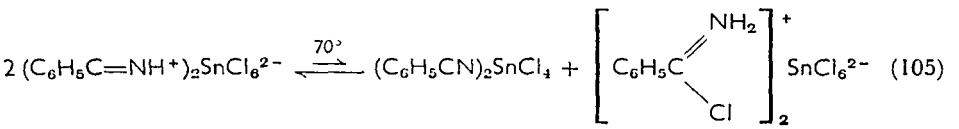
With metal halides, nitriles form stable complexes in solution[89], such as $(RCN)_2ZnCl_2$ or $RCN{\rightarrow}BF_3$. They also interact with hydrogen halides[87c,90]. It may be that the 1:1 complexes, RCN·HCl, are usually unstable in the absence of a second molecule of either a Brønsted or a Lewis acid. In the presence of excess of acid complexes like **23**, **24**, **25** and **26** are thought to form[90,91]. These species



(23) **(24)**

(25) **(26)**

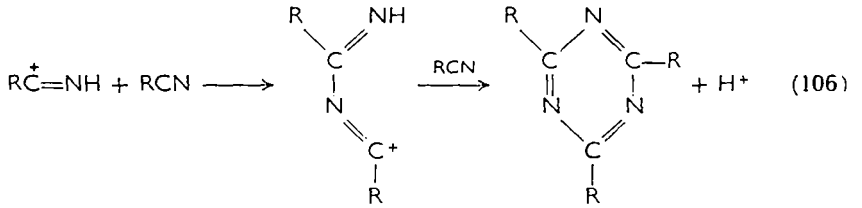
will exist as ion pairs in media of low dielectric constant and no doubt be further solvated by other molecules of nitrile and/or acid. With hydrogen chloride and acetonitrile it is considered that form **23** is more stable than **24**, with the reverse true for the corresponding hydrogen bromide system, but the balance between the two sorts of species appears to depend upon R, on the temperature and probably also on the solvent. With benzonitrile Klages[91] has observed equilibria like (105). Thus it seems probable that in solutions of



(105)

the nitrile and hydrogen chloride alone, species such as **23** or **24** exist, and when zinc or aluminium chlorides are added species like **25** or **26** are also formed. The most polar species are likely to result with aluminium chloride and this would account for the high reactivity observed with this catalyst. Electron withdrawal by R will increase the carbonium ion character of the complex but make its formation more difficult, because of the lowered electron density on nitrogen. The fact that electron withdrawal sometimes facilitates further reaction appears to indicate that the polarity of the complex when attacking the substrate is more important than the amount of complex available. However, substituent effects are still very uncertain[87c].

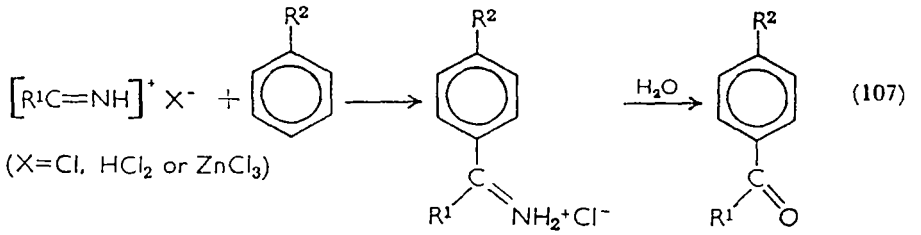
A complicating feature of the reactions, emphasized by the work of Grundmann[92], lies in the possibility of the polymerization of the nitrile. Species like **23** or **25** may be attacked by other nitrile molecules and perhaps (though this point is still debated[87c]) lead in stages to 1,3,5-triazines or their corresponding acid adducts (equation 106).



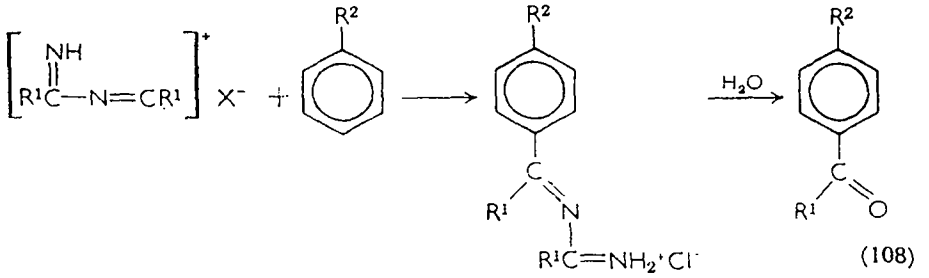
(106)

(27)

These processes appear normally rather slow and take place best in the presence of aluminium chloride, and when electron-withdrawing substituents are present in the nitrile. If it may be supposed that all the species **23** to **27** can attack the aromatic substrate, then the essentials of the second and third phases of the mechanism can be shown as in equations (107) and (108). The predominant species



(107)



(108)

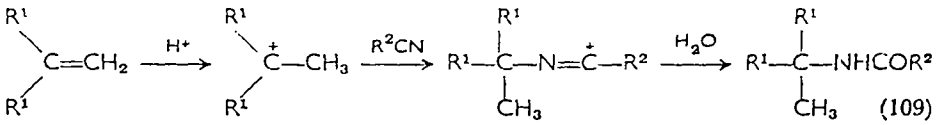
involved will clearly depend upon the system and the temperature. The choice of temperature is of great importance in these reactions[87c].

The depicted intermediate ketimine and substituted ketimine hydrochlorides may be isolated, though the relative importance of the latter in the ketone synthesis is not yet clear[87]. When formed, however, the yield based on RCN can never be 100% and the observation of increased yields in the presence of excess of nitrile may be a pointer to their frequent involvement. The extent to which a rapid preliminary polymerization to triazines and a subsequent slow depolymerization to provide the substituting agents may be concerned in some cases, is also not clear. This possibility is very much more important in the Gattermann synthesis (section III.B.4 below).

3. Acylation of olefins and saturated aliphatic hydrocarbons

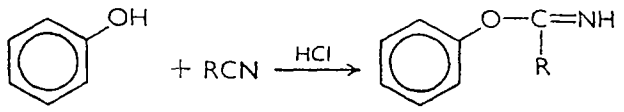
In contrast to the situation found with Friedel–Crafts reactions there appear to have been no successful acylations of olefins under Houben–Hoesch conditions[87]. The usual product is a substituted amide. It is relevant to the reaction mechanism to discover the reason for this.

In both types of reaction mixture there must always be some free Brønsted acid (and frequently some very powerful Brønsted acid like H_2ZnCl_4). The olefinic substrates, which are normally more basic than aromatic compounds, will, therefore, often be partially protonated to carbonium ions and these ions can then react with suitable basic entities in the system. In standard Friedel–Crafts syntheses there is usually little basic material available—apart from the anion of the acid which provided the proton—and therefore the olefin is eventually acylated, but under Houben–Hoesch conditions the nitrile reagent itself is particularly basic and it seems clear that here the favoured reaction is, therefore, that between the carbonium ions and the nitrile (equation 109) rather than between protonated nitrile and free olefin—the process which would lead to acylation.

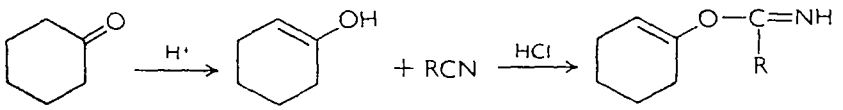


(109)

Among the few reactions attempted with saturated aliphatic compounds, that with cyclohexanone[93] is particularly instructive. Under the influence of acid catalysts some enol will form and this species provides both an unsaturated centre and a hydroxyl group. As with monohydric phenols under mild Houben–Hoesch conditions (equation 110)[87], it is the hydroxyl group which is attacked and an imino ester results (equation 111). In each case it is clear that the



(110)



(111)

most basic centre is oxygen (rather than carbon) and that this has been preferentially attacked by the reagent. (The cyclohexanone example is, in fact, more complex than is shown in (111), further reaction occurring at the double bond.) The reactions of various phenols under Houben–Hoesch conditions[87] illustrates how, in electrophilic substitutions generally, their behaviour often displays a balance of two effects. With polyhydric compounds the ring carbon atoms can be more basic than the phenolic oxygen atoms[94] and preferential nuclear substitution therefore results, whereas with monohydric phenols the oxygen atom is attacked. If, however, this atom is protected by coordination with any Lewis acid available in the system, nuclear substitution again results—provided that a sufficiently active attacking agent is also present (cf. section II.E.1.a).

4. Formylation of aromatic compounds

a. Scope and reaction conditions. In the Gattermann aldehyde synthesis[35,88] the reaction conditions are much the same as for acylation, except that hydrogen cyanide, or a suitable source of this substance, replaces the nitrile as reactant and that benzene and halobenzene solvents are more common than ether. Reactive aromatic compounds are substituted at temperatures below 40° but alkylbenzenes need temperatures closer to 100°. This fact may be associated with

available substituting agents at the different temperatures (see below). The use of free hydrogen cyanide as reactant, as in the original Gattermann method, provides experimental hazards and various modifications, beginning with that of Adams[95], who employed zinc cyanide, have been devised.

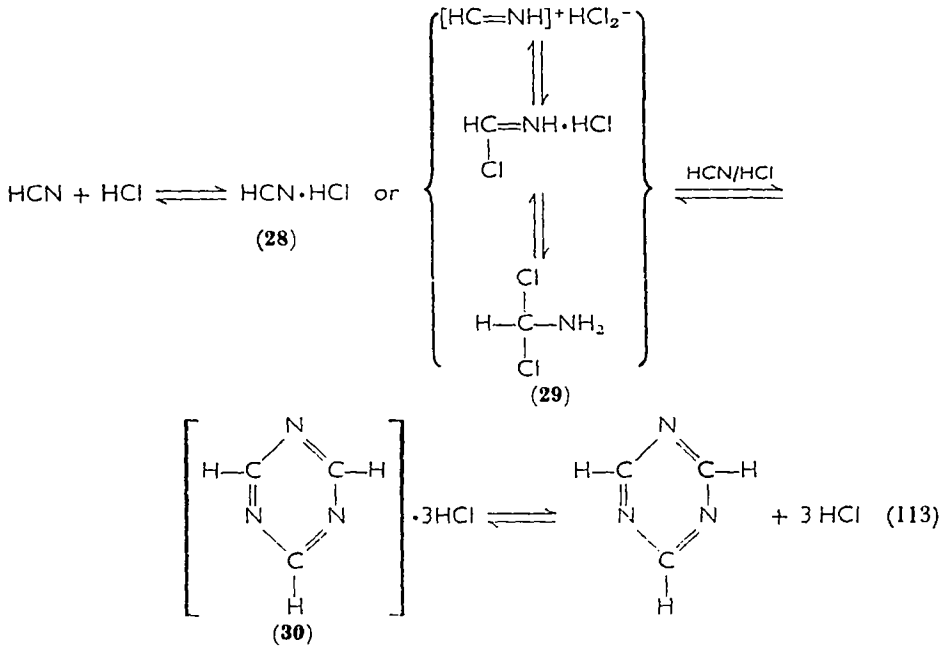
In the presence of hydrogen chloride, zinc cyanide provides both hydrogen cyanide and the zinc chloride catalyst *in situ* (equation 112). If more powerful catalysts are necessary (e.g. $AlCl_3$), these can be

$$Zn(CN)_2 + 2\,HCl \longrightarrow ZnCl_2 + 2\,HCN \qquad (112)$$

subsequently added. Other metal cyanides have also been used (e.g. NaCN and KCN) and a variation introduced by Karrer[96] involves BrCN with hydrogen chloride and a Lewis acid catalyst. Only Gattermann's original procedure and Adams' modification of it have, however, been extensively exploited. (No alternative procedures are necessary in the Houben–Hoesch reaction because, of course, hydrogen cyanide is not involved.)

The choice of solvent seems particularly important in the Gattermann synthesis and can affect both the yield and the position of substitution[35]. It is not at all clear exactly why this should be but in view of the complexity of the mechanism it is not unduly surprising.

b. Mechanism. This appears to be along the same general lines as

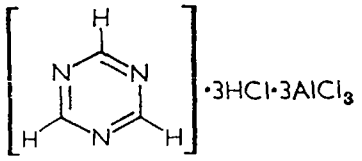


for acylation (cf. section III.B.2.b above) but the number of possible intermediates is now increased, hydrogen cyanide appearing more versatile than nitriles in this respect. Most of the investigations have concerned the behaviour in solution, either of hydrogen cyanide and hydrogen chloride alone, or of these substances in the presence of aluminium chloride. The zinc chloride systems have not received much study. This is unfortunate because they would probably provide more reproduceable phenomena than those containing aluminium chloride.

Hydrogen chloride and hydrogen cyanide alone interact with the eventual production of triazines and their acid derivatives[97]. In solution the positions of the various equilibria are uncertain and no doubt depend upon solvent and temperature. Intermediate stages in the polymerization may provide, apart from species **28** and **29**—which have probably never been isolated—species[98] such as **31** and **32**.

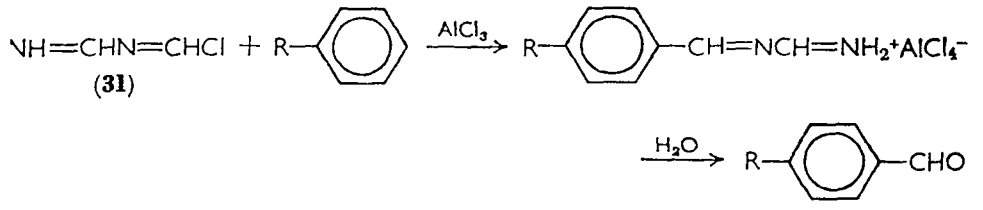
$NH{=}CHN{=}CHCl$ (**31**) $CHCl_2NHCHClNH_2$ (**32**)

In the presence of aluminium chloride, hydrogen cyanide alone is considered to form a complex $AlCl_3 \cdot 2HCN$, which on reaction with hydrogen chloride at moderate temperatures yields mainly[98] **31**. In general, mixtures of hydrogen chloride and hydrogen cyanide in the presence of aluminium chloride yield aluminium chloride derivatives of **30** (e.g. **33**) but these are rather unstable and at



(**33**)

moderate temperatures break down in stages to their precursors, **31** being considered the main intermediate[97]. Under these conditions the predominant substitution product with an aromatic substrate is a methyleneformamidine salt (equation 114); **31** may exist in solution

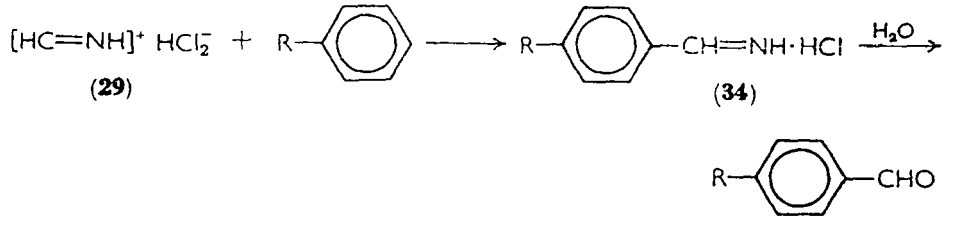


(**31**)

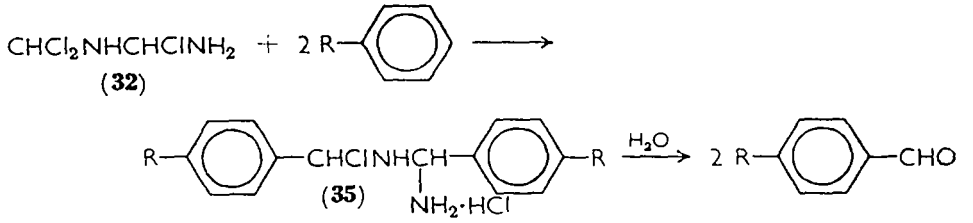
(114)

coordinated to aluminium chloride via nitrogen and excess of catalyst may, therefore, be beneficial. A variety of possible minor variations on equation (114) are clearly possible.

In the absence of Lewis acid or at low temperatures species **28**, **29** or **32** may participate primarily, leading to an aldimine (**34**) or dialdimine (**35**) salt respectively. Other complications exist, especially



(115)

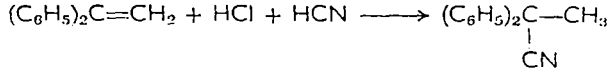


(116)

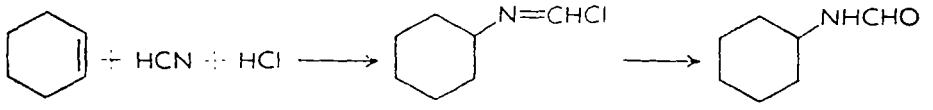
for phenols, when the hydroxyl group is often esterified (cf. section III.B.3 above). The Gattermann synthesis appears a remarkably involved process mechanistically in view of the simplicity of the reagents and the often excellent yield of product[35].

5. Formylation of olefins

As with the Houben–Hoesch procedures (section III.B.3 above) little success has been met with olefins[99]. Again the indications are of initial carbonium ion formation from the substrate followed by attack by the cyanide ion as in equation (117) or by the basic end of the iminoformyl chloride (equation 118).



(117)



(118)

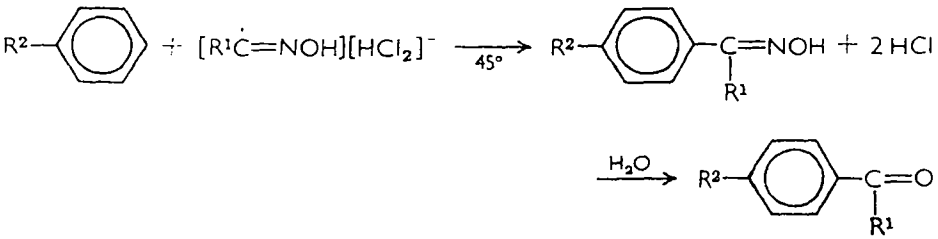
C. The Use of Metal Fulminates

Fulminates, especially that of mercury[100], form on treatment with hydrogen chloride a compound which may be considered the oxime of formyl chloride (equation 119). If a reactive aromatic compound

$$Hg(ONC)_2 + 4\,HCl \longrightarrow 2\,ClHC{=}NOH + HgCl_2 \qquad (119)$$

(e.g. phloroglucinol) is present the corresponding aldoxime is formed[101] and this may be hydrolysed to the aldehyde (equations 120 and 121 with $R^1 = H$). Nitrobenzene is a suitable solvent. With less reactive compounds (e.g. C_6H_6) the presence of (partially inactivated) aluminium chloride assists the reaction. It is clear that these processes

$$ClCR^1{=}NOH + HCl \rightleftharpoons R^1\overset{+}{C}{=}NOH[HCl_2]^- \qquad (120)$$



(121)

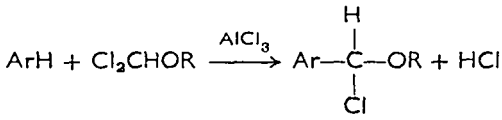
are similar to those discussed in section B above. In this case the unit —C(R)=NOH is being introduced and the probable substituting species, $[R\overset{+}{C}{=}NOH][HCl_2]^-$ or $[R\overset{+}{C}{=}NOH][AlCl_4]^-$, are very akin to the simplest involved in the Houben–Hoesch and Gattermann syntheses.

The useful processes are formylations, i.e. those in which R = H; otherwise the reagent is the oxime of an acyl halide and since free acyl halides are readily available (whereas formyl halides are not) no advantage is obtained in making the oxime. The method has, however, been little exploited as an aldehyde synthesis. If anhydrous aluminium chloride is used, it tends to dehydrate the oxime and nitriles become a prominent product[101].

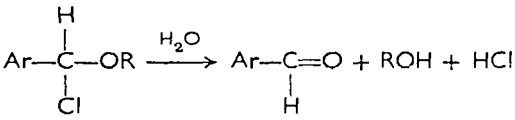
D. The Use of Dichloromethylalkyl Ethers

Dichloromethylalkyl ethers have the structure Cl_2CHOR. In solution in methylene chloride or carbon disulphide and in the presence of the usual Friedel–Crafts catalysts, these substances react with aromatic compounds to provide α-alkoxybenzyl chlorides

(equation 122). These substances are unstable and lead to the aldehyde on hydrolysis (equation 123). Reaction is relatively fast and



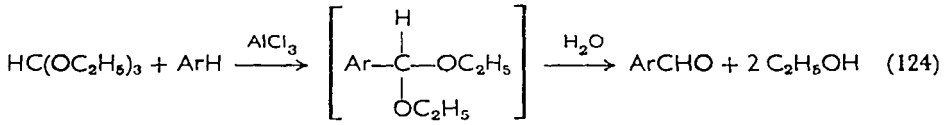
(122)



(123)

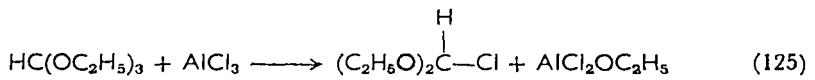
good yields are obtained with a wide variety of aromatic compounds. One or two molecular proportions of catalyst are used, though the reason is not apparent. This reaction is essentially a straightforward Friedel–Crafts alkylation, the resulting product being unstable. There seems no reason why the corresponding phenyl ethers should not be equally satisfactory, nor why compounds like Cl_2CROR should not lead to ketones by this route. The method discovered by Fischer[102] has so far been exploited mainly by Rieche, Gross and Hoeft[103]. Further details of mechanism can only be guessed at, at the present time, but an understanding of normal Friedel–Crafts alkylation (so far as it exists) should directly apply.

A related process also developed by the same authors[103] employs alkyl orthoformates and aluminium chloride. The overall reaction is given in (124). It seems very probable that the ketal of formyl

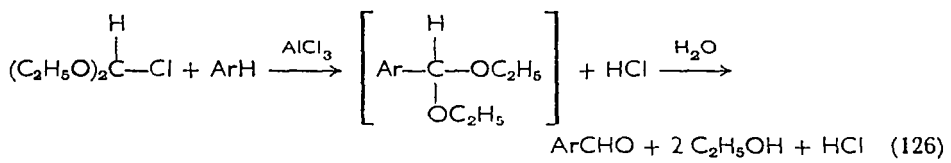


(124)

chloride is intermediately formed (125) which then acts as an alkylating agent in conjunction with more aluminium chloride (126).



(125)

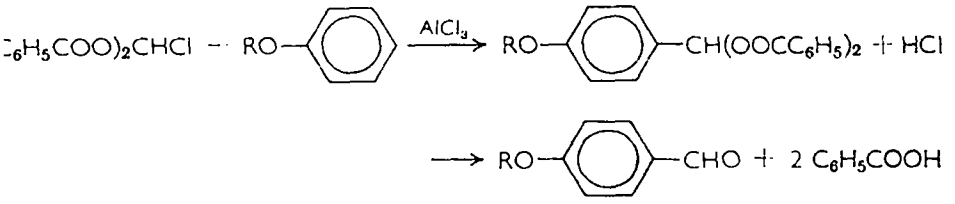


(126)

To date, the reaction has only been used with phenols as substrates.

E. The Use of Chloromethylene Dibenzoates

Reactive aromatic compounds (e.g. anisole) interact[104] with chloromethylene dibenzoates in the presence of aluminium chloride (and presumably other catalysts) to yield intermediates unstable to hydrolysis (equation 127). There appear only a few isolated applications of this process.



(127)

It is not difficult to invent other possible routes to aldehydes and ketones along the lines of those discussed in sections III.D and III.E; the principles are apparent. One such has recently appeared[105]; it employs benzotrichloride and leads to benzophenones.

F. The Use of Chloroform and Alkali

1. Introduction

Chloroform, in conjunction with powerful Lewis acids, is clearly a potential reagent for effecting reactions analogous to those discussed in sections III.D and III.E above. However, the powerful electron drain provided by the three chlorine substituents also renders the hydrogen atom in chloroform susceptible to attack by bases. It has been found that under aqueous alkaline conditions chloroform is hydrolysed, yielding eventually carbon monoxide, hydrogen chloride and formic acid. The initial step is considered[106] to be a rapid reversible formation of the carbanion CCl_3^- (equation 128) which subsequently rejects a chloride ion in a slow step (129). The intermediate dihalocarbene then undergoes further solvolysis (130).

$$HCCl_3 + OH^- \rightleftharpoons CCl_3^- + H_2O \quad (128)$$

$$CCl_3^- \longrightarrow :CCl_2 + Cl^- \quad (129)$$

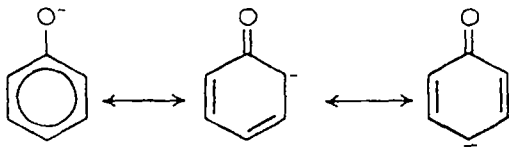
$$:CCl_2 \xrightarrow{H_2O} \text{Products} \quad (130)$$

When alkaline chloroform mixtures are used in formylation, this hydrolysis takes place but the carbene intermediates also attack the substrate. Formylation with chloroform and alkali is generally known

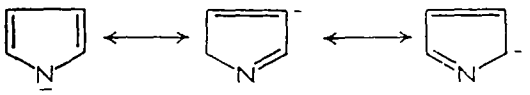
as the Reimer–Tiemann reaction after two of its earliest investigators[107].

2. Scope and reaction conditions

Suitable substrates are compounds which form carbanions readily under alkaline conditions and, to date, applications have been largely restricted to phenols and similar compounds, and to pyrroles (131, 132).

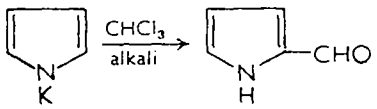


(131)

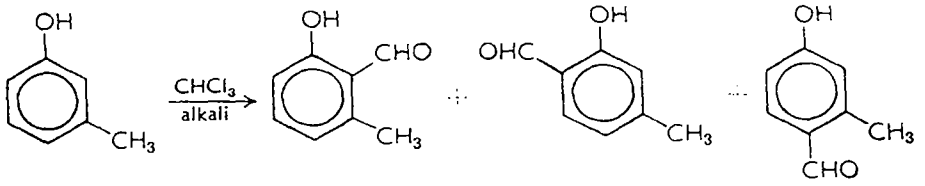


(132)

The usual reaction conditions[107] consist of heating the substrate with an excess of chloroform in the presence of 10% aqueous alkali for some hours at temperatures above 50°. Sometimes other solvents (e.g. ether, alcohol and pyridine) are added, though their effect is uncertain. Yields of aldehyde are low (rarely > 50%) and various, often highly coloured, by-products are formed in small amounts. The desired products are normally 2-substituted pyrroles (equation 133) and *o*- and *p*-substituted phenols (134). Among the by-products two



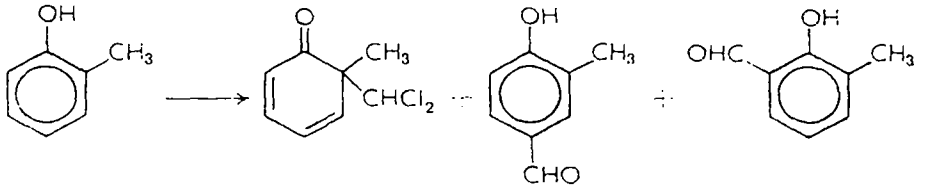
(133)



(134)

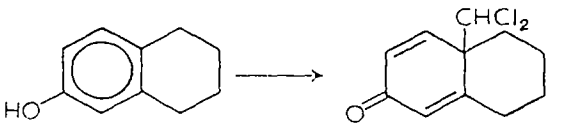
types are of particular importance and mechanistic significance. (*a*) When the usual site of substitution is blocked (i.e. occupied by a substituent other than a hydrogen atom) loss of aromaticity occurs

in addition to the normal formylations (equation 135). With poly-



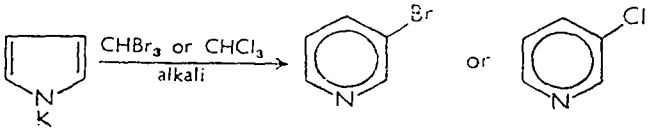
(135)

cyclic phenols, angular groups can be inserted[108] (equation 136). These products appear surprisingly stable towards hydrolysis. (*b*) In

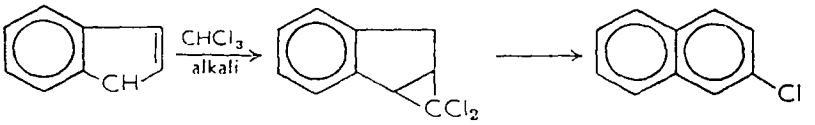


(136)

certain cases ring enlargement is observed, as shown for pyrrole in equation (137) and indene in (138).



(137)



(138)

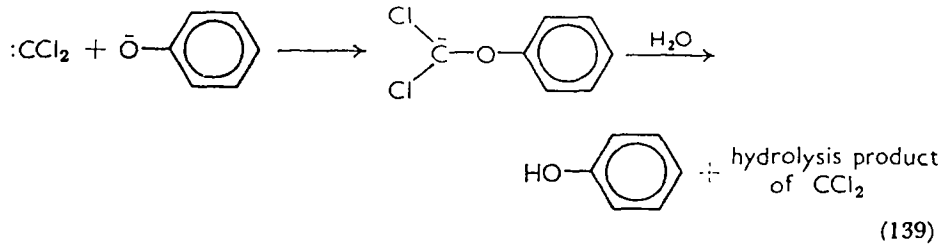
(36)

The effects of substituents in all these reactions is by no means clear[107]. This problem is made difficult by the very poor yields normally obtained, since these obscure inherent reactivities of the substrates towards the Reimer–Tiemann process.

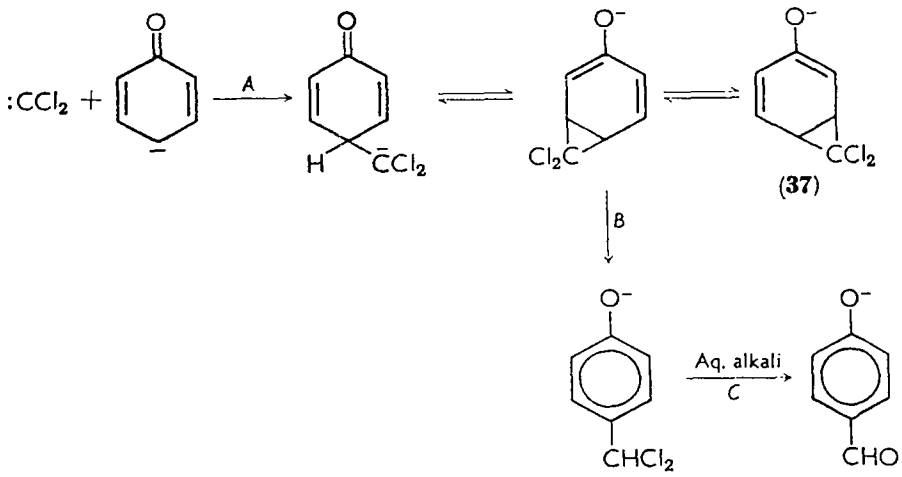
3. Mechanism

The allied work on the hydrolysis of chloroform[106] and the nature of the by-products outlined above both combine in a circumstantial implication of the dichlorocarbene as the active substituting agent. This species (like other radicals) apparently acts as a feeble electrophile (hence the necessity for anionic substrates) and attacks either

the phenolic oxygen atom (equation 139) or a ring position (140).

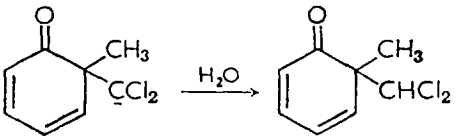


(139)



(140)

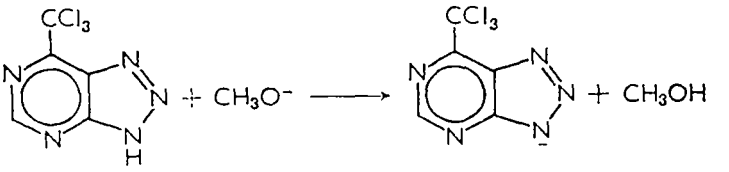
In (139) the phenoxide ion is only taking the role usually played by the hydroxide ion in catalysing the hydrolysis of chloroform. In (140) steps *A*, *B* and *C* lead to the aldehyde. Step *B* cannot occur when the substituted position carries no hydrogen[109] unless an external proton source, e.g. H_2O, is provided (equation 141). Species like **37**, for which there is evidence[110] (e.g. **36** in equation 138) can in suitable cases lead to the observed ring expansions.



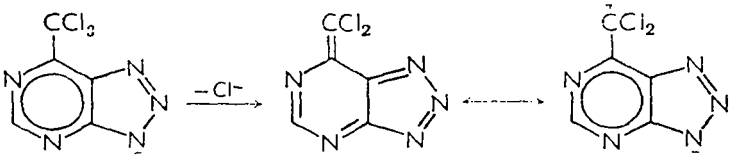
(141)

A recent interesting variation on the Reimer–Tiemann process employs 6-trichloromethylpurine in place of chloroform[111]. With sodium methoxide in methanol, this leads to the corresponding

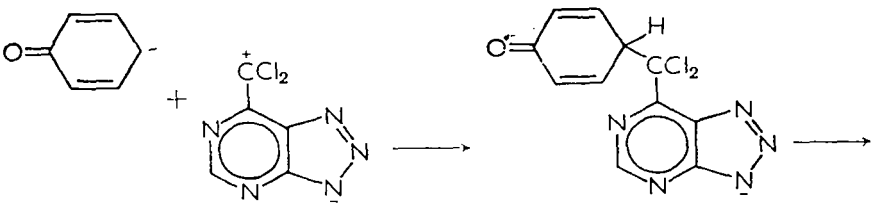
ketones on reaction with phenols (equations 142 to 144). As may be



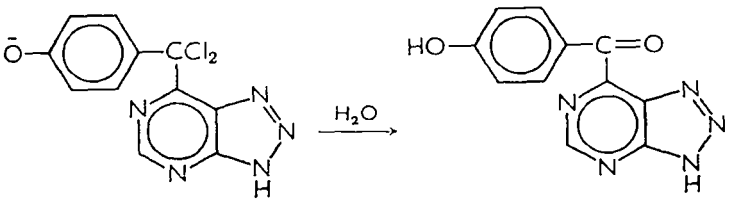
(142)



(143)



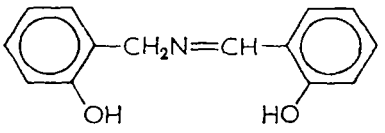
(144)



seen, a mechanism analogous to that given above for the Reimer–Tiemann process can be written[111]. The purine is effective because it contains an acidic hydrogen atom, together with a suitable conjugated system.

G. The Use of Hexamine in Formylation

The Duff reaction[112], which employs hexamine for the formation of *o*-hydroxyaldehydes from phenols and which may contain as a final step the hydrolysis of a species like **38**, could be considered an



(38)

indirect acylation. However, since this reaction—like the related Sommelet process[113]—involves an important prior oxidation stage, it is excluded from this chapter.

IV. CONCLUSION

The foregoing sections show that for reactive aromatic and heterocyclic compounds a variety of satisfactory procedures exist for acylation and formylation at carbon. It is this segment of the field which has received the most intensive study from both the preparative and mechanistic viewpoints. In comparison other classes of compound fare badly, though for olefins and for species containing acidic hydrogen atoms, one or two well-tried methods are available. It is clear that in principle, at least, the majority of the methods suitable for aromatic compounds should also be satisfactory for olefins, though with this class difficulties are often present owing to their tendency to undergo addition and polymerization. Nevertheless, in time, more than at present of the available aromatic substitutions should be extended to olefins and acetylenes. Those classes of compound for which the outlook is least promising are powerfully deactivated aromatic and saturated aliphatic hydrocarbons. In these the carbon atoms are so lacking in nucleophilicity that even the most powerful catalysts and reagents fail or, alternatively, destroy the substrate in subsidiary processes, rendering the yields poor and the products mixtures. For this group the other approaches to aldehyde and ketone synthesis given in this book appear likely to be the most rewarding.

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The Chemistry of the Carbonyl Group
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CHAPTER 6

Carbonyl syntheses through organometallics

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I. INTRODUCTION

The use of organometallic compounds for the synthesis of molecules containing the carbonyl group has been known for more than a century[1].

Organometallic derivatives of aluminum, cadmium, copper, lead, magnesium, mercury, sodium, tin and zinc have been shown[2-4] to react with acid halides to yield ketones, as represented by the general equation (1). The scope and limitations of the use of this reaction in

$$R^1\text{—}\overset{\overset{O}{\|}}{C}\text{—}X + R^2M \longrightarrow R^1\text{—}\overset{\overset{O}{\|}}{C}\text{—}R^2 + MX \qquad (1)$$

the laboratory-scale preparation of either simple ketones or various

polyfunctional derivatives containing a keto group have been reviewed[2-4] up to 1954. The reader is also referred to these reviews for detailed experimental considerations and procedures.

This chapter attempts to bring the subject up to date and deals largely with the mechanistic considerations and interpretations advanced for this reaction during the past ten years. In addition it has been considered pertinent to mention briefly the synthesis of organic carbonyl compounds by direct carbonylation reactions using metal carbonyls. The literature on this topic for the period to the end of 1960 has recently been reviewed[5].

II. THE USE OF ORGANOCADMIUM COMPOUNDS

A. Experimental Considerations

It was stated in the introduction that reaction (1) has been found to occur with the organic derivatives of a large number of metals. However, only a few of these organometallic reagents have been of general practical value. The organocadmium derivatives are thought to be most generally satisfactory[6].

The organocadmium compound is prepared from the respective Grignard reagent (preferably organomagnesium bromide) and anhydrous cadmium chloride in refluxing diethyl ether. (Organolithium compounds can be used instead of the Grignard reagents but this offers no particular advantage[6].) After all the organomagnesium compound has reacted (as checked by testing with Michler's ketone[3,6]) the ether solvent is replaced with anhydrous benzene and the acid chloride is then added to the organocadmium compound. The replacement of ether with benzene is advantageous for several reasons:

1. The ether tends to react with the acid chloride, in the presence of magnesium chloride, to form ethyl esters (equation 2).

$$RCOCl + C_2H_5OC_2H_5 \longrightarrow RCO_2C_2H_5 + C_2H_5Cl \qquad (2)$$

2. The side-reaction between the organocadmium reagent and the acid chloride (or the ketone formed) to yield a metallic enolate occurs less readily in benzene than in ether (equation 3).

$$R^1CH_2CdCH_2R^1 + R^2CH_2{-}\overset{O}{\overset{\|}{C}}R^3 \longrightarrow [R^2CH{=}\overset{O}{\overset{|}{C}}R^3]^-[R^1CH_2Cd]^+ + R^1CH_3 \qquad (3)$$

3. Efficient stirring of the heterogeneous reaction mixture (which is essential for good yields) is easier accomplished in the benzene solution.

4. The higher reflux temperature possible with benzene allows completion of the reaction in less than one hour, whereas several hours are necessary for completion with ether as solvent.

The experimental procedure is equivalent to a one-step process. The relatively ready availability of starting materials and good product yields make this a useful method for the synthesis of ketones.

These considerations have led to the use of this reaction for the syntheses of isotopically labeled carbonyl compounds[7].

B. Reaction with Acid Chlorides

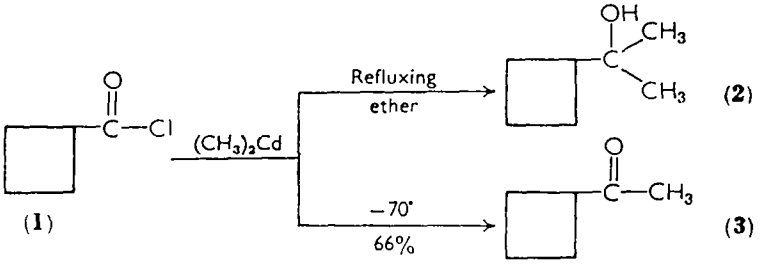
The first systematic investigation of the preparation of ketones by the reaction between organocadmium compounds and acid chlorides was carried out by Gilman and Nelson in 1936[6]. These authors obtained a number of dialkyl, alkyl aryl and diaryl ketones in yields ranging between 17–86%, but generally better than 50%. The

$$R^1X \xrightarrow[(\text{or Li})]{Mg} R^1MgX \xrightarrow[(\text{or } R^1Li)]{CdCl_2} R^1CdR^1 \xrightarrow{2\,R^2COCl} 2\,R^1COR^2 \qquad (4)$$

reactions involved in this preparation are shown in (4). The reaction occurs smoothly with both aliphatic and aromatic acid chlorides, though the former appear to be more reactive. However, one limitation of this reaction is that if the organic radical is alkyl it must be primary for satisfactory results[2].

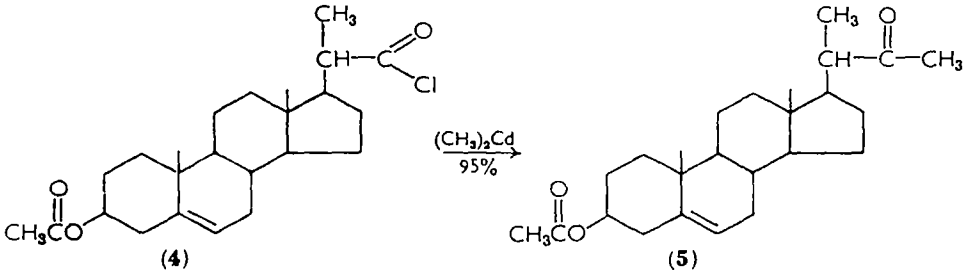
In general the reaction between the organocadmium compound and the acid chloride takes place with ketone formation. Carbinol formation through addition to the carbonyl group will occur only if the latter is unusually activated by some adjacent function. Even so this latter side-reaction can be minimized if the acid chloride is added to a solution of the organocadmium compound at low temperatures.

A typical example[8a] is provided by the reaction of dimethylcadmium with cyclobutanecarboxylic acid chloride (**1**). The use of a large excess of cadmium reagent and dropwise addition of the acid chloride **1** to a refluxing ether solution of dimethylcadmium furnished



exclusively the tertiary carbinol **2**. On the other hand, addition of the acid chloride (0·50 mole) to a well-stirred solution of the cadmium derivative (0·35 mole) at $-70°$ gave after a reaction time of one hour a yield of 66% of the desired ketone **3**.

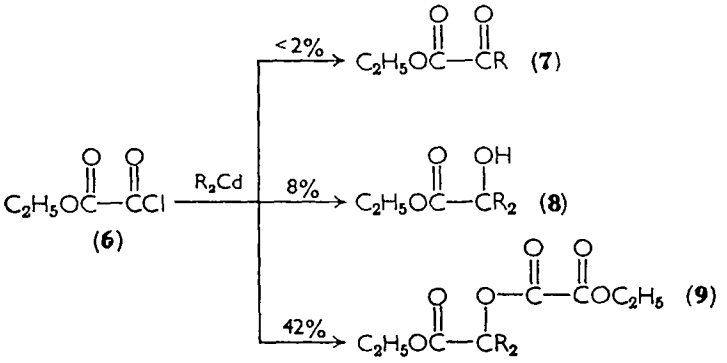
In contrast to the above conditions Cole and Julian[8b] reported that best yields (75–95%) of steroidal methyl ketones such as **5** were obtained when several times the theoretical amount of dimethylcadmium was used, even though an excess of the reagent might have been expected to be harmful through further action on the acetate or the ketone groups.



(4) (5)

The effect of activating adjacent groups in changing the course of the reaction in the synthesis of ketones through organocadmium compounds was demonstrated by the reported attempt to synthesize α-keto esters by this method[9].

Inverse addition of the organocadmium reagent to ethoxalyl chloride (**6**) accompanied by high-speed stirring at $-30°$ to $-40°$ gave less than 2% yields of the α-keto ester **7**. The main products were the α-hydroxy ester **8** and its ethoxalyl derivative **9**.



The same authors[9] investigated the possibility of changing the course of the reaction by steric inhibition of the addition reaction. The use of diisobutylcadmium raised the yield of the α-keto ester **7**, R = isoC$_4$H$_9$, to only 7%. On the other hand with di-*o*-tolylcadmium the α-keto ester **7**, R = *o*-CH$_3$C$_6$H$_4$, was obtained as the exclusive product in a yield of 50%.

In connection with the effect of activating adjacent groups, of interest are the results of reactions of organocadmium compounds with chlorides of dicarboxylic acids, where diketones are expected to be formed. The reaction of phosgene with dialkylcadmium gave[10] the expected symmetrical ketone (**10**) in yields of 20%. With oxalyl

$$COCl_2 \xrightarrow[20\%]{R_2Cd} \underset{(10)}{R_2CO}$$

chloride, the reaction does not stop at the diketone stage, the compound isolated[6,10] being the keto alcohol **11**. With higher diacid

$$(COCl)_2 \xrightarrow{R_2Cd} [RCOCOR] \longrightarrow \underset{(11)}{RCOCR_2OH}$$

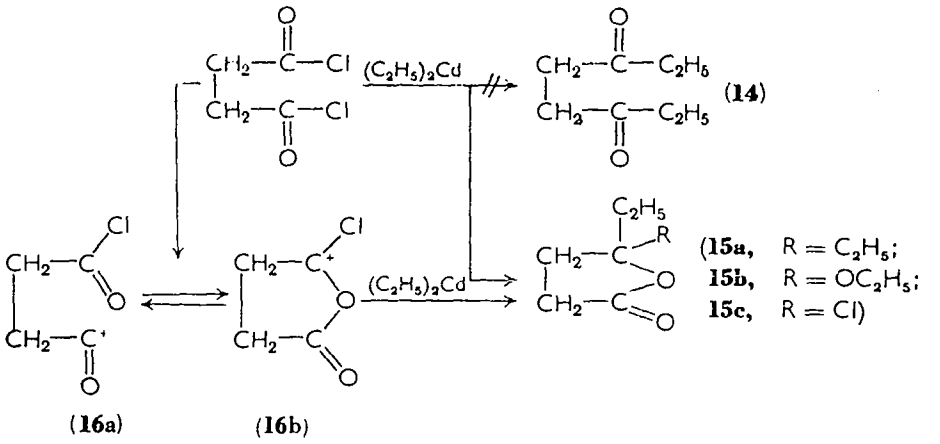
chlorides (**12**, $n \geq 4$) good yields of diketones **13** have been reported[10].

$$\underset{(12)}{ClCO(CH_2)_nCOCl} \xrightarrow{R_2Cd} \underset{(13)}{RCO(CH_2)_nCOR}$$

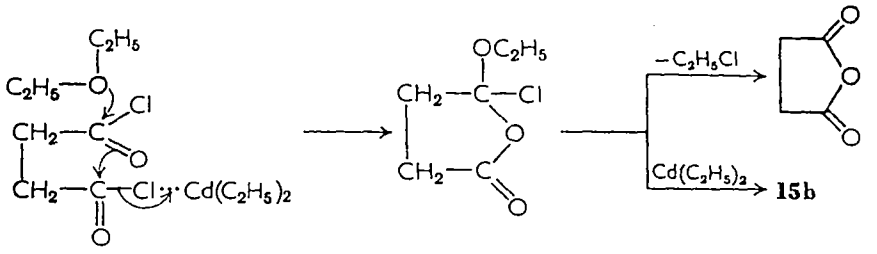
With the lower homologs (**12**, $n = 1, 2, 3$), side-reactions due to cyclizations appear to predominate and very poor yields of the diketones are obtained[10].

It is remarkable that the dichlorides of monoethyl- and diethylmalonic acids are recovered unchanged from the reaction with organocadmium compounds[10].

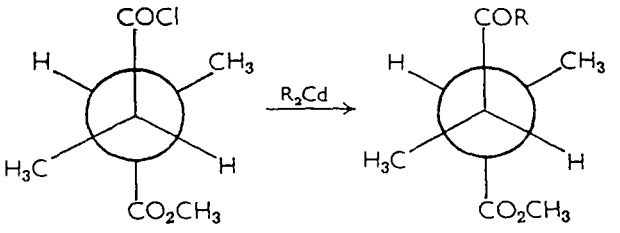
The reaction of diethylcadmium with succinyl dichloride[11] (**12**, $n = 2$) gives no 3,6-octanedione (**14**) but yields instead γ-ethyl-γ-caprolactone (**15a**) in addition to succinic anhydride and ethyl γ-oxocaproate isolated as a mixture of the normal open-chain ester and cyclic pseudo ester (**15b**). It is suggested that the initial reaction product from succinyl dichloride is the acylium ion (**16a** ↔ **16b**). Attack by the carbanion (or an equivalent species) from the cadmium reagent at the position of the charge in **16b** would yield the cyclic form (**15c**) of γ-oxocaproyl chloride. Attack at the position of charge in **16a** would yield the open-chain form of γ-oxocaproyl chloride which has been shown[12] to rearrange rapidly at room temperature



to the cyclic form **15c**. The reaction of the latter with the cadmium reagent results in the formation of γ-ethyl-γ-caprolactone (**15a**). The formation of the mixture of ethyl γ-oxocaproates as the major product (20–45% yields) in this case is not ascribed to the usually observed side reaction between an acid chloride and the ether solvent (*vide supra*). Instead, Cason and Reist[11] postulate a cyclic transition state such as **17**, in which there may be involved other Lewis acids than the organocadmium reagent. Such a transition state, if it exists, appears to be less favored in the case of glutaryl dichloride where small amounts (6–10%) of the expected 3,7-nonanedione are formed, accompanied by higher yields of the cyclic products analogous to **15a** and **15b**.

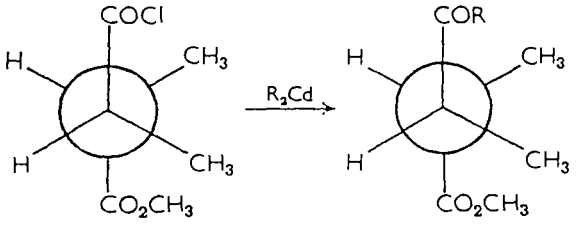


The reaction of a succinic acid derivative with an organocadmium reagent has been recently investigated[13] in order to ascertain whether epimerization occurs during organocadmium ketone synthesis. The reaction of either of the two diastereoisomeric ester acid chlorides of *s*-dimethylsuccinic acids, **19** and **21**, with dihexylcadmium yielded a



(**19**, *erythro*) (**20**, *erythro*)

(from *meso* succinic acid derivative)



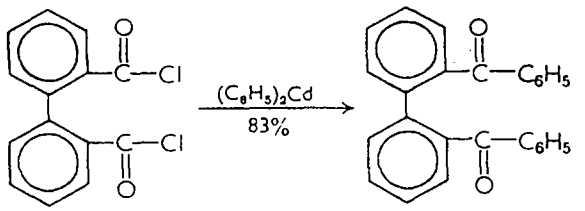
(**21**, *threo*) (**22**, *threo*)

(from *racemic* succinic acid derivative)

keto ester of the same geometry as the starting material with little or no epimerization. On this account Cason and Schmitz have suggested[13] that the highly variable amount of racemization (0–90%) observed by Mislow and Brenner[14] during the preparation of optically active α-phenylethyl methyl ketone (**24**) did not occur at the time of reaction between α-phenylpropionyl chloride (**23**) and dimethylcadmium. Such racemization might have occurred during the preparation and/or storage of the acid chloride[15,16].

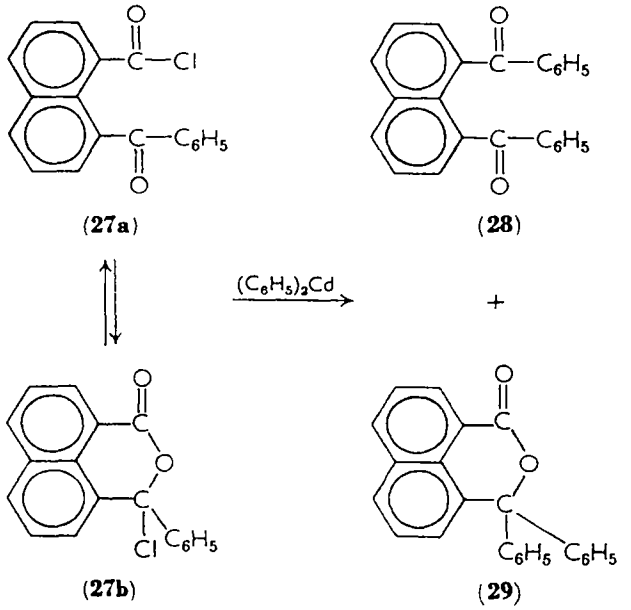
$$\underset{(\mathbf{23})}{C_6H_5CH(CH_3)COCl} \xrightarrow[50\text{–}70\%]{(CH_3)_2Cd} \underset{(\mathbf{24})}{C_6H_5CH(CH_3)COCH_3}$$

The results obtained by Cason and coworkers[11–13] for aliphatic diacid dichlorides can be compared to those obtained in the reactions of some polynuclear aromatic acid chlorides with organocadmium reagents[17a]. Thus, diphenic acid dichloride (**25**) reacted as the symmetrical dichloride with diphenylcadmium to form only 2,2′-dibenzoylbiphenyl (**26**) in 83% yield[17a]. On the other hand, 8-benzoyl-1-naphthoyl chloride (**27**) reacted with diphenylcadmium



(25) (26)

to form[17a] a mixture of 1,8-dibenzoylnaphthalene (**28**) and 3,3-diphenylnaphthalide (**29**). (Total yield of mixture was 60% but the two components were not separated from one another.) This was not



(27a) (28)

(27b) (29)

surprising since French and Kircher had already shown earlier[17b] that 8-benzoyl-1-naphthoyl chloride can be separated into two isomeric chlorides, one being an oil and the other a crystalline solid, m.p. 125–127°. French and Kircher[17b] ascribed the cyclic structure **27b** to the crystalline isomer. The isolation of compounds **28** and **29** from the reaction of the crystalline chloride with diphenylcadmium supports this assignment and is analogous to the isolation of cyclic compounds such as **15** from the reactions of aliphatic diacid dichlorides with organocadmium compounds.

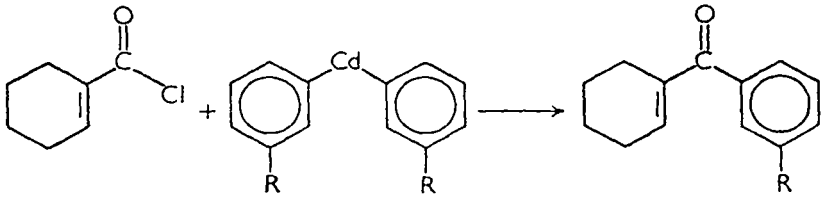
Attempts to prepare unsaturated ketones by reacting alkyl-

cadmiums with unsaturated acid chlorides such as crotonyl chloride and cinnamoyl chloride resulted in the formation of viscous oils or resins[18]. However, diphenylcadmium and cinnamoyl chloride (**30**) yielded benzalacetophenone (**31**) in 44% yield[18]. By analogy to

$$C_6H_5CH{=}CHCOCl \xrightarrow[44\%]{(C_6H_5)_2Cd} C_6H_5CH{=}CHCOC_6H_5$$

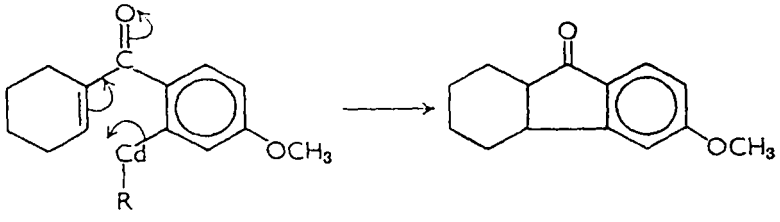
(**30**) (**31**)

this reaction Dauben and Colette attempted the synthesis of substituted tetrahydrobenzophenones (**34**) by reacting cyclohexenyl-1-carbonyl chloride (**32**) with an aromatic organocadmium reagent (**33**). When **32** was reacted with the cadmium reagent derived from *m*-bromoanisole (**33**, R = OCH_3) an 18% yield of analytically pure



(**32**) (**33**) (**34**)

material was obtained, but the spectral properties of this material did not correspond to the expected tetrahydrobenzophenone (**34**, R = OCH_3). The infrared spectrum showed, in addition to the expected[20] carbonyl band at 6·09 μ, another carbonyl band at 5·92 μ. This latter band was found to be due to the presence, in the isolated material, of a fluorenone derivative (**36**). The production of **36** is thought[19] to occur through the formation of an intermediate compound **35** which then undergoes addition to the α,β-unsaturated

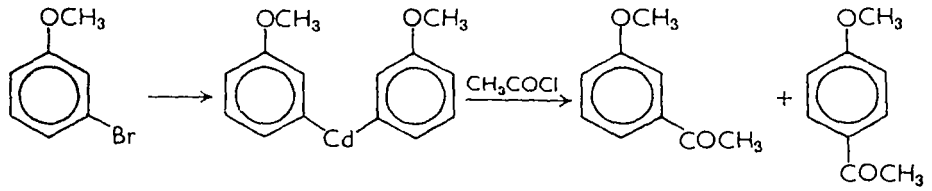


(**35**) (**36**)

ketone system. The isolation of **36** clearly indicates that in addition to the ring closure, a different isomer must have been formed at some stage of the reaction whereby the carbonyl group was placed on the

carbon atom adjacent to the position of that originally holding the halogen atom.

In an attempt to investigate the generality of the abnormal organocadmium reaction, the cadmium reagents derived from the three isomeric bromoanisoles were reacted with acetyl chloride[19]. It was observed that the *p*-bromoanisole reagent yielded only the expected, normal product, *p*-methoxyacetophenone. The *o*-bromoanisole reagent yielded a mixture containing 96% of the normal product, *o*-methoxyacetophenone, and 4% of the *p*-isomer. However, with the *m*-bromoanisole reagent (**33**, R = OCH_3) a mixture containing 35% *m*- (**37**) and 65% *p*-methoxyacetophenone (**38**) was isolated.



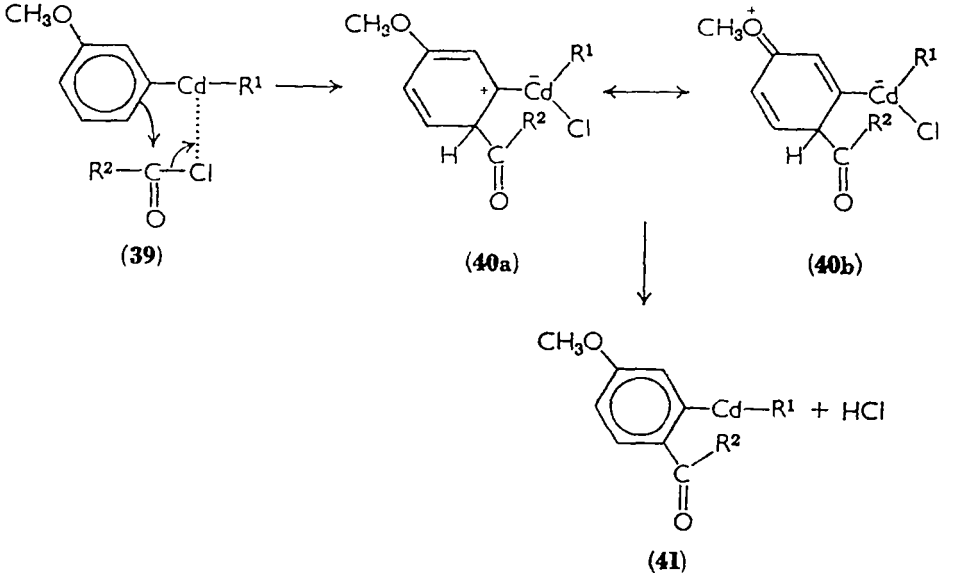
(**33**) (**37**) 35% (**38**) 65%

The same reaction carried out with other sets of isomeric aryl halides showed that only the *m*-methoxyphenylcadmium reagents gave the abnormal reaction. This indicates that the abnormal path requires a highly activated position adjacent to the carbon atom originally holding the bromine atom. The reaction was also found to be dependent on the nature of the acid chloride, since different isomer compositions were obtained with different acid chlorides. In order to determine whether isomerization occurs during the formation of the organocadmium reagent, that latter compound, derived from *m*-bromoanisole, was reacted with biacetyl. The product from this reaction, expected to be 3-hydroxy-3-(*m*-methoxyphenyl)-2-butanone, upon oxidation yielded *only* *m*-methoxybenzoic acid. This result shows that the cadmium reagent is of the expected orientation and the abnormal reaction must occur in the last step, namely during the reaction with the acyl halide.

Mention has already been made that the reaction of an organocadmium reagent with an acyl halide can be envisaged to proceed through the initial coordination of the cadmium to the halide atom with the resulting polarization of the carbon–halogen bond (see **17**).

This concept has also been used by Dauben and Collette[19] to formulate a mechanism explaining the formation of the *p*-substituted product from *m*-methoxyphenylcadmium reagent.

The mechanism presented by these authors is that of an electrophilic substitution in which the organocadmium reagent acts as an internal Lewis acid. Initially, the cadmium reagent coordinates with the chloride of the acid chloride to form an intermediate such as **39.**



(39) (40a) (40b) (41)

This coordination results in polarization of the carbonyl group and development of an acylium type of intermediate. Attack of this developing acylium ion can occur at the *m*- and *p*-position of the anisole ring. Substitution at the *p*-position would be favored due to the ability of the methoxyl group to lower the transition state energy in the intermediate (**40a** ↔ **40b**). The primary acylated material (**41**) in this mechanism would still retain the organocadmium bond, similarly to the intermediate **35** postulated in the mechanism for the formation of the fluorenone derivative **36.** Indeed, the isolation of the latter compound is taken[19] as evidence for the correctness of the postulated mechanism (**39** → **40** → **41**).

C. Reaction with Acid Anhydrides

Organocadmium reagents react with acid anhydrides in a similar manner to their reaction with acid chlorides (equation 5). However

$$R^1COOCOR^1 + R^2_2Cd \longrightarrow R^1COR^2 + R^1COOH \qquad (5)$$

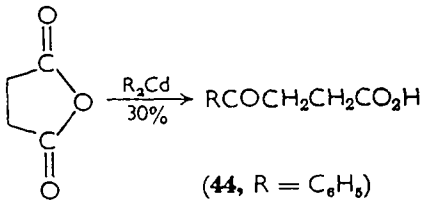
the yields from the acid anhydride reaction are less satisfactory than those obtained from the reaction with acid chloride and the former appears to have advantages only in cases where it is undesirable to prepare a carboxylic acid chloride.

A useful application of the anhydride reaction involves mixed carbonic anhydrides[21,22]. The mixed anhydrides **42** are prepared by the action of triethylamine and a chlorocarbonate ester on the carboxylic acid in ether or toluene at 0°. The triethylamine hydrochloride is removed by filtration and the mixed anhydride solution

$$R^1COOH + ClCOOC_2H_5 \xrightarrow{(C_2H_5)_3N} \underset{\textbf{(42)}}{R^1C(=O)-O-C(=O)OC_2H_5} \xrightarrow{R^2_2Cd} \underset{\textbf{(43)}}{R^1COR^2}$$

is added to the dialkylcadmium reagent. (Removal of the amine hydrochloride is essential since it appears to decompose the cadmium compound more rapidly than the latter reacts with the mixed anhydride.) Propiophenone (**43**, $R^1 = C_6H_5$, $R^2 = C_2H_5$) was obtained[21,22] in this manner in 60% yield.

The most interesting reaction of organocadmium reagents with acid anhydrides is that with cyclic anhydrides, leading to the synthesis of ketocarboxylic acids. Thus, succinic anhydride reacted with diphenylcadmium to give the keto acid **44** in 30% yield[23].

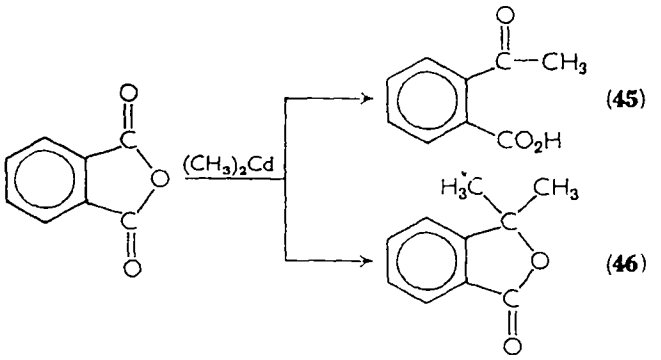


(**44**, $R = C_6H_5$)

This is a typical yield in the reaction of organocadmium reagents with cyclic anhydrides and it is usually more profitable to convert the acid anhydride first into the half-ester and then into the ester acid chloride[2–4]. Reaction of the latter with the organocadmium compound gives the keto ester corresponding to the keto acid obtained directly from the anhydride. This method is not suitable for phthalic and similar type compounds because of the reported[24] instability of the ester acid chlorides of such dibasic acids.

The reaction of phthalic anhydride with dimethylcadmium was reported[23] to yield 47% of *o*-acetylbenzoic acid (**45**). The same reaction was also reported[25] to yield 66% of 3,3-dimethylphthalide

(**46**). In a more recent reinvestigation of this reaction Jones and Congdon have shown[26] that the formation of **45** and/or **46** depends upon the reaction time and the type of organocadmium reagent employed in the reaction. Both **45** and **46** are formed even when the reaction time is relatively short and the ratio of **46**:**45** after 30 min was 0·02. However, the amount of **46** relative to **45** increased with reaction time. Thus, the yield ratio **46**:**45** was 0·5 after 6 h and after 17 h **46** was the only isolable product.



Jones and Congdon[26] also attempt to differentiate between 'dimethylcadmium', $(CH_3)_2Cd$, and 'monomethylcadmium chloride', CH_3CdCl, on the basis of the stoichiometry of their formation, namely on whether one or one-half molar equivalents of cadmium chloride were used in the preparation of the organocadmium reagent. Thus the highest conversion into products was achieved with two equivalents of 'monomethylcadmium chloride' rather than with one equivalent of 'dimethylcadmium'. Furthermore, the use of one equivalent of 'monomethylcadmium chloride' led to the formation of **45** as the only product. However, the authors[26] recognize that the distinction between the two reagents might be artificial and they point out that the apparent superior reactivity of 'monomethylcadmium chloride' could be due to purely mechanical reasons; with this reagent the mixture remained sufficiently fluid so that efficient stirring could be maintained throughout the reaction period.

It must be noted at this point that the use of the structure R—Cd—R to describe organocadmium compounds is largely a matter of convenience. Indeed, Fréon has recently pointed out[10] that the above structure could not possibly fit the known chemical reactivity of the 'normal' organocadmium reagents. Furthermore, he stresses the fact that doubling the quantity of cadmium halide, in

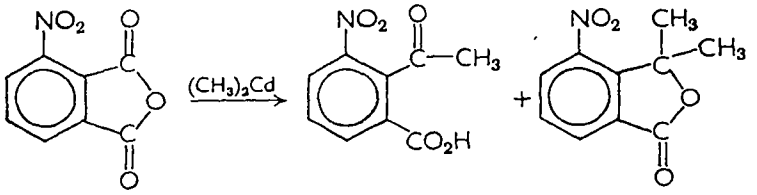
order to realize reaction (6) and thus arrive at the 'monoalkyl-

$$RMgX + CdX_2 \longrightarrow RCdX + MgX_2 \qquad (6)$$

cadmium halide', does not seem to change appreciably the behavior of the organocadmium reagent in its various applications. This is in contrast to the previously mentioned observations of Jones and Congdon[26] who, by halving the molar equivalent of the cadmium halide, changed the course of the organocadmium reaction.

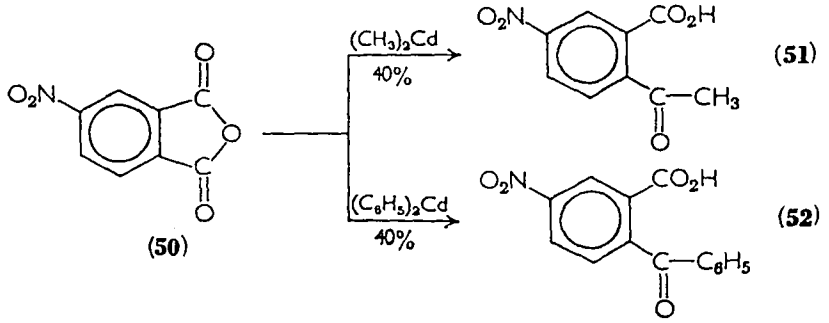
The 'abnormal' reaction (see p. 312) between the cadmium reagent of *m*-bromomethoxybenzene and an acid chloride has been found to take a similar course when the latter is replaced by an acid anhydride. The results have been interpreted to show that the process is intramolecular[19].

Potential synthetic interest may be found in the reports that organocadmium compounds do not react with a nitro group in an aromatic nucleus[25,27]. Dimethylcadmium and 3-nitrophthalic anhydride (**47**) gave 2-acetyl-3-nitrobenzoic acid (**48**) in 38% yield and a small amount (1%) of 3,3-dimethyl-4-nitrophthalide (**49**)[25].



(**47**) (**48**) (**49**)

In a similar manner, starting with 4-nitrophthalic anhydride (**50**) Tirouflet obtained[27] 2-acetyl-5-nitrobenzoic acid (**51**) and 2-benzoyl-5-nitrobenzoic acid (**52**).



(**50**)

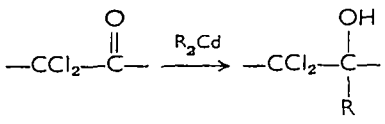
D. Reaction with Other Functional Groups

The fact that the organocadmium reaction can be used successfully for ketone synthesis is in itself proof of the lack of reactivity of ketonic carbonyls towards organocadmium reagents. On the other hand, it has already been mentioned that activating adjacent groups change the course of the reaction; witness the examples of ethoxalyl chloride (**6**) and oxalyl chloride. In the latter case the presence of an α-carbonyl group leads to attack of the cadmium reagent on a carbonyl group to form the carbinol grouping —CR_2OH. However, once this is formed the group activating the other carbonyl group is removed and the reaction stops at the keto alcohol stage (**11**). Similarly, ethyl pyruvate (**53**) reacts with organocadmium reagents to form the hydroxy ester **54** exclusively[10].

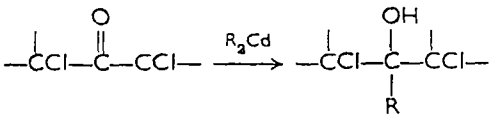
$$\underset{\textbf{(53)}}{CH_3COCOOC_2H_5} \xrightarrow[50\text{–}60\%]{R_2Cd} \underset{\textbf{(54)}}{CH_3CR(OH)COOC_2H_5}$$

The ester carbonyl is not attacked even in the presence of a large excess of cadmium reagent. Similar results have been reported for other keto esters[10].

The presence of an α-halogen atom (chlorine) does not appear to have a sufficient activating effect in order to lead to the addition of the organocadmium reagent to the carbonyl group[10]. On the other hand, the presence of two α-chloro atoms (**55**, **57**) leads to the production of 30–50% yields[10] of dichloro tertiary alcohols (**56**, **58**).



(55) **(56)**



(57) **(58)**

A similar situation appears to prevail in the case of α-chloroaldehydes[10].

The reaction of chloral (**59**) with organocadmium reagents results in the production of 45–70% yields of α-trichloro secondary

alcohols (**60**) and this appears to be[10] one of the best general methods for the preparation of compounds such as **60**.

$$\underset{(59)}{CCl_3CHO} \xrightarrow{R_2Cd} \underset{(60)}{CCl_3CH(OH)R}$$

III. THE USE OF ORGANOMAGNESIUM COMPOUNDS

A. General Considerations

The well known tendency of Grignard reagents to undergo addition to ketones to form tertiary alcohols causes, *a priori*, severe limitations on the use of organomagnesium compounds for ketone synthesis. However, in recent years a number of reports have appeared in which details are given for the use of Grignard reagents in the preparation of aromatic, alicyclic and sterically hindered ketones[4]. In particular high yields of ketones have been reported when the Grignard reagents have been used in conjunction with various catalytic agents; the following section will concentrate on this aspect of ketone synthesis through organomagnesiums.

B. Reaction with Acid Chlorides

About fifteen years ago, it was found[28] that the use of copper instead of glass reactors in the reaction of *t*-amylmagnesium chloride with isobutyryl chloride afforded the ketone 2,4,4-trimethyl-3-hexanone (**61**) in yields of up to 87% whereas previously only 10–15% yields had been realized from this reaction[29]. This dramatic

$$(CH_3)_2CHC(=O)Cl + CH_3CH_2C(CH_3)_2MgCl \xrightarrow[87\%]{} CH_3CH(CH_3)C(=O)C(CH_3)_2CH_2CH_3$$

(61)

change in yields was ascribed by Cook and Percival to the catalytic role played by cuprous chloride, formed *in situ* when the reaction was carried out in copper vessels. Indeed, the beneficial effect of cuprous chloride catalysis was demonstrated[29] when the addition of 5 g of cuprous chloride to the reaction between 5 moles of *t*-butylmagnesium chloride and 5 moles of trimethylacetyl chloride resulted in yields of 70–80% of hexamethylacetone (**62**). In the absence of cuprous

$$(CH_3)_3CCOCl + (CH_3)_3CMgCl \xrightarrow[70\text{–}75\%]{} (CH_3)_3CCOC(CH_3)_3$$

(62)

chloride and under otherwise similar reaction conditions, **62** was obtained in yields of only 1–2%. It is suggested[29] that cuprous chloride initiates a free-radical chain reaction as shown in the Scheme 1.

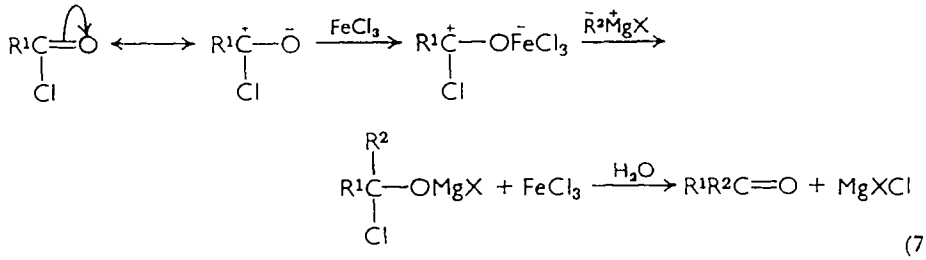
$$RCOCl + \cdot CuCl \longrightarrow R\dot{C}O + CuCl_2$$
$$R\dot{C}O + RMgCl \longrightarrow RCOR + \cdot MgCl$$
$$RCOCl + \cdot MgCl \longrightarrow R\dot{C}O + MgCl_2$$

SCHEME 1.

In a continuation of this work, Cook and coworkers[30] tested a number of other anhydrous metallic halides for catalytic activity in the reaction of acetyl chloride and *n*-butylmagnesium chloride to produce 2-hexanone. Ferric chloride was found to be superior to aluminum chloride, cuprous chloride, zinc chloride, manganese chloride, cobaltous chloride and magnesium bromide. The optimal conditions for the synthesis of straight-chain ketones appear to be addition of one mole of Grignard reagent to one or more moles of the acyl chloride at $-65°$ in the presence of a ferric chloride catalyst (1·5 g $FeCl_3$/mole acid chloride). Under these conditions the yield of 2-hexanone was in the range of 70–75% as compared to 31% yield in the absence of the catalyst[30].

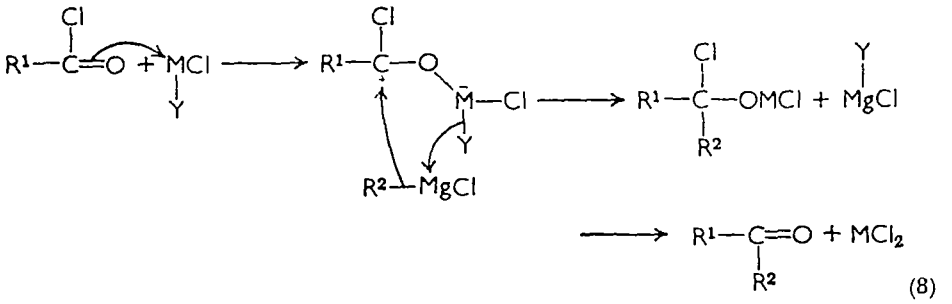
For the synthesis of highly branched ketones, the temperature of reaction does not seem to be as critical as in the case of straight-chain ketones[30]. The use of ferric chloride instead of cuprous chloride catalyst for the synthesis of di-*t*-butyl ketone (**62**) raised the yield of pure product to 84%.

Cook and coworkers[30] consider that in view of the stability of the complex formed at the end of the reaction (the complex was heated for several days with no liberation of ketonic product), it does not seem likely that ferric chloride is present as free-radical type catalyst as they suggested for cuprous chloride in the previous reaction[29]. Instead, for ferric chloride, but not specifically for the cuprous chloride-catalyzed reactions, an ionic mechanism is proposed, in which ferric chloride acts as a Lewis acid (equation 7).



(7)

An ionic mechanism involving a Lewis acid has been proposed also by Morrison and Wishman[31]. These authors[31] consider that addition of Grignard reagents to acid halides involves attack on a Grignard–acid halide complex by a second molecule of Grignard reagent, via a cyclic transition state (equation 8). By acting as strong

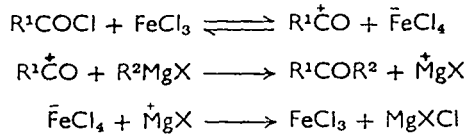


(8)

(M = magnesium or other metal;
Y = R^2 or halogen)

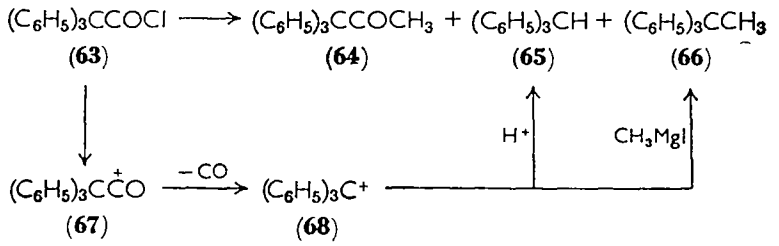
Lewis acids, certain metallic halides can take the place of Grignard reagent in forming the initial complex with the acid chloride. A stronger Lewis acid would form a higher concentration of the complex. The latter, being more reactive by virtue of the greater polarization of the carbonyl bond, would lead to an overall faster reaction.

Cason and Reist[11] have criticized both these suggested mechanisms[30,31] on the grounds that they both fail to differentiate between carbonyl in an acid chloride and in other structures such as a ketone. They consider that any intermediate involving coordination of the ferric chloride with oxygen is inconsistent with the observed fact that ferric chloride specifically catalyzes the Grignard reaction with an acid chloride in great preference to other carbonyl groups. To overcome this difficulty, Cason and Reist suggest a mechanism similar to that proposed[11,32] for the reaction of an organocadmium reagent with an acid chloride, namely extraction of halogen by the Lewis acid to give acylium ion and reaction of this ion with the Grignard reagent (Scheme 2). The same mechanism has been considered to be



SCHEME 2.

responsible for the resulting products in the reaction of methylmagnesium iodide with triphenylacetyl chloride (**63**)[33]. The products obtained from this reaction, as reported by Cason and Schmitz[33], were methyl trityl ketone (**64**) (17–21%), triphenylmethane (**65**) (17–21%) and triphenylethane (**66**) (31–40%).



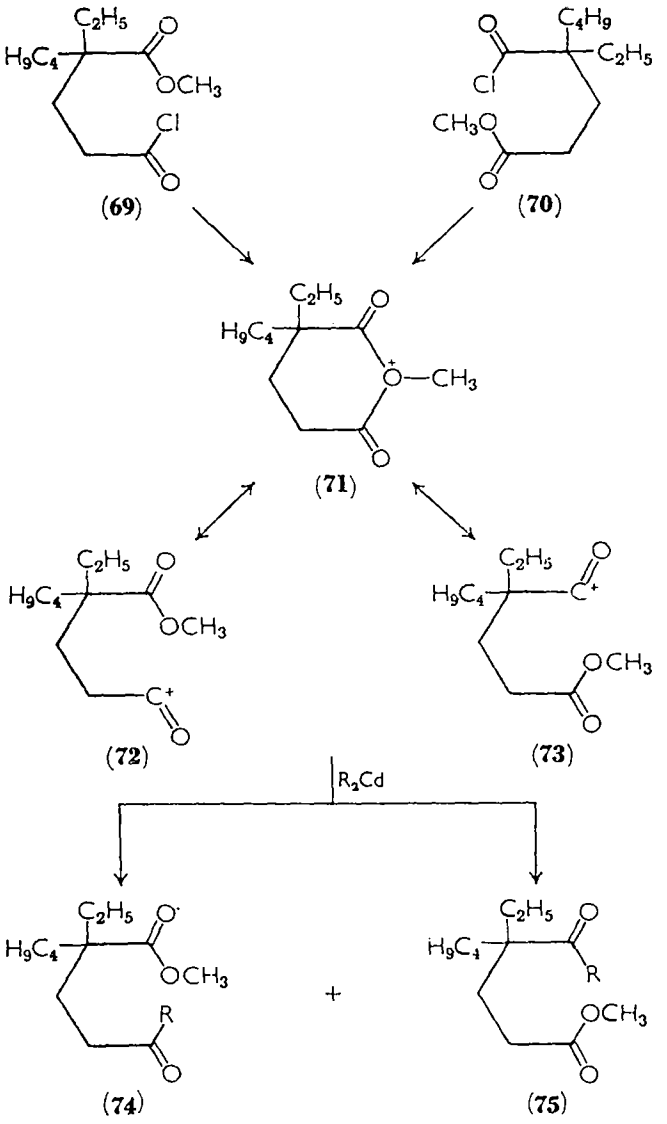
These results are quite different from the previously reported[34] isolation of ethyl triphenylacetate in 67% from the reaction between **63** and methylmagnesium iodide. The formation of ethyl triphenylacetate has been ascribed by Zook and coworkers[34] to the reaction between the acylium ion (**67**) and the diethylether solvent.

Cason and Schmitz could not isolate any ethyl triphenylacetate in their work[33]; this, it is stated, is not unexpected since the acylium ion **67** should react much more rapidly with the excess Grignard reagent present in the reaction mixture than it should with the ether solvent. These authors[33], whilst agreeing to the acylium ion intermediate **67**, ascribe a different fate to this ion to explain the formation of the isolated reaction products. Reaction of **67** with the Grignard reagent would yield the ketone **64**. Decarbonylation of **67** would result in the formation of the triphenylmethylcarbonium ion (**68**), which then leads to the formation of triphenylmethane (**65**) and triphenylethane (**66**).

It might be noted in parentheses that good yields of alkyl trityl ketones can be obtained by reacting triphenylacetyl chloride with a large excess of dialkylcadmium reagent[33].

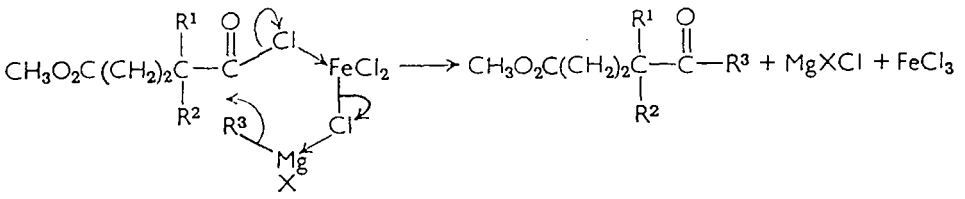
In a further attempt to test the plausibility of an acylium ion intermediate, Cason and Kraus[35] examined the ferric chloride-catalyzed Grignard reaction with the isomeric acid chlorides **69** and **70**. The acylium ion from either of these isomeric acid chlorides can be represented by the cyclic oxonium ion **71**, and its resonance forms **72** and **73**. This suggestion derives support from the fact that either of the isomers **69** or **70** reacts with an organocadmium reagent to give a mixture of the isomeric keto esters **74** and **75**. The same

mixture of isomers **74** and **75** should be expected from the ferric chloride-catalyzed Grignard reaction if the cyclic oxonium ion **71** is an intermediate. However, a similar mixture of isomers **74** and **75** could be formed in such a reaction if ferric chloride might induce the rearrangement of the acid chlorides **69** ⇌ **70** prior to the addition of the Grignard reagent to the reaction mixture; in which case the



cyclic oxonium ion would not necessarily be a required intermediate to explain the reaction products. Cason and Kraus[35] found that **69** and **70** rearrange into one another rapidly at room temperature in the presence of ferric chloride without solvent and somewhat slower in ether–toluene solvent. However at $-55°$ to $-60°$ rearrangement occurs at such a slow rate that any rapid reaction at these temperatures must involve an assisted process for the removal of halogen.

The reaction of one mole of **69** with two moles of the Grignard reagent at $-60°$ and in the presence of half a mole of ferric chloride gave after one hour a 40% yield of the keto ester **74** and none of the rearranged ester **75**. Under exactly the same reaction conditions, the isomer **70** gave 0·3% of **74** and 4% of **75**. When the temperature of the reaction with **70** was increased from $-60°$ to $-10°$ the yield of the rearranged product **74** was increased to 10% and that of **75** was about 4%. On the basis of these and similar additional data the authors[35] suggest a dual reaction path. One route, leading to rearrangement, involves formation of an intermediate acylium ion, such as **71**. This is the preferred route when the acid chloride function is hindered, as for instance in **70**, and the total reaction yield would be relatively very low. The second route, operating in the case of compounds such as **69** in which the acid chloride function is unhindered, involves a transition state such as formulated in **76** in which halogen is extracted by the Lewis acid from the acid chloride as the alkyl of the organometallic reagent attacks the carbonyl carbon. Such a concerted reaction might offer an explanation of the observed



(**76**)

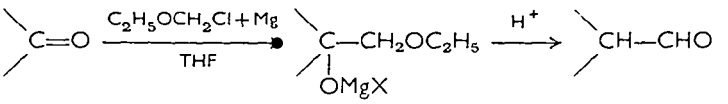
discrimination of ferric chloride in promoting reaction with the acid chloride in preference to other carbonyl groups. Furthermore, reaction via transition state **76** would be subject to steric hindrance whereas reaction via **71** would be relatively unaffected by such hindrance. In addition it is argued[35] that the dual reaction paths, involving transition states **71** and **76**, are consistent with the observation that the rate of the reaction route involving rearrangement is

more affected by temperature changes than is the rate by the second route. The negative entropy of activation would be expected to be larger for reaction via **76** and hence the concerted reaction would be expected to become more important as the temperature is lowered, and become dominant at low temperatures in the absence of steric hindrance.

On the basis of data obtained from the reactions of **69** and **70** with organocadmium reagents, Cason and Kraus[35] conclude that a dual mechanism also applies to the cadmium reactions, involving transition states similar to **71** and **76**.

For synthetic applications Cason and Kraus[35] suggest that for the ester acid chloride of an unsymmetrical dibasic acid the use of a Lewis acid with the cadmium reagent at low temperature appears specifically useful for avoiding rearrangements, provided that the acid chloride function is unhindered. At higher temperatures, where the ionization route becomes dominant and the cadmium reagent is no longer subject to hindrance, the yields are much better but rearrangement occurs in unsymmetrical compounds.

Mention should be made of what appears to be a rather versatile method for carbonyl synthesis involving organomagnesium intermediates. This is the reaction of either chloromethyl ethers or other α-halo ethers with carbonyl compounds in tetrahydrofuran in the presence of magnesium[36,37]. Both aldehydes and ketones have been prepared by this method (equation 9).



(9)

The various mechanistic suggestions for the reactions of organocadmium and organomagnesium compounds have been presented in a more or less chronological order. The reason for choosing this manner of presentation will have become obvious to the reader by now. The mechanism of these reactions is far from having been clarified and even though each mechanism presented seems plausible for the particular example being discussed by the various authors, none of the suggested mechanisms provide a satisfactory answer to the problem as a whole. Just to illustrate this statement, mention has been made that Cason and coworkers[11] have criticized the mechanisms of Percival and coworkers[30] and Morrison and coworkers[31] for not taking into consideration the difference between the carbonyl group in an acid chloride and that in other structures. On the other

hand, the mechanisms presented by Cason and coworkers give a ketone R^1COR^2 as the final product without really providing an adequate answer as to why this ketone should not react further with the excess organometallic reagent present in the reaction mixture. Cook and coworkers[30] have pointed out that the complex formed at the end of the reaction is very stable thermally and it only liberates the required ketone upon reaction with water.

In addition all the above-mentioned authors do not concern themselves with the structure of the organometallic reagent and it is quite clear that even less is known about organocadmium compounds than about organomagnesium compounds. In the case of the latter compounds only very recently has x-ray analysis shown the presence of RMgX units in crystalline organomagnesium compounds[38]. Although such evidence cannot be directly transferred to reactions in solution, it certainly opens anew the problem of the structure of organomagnesium[39] and by necessity of organocadmium compounds.

IV. THE USE OF ORGANOLITHIUM COMPOUNDS

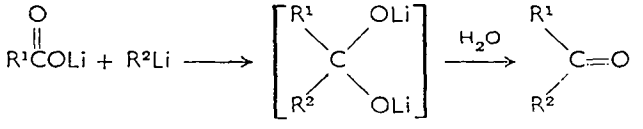
The use of organolithium compounds for ketone synthesis does not appear to have received much attention in the more recent literature despite the simplicity and potential of the method.

The observation made by Ziegler and Colonius[40] that carbonation of phenyllithium gave only traces of benzoic acid led Gilman and Van Ess[41] to reinvestigate this reaction. The latter authors[41] found that the poor yield of benzoic acid was accompanied by a high yield (> 70%) of benzophenone. This observation prompted Gilman and Van Ess to test the value of this reaction in the synthesis of ketones.

Carbonating an organolithium compound with solid carbon dioxide at low temperatures (−50° to −80°) gave the expected carboxylic acid according to equation (10). However, at higher

$$RLi + CO_2 \longrightarrow RCOOLi \qquad (10)$$

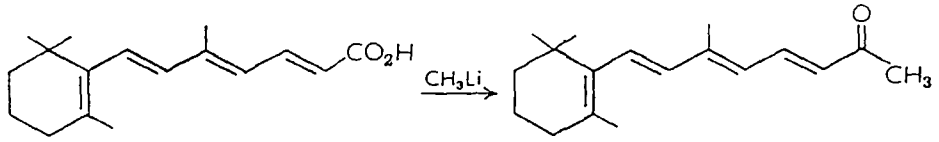
(room) temperatures, on bubbling carbon dioxide into or over the surface of the solution, the chief reaction product is a ketone and practically no tertiary alcohol is formed. This has been taken to indicate that the salt initially formed (**77**) adds another mole of the



(77) (78) (79)

organolithium reagent to form the dilithium derivative of a dihydroxymethane (**78**). The latter yields the ketone **79** on hydrolysis. The absence of carbinol formation is taken to indicate that **79** is not formed as such in this reaction, since it would then react further with the organolithium compound. Thus, benzophenone (**79**, $R^1 = R^2 = C_6H_5$) reacts rapidly and quantitatively with phenyllithium to give triphenyl carbinol. On the other hand, lithium benzoate (**77**, $R^1 = C_6H_5$) reacted with phenyllithium to give benzophenone in 70% yield[41]. Similarly, lithium n-butyrate (**77**, $R^1 = n\text{-}C_3H_7$) reacted with phenyllithium to give 62% yield of n-butyrophenone (**79**, $R^1 = n\text{-}C_3H_7$, $R^2 = C_6H_5$). This latter example shows up the possibility of using this reaction for the synthesis of unsymmetrical ketones.

In 1946 Van Dorp and Arens[42] used this reaction for the synthesis of the C_{18} ketone **81**, one of the compounds of interest in vitamin A chemistry. By adding a solution of β-ionylidenecrotonic acid (**80**) in ether to 2 moles of methyllithium in ether **81** was obtained in over 90% yield.



(**80**) (**81**)

A similarly high yield (90–95%) of a methyl ketone was obtained[43] upon reacting lithium cinnamate with methyllithium. The compound, benzalacetone, thus obtained was very pure and therefore this method was used to prepare isotopically labeled benzalacetone as an intermediate in the synthesis of α-^{14}C-alanine.

The same reaction was investigated by Tegner[44], who wanted to compare the yields of methyl ketone when using the free cinnamic acid, or the lithium salt. In both cases practically the same yield (~77%) was obtained; since the lithium salts of carboxylic acids are rather difficult to prepare, the free acid can be used directly in this reaction. From the reaction of a number of acids with methyllithium (see Table 1), Tegner concludes[44] that this is a useful method for the synthesis of methyl ketones in high yields, even when carbon–carbon double bonds are present in the structure of the acid. In addition it appears that acids having electron-withdrawing substituents give a higher yield of the ketone than those containing an electron-repelling substituent.

TABLE 1. Yields of methyl ketones obtained by the reaction of methyllithium with carboxylic acids[44].

R in acid RCO_2H	Yield of $RCOCH_3$ (%)
CH_3	0
CH_3CH_2	~1
CH_3OCH_2	16
$CH_3(CH_2)_3CH_2$	83
C_6H_5	82
$C_6H_5CH_2$	76
$C_6H_5CH_2CH_2$	100
$C_6H_5CH{=}CH$	77
80[42]	90

V. THE USE OF METAL CARBONYLS

The hydroformylation of olefins, the so-called 'Oxo synthesis', for the preparation of aldehydes is the best known example of the use of metal carbonyls to prepare organic carbonyl compounds (equation 11)[45].

$$RCH{=}CH_2 \xrightarrow[H_2/CO]{Co_2(CO)_8} RCH(CHO)CH_3 + RCH_2CH_2CHO \qquad (11)$$

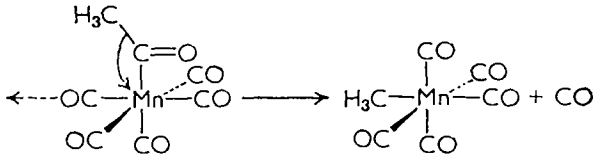
The role played by dicobalt octacarbonyl in these reactions has been extensively investigated and this in turn has led to the investigation of other metal carbonyls as potential catalysts for carbonyl insertion[5].

An excellent review[5] on this subject was published in 1962. In addition several examples are mentioned in passing in a chapter in the first volume of this series[46]. We shall limit ourselves to giving a few selected examples in order to demonstrate the potentiality of the method.

An interesting example of carbonyl insertion in the presence of a metal carbonyl is that in which methylmanganese pentacarbonyl (**82**) is converted into acetylmanganese pentacarbonyl (**83**) by treatment with carbon monoxide at elevated pressure and room temperature[47]. This process was found to be reversible, **83**

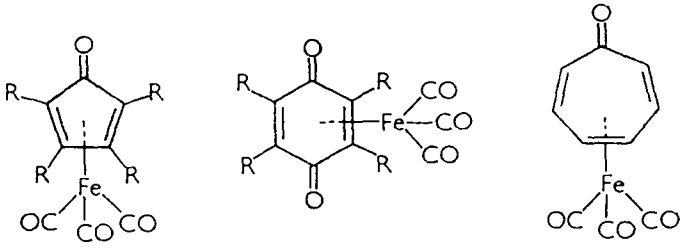
$$\underset{(\mathbf{82})}{CH_3Mn(CO)_5} + CO \rightleftharpoons \underset{(\mathbf{83})}{CH_3C({=}O)Mn(CO)_5}$$

undergoing fast decarbonylation to **82** on heating; the mechanism of this reaction has been investigated by a number of workers[48–50] in an



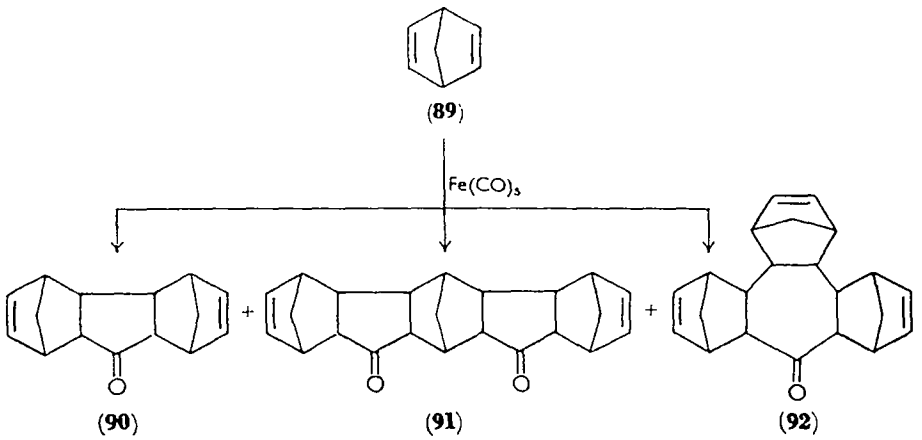
(**84**) (**85**)

attempt to learn more about the general process of carbonyl insertion in the presence of metal carbonyls. The use of radioactive carbon



(**86**) (**87**) (**88**)

monoxide in the carbonylation reaction[48] and several kinetic studies[49,50] have led to the suggestion[50] that the decarbonylation step occurs by a mechanism of methyl migration (**84** → **85**). Similar



(**89**)

(**90**) (**91**) (**92**)

carbonylation reactions have been observed with other organometallic compounds such as iron, cobalt, platinum, palladium and nickel derivatives[5]. Reactions of acetylene and substituted acetylenes

with iron carbonyls have been shown[5,51] to form compounds such as **86** to **88**. A further interesting example of carbonyl insertion is the reaction between bicyclo[2.2.1]heptadiene (**89**) and iron pentacarbonyl where the metal-free ketones **90** to **92** were found among the reaction products[5,46]. The isolation of compounds such as **90** to **92** together with the fact that the reaction of organoiron tricarbonyl complexes such as **86** to **88** with ferric chloride[52,53] breaks up the complex to release the metal-free organic moiety in good yields, completes a reaction sequence which may provide a useful method for the introduction of the carbonyl group into organic compounds. The potentiality of this method has been very little investigated so far.

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The Chemistry of the Carbonyl Group
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CHAPTER 7

Biological formation and reactions of carbonyl groups

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I. INTRODUCTION

Virtually every class of organic compounds of biochemical interest includes among its members compounds containing the carbonyl group. In the myriad of metabolic reactions that have been described in all forms of microbial, plant and animal life carbonyl compounds appear either as end-products in themselves or as intermediates in the formation of other substances. It is fitting, therefore, to divide a discussion of the biochemistry of the carbonyl group into two categories: formation and reactions. Each of these divisions can be further subdivided into reaction types that follow the lines of classical organic chemistry, with the restriction in mind that these reactions are, with few exceptions, catalyzed by enzymes. In considering the mechanism of these reactions the role of the enzyme as a transitory participant must be recognized, and in many instances a coenzyme will be an additional essential component of the reaction.

It is obviously impossible in a chapter of this kind to include every reaction which is known to involve the biological formation or fate of carbonyl groups. The carbohydrates, for example, comprise one of the largest class of biologically important compounds and are characterized by the presence of an aldehydic or ketonic carbonyl group, the focal point of their reactivity. Since many reviews of carbohydrate chemistry and metabolism have appeared and continue to appear, only reactions of recent origin will be discussed. Where a carbonyl compound is formed as an intermediate in the synthesis of another compound, a clear distinction between formation and reaction will not be attempted. Such cyclic processes as the Embden–Meyerhof pathway, the Krebs tricarboxylic cycle, or the glucuronic acid pathway can best be treated as intact units.

Only *de novo* formation of carbonyl groups will be considered and only those compounds in which the carbonyl group is actually or potentially aldehydic or ketonic and plays a central metabolic role will be included. Carbonyl groups in quinones, carboxylic acids, esters, amides, and sulfur analogs have been excluded.

II. BIOLOGICAL FORMATION OF CARBONYL GROUPS

A. Reduction of Carboxylic Acids, Esters, and Anhydrides

Although few carbonyl compounds are synthesized by this route, it ranks among the most important, since it leads to ketones and aldehydes that play central roles in the metabolism of plants, the ultimate source of metabolic fuel for the animal kingdom.

1. Pyruvate synthase

In spite of its recent discovery[1] this reaction will be presented first since it may represent the primordial carbonyl synthesis in nature. Cell-free extracts of the photosynthetic bacterium *Chromatium* will reductively couple carbon dioxide to acetyl-P* in the presence of hydrogen gas, ferredoxin, and CoA to produce pyruvate, a key carbonyl intermediate in biological systems (equation 1). To demon-

$$CH_3COOP^{2-} + CO_2 + H_2 \rightleftharpoons CH_3COCOO^- + H_2OP^- \qquad (1)$$

strate the formation of pyruvate it is necessary to include a carbonyl trapping agent, semicarbazide, without which pyruvate would go on to form amino acids and other cellular material. In *Clostridium pasteurianum*, another photosynthetic organism, no trapping agent is needed for the accumulation of pyruvate.

The energy to drive this reaction in the dark is supplied by the concerted action of the energy-rich organic phosphate and the high reductive potential of hydrogen gas, whose electrons are carried by ferredoxin, a low molecular weight protein, the most electronegative electron carrier yet discovered in living systems. In the light, pyruvate can be synthesized from simple carbon precursors, acetate and carbon dioxide. Radiant energy captured by chlorophyll, the green pigment of *Chromatium* and higher plants, photophosphorylates ADP to ATP, which in turn phosphorylates acetate to acetyl-P; the sequence then follows equation (1) to produce pyruvate.

This reaction thus illustrates the fundamental role played by photosynthetic organisms in capturing radiant energy for the synthesis of reduced substrates which then serve as sources of oxidative energy for higher organisms.

The reverse reaction, known as the phosphoroclastic reaction, will be discussed in section III.A.2.

2. Glyceraldehyde-3-P dehydrogenase[2]

A major route of carbohydrate catabolism and synthesis in living systems is the glycolytic pathway (Figure 1), which traverses a series

* The following abbreviations will be used in this chapter: P = phosphate, CoA = coenzyme A, AcCoA = acetylcoenzyme A, AcAcCoA = acetoacetyl-coenzyme A, ADP = adenosine diphosphate, ATP = adenosine triphosphate, NAD = nicotinamide-adenine dinucleotide, NADH = reduced NAD, NADP = nicotinamide-adenine dinucleotide phosphate, NADPH = reduced NADP, FMN = flavin mononucleotide, FAD = flavin-adenine dinucleotide.

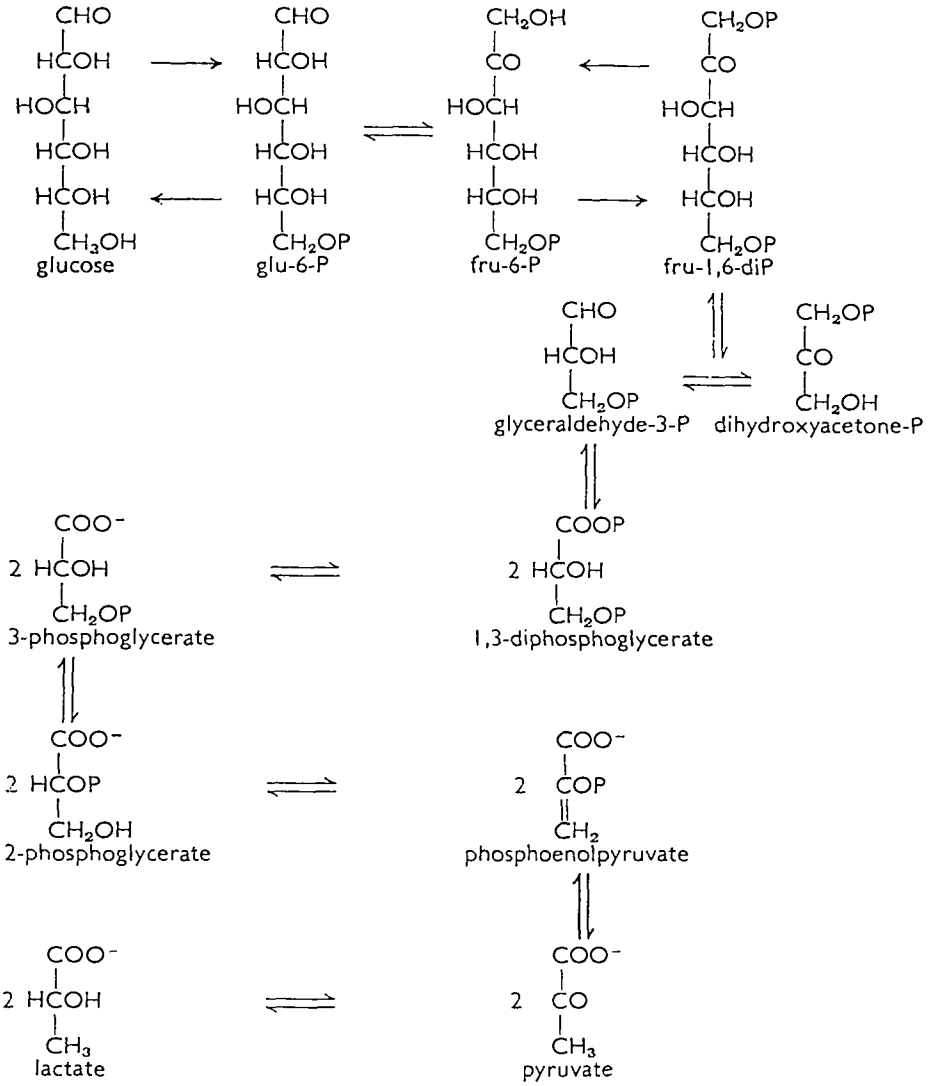


FIGURE 1. The Embden–Meyerhof glycolytic sequence.

of reversible steps from glucose, the principal fuel, to pyruvate and lactate. One of these steps involves the freely reversible interconversion (K_{equ} = 1 at pH 7·4) of 1,3-diphosphoglycerate and glyceraldehyde-3-P (equation 2). The reaction is coupled to the oxidoreduction of NAD. The reaction as shown in the direction of aldehyde

1,3-Diphosphoglycerate + NADH + H^+ $\rightleftharpoons$ Glyceraldehyde-3-P + NAD^+ + HOP (2)

synthesis occurs in photosynthetic organisms and gives rise to a precursor of hexose through reversal of the glycolytic scheme.

Photosynthetic organisms thus utilize the reduction of a mixed anhydride of phosphoric acid and a carboxylic acid for the generation of an essential aldehyde (equation 2) as well as a ketone (equation 1).

3. Aspartate β-semialdehyde dehydrogenase[3]

Extracts of the bacterium *Escherichia coli*, yeast, and mutants of the mold *Neurospora* catalyze the reduction of β-aspartyl-P to aspartate β-semialdehyde, NADPH serving as the reducing agent. This reaction is a link in the chain of reactions leading to the formation of threonine and lysine, amino acids essential to the growth and repair of the animal organism. An important biosynthetic function is subserved by this reaction since the carbon skeleton of so-called essential amino acids can not be synthesized by animal tissues and must be supplied in the diet, which is ultimately of vegetable origin. Without this dietary supply of essential amino acids the animal organism is unable to synthesize protein for growth and maintenance.

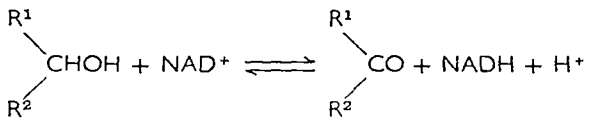
B. Oxidation of Alcohols

In this category is found the great majority of reactions leading to aldehydes and ketones. Many of the important metabolic pathways involve at least one reaction in which a carbonyl compound arises by oxidation of an alcohol. Of especial interest in this group are the primary alcohols, e.g. ethanol, the prototype for studies of enzyme-catalyzed stereospecific hydrogen transfer.

1. Alcohol dehydrogenases[4]

Since a complete review of these enzymes has appeared recently, this discussion will deal mainly with stereospecific hydride ion transfer. Although stereospecificity has long been recognized as a concomitant of enzyme catalysis, the underlying principles remain obscure and many misconceptions persist in the literature.

Alcohol dehydrogenases occur in all living systems and were among the first enzymes to be recognized and studied. Most work, however, has been done on the yeast and horse-liver enzymes, both of which have been crystallized. They catalyze the general reaction shown in equation (3), where the alcohol is either primary or secondary,



(3)

leading to aldehydes and ketones, respectively. An alcohol dehydrogenase recently found in a pseudomonad grown on methanol as sole carbon source has been shown to require no pyridine nucleotides for activity but required phenazine methosulfate as hydrogen acceptor[5]. The substrate specificities of the yeast and liver enzymes are different, the latter having the lesser specificity. An important substrate of alcohol dehydrogenase is vitamin A which is oxidized to the aldehyde[6].

Although the two enzymes are distinct proteins they have several properties in common, apart from their catalytic function. Both enzymes contain zinc which is involved in the binding of enzyme, coenzyme, and substrate and both display stereospecificity toward hydrogen transferred directly as hydride ion from substrate to coenzyme. From the standpoint of classical organic chemistry the carbinol hydrogen atoms of a primary alcohol would appear to be chemically indistinguishable and yet are completely differentiable in enzymatic reactions. The remainder of the discussion of alcohol dehydrogenases will dwell on this subject.

Implicit in the Van't Hoff–LeBel tetrahedral model of the carbon atom is the notion of asymmetry which is apparent when the apexes of the tetrahedron are occupied by four structurally distinct groups (Cabde). Interchange of any two of the groups generates the non-superimposable mirror image or enantiomer of the original configuration. The preferential reactivity of enzymes toward one enantiomer, usually to the exclusion of the other, has been known from the earliest years of organic chemistry and is ascribed to the asymmetric nature of the enzyme protein. That it is in fact the asymmetry of the enzyme which enables it to distinguish one enantiomer from the other is seen from the capacity of nonenzymic asymmetric molecules to differentiate similarly but usually less completely. For example, chromatography on paper[7] and on columns of lactose[8] and of starch[9] has been used to resolve racemic mixtures more or less completely.

The advent of isotopes and their application to biochemical problems brought to light phenomena that were not previously detected. One of these was the puzzling observation that citrate, enzymatically labeled with ^{14}C, contained the label in only one of its terminal carboxyl groups and not randomly in both in accord with expectation from the symmetry of the molecule[10]. Apparently another kind of asymmetry characterized the citrate molecule, recognizable by enzymes but unnoticed by the observer until isotopic labeling became available. It must be emphasized at the outset that

optical activity resulting from introduction of the isotopic marker, although often measurable, does not explain nor is it related to the asymmetry implied in the differentiation of like groups in symmetrical molecules. The role of the isotope lies solely in the detection of the phenomenon.

The paradox of the asymmetric behavior of seemingly symmetrical molecules was resolved in two stages, first by Ogston[11] and later by Schwartz and Carter[12]. Ogston explained the asymmetry of such molecules as a manifestation of the geometry of binding of substrate to enzyme. A molecule with symmetry of the citrate type could only bind to the enzyme surface so that one of the like groups was asymmetrically located with respect to the other. Schwartz and Carter

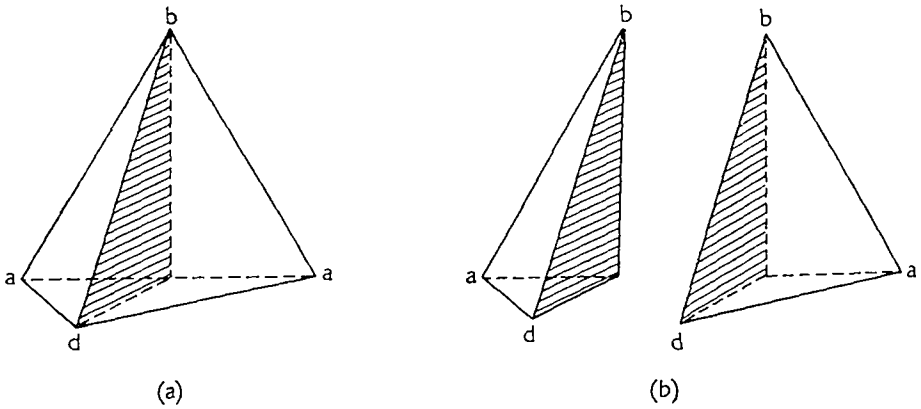


FIGURE 2. The *meso* carbon atom.

placed Ogston's hypothesis on a simpler and more fundamental basis by their perceptive recognition that like groups in unlike asymmetric environments are differentiable by enzymes whether the groups reside in the same molecule or in different molecules.

How is it possible to find asymmetry in a molecule devoid of optically active centers? For this purpose Schwartz and Carter recognized the *meso* carbon atom in analogy to the *meso* molecule in which equal and opposite asymmetries compensate to render the molecule optically inactive. Figure 2a shows a *meso* carbon atom, Caabd. One restriction in this definition, often ignored but essential to the argument that follows, is that all four substituents must be symmetrical, that is it must be possible to pass a plane through the molecule which will bisect the groups b and d. The resulting halves shown in Figure 2b are now tetrahedra with four unlike groups at

the apexes arranged in familiar antipodal relation to each other. Each a group resides in an environment of equal and opposite asymmetry and an asymmetric reagent, e.g. an enzyme, should behave toward these enantiomers just as it does toward a racemic mixture of molecules. Schwartz and Carter demonstrated this fact experimentally by showing that a simple asymmetric reagent, *l*-phenylethylamine, formed unequal amounts of diastereomers with β-phenylglutaric anhydride, a compound like citrate containing a *meso* carbon atom. It is to be noted also that the reaction was selected such that an effect could be detected optically without recourse to isotopic labeling, thus eliminating isotopic asymmetry from consideration.

It follows from the discussion just presented that ethanol, a compound with a *meso* carbon atom, should show stereospecificity of hydrogen transfer in enzymatic oxidation to acetaldehyde. That this is in fact true has been demonstrated experimentally with deuterium-labeled ethanol in a reaction[13] catalyzed by alcohol dehydrogenase (equation 4). When unlabeled ethanol was incubated with the

$$CH_3CD_2OH + NAD^+ \rightleftharpoons NADD + CH_3CDO + H^+ \quad (4)$$

enzyme and coenzyme in D_2O, no deuterium was taken up in any product, showing that the transfer of hydrogen is direct and does not involve solvent protons.

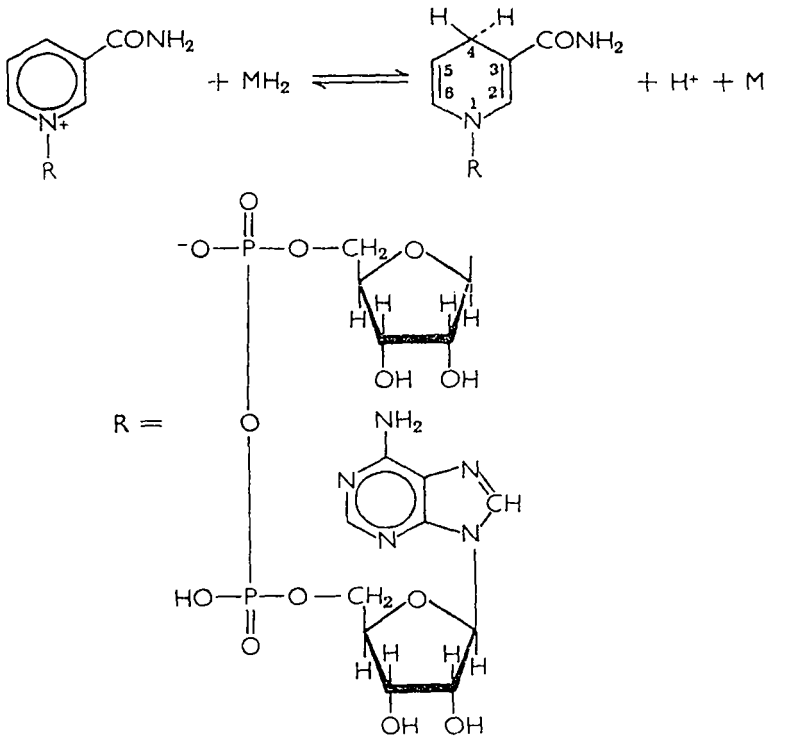
In further studies[14] the reverse enzymatic reactions were run with labeled acetaldehyde (equation 5) and labeled coenzyme (equation 6). It is obvious from the two kinds of labeled ethanol produced that

$$H^+ + CH_3CDO + NADH \rightleftharpoons CH_3CDHOH + NAD^+ \quad (5)$$

$$H^+ + CH_3CHO + NADD \rightleftharpoons CH_3CHDOH + NAD^+ \quad (6)$$

stereospecificity is directed not only toward ethanol but also toward NAD. In a review of stereospecific enzymatic hydrogen transfer at *meso* carbon atoms Levy, Talalay, and Vennesland[15] discuss these reactions and classify $C_{(4)}$ of the pyridine ring of NADH, the site of hydrogen transfer, as a *meso* carbon atom (Figure 3). Although it resembles a *meso* carbon in having two like (H, H) and two unlike groups, the latter are not symmetrical nor is the molecule symmetrical. $C_{(4)}$ is therefore not a *meso* carbon atom since it does not fit the definition of Schwartz and Carter.

Hirschmann[16] has explored the question of selection of like groups at non-*meso* carbon in symmetrical compounds. Although the central carbon atom of citrate is *meso*, the methylene carbons are not since they can not be bisected by a plane of symmetry; Hirschmann has



MH_2 is any reduced substrate capable of enzymatic dehydrogenation by NAD

FIGURE 3. The oxidoreduction of NAD.

shown that like groups on such carbons can be differentiated by any reagent, symmetrical or unsymmetrical. The same argument can be extended to $C_{(4)}$ of NAD, an asymmetric molecule; any reagent should be able more or less to distinguish the transferable hydrogens. It is therefore not unexpected[17] that dithionite reduction of NAD in D_2O yielded an unequal mixture of the two isomers (A and B) of NADD. A and B refer to the two approaches an incoming hydride ion can take in an attack of the $C_{(4)}$ position. From a study of the absolute configuration of degradation products of pyridine nucleotides reduced by A and B specific enzymes, Cornforth and colleagues[18] have deduced the absolute configuration of $C_{(4)}$ and formulate their findings in a rule which states that enzymes with A specificity transfer hydrogen from substrate to coenzyme on the side of the nicotinamide ring in which numbering is counterclockwise.

The question that follows from this discussion concerns the contribution of the enzyme to stereospecific transfer of hydride ions. In

the oxidation of alcohol by NAD with alcohol dehydrogenase the requirements for differentiation of hydrogen atoms in both substrate and coenzyme are theoretically fulfilled by the compounds themselves since they are complementary to each other; that is oxidized coenzyme is the asymmetric reagent needed for stereospecific recognition of *meso* carbon-bound hydrogen in the substrate, and the substrate is the indifferent reagent for selection of non-*meso* carbon-bound hydrogen in reduced coenzyme (equation 7). Further experimental work is necessary to define the role of the enzyme. It may act

$$\underset{(meso)}{\text{Ethanol}} + \underset{(asymmetric)}{\text{NAD}^+} \rightleftharpoons \underset{(meso)}{\text{Acetaldehyde}} + \underset{(asymmetric)}{\text{NADH}} + \text{H}^+ \qquad (7)$$

directly as the asymmetric agent required for selection of substrate hydrogen or it may act indirectly by augmenting the asymmetry of the coenzyme sufficiently to make the selection absolute. The latter alternative is possible on the basis of nuclear magnetic resonance studies which can detect no spectral difference between the hydrogen atoms at $C_{(4)}$ of NAD[19].

2. Galactose oxidase

In contrast to the action of glucose oxidase, which catalyzes the oxidation of the terminal aldehyde group of glucose, galactose oxidase mediates an attack on the terminal alcoholic group of galactose to produce a dialdose[20] (equation 8). An analogous reaction has been observed in the oxidation of fructose to a ketaldose[21].

$$HOCH_2(CHOH)_4CHO + O_2 \longrightarrow OHC(CHOH)_4CHO + H_2O_2 \qquad (8)$$

Reactions of this type are of great interest to chemists and biochemists since they make possible the preparation of dicarbonyl compounds hitherto attainable only by laborious and indirect chemical methods[22]. Chemical or enzymatic oxidation of aldoses suitably blocked at the terminal aldehyde group have in previous attempts led invariably to uronic acids; the specificity of these newly discovered enzymes for the primary alcoholic group obviates the necessity of protecting the existing carbonyl group.

Galactose oxidase is a copper-containing protein which has been crystallized from extracts of the mold *Dactylium dendroides*. Specificity studies with monosaccharide substrates have shown that the galactose configuration at $C_{(4)}$ (axial OH) is essential since glucose ($C_{(4)}$ equatorial) is inert. From the observation that 2-deoxygalactose, talose ($C_{(2)}$ axial), and galactosamine are all active substrates it was concluded that configuration at $C_{(2)}$ is not critical.

Since talose and galactose have the same configurations at $C_{(3)}$ and $C_{(4)}$, a theoretically more interesting interpretation is that the galactose configuration at $C_{(3,4)}$ is the essential structure.

An important application of the galactose oxidase reaction has been found in elucidation of polysaccharide structure where specific 6-oxidation of terminal galactose residues leads to formation of aldehydic side-chains susceptible to oxidation with Br_2 to galacturonosides. The relative resistance of galacturonosidic linkages to subsequent acid hydrolysis compared to other glycosidic linkages present permits the isolation of uniquely ordered fragments reflecting the sequence of monosaccharide units in the parent polymer[23].

3. Lactate dehydrogenase

The end-product of aerobic glycolysis is pyruvate (Figure 1) which is then further oxidized by the Krebs tricarboxylic acid cycle in animal tissues (Figure 4). During periods of strenuous exercise the tissues become deficient in oxygen, and this results in the accumulation of reduced coenzymes to the extent that pyruvate is reduced to lactate, which accumulates. On readmission of oxygen, lactate is oxidized to pyruvate; the enzyme catalyzing this oxido-reduction (equation 9) is lactate dehydrogenase[24]. Since the D-isomer

$$\text{L-Lactate} + \text{NAD}^+ \rightleftharpoons \text{Pyruvate} + \text{NADH} + \text{H}^+ \qquad (9)$$

is not a substrate for the enzyme the system exhibits absolute specificity of hydrogen transfer. A bacterial NAD-dependent lactate dehydrogenase has been described which is specific for the D-isomer[25].

Yeast contains lactate dehydrogenases which differ from the animal enzyme in that they are flavin-linked proteins[26]. Both isomers are oxidized but by two distinct enzymes, both of which transfer electrons directly to cytochrome C. They are therefore called D-lactate and L-lactate cytochrome C reductases. The L-enzyme has been crystallized and is a flavohemoprotein with FMN and protoheme as prosthetic groups; the D-enzyme is associated with mitochondria but has been solubilized and partially purified. The prosthetic group is FAD.

The crystalline animal enzyme has been found to exist in several molecular forms known as isozymes, a term used to denote the different proteins which may coexist to catalyze the same reaction. Lactate dehydrogenase was one of the first enzymes to be recognized as a complex of isozymes; many other enzymes are known to be

isozymic mixtures, a property which is now regarded as a common characteristic and another manifestation of their protein nature. Since isozymes may have different affinities for a substrate and display different degrees of product inhibition[27] they serve as a means of regulating metabolic activity.

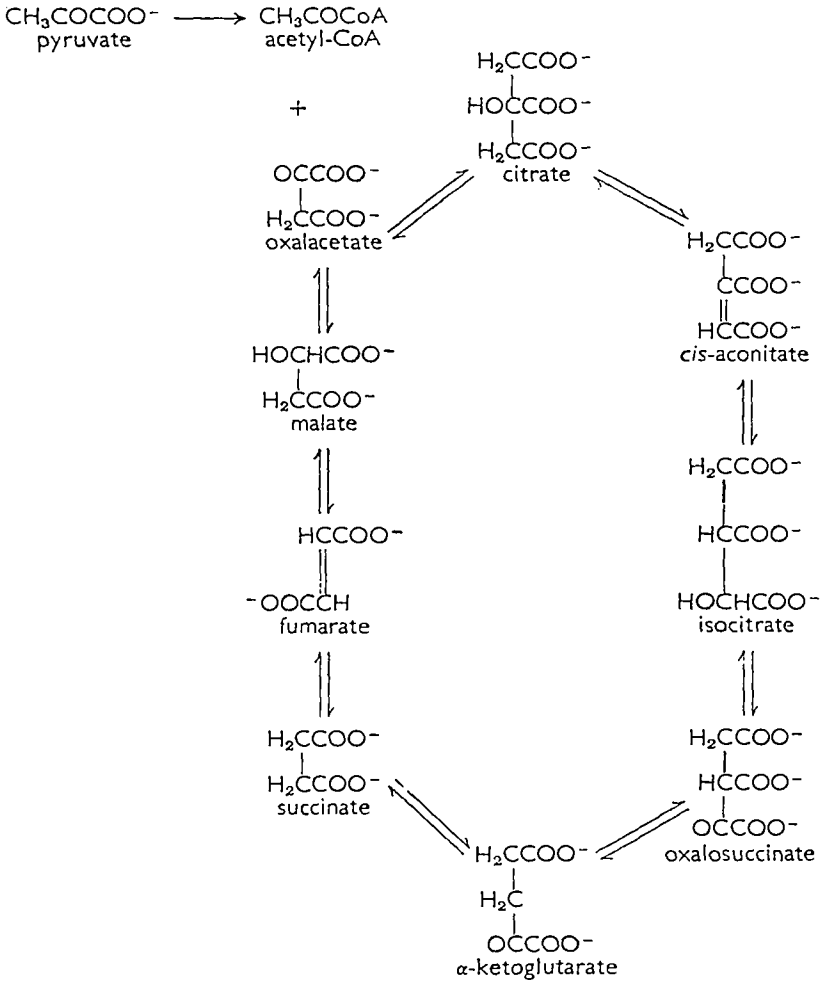


FIGURE 4. The Krebs tricarboxylic acid cycle.

4. Malate dehydrogenase[28]

Another critical conversion of an alcohol into a ketone is the oxidation of malate to oxalacetate catalyzed by malate dehydrogenase. This reaction constitutes the last segment of the tricarboxylic

acid cycle (Figure 4) and supplies oxalacetate for condensation with acetyl-CoA to form citrate, the first of the tricarboxylic acid intermediates of pyruvate oxidation. The enzyme is NAD-dependent, stereospecific for hydrogen transfer, and catalyzes the reaction shown in equation (10).

$$\text{L-Malate} + \text{NAD}^+ \rightleftharpoons \text{Oxalacetate} + \text{NADH} + \text{H}^+ \qquad (10)$$

5. Oxidative decarboxylases

Associated with oxidation of secondary alcohols to ketones is an important biochemical reaction, decarboxylation. Carbon is supplied

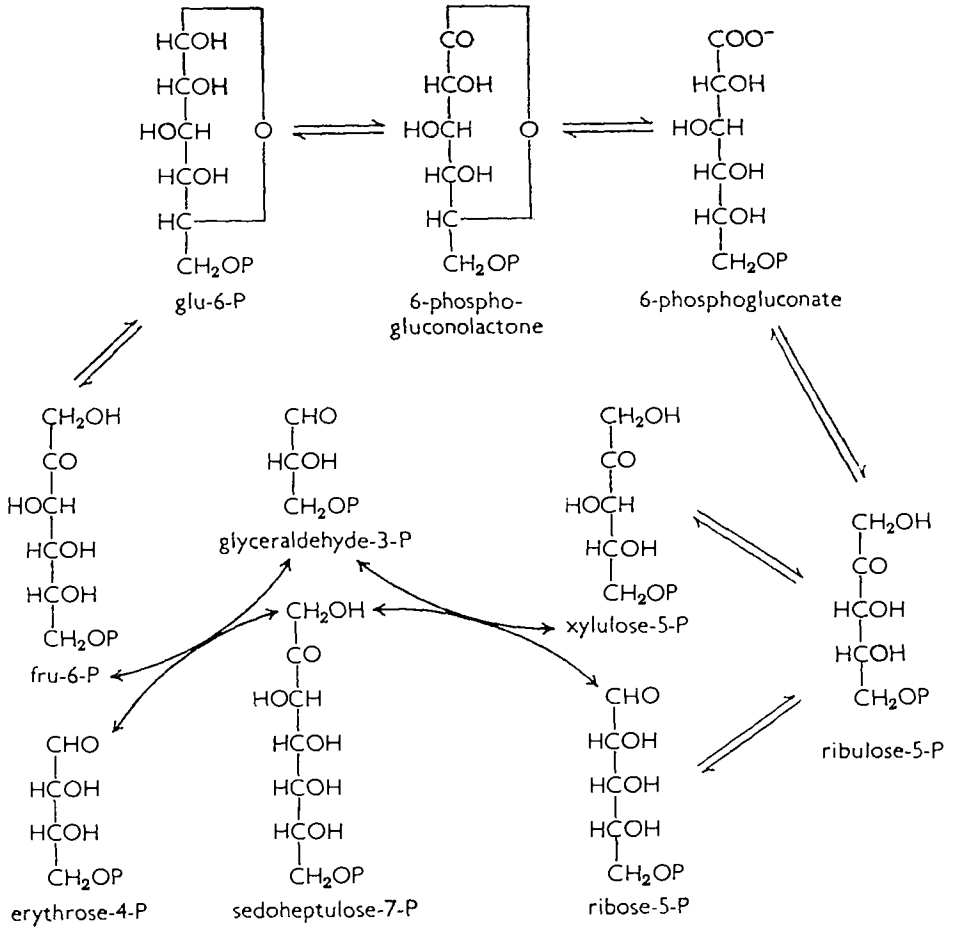


FIGURE 5. The phosphogluconate oxidative pathway.

as fuel for living tissues in a reduced state and through oxidation energy is released for synthetic processes in the organism; the state of lowest energy is carbon dioxide, ultimate catabolic product of carbon. Although oxygen is required finally to remove electrons from reduced carbon compounds, direct combination of oxygen with these compounds is relatively rare and never occurs to form carbon dioxide. Instead, carbon dioxide is evolved as a result of decarboxylation, a reaction represented in each of the major catabolic pathways. In many cases the precursor is a β-hydroxy acid and the product of decarboxylation is an essential metabolite. In the Krebs cycle (Figure 4) there are two such reactions, one catalyzed by the malic enzyme and the other by isocitrate dehydrogenase. The decarboxylation products are pyruvate and α-ketoglutarate, respectively, both of which are key intermediates in the cycle and supply carbon for the amino acids alanine and glutamate, respectively (section III.F.3). In the phosphogluconate oxidative pathway (Figure 5) a similar oxidative decarboxylation occurs in the formation of ribulose-5-P from 6-phosphogluconate by 6-phosphogluconate dehydrogenase. The pentulose is important as a precursor of pentose required by the organism for nucleic acid synthesis. Although the tendency to decarboxylate is characteristic of β-keto acids no evidence for these intermediates has been found.

a. Malic enzyme[28]. This system is distinct from malate dehydrogenase (section II.B.4) and catalyzes the reaction shown in equation (11).

$$\text{-Malate}^{2-} + \text{NADP}^{+} \overset{Mn^{2+}}{\rightleftharpoons} \text{Pyruvate}^{-} + \text{NADPH} + CO_2 \qquad (11)$$

b. Isocitrate dehydrogenase[29]. The requirements for this enzyme are similar to the previous one. Although oxalosuccinate is decarboxylated by this enzyme there is no evidence for its existence as a free intermediate in the reaction given by equation (12). A detailed

$$\text{Isocitrate}^{3-} + \text{NADP}^{+} \overset{Mn^{2-}}{\rightleftharpoons} \alpha\text{-Ketoglutarate}^{2-} + \text{NADPH} + CO_2 \qquad (12)$$

study[30] of the mechanism of this reaction has shown that a carbanion intermediate is formed with retention of configuration during replacement of the central carboxyl group by a proton generating a central *meso* carbon atom in α-ketoglutarate (Figure 6).

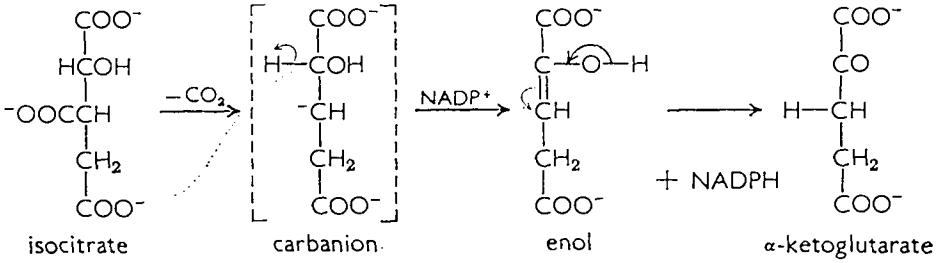


FIGURE 6. Mechanism of oxidative decarboxylation of isocitrate.

c. 6-Phosphogluconate dehydrogenase[31]. In this reaction NADP is again the cofactor but the metal requirement is not absolute (equation 13). A study of the mechanism of this reaction showed that decar-

$$\text{6-Phosphogluconate}^{3-} + \text{NADP}^{+} \longrightarrow \text{Ribulose-5-P}^{2-} + \text{NADPH} + \text{CO}_2 \quad (13)$$

boxylation was accompanied by inversion of configuration during replacement of the carboxyl group by a proton[32] (Figure 7).

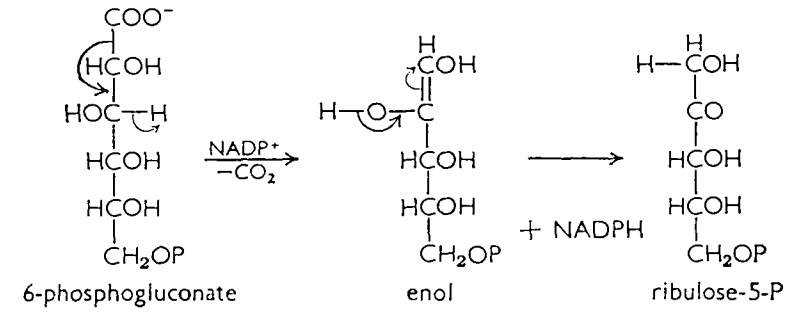


FIGURE 7. Mechanism of oxidative decarboxylation of 6-phosphogluconate.

d. Enzymes of the glucuronic acid pathway[33]. The identification of L-xylulose in the urine of pentosurics led to the discovery of another metabolic system known as the glucuronic acid pathway (Figure 8). L-Xylulose was found to arise from the decarboxylation of 3-keto-gulonate which in turn resulted from the oxidation of L-gulonate by NAD and the kidney enzyme, L-gulonate dehydrogenase. Here again is an example of carbon dioxide formation by decarboxylation but in contrast to the previous reactions a β-keto acid is clearly implicated.

Normally L-xylulose is reduced by NADPH to xylitol which is then oxidized at the other penultimate carbon by NAD to D-xylulose. In the condition known as pentosuria the reduction of L-xylulose is blocked, the compound accumulates in the blood, and is ultimately

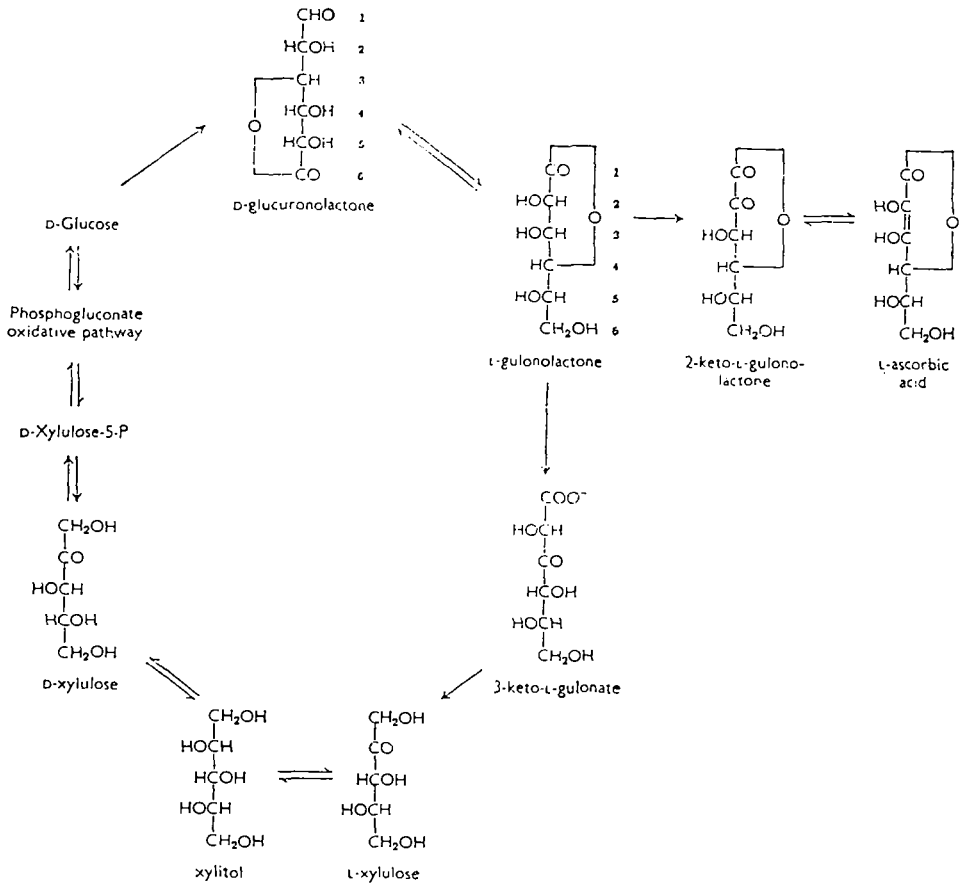


FIGURE 8. The glucuronic acid pathway.

excreted in the urine. Xylitol is a *meso* compound since $C_{(2)}$ and $C_{(4)}$ are compensated centers of asymmetry; they are therefore differentiable by asymmetric reagents (enzymes or possibly coenzymes) giving rise to the enantiomeric xyluloses.

In the liver of all species except man, monkey, and guinea pig L-gulonate undergoes an entirely different conversion; the first step is enzymatic γ-lactonization followed by atmospheric oxidation catalyzed by an oxygenase to 2-keto-L-gulonate which then enolizes to ascorbic acid.

For a long time biochemists were puzzled by the configurational changes in these reactions which suggested the existence of a complicated series of epimerizations. It can be seen from Figure 8 that

these changes are simply the result of reversal of the numbering system in going from D-glucuronate to L-gulonate and of stereospecific selection in going from xylitol to either ketopentose.

6. Glycerophosphate dehydrogenase[34]

A recently recognized important cyclic process utilizes the redox couple L-glycerophosphate/dihydroxyacetone-P and occurs in musculature with high energy requirements such as insect flight and saltatory muscles and vertebrate tissues. The reaction in the cytoplasm is NAD-dependent and reversible (equation 14). In mitochondria it is unidirectional and NAD-independent (equation 15). The net reaction (equation 16) is the sum of equations (14) and (15).

$$\text{Dihydroxyacetone-P} + \text{NADH} + \text{H}^+ \rightleftharpoons \text{NAD}^+ + \alpha\text{-Glycerophosphate} \quad (14)$$

$$\alpha\text{-Glycerophosphate} + \tfrac{1}{2}\,\text{O}_2 \longrightarrow \text{Dihydroxyacetone-P} + \text{H}_2\text{O} \quad (15)$$

$$\text{NADH} + \text{H}^+ + \tfrac{1}{2}\,\text{O}_2 \longrightarrow \text{NAD}^+ + \text{H}_2\text{O} \quad (16)$$

This shuttle thus provides for the conveyance of hydrogen from substrates via pyridine nucleotides in the cytoplasm to sites of atmospheric oxidation in respiratory particles (mitochondria).

7. β-Hydroxyacyl-CoA dehydrogenase[35]

A critical step in the degradation of fatty acids is the oxidation of β-hydroxyacyl-CoA by NAD to the β-keto ester (equation 17) which then undergoes thiolytic cleavage by CoA to yield acetyl-CoA and an acyl-CoA shorter by two carbon atoms (equation 18).

$$\text{RCHOHCH}_2\text{COSCoA} + \text{NAD}^+ \rightleftharpoons \text{RCOCH}_2\text{COSCoA} + \text{NADH} + \text{H}^+ \quad (17)$$

$$\text{RCOCH}_2\text{COSCoA} + \text{HSCoA} \rightleftharpoons \text{RCOSCoA} + \text{CH}_3\text{COSCoA} \quad (18)$$

8. Methyl ketone formation[36]

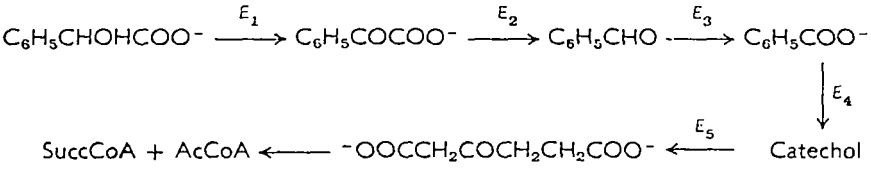
Resting cell suspensions of *Penicillium roqueforti*, the mold used in the manufacture of bleu cheese, catalyze the oxidation of fatty acids to the methyl ketone shorter by one carbon atom. The characteristic aroma and flavor of this cheese is attributed to these compounds, the main one being 2-heptanone. The nature of the end-product suggests that this pathway of fatty acid degradation involves hydrolytic removal of CoA from acylacetyl-CoA (equation 17) to form a β-keto acid which then undergoes decarboxylation.

9. Regulation of a series of carbonyl reactions

Although biochemical reactions of many kinds are essential to the functioning of living cells, the cell contents are not chaotic mixtures

of independently metabolizing enzymes. One aspect of metabolic activity of paramount importance is the maintenance of the steady-state composition of the cell, homeostasis. Since enzymes are the catalysts for cellular reactions, control of these catalysts will regulate the steady-state composition. Several mechanisms are available for this regulation; one has already been alluded to in the discussion of isozymes (section II.B.3). Another device is feedback inhibition in which the activity of an enzyme is diminished by interaction with an intermediate or end-product of a sequence of reactions. Still another is control of synthesis of an enzyme; this can be an increase in synthesis, known as induction, or a decrease, repression. Although all of these processes are of great current interest, the last is probably the most interesting since it is thought that this kind of control is effected at the level of messenger RNA (ribonucleic acid) and is therefore under genetic direction.

An example of dual control of enzyme synthesis is seen in the bacterium *Pseudomonas fluorescens* in which a pathway of oxidation of a secondary alcohol, mandelate, is regulated through the effect of substrate as well as products (equation 19)[37]. Both mandelate and



(19)

benzoyl formate are inducers of E_1. Benzoate repressed E_1, E_2, and E_3 but induced E_4 and E_5. Catechol repressed E_{1-4} but induced E_5. Both succinate and acetate repressed E_{1-5}. All repressive effects could be reversed by increasing concentrations of mandelate.

10. Inositol dehydrogenase

Several species of microorganisms[38] as well as mammalian tissues[39] contain a system for the oxidation of myoinositol to inosose. Since this is an NAD-linked dehydrogenation the reaction has been used

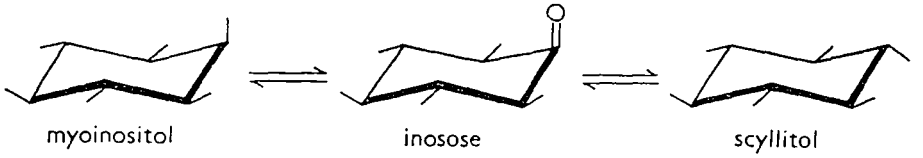


FIGURE 9. The interconversion of myoinositol, inosose, and scyllitol.

as an assay for inositol. In mammalian tissues inosose has been shown to be the intermediate through which myoinositol and its 2-epimer, scyllitol, are interconverted (Figure 9).

II. Hydroxy steroid dehydrogenases[40]

Microorganisms and animal tissues contain enzymes which catalyze the oxidation of hydroxyl groups substituted at all positions where they occur in the steroid nucleus: 3α, 3β, 11β, 17α, 17β, 20α, 20β, and 21. Both NADP (equation 20) and NAD (equation 21) are coenzymes for these reactions. In addition to their dehydrogenating function these enzymes are capable of transferring hydrogen between the two coenzymes at catalytic concentrations of the steroids (equations 20, 21, and 22). Stereospecificity of hydrogen transfer has

$$\text{Keto steroid} + \text{NADPH} + \text{H}^+ \rightleftharpoons \text{Hydroxy steroid} + \text{NADP}^+ \quad (20)$$

$$\text{Hydroxy steroid} + \text{NAD}^+ \rightleftharpoons \text{Keto steroid} + \text{NADH} + \text{H}^+ \quad (21)$$

$$\text{Sum:} \quad \text{NADPH} + \text{NAD}^+ \rightleftharpoons \text{NADP}^+ + \text{NADH} \quad (22)$$

been demonstrated for these enzymes, all of those examined showing B specificity; that is hydrogen is transferred to the side of the pyridine ring on which numbering is clockwise[18].

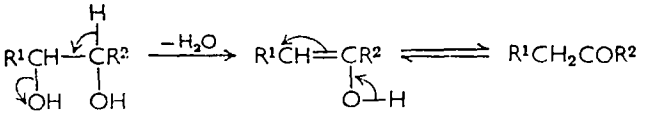
C. Oxidation of an Enediol to a Diketone

Plants and animals both contain systems for the oxidation of L-ascorbic acid to dehydroascorbic acid. In the rat and guinea pig the oxidation can occur nonenzymically, catalyzed by a heat-stable particulate factor from liver[41]; in plants a copper-containing oxidase has been described. The unusual feature of the plant reaction[42] is that water and not H_2O_2 is formed as a by-product (equation 23).

$$\text{Ascorbic acid} + \tfrac{1}{2}\,O_2 \longrightarrow \text{Dehydroascorbic acid} + H_2O \quad (23)$$

D. Dehydration[43]

Another series of reactions involving alcoholic substrates is the disproportionation of vicinal glycols to carbonyl products with the concomitant formation of a deoxy function. The net change is a dehydration catalyzed by enzymes known as dehydrases. Two mechanisms can be written for this reaction for each of which there are examples. The reaction illustrated by equation (24) proceeds through liberation of a carbon-bound hydrogen as a proton with release of a hydroxyl group to form water and an enol which then tautomerizes. In equation (25) the same hydrogen is liberated as a



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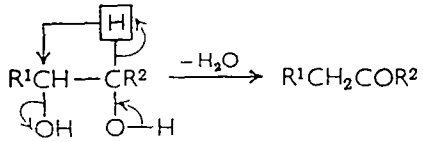
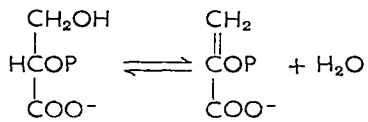


(25)

hydride ion displacing the hydroxyl group which then combines with the proton liberated from the other alcoholic group. Although this class of reactions is peculiar to microbial systems there is one notable exception, the enolase reaction, found in all classes of living matter.

1. Enolase[44]

A central reaction of the glycolytic sequence (Figure 1) is the dehydration of D-2-phosphoglycerate to phosphoenolpyruvate, a variant of equation (24) in which the enol form is unable to undergo ketonization (equation 26). A second enzymatic reaction catalyzed



(26)

by pyruvate kinase dephosphorylates the enol to pyruvate coupled to the phosphorylation of ADP to ATP. The importance of these reactions to the organism is that energy unavailable in the form of secondary phosphate is rendered available in the conversion to enol phosphate, which is capable of generating ATP, the principal store of energy for all manner of biochemical reactions.

2. 6-Phosphogluconate dehydrase

A pathway of glucose dissimilation in microorganisms, elucidated by Entner and Doudoroff[45], contains a dehydration step in which 6-phosphogluconate is converted into 2-keto-3-deoxy-6-phosphogluconate.

3. Dihydroxy acid dehydrase[46]

Extracts of *Neurospora crassa* and *E. coli* dehydrate α,β-dihydroxy-β-methylvalerate to α-keto-β-methylvalerate and α,β-dihydroxyiso-

valerate to α-ketoisovalerate, precursors of isoleucine and valine, respectively.

4. Diol dehydrase[47]

In other microorganisms 1,2-propanediol is converted into propionaldehyde and ethylene glycol into acetaldehyde. Cobamide is a required cofactor for these enzymes. Evidence for equation (25) has been adduced by Brownstein and Abeles[48] who found no incorporation of deuterium when the reaction was carried out in D_2O. An enol intermediate required by equation (24) would have introduced isotope into the product.

5. Glycerol dehydrase[49]

A reaction of economic importance is the analogous dehydration of glycerol to β-hydroxypropionaldehyde by a species of *Lactobacillus* found in fermenting grain mash. The product is readily dehydrated nonenzymically to acrolein, an undesirable product in the manufacture of whiskey.

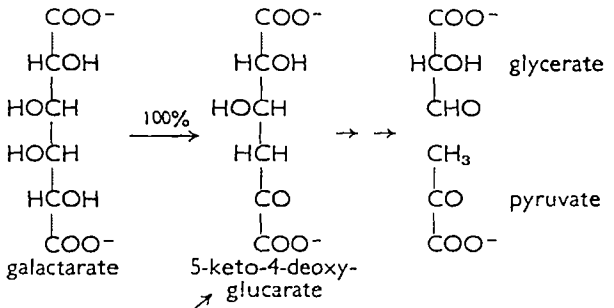
6. L-Tartrate dehydrase[50]

Dehydration of L-tartrate to oxalacetate has been demonstrated recently in a genus of *Pseudomonas*.

7. Galactarate dehydrase[51]

An homologous reaction has been found recently in *E. coli* in which galactarate (equation 27) and glucarate (equation 28), the dicarboxylic acid derivatives of galactose and glucose, respectively, are dehydrated enzymatically to the corresponding α-keto-β-deoxy acid. Further reactions split the compound centrally to pyruvate and glycerate.

The stereochemistry of these reactions is interesting and merits further consideration. Galactarate-1-^{14}C gave rise to labeled glycerate and unlabeled pyruvate while galactarate-6-^{14}C yielded labeled pyruvate. It is clear that galactarate, a *meso* compound, is dehydrated asymmetrically in a reaction reminiscent of the asymmetric oxidation of xylitol (section II.B.5.d). Glucarate on the other hand is dehydrated less specifically, 15% resulting in 2-keto-3-deoxy- and 85% in 5-keto-4-deoxyglucarate. A possible explanation for the latter observation is the existence of two glucarate dehydrases of opposite stereospecificity.



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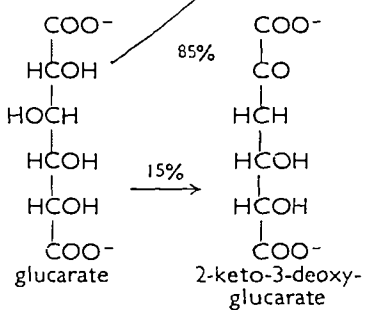
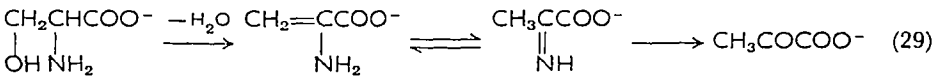


(28)

8. Amino acid dehydrases[52]

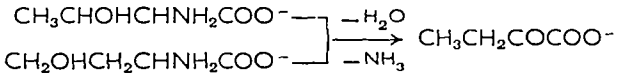
Although the net reaction is the elimination of the elements of ammonia, the mechanism probably involves dehydration followed by hydrolysis of the imino compound. Pyridoxal-P is the coenzyme for these reactions.

a. Serine dehydrase. The formation of pyruvate from serine has been observed in mammalian liver (equation 29).



(29)

b. Threonine and homoserine dehydrases. The liver is similarly capable of catalyzing the formation of α-ketobutyrate from the isomeric amino acids, threonine and homoserine (equation 30).

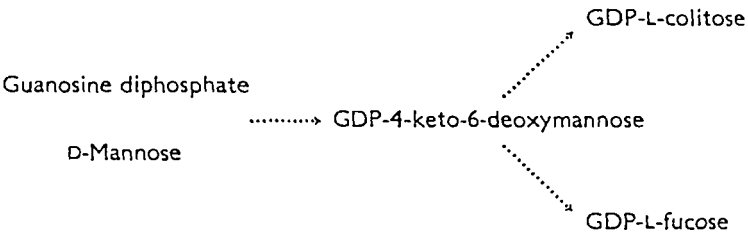


(30)

9. Deoxy sugar synthesis[53]

In contrast to the simplicity of D and L interconversions discussed in section II.B.5.d, the formation of 6-deoxy and 3,6-dideoxy sugars with L configuration from D-sugars is complicated and involves several epimerization steps. In further contrast is the fact that the

sugars are not free as in the uronic acid pathway but nucleotide-bound. An intermediate has been isolated in these reactions and identified as the 4-keto-6-deoxy compound, as shown in equation (31). Since the net change in conversion of hexose into the inter-



(31)

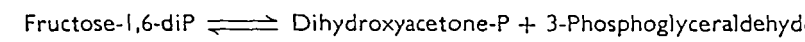
mediate is loss of a molecule of water with formation of keto and deoxy functions, the reactions bear a formal resemblance to the other dehydrations. The complete mechanism of these reactions, however, remains unknown.

E. Carbon–Carbon Cleavage

A number of enzymes catalyze the cleavage of carbon–carbon bonds to give rise to important intermediary carbonyl compounds.

1. Aldolase

A critical step in the glycolytic pathway (Figure 1) is the splitting of hexose diphosphate to triose phosphates, achieved through a reverse aldol reaction catalyzed by aldolase. The literature pertaining to this enzyme has been reviewed by Rutter[54]. Although the aldolase reaction operates with many substrates the reaction of principal interest is shown in equation (32). The newly formed carbonyl

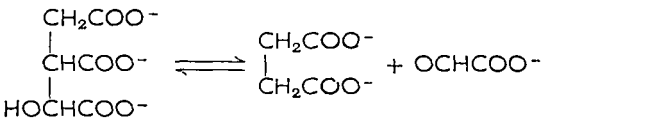


(32)

group resides in the aldehyde. The stereospecificity of this reaction will be discussed in section III.C.4.

2. Isocitrate lyase[55]

The accumulation of glyoxylate and oxalate in certain species of molds has been found to result from the cleavage of isocitrate to succinate and glyoxylate, subsequently oxidized to oxalate (equation 33). The reaction in the direction of synthesis resembles a Stobbe



(33)

condensation stopped short of the dehydration step which ordinarily leads to an unsaturated product. That this reaction cannot be classed as an aldol condensation is seen from the failure of succinate to incorporate tritium in the half reaction between enzyme and succinate in T_2O.

The importance of this reaction is its key position in the glyoxylate cycle (Figure 10) by which acetate gives rise to four-carbon acids for carbohydrate and protein synthesis. The first occurrence of the enzyme in a multicellular organism has been reported recently[56].

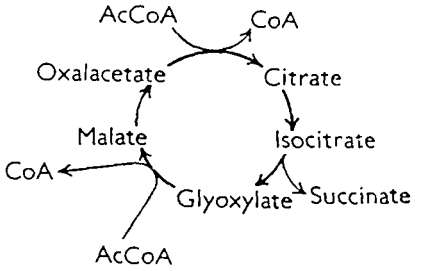


FIGURE 10. The glyoxylate cycle.

3. Inositol oxygenase[57]

An interesting reaction in which a carbonyl and carboxyl group are generated simultaneously is the atmospheric oxidation of myo-inositol, catalyzed by an enzyme in rat kidney. The product is

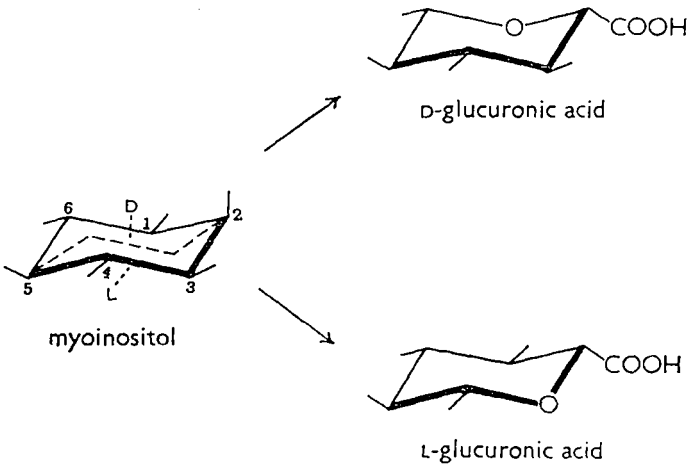


FIGURE 11. Oxidation of inositol to DL-glucuronic acid.

D-glucuronic acid, the aldehyde group originating from $C_{(6)}$ of inositol and the carboxyl group from $C_{(1)}$. Ferrous ions are essential for the reaction. By means of ^{18}O labeling it was shown that the added oxygen appeared in the carboxyl group.

An unusual aspect of this reaction is its stereospecificity; with the crude kidney enzyme the product was a racemic mixture of glucuronic acids, presumably arising by cleavage of corresponding bonds across the plane of symmetry of inositol catalyzed by specific enzymes (Figure 11). Purification of the enzymes revealed that the D-enzyme was the more stable. Although the formation of D-glucuronate from inositol has been repeated in many laboratories, the formation of the L-isomer remains unconfirmed.

F. Oxidative Deamination

Analogous to the oxidation of alcohols to aldehydes and ketones is the oxidation of amino compounds to metabolically important carbonyl compounds.

1. Spermidine oxidase[58]

The bacterium *Serratia marcescens* contains an enzyme which catalyzes the atmospheric oxidation of spermidine to γ-aminobutyraldehyde and trimethylenediamine (equation 34).

$$NH_2(CH_2)_3NH(CH_2)_4NH_2 + H_2O + O_2 \longrightarrow NH_2(CH_2)_3CHO + NH_2(CH_2)_3NH_2 + H_2O_2 \quad (34)$$

2. L-Glutamate dehydrogenase[59]

The most important reaction in this class is the reversible oxidative deamination of L-glutamate to α-ketoglutarate and NH_4^+ by NAD or NADP, catalyzed by glutamate dehydrogenase.

The reaction supplies the chief link between protein and carbohydrate metabolism and in conjunction with transamination (section III.F.3) provides for the oxidative deamination of many other amino acids. Although the actual reaction mechanism remains obscure the enzyme is known to be B stereospecific with respect to hydrogen transfer to both coenzymes and like liver alcohol dehydrogenase, the liver enzyme contains zinc.

Glutamate dehydrogenase has become one of the model systems for the study of reversible dissociation of proteins into subunits. An interesting observation pertinent to this dissociation is that, whereas the tetrameric form of the enzyme has glutamate specificity, the monomer is specific for alanine. Moreover conditions which change

the rate of the glutamate reaction cause complementary changes in the alanine reaction.

3. D- and L-Amino acid oxidases[60]

Enzymes are found in most living systems which catalyze the oxidation of amino acids to α-keto acids according to equation (35).

$$RCH(NH_3^+)COO^- + EnzFAD + H_2O \rightleftharpoons RCOCOO^- + NH_4^+ + EnzFADH_2 \quad (35)$$

$EnzFADH_2$ is then oxidized by atmospheric oxygen to EnzFAD and H_2O_2. Both the D- and L-enzymes show absolute optical specificity.

G. Prostaglandins

A class of compounds originally thought to be elaborated by the prostate gland has been isolated from human and ovine sperm plasma. Prostaglandins are characterized by the presence of a cyclopentanone

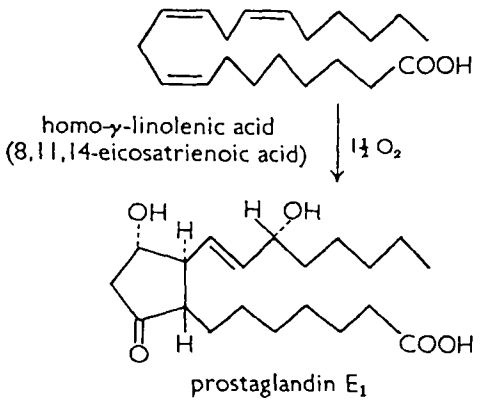


FIGURE 12. Biosynthesis of prostaglandin.

ring and have pharmacological activity on smooth muscle. Recent work on the biosynthesis[61] of these compounds has disclosed that they arise from the essential fatty acids and may explain the dietary requirement for such compounds as linolenic and arachidonic acids, etc. The detailed mechanism of their synthesis remains unknown but the overall reaction is the uptake of three atoms of oxygen (Figure 12).

III. BIOLOGICAL REACTIONS OF CARBONYL GROUPS

A. Oxidation to Acids, Esters, Anhydrides, and Lactones

1. Aldehyde dehydrogenases

These enzymes have been reviewed[62] and will not be discussed in detail. They have a wide range of specificity and like the alcohol

dehydrogenases occur in many forms of life. The coenzyme is either NAD or NADP and the reaction proceeds according to the general pattern of equation (36), where A is hydroxyl, phosphate, arsenate

$$RCHO + NAD(P)^+ + HA \rightleftharpoons RCOA + NADH(P) + H^+ \qquad (36)$$

or mercaptan. A recent addition to the known substrates for these enzymes is retinal which is oxidized to vitamin A acid[63].

2. Phosphoroclastic reaction[64]

Cleavage of pyruvate by phosphate was observed long before the reverse pyruvate synthase reaction (equation 1). The net reaction is an internal oxidoreduction in which the carbonyl group is oxidized to carboxyl and two protons are reduced to molecular hydrogen.

3. α-Keto acid dehydrogenases[65]

Pyruvate and α-ketoglutarate are the principal α-keto acids encountered in living systems and both are intermediates in the Krebs tricarboxylic acid cycle (Figure 4). The systems for oxidation of these compounds are extremely complicated and not entirely under-

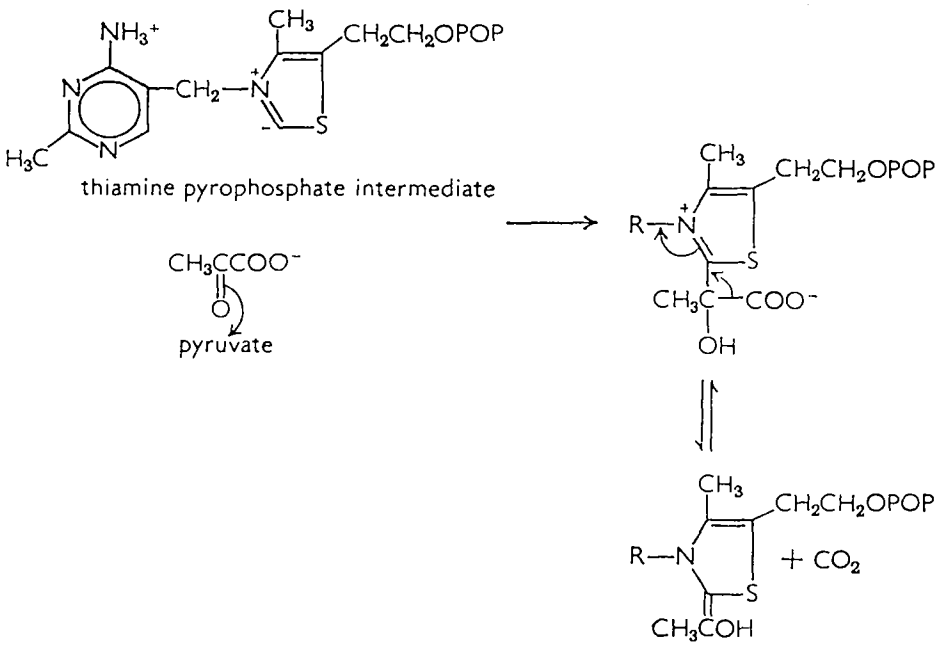


FIGURE 13. Mechanism of decarboxylation of pyruvate by thiamine pyrophosphate.

stood. It is known that lipoic acid (6,8-dithiooctanoic acid) and thiamine pyrophosphate (cocarboxylase) are required for the several enzymes. The first step, decarboxylation, has largely been elucidated[66]. It had been shown earlier that thiamine in basic solution will decarboxylate pyruvate to form acetoin; later it was found that 3,4-dimethylthiazole at alkaline pH will catalyze the same reaction. It was further shown by nuclear magnetic resonance spectroscopy in D_2O that $H_{(2)}$ of dimethylthiazole is exchangeable with solvent protons; the thiazole moiety is thus the catalytically active part of the coenzyme and effects decarboxylation by the mechanism illustrated in Figure 13. The addition product, containing a two-carbon fragment at the aldehyde level of oxidation, transfers the fragment to lipoate to form 8-(*S*-acetyl)-6,8-dimercaptooctanoate and thiamine pyrophosphate. The acetyl group is then transferred enzymatically to CoA forming acetyl-CoA and reduced lipoate which is then reoxidized to lipoate with NAD[67]. A similar series of reactions converts α-ketoglutarate to succinyl CoA and CO_2.

4. Glucose-6-P dehydrogenase[31]

This enzyme is spread throughout the biological kingdoms and has been the subject of intensive study from all aspects of enzymology. The reaction catalyzed is the oxidation of D-glucopyranose-6-P by NADP to give δ-gluconolactone-6-P, NADPH, and H^+. The reaction is important not only in the catabolism of glucose (Figure 5) but also as a sensitive analytical tool for the assay of compounds and enzymatic reactions which can be coupled to the dehydrogenase. The increase in light absorbancy at 340 mμ is a measure of NADPH formation and constitutes the basis for the analytical method.

5. Glucose oxidase[68]

Microorganisms have long been known to oxidize glucose to gluconate with concomitant formation of H_2O_2. Further studies of the reaction have shown a requirement for FAD which as the primary hydrogen acceptor is subsequently dehydrogenated by O_2. Glucose oxidase has been identified with notatin, elaborated by *Penicillium notatum*, deriving its antibiotic activity from the lethal peroxide generated.

The enzyme is specific for β-D-glucopyranose which is oxidized to δ-gluconolactone; the lactone is then spontaneously hydrolyzed to D-gluconate as shown in Figure 14.

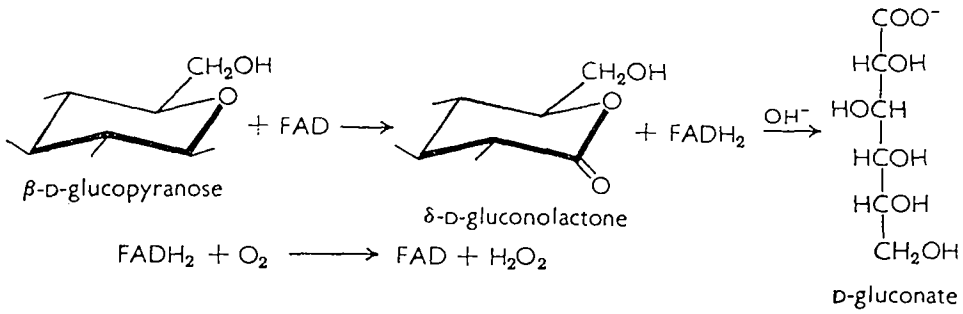


FIGURE 14. The glucose oxidase reaction.

6. Bioluminescence[69]

Straight-chain aldehydes from C_7 to C_{18} have been implicated in the reactions leading to light emission in luminous bacteria. In these reactions light is produced when reduced FMN and aldehyde are incubated with the enzyme luciferase in the presence of O_2. The aldehyde apparently combines with oxygen to form a peroxide intermediate which in its rearrangement to the corresponding acid liberates sufficient energy to excite some product of the reaction to fluoresce.

B. Reduction to Alcohols

The general reactions presented in section II.B.1 are reversible and therefore will not be discussed further. Certain reductive reactions of carbonyl compounds of particular metabolic significance will be considered, however.

1. Glucuronolactone reductase[33]

The first step in the catabolism of glucuronic acid (Figure 8) is the reduction of the terminal aldehyde group of D-glucuronolactone by NADPH to an alcohol, L-gulonolactone. All species of animals tested demonstrate this conversion so that the block in the synthesis of ascorbic acid by man, monkey and guinea pig does not occur at this step but in the further catabolism of L-gulonolactone.

2. Aldose and ketose reductases

Hers[70] has described two enzymes present in sheep seminal vesicle which catalyze reversibly the reduction of glucose (equation 37) and fructose (equation 38) to sorbitol by NADPH and NADH, respectively. Since NADP occurs in tissues largely in the reduced form and

NAD, largely oxidized, the reaction tends toward the conversion of glucose into fructose with sorbitol the intermediate (equation 39).

$$\text{Glucose} + \text{NADPH} + \text{H}^+ \xrightleftharpoons{\text{Aldose reductase}} \text{Sorbitol} + \text{NADP}^+ \quad (37)$$

$$\text{Sorbitol} + \text{NAD}^+ \xrightleftharpoons{\text{Ketose reductase}} \text{Fructose} + \text{NADH} + \text{H}^+ \quad (38)$$

$$\text{Sum: Glucose} + \text{NADPH} + \text{NAD}^+ \rightleftharpoons \text{Fructose} + \text{NADH} + \text{NADP}^+ \quad (39)$$

3. Reduction of ketones

Prelog[71] and coworkers have studied the steric course of reduction of bicyclic ketones by NADH in microbial systems. They have

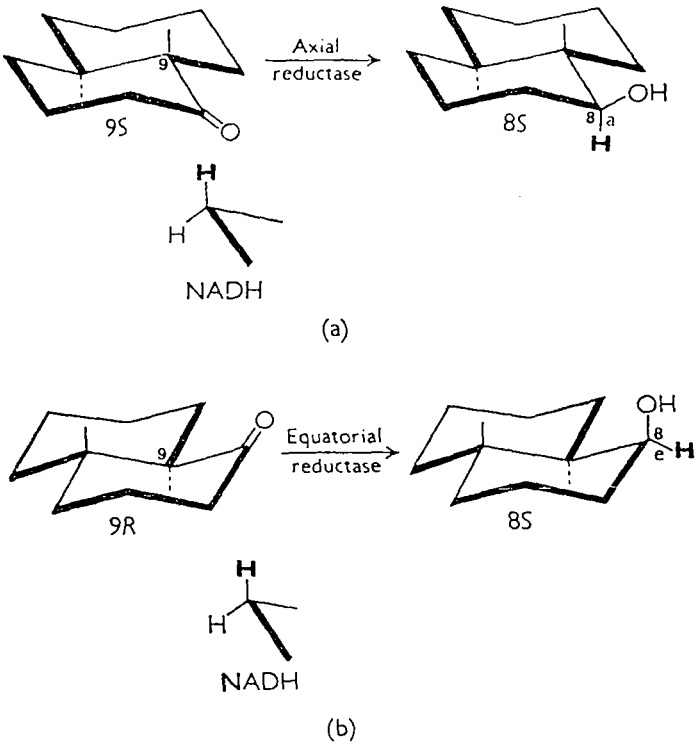


FIGURE 15. Stereospecific reduction of bicyclic ketones.
(a) 9*S*-axial approach favorable.
(b) 9*R*-equatorial approach favorable.

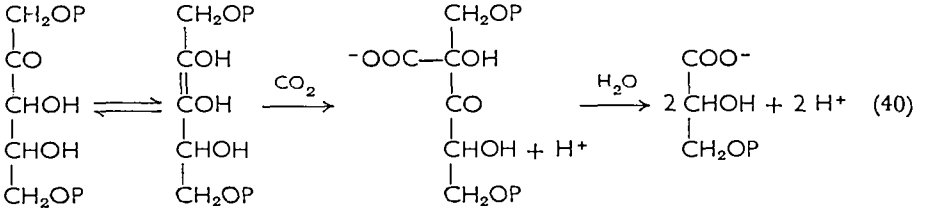
observed that in the pair of enantiomers illustrated in Figure 15, where configuration of $C_{(9)}$ is *S*[72] in (a) and *R* in (b), the configuration of the secondary alcohol at $C_{(8)}$ is *S* in both (a) and (b), that is

$H_{(8)}$ is axial in (a) and equatorial in (b). To account for these results they propose that a specific hydrogen at $C_{(4)}$ of the nicotinamide ring of the coenzyme (Figure 3) approaches the carbonyl group of the ketone in a preferred configuration, axial when $C_{(9)}$ is *S* and equatorial when *R*. Substrate, coenzyme, and enzyme are thought to be held in proper alignment for these approaches by hydrophilic and hydrophobic bonds. Prelog has enlarged on this concept[73] by comparing the structures of various substrates of a given enzyme. When the carbon skeletons of mono-, bi-, and tricyclic cyclohexanones are superimposed such that the carbonyl groups are always in the same position for attack by the coenzyme–enzyme complex, a diamond lattice section is obtained which defines that space not occupied by enzyme, coenzyme, inhibitor, or adsorbed solvent in the transition complex. From the characteristics of this space and the structure of nonsubstrate analogs, some notion concerning the structure of the complex can be obtained.

C. Carbon–Carbon Bond Formation

1. Carboxylation[74]

Only one reaction is known in which addition of carbon dioxide occurs at a carbonyl group. This is the photosynthetic carboxylation of ribulose-1,5-diP with the ultimate formation of two molecules of 3-phosphoglycerate, the precursor of 1,3-diphosphoglycerate (section II.A.2). Spinach leaves are a particularly rich source of the carboxylase to the extent that highly purified preparations represent only a 10- to 20-fold concentration of the crude enzyme. There is evidence that the reaction proceeds according to equation (40).



(40)

2. Synthases

There are three analogous reactions known in which AcCoA condenses by an aldol-like reaction with a carbonyl compound to form an essential metabolic intermediate. Reaction (41) is catalyzed by condensing enzyme[75] for the operation of the tricarboxylic acid

cycle (Figure 4). Reaction (42) is an integral part of the glyoxylate cycle (Figure 10) of plants and microorganisms. Reaction (43) is essential to the biosynthesis of isoprenoid compounds and ultimately the steroids[76].

$$\text{AcCoA} + \text{Oxalacetate}^{2-} + H_2O \rightleftharpoons \text{Citrate}^{3-} + \text{CoA} + H^+ \quad (41)$$

$$\text{AcCoA} + \text{Glyoxylate}^{-} + H_2O \rightleftharpoons \text{Malate}^{2-} + \text{CoA} + H^+ \quad (42)$$

$$\text{AcCoA} + \text{AcAcCoA} + H_2O \longrightarrow \beta\text{-Hydroxy-}\beta\text{-methylglutaryl-CoA}^{-} + \text{CoA} + H^+ \quad (43)$$

3. Cyclization reactions

Formation of a carbon–carbon bond within a molecule leads to a cyclic compound. Examples of this type of reaction are found in the microbial synthesis of aromatic rings and the ubiquitous biosynthesis of cyclitols. Both pathways originate with glucose.

a. 5-Dehydroquinate synthesis[77]. Cyclization of 2-keto-3-deoxy-7-phosphoheptonate, formed from erythrose-4-P and phosphoenolpyruvate, leads to the formation of 5-dehydroquinate, the precursor of shikimic acid and the aromatic amino acids. The overall reaction involves loss of water (as phosphoric acid) and an intramolecular oxidoreduction for which NAD is required.

b. Myoinositol synthesis. Another cyclization occurs in animals[78], plants[79,80], and microorganisms[81]. By degradation of inositol-^{14}C formed from specifically labeled glucose it has been shown that the cyclitol arises through cyclization of an intact hexose chain[82] (Figure 16), contrary to earlier results which suggested that the conversion

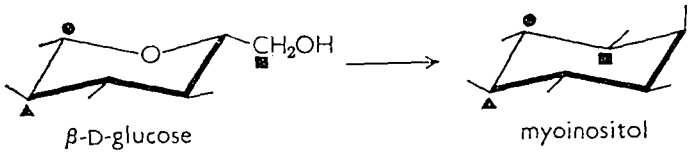


FIGURE 16. Biosynthesis of inositol from glucose. The symbols indicate source of product carbon atoms in precursor.

of glucose into inositol occurred with fragmentation of the hexose molecule[83]. In this reaction there is no change in composition; the conversion of glucose into inositol is an isomerization. In both the yeast and plant systems glucose-6-P is an intermediate and NAD is

required, which suggests that there may be transitory oxidoreduction necessary for activation of $C_{(6)}$ of the hexose. Although there is as yet no evidence in support of a mechanism, it is likely that there is stereospecific activation of hydrogen bound to the alcoholic terminal of glucose to produce myoinositol.

4. Aldolase[54]

Studies on the stereospecificity of this enzyme have been carried out with triose phosphates in the direction of synthesis (equation 32). The mechanism of base-catalyzed aldol condensation requires a nucleophilic attack on the α-carbon atom of one reactant to produce a carbanion which then reacts with the carbonyl carbon of the other reactant. With dihydroxyacetone and D-glyceraldehyde the products were D-fructose and D-sorbose (both 3,4-*trans*); neither of the other isomers, tagatose and psicose (both 3,4-*cis*), were formed showing geometrical specificity of the nonenzymatic reaction.

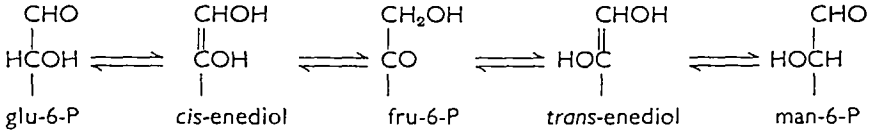
The enzymatic reaction in which phosphorylated substrates were used proceeded by the same mechanism but was even more selective since only fructose-diP (4,5-*cis*) and no sorbose-diP (4,5-*trans*) was formed. When the enzyme was incubated with dihydroxyacetone-P in D_2O or T_2O one atom of isotope was incorporated showing exchange of a carbon-bound hydrogen in accord with the carbanion mechanism. The resultant fructose-diP, generated upon addition of unlabeled phosphoglyceraldehyde, was unlabeled indicating that an exchangeable position on the carbanion was involved in synthesis. From the absolute configuration of the enzymically tritiated dihydroxyacetone-P it is concluded that the intermediate carbanion is of *S* configuration, that is reading counterclockwise on the face of the $C_{(1)}$ tetrahedron opposite the hydrogen atom, the groups are in the order OH, $POCH_2CO$, and negative charge.

D. Isomerization

Four isomerizations have already been discussed: the interconversion of glucose and fructose via sorbitol (section III.B.2), the analogous interconversion of D- and L-xylulose through xylitol (section II.B.5.d), the reversible epimerization of myoinositol and scyllitol through inosose (section II.B.10), and the cyclization of glucose to inositol (section III.C.3.b). These are relatively indirect changes compared to those that are catalyzed by the isomerases and mutarotase.

I. Isomerases[84]

The isomerases catalyze the interconversion of α-hydroxy aldehydes and α-hydroxy ketones among the carbohydrates and their derivatives, the phosphate esters, uronic acids, and the amino sugars. Studies on the enzymatic interconversion of glucose-6-P, fructose-6-P, and mannose-6-P have shown that, whereas the fructose ester is attacked by either phosphoglucose isomerase (PGI) or phosphomannose isomerase (PMI), the aldose esters are specific for their respective isomerase, each of which labilizes a different specific terminal α-hydrogen of fructose-6-P, as indicated with deuterium labeled substrates. Topper has proposed specific enzyme-bound enediols, one *cis*, the other *trans*, as intermediates in these reactions (equation 44).



(44)

Now the mechanism depicted above is incomplete since it fails to explain enzyme specificity in the direction from fructose ester to enediols. Selection of the correct hydrogen atom of fructose-6-P for release as a proton may be only a minor part of the specificity demanded of the isomerases, since these hydrogens by virtue of their asymmetric environment are inherently differentiable. Moreover it is unlikely that straight-chain forms of the sugar phosphates are involved, although to explain proton transfer, enediols are the most likely intermediates. These reactions thus combine two kinds of stereospecificity, optical, in the selection of the proton, and geometric, in the selection of the enediol. The remainder of the discussion will be devoted to a possible basis for the latter specificity.

From a consideration of the conformational formulas of the various substrates involved, it can be seen readily that the anomeric forms of the sugar phosphates might well be the determinants for geometric selection. If it is assumed that the most stable conformation is that in which oxygen atoms (including the ring oxygen) on $C_{(1)}$ and $C_{(2)}$ occupy positions in space as remote from each other as possible, then β-fructose-6-P must be the precursor of the *trans*-enediol and the α-anomer of the *cis*-enediol (Figure 17). The *trans*-enediol then is the precursor of either β-glucose-6-P (*trans*-1,2-diequatorial) or α-mannose-6-P (*trans*-1,2-diaxial); the *cis*-enediol gives rise to either α-glucose-6-P (*cis*-1-axial;-2-equatorial) or β-mannose-6-P (*cis*-1-equatorial; -2-axial). PGI and PMI are aldose-specific, however, so

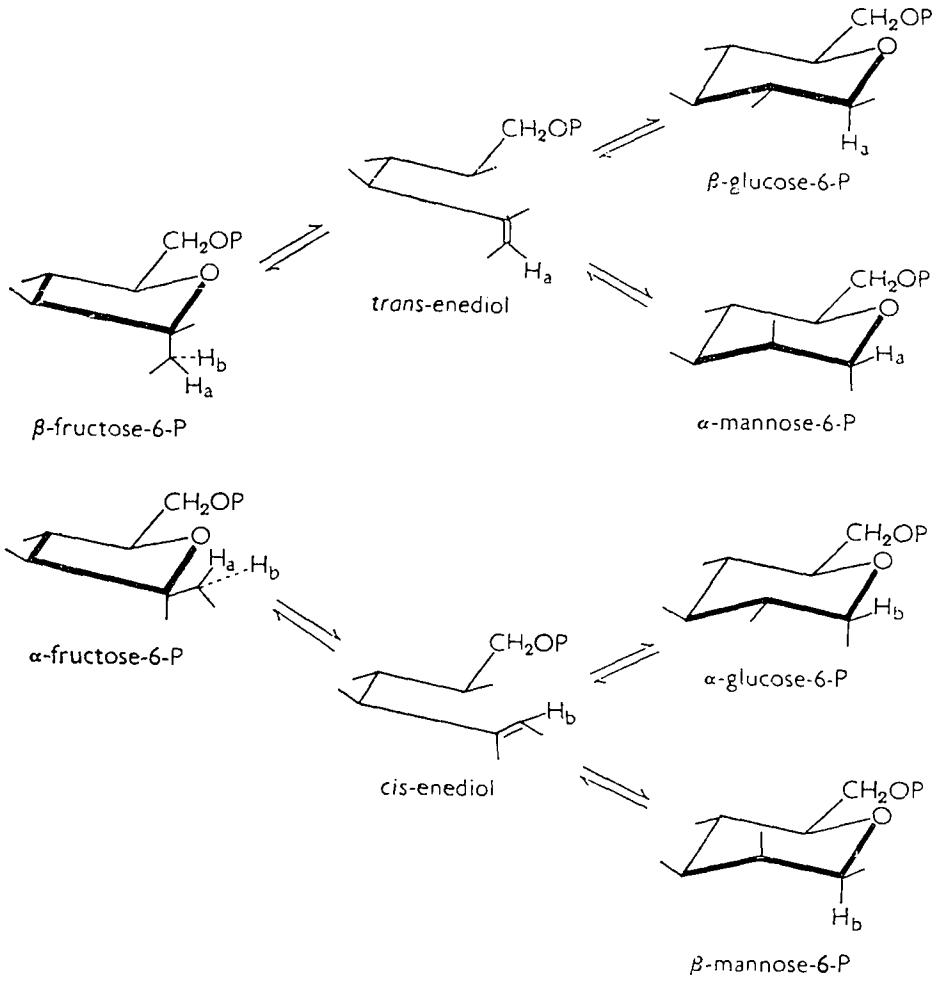


FIGURE 17. A proposed mechanism of action of isomerase.

that only one product in each pair can be formed. Which series is related to a given enzyme can only be ascertained by experimental test. Should it prove feasible to prepare the anomeric forms of each aldose-P, a comparison of their reaction rates with the two isomerases would establish absolute relationships.

2. Mutarotases

Isomerism uniquely related to the carbonyl group of carbohydrates is seen in the α- and β-anomers of the cyclic forms of the sugars.

Enzymes which catalyze the interconversion of these forms are known as mutarotases and have been described for many sugars[85,86]. The work of Swain and coworkers[87] in model systems for enzymatic mutarotation is well known and will not be reviewed further.

E. Reactions of Acetals

A general property of carbonyl compounds is reaction with an alcohol to form a hemiacetal and further reaction to form an acetal. The simple carbohydrates comprise the largest class of hemiacetals, originating from intramolecular condensation of hydroxyl and carbonyl groups. The acetals are likewise represented by the carbohydrates and are seen in the structure of glycosides and their polymers, the polysaccharides. Acetal-like compounds formed from simple sugars and phosphoric acid, carboxylic acids, and nitrogen compounds are important in biological systems; the *N*-glycosides are abundantly represented by the nucleic acids. Because of the great number and variety of acetal reactions it is beyond the scope of this chapter to consider more than a few.

1. Carbonyl carbinol acetals

This class comprises the bulk of the glycosides which in general are synthesized by transfer[88] of a hemiacetal moiety from a nucleotide to an alcoholic group. Although most of the nucleotides have been implicated in these transfers, the general reaction can be illustrated with uridine diphosphate glucose (equation 45).

$$\text{UDPG} + \text{ROH} \longrightarrow \text{UDP} + \text{ROG} \qquad (45)$$

a. Biosynthesis of cellulose[89]. Although bacterial systems capable of synthesizing cellulose have been known for some time, only recently has this reaction been achieved in higher plants. A particulate fraction of mung beans (*Phaseolus aureus*) catalyzes the synthesis of cellulose from guanosine diphosphate glucose. Other nucleotides are inactive in this transfer of glucose.

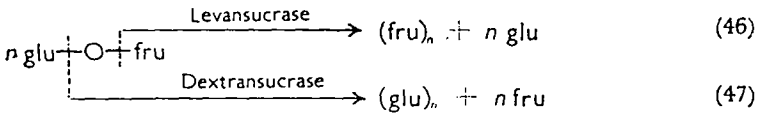
b. Biosynthesis of galactinol[90]. A galactoside of inositol is formed by transfer of galactose from UDPgalactose in an extract of pea seeds.

2. Carbonyl carbonyl acetals

This class consists of compounds formed from the union of hemiacetals through the potential carbonyl groups. The best known example of this type is sucrose, α-glucosido-β-fructoside. Some of the enzymatic reactions of this sugar will be described.

a. Dextransucrase and levansucrase. The sucrases are microbial enzymes which catalyze the polymerization of glucose to dextran and of fructose to levan, both obtained from sucrose. The energy for these reactions is derived from the high energy interglycoside linkage in the substrate.

The two series of reactions have provided a convenient approach to further studies of the nature of glycosidic bond cleavage by enzymes. Koshland[91] has observed that in enzymatic hydrolysis of a glycoside the bond cleaved is that which links oxygen to the enzyme-specific moiety. For example, in a series of glucosides the bond between oxygen and $C_{(1)}$ of glucose, and not between oxygen and the aglycone, is hydrolyzed by glucosidase. It was of interest to determine if the same rule applied to the transfer enzymes and the sucrases were chosen for this study with ^{18}O as a tracer to follow the interglycoside oxygen atom[92]. The results of the investigation showed that both enzymes catalyze the cleavage of the oxygen linkage to their respective enzyme-specific moiety (equations 46 and 47).



(46)

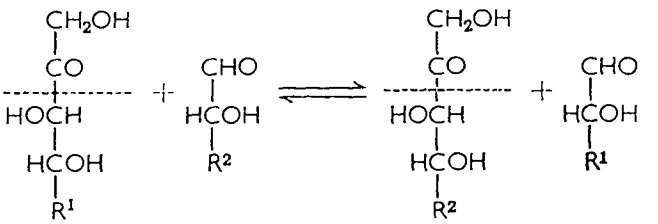
(47)

F. Transferases

The previous section has dealt with transfer reactions characterized by C—O cleavage. This section will be devoted to transfers in which C—C and C—N bonds are broken and reformed.

1. Transketolase[93]

An important reaction of aldehydes is enzymatic exchange with ketols as shown in equation (48). Although examples of this type of



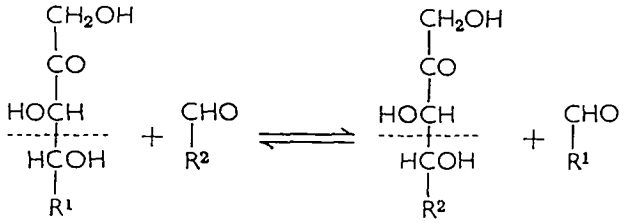
(48)

reaction are numerous, the most important is the exchange between D-xylulose-5-P and ribose-5-P to give sedoheptulose-7-P and glycer-

aldehyde-3-P, for which K_{equ} is nearly unity. Required for the reaction are Mg^{2+}, thiamine pyrophosphate and 3,4-*trans* configuration in the donor substrate. The coenzyme serves as carrier of 'active glycolaldehyde' in analogy to its role as carrier of 'active acetaldehyde' in the decarboxylation of pyruvate (section III.A.3).

2. Transaldolase[94]

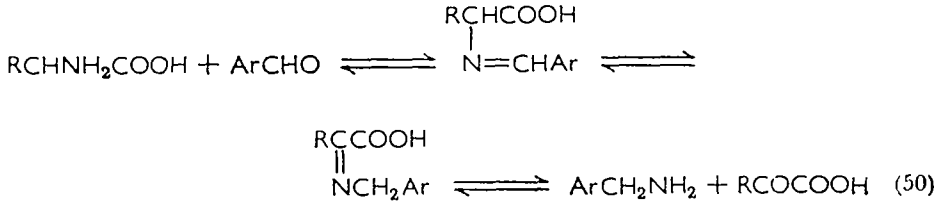
A similar reaction of aldehydes with ketols is mediated by transaldolase, exchange occurring one carbon removed from the donor carbonyl (equation 49). The principal example of this reaction is found in the phosphogluconate oxidative pathway (Figure 5) in the exchange between sedoheptulose-7-P and glyceraldehyde-3-P to give fructose-6-P and erythrose-4-P. No metal or cofactor requirement has been found for the enzyme. $K_{equ} = 0{\cdot}95$.



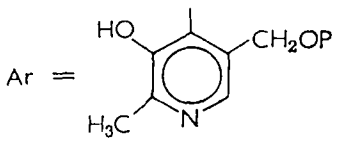
(49)

3. Transaminase[95]

In these reactions both substrate and coenzyme are carbonyl compounds. In general the reaction involves the transfer of an amino group, which never appears as free NH_3, from an amino acid to pyridoxal-P[96] and then to a keto acid (equation 50). By reversal of



(50)



the reaction the amino group of pyridoxamine-P can be transferred to another keto acid to form a new amino acid. Transamination provides a link between Krebs cycle α-keto acids, oxalacetate and α-ketoglutarate and amino acids, aspartate and glutamate.

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The Chemistry of the Carbonyl Group
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CHAPTER 8

Chemical and physical methods of analysis

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I. INTRODUCTION

As might be expected from the great reactivity of the carbonyl group and the wide distribution of carbonyl compounds in natural and manufactured materials, the analytical literature on these compounds is extensive. No attempt is made in this chapter to obtain a comprehensive coverage of all the methods. Instead, emphasis is given to the discussion of those methods which can be applied most generally. Included are methods which differentiate between aldehydes and ketones and between aliphatic and aromatic compounds. Both representative chemical and physical methods are discussed and procedural details are given for those that are most widely applicable.

The general methods most commonly used for quantitative analysis are volumetric and often involve reactions also used for the characterization of aldehydes and ketones. Addition reactions and reactions involving the oxidation and reduction of the carbonyl group are used, followed by a determination of one of the products of the reaction or of the excess reagent used. Gravimetric methods are useful for separating and determining carbonyl compounds in mixtures. The formation of colored derivatives with subsequent determination by spectroscopic methods is a sensitive technique for trace carbonyl analysis. Polarography is used often to determine particular carbonyl compounds directly or to examine the derivatives of carbonyl compounds. Chromatographic procedures are not only valuable for the direct identification and determination of aldehydes and ketones but also for separating these compounds for subsequent identification and characterization by other techniques. Ultraviolet spectroscopy is applied directly in some cases for analysis but its most important

application is to the derivatives of carbonyl compounds. Mass spectrometry and infrared and nuclear magnetic resonance spectroscopy, either alone but especially in conjunction with one another, are powerful tools for structure elucidation. In certain special cases the last three techniques are applicable to quantitative determinations.

II. CHEMICAL METHODS

A. Qualitative

1. Hydrazone formation

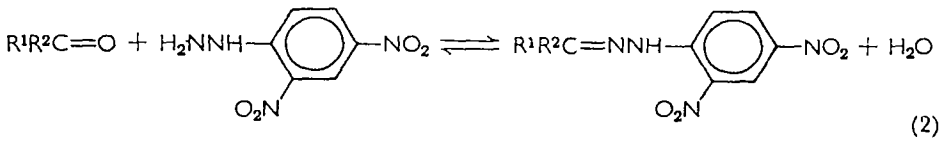
The reaction of phenylhydrazine with aldehydes and ketones to form phenylhydrazones is used frequently as a test for the presence of carbonyl compounds (equation 1). In most cases the phenylhydra-

$$R^1R^2C{=}O + H_2NNHC_6H_5 \rightleftharpoons R^1R^2C{=}NNHC_6H_5 + H_2O \qquad (1)$$

zones precipitate immediately when the sample and reagent are mixed. However, some phenylhydrazones, especially the derivatives of simple ketones, are oils; and the absence of a precipitate does not necessarily indicate the absence of these compounds.

The test reagent is prepared as a 10% solution in water by adding acetic acid to dissolve the phenylhydrazine. To make the test, about 0·5 ml of the sample is added to 5 ml of the reagent. If a cloudiness does not form immediately, the mixture is heated gently, an additional 1–2 ml of water is added, and the mixture is cooled. The phenylhydrazones can be isolated and the parent carbonyl compound identified from the melting point of the derivative. The derivatives of aryl carbonyl compounds are particularly useful for this purpose because of their convenient melting points.

The 2,4-dinitrophenylhydrazones are the most widely used derivatives for the identification of carbonyl compounds (equation 2).



(2)

Because of their higher melting points, they are more useful than the corresponding phenylhydrazones, especially for the characterization of the lower molecular weight compounds.

A convenient reagent is a saturated solution of 2,4-dinitrophenylhydrazine in 2 N hydrochloric acid. An aliquot of the sample in 95%

ethanol is added dropwise to 20–60 ml of the reagent containing 50–100% dinitrophenylhydrazine in excess of that needed for complete reaction. Fifty ml of 2 N hydrochloric acid are added. When precipitation is complete, the precipitate is filtered, washed with 2 N hydrochloric acid, then with distilled water, and finally dried.

The tendency of this group of derivatives to polymorphism, to form geometric isomers and mixed crystals, and to undergo structural rearrangements can cause difficulties when identifications are attempted by evaluation of the melting points using published data. However, if reference derivatives of pure carbonyl compounds are prepared, employing techniques identical to those used for the test sample, these difficulties are minimized.

Sensabaugh, Cundiff, and Markunas[1] demonstrated the feasibility of titrating the 2,4-dinitrophenylhydrazones as weak acids in pyridine. From such a titration a calculation of the equivalent weight is possible, which furnishes important additional information for the characterization of the parent carbonyl compound. Either 0·01 or 0·02 N tetrabutylammonium hydroxide is used as the titrant, and 2–20 mg samples of the derivative in 50 ml of pyridine are titrated potentiometrically in an inert atmosphere.

Cowell and Selby[2] titrated the 2,4-dinitrophenylhydrazones of aliphatic ketones potentiometrically as bases with 0·2 N perchloric acid, using acetic anhydride as the solvent. They also applied this titration to some semicarbazones, phenylhydrazones, and 4-nitrophenylhydrazones. However, the method is limited by the low solubilities of many of the derivatives in acetic anhydride.

2. Oxime formation

Duke[3] has suggested that the appearance of the liberated hydrochloric acid when carbonyl compounds react with hydroxylamine hydrochloride to form oximes (equation 3) could be used as a test for the presence of aldehydes or ketones. A suitable acid–base indicator, added to the reaction mixture, indicates the liberation of

$$R^1R^2C{=}O + NH_2OH{\cdot}HCl \rightleftharpoons R^1R^2C{=}NOH + H_2O + HCl \qquad (3)$$

hydrochloric acid by a color change. When combined with a test specific for aldehydes, for example the Tollen's test, the presence of a ketone can be established in the absence of aldehydes. A reagent solution containing 5 g of hydroxylamine hydrochloride and 3 ml of Universal indicator per liter in 95% alcohol is used. The color of the solution is adjusted to a bright orange (pH 3·7–3·9) with alcoholic

sodium hydroxide. If acids or bases are present in the test sample, indicator is added and the color also adjusted to a bright orange. A change of color to red on mixing the sample and reagent is a positive test. A pH meter to indicate the pH change can be used conveniently in place of the indicator.

Oximes are often used as derivatives, especially for the higher molecular weight compounds. They have lower melting points than the semicarbazones and substituted phenylhydrazones. An adaptation of the quantitative procedure of Bryant and Smith[4] can be used conveniently to prepare these derivatives. About 0·5 g of carbonyl compound and 0·5 g of hydroxylamine hydrochloride are dissolved in a mixture containing 4 ml each of pyridine and absolute ethanol. The mixture is heated on a steam bath for 2 h. The solvents are then evaporated in a current of air and the residue is washed well with water. The derivatives can be recrystallized from ethanol or from an ethanol/water mixture.

3. Semicarbazone derivatives

The semicarbazone derivatives of aldehydes and ketones (equation 4) are generally highly crystalline compounds with sharp melting points and are easily obtained in a nearly pure state. The derivatives

$$R^1R^2C{=}O + H_2NNHCONH_2 \rightleftharpoons R^1R^2C{=}NNHCONH_2 + H_2O \qquad (4)$$

of unsubstituted aldehydes in the C_2 to C_{12} range are difficult to identify because their melting points are so close together.

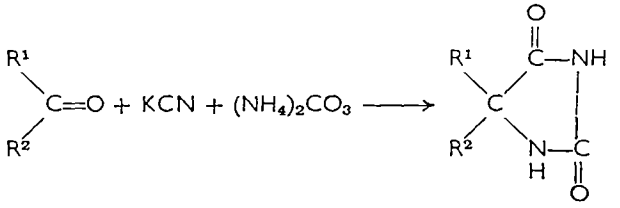
The semicarbazones can be formed by adding 1 g each of semicarbazide and sodium acetate to 1 ml of the carbonyl compound dissolved in 10 ml of water. If the carbonyl compound is water-insoluble, it is dissolved in ethanol with just enough water added to obtain a cloud point and the turbidity just removed with ethanol. In either case the mixture is agitated well, heated in a boiling water bath, and then cooled in ice. The crystals are filtered and recrystallized from ethanol/water mixtures.

The reaction as indicated in equation (4) is reversible, and the rate and position at equilibrium are dependent upon a composite of the hydrogen ion concentration and acidity of the solution. The kinetics and mechanism of the reaction have been studied carefully by Conant and Bartlett[5] and by Westheimer[6]. Jamieson[7] and Smith and Wheat[8] suggested hydrolyzing the semicarbazone derivatives with aqueous hydrochloric acid and titrating with standard iodate

solution to obtain the equivalent weights of the parent carbonyl compounds.

4. Hydantoin derivatives

Henze and Speer[9] used the procedure first described by Bucherer and Libe[10] to prepare the hydantoins from aldehydes and ketones. They published melting points of some of these derivatives and recommended them for identification purposes. Hydantoins are formed when carbonyl compounds react with potassium cyanide and ammonium carbonate (equation 5).



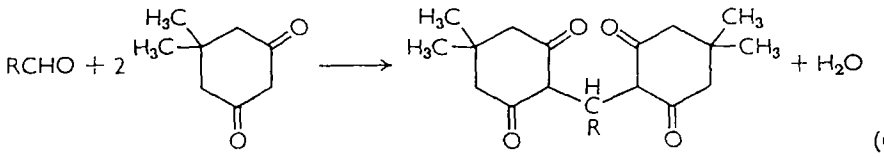
(5)

The sample containing 0·02 mole of carbonyl compound is dissolved in 50% alcohol, and 9·1 g of ammonium carbonate and 2·6 g of potassium cyanide are added. The mixture is warmed under reflux at about 60°c for 2 h. The solution is concentrated to about 35 ml, chilled in an ice bath, and the precipitate recovered by filtration.

The method cannot be used for formaldehyde, certain unsaturated aldehydes, some substituted aryl aldehydes, and pyruvic acid.

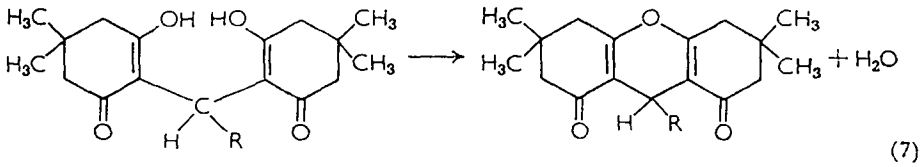
5. Dimedone derivatives of aldehydes

Dimedone, also known as methone (5,5-dimethylcyclohexane-1,3-dione), is used as a reagent specifically for the identification of aldehydes[11–14]. The derivatives, aldemedones, are highly crystalline compounds with sharp melting points. The aldomedones, except the derivative obtained from formaldehyde, can be cyclized by dehydration of their enolic forms, resulting in other useful



(6)

crystalline derivatives, octahydroxanthenes (equation 7). Thus two derivatives are obtained from a single sample of the original aldehyde.



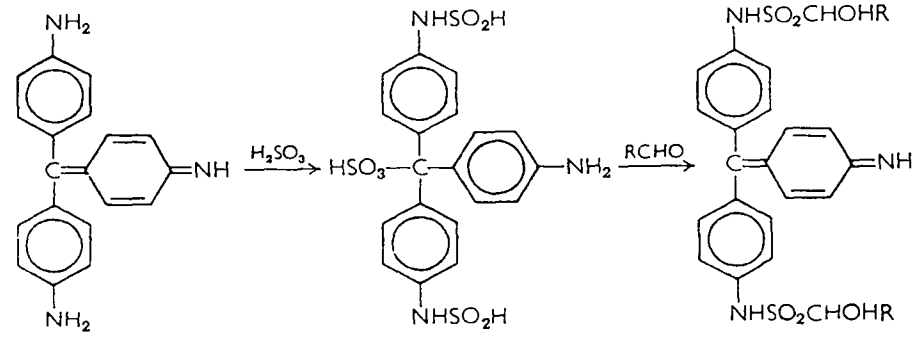
(7)

The procedure of Horning and Horning[14] is as follows. A 0·1 ml sample of the aldehyde is added to 4 ml of a solution of 400 mg of dimedone (300 mg for aromatic aldehydes) in 50% ethanol/water. One drop of piperidine is added as a catalyst and the mixture is refluxed for 5 min. The aldomedone is filtered from the chilled solution. To form the anhydride, 100 mg of the aldomedone is dissolved in 3–4 ml of hot 80% ethanol. One drop of concentrated hydrochloric acid is added and the mixture is refluxed for 5 min. Water is added until a cloud point is obtained, the mixture is chilled, and the precipitate filtered.

o-Hydroxy aromatic aldehydes and α,β-unsaturated aldehydes give derivatives which differ in structure from the normal aldomedones and cannot be dehydrated. These derivatives, however, serve equally well for identification purposes.

6. Schiff's reagent for aldehydes

The use of Schiff's reagent is one of the oldest tests for aldehydes[15]. The reagent is prepared by treating the red dye basic fuchsin (rosaniline hydrochloride) with aqueous sulfur dioxide, forming the



(8)

colorless addition product. Reaction with an aldehyde results in the loss of sulfurous acid and the formation of a red quinoid dye. The reactions can be formulated as in equation (8).

Schiff's reagent is prepared by dissolving about 0·3 g of basic fuchsin in 250 ml of water and filtering. To this solution is added 250 ml of water saturated with sulfur dioxide. The solution is allowed to stand overnight. To make the test, 1 or 2 drops of the sample solution are added to 2 ml of the reagent. The development of a color in about 4 min is a positive test.

7. Tollen's reagent for aldehydes

Tollen's reagent, an ammoniacal silver nitrate solution, is extensively used to test specifically for aldehydes. The reaction involves oxidation of the aldehyde to the corresponding acid and reduction of the metal ion to metallic silver (equation 9). The silver is usually deposited in the form of a mirror on the surfaces of the container. Ketones do not undergo this reaction, and acetals are not hydrolyzed under the basic conditions of the reagent.

$$RCHO + 2\,Ag(NH_3)_2OH \longrightarrow RCOONH_4 + 2\,Ag + 3\,NH_3 + H_2O \qquad (9)$$

The reagent is prepared by precipitating silver oxide from a 5% solution of silver nitrate by the dropwise addition of 10% sodium hydroxide. A 2% solution of ammonium hydroxide is added until the silver oxide just dissolves. An excess of ammonia reduces the sensitivity of the reagent. A positive test is indicated when 1 or 2 drops of the sample added to 5 ml of the reagent produce a precipitate of metallic silver or a silver mirror on the surfaces of the container. The reagent must be freshly prepared for each use. *It has shown a tendency to deteriorate on standing, forming an explosive compound; therefore, any excess reagent should be discarded immediately and any silver mirrors obtained should be dissolved in nitric acid and the solution discarded.*

8. Cupric salts for aldehydes

Cupric salts in an alkaline medium form blue complexes with tartrate and citrate. Aliphatic aldehydes reduce the copper to red insoluble cuprous oxide (equation 10). Fehling's solution, using

$$RCHO + 2\,CuO \longrightarrow RCOOH + Cu_2O \qquad (10)$$

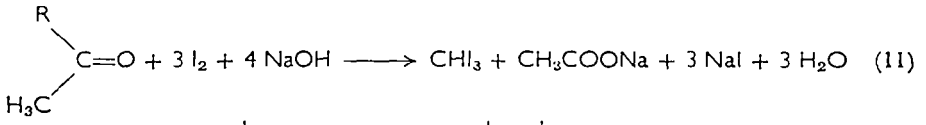
tartrate, and Benedict's solution, using citrate, are specific for aliphatic aldehydes and α-ketols and, when used in conjunction with Tollen's reagent, distinguish between aliphatic and aromatic aldehydes.

Fehling's solution is prepared by mixing equal volumes of tartrate solution and copper sulfate solution immediately before use. The copper sulfate solution contains 34·7 g of the hydrated copper salt in 500 ml of water. The second solution is prepared by dissolving 173 g of potassium sodium tartrate and 70 g of sodium hydroxide in 500 ml of water.

Benedict's solution is prepared by first dissolving 173 g of sodium citrate and 100 g of anhydrous sodium carbonate in 800 ml of water with the aid of heat. This solution is filtered if necessary and diluted to 850 ml with water. A second solution is prepared by dissolving 17·3 g of hydrated copper sulfate in 100 ml of water. The latter solution is poured, with stirring, into the first solution and the volume adjusted to 1 liter with water.

9. Iodoform reaction

Hypoiodite reacts with certain organic compounds to give iodoform (equation 11). The iodoform is easily identified by its light lemon color and its melting point, 119–121°c. Compounds containing



the structures $CH_3\overset{|}{C}{=}O$ and $CH_2{=}\overset{|}{C}{-}\overset{|}{C}{=}O$ and other compounds, including CH_3CH_2OH, CH_3CHOHR, $RCOCH_2COR$ and $RCHOHCH_2CHOHR$, where R is either an alkyl or aryl radical, give the test. Fuson and Bull[16] have given a general discussion of this test. Fuson and Tullock[17] recommend the use of dioxane as the solvent.

The compound to be tested is dissolved in 5 ml of dioxane, and 1 ml of 10% aqueous sodium hydroxide solution is added. A slight excess of iodine/potassium iodide solution is added. The iodine solution is prepared by dissolving 50 g of iodine and 100 g of potassium iodide in 400 ml of water. The sample mixture is warmed 2 min at 60°c and the excess iodine discharged, using alkali. Water is then added to precipitate the iodoform.

10. Peroxytrifluoracetic acid for ketones

A test which gives positive results only with ketones has been proposed by Drucker and Rosen[18]. These workers first oxidized the ketones with peroxytrifluoroacetic acid to produce esters and

lactones (equation 12) and they detected these products using the characteristic purple color of the ferric hydroxamates[19] (equations 13 and 14).

$$R^1COR^2 + CF_3COOOH \longrightarrow R^1COOR^2 + CF_3COOH \quad (12)$$

$$R^1COOR^2 + NH_2OH \longrightarrow R^1CONHOH + R^2OH \quad (13)$$

$$3\,RCONHOH + FeCl_3 \longrightarrow (RCONHO)_3Fe \quad (14)$$

The peroxytrifluoracetic acid reagent is prepared by first dissolving 1 drop of 90% hydrogen peroxide in 1 ml of methylene chloride. While cooling in an ice bath, 6 drops of trifluoroacetic anhydride are added and the mixture agitated for about 30 sec until a homogeneous mixture is obtained. The oxidation of any ketone in the test sample is then performed by adding the methylene chloride solution of peroxy acid to a 0·2 ml or 0·2 g sample and refluxing on a steam bath for 5 min. The mixture is cooled and washed twice with 10 ml portions of 0·5 M sodium carbonate solution, then twice with 10 ml of 10% sodium bisulfite, and finally once with 10 ml of water. The methylene chloride is evaporated on a steam bath. The hydroxamic acid test is then performed as follows. The residue is dissolved in 1 M hydroxylamine hydrochloride reagent (70 g of hydroxylamine hydrochloride, 0·2 g of thymolphthalein, 0·1 g of methyl yellow in 1 liter of methanol). One-half ml of 2 M methanolic potassium hydroxide is added in excess of that necessary to just form a blue color. The mixture is boiled for 30 sec, cooled, and 2 M methanolic hydrochloric acid added until a pink color is just formed. Two drops of 10% ferric chloride are added. A positive test is indicated by a red-purple color. Esters must be absent from the sample or they will cause the test to be positive in the absence of ketones.

11. Chromotropic acid for formaldehyde

An almost specific test for formaldehyde was proposed by Eegriwe[20], based on the deep purple-violet color formed when the aldehyde is condensed with chromotropic acid (1,8-dihydroxynaphthalene-3,6-disulfonic acid). The chemistry of this color reaction is not known with certainty. Formals and other compounds which split off formaldehyde also give a positive test. A drop of the sample solution is mixed with 1–2 ml of concentrated sulfuric acid containing a little solid chromotropic acid and the mixture heated at 60°C for 10 min. The formation of a purple-violet color constitutes a positive test for formaldehyde.

B. *Quantitative*

1. Oximation methods

Oximation reactions between carbonyl compounds and hydroxylamine or its salts have been thoroughly studied, and quantitative methods based on these reactions are the most extensively used for the determination of aldehydes and ketones. The hydroxylamine reagents are attractive because they are generally applicable to both ketones and aldehydes, and the reagent or the reaction products, free acid and water, are determined easily. Most investigations have been concerned with overcoming the instability of the free hydroxylamine, eliminating the adverse equilibrium effects encountered in the use of the hydroxylamine salts, and obtaining satisfactory end-points in the final titrations. Although the reaction of carbonyl compounds with free hydroxylamine, in general, is complete (equation 15), the instability of this reagent due to air oxidation

$$R^1R^2C{=}O + NH_2OH \longrightarrow R^1R^2C{=}NOH + H_2O \qquad (15)$$

discourages its use. On the other hand, although the hydroxylamine salts are relatively stable, an equilibrium is involved in their reactions with carbonyl compounds (equation 3) and special conditions are necessary in many cases to obtain substantially complete reactions. Siggia[21] has pointed out, however, that for many aldehydes the equilibrium is sufficiently favorable for satisfactory results to be obtained without special precautions, using a variety of solvents such as water, glycol, isopropanol, and mixtures of glycol or isopropanol with benzene or petroleum ether. Hydroxylamine is used as the reagent and the liberated hydrochloric acid is titrated, usually potentiometrically, because the system is often too highly buffered to yield sharp pH changes at the end-point. Roe and Mitchell[22] used a differential pH method to determine small concentrations of carbonyl compounds in water, methanol, dioxane, and benzene systems. The pH of a 0·5 N hydroxylamine hydrochloride solution is measured before and after the addition of the sample. The change in pH is compared with a working curve prepared using measured concentrations of pure carbonyl compounds. The method can be used to determine 0·0 to 0·23 millimole of aldehydes and methyl ketones per ml to ±2% relative. The procedure is subject to interference from acids and buffering materials.

In most cases it is necessary to use systems that will force the reaction to completion. Since water is one of the products of the

reaction, the use of nearly nonaqueous systems is advantageous. Higuchi and Barnstein[23] investigated hydroxylammonium acetate as a reagent. The oximation was performed in glacial acetic acid and the excess reagent titrated potentiometrically with standard perchloric acid solution. Because of the basicity of the oximes of the lower aliphatic carbonyl compounds, the titrations in these cases produced poor end-points. Pesez[24] used hydroxylammonium formate in a methanolic medium and titrated the unreacted reagent with perchloric acid in dioxane to the thymol blue end-point. Results in some cases were 1 to 2% low, which has been attributed to the presence of peroxides. Ruch, Johnson, and Critchfield[25] changed the titration solvent of the Pesez procedure to a 2:1 mixture of methylcellosolve and methanol and replaced the perchloric acid titrant with nitric acid solution. Their preference for the nitric acid titrant was based on the observation that the hydrolysis of acetals did not occur as readily in the presence of this acid as when the stronger hydrochloric or perchloric acids were used. An outline of the procedure of Ruch and coworkers follows.

Exactly 50 ml of 0·5 N hydroxylammonium formate are pipetted into each of two flasks. One is reserved as a blank. The sample containing 15 milliequivalent or less of carbonyl compound is added to the other flask. The reaction mixture is allowed to stand at room temperature until the reaction is complete. Fifty ml of methanol, 75 ml of methylcellosolve, and 5 or 6 drops of thymol blue indicator are added. The blank is titrated with 0·5 N nitric acid in methylcellosolve until the color changes to a definite orange. The sample is titrated until the color matches that of the blank.

To prepare the hydroxylammonium formate, 32 g of potassium hydroxide are added to 350 ml of methylcellosolve. Twenty ml of 90% formic acid are added to bring about solution. Formic acid is then added until the solution is neutral to phenolphthalein, and then 2 or 3 more pellets of potassium hydroxide are added and dissolved. A second solution is prepared by dissolving 34 g of hydroxylamine hydrochloride in 650 ml of methylcellosolve. The two solutions are mixed, the mixture cooled to 15°C, and the potassium chloride filtered.

The 0·5 N nitric acid solution is prepared by adding 33 ml of concentrated acid to 500 ml of methylcellosolve. One g of urea (to destroy any nitrous acid) and 0·1 g of *p*-diethoxybenzene (to retard peroxide formation) are added and dissolved and the mixture diluted to 1 liter with additional methylcellosolve.

The procedure has been adapted to the semimicro scale by sub-

stituting more dilute reagents: 0·22 N nitric acid solution and 0·1 N hydroxylammonium formate solution. Carbonyl-free methanol was used as the diluent for both titrant and reagent. Trace carbonyl present in the methylcellosolve interferes if this reagent is used as the diluting agent.

Another technique is to include an acid acceptor in the oximation system to tie up the acid liberated as the reaction proceeds and displace the equilibrium in the direction of complete reaction. The Bryant and Smith method[4], which has been used for many years, is based on the use of pyridine as the acid acceptor. The pyridine hydrochloride produced by the reaction is titrated with a standard alcoholic solution of sodium hydroxide, using bromphenol blue as the indicator. The end-point determination depends upon matching the color of the sample reaction mixture with that of a blank solution. However, the color change is gradual and precise matching is difficult. Fritz, Yamamura, and Bradford[26] proposed the use of 2-dimethylaminoethanol in an amount necessary to approximately half-neutralize the hydroxylamine hydrochloride. The solvent medium was methanol/isopropanol. The base is neutralized by the hydrochloric acid liberated by the reaction, and excess base is titrated with perchloric acid in methylcellosolve to an indicator end-point. Acetals, ketals and vinyl ethers will interfere if present in major amounts. The procedural details of this method follow.

Exactly 20 ml of 0·25 M 2-dimethylaminoethanol and then 25 ml of 0·4 M hydroxylamine hydrochloride are added to the sample containing 1·5 to 2·5 millimole of carbonyl compound. For most aldehydes and simple aliphatic ketones, the solution is allowed to stand at room temperature for 10 min. Aryl ketones, hindered aliphatic and dicarbonyl compounds are held at 70° for 45 min or longer. The completeness of reaction of doubtful compounds can be checked by using longer reaction times. Five drops of indicator (0·0667 g of Martius yellow and 0·004 g of methyl violet in 50 ml of ethanol) are added and the excess amine titrated with 0·2 M perchloric acid in methylcellosolve. A similar mixture except that the sample is omitted is carried through the procedure as a blank and is also titrated.

Mitchell, Smith, and Bryant[27] based a method for the analysis of carbonyl compounds on a titration of water formed in the oximation reaction. Although Karl Fischer reagent reacts with the hydroxylamine salts to produce water, the oximes are not affected. For this reason, excess hydroxylammonium ions are converted into the

pyridine salts of sulfamic acid by adding a solution of sulfur dioxide and pyridine in methanol. Then only the water formed by the oximation reaction is titrated. The sample, containing up to 10 milliequivalent of carbonyl, is added to exactly 30 ml of 0·5 N hydroxylamine hydrochloride in dry methanol containing 5 ml of pyridine. The sample mixture is maintained at 60° ± 1°C for 2 h and then cooled to room temperature. Twenty-five ml of 1 M pyridine/sulfur dioxide in methanol are added and the resulting solution titrated with Karl Fischer reagent. After applying the correction for the water originally present in the sample and in a blank, the carbonyl concentration is equivalent to the net water found.

Fowler and coworkers[28,29] presented a method for the determination of aromatic aldehydes in the presence of aromatic ketones based on the competing rates of oxime formation. The difference in reaction rates for these two types is normally large, and oximation of the aldehyde is complete when a very small amount of the ketone has reacted. These workers prepared calibration curves using mixtures of known concentrations reacted for a given period of time. The composition of the sample mixture was then read from this graph, relating the amount of reaction to the original composition. Siggia and Hanna[30] proposed a more general reaction rate method which permits the quantitative resolution of binary mixtures of aliphatic as well as aromatic aldehydes and ketones and also mixtures of aldehydes and mixtures of ketones. They added the sample to a hydroxylamine hydrochloride solution and maintained the pH of this solution at 3·5 by the addition of a standard sodium hydroxide solution. The amount of alkali consumed at successive time intervals is a measure of the amount of reaction at these intervals. They then extrapolated the final straight-line portion of the standard second-order rate plot to zero time and calculated the amount of slower reacting component.

2. Bisulfite addition methods

Analyses based on the formation of the bisulfite addition products of aldehydes can be divided into two general methods. In one method, after the carbonyl compound has reacted with excess bisulfite to form the addition compound, the residual bisulfite is determined by titration with a standard iodine solution. This technique was first

$$RCHO + NaHSO_3 \rightleftharpoons RCHOHSO_3Na \qquad (16)$$

used by Ripper[31] to analyze formaldehyde. Air oxidation of the bisulfite and the equilibrium indicated (equation 16) make this

method subject to serious errors. As iodine is added in the end titration, the excess bisulfite is reduced and a shift takes place in the equilibrium in favor of free aldehyde and free bisulfite. The method is satisfactory only for formaldehyde, for which the rate of dissociation of the bisulfite addition product is slow, but is unsatisfactory for other aldehydes and ketones. Parkinson and Wagner[32] improved the accuracy of the procedure somewhat by using a back-titration approach. These workers added an excess of iodine to react rapidly with the free bisulfite and immediately titrated the excess iodine with sodium thiosulfate.

The other general method involving the formation of the bisulfite addition product is based on the increase in alkalinity of the system when sodium sulfite is used as the reagent (equation 17). Direct

$$RCHO + Na_2SO_3 + H_2O \rightleftharpoons RCHOHSO_3Na + NaOH \qquad (17)$$

titration with standard acid was used by Lemme[33] to determine the increase in alkalinity. Here again, equilibrium difficulties are encountered and although various modifications have been proposed[34–37], the direct neutralization methods are reliable only for formaldehyde analysis. Reynolds and Irwin[38] gained some improvement in the accuracy of the method for formaldehyde by reducing the temperature of the system to 0–5° by the addition of clean ice. The solution is finally titrated with standard 0·5 N acid and the formaldehyde content calculated.

To overcome the reagent instability and to obtain a more favorable equilibrium situation, Siggia and Maxcy[39] added a measured volume of standard sulfuric acid to a solution of sodium sulfite to produce sodium bisulfite immediately before the addition of the sample. After complete reaction, the free excess acid was titrated potentiometrically with standard alkali. A large excess of sulfite drives the reaction substantially to completion and also aids in the dissolution of many of the higher boiling aldehydes. Of the ketones, only cyclohexanone can be determined by this method. Other ketones and furfural give shallow titration curves showing no definite end points. In general, ketones will not interfere in the determination of aldehydes if they are present in less amounts than 10 mole percent. The system is not sufficiently acidic at any time for acetals to hydrolyze and interfere. The method, therefore, is almost specific for aldehydes. Once the end-point pH for a particular aldehyde has been established, it is often more convenient and more rapid to titrate the reaction mixtures of subsequent determinations to this

predetermined pH with a slight loss in accuracy. The reproducibility of the method is ±0·2% if the entire curve is plotted and ±0·4% if the rapid method is used. The procedure of Siggia and Maxcy[39] is as follows. To 250 ml of 1 M sodium sulfite solution neutralized to pH 9·1 are added exactly 50 ml of 1 N sulfuric acid. The sample, containing 0·02 to 0·04 mole of aldehyde, is added and the mixture shaken for 2–3 min for the more soluble aldehydes and 5 min for the less soluble compounds. The titration is made with 1 N sodium hydroxide to a predetermined pH or by stepwise addition, followed by plotting pH *versus* ml. A blank is run and the percent aldehyde calculated, based on the difference in ml of titrant between that used for the blank and that used in the presence of the sample.

3. Hydrazone formation

Many procedures have been proposed using hydrazine compounds for the volumetric and gravimetric determination of carbonyl compounds. Kleber[40] added an excess of phenylhydrazine to the sample and titrated the excess with standard acid. Air oxidation of the reagent necessitated the use of large blank corrections in this method. Ardagh and Williams[41] determined the excess phenylhydrazine iodometrically but also experienced difficulties due to oxidation by air and by dissolved oxygen. In addition, because the phenylhydrazone formed reacts with the iodine added in the end determination, they found it necessary to extract the product before the excess phenylhydrazine was titrated. Various methods have been proposed based on oxidation of the unreacted phenylhydrazine with Fehling's solution to liberate nitrogen, which is collected and measured[42–46]. However, these procedures do not produce precise and accurate results for most carbonyl compounds. Fuchs[47,48] and Monti[49] and their associates titrated the acid liberated after reaction of hydrazine sulfate with carbonyl compounds. Long reaction times were needed for quantitative reactions.

Gravimetric 2,4-dinitrophenylhydrazine methods are useful for determining carbonyl compounds in complex mixtures. The reaction is specific and the 2,4-dinitrophenylhydrazones, because of their low solubilities, can be prepared essentially quantitatively. Iddles and coworkers[50,51] recommended the use of a standard 2,4-dinitrophenylhydrazine solution in 2 N hydrochloric acid as the reagent. Aqueous solutions of water-soluble carbonyl compounds were prepared, while 95% ethanol was used for water-insoluble compounds. Ten ml aliquots of the sample solutions are added dropwise to 20–60

ml of the reagent containing 50–100% dinitrophenylhydrazine in excess of that needed for complete reaction. The alcohol solutions are diluted with 50 ml of 2 N hydrochloric acid solution. The mixtures are then allowed to stand at room temperature until precipitation is complete. The precipitates are filtered and washed with 100–150 ml of 2 N hydrochloric acid and then with distilled water until the filtrates are free of chloride. The precipitates are dried and weighed.

The method gives slightly low recoveries, especially for the low molecular weight aldehydes, because of the slight solubilities of their hydrazones. Interferences consist mainly of material that will oxidize the hydrazones to form tars, which are weighed with the hydrazones. Because of the acidity of the reaction mixture, acetals and vinyl ethers are hydrolyzed, forming aldehydes, and if present will interfere.

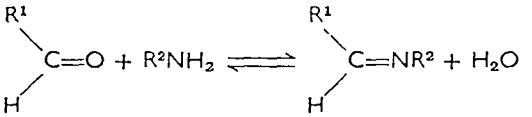
Clift and Cook[52] dissolved the 2,4-dinitrophenylhydrazones of keto acids in excess caustic solution and back-titrated the excess with standard acid. Epsil and coworkers[53,54] used titanous chloride to reduce the dinitrophenylhydrazones. Strict precautions must be observed to eliminate air oxidation of the titanous chloride reagent. Schoeniger and Lieb[55] determined excess 2,4-dinitrophenylhydrazine with titanous chloride. Sensabaugh and associates[1] titrated the 2,4-dinitrophenylhydrazone potentiometrically, using pyridine as the solvent. They recommended this method primarily for identification purposes (see section II.A.1). Baldinus and Rothberg[56] demonstrated that the ketone derivatives can be titrated potentiometrically, using a sodium nitrite titrant in a tetrahydrofuran medium containing sulfuric and hydrochloric acids. However, since the 2,4-dinitrophenylhydrazone derivatives can be obtained in essentially pure form and errors involved are due almost exclusively to their solubilities and are not overcome by these titration methods, it appears more logical to make the final determinations gravimetric rather than titrimetric.

Siggia and Stahl[57] introduced the use of unsymmetrical dimethylhydrazine for the determination of aldehydes. This reagent is stable toward decomposition and oxidation and, because it is alkaline, acetals do not interfere in the determination of aldehydes. An excess of the reagent is added to the sample and, after reaction, the unreacted excess is titrated potentiometrically with standard acid. The precision and accuracy are within 1%. Ketones cannot be determined and will interfere in the determination of aliphatic aldehydes. Three different reagent mixtures are recommended for different types of samples: 0·2 M dimethylhydrazine in ethylene glycol for

aliphatic aldehydes, 1 M in ethylene glycol for aromatic aldehydes, and 1 M in methanol for disubstituted benzaldehydes. A 25 ml aliquot of the reagent is reacted with 0·002 mole of aliphatic aldehyde or 0·01 mole of aromatic aldehyde at room temperature for 15 min or longer (2 h for aromatic aldehyde). Fifty ml of methanol are used to wash the mixture into the titration beaker, and the titration is made potentiometrically, using 0·1 N hydrochloric acid in methanol for the 0·2 M reagent and 0·5 N hydrochloric acid in methanol for the 1 M reagent. A blank is run.

4. Schiff base formation

The characteristic reaction of carbonyl compounds with amines to form imines, commonly called Schiff bases[58], has been used by Siggia and Segal[59] to determine certain aldehydes (equation 18).

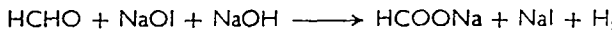


(18)

Because water is a product of the reaction and an equilibrium is involved, a nonaqueous system is used to obtain the most favorable conditions for complete reaction. Salicylic acid is used to titrate excess amine potentiometrically after the reaction is complete. If stronger acids are used as titrants, the Schiff base hydrolyzes to free amine and aldehyde and low results are obtained. Laurylamine is used as the reactant because of its availability and high boiling point. The equilibrium position for the reaction of ketones or aliphatic aldehydes excepting formaldehyde is in favor of the free amine and carbonyl; and as the reaction mixture is titrated with acid, the product is decomposed and no definite end-point is obtained. The presence of ketones tends to obscure the end-point for aldehyde determinations. Exactly 20 ml of 2 M laurylamine in a 1:1 mixture of ethylene glycol/isopropanol are added to 0·02 mole of aldehyde, mixed and allowed to stand for 1 h. The excess laurylamine is then titrated potentiometrically with 1 N salicylic acid solution which is also prepared in a 1:1 ethylene glycol/isopropanol medium. A blank is run.

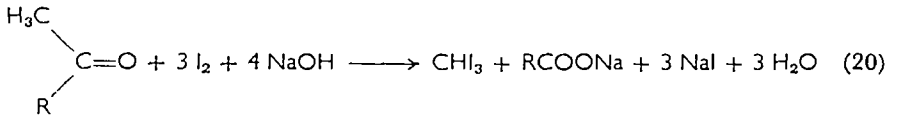
5. Oxidation methods

a. Hypohalite oxidation. Romijn[60] was the first to use the hypoiodite reaction (19) for the determination of formaldehyde. After the



(19)

reaction was complete, he acidified the excess hypoiodite and titrated the iodine with standard sodium thiosulfate solution. Iodoform is the primary reaction product of compounds containing the structures $CH_3\overset{|}{C}{=}O$ and $CH{=}\overset{|}{C}{-}\overset{|}{C}{=}O$ or structures oxidizable to these groups (equation 20). The hypoiodite reaction has been studied



$$\begin{matrix} H_3C \\ \diagdown \\ \quad C{=}O \\ \diagup \\ R \end{matrix} + 3\,I_2 + 4\,NaOH \longrightarrow CHI_3 + RCOONa + 3\,NaI + 3\,H_2O \qquad (20)$$

extensively[61–67] since Messinger[68] used it for the determination of acetone. Because the reagent oxidizes many noncarbonyl compounds, analyses based on this reaction suffer from interferences and side-reactions. Such methods are useful primarily for determining small concentrations of formaldehyde, acetaldehyde, or acetone. For example, Bose[61] determined 3–5 p.p.m. acetaldehyde, in water as follows. The sample containing 0·5–1·0 mg of aldehyde is diluted to 200 ml with water and cooled in ice water, and 6–12 ml of 0·0125 N iodine are added. Then 4 ml of 4 N sodium hydroxide are added and the mixture kept cold for 2 h, after which the temperature is raised to 20°C for another hour. The mixture is acidified with 5 ml of 4 N sulfuric acid and the excess iodine titrated with 0·025 N thiosulfate. Goltz and Glew[62] used a similar method to analyze dilute solutions of acetone in water and in benzene.

Grover and Mehrota[69] used alkaline bromine as a volumetric reagent for the estimation of acetone. Hashmi and Ayez[70] determined low concentrations of methyl ketones and acetaldehyde by direct titration with hypobromite, using Bordeaux as an internal indicator. To use the latter procedure, 2 ml of a solution containing about 0·001 mole of sample are added to 3 ml of 3 N NaOH, and the mixture is diluted with 2 ml of water. The titration is done using 0·1 N hypobromite solution and 3 drops of a 0·2% aqueous solution of Bordeaux.

b. Silver oxidation. Siggia and Segal[71] applied Tollen's reagent as an oxidant for aldehydes and determined the residual silver ions by titration with 0·1 N potassium iodide potentiometrically. The oxidation reaction is shown in equation (9). A silver and calomel electrode system with a potassium nitrate bridge was used. Although the alkalinity of the reaction medium eliminates the hydrolysis and

interference of acetals and vinyl ethers, it promotes the Cannizzaro-type reactions among aromatic aldehydes, causing low results. In general the method is applicable only to water-soluble samples. Ketones, excepting cyclohexanone, do not react and do not interfere in the determination of aldehydes. The principal disadvantage connected with the method is the instability of the reagent. *The reagent is potentially hazardous because of the occasional formation of an explosive silver compound which can explode with violence. Therefore, long reaction times and elevated reaction temperatures are not advisable*, and aldehydes, such as salicylaldehyde, which are difficult to oxidize cannot be determined.

Mitchell and Smith[72] oxidized aldehydes to their corresponding acids with silver oxide (equation 21). In their procedure about

$$2\,RCHO + 3\,Ag_2O \longrightarrow 2\,RCOOAg + H_2O + 4\,Ag \qquad (21)$$

5 milliequivalent of aldehyde is heated with solid silver oxide for about 30 min at 60°C. A measured amount of 0·5 N sodium hydroxide is added to displace the silver salt, the mixture is filtered, and the excess alkali is titrated with 0·2 N hydrochloric acid. This method gives low recoveries for formaldehyde and suffers from interference if acids or esters are present. Bailey and Knox[73] also applied silver oxide as a reagent. In their procedure the sample containing about 0·2 milliequivalent of aldehyde is dissolved in 1 to 5 ml of isopropanol or water and passed through solid silver oxide packed in a glass column. The column is washed with 25 ml of water and the eluant containing the silver salt of the acid is titrated with 0·02 N potassium thiocyanate to the ferric alum end-point. For saturated aliphatic aldehydes up to hexaldehyde, agreement within 2% of the values obtained by an oximation procedure was reported by the authors. The hydrolysis of esters, if present, constitutes an interference.

Ponndorf[74] developed a method for acetaldehyde in which sodium hydroxide is added to a mixture containing the sample and dilute silver nitrate. The unreduced silver is determined in the filtered reaction mixture after acidification to redissolve the silver oxide by titration with potassium iodide solution. Siegel and Weiss[75] extended the Ponndorf procedure to the determination of formaldehyde, propionaldehyde, n-butyraldehyde, benzaldehyde, and valeraldehyde and reported an accuracy of ±2% in the following procedure. Five ml of 0·5 sodium hydroxide are added to a mixture of the sample containing 0·5 milliequivalent of the aldehyde and 25 ml of 0·1 N of silver nitrate solution in a 100 ml volumetric flask. After shaking for

15 min, 2 ml more of 0·5 N sodium hydroxide are added and the mixture shaken again for 10 min. Then the mixture is acidified with 5 ml of 18 N sulfuric acid, cooled, diluted to the mark, and filtered. A 50 ml aliquot of the filtrate is titrated with 0·05 N thiocyanate using ferric alum indicator. Because the reaction is kept dilute with respect to sample and made strongly alkaline only in the last stages of oxidation, no side-reactions are experienced. There is no interference from ketones excepting cyclopentanone and cyclohexanone.

The reactions with silver oxide are heterogeneous with the attendant difficulties of reaction time and particle size of the reagent. Mayes, Kuchar, and Siggia[76], to overcome these difficulties and also to circumvent the use of the potentially hazardous Tollen's reagent, investigated silver oxide–amine complexes and used the complex formed with *t*-butylamine. This system is adaptable to the analysis of water-insoluble aldehydes and retains the advantages of the silver oxide systems, since it permits the determination of aldehydes in the presence of ketones, carboxylic acids, and acetals. The reagent is prepared by vigorously stirring a mixture of 24·5 g of silver oxide, 500 ml of deionized water, and 72·0 ml of *t*-butylamine until nearly all of the silver oxide is dissolved. An excess of amine is avoided and the excess silver oxide removed by filtration. Dilution with water to 1 liter results in a 0·2 N solution suitable for the determination of aromatic aldehydes, and dilution to 2 liters results in a 0·1 N reagent for aliphatic aldehydes. A 10 ml aliquot of the sample in 2B alcohol* containing about 0·002 mole of aldehyde is added to 50 ml of the reagent. After standing at room temperature with periodic shaking until reaction is complete (0·5 to 2 h), the mixture is filtered and the filtrate acidified with 10 ml of concentrated nitric acid and the excess silver ion is titrated with 0·1 N potassium thiocyanate solution. A blank is also run. Carboxylic acids and ketones do not interfere. Anisaldehyde yields low results, and acrolein and cinnamaldehyde give erratic results.

c. Mercurimetric oxidation. The oxidation of aldehydes with an alkaline solution of potassium mercuric iodide, a modification of Nessler's reagent, and determination of the liberated mercury has been extensively studied[77–83] (equation 22). These methods offer no

$$RCHO + K_2HgI_4 + 3\,KOH \longrightarrow RCOOK + Hg + 4\,KI + 2\,H_2O \qquad (22)$$

advantages over the silver methods, and the disadvantages are

* Formula 2B alcohol is a specially denatured alcohol consisting of a mixture of 0·5 volume part benzene and 100 volume parts 95% ethanol.

similar. The most effective of the mercury methods is that of Ruch and Johnson[82]. In this method the free mercury produced is maintained in the colloidal state with agar, acidified with acetic acid, and reacted with 0·1 N iodine. Excess iodine is titrated with 0·1 N sodium thiosulfate. Yamagishi, Yokoo, and Inoue[84] demonstrated a micromethod involving the determination of unreacted Nessler's reagent by adding hydrazine and measuring the liberated nitrogen gas.

6. Reduction methods

Higuchi and his coworkers[85–88] proposed lithium aluminum hydride as a reagent for the quantitative reduction of aldehydes and ketones. A known amount of the hydride in tetrahydrofuran is

$$4\,R_2C{=}O + LiAlH_4 \longrightarrow (R_2CHO)_4LiAl \qquad (23)$$

reacted with the sample (equation 23) and the excess determined by electrometric titration with a standard solution of one of the lower primary alcohols in benzene. The nonspecificity of the hydride reagent limits its utility. It is sensitive to such compounds as alcohols, amines, amides, water, mercaptans, acids, esters, nitriles, oxygen, and carbon dioxide in addition to the carbonyl compounds.

Sodium borohydride has the advantage as a quantitative reducing agent for carbonyl groups in that it is relatively stable in water or alcohol solutions (equation 24). Jensen and Struck[89] added known

$$R_2C{=}O + NaBH_4 + 2\,NaOH + H_2O \longrightarrow Na_3BO_3 + 4\,R_2CHOH \qquad (24)$$

amounts of 0·5 N sodium borohydride solution to the sample and determined the excess by titration of the iodine liberated when a mixture of potassium bromate and potassium iodide was added. Sobotka and Trutnovsky[90] used a gasometric method wherein the excess aqueous borohydride is decomposed with hydrochloric acid in propanol and the volume of hydrogen evolved is measured (equation 25). Borohydride solutions decompose slowly, and frequent standardization of the reagent is necessary.

$$NaBH_4 + HCl + 3\,H_2O \longrightarrow 4\,H_2 + NaCl + H_3BO_3 \qquad (25)$$

7. Dimedone method for formaldehyde

The dimedone derivative of formaldehyde (see section II.A.5 and equation 6) precipitates quantitatively and can be used for the gravimetric determination of the aldehydes[91–93]. This technique is particularly useful for the determination of formaldehyde in the presence of ketones. Yoe and Reid[93] showed that careful control of

the pH of the solution is necessary. A sample containing about 0·025 g of formaldehyde is added to a solution buffered at pH 4·6 by means of sodium acetate/hydrochloric acid mixture and containing about a 10% excess of dimedone. After standing for 12 h or longer, the precipitate is filtered and dried to constant weight at 60°c.

III. PHYSICAL METHODS

A. Chromatographic Techniques

1. Gas chromatography

The gas chromatographic separation, identification, and determination of volatile aldehydes and ketones is normally uncomplicated. Because of the large variety of column substrates and operating conditions used by various workers, no specific procedure will be given here. Certain conditions reported apply to specific compounds and to compounds in specific mixtures. The reader is referred to the literature cited in this section for the selection of the method most pertinent to his needs.

The time necessary for an unknown carbonyl compound to pass through a chromatographic column when compared with data for known compounds is often sufficient for its identification. The quantitative interpretation of the chromatograms is based on either peak height or peak area. Retention-time data for various types of columns and conditions have been published for aldehydes and ketones[94–101]. The eluted fractions also may be trapped and further characterized by chemical reagents or by physical measurements such as infrared and ultraviolet spectroscopy. Lewis, Patton, and Kaye[102] presented a technique applicable to the identification of aldehydes in complex mixtures whereby the elution times of known compounds from two partition columns having different characteristics are plotted against each other on logarithmic paper. Each compound studied had a different location on the plot. Young[103] has pointed out that there is a linear relationship between the number of carbon atoms in alkyl ketones and the logarithm of their retention volumes on dinonyl phthalate columns. Methyl n-alkyl ketones give a linear plot for all members. Ethyl n-alkyl, n-propyl n-alkyl, and isopropyl n-alkyl ketones each give linear plots except for the first member of each series, which is low; all the straight lines have the same slope. Compounds containing branched groups fall below the corresponding unbranched groups. An unknown can be

tentatively identified from its position on the plot. Results given by other workers[94,95,100] indicate that such linear relationships also exist for aldehydes.

Difficulties are often associated with the gas chromatographic analysis of formaldehyde, because it polymerizes on many stationary phases before it is eluted. Using special substrates, however, it is possible to obtain peaks. Kelker[104] used *o*-acetyltriethylhexyl citrate; Sandler and Strom[105] used a surface-active agent extracted from a commercial detergent; and Bombaugh and Bull[106] used a polyoxyethylene monostearate containing an average of 15 ethylene oxide units per molecule.

Ralls[107] and Stephens and Teszler[108] formed the 2,4-dinitrophenylhydrazones of carbonyl compounds and identified and determined the parent carbonyls by exchange with α-ketoglutaric acid followed by gas chromatography. This method is useful for concentrating small amounts of carbonyl compounds in large volumes of solvent or gas. Cason and Harris[109] showed that low molecular weight carbonyl compounds can be identified conveniently by gas chromatography of their oximes. These workers used di-2-ethylhexyl phthalate as a partitioning agent and showed that it is possible to identify C_2 to C_4 aldehydes, acetone, butanone, and 3-methyl-2-butanone in the presence of each other. Gray[110] separated long-chain fatty aldehydes by converting them into dimethyl acetals, which have better stability and lower boiling points than the aldehydes themselves. He then plotted the logarithm of the relative retention volumes for the acetals for separations, using Apiezon L grease as a stationary phase against values obtained using a Reoplex 400 stationary phase, and obtained parallel straight lines for each series. A tentative identification of an unknown is made from its position on such plots.

Another technique useful for determining the carbon skeleton and other structural features of micro amounts of carbonyl compounds is catalytic hydrogenation followed by gas chromatography. Hydrogenation of microgram amounts of C_n aldehydes produces mainly the C_{n-1} hydrocarbon corresponding to the original compound less the CHO group, and hydrogenation of ketones produces the parent hydrocarbon. Thompson and colleagues[111] hydrogenated fractions trapped from a column and passed the hydrogenated fractions again through the column. Beroza[112] simplified this technique by hydrogenating the original sample and passing it directly into the column, omitting the trapping steps. Depending upon the catalyst used,

aldehydes up to at least C_{11} and ketones up to at least C_7 are distinguishable[113].

2. Paper chromatography

The isolation and identification of aldehydes and ketones by paper chromatography is generally performed using their 2,4-dinitrophenylhydrazone derivatives. Identification is normally made by comparing the R_f values, the ratio of the compound movement to the developing solution movement, to the R_f values of known compounds. The method is valuable particularly for small amounts of carbonyl compounds in natural products. The use of the 2,4-dinitrophenylhydrazones is advantageous in that the separated spots can be located easily because of the yellow color of the derivatives. Rice, Keller, and Kirchner[114] used ascending development with ethyl ether in petroleum ether and sprayed the chromatograms with a 10% solution of potassium hydroxide to enhance the colors of the separated compounds. Kirchner and Keller[115] impregnated the paper with silicic acid and again used the same developing solution. Sýkora and Procházka[116] used kerosine as the immobile phase and 80% ethanol or 65% propanol as the developer, mainly for the 2,4-dinitrophenylhydrazones of the lower aldehydes and ketones. Seligman and Edmonds[117] impregnated paper with olive oil and developed the chromatograms of the 2,4-dinitrophenylhydrazones of C_8, C_9, and C_{12} aldehydes, and C_{11} and C_{13} ketones with either methyl acetate/water or isopropanol/water solutions. Acetylated paper was used by Koštíř and Slavic[118] and by Burton[119] and the chromatograms developed with various organic solvents. Klein and de Jong[120] separated the 2,4-dinitrophenylhydrazones of aliphatic carbonyl compounds having 7 or more carbon atoms, using paper impregnated with paraffin oil and 4:1 dioxane/water as the mobile phase.

Nano and Sancin[121] used thin-layer chromatography to separate the 2,4-dinitrophenylhydrazones of some short-chain carbonyl compounds. A thin layer of neutral alumina was used as the adsorbent and a 2:1 mixture of cyclohexane/nitrobenzene or an 8:2:1 mixture of hexane/chloroform/nitrobenzene as the developing solvent.

3. Column chromatography

Smith and LeRosen[122] have studied the straight-chain ketones, using adsorption on carbon, calcium carbonate, silicic acid, and

Florisil, a synthetic magnesium silicate. They found that the adsorption of these materials becomes progressively stronger as the length of the chain is increased. LeRosen and May[123] studied the chromatographic behavior of aldehydes on silicic acid from benzene and found that the rate of movement of zones increased with the length of the chain, and decreased with unsaturation in it. The position of the zones was found by streaking the column after extrusion with Schiff's reagent. Stoll[124] separated aldehydes with an activated alumina column.

Gabrielson and Samuelson[125] used an ion-exchange column in the bisulfite form to separate aldehydes from ketones. Ketones are readily removed by washing with water, while aldehydes are retained on the column. With such columns, Sjostrom[126,127] separated ketones by fractional elution with water. To separate and recover volatile carbonyl compounds, as well as ones which tend to polymerize or oxidize, Huff[128] used increasing concentrations of sodium or potassium bisulfite in water as the eluent.

However, a major portion of the studies performed on the column chromatography of carbonyl compounds has been concerned with their derivatives. Roberts and Green[129] used a silicic acid/Super Cell adsorbent mixture in a 2:1 ratio to separate any mixture of the 2,4-dinitrophenylhydrazone derivatives of acetaldehyde, acetone, propionaldehyde, and methyl ethyl ketone except that of acetone and propionaldehyde. They used ethyl ether in petroleum ether to elute the fractions. White[130] separated the aldehyde and ketone derivatives on a mixture of bentonite and diatomaceous filter aid. Gordon and coworkers[131] separated aldehydes and ketones from C_1 up to C_4 on a 2:1 silicic acid/Celite column, using ether/petroleum ether mixtures. The range of this procedure was extended by Pippin, Eyring, and Nonaka[132], who separated adjacent members of the homologous series of saturated normal aldehydes as high as C_{11} on long columns. Kramer and Van Duin[133] used silica gel to separate the derivatives of up to and including C_{18} normal aliphatic aldehydes and normal methyl ketones. These authors used nitromethane as a stationary phase and purified hexane as the mobile phase. They plotted retention volumes against the number of carbon atoms in the parent compound of two homologous series and obtained practically straight lines. Monty[134] modified this method by using diatomaceous earth as the supporting medium. Nitromethane absorbs light in the same region as the 2,4-dinitrophenylhydrazones and has to be removed before spectrophotometric identification. Corbin, Schwartz, and

Keeney[135] replaced the nitromethane with acetonitrile to overcome this interference. Corbin[136] separated mixtures of dicarbonyl compounds, using acetonitrile and water as the stationary phase on Celite columns. Elution was done with methylcyclohexane alone or in mixtures with ethyl acetate. Wolfrom and Arsenault[137] separated highly oxygenated C_2 and C_3 carbonyl compounds on a silicic acid/Celite column. Schwartz, Parks, and Keeney[138] separated 2,4-dinitrophenylhydrazones into classes on a magnesia/Celite column. The classes elute in the sequence: methyl ketones, saturated aldehydes, 2-enals, and 2,4-dienals. Characteristic colors for each class are displayed on the adsorbent and aid in their identification.

B. Visible and Ultraviolet Spectroscopy

1. Qualitative

Except in some special cases, for example glyoxal, which absorbs at about 440 mμ, direct optical examination of aldehydes and ketones in the visible range is of little analytical utility because of the colorless or transparent nature of these compounds.

Compounds containing unsaturated bonds exhibit resonance and therefore are likely to have characteristic absorptions bands in the ultraviolet region. For this reason, aldehydes and ketones, because of the presence of the carbonyl group, show an absorption that is usually in the region 270–300 mμ. A low relative intensity absorption in this range and the nature of the spectrum, usually structureless, are criteria for the presence of an aldehydic or ketonic group. The ultraviolet spectrum is a useful supplement to the infrared spectrum, especially to distinguish between these groups and esters, which is normally difficult to do from the infrared spectrum alone.

The ultraviolet spectra are subject to environmental influence; for example, substitution of halogen for hydrogen in ketones displaces the band toward longer wavelengths and substitution with hydroxyl displaces the band toward shorter wavelengths[139]. These effects are illustrated in Table 1.

Ethylenic unsaturation conjugated with the carbonyl group shifts the spectrum toward the visible range[140]. The presence of two bands, one of low intensity at 320–340 mμ due to C=O absorption and the other of high intensity at 200–250 mμ due to C=C—C=O absorption, is good evidence of the conjugated linkage.

Medium effects must also be considered when identification is attempted using the ultraviolet region. The polarity of the solvent and

TABLE 1. Environmental effects on the band position of ketones in the ultraviolet region[139].

Compound	Formula	Wavelength (max) (mμ)
Acetone	CH_3COCH_3	278
Methyl ethyl ketone	$CH_3COCH_2CH_3$	279
Monochloroacetone	$CH_2ClCOCH_3$	292
sym-Dichloroacetone	$CH_2ClCOCH_2Cl$	294
Acetoin	$CH_3COCHOHCH_3$	273
Desoxybenzoin	$C_6H_5CH_2COC_6H_5$	326
Benzoin	$C_6H_5CHOHCOC_6H_5$	316

hydrogen ion concentration influence the spectral absorption[141,142]. In general an increase in polarity or hydrogen ion concentration of the solvent results in a displacement of the absorption band to shorter wavelengths. The solvent also can affect the equilibrium between the enol and keto forms of 1,3-diketone, resulting in a change in the absorption spectra. The enol form has the characteristic conjugated structure which is absent in the keto form and is evidenced in the ultraviolet spectrum. The formation of hydrates can also influence the spectra. Formaldehyde shows carbonyl absorption in the vapor state but fails to show significant absorption in aqueous solution because of the formation of the hydrate, $H_2C(OH)_2$.

The high molar absorptivities in the far-ultraviolet region, 222–175 mμ for carbonyl compounds, make this region attractive, especially for the examination of small quantities[143,144]. Not only is differentiation between classes of carbonyl compounds possible, but also differentiation between homologs. The spectra of vapor samples are to be preferred, because then the vibration fine structure is revealed and solvent absorption is avoided.

Informative qualitative data can be obtained from the visible and ultraviolet spectra of derivatives of carbonyl compounds. Jones, Holmes, and Seligman[145] have made a detailed spectrophotometric study of various 2,4-dinitrophenylhydrazones of aldehydes and ketones in neutral and in basic solution. Differentiation among classes of carbonyl compounds is possible. Table 2 shows the general band positions for the 2,4-dinitrophenylhydrazones of carbonyl compounds of differing structures. In addition to these maxima for aliphatic aldehydes and ketones, smaller maxima occur at 520–525 mμ in alkaline media. These maxima are stable in the case of ketone

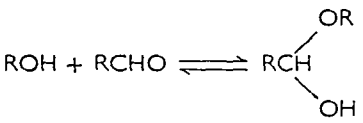
TABLE 2. Absorption of classes of aldehyde and ketone 2,4-Dinitrophenylhydrazones[145].

Compound class	λ_{max} Range (mμ)	
	Neutral solution	Basic solution
Aliphatic aldehydes	344–358	426–438
Aliphatic ketones	364–367	431–444
Aromatic aldehydes	378–390	462–486
Aromatic ketones	382–392	452–508
Olefinic aldehydes and ketones	368–385	452–459
Furanic aldehydes and ketones	380–404	468–490

derivatives, but deteriorate in 60 to 90 min in the case of aldehyde derivatives, and this deterioration is the deciding factor in differentiating between these classes.

Phillips[146] has compiled charts of the absorption maxima in the ultraviolet region of several hundred 2,4-dinitrophenylhydrazones in chloroform and of several hundred semicarbazones, mostly in ethanol. In general the semicarbazones appear insensitive to most minor structural influences on their spectra compared with the 2,4-dinitrophenylhydrazones.

The temperature-sensitive equilibrium reaction between aldehydes and alcohols (equation 26) can be used to detect these carbonyl



(26)

compounds in complex mixtures by comparing the ultraviolet spectrum at two different temperatures and noting the equilibrium shift[147].

2. Quantitative

Only limited use has been made of the direct determination of carbonyl compounds using ultraviolet absorption spectroscopy. Barthauer, Jones, and Mettler[148] determined acetone in mixtures with diisopropyl ether, isopropyl alcohol, and low molecular weight olefins. Rees and Anderson[149] determined benzaldehyde in benzyl alcohol. Englis and coworkers[150,151] determined vanillin and Pepe, Kniel, and Czuha[152] determined isopropenyl ketone in polymers, using direct ultraviolet absorbance measurements. The band in the

170–200 mμ far-ultraviolet region has been applied to the analysis of acetone in acetylene[153].

The most generally used technique for determining trace quantities of carbonyl compounds is based on the spectrophotometric measurement of the 2,4-dinitrophenylhydrazone derivatives. The main difficulty in these procedures has been the interference from the excess 2,4-dinitrophenylhydrazine, which absorbs in the same region as the derivatives. To minimize this, two general approaches have evolved. One involves the selective extraction of the derivative, using a hydrocarbon solvent, and subsequent measurement of the absorbance at about 340 mμ. The other is based on the measurement of the wine-red complex formed on addition of alkali to a solution of the derivative, shifting the maximum absorbance to the 430–480 mμ region, where the reagent interference is decreased. One objection to the direct measurement of the 2,4-dinitrophenylhydrazone derivatives, even after extraction, is that the absorption maximum and the molar absorptivity change significantly with the saturated and unsaturated nature, as well as the structural variations of carbonyl compounds. This causes difficulties when attempts are made to determine the total carbonyl content of mixtures. However, the method is satisfactory for single aldehydes or ketones, when comparison is made with calibration curves based on the compound being determined. In contrast to this, where the color is stable, the color of the complex formed in the presence of alkali decreases in intensity with time for any given concentration and a prescribed reading interval must be observed to limit the error incurred to within the accuracy of the method. However, in this latter case, no significant shift in absorbance maximum is observed with aliphatic and most simple aromatic aldehydes and ketones.

The determination of small amounts of carbonyl compounds based on the formation of 2,4-dinitrophenylhydrazone was first reported by Mathewson[154]. He applied it to the determination of acetone in water-soluble samples only. Toren and Heinrich[155] selectively extracted the 2,4-dinitrophenylhydrazone of a butadiene–furfural condensation product with isooctane and determined its concentration by absorption measurement at 340 mμ. Lohman[156] presented a more general procedure, using hexane to extract the 2,4-dinitrophenylhydrazone derivative. Carbonyl compounds in the range 3 to 300 p.p.m. of carbonyl oxygen are determined. This range can be extended to lower limits by use of large samples for the hydrazone formation, followed by a chromatographic adsorption on a silicic

acid/Celite column to concentrate the hydrazone. This technique has been used to determine aldehydes down to the 0·1 p.p.m. level in 100 g samples[157]. The details of Lohman's procedure[156] are as follows.

Ten ml of 2,4-dinitrophenylhydrazine solution, 1 mg per ml in purified ethanol (500 ml of anhydrous ethanol refluxed with 5 g of 2,4-dinitrophenylhydrazine and a few drops of concentrated hydrochloric acid for 2 h and distilled), and 5 ml of hexane are pipetted into a 50 ml glass-stoppered flask and one drop of concentrated hydrochloric acid added. The sample is diluted with mineral oil, if necessary, to contain about 1 mg of aldehyde or ketone per gram. Approximately 0·25 to 0·5 g of the sample solution is added to the flask and the exact sample weight obtained by difference. The mixture is kept at 50°c for 1 h and then transferred to a separatory funnel containing 15 ml of methanol and 10 ml of 1% sodium bicarbonate solution. The mixture is extracted 5 times with 15 ml portions of hexane. The combined extracts are dried with a little sodium sulfate and diluted to exactly 100 ml. The absorbance of this solution is read at 340 mμ in a 1 cm cell, using hexane as the reference solution. The concentration of carbonyl is read from a calibration plot of absorbance *versus* concentration, prepared using the carbonyl compound being determined.

Pool and Klose[158] eliminated the interference from excess reagent by carrying out the condensation on an alumina column. The 2,4-dinitrophenylhydrazone was eluted with benzene, made alkaline, and the colored product determined spectrophotometrically at 435 mμ. Lappin and Clark[159] determined carbonyl compounds at a wavelength of 480 mμ as the 2,4-dinitrophenylhydrazone in alkaline solution. Mendelowitz and Riley[160] pointed out that, for most aldehydes and ketones, the maximum absorbance occurs near 430 mμ instead of the 480 mμ used by Lappin and Clark. They also observed inorganic chloride precipitation upon the addition of potassium hydroxide. By adding water to ensure solution of inorganic chloride, Jordan and Veatch[161] eliminated this objection. The Jordan and Veatch procedure was developed primarily for carbonyl compounds in alcohols, but is also applicable for most hydrocarbons, organic esters and acids, aromatic compounds, petroleum distillates and some ethers. An appropriate size sample is weighed into a 25 ml volumetric flask. Five ml of a 3:7 n-hexane/Formula 30 alcohol*

* Formula 30 alcohol is a specially denatured alcohol consisting of a mixture of 10 volume parts methanol and 100 volume parts 95% ethanol.

and 0·1 ml of concentrated hydrochloric acid are added. The Formula 30 alcohol and the n-hexane are previously purified by refluxing with an excess 2,4-dinitrophenylhydrazine (1 h for the alcohol and overnight for the n-hexane) and then distilled. The sample mixture and reference solution are heated at 55 ± 1°c for 30 min. They are cooled rapidly to room temperature and diluted to volume with a solution containing 59 g of potassium hydroxide and 180 ml of water diluted to 1 liter with Formula 30 alcohol. The absorbance of each solution is read, using 1 cm cells at 480 mμ between 8 and 15 min after diluting to volume. The concentration of carbonyl is obtained by reference to a calibration curve prepared using pure aldehyde or ketone.

Chromotropic acid is an almost specific reagent for formaldehyde (see section II.A.11). Spectrophotometric methods based on the deep purple-violet color produced are primarily useful for determining small amounts of formaldehyde in the presence of large concentrations of various organic compounds. Methods were developed by Bricker and Johnson[162] and by Bricker and Vail[163]. West and Sen[164] presented a procedure as follows.

One ml of a 1% sulfuric acid solution of chromotropic acid is added for each ml of aqueous formaldehyde solution. Immediately, sufficient concentrated sulfuric acid is added to insure that the acid is present in a concentration of at least 86% during the color development. This is mixed, allowed to stand for a few minutes, diluted cautiously with distilled water to almost the desired volume, and again mixed. After the mixture is cool, final adjustment of volume is made and the color measured at 570 mμ. Using cells of 1 cm light path, solutions containing 0·05 μg to 2·0 μg of formaldehyde per ml follow Beer's law. The method is sensitive not only to free formaldehyde, but also to any substance which will yield formaldehyde upon hydrolysis in concentrated sulfuric acid. Only acrolein interferes seriously; other aldehydes react with chromotropic acid but the purple color is specific for formaldehyde.

Altshuller, Miller, and Sleva[165] adapted the method of West and Sen with slight modifications to determine formaldehyde in air at the 0·5 p.p.m. level.

Although the use of Schiff's reagent is one of the earliest tests for aldehydes (see section II.A.6) and is widely used, the method suffers from many defects. As a result, numerous studies have been made to arrive at acceptable quantitative procedures. Careful attention must be given to the ratio of sulfur dioxide to fuchsin, and the solution

must be specially treated by adsorbents to remove residual color before it is suitable for use[166–168]. Kramm and Kolb[169] found that the most sensitive reagent results when a dye concentration of 300 mg per 100 ml and a sulfur dioxide concentration of 2·8 to 4·8 millimole in the form of sodium metabisulfite is used. This solution is decolorized with 1 g of carbon for each 500 ml of solution, followed by vacuum filtration. Tobie[170] recommended the addition of ethanol; Hoffpauir and O'Connor[171] suggested the addition of acetone to intensify the color of the reaction product with aldehydes. Fishbeck and Neundeubel[172] applied the reaction for the determination of formaldehyde, acetaldehyde, and propionaldehyde. Deniges[173] observed that Schiff's reagent reacts with formaldehyde in acidified solution to give a blue color, fairly stable for several hours, while the color formed with higher aldehydes faded within a few hours. Blaedel and Blacet[174] used this observation to determine formaldehyde in the presence of other aldehydes. Hoffpauir, Buchaloo, and Guthrie[175] refined the procedure of Blaedel and Blacet[174] and obtained a reproducible curve for transmittance at 550–585 mμ against mg of formaldehyde. Rayner and Jephcott[176] used Schiff's reagent to determine formaldehyde in air in concentrations as low as 0·05 p.p.m. Precise control of reaction conditions and the use of standards prepared under identical conditions and at the same time as the experimental samples are necessary. Temperature and time affect the rate of color development, and Beer's law is not obeyed in any of the modifications of the methods discussed. Therefore, no general procedure can be given to cover all specific situations.

An ultraviolet spectrophotometric method for acetaldehyde and acetone based on the iodoform reaction (see section II.A.9) has been described by Dal Nogare, Norris, and Mitchell[177]. Using controlled conditions, the reaction of acetaldehyde and acetone with hypoiodite gives iodoform, which is measured at 347 mμ. This peak is most sensitive and shows good agreement with Beer's law for amounts of iodoform from 0 to 3 mg. The procedure can probably be used for other methyl ketones. Ten ml of 20% iodine solution are pipetted into a 125 ml separatory funnel and 3·3 ml of 20% sodium hydroxide added. If the resulting solution is not distinctly orange, the color is adjusted by dropwise addition of iodine solution. To this solution, 1 to 5 ml of solution containing no more than 0·4 mg of acetone or acetaldehyde are added and immediately mixed. This is allowed to stand for 5 min. Iodine solution is added dropwise to maintain the orange-yellow color. After reaction, the iodine color is discharged

with a few drops of 5% sodium thiosulfate solution. The iodoform is extracted, using 22 to 24 ml of chloroform. The chloroform extract is washed by shaking with an approximately equal volume of water. The chloroform extract is dried by passing it through a bed of anhydrous sodium sulfate supported on a glass-wool plug in a funnel. The extract is diluted to 25 ml in a volumetric flask, using chloroform, passing it first through the sodium sulfate to wash down the retained extract. The absorbancy of the solution is measured at 347 mμ *versus* chloroform in 2·5 cm silica cells. The absorbance of a blank is determined and subtracted from all sample readings. Equation (27) or (28) is used for the calculation, where A is the absorbance

$$\% \text{ Acetaldehyde} = \frac{A \times 0{\cdot}421 \times 100}{\text{mg of sample}} \tag{27}$$

$$\% \text{ Acetone} = \frac{A \times 0{\cdot}284 \times 100}{\text{mg of sample}} \tag{28}$$

corrected for the blank, and 0·421 and 0·284 are the reciprocals of the slopes of the respective acetaldehyde and acetone calibration curves. These calibration curves are plots of absorbancy *versus* mg compound, the data obtained by application of the outlined procedure to pure acetaldehyde and pure acetone.

Cochran and Reynolds[178] used sodium borohydride in dimethylformamide for the direct photometric titration of aldehydes. The sample was dissolved in a water/isopropyl alcohol solution and titrated with standardized reagent to the disappearance of the ultraviolet absorption peak characteristic of the particular aldehyde being determined.

C. *Infrared Spectroscopy*

1. Qualitative

The carbonyl group appearing in a number of different classes of compounds, including aldehydes, ketones, carboxylic acids, esters, amides, and anhydrides, exhibits under normal conditions a strong band in the region between 5·45 and 6·5 μ. Aldehydes and ketones absorb, in general, in the range 5·7 to 6·0 μ and overlap the absorption bands for acids and esters. Therefore, differentiation among the different classes using the maxima in this region only is usually difficult, if not impractical. Aldehydes also exhibit C—H stretching of the formyl groups, and characteristic bands appear near 3·7 μ which can be used to differentiate aldehydes from other types. Esters

can be eliminated in the absence of a band at 7·7 to 8·8 μ due to C—O stretching, and acids can be eliminated if the OH absorption at 2·82 μ is missing.

The structural configuration adjacent to the carbonyl group affects the observed spectra in the 14 to 25 μ region in a specific manner[179,180]. The spectral behavior of aldehydes and ketones in this region is very similar. Each possess a vibration involving a C=O bending motion slightly below 20·0 μ. This absorption occurs in nearly the same position in both α-branched and non-α-branched members of the two classes. Each class possesses a C—C—C bending motion in which one of the carbon atoms is the carbonyl carbon. The wavelength of this vibration is not the same in the two classes, about 16·0 μ for ketones compared to about 14·7 μ for aldehydes. In both classes α-branching tends to shift the absorption to higher wavelengths.

The near-infrared region can be used to confirm the presence of the aldehyde group and to provide information concerning its environment[181,182]. This portion of the spectrum shows characteristic absorptions which are combinations of the C=O and formyl C—H bands and appear in the 2·25 μ region. This region is comparatively free of absorptions by other functions, and the presence of a band here in addition to the C—H and C=O bands is good indication of the presence of an aldehyde. Alternatively, the absence of this band in the near-infrared, although the C—H and C=O bands are present, would appear to exclude the possibility of the presence of an aldehyde.

Special advantages often are gained by separating the aldehyde or ketone as the 2,4-dinitrophenylhydrazone or as the semicarbazone and examining the infrared spectrum of the derivative. The spectra are, in general, unique for the 2,4-dinitrophenylhydrazones of the common aldehydes and ketones and of the 2,4-dinitrophenylhydrazine reagent[183]. Even closely related aldehydes or ketones differing by only one CH_2 group exhibit markedly different infrared spectra. Derivatives containing as much as 5 to 10% of an impurity as another derivative may be characterized readily. The N—H stretching band is found at shorter wavelengths in the ketone 2,4-dinitrophenylhydrazones than in the aldehyde derivatives[145] and is useful for distinguishing the two classes. Use can be made of the ratio of absorbance of the CH_2 and NH band to distinguish among n-alkanals, 2-alkenals, and 2,4-dienals and to differentiate individual members within each of these groups[184,185]. Lento and Ford[184]

demonstrated that there is a linear relationship between the ratio of the CH_2 to NH stretching modes and the chain length of the parent carbonyl compound and, using calibration curves, showed that the chain length of an unknown can be estimated. Using the semicarbazones, it is not possible to differentiate ketones from aldehydes as a class[186]. However, the semicarbazones appear to be even more readily differentiated from one another than are the 2,4-dinitrophenylhydrazones. Crystalline modifications of both the 2,4-dinitrophenylhydrazones and semicarbazones yield different spectra, but if the crystallizations are performed under identical conditions as those used to obtain the reference spectra, no difficulties are experienced.

2. Quantitative

It has been demonstrated that, with suitable attention to corrections for mutual interferences, satisfactory semiquantitative analyses of mixtures of oxygenated hydrocarbons are possible[187–189]. The band positions used by Saier and Hughes[189] for the analysis of such a mixture are shown in Table 3. The band position used for the

TABLE 3. Wavelengths used for analysis of oxygenated hydrocarbon mixtures[189].

Compounds	Wavelength (μ)
Aldehydes	3·68
Ketones	5·80
Acids	2·82
Esters	7·7–8·8
Ethers	8·3–9·4

aldehyde determination corresponds to the C—H stretching of the formyl group. The C=O vibration band was used for the ketone determination, which introduces difficulties because of the absorption in the same region of other compounds containing the carbonyl group and, in addition, all the others except aldehydes have greater absorptivities. A correction for the ester absorption in this region was made, using the 7·7 to 8·8 μ C—O stretching band position, and a correction for the presence of acids was made, based on their O—H absorption at 2·82 μ. In such a complex mixture the average error to be expected is about 9% for aldehydes and 23% for ketones[189]. The use of bandwidth curves[187], substitution of the data into a

special matrix[189], or the use of integrated absorptivities of the C—H stretching vibration[188] aids in the resolution of such mixtures and increases the accuracy of the method. The application of this scheme to other types of mixtures should be preceded by careful testing of synthetic mixtures to evaluate mutual interferences of the components.

Powers, Harper, and Tai[182] used the absorption of the aldehyde group in the near infrared to determine benzaldehyde in the presence of aromatic ketones and to analyze mixtures of nitrobenzaldehydes. Although the position of the combination bands for *m*- and *p*-nitrobenzaldehyde are practically identical, the difference in their position from the *o*-nitrobenzaldehyde band position is sufficient to make possible the determination of a mixture of either the *ortho* and *para* isomers or the *ortho* and *meta* isomers.

In many cases a preliminary distillation[190] or chromatographic separation of a mixture, followed by infrared examination of the fractions, results in a decrease in complexity of the spectra and an increase in the accuracy of the determination. Also, separation of interfering compounds by chemical means, where practical, simplifies the spectra of the remaining mixture. The quantitative determination of a mixture of acetaldehyde and propionaldehyde by means of their 2,4-dinitrophenylhydrazones in solution has been demonstrated by Ross[191].

Goddu[192] points out that oxime derivatives of aldehydes and ketones have a very intense fundamental band at 2·78 μ, which can probably be used as a basis for quantitative determinations. Alcohols, which absorb at 2·74 to 2·76 μ, hydroperoxides, which absorb at 2·81 to 2·84 μ, and most nitrogen-containing compounds, which absorb at 2·8 to 3·0 μ, would not be expected to interfere. Phenols would probably interfere.

D. Mass Spectroscopy

Although more certain identifications from the mass spectra of carbonyl compounds are obtained by matching the spectra of the unknown with reference spectra of known compounds, much structural information can be obtained using certain structural correlations, even if pertinent reference spectra are not available. Structural correlations can be obtained from such works as those of Gilpin and McLafferty[193] for aliphatic aldehydes, Aczel and Lumpkin[194] for aromatic aldehydes, and those of Sharkey, Shultz and Friedel[195] and Beynon, Saunders, and Williams[196] for ketones. The observations of these workers can be summarized only very

generally here. Readers interested in more detailed information are referred to the original papers.

The mass 29 peak, from the aldehyde group —CHO, is the highest peak in the spectra of formaldehyde, acetaldehyde, and n-propionaldehyde. In most cases aldehydes give a major cleavage at the bond β to the aldehyde group, accompanied by a shift of one hydrogen to the oxygen-containing fragment to give mass 44. Mass 44 is the highest peak in the spectra of straight-chain C_4 to C_7 aldehydes; β cleavage is increased by chain-branching adjacent to the β bond. For aromatic aldehydes, the loss by α cleavage of the functional group often gives the most intense peak. Major fragmentation peaks are produced by splitting on either side of the carbonyl group. Asymmetrical ketones show two such peaks, since either alkyl substituent may be lost. These peaks are useful for establishing the position of the carbonyl group. For cyclic ketones, the spectra show the tendency to give a large peak corresponding to loss of C_2H_4, C_2H_5 and C_2H_4O fragments from the molecular ions. $(C_3H_3O)^+$ ions predominate in the single-ring systems.

E. Polarography

The direct polarographic determination of carbonyl compounds is limited, in general, to aliphatic aldehydes, which readily reduce at voltages just below the reduction voltages of the more common supporting electrolytes. Ketones, on the other hand, are reduced at potentials much more negative than those obtainable in the usual supporting electrolytes. Ketones can be directly determined in solutions of specially prepared quaternary ammonium salts, as recommended by von Stackelberg and Stracke[197].

The direct technique has its most extensive application in the analysis of formaldehyde and acetaldehyde, either alone or in mixtures. Formaldehyde reduces at about $-1{\cdot}6$ v, while the saturated aldehydes reduce at about $-1{\cdot}8$ v, making the determination of formaldehyde in the presence of other aldehydes feasible. Boyd and Bambach[198] used a supporting electrolyte solution, 0·5 N in potassium hydroxide and 0·01 N in potassium chloride, to determine formaldehyde. An alkaline medium is used because formaldehyde exists predominantly in the hydrated and therefore nonreducible form in acidic aqueous solutions. Shikata and his coworkers[199,200] described the polarographic determination of small amounts of aldehydes, including acetaldehyde, in alcoholic beverages. Elving and Rutner[201] used the polarographic technique to determine acetaldehyde in the

presence of formaldehyde or unsaturated aldehydes, based on the difference in diffusion currents. The effect of the presence of other aldehydes, such as acrolein, acetaldehyde, and propionaldehyde on the determination of formaldehyde was investigated by Whitnack and Moshier[202]. They found that the most satisfactory results are obtained in 0·1 N lithium hydroxide containing 0·01 N lithium chloride. Warshowsky and Elving[203] used this method for the simultaneous determination of formaldehyde and acetaldehyde resulting from the periodate oxidation of mixtures of ethylene and 1,2-propylene glycols. Neĭman and Gerber[204] analyzed solutions containing both formaldehyde and acrolein by using dimedone to remove the wave due to formaldehyde. Sandler and Chung[205] determined formaldehyde in mixtures containing hydrogen peroxide and acetaldehyde. Titanium tetrachloride was added to eliminate peroxide interference.

Van Atta, Harrison, and Sellers[206] developed an amperometric method for the titrimetric determination of acetaldehyde using hydroxylamine hydrochloride solution. The sample is titrated at constant voltage using a dropping mercury electrode. Braddock and coworkers[207] studied the 2,4-dinitrophenylhydrazones of a series of aldehydes in an acetone/water solution. They found that, in the range 5×10^{-5} to 4×10^{-4} M concentration, the diffusion current varies directly with the concentration, providing a means of quantitative analysis of these compounds. The semicarbazones of aldehydes and ketones give well-defined polarographic waves in solutions buffered in the pH range 4 to 5. Coulson[208] applied this technique to the determination of volatile compounds in the atmosphere.

Ketones are usually determined polarographically by first reacting them with a reagent to form a product which is reducible within the range of potentials available with the ordinary electrolyte systems. The bisulfite method used by Strnad[209] is based upon the extent to which the presence of a ketone decreases the bisulfite wave. Souchay and Graizon[210] presented a method involving the polarographic measurement of acetone after condensation with semicarbazide. The imine produced by the reaction of ketones with amines has been measured[211–216] and used quantitatively.

Adkins and his associates[217,218] worked with diaryl and alkyl aryl ketones and found that, in some two-ketone systems, the diffusion current was quantitatively proportional to the concentration of ketone being determined and independent of other ketones present; for example, n-propyl phenyl ketone and benzophenone, and iso-

propyl phenyl ketone and benzophenone. However, this was not the case for other ketones; for example, acetophenone and benzalacetone, in which case benzalacetone had a marked effect on the wave height of acetophenone. Boyd and Amell[219] found that, in 0·1 M lithium hydroxide in 50% ethanol/water solvent, the diffusion current is directly proportional to the benzaldehyde concentration and to the concentration of isopropyl phenyl ketone and *t*-butyl phenyl ketone.

F. Nuclear Magnetic Resonance Spectroscopy

1. Qualitative

High-resolution nuclear magnetic resonance chemical shifts and spin–spin splittings provide information concerning the chemical environment and numbers of each type of hydrogen present in a molecule. It is a valuable tool for the identification of organic structures. The chemical shifts indicate the chemical nature of the hydrogens and provide some information about their spatial positions. Further information about the spatial positions of the hydrogens are obtained from the band multiplicities produced by spin–spin interaction. The number of hydrogen atoms contributing to a band can be counted, since the area under an absorption band is directly proportional to the number of hydrogen atoms contributing to the band. Identification is made when an unknown exhibits the same characteristic chemical shifts and relative intensities as a known sample. The technique is useful alone, but is used best with other tools, especially with infrared spectroscopy.

Various listings of nuclear magnetic data and reviews of the technique are found in the literature[220–224]. The aldehydic proton shift in aliphatic carbonyl groups occurs at about −2·3 p.p.m. relative to benzene as an external standard and at about −2·7 p.p.m. in aromatic compounds. The shift for the protons in a methyl group α to the carbonyl group in aliphatic compounds is at about 5·2 p.p.m. and at about 6·3 p.p.m. in a methyl group β to the carbonyl group. Methylene groups α to the carbonyl group in aliphatic compounds have their proton shift at 4·9 p.p.m., while those in the β-position have the proton shift at 5·9 p.p.m. For a methyl group β to an aromatic ring, the proton shift is at about 4·8 p.p.m., while for a methylene group α to the ring, it is at about 2·8 p.p.m.

Curtin and coworkers[225] showed that nuclear magnetic resonance spectroscopy can be used to differentiate between aldehydes and ketones, based on the presence or absence of the aldehydic hydrogen

in their 2,4-dinitrophenylhydrazone and semicarbazone derivatives. The proton resonance of the N=C—H group in methylene chloride solutions of the 2,4-dinitrophenylhydrazones and the semicarbazones occurs at −0·2 to −0·4 p.p.m. and 0·34 to 0 p.p.m. relative to benzene, respectively.

2. Quantitative

The number of hydrogen nuclei contributing to a band can be counted by integration of the area under an absorption band. The total hydrogen can be determined by comparison with samples of known hydrogen content, and quantitative analysis becomes possible. Jungnickel and Forbes[226] used this technique to analyze diethyl ketone, among other illustrative examples of organic compounds. Karabatsos, Graham, and Vane[227] used the same technique to determine the percentage of stereoisomeric forms of the 2,4-dinitrophenylhydrazone and semicarbazone derivatives of ketones.

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CHAPTER 9

Basicity of carbonyl compounds

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I. INTRODUCTION

It is not usually obvious to a chemist working in the field of organic synthesis that questions about the basicity of the carbonyl group are of any importance at all. According to the familiar general concepts of basicity, it would seem that carbonyl compounds do not behave like bases in common practice, and even if they did hardly anything would seem to be relevant to this subject besides a list of the values of basicity constants for different carbonyl compounds. But in spite

of these common assumptions, recent investigations have shown that the basicity of the carbonyl group is by no means a simple problem. To demonstrate this, Table 1 lists the pK_a values (the negative

TABLE 1. The pK_a values for acetone according to different sources.

pK_a	Ref.	pK_a	Ref.
−7·2	1	−1·6	4
−4	2	−0·66	5
−2	3		

logarithm of the basicity constant) for acetone, according to different authors. The result is striking: anybody is at liberty to choose a 'right' value within the limits of seven powers of ten. Such freedom of choice is rather disappointing, especially if we take into consideration the fact that the discrepancies (to several powers of ten!) cannot be attributed to experimental errors.

Several questions now arise. What do we mean when we speak about the basicity of carbonyl compounds? What does 'basicity' itself mean? Is it one definite thing or are there several different basicities?

In this chapter we shall try to find some possible answers to these problems. We shall also try to show that the study of the basicity of carbonyl compounds is extremely important for the development of the general concepts of basicity.

II. THE CLASSICAL ACID-BASE CONCEPT AND THE QUANTITATIVE MEASURE OF BASICITY

Classical definitions of a base were given by Brönsted[6] and by Lowry[7,8] from one point of view, and by Lewis[9] from another. The first two authors considered bases as compounds capable of forming a protonated entity; the more general definition of Lewis considered basicity as the ability of an electron donor to donate an electron pair to form a covalent bond with the acceptor. From the point of view of the bases themselves, however, these two concepts are equivalent. The electron pairs donated by bases are usually presented as unshared electron pairs, but this is not a rigid requirement and π electrons could be used as well. Consequently, all carbonyl compounds should

be considered as bases, with their basic behavior related to the unshared electron pairs of the oxygen atom.

There are some important details in the Brönsted basicity concept which should be outlined. The acid–base interaction is considered to follow the general scheme (1), where n and m denote the charges

$$\underset{\text{base}}{B^n} + \underset{\text{acid}}{AH^m} \rightleftharpoons \underset{\text{acid}}{BH^{n+1}} + \underset{\text{base}}{A^{m-1}} \tag{1}$$

on the base and acid, respectively. According to this scheme, the general property of a base is its ability to form a protonated particle BH^{n+1}. The charge on the latter is more positive by one unit than the charge on the original base. Uncharged bases, for example carbonyl compounds, give protonated particles (cations) with a unit positive charge. Consequently, there should be important differences between the electronic structure of the base and that of its protonated form (conjugate acid).

It is easy to represent this simple concept, since the equilibrium (1) with a standard acid under standard conditions can be used to estimate base strengths quantitatively. When the standard acid is water, the equilibrium (1) for uncharged bases is reduced to the equilibrium (2), so that the basicity constant K_b in pure water at 25°

$$B + H_2O \rightleftharpoons BH^+ + OH^- \tag{2}$$

can be used to measure the base strength (equation 3). The concentration of the base must be small enough to assume activity coefficients of unity; the concentration of water is 'included' in the value of K_b.

$$K_b = \frac{[BH^+][OH^-]}{[B]} \tag{3}$$

If H_3O^+ is chosen as the standard acid, the equilibrium (1) for uncharged bases becomes the equilibrium (4), so that the dis-

$$B + H_3O^+ \rightleftharpoons BH^+ + H_2O \tag{4}$$

sociation constant K_a for the conjugate acid BH^+ can be used to measure the base strength (equation 5). The simple relationship (6)

$$K_a = \frac{[B][H_3O^+]}{[BH^+]} \tag{5}$$

$$K_a \times K_b = K_w \tag{6}$$

exists between the K_b and K_a values, where $K_w = [H_3O^+][OH^-]$. For weak bases the value of K_b is too small to be detected experimentally, and the only directly measurable quantity is K_a.

Further developments of this concept by Hammett[10,11] led to the possibility of measuring K_a values for extremely weak bases. Simultaneously, the extended quantitative acidity scale was suggested as a continuation of the pH scale. The basic assumption made by Hammett (equation 7) was that the ratios of activity coefficients

$$\frac{f_{B_1}}{f_{B_1H^+}} = \frac{f_{B_2}}{f_{B_2H^+}} \tag{7}$$

for the base and protonated base were equal for all bases of the same charge n. Equation (5), therefore, can be expanded to the general equation (8).

$$K_a = \frac{[B]}{[BH^+]} \cdot a_{H^+} \cdot \frac{f_B}{f_{BH^+}} \tag{8}$$

The quantity $h_0 = a_{H^+} \cdot f_B/f_{BH^+}$ is independent of the nature of the base involved and was interpreted as a quantitative measure of the acidity of the medium. The quantity H_0 (equation 9) is called

$$H_0 = -\log h_0 \tag{9}$$

the acidity function*.

If the ratios of the concentrations of B and BH^+ can be determined by some experimental method (spectrophotometry is usually employed), it is possible to measure the stepwise change in H_0 values for increasing acidity of the solution, beginning in the range where the pH scale is still applicable. Or, alternatively, if the H_0 values are known, K_a values can be estimated by using equation (10). So, from

$$H_0 = pK_a + \log \frac{[B]}{[BH^+]} \tag{10}$$

the point of view of the concept presented in this section, the problem of the basicity of carbonyl compounds reduces itself to the estimation of their pK_a values; this estimation is based on the H_0 values determined by the use of indicator bases.

III. MODERN VARIATIONS IN THE ACIDITY–BASICITY CONCEPT

There has been a surprising development in the concept of acid–base interaction during recent years[12–18], the main difference from the

* The subscript zero denotes that H_0 is the acidity function for uncharged bases. It is possible to introduce acidity functions H_+, H_-, etc., for bases of different charge types[11a].

classical theory being in the definition of an acid–base interaction itself. The protonated (or 'fully protonated') base resulting from this interaction is considered as only one of several possibilities—namely the extreme one, which is formed when the acid–base interaction is completed to its full theoretical extent. But there are thought to be many examples where such a completion is not achieved and the 'partly protonated' base or a complex between acid and base is formed by hydrogen bonding only. This can be represented by the scheme (11) (neglecting solvation). It is assumed that some acid–base

$$B + HA \rightleftharpoons B\cdots HA \rightleftharpoons BH^+\cdots A^- \rightleftharpoons BH^+ + A^- \qquad (11)$$

pairs are able to form only the complexes B····HA; for such complexes, equations (5) and (8) obviously cannot be used, and in this connection the pK_a value becomes meaningless. Even if all the equilibria represented by (11) are real, difficulties still arise. When the concentration of the complexes B····HA is of the same or higher order of magnitude than the concentration of BH^+, equations (5) and (8) are also useless, if the concentrations of BH^+ and B····HA cannot be determined independently.

Other authors[19–24] stress the importance of the solvation of the protonated base, and hydration in aqueous solutions is especially considered in detail. Since the activity of water in dilute aqueous solutions remains constant, the phenomena connected with hydration become important in concentrated mineral acids where the activity of water rapidly decreases with increasing acid concentration. Therefore equation (8) should be modified by introducing the term a_{H_2O} for the water activity. Equation (10) thus becomes equation (12),

$$H_0 = pK_a + \log \frac{[B]}{[BH^+ \cdot nH_2O]} + (n - m) \log a_{H_2O} \qquad (12)$$

where n and m represent, respectively, the number of water molecules involved in the solvation of the protonated forms of the base and the indicator used in the determination of H_0.

It is obvious that if H_3O^+ (or any lyonium ion) is considered as the acid HA, the two concepts in this section are indistinguishable. Indeed, particles like $B\cdots H^+ \cdot nH_2O$ can be considered either as the complex of the base B with the acid $H_3O^+ \cdot (n - 1)H_2O$, or as the protonated base BH^+ with a hydration shell of n H_2O molecules. Moreover, even the complexes B····HA can be considered as indistinguishable from the protonated base BH^+ 'solvated' by the anion A^- (the ion pair BH^+A^-).

This equivalence has to be considered in the formal quantitative laws of the equilibrium; but if there are independent methods (e.g. spectral ones) to distinguish between the molecular structures of 'fully' and 'partly' protonated forms, the equality of the two concepts disappears.

IV. BASICITY AND ACID CATALYSIS

The existence of acid catalysis is the reason why the basicity of even very weak bases is of great importance for organic chemistry. An arbitrarily chosen acid-catalyzed process could be represented by the formal scheme (13). According to this scheme the first step of every

$$\text{Substrate (base)} + \text{acid} \overset{\text{Fast}}{\rightleftharpoons} \text{Intermediate} \tag{13a}$$

$$\text{Intermediate (+ reagent)} \xrightarrow{\text{Slow}} \text{Products} \tag{13b}$$

acid-catalyzed reaction is like an ordinary acid–base equilibrium. In practice the substrate is usually a base having a heteroatom with an unshared electron pair. If the catalyst is a protonic acid, at least for the cases considered in this chapter, it should not be a pseudoacid, so that the first step can be considered a fast one[25]. This could be any of the possible acid–base interactions discussed in section III of this chapter. The rate-determining second step could be a unimolecular ($A1$) or bimolecular ($A2$) process. In the latter case the 'reagent' is likely to be a nucleophile because 'full' or 'partial' protonation obviously increases the electrophilic reactivity of the substrate. (The possibility of the termolecular concerted attack of acid and 'reagent' on the substrate is not discussed in this section and will be considered in connection with concrete situations only.)

Two fundamental formal relationships exist in the quantitative aspect of acid catalysis. Accordingly, acid-catalyzed reactions can be divided into two classes: those following the laws of 'specific' acid catalysis; and those which are consistent with 'general' acid catalysis[26].

In the case of specific acid catalysis the observed value of the rate coefficient k is proportional only to the oxonium (lyonium) ion concentration in dilute solutions of acids, and to the acidity h_0 as defined in equation (9) in concentrated solutions of acids. Since in dilute solutions of acids $h_0 = [H_3O^+]$, the overall relationship (14)

$$\log k = C - H_0 \tag{14}$$

is obeyed[27], where C is a constant. In the case of general acid catalysis the observed value of the rate coefficient equals a sum of terms, each being proportional to the concentration of some acid present in the system (equation 15).

$$k = k_0 + \sum_i k_i[A_iH] \tag{15}$$

Here k_0 is the rate coefficient of the noncatalytic 'spontaneous' reaction, and each k_i is a 'catalytic constant' for the acid A_iH.

The interpretation of equation (14) is simple. Assuming that the substrate–acid interaction leads to the 'fully' protonated form and the reaction rate is proportional to the concentration of the latter, (14) can be easily derived from (11) by assuming that $[BH^+] \ll [B]$. The value of the constant C in (14) is given by equation (16), where

$$C = \log \frac{k_0}{K_a} \tag{16}$$

k_0 is the rate coefficient for the rate-determining reaction of the protonated substrate and K_a is the basicity constant for the same.

In the case where media of high acidities are involved and the limitation $[BH^+] \ll [B]$ is not obeyed, the more general equation (17)[28] is used. If $h_0 \ll K_a$, equation (17) is reduced to equation (14);

$$k = \frac{k_0 h_0}{h_0 + K_a} \tag{17}$$

if $h_0 \gg K_a$, then $k = k_0$ and the further increase of the acidity has no influence on the value of k.

The problem of the interpretation of equation (15) is much more complex. The naïve assumption that different acids react with the substrate at different rates should be discarded because it would require the acid–base interaction to be the slow step of the reaction.

The two methods given below can be used to derive equation (16) from the concepts considered in sections II and III.

A. Prototropic Reactions[29]

The acid-catalyzed process can be represented by the scheme (18),

$$BH + A_iH \underset{\text{Fast}}{\overset{\text{Fast}}{\rightleftharpoons}} HBH^+ + A_i^- \tag{18a}$$

$$HBH^+ + A_i^- \xrightarrow{\text{Fast}} HB + A_iH \tag{18b}$$

where BH is the substrate, A_iH denotes any acid present in the system, and HB is the product. Assuming that the value of k_i is different for different A_i^- in equation (18) and that the reaction with each A_i^- is independent of the other ones, the relationship (19) can be derived for the observed value of the first-order rate coefficient.

$$k = \frac{h_0(k_{OH^-}[OH^-] + k_{H_2O}[H_2O] + \sum_i k_i^-[A_i^-])}{h_0 + K_a} \tag{19}$$

In dilute aqueous solutions of acids $h_0 = [H_3O^+] \ll K_a$. Consequently k_0, k_{H^+}, and k_i may be defined by the following equations:

$$\frac{k_{OH^-}[OH^-]h_0}{K_a} = \frac{k_{OH^-}K_w}{K_a} = k_0$$

$$\frac{k_{H_2O}[H_2O]h_0}{K_a} = \frac{k_{H_2O}[H_2O][H_3O^+]}{K_a} = k_{H^+}[H_3O^+]$$

where k_{H^+} is the catalytic constant for hydrogen ion, and

$$\frac{k_i^-[A_i^-]h_0}{K_a} = \frac{k_i^-[A_i^-][H_3O^+]}{K_a} = \frac{k_i^-K_i[A_iH]}{K_a} = k_i[A_iH]$$

Substituting these values into equation (19), the equation (20) is obtained, analogous to (15). The formal analogy between (15) and (20) is complete with the understanding that the term $k_{H^+}[H_3O]$ is included in the sum in (15) but exhibited separately in (20).

$$k = k_0 + k_{H^+}[H_3O^+] + \sum_i k_i[A_iH] \tag{20}$$

Instead of A_i^- and A_iH, the bases B_i and their conjugate acids B_iH^+ could be considered in the same way.

B. Other Reactions[30]

If only one definite 'reagent' is participating in equation (13b) and the 'intermediate' is a 'fully' protonated base BH^+, general acid catalysis is excluded. Consequently in the case of nonprototropic reactions sensitive to general acid catalysis, the intermediate is not a 'fully' protonated base, but either a hydrogen-bonded acid–base complex B····HA or an ion pair BH^+····A^- (see scheme 11). If the reactivity of the complexes of the substrate with different acids is sufficiently different and/or the equilibrium constants for the

formation of such complexes depend considerably upon the nature of the acid, general acid catalysis follows.

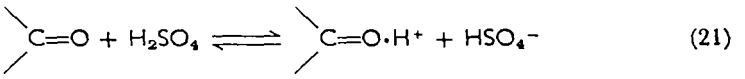
The quantitative treatment of this interpretation will be presented in relation to experimental data about the behavior of carbonyl compounds.

V. THE EQUILIBRIUM INTERACTION BETWEEN CARBONYL COMPOUNDS AND ACIDS IN AQUEOUS SOLUTIONS

In this section we present the main results of the experimental study of processes and phenomena (excluding acid catalysis) connected with the basicity of carbonyl compounds.

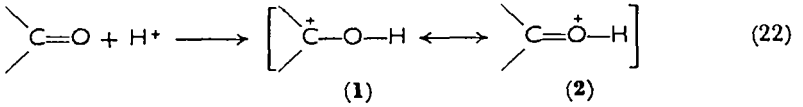
Carbonyl bases will shift equilibrium (2) to the left to such an extent that there is no experimental method for detecting the increase of the hydroxyl ion concentration after the carbonyl compound is added, so that the K_b value cannot be directly estimated. All the observations in the field of acid–base equilibria involving carbonyl compounds, therefore, are related to aqueous solutions of acids.

The first experimental observation in the field of the basicity of carbonyl compounds was made by Hantzsch[31] in 1909, who found that in 100% H_2SO_4 acetophenone and benzil behave like strong bases and the equilibrium (21) is shifted completely to the right.



(21)

A more extended study of the basicity of carbonyl compounds was performed after the indicator method for detecting pK_a values by the use of the acidity-function concept had been elaborated by Hammett and Deyrup (see section II). This study was based almost completely on the investigation of the acidity dependence of the electronic absorption spectra of carbonyl compounds in acid media. It is assumed that major differences between the spectra of non-protonated and protonated carbonyl compounds should be observed, due to the considerable change in the electronic structure of the carbonyl group after the protonation depicted in equation (22).



(22)

(1) (2)

If the resonance structure **1** has a much greater contribution than

structure **2**, the ultraviolet carbonyl absorption band ($n \rightarrow \pi^*$ transfer) should disappear. For saturated aliphatic carbonyl compounds this band is the most intense one in the region of 270 mμ and the protonation should be easy to detect. In compounds where the carbonyl group is directly connected with an aromatic ring the latter is mainly responsible for the very intense ultraviolet absorption. Now the appearance of the contributing resonance structures

causes considerable changes in the ultraviolet absorption spectrum.

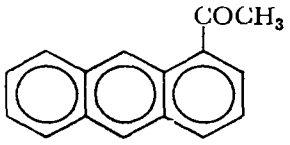
Assuming that the observed changes in the ultraviolet or visible spectra are caused by reactions (4) or (22), the ratios of $[B]/[BH^+]$ were determined from the spectral data and the pK_a values for a number of carbonyl compounds were calculated using equation (10); these are shown in Table 2. Besides the values of pK_a the concentra-

TABLE 2. Spectrophotometric pK_a and pK_h values for carbonyl compounds.

Compound	pK_a	% H_2SO_4 at half ionization	Ref.	pK_h[c]
C_6H_5CHO	−6·99[b]	80	36	−2·30
	−7·10[a]	81	37	−2·40
o-$CH_3C_6H_4CHO$	−6·50[a]	76·5	37	−1·95
m-$CH_3C_6H_4CHO$	−7·06[a]	80·5	37	−2·36
p-$CH_3C_6H_4CHO$	−6·32[a]	75	37	−1·82
2,4,6-$(CH_3)_3C_6H_2CHO$	−4·7[a]	62	37	−0·90
2,4,6-$(C_2H_5)_3C_6H_2CHO$	−5·0[a]	64	37	−1·00
2,4,6-$(i\text{-}Pr)_3C_6H_2CHO$	−5·2[a]	66	37	−1·11
m-ClC_6H_4CHO	−7·68[a]	85	37	−2·90
p-ClC_6H_4CHO	−7·26[a]	82	37	−2·53
p-$NO_2C_6H_4CHO$	−6·45[a]	76	37	−1·92
p-$CH_3OC_6H_4CHO$	−5·45[a]	68	37	−1·26
α-$C_{10}H_7CHO$	−6·34[b]	75	36	−1·84
β-$C_{10}H_7CHO$	−6·68[b]	78	36	−1·94
1-Anthrylaldehyde	−5·71[b]	70·5	36	−1·44
9-Anthrylaldehyde	−4·81[b]	63	36	−0·94
9-Phenanthrylaldehyde	−6·39[b]	76	36	−1·88
CH_3COCH_3	−7·2[a]	81·5	1	−2·48
CH_3COCH_3	−1·58		4	–
$CH_3COC_2H_5$	−7·2[a]	81·5	1	−2·48
$CH_3COCH(CH_3)_2$	−7·1[a]	81	1	−2·40

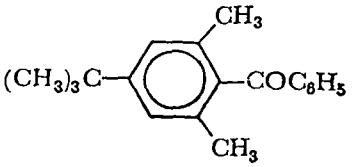
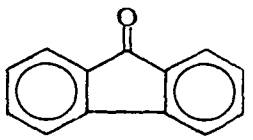
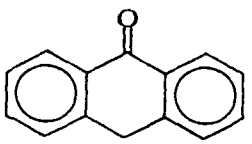
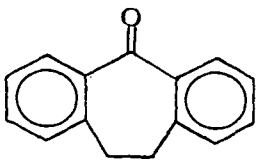
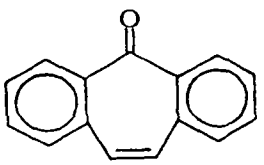
(*Table continued*)

TABLE 2—*cont.*

Compound	pK_a	% H_2SO_4 at half ionization	Ref.	pK_h[c]
$CH_3COC(CH_3)_3$	−7·1[a]	81	1	−2·40
Cyclobutanone	−9·5[a]	98·5	1	–
Cyclopentanone	−7·5[a]	84	1	−2·74
Cyclohexanone	−6·8[a]	78·5	1	−2·16
Cycloheptanone	−6·6[a]	77	1	−2·03
Cyclooctanone	−6·2[a]	74	1	−1·74
$C_6H_5COCH_3$	−6·15[a]	74	35	−1·71
m-$CH_3C_6H_4COCH_3$	−6·02[a]	72·5	35	−1·63
p-$CH_3C_6H_4COCH_3$	−5·47[a]	69	35	−1·29
p-$C_2H_5C_6H_4COCH_3$	−5·61[a]	70	35	−1·37
m-$CH_3OC_6H_4COCH_3$	−6·70[a]	78	35	−2·10
p-$CH_3OC_6H_4COCH_3$	−4·81[a]	63	35	−1·24
m-$C_2H_5OC_6H_4COCH_3$	−6·70[a]	78	35	−2·10
p-$C_2H_5OC_6H_4COCH_3$	−4·90[a]	63·5	35	−0·97
m-$HOC_6H_4COCH_3$	−6·59[a]	77	35	−2·02
p-$HOC_6H_4COCH_3$	−4·73[a]	62	35	−0·90
p-$FC_6H_4COCH_3$	−6·06[a]	73	35	−1·65
m-$ClC_6H_4COCH_3$	−7·01[a]	80	35	−2·32
p-$ClC_6H_4COCH_3$	−6·52[a]	76·5	35	−1·96
m-$BrC_6H_4COCH_3$	−6·90[a]	79	35	−2·24
p-$BrC_6H_4COCH_3$	−6·52[a]	76·5	35	−1·96
m-$NO_2C_6H_4COCH_3$	−7·62[a]	85	35	−2·90
p-$NO_2C_6H_4COCH_3$	−7·92[a]	87	35	−3·12
α-$C_{10}H_7COCH_3$	−5·86[b]	71·5	36	−2·44
β-$C_{10}H_7COCH_3$	−5·71[a]	71	35	−1·43
	−6·04[b]	73	36	−1·64
	−5·65[b]	70	36	−1·37
$(C_6H_5)_2CO$	−6·16[a]	73·8	31	−1·68
	−5·5[b]	68·5	33	−1·28
	−6·18[a]	74·1	34	−1·72
$(p\text{-}CH_3C_6H_4)_2CO$	−5·67[a]	70	32	−1·40
$(p\text{-}CH_3OC_6H_4)_2CO$	−4·39[a]	59·5	32	−0·78
$(p\text{-}HOC_6H_4)_2CO$	−4·19[a]	57·6	32	−0·70
$(p\text{-}ClC_6H_4)_2CO$	−6·64[a]	77·6	32	−2·05
$(m\text{-}ClC_6H_4)_2CO$	−6·95[a]	80·0	32	−2·30
$(m\text{-}NO_2C_6H_4)_2CO$[d]	−9·85[a]	99·3	32	–
$(p\text{-}NO_2C_6H_4)_2CO$[d]	−10·12[a]	99·6	32	–
m-$CH_3C_6H_4CH_2COC_6H_5$	−6·89[a]	79	34	−2·23
p-$CH_3C_6H_4CH_2COC_6H_5$	−6·86[a]	79	34	−2·20

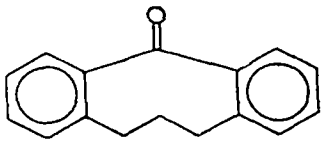
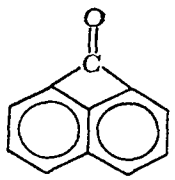
(*Table continued*)

TABLE 2.—*cont.*

Compound	pK_a	% H_2SO_4 at half ionization	Ref.	pK_h[c]
$C_6H_5CH_2COC_6H_5$	−6·92[a]	79	34	−2·27
m-$FC_6H_4CH_2COC_6H_5$	−7·07[a]	81	34	−2·37
p-$FC_6H_4CH_2COC_6H_5$	−7·04[a]	80·5	34	−2·34
m-$ClC_6H_4CH_2COC_6H_5$	−7·11[a]	81	34	−2·40
p-$ClC_6H_4CH_2COC_6H_5$	−7·07[a]	81	34	−2·37
m-$NO_2C_6H_4CH_2COC_6H_5$	−7·39[a]	83	34	−2·64
p-$CH_3C_6H_4COC_6H_5$	−5·91[a]	72	34	−1·54
p-$(CH_3)_3CC_6H_4COC_6H_5$	−6·02[a]	73	34	−1·63
2,6-$(CH_3)_2C_6H_3COC_6H_5$	−6·57[a]	77	34	−2·01
2,4,6-$(CH_3)_3C_6H_2COC_6H_5$	−6·15[a]	74	34	−1·71
	−6·36[a]	76	34	−1·85
	−6·65[a]	77·6	32	−2·05
	−5·02[a]	64·7	32	−1·01
	−5·69[a]	70·2	32	−1·42
	−5·25[a]	66·6	32	−1·14

(*Table continued*)

TABLE 2.—*cont.*

Compound	pK_a	% H_2SO_4 at half ionization	Ref.	pK_b[c]
	−5·80[a]	71·1	32	1·48
	−1·40[b]	25	36	—

[a] At 25°C.
[b] At room temperature.
[c] $pK_b = \log a_{H_2O}$ at $H_0 = pK_a$ (see section VI).
[d] The observed spectral phenomena could be connected with the protonation of the NO_2 group (I. C. D. Brand, *J. Chem. Soc.*, 997 (1950)).

tions of H_2SO_4 (in weight %) at the point of half ionization ($[BH^+] = [B]$, $pK_a = H_0$) are also tabulated. These data for fifty-six ketones and seventeen aldehydes show that carbonyl compounds are bases which undergo protonation according to the schemes (4) or (22). There is an inconsistency in the case of acetone, for which two different pK_a values based on ultraviolet spectrum measurements were reported by Nagakura, Minegishi, and Stanfield[4] (−1·58), and by Campell and Edward[1] (−7·2).

Let us consider how such a difference (running to six powers) arises. For this purpose it is useful to follow the changes in the ultraviolet spectrum of acetone beginning from the pure water solution and then through different concentrations of H_2SO_4, covering the whole range investigated. Figure 1 illustrates three ranges of H_2SO_4 concentrations at which the spectral behavior of acetone is different. Up to 7% H_2SO_4 ($H_0 = 0$) the spectrum is identical to that of the neutral aqueous solution. In the range from 7% to 64% H_2SO_4 the carbonyl-bond absorption maximum is gradually shifted to shorter wavelengths. By increasing the H_2SO_4 concentration to over 65% ($H_0 < -6$) this absorption maximum gradually disappears. There are two approaches to the interpretation of these data: if the disappearance of the carbonyl-group absorption maximum alone is considered to be connected with protonation, a

pK_a value in the order of magnitude of -7 is obtained; but if any changes in the absorption spectrum are related to the protonation, one could also conclude that the formation of the protonated particles becomes relevant at much lower concentrations of H_2SO_4.

The changes in the spectra of bases relating to their protonation can clearly be detected in the range $H_0 = pK_a \pm 1{\cdot}0$–$1{\cdot}5$*. The positions of the maxima in the spectra of acetone begin changing in the range $H_0 = 0{\cdot}0 \pm 0{\cdot}5$. If this change is assumed to be related to

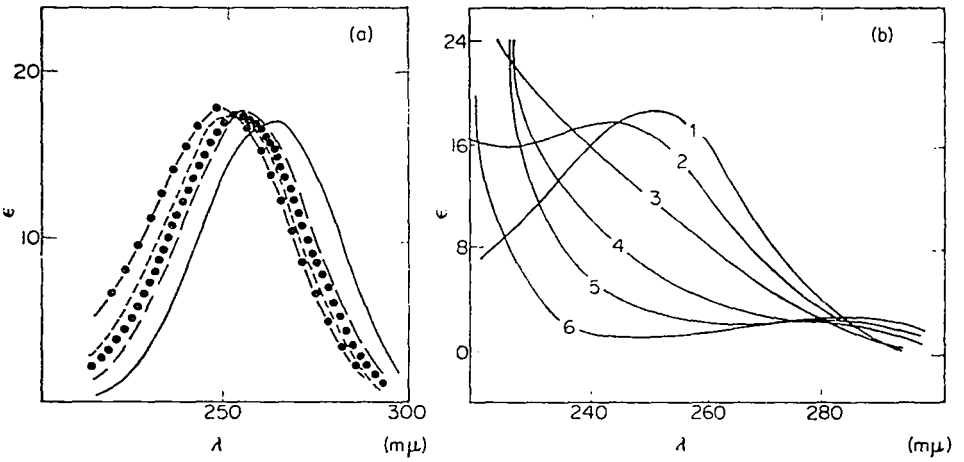


FIGURE 1. Dependence of the ultraviolet absorption of acetone on the concentration of H_2SO_4[1].

(a) ——— pure water
— — — 46·6% H_2SO_4
····· 53·2% H_2SO_4
– – – – 58·5% H_2SO_4
–·–·–·– 64·0% H_2SO_4

(b) 1 65·3% H_2SO_4
2 74·1% H_2SO_4
3 80·0% H_2SO_4
4 84·7% H_2SO_4
5 89·2% H_2SO_4
6 98·2% H_2SO_4

protonation, the pK_a value for acetone in the range $-0{\cdot}5$ to $-1{\cdot}5$ could be found, if no measurements are carried out at high H_2SO_4 concentrations[4]. In aqueous HCl the high concentration necessary to observe the disappearance of the carbonyl absorption maximum cannot be achieved at all[38], and the shift of the wavelength of this maximum is the only observable spectral change. These complications are not too significant by themselves. Many examples are known where spectral shifts are due to some change in the charac-

* Assuming that the presence of 3–10% of the forms B or BH^+ can be detected in an abundance of the other form.

teristics of the solvent without involving acidity and hence the assumed $pK_a \approx -1$ value for acetone may be due to a misunderstanding.

But let us proceed considering the facts. As early as 1940 it was found that shifts of the infrared maximum for the O—D bond in CH_3OD are linearly related to the pK_a values of the bases dissolved in deuteromethanol[39]. It should be stressed that the pK_a values in water were used and therefore the method is useful for the indirect estimation of these values. For acetone the value -4 was obtained. The inconsistence of this with both values cited before is obvious.

It would be desirable to have some additional experimental data. Those which are as directly related to the possibility of protonation are naturally preferred. Clearly, if equilibrium (22) really occurs, one of the main results would be the substitution of charged particles of one type ($>C^+—OH$) for those of another type (H_3O^+). The appearance of the charge on the carbonyl compound by protonation should be detectable conductometrically. If ions of one sort are substituted for ions of a different nature but with the same charge, the change in the conductivity of the solution should be proportional to the difference between the equivalent conductivities of the ions considered. Therefore, on addition of base B to an aqueous solution of a mineral acid the change in conductivity should be proportional to the concentration of the base B and to the degree of its protonation, and could be used for the determination of the $[B]/[BH^+]$ ratio.

The conductometric method was first used for the study of the behavior of acetone in aqueous HCl[5]. Conductometric apparatus[40] with a sensitivity of 0·001% and a means of thermostating the conductivity cell to $\pm 0{\cdot}003°$ is required to achieve the necessary precision of the measurements. The conductometric values of y were

$$y = \frac{1}{[B]_0}(\varkappa_1 - \varkappa_2) = \frac{[BH^+]}{[B]_0} y_\sim \tag{23}$$

calculated from equation (23), where $[B]_0$ is the concentration of the base added, $\varkappa_1$ is the conductivity calculated on the assumption that the only effect of the addition of the base is the dilution of the solution, $\varkappa_2$ is the measured value of conductivity after the base is added, and $y_\sim$ is the extreme value of y reached at high acidities when the base is completely protonated ($[BH^+] \gg [B]$). The highest experimentally observed value of y was chosen for $y_\sim$, because the increase of viscosity at high acid concentrations has an adverse influence on the y value.

The pK_a value of the base B can be calculated by substituting the values obtained from equation (24) into equation (10).

$$\frac{y_\sim - y}{y} = \frac{[B]}{[BH^+]} \tag{24}$$

Plots of y *versus* H_0 for *p*-nitroaniline, *o*-nitroaniline, and acetone are shown in Figure 2. The first two of these bases are common indicators and their pK_a values are determined from spectral data, so that the 'conductometric' pK_a values can be compared with the 'spectrophotometric' ones in order to verify the method described

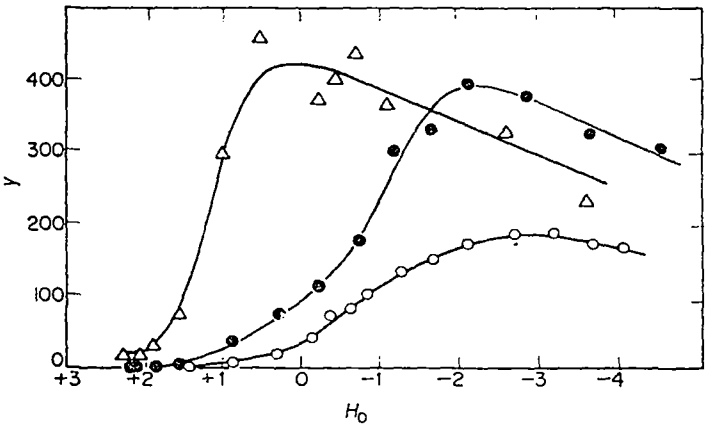


FIGURE 2. Dependence of the conductometric y value (defined by equation 23) on the acidity function H_0.

△ *p*-nitroaniline in aqueous HCl at 40°
● *o*-nitroaniline in aqueous H_2SO_4 at 60°
○ acetone in aqueous HCl at 25°

above. This has been done in Table 3. For *p*- and *o*-nitroaniline the agreement between the conductometric and spectrophotometric values is excellent. This is taken as proof that the conductometric phenomena are really related to the protonation of these bases, and this should also be true in the case of acetone. The 'conductometric' $pK_a = -0{\cdot}66$ obtained for the latter is close to the value obtained by assuming that the shift of the absorption maximum is related to the protonation and differs from the value of $-7{\cdot}2$ obtained by using the ordinary procedures of the indicator method.

If protonation of acetone occurs to a considerable extent according to the acidity function values in the H_0 range from 0·0 to $-1{\cdot}0$

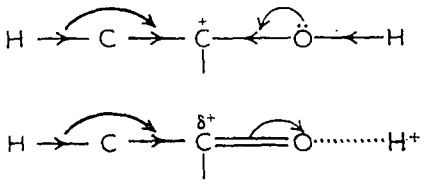
(and this is impossible if the pK_a value of $-7{\cdot}2$ is the correct one), a considerable transport of acetone should be observed if a constant electrical field is applied, and the acetone concentration should increase around the cathode compartment. Experiments to verify this idea were performed at different concentrations of sulphuric acid[42]. It was found that the acetone was indeed transported to the cathode. The quantitative treatment of these data permits a pK_a value for acetone to be calculated which was found to be equal to $-0{\cdot}43$ and in agreement with the conductivity data.

TABLE 3. Conductometric and spectrophotometric values of pK_a.

Base	Medium	Temp. (°c)	pK_a	
			Conducto-metric[5]	Spectro-photometric[41]
p-Nitroaniline	H_2O/HCl	40	+0·90	+0·91
o-Nitroaniline	H_2O/H_2SO_4	60	−0·49	−0·43
Acetone	H_2O/HCl	5	−0·55	
		15	−0·60	
		25	−0·66	
		40	−0·81	

VI. ACID-CATALYZED REACTIONS OF CARBONYL COMPOUNDS

There are two types of reactions characteristic of carbonyl compounds: the first one is connected with the nucleophilic attack on the carbonyl carbon, leading to addition or, after elimination, to substitution; the second type is the abstraction of a proton from a C—H bond in the position α to the carbonyl group. Both these reaction types are subject to acid catalysis. Indeed, if the carbonyl oxygen is 'fully' or 'partly' protonated, the positive charges on the carbonyl carbon atom and on the α-hydrogen atoms should be increased as well as their electrophilic reactivity:



The second type of reaction is represented by the enolization of carbonyl compounds which is subject to general acid catalysis[43,44].

General acid catalysis also influences many reactions of the first type, e.g. the hydration of the carbonyl group[45–47], and the formation of semicarbazones[48,49], hydrazones[50], and Schiff bases[51]. Other reactions of carbonyl compounds are subject to specific acid catalysis. These are, for example, some isomerizations of carbonyl compounds[52–55], acid-catalyzed aldol condensations[56–59], and the formation of acetals, although the formation of hemiacetals is subject to general acid catalysis[60].

So the picture is rather confused and complicated. According to the scheme (18) and to equation (19), the prototropic reaction is subject to general acid catalysis if the 'fully' protonated substrate is formed during the fast step of the reaction with acid. The 'fully' protonated substrate is also required for specific acid catalysis, but general acid catalysis of the nucleophilic attack on the carbonyl carbon could not be related to the formation of the 'fully' protonated reagent, as was shown in section IV.

Valuable additional information was obtained during the study of enolization reactions in concentrated acids. If equation (19) is obeyed there should exist a phenomenon of saturation of the acid catalytic effect at $h_0 \gg K_a$. Therefore, the acidity dependence of the observed value of the rate coefficient could be used to find what value of pK_a is related to the acid catalysis in this case. In the enolization of acetone in aqueous solutions of HCl the dependence of the observed value of the rate coefficient on the acidity is shown in Figure 3[29,38]. The linear dependence of the log k value on H_0 is disturbed in the region where $H_0 < 0$, and on reaching the $H_0 < -2$ region the reaction seems to become acidity independent with the rate coefficient being approximately proportional to the Cl^- concentration. With aqueous sulphuric acid[61] the picture is analogous, excluding the range of acidities $H_0 < -4$ which could not be studied in aqueous HCl. Although the experimental data considered are only preliminary ones, the decrease of the rate coefficient at high concentrations of sulphuric acid can be considered as a real phenomenon.

The behavior of the acetaldehyde enolization reaction in aqueous HCl is completely analogous to the results obtained for acetone[62,63].

It is easy to see that these kinetic results are rather consistent with the conductometric value of pK_a and do not support the much more negative spectrophotometric value. On the other hand, the enoliza-

tion kinetics of D-α-phenylisocaprophenone[70] is satisfactorily consistent with equation (17) in the concentration range of 85 to 94% H_2SO_4. Consequently, in this case the order of magnitude of the spectrophotometric pK_a seems to be applicable.

The above discussion seems sufficient to show that the kinetic data relating to acid catalysis do not lead to a simple solution of the basicity problems of carbonyl compounds.

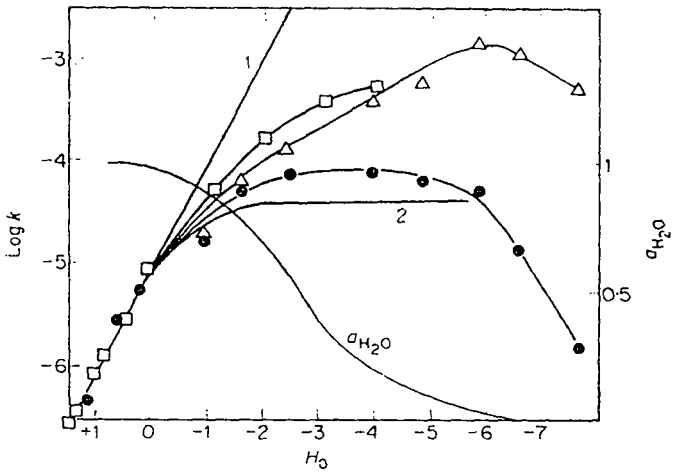


FIGURE 3. Dependence of the enolization rate of acetone and of the water activity on the acidity function.

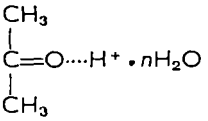
1 Line with unit slope, corresponding to equation (14)
2 Line calculated using equation (17) and accepting the conductometric pK_a value for acetone
□ Experimental data in aqueous HCl at 15° (unimolecular rate coefficients)
● Experimental data in aqueous H_2SO_4 at 15° (unimolecular rate coefficients)
△ Experimental data in aqueous H_2SO_4 at 15° in aqueous H_2SO_4 (bimolecular rate coefficients: ratio k/a_{H_2O})

VII. GENERAL SCHEME FOR THE INTERACTION OF CARBONYL COMPOUNDS WITH ACIDS IN AQUEOUS MEDIA

Although the most important experimental observations have now been presented, their general interpretation is still lacking. This is not an easy task, since we do not agree to accept different standpoints

on the nature of the process for the interpretation of different kinds of experimental data.

In the first place the inconsistency between the pK_a values of acetone as determined by the spectral indicator method, or conductometrically, or based on the kinetic data for the enolization, should be explained. It was suggested[19,42] that different processes were detected by using different methods. It is obvious that conductometric measurements offer proof of the formation of some kind of charged particles from acetone. These are assumed to be hydrated and protonated acetone molecules or hydrogen bonded complexes between acetone and hydrated oxonium ions (see scheme 13):



As stated in section III, the formation of such particles should follow the classical laws of protonation equilibrium, except for the additional

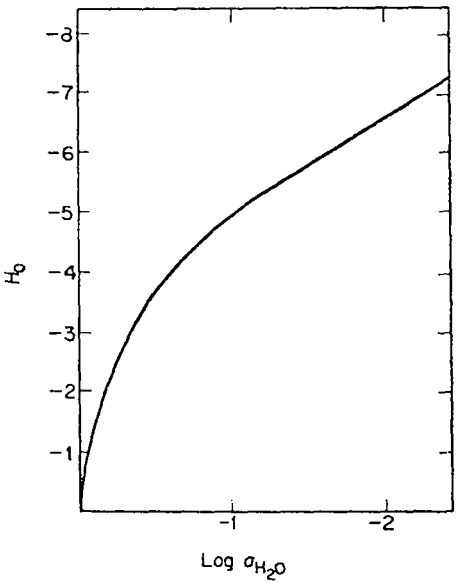
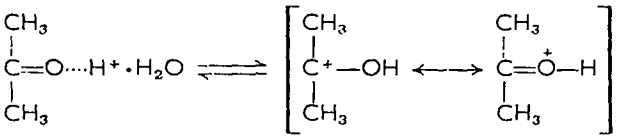


FIGURE 4. The interrelation between the acidity function H_0 and the water activity in aqueous H_2SO_4.

influence of the activity of H_2O. As there is not a 'full' covalent bonding between the carbonyl oxygen and the proton, the carbonyl

double bond is preserved and therefore the relevant ultraviolet absorption maximum does not disappear. The shift of this maximum is related to minor changes in the electron distribution caused by the bonding with a proton. Nevertheless, this sufficiently increases the positive charges of the α-hydrogens to bring about a large catalytic effect. For example, when comparing the rates of enolization of hydrated protonated acetone molecules on the one hand with formation of the enolate ion from unprotonated acetone on the other, both in aqueous solutions of acetate buffer, the bimolecular rate of the former reaction is found to be greater than that of the latter by a factor of two million[64].

As the concentration of the acid is increased the water activity decreases. The rapid increase of acidity and the considerable decrease of water activity are related to each other. This is illustrated by the plot of the H_0 values *versus* log a_{H_2O} represented in Figure 4. Therefore the hydrated protonated particles will gradually loose water molecules from the hydrate shell, causing the shift of the ultraviolet absorption maximum after practically all the acetone molecules are protonated. In the presence of even higher acid concentrations the last molecule of H_2O is lost and the 'fully' protonated particle is formed (equation 25). This is the equilibrium observed spectrally by



(25)

the disappearance of the ultraviolet maximum of the carbonyl group. It is clear in Figure 4 that for aqueous H_2SO_4 H_0 and log a_{H_2O} are approximately linearly related at the high acid concentrations where this spectral change is observed. The equations (26) and (27),

$$\log \frac{[B]}{[BH^+]} = H_0 - pK_a \tag{26}$$

$$\log \frac{[B\cdots H^+ \cdot H_2O]}{[BH^+]} = \log a_{H_2O} + \log K_h \tag{27}$$

where K_h is the equilibrium constant for the dehydration reaction, are formally indistinguishable in so far as both B and $B\cdots H^+ \cdot H_2O$ are assumed to have similar spectral characteristics. This leads to the conclusion that the pK_a values represented in Table 2 are

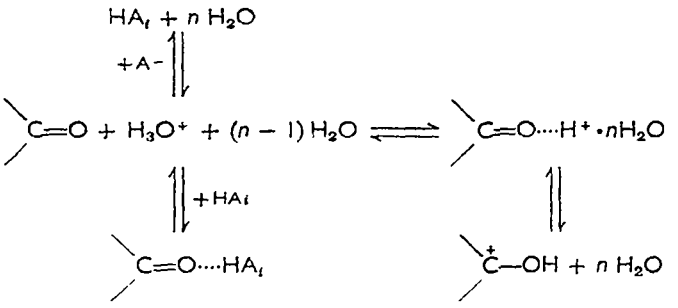
meaningless as a measure of the classical basicity of carbonyl compounds. They are simply equal to the values of H_0 at the concentrations of H_2SO_4 which correspond to the half-completion of the equilibrium (25) (i.e. $[B\cdots H^+ \cdot H_2O] = [BH^+]$). The equilibrium

$$\text{>C=O} + H_3O^+ + (n-1)H_2O \rightleftharpoons \text{>C=O}\cdots H^+ \cdot nH_2O \qquad (28)$$

(28) is indistinguishable from the classical protonation equilibrium (4) in the range of acid concentrations where a_{H_2O} remains practically constant. Therefore in this range equation (10) represents the dependence of the ratio $[B]/[B\cdots H^+ \cdot nH_2O]$ on the acidity of the medium if the Hammett postulate (7) is also valid for the hydrated protonated base. This is why the conductometric results are in agreement with the classical scheme of protonation.

If the value of a_{H_2O} begins to decrease to a considerable extent, the relative concentration of the particles $\text{>C=O}\cdots H^+ \cdot nH_2O$ with different values of n will also be changed; thus the concentration of the particles with any given value of n could be highly sensitive to the changes in water activity. Nevertheless, the *total* equilibrium concentration of the particles having different values of n is likely to be less sensitive to the changes in the activity of H_2O. Therefore it can be assumed that the equilibrium (28) follows equation (10) even in the ranges of acid concentrations where the changes in the a_{H_2O} value become significant, by treating n as a variable. Thus we have arrived at the conclusion that the equilibrium (28) can be considered formally like a classical protonation equilibrium, if for practical purposes the only acid present in the medium is the oxonium or lyonium ion.

Furthermore, assuming that the protonated particles hydrated by different number of H_2O molecules are in equilibrium with each other, it would be logical to consider the 'fully' protonated form ($n = 0$) as being equilibrated with them; this equilibrium should be highly sensitive to water activity. Therefore, even in dilute aqueous solutions of acids, $\text{>C}^+\text{—OH}$ ions are present, but their concentration should be extremely low. If a buffer is added, complexes of the type $C{=}O\cdots HA_i$ containing different acids HA_i should be considered as different species with different properties. Accordingly, the qualitative picture of protonation of carbonyl compounds could be represented by scheme (29) which is actually a special case of the general scheme (12). It should be stressed once more that in principle



(29)

particles with different values of n could be represented as being equilibrated with each other.

To distinguish between the equilibrium constant for reaction (28) and the classical K_a it was suggested that the former should be written as K_α[42]:

$$K_\alpha = \frac{a_{B\cdot sH_2O} \cdot a_{H^+\cdot xH_2O}}{a_{B\cdots H^+\cdot nH_2O} \cdot a_{H_2O}^{s+x-n}}$$

where s, x and n denote the numbers of water molecules in respective hydrated particles. This relationship can be represented as follows:

$$K_\beta = \frac{a_B \cdot a_{H^+}}{a_{B\cdots H^+\cdot nH_2O}} \tag{30}$$

where

$$a_{H^+} = \frac{a_{H^+\cdot xH_2O}}{a_{H_2O}^x}$$

and

$$K_\beta = K_\alpha \cdot a_{H_2O}^{s-n}$$

In pure water a_{H_2O} is assumed equal to unity and then the numerical value of K_β equals the value of K_α. In the range of concentrations where the water activity remains approximately constant there should be full formal analogy between K_β and K_α and the classical K_a.

In spite of this formal analogy between the K_β and K_a values there are quite important differences between them. The K_a values are usually very sensitive to structural changes in the bases, because of the great differences between the electronegativities of the reaction center in the initial and final states. In the formation of hydrated protonated particles from carbonyl compounds this difference should be much less because the bonding of the base with a proton is much

weaker. This is true not only of carbonyl compounds. The results of conductometric measurements lead to the conclusion that the K_β value for oxonium bases of different types (acetone, nitromethane, aliphatic alcohols, phenol, and benzamide) are usually all in the range $1 < K_\beta < 10$ which corresponds to the pK_β range $0{\cdot}0 < pK_\beta < -1{\cdot}0$[42]. The changes in the K_β values, when only substituents are varied adjacent to a constant reaction center (e.g. different ketones and aldehydes) should consequently be even less. Therefore the problem of the dependence of the K_β value upon the structure of carbonyl compounds seems to be of minor practical importance.

Besides K_β or K_α, the K_h values in equation (27) are important to describe quantitatively the behavior of carbonyl compounds in acidic media. K_h is defined in equation (31). It is not difficult to

$$K_h = \frac{a_{B\cdots H^+ \cdot nH_2O}}{a_{BH^+} \cdot a^n_{H_2O}} \tag{31}$$

show that the K_h values could be easily obtained from the data in Table 2 (if the $a_{H_2O} - [H_2SO_4]$ dependence or the a_{H_2O}–H_0 dependence is known). As the pK_h values and the respective concentrations of H_2SO_4 determine the conditions (H_0 or $[H_2SO_4]$) at which the concentrations of $[B\cdots H^+ \cdot H_2O]$ and $[BH^+]$ are equal, and at which the ratio of the respective activities could be assumed to equal unity, the relationship (32) follows, where a_{H_2O} is the water

$$pK_h = n \log a_{H_2O} \tag{32}$$

activity at the value of H_0 or the concentration of H_2SO_4 mentioned. The pK_h values calculated by the use of equation (32) are also represented in Table 2, assuming that $n = 1$, which should be a satisfactory approximation for concentrated sulfuric acid solutions.

It is easy to realize that the precise relationship between the total concentration of $B\cdots H^+ \cdot nH_2O$ (or of BH^+) and the acidity of the medium and the water activity should be quite complex. We will not try to discuss this relationship here, owing to the lack of information about the ratios of particles with different values of n at different water activities. The values of the respective equilibrium constants cannot be estimated, and hence the precise relationship becomes useless in practice, but it is reasonable to consider the following rough approximation.

Assuming that equation (31) and the Hammett postulate (7) are valid for the total concentration of $B\cdots H^+ \cdot nH_2O$ and also for BH^+

(n being a variable), and that $s = 0$*, the approximate relationships (33) and (34) can be derived, where $[B]_0$ is the total concentration of

$$[B\cdots H^+ \cdot nH_2O] = \frac{h_0 K_h a_{H_2O}^n}{h_0(1 + K_h a_{H_2O}^n) + K_h K_\alpha} [B]_0 \qquad (33)$$

$$[BH^+] = \frac{h_0}{h_0(1 + K_h a_{H_2O}^n) + K_h K_\alpha} [B]_0 \qquad (34)$$

the base (carbonyl compound) and n should be considered as some effective mean value, depending on a_{H_2O}. It is easy to show that†

$$K_h K_\alpha = K_a \qquad (35)$$

Concerning these relationships in general, an interesting conclusion can be drawn. Let $a_{H_2O} = 1$ be the standard in pure water. Now, if $K_h \ll 1$, the value of (33) equals zero and compound B behaves like a 'classical' base. If $K_h \gg 1$ the $[BH^+]$ is negligible in dilute aqueous solutions of acids and only the hydrated protonated particles are presented. We have seen that the carbonyl compounds belong to the latter class of bases.

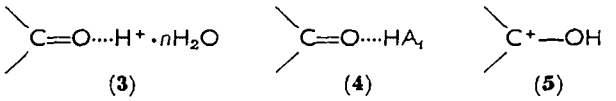
Equation (35) shows that the K_h and K_a values are not independent. Taking into account the very low sensitivity of K_α to the variations in the structure of the base, one can assume it to be a constant. Consequently the relative changes in the pK_h values could approximately represent the relative changes in the pK_a values. But it should be kept in mind that equation (35) cannot be used for calculation of K_a values by substituting in it the experimental values of K_h and K_α, since these are dependent on the mean value of n which is variable and certainly differs in conditions where K_α and K_h can be determined from experimental data. Indeed, K_α is determined in dilute solutions of sulphuric acid where $a_{H_2O} = 1$, but K_h is obtained in conditions where $a_{H_2O} < 1$.

* This assumption is made only for the sake of simplicity in the equations, and it is certainly incorrect in general. If $s \neq 0$ and the hydration of the indicator used for determining the H_0 value is taken into consideration, n in equations (33) and (34) should be replaced by the more complex quantity $m = n - n' - s + s'$, where n' and s' are the hydration numbers of the protonated and unprotonated indicator respectively.

† This follows from equations (17), (33), and (34), since in these the ratio $[B]/[BH^+]$ is equal to $K_h K_\alpha / h_0$ on the one hand and to K_a / h_0 on the other.

VIII. INTERPRETATION OF ACID CATALYSIS

Acid-catalyzed reactions of carbonyl compounds considered in section VI should find their explanation by using scheme (29), in order to prove the validity of the latter. According to this scheme the three types of particles **3**, **4**, and **5** are relevant to acid catalysis.

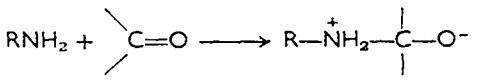


(3) **(4)** **(5)**

Enolization, being a prototropic process, could proceed through particles **3** or **5** only. The reactivity of **3** should be much higher than the reactivity of **4**, whatever the nature of the acid HA_i. If the reverse is true, a more complicated equation than (15) should be used, with the terms $k_i[HA_i][A_i^-]$ instead of $k_i[HA_i]$ [65]. It was shown that such termolecular terms could be present, but they are by no means the major ones[66,67]. Hence, it should be concluded that **4** is indeed considerably less reactive than **3**. General acid catalysis affecting electrophilic reactions of the carbonyl group could not be related to **3** or **5** although **3** could be involved as a specific case of complexes like **4**. Specific acid catalysis could proceed through **3** or **5**, like the enolization.

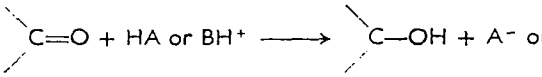
Let us consider some details of these variants. Acid catalysis in the case of nucleophilic additions to the carbonyl group should involve the following processes:

1. Addition of the nucleophile to the carbonyl carbon, e.g.



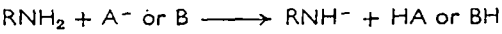
(36a)

2. Addition of a proton to the carbonyl oxygen:



(36b)

3. Removal of a proton from the basic heteroatom of the nucleophile:



(36c)

The order of these processes can, in principle, differ, but the fact of general acid catalysis and of a deuterium isotope effect ($k_H/k_D = 1{\cdot}2$ [49]) exclude all other combinations except from the possibility of reactions (36a) and (36b) taking place simultaneously. This is equivalent to

accepting scheme (37)[49,51,68,69]. Hence the formation of the com-

$$\text{>C=O} + HA_i \overset{\text{Fast}}{\rightleftharpoons} \text{>C=O}\cdots HA_i \qquad (37a)$$

$$RNH_2 + \text{>C=O}\cdots HA_i \xrightarrow{\text{Slow}} R\overset{+}{N}H_2\text{—}\underset{|}{C}\text{—OH} + A_i^- \qquad (37b)$$

$$R\overset{+}{N}H_2\text{—}\underset{|}{C}\text{—OH} + A_i^- \overset{\text{Fast}}{\rightleftharpoons} RNH\underset{|}{C}OH + HA_i \qquad (37c)$$

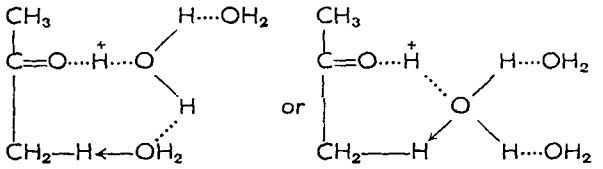
plexes $\text{>C=O}\cdots HA_i$ should be accepted as a fact. Nevertheless, the acid-catalyzed enolization by-passes these complexes. Let us consider whether particles of type **3** or **5** are involved. In dilute solutions of acid, where water activity remains constant, the equilibrium (38) causes a proportionality of the concentrations of **5** and **3**.

$$\text{>C=O}\cdots H^+ \cdot nH_2O \rightleftharpoons \underset{|}{C^+}\text{—OH} + n\,H_2O \qquad (38)$$

Considering **3** to be a specific case of **4** and taking into account the fact that these do not participate in the enolization, it follows that the enolization should be connected with the 'fully' protonated form **5**. As shown in section VII, the formation of the latter to a considerable extent is possible in concentrated sulfuric acid only. Therefore up to $H_0 = -6$, in aqueous sulfuric acid, the concentration of $\text{>C}^+\text{—OH}$ should be inversely proportional to the a_{H_2O} value* and the rate of bimolecular reaction with water should not to the first approximation depend upon the water activity. In Figure 3 the real situation of the acetone enolization in aqueous sulfuric acid solutions is illustrated. The observed value of the first-order rate coefficient k follows equation (14) (represented in Figure 3 by line 1) only when $H_0 > 0$. At $H_0 < 0$ the k value becomes lower than defined by equation (14). Curve 2 represents the $\log k$ dependence on H_0 calculated by the use of equation (17) assuming that k is independent of a_{H_2O} (unimolecular reaction) and accepting the conductometric K_a value. Experimental values of $\log k$ are quite close to curve 2 in the wide range $0 > H_0 > -6$, the maximum k being 65% higher than calculated using equation (17). This is consistent with an interpretation where complexes like **3** are considered to be reactive intermediates in a unimolecular reaction. The proton

* For acetone the exact relationship at high concentrations of H_2SO_4 is[20]
$\log [\mathbf{3}]/[\mathbf{5}] = -3{\cdot}60 + 1{\cdot}5 \log a_{H_2O}$.

abstractor should be in this case one of the n water molecules in the hydration shell of particle **3**:



If the hydration number n becomes smaller, the bond between the carbonyl oxygen and the proton becomes stronger and the positive charge of the methyl hydrogen increases. The result should be an increase in the rate coefficient k with the decrease of a_{H_2O}, as observed. In the region $H_0 < -6$ the decrease of the concentration of particle **3** becomes considerable (see equilibrium 25) and the rate of unimolecular reaction should decrease. The rate of bimolecular reaction between particle **5** and H_2O should remain approximately constant in the region of $H_0 > -6$ because the increase of the concentration of **5** will be compensated by the decrease of a_{H_2O}. In the region $H_0 < -6$, the increase of the concentration of **5** becomes less than the decrease of a_{H_2O} and the reaction rate should decrease. (Actually the H_0 value has no immediate influence as far as the phenomena connected with the dehydration of complex **3** are considered. At $H_0 < -6$ the water activity in aqueous sulfuric acid becomes very low and the concentration of **5** becomes comparable to the total concentration of acetone.) The ratio k/a_{H_2O}, which could be considered as a bimolecular rate coefficient, passes through a maximum in the $H_0 \approx 6$ region (see Figure 3), and its increase in the $-2 > H_0 > -6$ range could be explained by assuming that the n value is higher than unity (which is very likely in this case). If so, the concentration of complex **5** will increase faster than the water activity.

While it cannot be definitely ascertained whether particles **3** or **5** are the main reactive intermediates, it is most likely that they are of the type **3**, especially if we give any significance to the proximity of the experimental k values to the calculated curve 2 in Figure 3.

The principal differences between the reactivities of complexes **3** and **4** should be as follows: complex **3** may react by intermolecular attack of a water molecule from the hydration shell (unimolecular rate-determining step), but a similar reaction is impossible in the case of complex **4** because it is not hydrated like **3**. Complex **3**

may also react with water bimolecularly; this possibility cannot be excluded and will be considered later.

In the case of bimolecular interaction, the reactivity of complex **4** should be much lower than the reactivity of **3**. If the intermolecular attack of the water molecule in complex **3** is retarded, as in the case of sterically hindered carbonyl compounds, the differences between the reactivities of **3** and **5** should be detected by the relevant treatment of experimental data. From this viewpoint it is interesting to consider the enolization of D-α-phenylisocaprophenone in 85–94% H_2SO_4[70]*. In this range of H_2SO_4 concentrations all the activity coefficients can be considered constants[71], and the concentrations of H_2O and HSO_4^- can therefore be used instead of activities. Assuming the reaction to be bimolecular and the reactivity of complex **3** with $n = 1$ to be negligible in comparison with the reactivity of form **5**, equation (39) holds for the observed first-order rate coefficient k_1.

$$k_1 = \frac{k_{H_2O}[H_2O] + k_{HSO_4^-}[HSO_4^-]}{1 + K_h[H_2O]} \tag{39}$$

Here K_h is presented in concentration units and its absolute value is not comparable with those listed in Table 2. The K_h value can be calculated from the ratio of concentrations of **3** and **5** (equation 40)

$$\log [\mathbf{3}]/[\mathbf{5}] = -0{\cdot}94 \tag{40}$$

in 90·6% H_2SO_4 where $[H_2O] = 0{\cdot}234$; the value of K_h obtained is 0·49.

Equation (39) can be rewritten as (41). The plot of the left-hand

$$\frac{k_1(1 + K_h[H_2O])}{[HSO_4^-]} = k_{HSO_4^-} + k_{H_2O}\frac{[H_2O]}{[HSO_4^-]} \tag{41}$$

side of (41) *versus* the ratio of $[H_2O]/[HSO_4^-]$ should be linear and it really is (Figure 5). So the suggested scheme for this reaction seems very likely to be the correct one and the existence of the equilibrium between **3** and **5** is also verified by the kinetic data. The k_{H_2O} and $k_{HSO_4^-}$ values obtained equal $4{\cdot}05 \times 10^{-4}$ and $2{\cdot}00 \times 10^{-6}$ respectively.

Specific acid catalysis can be connected either with form **3** or **5**, if the reaction is not a prototropic one. No nucleophilic reaction with carbonyl is known to occur in concentrated sulfuric acid, possibly owing to the protonation of all active nucleophiles in this medium.

* In the original paper the data obtained were treated assuming the classical protonization scheme and that $pK_a = -7{\cdot}39$.

In dilute aqueous solutions of acids the concentration of particle **5** is probably too low to have any real importance. Significant differences must again exist between the reactivities of forms **3** and **4** to account for specific acid catalysis. Here the selectivity relationship could be used[71a]. According to this law the differences between the rate coefficients for **3** and **4** should increase with decreasing reaction rates. So in the case of a nucleophilic attack on the carbonyl carbon, reactions with highly nucleophilic reagents should show general acid catalysis, and with much less nucleophilic reagents specific acid catalysis. This leads to the following general conclusions. In the case

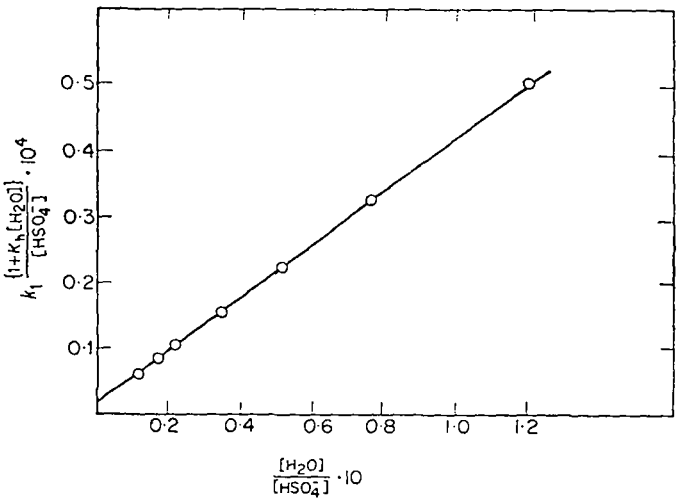


FIGURE 5. Treatment of the experimental data[70] for the enolization of D-α-phenylisocaprophenone in 85–94% H_2SO_4.

of nucleophilic additions to the carbonyl group or unimolecular isomerizations high reactivities (low free energies or heats of activation) should be connected with general acid catalysis; low reactivities (high free energies or heats of activation) should be connected with specific acid catalysis. In the case of enolization high reactivities (low heats of activation) should be connected with the termolecular kinetic law, and low reactivities (high heats of activation) with general acid catalysis.

These conclusions cannot be fully proved by a comparison of existing data, because the literature does not report any acid-catalyzed nucleophilic addition to a carbonyl group with a heat of activation higher than 10 kcal. On the other hand, it also seems that

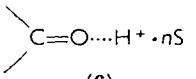
there are no enolization and isomerization reactions of carbonyl compounds with low heats of activation. Nevertheless the data listed in Table 4 show that in all cases nucleophilic addition to the carbonyl group is connected with low heats of activation and general acid catalysis. Enolization reactions with high heats of activation exhibit general acid catalysis; isomerization reactions with high heats of activation are connected with specific acid catalysis only. So the data listed in Table 4 do not contradict the general conclusions mentioned above.

From the point of view of reactivity, also, complex **3** is a real entity and can be considered either as a hydrated 'fully' protonated form or a specific case of complex **4**, depending upon the process occurring.

The authors of this chapter realize that the general explanation they suggest for the phenomena under consideration is not the only possible one. The goal they desired to achieve was to show that such an explanation could be presented encompassing the main experimental data even though these seem to be inconsistent with each other.

IX. BASICITY OF CARBONYL COMPOUNDS IN NONAQUEOUS MEDIA

The basicity of carbonyl compounds in nonaqueous media can in principle be considered using the conceptions developed for aqueous solutions. Complex **3** should be substituted by the protonated form



(**6**)

solvated by the molecules of the solvent or by the equivalent complexes (**6**, S = solvent molecule) of carbonyl compounds with the solvated lyonium ions, if the existence of these particles is possible in the given solution. The 'fully' protonated form could be formed in solutions of very strong acids where the activity of the basic components of the medium is small. Most experimental investigations deal with solutions of carbonyl compounds in media of comparatively weak acidity, where the carbonyl compound is probably present in the form **4** or **6**. These were mostly interpreted as hydrogen bonding of the medium or of proton-donating solutes with the carbonyl compound. The experimental methods usually employed for such a study are ultraviolet, infrared, and nuclear magnetic resonance spectroscopy or the determination of the heats of solvation[14,15,77,78].

TABLE 4. Comparison of the activation heats for different types of acid-catalyzed reactions of carbonyl compounds.

Carbonyl compound	Reagent	Conditions	Reaction type[a]	Heat of activation (kcal)	Ref.
Acetone	semicarbazide	H_2O, Na_2HPO_4/NaH_2PO_4 buffer, pH = 7	Nucleophilic substitution, g.a.c.	2·0	72
Diethyl ketone	semicarbazide	H_2O, Na_2HPO_4/NaH_2PO_4 buffer, pH = 7		1·4	72
Cyclopentanone	semicarbazide	H_2O, Na_2HPO_4/NaH_2PO_4 buffer, pH = 7		4·0	72
Cyclohexanone	semicarbazide	H_2O, Na_2HPO_4/NaH_2PO_4 buffer, pH = 7		1·1	72
Acetone	hydroxylamine	H_2O, Na_2HPO_4/NaH_2PO_4 buffer, pH = 7		4·5	73
Diethyl ketone	hydroxylamine	H_2O, Na_2HPO_4/NaH_2PO_4 buffer, pH = 7		4·1	73
Cyclopentanone	hydroxylamine	H_2O, Na_2HPO_4/NaH_2PO_4 buffer, pH = 7		5·4	73
Cyclohexanone	hydroxylamine	H_2O, Na_2HPO_4/NaH_2PO_4 buffer, pH = 7		1·9	73
Methyl ethyl ketone	hydroxylamine	H_2O, Na_2HPO_4/NaH_2PO_4 buffer, pH = 7		6·1	73
Acetone	thiosemicarbazide	H_2O, Na_2HPO_4/NaH_2PO_4 buffer, pH = 7		0·9	74
Diethyl ketone	thiosemicarbazide	H_2O, Na_2HPO_4/NaH_2PO_4 buffer, pH = 7		3·4	74
Cyclopentanone	thiosemicarbazide	H_2O, Na_2HPO_4/NaH_2PO_4 buffer, pH = 7		3·0	74
Cyclohexanone	thiosemicarbazide	H_2O, Na_2HPO_4/NaH_2PO_4 buffer, pH = 7		1·1	74
Methyl ethyl ketone	thiosemicarbazide	H_2O, Na_2HPO_4/NaH_2PO_4 buffer, pH = 7		2·9	74

Acetone	Bromine	H_2O, 0·04–11·2 M HCl	Enolization, g.a.c.	20·9	38
Cyclopentanone	Bromine	90% acetic acid, 0·05 M HCl		20·4	75
Cyclohexanone	Bromine	90% acetic acid, 0·05 M HCl		20·1	75
Acetaldehyde	Iodine	H_2O, 0·71–15 M H_2SO_4		19·5	63
cis-2,4-Dimethoxychalcone	–	H_2O, 5% dioxane, 0·0017–0·0038 M H_2SO_4	Unimolecular isomerization, s.a.c.	15·3	53
cis-2,4,6-Trimethoxychalcone	–	H_2O, 5% dioxane, $2·85 \times 10^{-4}$ M H_2SO_4		15·8	53
cis-2,7-Dimethoxychalcone	–	H_2O, 5% dioxane, 2·83 M H_2SO_4		22·3	53
cis-2-Methoxychalcone	–	H_2O, 5% dioxane, 1·00–2·83 M H_2SO_4	Bimolecular isomerization, s.a.c.	18·5	54
cis-Chalcone	–	Acetic acid, 0–0·4 M H_2SO_4		18·1	76

[a] g.a.c. = general acid catalysis, s.a.c. = specific acid catalysis.

Investigations of infrared spectra of carbonyl compounds are quite extensive[78,79] and a considerable amount of work was done in the study of hydrogen bonding. It is known[78–80] that if formation of a hydrogen bond between the carbonyl group and some proton-donating component of the medium occurs, the infrared absorption frequencies for both the carbonyl group ($\nu_{C=O}$) and for the proton-donating group (ν_{AH}) are shifted to lower frequencies. These $\Delta\nu_{C=O}$ and $\Delta\nu_{AH}$ shifts are used by different authors for the qualitative or semiquantitative estimation of the relative basicity of different carbonyl compounds. It was concluded by Fox and Martin[81] and Badger and Bauer[82] that the magnitude of the shift to a lower frequency should depend upon the strength of the hydrogen bond: the stronger the bonding, the greater the shift. Accordingly, Gordy and Stanford[2,83–85] suggested the use of the shift of O—D bond frequency in CH_3OD (or in D_2O + HCl) as a measure of the basic strength of the dissolved base. It has already been mentioned in this chapter that a linear correlation was observed between the shift magnitudes and the pK_a values of the respective bases. However, further reexamination[86,87] shows this relationship to be more complex.

The detection of carbonyl-bond shifts for the estimation of the relative basicities of carbonyl compounds was employed also by Denisov[88], who studied the shift caused by hydrogen bonding with CF_3COOH in CCl_4 solution. Ketones for which the higher basicity could be assumed were characterized by greater shifts to the lower frequencies (see Table 5).

TABLE 5. Shifts of the infrared bond frequencies of the carbonyl group by the interaction between ketones and CF_3COOH in CCl_4[88].

Ketone	$\Delta\nu_{C=O}$ (cm^{-1})[a]
$(CH_2Cl)_2CO$	6
$CH_2ClCOCH_3$	15
$(CH_3)_2CO$	25
Cyclopentanone	29
Camphor	33

[a] The difference between the observed frequencies before and after addition of CF_3COOH.

The other method employing infrared spectroscopy for the study of acid–base interactions in nonaqueous media is based on bond-intensity measurements. This method is analogous to the indicator method described in section II of this chapter and the relevant equilibrium constants can be calculated. This method was applied by Widom, Philippe, and Hobbs[80] for determining the dissociation constants of complexes between phenol (A) and bases (B) in CCl_4 solutions (equation 42). The values obtained are listed in Table 6.

$$K = \frac{[A][B]}{[AB]} \tag{42}$$

TABLE 6. Dissociation constants K of complexes between phenol and various ketones in CCl_4 at 24·6 ± 0·1°[80] and the respective OH bond frequency shifts.

Ketone	K	$\Delta\nu_{OH}$ (cm^{-1})
$(CH_3)_2CO$	0·118	266
$CH_3COC_2H_5$	0·125	230
$(C_2H_5)_2CO$	0·136	209
$(C_3H_7)_2CO$	0·139	197
$C_6H_5COCH_3$	0·146	243

Although the variations in the K values are rather small, there seems to be a correlation between the values of K and $\Delta\nu_{OH}$. The deviation of acetophenone was explained by the authors as a result of the influence of steric factors.

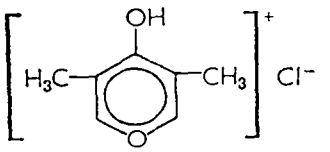
By the application of ultraviolet spectroscopy[89,90], nuclear magnetic resonance spectroscopy, and measurements of the heats of mixing[14,78] only qualitative or semiquantitative information can be obtained in the field under consideration.

X. OXONIUM SALTS AND THE INTERACTION OF CARBONYL COMPOUNDS WITH APROTONIC ACIDS

According to the conception developed by Lewis all acids (electrophiles) can be divided into two sharply different groups: the protonic and aprotonic acids. In the previous sections only the interaction of carbonyl compounds with protonic acids was considered. In this section some facts of the basic behavior of carbonyl compounds in

the reactions with aprotonic acids will be presented. Since there is almost a complete lack of quantitative data in this field, we present the available information which can be used to indicate that such an interaction exists.

Examples of ketones capable of forming stable crystalline salts with protonic acids are restricted to highly resonance-stabilized systems, such as pyrone, chromone, flavone, and xanthone derivatives. For example, dimethylpyrone forms a crystalline compound[91] with HCl having the structure **7**. These compounds can be classified



(7)

as salts of carbonyl compounds only by convention, because only a minor part of the positive charge is located on the former carbonyl group.

Stable complexes of carbonyl compounds with such aprotonic acids as $MgBr_2$, MgI_2, and BF_3 are, on the other hand, quite common. Many ketones and aldehydes form stable complexes, having definite melting points, with $MgBr_2$, MgI_2[92], and BF_3[93]. Tshelintsev[94] investigated calorimetrically the interaction between C_2H_5OMgI and carbonyl compounds. The values of the heats of addition of the first molecule of C_2H_5OMgI to some ketones are listed in Table 7.

TABLE 7. Heats of addition (ΔH) of the first molecule of C_2H_5OMgI to some ketones[94].

Compound	ΔH (kcal/mole)
CH_3COCH_3	17·26
$CH_3COC_2H_5$	14·36
1,4-Benzoquinone	11·32
2,6-Dimethyl-1,4-pyrone	10·69

An interesting reaction where ketones are involved as bases is reported by Meerwein[95] (equation 43). The analogous oxonium compound with $[SbCl_6]$ instead of $[BF_4]^-$ can also be obtained[95].

$$R_2C{=}O + [(C_2H_5)_3O]^+[BF_4]^- \longrightarrow [R_2C{-}O{-}C_2H_5]^+[BF_4]^- + (C_2H_5)_2O \quad (43)$$

Different complexes of carbonyl compounds with aprotonic acids are assumed to be reactive intermediates in reactions, catalyzed by aprotonic acids; *e.g.* complexes with SO_3 in the sulfonation of aldehydes and ketones[96], with metal cations in the Cannizzaro reaction[97], with Cu^{2+}, Al^{3+}, or Ni^{2+} in the decarbonylation of ketodicarboxylic acid anions $^{-}O_2CCOC(CH_3)_2CO_2^{-}$[98], and with $(RO)_3Al$ in the Tishtschenko[99], Meerwein–Ponndorf–Oppenauer[100], and Meerwein–Ponndorf–Verley[101] reactions. The formation of an acceptor–donor bond between the carbonyl oxygen and the metal atoms is assumed in the activated state, in the course of the reduction of carbonyl compounds by Grignard reagents[102,103] and by $LiAlH_4$[104].

Even this short and incomplete review indicates that the interaction between carbonyl compounds and aprotonic acids is very important. Therefore an extensive and quantitative systematic study in this field is urgently needed.

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CHAPTER 10

Oxidation of aldehydes by transition metals

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I. INTRODUCTION

Of the many oxidation reactions of carbonyl compounds, the oxidation of aldehydes with transition metals seems to be at present in the greatest need of a detailed discussion: enough work has been done in the field to reveal, on the one hand, some of the basic features and to show, on the other hand, how much more has to be done.

With the intention of giving a detailed discussion of the experimental findings and of the possible interpretations as well as of open questions and unresolved problems, this chapter is restricted to several oxidants only; namely to the compounds derived from chromium, manganese, vanadium, cerium, and cobalt.

II. CHROMIC ACID

A. Aromatic Aldehydes

The chromic acid oxidation of aldehydes has been studied most intensely in the aromatic series. Lucchi[1–5] measured the oxidation rates, activation energies, and frequency factors for the oxidation of benzaldehyde and the *ortho*-, *meta*-, and *para*-monosubstituted benzaldehydes with CH_3, Cl, Br, NO_2, OH, and OCH_3 as the substituent. With the exception of the phenolic aldehydes, all reactions were of second order. In the case of the hydroxybenzaldehydes the facile attack on the phenolic ring complicates the picture[3]. Lucchi showed clearly that electron-attracting substituents increase the rate of oxidation and electron-donating groups retard the reaction*. Graham and Westheimer[7] later used Lucchi's data to calculate the Hammett reaction constant[8] and obtained the value $\rho = +1{\cdot}06$. This value is in excellent agreement with the value $\rho = +1{\cdot}02$ which Wiberg and Mill[9] obtained from their measurements of the oxidation in 91% acetic acid in the presence of perchloric acid.

Another interesting observation which Lucchi made is that most electron-attracting groups seem to be more effective in the *para* than in the *ortho* position (Table 1). Since the polar effect of substituents in

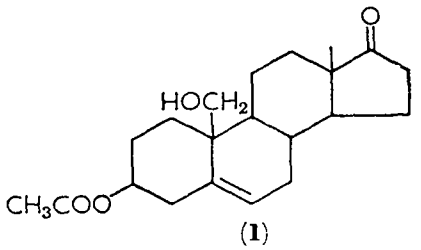
TABLE 1. Relative rates for the chromic acid oxidation of *ortho*- and *para*-substituted benzaldehydes[1–5] in aqueous acetic acid at 20°.

Substituent	k_o/k_p
CH_3O	3·2
CH_3	0·93
Cl	0·85
Br	0·74
NO_2	0·36

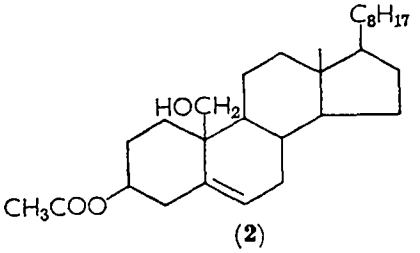
* This is probably true only up to a certain point. Jayaraman[6] has recently observed that 2,4-dinitrobenzaldehyde is extremely unreactive towards chromic acid, despite the fact that both *ortho*- and *para*-nitrobenzaldehyde react faster (1·4 and 4·1 times, respectively) than benzaldehyde itself.

the *ortho* and *para* position is usually very similar[10], the results given in Table 1 indicate that the reaction is hindered by bulky *ortho* substituents. In this respect the oxidation of aldehydes differs dramatically from other oxidations involving chromic acid: the well-investigated oxidation of alcohols and hydrocarbons is subject to steric hindrance only in the most extreme cases[11–13]. On the other hand, the decrease in the k_o/k_p ratio does not exactly parallel the steric requirements of the substituents as these have been determined from other reactions. For example, Taft's steric substituent constants[10], E_s, for the methyl group and a bromine atom are of the same magnitude, whereas Table 1 shows that in the oxidation of substituted benzaldehydes a bromine atom in the *ortho* position will decrease the reaction rate more effectively than does a methyl group. Also, the effect of the methoxy group is anomalous and indicates the operation of special factors, e.g. hydrogen bonding, in the reaction intermediate or transition state.

The amount of experimental data available at the present time, therefore, do not demonstrate unambiguously the operation of steric hindrance in the oxidation of aldehydes, and the observed change in relative reactivities of *ortho*- and *para*-substituted benzaldehydes could also be interpreted partially or wholly in terms of dipolar interactions between the carbonyl group and the substituent. There are, however, some qualitative observations available which further support the view that the oxidation of an aldehyde group is sensitive to steric hindrance. If the oxidation of aldehydes is sterically hindered and that of alcohols is not, then one should expect good yield of aldehydes in the oxidation of sterically hindered alcohols. Such a conclusion appears to be justified in the oxidation of certain aliphatic aldehydes. For example, Tanabe and coworkers[14] observed that although 3β,19-dihydroxyandrost-5-en-17-one 3-acetate (**1**) can be easily oxidized to the aldehyde, the latter is resistant to further



(**1**)



(**2**)

oxidation by chromic acid; only a very small amount of the corresponding acid was obtained even under relatively drastic conditions. Similarly, Δ^5-cholestene-3β,19-diol 3-acetate (**2**) is easily oxidized to the corresponding aldehyde in very good yield, but less than 1% of the acid could be obtained even under much more forceful conditions[15]. Even though no kinetic data on the oxidation of the C_{19} steroid aldehydes are available and other interpretations for their surprisingly low reactivity cannot be excluded, steric hindrance suggests itself as a very plausible explanation considering that the aldehyde group in the two above examples is axial and flanked by four coaxial hydrogen atoms.

The chromic acid oxidation of aldehydes, like all other oxidations by chromic acid, is an acid-catalyzed reaction. Graham and Westheimer[7] carried out a detailed study of the kinetics of the chromic acid oxidation of benzaldehyde in aqueous solution at 80°. Their results were consistent with the rate equation (1), which is very similar to that previously derived for the oxidation of isopropyl

$$-\mathrm{d}[CrO_3]/\mathrm{d}t = k[HCrO_4^-][C_6H_5CHO](k_3[H^+] + k_4[H^+]^2) \quad (1)$$

where $k_3 = 0{\cdot}147\ (\mathrm{mole/l})^{-2}\ \mathrm{min}^{-1}$

and $k_4 = 0{\cdot}95\ (\mathrm{mole/l})^{-3}\ \mathrm{min}^{-1}$

alcohol[16]. One point of interest is that only that part of the total hexavalent chromium which is present in the monomeric form (as $HCrO_4^-$) is involved in the oxidation whereas the chromic acid present as dichromate ($Cr_2O_7^{2-}$) is not. Although this phenomenon has been known in the chromic acid oxidation of alcohols for more than twenty years[17], no satisfactory explanation has been offered.

The rate of oxidation depends both on the first and second power of the hydrogen ion concentration. Because chromic acid is a very strong acid and the monochromate anion is a rather weak one[18], in moderately acidic solutions practically all monomeric chromium will be in the form of the anion $HCrO_4^-$ (equations 2 and 3).

$$H_2CrO_4 \rightleftharpoons H^+ + HCrO_4^- \quad K_1 = 10 \quad (2)$$

$$HCrO_4^- \rightleftharpoons H^+ + CrO_4^{2-} \quad K_2 = 3{\cdot}2 \times 10^{-7} \quad (3)$$

The first- and second-order term in hydrogen ion concentration in the rate expression therefore corresponds to H_2CrO_4 and $H_3CrO_4^+$, respectively. Both chromic acid and its conjugate acid or their derivatives can therefore be regarded as the active oxidizing species.

In acetic acid the rate of oxidation is approximately proportional to the first power of the Hammett acidity function[19,20], h_0, and no second-order term has been detected[9].

In order to obtain information on the role of the aldehydic hydrogen in the oxidation reaction, the effect of isotope substitution was investigated. Wiberg[21] observed a primary kinetic isotope effect when replacing the aldehydic hydrogen by deuterium; C_6H_5CDO reacts 4·3 times slower than benzaldehyde. Hodnett[22] determined the isotope effect for the tritated compound; at 80°, k_H/k_T is 7·9. Both these results strongly indicate that the aldehydic C—H bond is broken in the rate-limiting step of the reaction.

Because only very few solvents resist the oxidizing action of chromic acid, the choice of solvent is restricted. Pyridine[23], *t*-butyl alcohol[24], acetic anhydride[25], acetone[26], and dimethylformamide[27] are sometimes used instead of water, but acetic acid is certainly the solvent most widely used for water-insoluble substrates. Acetic acid has not only the advantage of being fairly, though not completely[28], resistant to the oxidation by chromic acid, but also increases the oxidative power of chromic acid considerably. Isopropyl alcohol is oxidized 250 times faster in 86·5% acetic acid of the same acidity (as measured by the acidity function H_0) than in water[29]. The rate of oxidation of methylcyclohexane is increased by a factor of 10 by increasing the acetic acid concentration from 90 to 99% and by another power of 10 by changing from 99 to 100% acetic acid as solvent[30] (always keeping the H_0 acidity constant).

Aromatic aldehydes exhibit an exceptional behavior in this respect. Even though they are oxidized faster in acetic acid than in aqueous solution, the increase is relatively small. The increase in the oxidation rate of benzaldehyde from 75 to 95% acetic acid parallels the change in acidity function, though at lower acetic acid concentrations the change in rate is steeper than that of the acidity[9]. From the measurements of Westheimer[7] and Wiberg[9] one can roughly estimate the difference in reaction rate in water and 91% acetic acid. Because of the presence of the quadratic term in hydrogen ion concentration in aqueous solution and its absence in acetic acid, the rate ratio depends on acidity. At $H_0 = 1$ the oxidation of benzaldehyde will proceed about 3 times faster in 91% acetic acid (at 80°) than in water; at a higher acidity ($H_0 = 0$) the rate increase will be only by a factor of about 1·5.

The effect of solvent composition on the oxidation rate of aromatic aldehydes is also the subject of a recent study by Jayaraman[31].

Unfortunately, his data are not corrected for changes in acidity and are therefore difficult to interpret.

B. Aliphatic Aldehydes

The pattern observed in the oxidation of benzaldehyde was also found in a study of the oxidation of formaldehyde in aqueous solution by Chatterji and Mukherjee[32] and by Kemp and Waters[33]. The second group of investigators also determined the primary isotope effect to be 6·8 at 25° in 0·314 M perchloric acid. The isotope effect was found to decrease not only with temperature, as would be expected[34], but also with increasing perchloric acid concentration. Also, a large solvent isotope effect has been found. The reaction is 5·37 ± 0·2 times faster in D_2O than in water, a value in good agreement with that expected for a reaction involving two protonation equilibria. Even in this respect the oxidation of aldehydes resembles that of alcohols[35]. Rate data for the oxidation of some other aliphatic aldehydes have been obtained by Chatterji and Antony[36]. Qualitatively, a 'considerable' primary isotope effect in the oxidation of 1-deuteroacetaldehyde has been reported[37] as early as 1949.

No detailed study of any higher aliphatic alcohol is available. However, Barnard and Karayanis[37a] investigated the chromic acid oxidation of propionaldehyde and n-butyraldehyde from the analytical point of view and made some interesting observations. The above authors found that propionaldehydes reduced 170% of the expected amount of chromic acid and that acetic acid was produced beside propionic acid. In the oxidation of n-butyraldehyde about 190% of the theoretical amount of the oxidant was consumed and both propionic and, to a lesser extent, acetic acid were formed. As carboxylic acids are very resistant to oxidation, the obvious conclusion is that about 25 to 30% of the aldehyde undergoes oxidation on the alkyl group rather than on the carbonyl function. Barnard and Karayannis interpret their observation in terms of an enol intermediate (equation 4). This interpretation is very

$$\begin{array}{ccccccc} RCH_2{-}CH{=}O & \xrightarrow{\text{Oxidation}} & RCH_2{-}CO_2H & & & & \\ \uparrow\downarrow & & & & & & \\ RCH{=}CH{-}OH & \xrightarrow{\text{Oxidation}} & RCH(OH){-}CH{=}O & \longrightarrow & RCH{=}O & \longrightarrow & RCO_2H \end{array} \qquad (4)$$

attractive, particularly in the light of the recent finding that chromic acid oxidation of ketones proceed through an enol intermediate[37b]. Also, we shall see later that other reagents oxidize aldehydes via enol intermediates.

C. Reaction Mechanism

1. The role of aldehyde hydrates

Roček[38] measured the rate of chromic acid oxidation for a series of negatively substituted aliphatic aldehydes, namely mono-, di-, and trichloroacetaldehyde. All of these aldehydes are practically completely hydrated in aqueous solution. It was found that electronegative substituents in this case decrease rather than increase the rate of reaction. Including the oxidation rate for acetaldehyde hydrate, he obtained a fairly good linear log k *vs.* σ^* dependence giving a value of $\rho^* = -1{\cdot}2$, which is very similar to that obtained for the oxidation of primary alcohols[40]. This finding shows that the positive ρ value is not typical of aldehyde oxidation but is rather restricted to aldehydes existing predominantly in the form of a free carbonyl compound. The clear inference is that electronegative substituents increase the oxidation rates indirectly by increasing the equilibrium concentration of the chromic acid ester of the aldehyde hydrate.

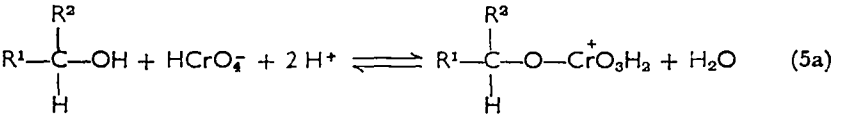
At this point it is of considerable interest to compare the oxidation rates of aldehydes with those of the corresponding alcohols. Formaldehyde can be estimated from Waters's[33] and Roček's[40] data to react more than 100 times faster than methanol. Acetaldehyde[36] and other simple aliphatic aldehydes react very roughly 5 times faster than the corresponding primary alcohols. On the other hand, benzaldehyde[7] reacts about 100 times slower than benzyl alcohol[40] in aqueous solution; from our previous discussion of the effect of solvent composition on the oxidation rates of alcohols and aldehydes it is evident that the relative rate of benzaldehyde should decrease at least by another order of magnitude in moderately concentrated acetic acid.

Inspection of these relative rates leads directly to one important conclusion about the reaction mechanism. Considering the high reactivity of formaldehyde in conjunction with the fact that it is practically fully hydrated in aqueous solution[41] with only about 0·1% of the free aldehyde present, makes any mechanism which would *directly* involve the free aldehyde seem very improbable. For

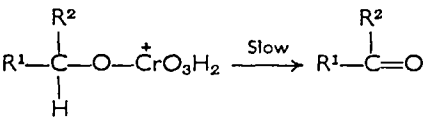
this reason the recently proposed[42] 'S_N2-like' mechanism in which a water molecule 'displaces' a hydride ion from an aldehyde molecule can be ruled out. Either the aldehyde hydrate or its simple derivative is the most likely intermediate.

Because the aldehyde hydrates so closely resemble alcohols both in structure as well as in practically every facet of the oxidation, it is reasonable to expect a similarity in the reaction intermediate and transition state of the two oxidation reactions as well.

Strong support has recently been offered[12] for the mechanism of the chromic acid oxidation of alcohols shown in equation (5). The



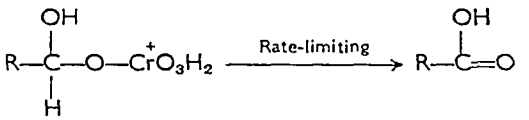
(5a)



(5b)

rate-limiting* step of the reaction is the decomposition of the protonated acid chromate ester.

Analogously, the oxidation of aldehydes can best be interpreted by assuming the reversible formation of a similar intermediate, an ester of the aldehyde hydrate, which then will decompose in the rate-limiting step (equation 6). In solutions of very low acidity, most of



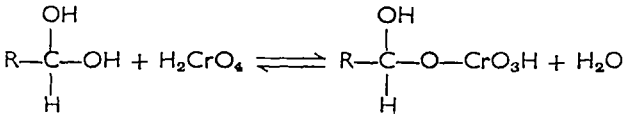
(6)

the product will be formed by decomposition of the unprotonated ester. In the presence of acetic acid the situation is complicated by the possibility of formation of acetochromic acid, $CH_3COOCrO_3H$,

* The usual terms, 'rate-determining', 'rate-controlling', 'slow' and 'fast' steps are sometimes loosely used, and may lead to ambiguity. The author of this chapter therefore prefers to use the term 'rate-limiting step' which has been recently defined by Roček, Westheimer, Eschenmoser, Moldovaniy, and Schreiber[12] as follows:

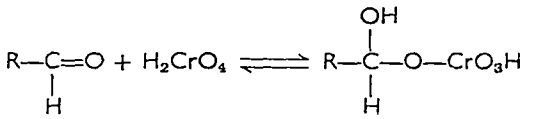
The kinetic equation for a complex reaction will contain rate coefficients of some or all of the successive steps. The last step in the series for which the rate coefficients appears in the kinetic equation is 'rate-limiting'; variations in the magnitude of rate coefficients of subsequent steps have no effect on the overall reaction rate.

which is assumed to be a stronger acid and a much more powerful oxidizing agent[30]. As long as the chromic acid ester is in rapid equilibrium with the aldehyde and the aldehyde hydrate, it is immaterial whether it is formed by esterification of the hydrate (equation 7) or by a carbonyl addition reaction to the free aldehyde



(7)

(equation 8). Defining the equilibrium constants for the three



(8)

reactions involved by equations (9), (10), and (11), we can easily see

$$K_{\text{hydration}} = \frac{[\text{hydrate}]}{[\text{aldehyde}][H_2O]} \tag{9}$$

$$K_{\text{esterification}} = \frac{[\text{ester}][H_2O]}{[\text{hydrate}][H_2CrO_4]} \tag{10}$$

$$K_{\text{addition}} = \frac{[\text{ester}]}{[\text{aldehyde}][H_2CrO_4]} \tag{11}$$

that $K_{\text{addition}} = K_{\text{esterification}} \times K_{\text{hydration}}$. The concentration of the ester intermediate, to which the reaction rate will be proportional, can therefore be expressed in two equivalent ways: (12) and (13).

$$[\text{ester}] = K_{\text{addition}}[\text{aldehyde}][H_2CrO_4] \tag{12}$$

$$[\text{ester}] = K_{\text{esterification}}K_{\text{hydration}}[\text{aldehyde}][H_2CrO_4] \tag{13}$$

K_{addition} refers to a carbonyl addition reaction which is, at least at present, inaccessible to direct measurement and certainly very sensitive to structural changes. The hydration of aldehydes, on the other hand, has been studied fairly extensively at least in the aliphatic series[41,43] and the change of the degree of hydration with changing solvent composition could be easily determined. Esterification reactions depend much less than carbonyl addition processes upon structural changes[39] and, as a very crude approximation, $K_{\text{esterification}}$ can be regarded as structure independent. Moreover, the esterification equilibria of alcohols and the related *gem*-diols can be expected

to vary in the same way. We can therefore see that it is very useful to keep the role of the ester hydration in mind in the discussion of the oxidation of aldehydes. All the apparent differences between the chromic acid oxidation of alcohols and aldehydes then disappear and we are fully justified to make use in this discussion of the results of the much more extensively studied oxidations of alcohols*.

The question whether the ester intermediate is indeed formed by esterification of the hydrate or by a direct carbonyl addition of chromic acid cannot be decided as long as no example of an aldehyde can be found which will be sufficiently hindered to make the formation rather than the decomposition of the *gem*-hydroxy ester rate-limiting.

Although the formation of the ester intermediate, suggested first by Wiberg[21], is now almost generally accepted, its exact mode of decomposition is still very much a matter for discussion and, particularly, for further research.

2. The valency change of chromium

The first point of interest in the detailed discussion of the reaction mechanism is the valence change which chromium undergoes (*a*) in the rate-limiting step and (*b*) on the way from the first product to the final stable species.

In an oxidation reaction chromium undergoes a valency change from VI to III, i.e. a three-electron change. On the other hand, the aldehyde which is oxidized to an acid undergoes a two-electron change only. It is therefore obvious that intermediate chromium valence states will have to appear and take part in the oxidation reaction; these intermediate compounds must be unstable and much more reactive than chromic acid.

Obviously, it is of considerable interest for the understanding of the oxidation process to determine whether the chromium intermediate is a compound of penta- or tetravalent chromium. Or, to

* It is of interest to recall in this connection Oppenauer's observation that aliphatic primary alcohols can be oxidized in practically quantitative yields to the corresponding aldehydes in *t*-butanol solution[24]. The evidently greatly reduced reactivity of the aldehydes as compared with the alcohols can easily be interpreted in terms of a probably very low concentration of the *t*-butyl hemiacetal $RCH(OH)OC(CH_3)_3$. In alcoholic solutions the role of the hemiacetal will be expected to be analogous to that of the hydrate in aqueous solution. The pronounced steric effect in the formation of hemiacetals is demonstrated, for example, by finding that chloral, which forms a very stable hydrate and hemiacetals with primary and secondary alcohols, fails to react with *t*-butanol[44].

rephrase the question, whether the oxidation is a one-electron process, leading to a free-radical intermediate, or whether it is a two-electron reaction. Unfortunately, this question cannot be answered by kinetic studies alone. The domain of kinetics ends at the transition state of the rate-limiting step. Whatever happens beyond this point is without influence on the reaction rate and therefore also inaccessible to exploration by rate measurements.

An ingenious approach to the solution of this complex problem has been opened by Watanabe and Westheimer[45] who exploited the effect of induced oxidation[46]. This term refers to a situation where a compound would not undergo direct oxidation under certain conditions, but can be oxidized in the presence of another reducing agent, the inductor. For example, manganous sulfate or ceric sulfate are stable towards chromic acid, but will be attacked and oxidized in the presence of isopropyl alcohol.

Watanabe and Westheimer investigated the induced oxidation of manganous salts in the presence of isopropyl alcohol. They found that even if the ratio of manganous salts to the alcohol is very high, a maximum of one molecule of MnO_2 will be formed for two molecules of acetone. Hence, two thirds of the oxidizing capacity of chromic acid is used up in the reaction with the alcohol before the intermediate chromium compound is released to react with the manganese ion. This result leads to the conclusion that chromium undergoes a VI to IV valence change during the oxidation of the alcohol (equations 14–16). In the absence of manganous ions or

$$(CH_3)_2CHOH + Cr^{VI} \longrightarrow (CH_3)_2CO + Cr^{IV} \quad (14)$$

$$Cr^{IV} + Mn^{2+} \longrightarrow Cr^{III} + Mn^{3+} \quad (15)$$

$$2\,Mn^{3+} + 2\,H_2O \longrightarrow MnO_2 + Mn^{2+} + 4\,H^+ \quad (16)$$

another compound capable of reacting directly with Cr^{IV}, reactions (17) and (18) can take place[45]. In the absence of manganous ions,

$$Cr^{IV} + Cr^{VI} \longrightarrow 2\,Cr^{V} \quad (17)$$

$$Cr^{V} + (CH_3)_2CHOH \longrightarrow Cr^{III} + (CH_3)_2CO \quad (18)$$

for each molecule of chromic acid reduced in a rate-limiting step by the alcohol (or aldehyde) another chromic acid molecule will be reduced by an unstable, highly reactive intermediate. Hence, twice as many molecules of chromic acid than before will be reduced for each initial slow reaction between the alcohol and chromic acid. In agreement with this conclusion it was found that the addition of manganous salts reduced the rate of chromic acid oxidation of an alcohol to about one-half[45].

In the oxidation of aldehydes no detailed study of induced oxidation is available. It has, however, been found that manganous or ceric ions decrease the rate of oxidation of aldehydes and alcohols in about the same manner[7,9]. There is therefore very little reason to doubt that the two reactions are analogous even in this respect and that the oxidation of aldehydes leads to carboxylic acids and a tetravalent chromium species as the first detectable products.

Even though the fate of the Cr^{IV} intermediate formed in the oxidation process cannot be directly studied by kinetic methods, it is of considerable interest, particularly if one keeps in mind (cf. equations 14, 17, and 18) that only one-third of the aldehyde is actually oxidized by the kinetically investigated reaction with hexavalent chromium, whereas two-thirds of it are oxidized by chromium compounds of intermediate valence states.

The first insight into the behavior of the lower chromium valences as oxidants in the oxidation of aldehydes was made available through the elegant investigations of Wiberg and Richardson[47]. Their approach can be explained as follows. The acid which is produced in the oxidation of an aldehyde is formed by (at least) two reactions. One part of the acid originates from the oxidation of the aldehyde with Cr^{VI}, whereas a second part results from an oxidation by Cr^{V}. The first reaction yields one-third and the second two-thirds of the total amount of acid formed. Using a mixture of two aldehydes the reactions taking place can be expressed by reactions (19) to (22).

$$R^1CHO + Cr^{VI} \xrightarrow{k_1} R^1CO_2H \tag{19}$$

$$R^2CHO + Cr^{VI} \xrightarrow{k_2} R^2CO_2H \tag{20}$$

$$R^1CHO + Cr^{V} \xrightarrow{k_3} R^1CO_2H \tag{21}$$

$$R^2CHO + Cr^{V} \xrightarrow{k_4} R^2CO_2H \tag{22}$$

Of the four rate coefficients, k_1 and k_2 are the only two that can be measured directly. The ratio and amounts of the acids formed in reaction (19) and (20) can be calculated from the value of the rate coefficients k_1 and k_2 and the concentrations of the two aldehydes. (As long as the concentrations of the two aldehydes can be considered equal, the ratio R^1COOH/R^2COOH formed by Cr^{VI} will be equal to k_1/k_2.) Subtracting now the calculated yield of reaction (19) and (20), respectively, from the actually determined yields of the two acids leaves a new ratio of products which will be related to the ratio

k_3/k_4. Even though the actual values of k_3 and k_4 still remain inaccessible, their ratio can thus be obtained by a combination of rate measurements and product analysis.

Using the principle which we have just outlined, Wiberg and Richardson[47] studied the oxidation of a mixture of benzaldehyde and 1-deuterobenzaldehyde and found that the deuterium isotope effect for Cr^{V} ($k_H/k_D = 4{\cdot}1$) is practically identical with that for Cr^{VI} ($k_H/k_D = 4{\cdot}3$), indicating that breaking of the C—H bond is the rate-limiting step in both reactions. This result is somewhat surprising when compared with the big difference in the tritium isotope effect which Kaplan, using basically the same method, found earlier for the oxidation of isopropyl alcohol[48]: Cr^{VI}, $k_H/k_T = 25$; Cr^{V}, $k_H/k_T = 3{\cdot}6$.

The study of the competitive oxidation of pairs of substituted benzaldehydes lead to the determination of the Hammett reaction constants. Assuming as before that the aldehydes are oxidized only by Cr^{VI} and Cr^{V}, the value of ρ for the latter is $+0{\cdot}45$ which is somewhat lower than the value $+0{\cdot}77$ for Cr^{VI}.

This decrease in the value of the reaction constant is contrary to expectation. Wiberg and Richardson therefore proposed to consider the more complicated reaction sequence (23) to (26) which includes three different oxidation states of chromium as oxidants. In this

$$RCHO + Cr^{VI} \longrightarrow RCO_2H + Cr^{IV} \quad (23)$$

$$RCHO + Cr^{IV} \longrightarrow R\text{—}\dot{C}{=}O + Cr^{III} \quad (24)$$

$$R\dot{C}{=}O + Cr^{VI} \longrightarrow RCO_2H + Cr^{V} \quad (25)$$

$$RCHO + Cr^{V} \longrightarrow RCO_2H + Cr^{III} \quad (26)$$

scheme each of the three oxidation stages of chromium consumes one-third of the aldehyde used up in the reaction. Two of the reactions include two-electron transfer reaction, whereas the oxidation by Cr^{IV} consists of a single-electron transfer and leads to a free-radical intermediate. Using this mechanistic scheme and assuming a reaction constant $\rho = -0{\cdot}5$ to $-1{\cdot}0$ for the radical-forming step, Wiberg and Richardson derived a more satisfying value of $\rho = +1{\cdot}6$ to $+2{\cdot}2$ for Cr^{V}. The selection of the above value for ρ of reaction (24) is based on the analogy with autoxidation of aromatic aldehydes.

Though this scheme has been suggested only tentatively it seems to be supported by the remarkable finding that oxidation of triphenylacetaldehyde is accompanied by decarbonylation of about one-third

of the substrate (equation 27), while two-thirds is oxidized to

$$(C_6H_5)_3CCHO \xrightarrow{CrO_3} (C_6H_5)_3COH + CO \qquad (27)$$

triphenylacetic acid. On the other hand, ceric ion, which can be regarded as a typical one-electron oxidant, leads to decarbonylation (presumably via the free radical) as the only observable reaction.

The role of Cr^{IV} in the oxidation of aldehydes has recently been tested[48a]. Assuming that benzyl alchohol reacts with chromic acid by the same mechanism as isopropyl alcohol, then the first step of the oxidation will produce a molecule of benzaldehyde and of Cr^{IV} (equation 27a).

$$C_6H_5CH_2OH + Cr^{VI} \longrightarrow C_6H_5CHO + Cr^{IV} \qquad (27a)$$

According to equation (24) these two species can react further in a reaction which is very fast even at low concentrations of chromium (IV). In the case where the two molecules are actually in direct contact when formed, they should interact immediately. The overall reaction would then be a three-electron oxidation of benzyl alcohol (equation 27b)

$$C_6H_5CH_2OH + Cr^{VI} \longrightarrow C_6H_5\dot{C}{=}O + Cr^{III} \qquad (27b)$$

followed by reactions (25) and (27c)

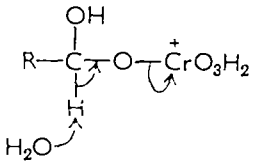
$$C_6H_5CH_2OH + Cr^{V} \longrightarrow C_6H_5CHO + Cr^{III} \qquad (27c)$$

Therefore only a 50% yield of benzaldehyde could be expected, the other part of benzyl alcohol being oxydized directly to benzoic acid. The results have shown, however, that almost quantitative yields of benzaldehyde can be obtained in the oxidation of benzyl alcohol, thus making the direct reaction of Cr^{IV} with aromatic aldehydes according to equation (24) seem very unlikely.

3. The nature of the carbon–hydrogen bond cleavage

Let us now discuss the fate of the aldehydic hydrogen which is lost during the oxidation reaction. From the primary isotope effect it is clear that the C—H bond is broken during the rate-limiting step. It is, however, far less clear whether it leaves as a proton, an atom, or an anion. In the original scheme[21] and in the later work by Westheimer[7] and Wiberg[9] it was assumed that the decomposition of

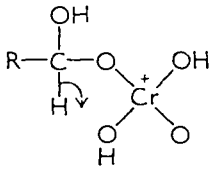
the ester intermediate is a base-induced reaction in which the hydrogen atom is abstracted as a proton by a solvent molecule (**3**).



(**3**)

This assumption was based primarily on the accelerating influence which electronegative groups have on the oxidation of aromatic aldehydes (positive ρ value) and on the oxidation of alcohols where base catalysis by pyridine had been claimed[16]. It was, however, demonstrated that the rate-accelerating effect of electronegative substituents in aromatic aldehydes can be easily interpreted in terms of greatly increased hydration. Aliphatic aldehyde hydrates also show the normal negative ρ value. The pyridine catalysis observed in the oxidation of isopropyl alcohol was shown to be a rather complicated artifact and not to represent real base catalysis[49,50].

Roček[38] argued in favor of a hydride transfer. He claimed that the ρ value of the oxidation step is actually negative and that the positive value observed experimentally for aromatic aldehydes is only apparent and is due to a superimposed effect of ring substituents on the hydration equilibrium. He concluded that an oxidation reaction having a negative ρ value is much better interpreted in terms of a hydride than in terms of a proton transfer. Also, the reaction is strongly acid-catalyzed with the rate depending upon the H_0 acidity function in strongly acid solutions[33]. In order to bring a hydride transfer in accord with the ester intermediate, a cyclic mechanism (**4**) has to be assumed. However, once we accept the

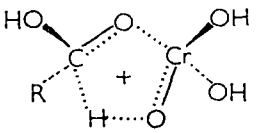


(**4**)

cyclic model for the decomposition of the ester intermediate, the differences between various modes of breaking of the carbon–hydrogen bond become much less clearly defined. Basically, the

mechanism has to indicate the migration of the hydrogen atom and the transfer of electrons, both towards chromium. Whether now the electrons migrate entirely with the hydrogen atom (hydride anion transfer), partially or completely through the oxygen bridge (proton and hydrogen atom transfer, respectively), is a secondary and rather subtle question. Indeed, it might well be argued that all these modes participate to some extent, thus leading to a resonance-stabilized transition state and that it is this very multitude of mechanistic pathways which leads to a particularly advantageous low energy transition state with extensive electron delocalization.

The transition state can then be represented as **5** or **6** depending upon whether one assumes a synchronous or consecutive breaking of the oxygen–chromium bond. This, incidentally, is another point of the mechanism which is not clearly understood, even though the absence of an ^{18}O isotope effect[51] makes the second alternative more attractive.



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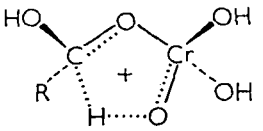

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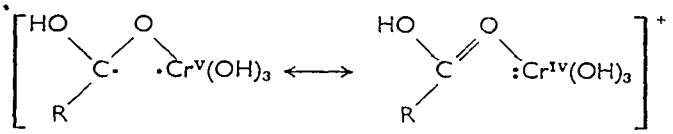
In the author's opinion only a certain resonance contribution of proton transfer in the transition state seems acceptable along with contributions from hydride and hydrogen atom transfer. On the other hand, a pure cyclic proton transfer mechanisms seem unlikely on several accounts: water has a basicity comparable to the acid chromate anion (H_3O^+ and H_2CrO_4 are acids of comparable strengths) and can therefore be expected to be some 10^{10} times more basic than $H_3CrO_4^+$ or $ROCrO_3H_2^+$. Even though there can be an expected entropy factor in favor of the intramolecular proton transfer, it is very unlikely to overcome this disparity. Another pronounced difficulty with any strictly proton-transfer mechanism for the chromic acid oxidation of aldehydes and alcohols is that it would set it completely apart from the oxidation of compounds where a mechanism of this type is unthinkable, e.g. the oxidation of hydrocarbons, and this in spite of the many similarities among these oxidation processes which have been demonstrated. Finally, as has been stressed before, any proton-transfer mechanism makes the negative sign of the ρ constant for the oxidation of aldehyde hydrates hard to interpret.

Assuming the second of the two representations of the transition state to be the correct one, the decomposition of the ester intermediate could lead to an intermediate (**7**) which itself would be resonance stabilized.



(7)

The concept of a resonance stabilized intermediate with contributing penta- and tetravalent chromium structures has earlier been applied in the interpretation of the oxidation of hydrocarbons[52]. Its justification lies in the observation that tetravalent chromium compounds have two unpaired electrons[53].

III. CHROMYL ACETATE

Wiberg and Lepse[54] recently published a study of the oxidation of benzaldehyde with chromyl acetate, $(CH_3CO_2)_2CrO_2$, in acetic anhydride solution. The reaction under these conditions differs drastically from the oxidation in aqueous acetic acid. First, Cr^{VI} is reduced even in the presence of an excess of benzaldehyde only to Cr^{IV} which is fairly stable in acetic anhydride and undergoes only a very slow further reduction to Cr^{III}. Second, the reduction of chromyl acetate clearly proceeds in two steps and the presence of intermediary Cr^{V} can be demonstrated both by ultraviolet and by electron spin resonance spectroscopy. Third, electronegative substituents in substituted benzaldehydes decrease the rate of oxidation, whereas the opposite is true in aqueous acetic acid. Fourth, benzaldehyde and toluene react at about the same rate with chromyl acetate, whereas the oxidation of benzaldehyde in 95% acetic acid is about 600 times faster[55] than that of toluene. Fifth, the oxidation of triphenylacetaldehyde leads almost only to carbon monoxide and triphenyl carbinol. No triphenylacetic acid could be isolated. This cleavage is typical for one-electron oxidants leading to the triphenylacetyl radical.

All these differences lead to the conclusion that the oxidation of aldehydes by chromic acid and by chromyl acetate must have very different mechanisms. For the latter, a simple hydrogen atom abstraction leading to an aroyl radical (equation 28) seems to be

$$ArCHO + (CH_3CO_2)_2CrO_2 \longrightarrow Ar\dot{C}{=}O + (CH_3CO_2)_2CrO_2H \qquad (28)$$

most likely. This mechanism is also in agreement with the deuterium isotope effect observed in the oxidation of benzaldehyde-d_1 which supports a mechanism with a rate-limiting C—H bond cleavage. The exact fate of the intermediates in the further process of the reaction is not quite clear. It is, however, of interest to note that Wiberg and Lepse found that the oxygen added to a molecule of benzaldehyde in its oxidation to benzoic acid comes from the chromyl acetate and not from the solvent.

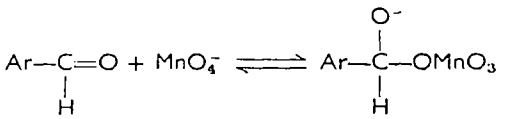
IV. PERMANGANIC ACID

A. *Aromatic Aldehydes*

1. Acid and neutral oxidation

The oxidation of aromatic aldehydes can be measured conveniently only in approximately neutral solutions, where good second-order rate behavior has been observed. In acid solutions the reaction becomes autocatalytic, probably because of the intervention of lower oxidation states of manganese which act as more powerful oxidants than the permanganate ion itself. Nevertheless, Tompkins[56] was able to study at least the initial rates of the permanganate oxidation of benzaldehyde in the range from pH 4·1 to pH 0·40 and could observe only a very moderate increase of the initial rate of oxidation. Even though the concentration of hydrogen ions in the range studied increases about 5000 times, the oxidation rate of benzaldehyde increased less than 5 times. Taking into account the experimental uncertainty of determining initial rates in autocatalyzed reactions, it seems justified to state that the oxidation rate of benzaldehyde by the permanganate ion is, in the region which has been investigated, independent of the hydrogen ion concentration. We shall see later that a similar situation is found in the oxidation of fluoral hydrate.

On the basis of this result and in analogy with the previously investigated oxidation of formic acid, Tompkins proposed the mechanism (29) to (32). He considered as rate-limiting the unimole-



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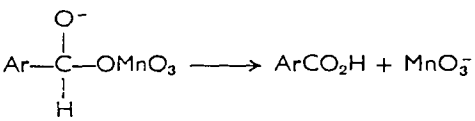


(30)

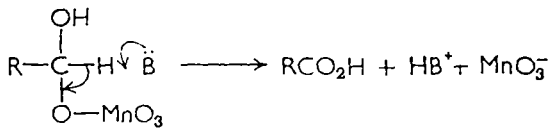
$$2\,MnO_3^- + H_2O \longrightarrow MnO_2 + HMnO_4^- + OH^- \quad (31)$$

$$ArC(H)=O + HMnO_4^- \longrightarrow ArCO_2^- + MnO_2 + H_2O \quad (32)$$

cular decomposition of the permanganate ester of the aldehyde hydrate monoanion (equation 30). Based on the amount of information Tompkins had available, this mechanism could hardly be regarded as anything more than an inspired guess. However, it predicted two facts, which could be verified using isotopically labeled compounds. The breaking of the carbon–hydrogen bond in the rate-limiting step should lead to a kinetic isotope effect if the aldehydic hydrogen is replaced by deuterium. Use of ^{18}O should determine whether the oxygen atom in the product came from the oxidant or from the solvent. Both these experiments have been carried out in a very elegant study by Wiberg and Stewart[57] and their finding agreed fully with the prediction based on the mechanism proposed by Tompkins. Wiberg and Stewart found that benzaldehyde-d_1 is oxidized up to 7·5 times slower than the protio compound, and that up to 75·8% of the oxygen in the benzoate ion formed in the oxidation of benzaldehyde with ^{18}O-labeled permanganate stems from the oxidant rather than from the solvent. Besides that, Wiberg and Stewart studied a number of substituted benzaldehydes and found a very moderate decrease of oxidation rate with increasing electronegativity of the substituent; in a Hammett plot a value $\rho = -0{\cdot}248$ was obtained.

Wiberg and Stewart also investigated the oxidation of the aromatic aldehydes over a wide range of acidities using buffered solutions. They found that in more alkaline media (pH 9 to 13) the reaction rate did not depend upon the nature of the buffer system used. On the other hand, in the region between pH 5 to 8, they observed a clear, albeit not very dramatic, dependence upon the nature of the ions present in the buffer system. For two of the buffers, namely phosphate and pyrophosphate, they could demonstrate a rate increase roughly proportional to the concentration of the buffer. Both the dependence on the nature of a buffer solution as well as the increase in the rate coefficient with increasing buffer concentration are suggestive of a general acid-catalyzed reaction. Wiberg and Stewart therefore proposed the mechanism (33) to (35). The rate-limiting

$$RCHO + H^+ + MnO_4^- \rightleftharpoons R{-}\underset{\displaystyle OMnO_3}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}{-}H \quad (33)$$



$$R{-}\underset{\underset{O{-}MnO_3}{|}}{\overset{OH}{\overset{|}{C}}}{-}H \cdots B \longrightarrow RCO_2H + HB^+ + MnO_3^- \qquad (34)$$

$$3\,MnO_3^- + H_2O \longrightarrow 2\,MnO_2 + MnO_4^- + 2\,OH^- \qquad (35)$$

step in this mechanism is the second step (34), the base-catalyzed decomposition of the permanganate ester of the aldehyde hydrate.

The rate equation derived from this mechanism is equation (36),

$$\begin{aligned} v &= k[\text{ester}][B] \\ v &= kK_E[RCHO][MnO_4^-][H^+][B] \\ v &= kK_EK_{HB^+}[RCHO][MnO_4^-][HB^+] \end{aligned} \qquad (36)$$

where K_E denotes the equilibrium constant for the formation of the permanganate ester (reaction 33) and K_{HB^+} is the acid dissociation constant of any acid present.

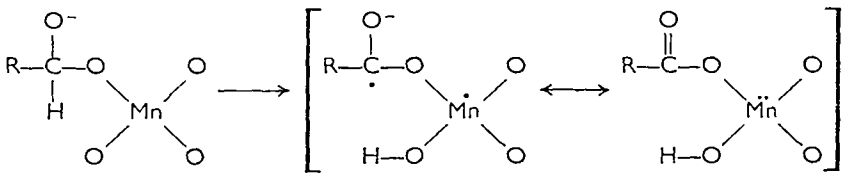
The rate equation (36) correctly predicts general acid catalysis. On the other hand, it is hard to understand why an oxidation process which, after all, consists in the transfer of electrons from the substrate to the oxidant should proceed faster in the neutral molecule as proposed by Wiberg and Stewart than in the anion as suggested by Tompkins. This assumption stands in sharp contrast with the oxidation of fluoral hydrate, which we will discuss later, and also with the oxidation of formic acid[58,59] where the formate anion, but not formic acid, undergo oxidation by the permanganate anion; this is so in spite of the fact that the latter reaction requires the interaction of two anions, a definite handicap which is absent in the oxidation of aldehydes. Also, the mechanism of Wiberg and Stewart consists of two reactions: a reversible carbonyl addition of permanganic acid to the aldehyde and the irreversible proton transfer to the base. Both of these reactions would be expected to exhibit a positive sign of the ρ constant and the overall ρ for the reaction should be large and positive; in contrast a small negative value has been found.

Moreover, the general acid catalysis which constitutes the only experimental support and justification of the above mechanism (33–35) has not been demonstrated conclusively. In general acid-catalyzed reactions the catalytic effects of individual acids are by Brønsted's law required to parallel the respective acid dissociation constants. This rule is violated in the permanganate oxidation of

benzaldehyde where the effectiveness of pyrophosphate and carbonate buffers (calculated for pH 8) is in the wrong order. Further, the increase in rate with the increase in buffer concentration indicative of general acid catalysis has been observed only for the two buffers, but is absent for the carbonate buffer. Most importantly, hydrogen ions, which in a general acid-catalyzed reaction should play a very important role and strongly accelerate the reaction at higher acidities, are either completely without effect on the reaction of the aldehyde with permanganate ion or have only a very moderate accelerating influence even in rather strongly acid solutions (up to pH 0·4).

One is therefore inclined to ascribe the effect observed with phosphate and pyrophosphate buffers to specific interactions of these anions with some form of manganese rather than to general acid catalysis. Pyrophosphate, for example, is known to form strong complexes with trivalent manganese (section IV) and could therefore easily affect the overall reaction rate by upsetting the complex interplay of reactions between the unstable manganese intermediates.

The present author therefore prefers to retain Tompkins's mechanism and to interpret the decomposition of the intermediate as a cyclic transfer of either a hydride anion or of a hydrogen atom. It is also possible that a resonance-stabilized intermediate (equation 37)



(37)

can best explain the particular reactivity of the permanganate ion in the aldehyde oxidation.

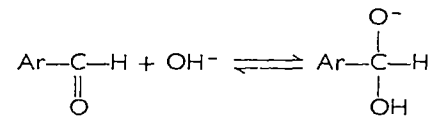
It is, however, clear that the question of general acid catalysis in the permanganate oxidation of aromatic aldehydes is of crucial importance and has to be reexamined before one of two mechanisms can be accepted or rejected.

2. Alkaline oxidation

In alkaline solution the oxidation of aromatic aldehydes is more complicated. A definite hydroxide ion catalysis has been observed, even though conflicting reports about its nature have been published. Tompkins[56] found the oxidation of benzaldehyde to be first-order in hydroxide ions up to a sodium hydroxide concentration of 0·15 M.

Wiberg and Stewart[2], on the other hand, found the oxidation of benzaldehyde and some other aromatic aldehydes to depend on the square root of the concentration of hydroxide ions. They also observed that in alkaline solution the mechanism of the reaction undergoes a drastic change as evidenced by these additional facts: (*a*) The deuterium isotope effect is small or negligible; (*b*) most, or possibly all, oxygen introduced into the aldehyde arises from the solvent; (*c*) the reaction has a large positive ρ value ($+1{\cdot}83$); and (*d*) no prominent salt effect has been observed.

Two different mechanisms have been proposed for the alkaline oxidation of aldehydes. Tompkins suggested a mechanism consisting of the oxidation of the hydrate anion. The rate-limiting step in his mechanism consisted of a hydride transfer from the substrate to the permanganate anion (39). This mechanism is well suited to explain



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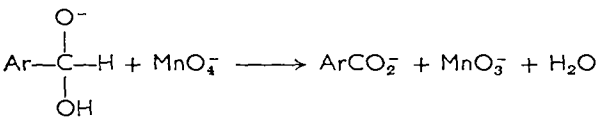


(39)

the observed large positive constant for the oxidation of substituted benzaldehydes as well as the absence of oxygen transfer. Nevertheless, it is unacceptable on several grounds. First, it predicts a first-order dependence of the oxidation rate on the hydroxide ion concentration. Second, there is little reason to doubt that the hydride transfer according to equation (39) should exhibit a deuterium isotope effect. Third, the reaction is one between two anions and should therefore be subject to an appreciable positive salt effect. As pointed out above none of these requirements is fulfilled.

Wiberg and Stewart assume that the oxidation is a free-radical chain process and tentatively formulate the individual steps as in (40) to (44). Even though this mechanism predicts correctly the half-power dependence on hydroxide ions, it has several drawbacks. In the opinion of the present author the least acceptable step is represented in equation (42). In this reaction the radical intermediate simply looses a hydrogen atom. The most logical way in which this could be done would be a simple transfer to the permanganate ion to yield a manganate anion $HMnO_4^-$. However, in order to regenerate a hydroxyl radical the reaction is actually formulated as producing a

Initiation

$$MnO_4^- + HO^- \xrightarrow{k_1} MnO_4^{2-} + HO\cdot \quad (40)$$

Propagation

$$HO\cdot + RCHO \xrightarrow{k_2} R{-}\overset{\overset{O\cdot}{|}}{\underset{\underset{H}{|}}{C}}{-}OH \quad (41)$$

$$R{-}\overset{\overset{O\cdot}{|}}{\underset{\underset{H}{|}}{C}}{-}OH + MnO_4^- \xrightarrow{k_3} RCO_2H + MnO_3^- + HO\cdot \quad (42)$$

Termination

$$2\,HO\cdot \xrightarrow{k_4} H_2O_2 \quad (43)$$

$$H_2O_2 + MnO_4^- \xrightarrow{\text{Fast}} O_2 + H^+ + HMnO_4^{2-} \quad (44)$$

much less stable hypomanganate anion, MnO_3^-, together with the required hydroxyl radical. Besides that, as Wiberg and Stewart themselves have pointed out, the rate equation derived for the above scheme predicts a square-root dependence upon the permanganate ion concentration, a conclusion which is in disagreement with the observed kinetics.

Obviously, the oxidation of aldehydes in alkaline solution also presents a complex and challenging problem and stands in need of further investigation.

B. Aliphatic Aldehydes

Only a few kinetic measurements of permanganate oxidation of simple aliphatic aldehydes have been published[60-62]. None of them contain enough information to allow drawing any conclusions about the reaction mechanism.

Holluta and Mutshin[62] found that the permanganate oxidation of formaldehyde displayed complicated kinetic behavior due to the further oxidation of formic acid and the intervention of lower oxidation states of manganese. They established that the reaction is base-catalyzed.

On the other hand, a very detailed elegant study of the permanganate oxidation of fluoral hydrate recently became available and deserves detailed discussion.

Stewart and Mocek[63] determined the pH profile of the permanganate oxidation of fluoral hydrate over a range of almost 20 pH units. The study revealed the existence of four distinctly different

oxidation routes, differing from each other by the total number of negative charges of the transition state (Table 2). Stewart and Mocek's results represent probably the best example available in the literature to demonstrate what seems to be a general rule in the chemistry of oxidation reactions. Namely, that the oxidation process is facilitated by (*a*) *an increase in the number of positive charges on the oxidant* and (*b*) *by an increase in the number of negative charges on the substrate.* The oxidizing power of an oxidant is therefore increased by protonation, whereas the reactivity of a substrate is increased by proton removal. This rule is an obvious consequence of the fact that an oxidation reaction is, in principle, a transfer of electron from the substrate to the oxidant.

TABLE 2. Principal reacting species in the oxidation of fluoral hydrate by potassium permanganate.

Substrate	Oxidant	pH range
$CF_3CH(OH)_2$	$HMnO_4$	−4–0 (H_-)
$CF_3CH(OH)_2$	MnO_4^-	0–6
$CF_3CH(OH)O^-$	MnO_4^-	6–11
$CF_3CH(O^-)_2$	MnO_4^-	11–14

As a consequence of the rule discussed in the previous paragraph, it is obvious that the permanganate ion will be the poorest oxidant and fluoral hydrate the least reactive substrate available in the system. The slowest reaction is therefore observed in solutions of medium acidity where these two species are prevalent. At high acidities enough of free permanganic acid, $HMnO_4$, will be present to participate noticeably in the oxidation and the oxidation rate will therefore increase with increasing acidity. In alkaline solution fluoral hydrate will loose a proton to form the much more reactive anion. As a consequence the reaction is both acid- and base-catalyzed (Figure 1).

In strongly basic solutions all the fluoral hydrate is converted into its monoanion; one should therefore expect the rate to become independent of further changes in basicity of the solution. A small plateau around pH 11 is indeed observed, but as the base concentration is increased further the second ionization sets in to form the highly reactive dianion. It is satisfying to note that this latter change in mechanism is reflected in a predictable change in the activation parameters. The activation enthalpy for the hydrogen transfer of the dianion is considerably smaller than for the monoanion; on the other

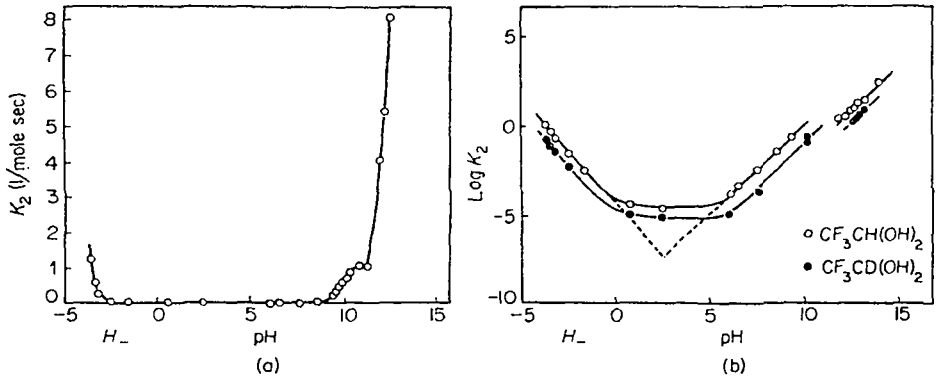


FIGURE 1. (a) Rate of permanganate oxidation of fluoral hydrate as a function of the acidity of the medium. (b) The logarithm of the rate of permanganate oxidation of fluoral hydrate as a function of the acidity of the medium. [Reproduced, by permission, from *Can. J. Chem.*, 41, 1164 (1963).]

hand, the activation entropy is markedly decreased by the introduction of the second negative charge (Table 3).

TABLE 3. Activation parameters for the reaction of fluoral hydrate with the permanganate anion.

Substrate	$\Delta H^{\ddagger}$ (kcal/mole)	$\Delta S^{\ddagger}$ (e.u.)
$CF_3-C(O^-)(OH)-H$	12·4	−18·4
$CF_3-C(O^-)(O^-)-H$	6·6	−31·4

The permanganate oxidation of fluoral hydrate exhibits a clear primary kinetic deuterium isotope effect at all acidities (Table 4). One can therefore conclude that the aldehyde C—H bond is broken in the rate-limiting step under all investigated conditions. The actual magnitude of the isotope effect varies considerably, however, with the acidity of the solution. A particularly high value is observed at pH 7·6; it is about twice as high as that predicted from the difference

TABLE 4. Kinetic isotope effect in the permanganate oxidation of fluoral hydrate at 25°.

Acidity	Principal reactants	k_H/k_D
0·12 M NaOH	MnO_4^-, $CF_3CHO_2^{2-}$	5·1
pH 10·2	MnO_4^-, $CF_3CH(OH)O^-$	10·1
pH 7·6	MnO_4^-, $CF_3CH(OH)O^-$	13·6
44·1% H_2SO_4	$HMnO_4$, $CF_3CH(OH)_2$	6·3

in the zero-point energies of the stretching mode of vibration. No clear explanation of this effect is available, but the observation does not stand isolated: unusually high isotope effects are frequently observed in oxidations of highly fluorinated compounds.

In strongly basic solution the isotope effect is much smaller. This decrease in the isotope effect can well be understood if one remembers that the reacting species under these conditions is the dianion. The dianion is clearly a very reactive intermediate which requires only a small amount of energy to reach the transition state (cf. low value of $\Delta H^{\ddagger}$ in Table 3). In a situation such as this only a moderate degree of bond breaking will be required to reach the transition state, according to Hammond's[64] postulate. The transition state will then resemble the ground state and the C—H bond will be stretched only to a small extent. As a consequence, only a part of the zero-point energy will be lost. The most puzzling feature of Table 4 is, however, the change in the magnitude of the isotope effect from pH 7·6 to pH 10·2 without any evident change in mechanism. No satisfactory explanation has been advanced for this behavior.

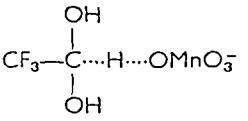
The mechanism of the reaction can best be described in terms of a direct hydrogen transfer between the substrate–oxidant pair as represented in Table 2. Several questions, however, remain undecided. One of them is whether the aldehyde hydrate and the oxidant form an intermediate in a way similar to that envisioned for aromatic aldehydes. Unfortunately, no studies with ^{18}O-labeled permanganate have been published. Also, no attempt has been made to give a detailed account of the fate of the intermediate manganese species formed in the initial process. And most importantly, the mode in which the hydrogen is transferred is open to discussion, as we have seen in all previous instances. Even though the hydride anion transfer would seem by far the simplest and most satisfying solution, there are certain factors which argue against it[63]. The most serious of these is the strange insensitivity of the oxidation rates of the related aryl

trifluoromethyl carbinolate anions, $ArCH(O^-)CF_3$, towards changes in the structure of the aryl group. For example, the *m*-nitro and the *p*-methoxyphenyl alcoholate are equally reactive towards the permanganate anion[65]. However, the edge of this argument is somewhat blunted if we recall that the relative rates of oxidation of $CF_3CH(OH)_2$, $CF_3CH(OH)O^-$, and $CF_3CHO_2^{2-}$ are $1:6 \times 10^3:10^7$.

Recently, an extremely interesting approach to the problem of the nature of the hydrogen transfer has been taken by Kurz, who demonstrated[66] that, as a direct consequence of the transition state theory, the apparent acid dissociation constant of the transition state of a given reaction can be calculated from a pair of rate coefficients for the uncatalyzed and catalyzed reaction. For example, in moderately acid solutions, where the oxidation proceeds through fluoral hydrate and both permanganic acid and the permanganate ion (cf. Table 2), the rate of the oxidation can be expressed by the rate equation (45). Assuming that the reaction proceeds by the same

$$\begin{aligned} v &= k_0[CF_3CH(OH)_2][MnO_4^-] + k_1[CF_3CH(OH)_2][HMnO_4] \\ &= [CF_3CH(OH)_2][MnO_4^-](k_0 + k_1[H^+]) \end{aligned} \tag{45}$$

mechanism in both cases, the structures of the two transition states will differ only in the absence or presence of one proton on the permanganate moiety (**8** and **9**). Even though the two transition



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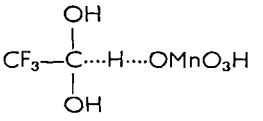


(9)

states are not in direct equilibrium, they are in an indirect equilibrium through their components (permanganic acid and the permanganate ion), and an acid dissociation constant for the transition state can therefore be defined (equation 46), where T^- and TH represent

$$K_a^{\ddagger} = \frac{[T^-][H^+]}{[TH]} \tag{46}$$

the two activated complexes **8** and **9**, respectively. The activated complexes are assumed to be in equilibrium with the reactants, e.g. equation (47).

$$K^{\ddagger} = \frac{[T^-]}{[MnO_4^-][CF_3CH(OH)_2]} \tag{47}$$

The absolute rate theory postulates that a reaction rate depends only* upon the concentration of the activated complex and upon a factor $k^{\ddagger} = kT/h$ which, at any given temperature, is independent of the nature of the reaction. For the reaction under discussion which proceeds through two different activated complexes, the rate will be

$$v = k^{\ddagger}[T^-] + k^{\ddagger}[TH] \tag{48}$$

From equation (46), (47), and (48) it follows that

$$\begin{aligned} v &= k^{\ddagger}[T^-] + k^{\ddagger}[T^-][H^+]/K_a^{\ddagger} \\ &= [MnO_4^-][CF_3CH(OH)_2](k^{\ddagger}K^{\ddagger} + k^{\ddagger}K^{\ddagger}[H^+]/K_a^{\ddagger} \end{aligned} \tag{49}$$

Comparison of equations (45) and (49) will reveal that both of them express the rate of oxidation of fluoral hydrate as a function of the concentrations of the substrate, of the permanganate ions, and of hydrogen ions. Moreover, the form of the two equations is the same, the only difference being in the factors of the variables. A relationship of mathematical identity therefore exists between the two expressions and, as a consequence, the coefficients of the concentration terms must be equal. Hence

$$k_0 = k^{\ddagger}K^{\ddagger}, \qquad k_1 = k^{\ddagger}K^{\ddagger}/K_a^{\ddagger} \tag{50}$$

$$K_a^{\ddagger} = \frac{k_0}{k_1} \quad \text{or} \quad pK_a^{\ddagger} = \log \frac{k_1}{k_0} \tag{51}$$

Equation (51) makes the acid dissociation constant of the activated complex easily accessible. Kurz's procedure of estimating the acidity of the activated complex opens a completely new source of information about the structure of the transition state. As we generally assume the structure and all the properties of the transition state to lie in between that of the starting materials (i.e. substrate plus reagent) and of the products, we will anticipate that also the acidity of the transition state must lie within the limits defined by the respective acidities of the reactants and products. We assume further that the acidity of the transition state will be close to that of the reactants if only very little bond breaking and bond making took place before the transition state has been reached. On the other hand, the acidity of the activated complex should resemble that of the products if the bond-breaking and bond-making process is virtually completed. The acidity of the activated complex allows us therefore to estimate

* Assuming the transmission coefficient to be unity.

quantitatively how far the reaction has progressed along the reaction coordinate. However, should we find that the acidity determined for the transition state is outside the predicted range, we have to conclude that the mechanism on the basis of which the range has been predicted was incorrect.

Let us now apply this approach, as Kurz[67] did, to the permanganate oxidation of fluoral, discussing the two possible modes of hydrogen transfer. The transition state of the acid-catalyzed reaction, TH, differs from that of the uncatalyzed process, T^-, by the presence of a proton on one of the oxygens of an Mn—O bond in TH. It is therefore the acidity of this particular O—H bond which we have to discuss. At the outset of the reaction, before the hydrogen transfer began, the acidity of this hydrogen will be identical with the acidity of permanganic acid. For permanganic acid two widely differing values are available, $-2{\cdot}3$[68] and $-5{\cdot}1$[63], the latter being determined under conditions more closely corresponding to the conditions of the fluoral hydrate oxidation. If the transfer of hydrogen were complete (100% hydrogen transfer), the acidity of the transition state should correspond either to that of $H_2Mn^{VI}O_4$ or of $H_2Mn^{V}O_4$, depending upon whether the reaction proceeds by way of a hydrogen atom or hydride anion transfer. Unfortunately, the pK_a values of neither manganic acid nor of the hypomanganous monoanion are known and one has therefore to resort to estimated values. Assuming that the two species will have similar acidities as chromic acid, H_2CrO_4, and the vanadate monoanion, $H_2VO_4^-$, which they resemble, the pK_a values can be estimated to be $-1{\cdot}0$ for $H_2Mn^{VI}O_4$ and $+9{\cdot}0$ for $H_2Mn^{V}O_4^-$.

The $pK_a^{\ddagger}$ value for the transition state calculated from the rate coefficients for the neutral and acid-catalyzed reaction by Kurz's method is $+0{\cdot}4$. This value fits neatly into the acidity range of -5 to $+9$ predicted for the hydride anion transfer and corresponds to about 40% bond breaking in the transition state. It lies, however, outside of the -5 to -1 range predicted for the hydrogen atom transfer and is thus incompatible with the latter mechanism.

An approach similar to the one outlined above has been used also to compute the second and third dissociation constant of the transition state, using rate coefficients derived from hydroxide ion catalysis. All these calculations agreed in so far as they are suggestive of a mechanism consisting of a hydride anion transfer which is about 30 to 40% completed in the transition state.

Even though this original approach taken by Kurz clearly favors

the hydride transfer mechanism, it must be emphasized that the validity of the conclusion depends upon the correctness of the estimated acidities of the primary products and that the method has, until now, been applied to only a very limited number of reactions.

The conclusion that the permanganate oxidation of aliphatic aldehydes consists of hydride anion rather than hydrogen atom transfer is also supported by Wiberg and Richardson's[47] study of the oxidation of triphenylacetaldehyde. The radical which is formed from this aldehyde by hydrogen atom abstraction is known to be unstable and to lose carbon monoxide readily (equation 52). The

$$(C_6H_5)_3C\underset{\displaystyle H}{\underset{|}{-}}C{=}O \longrightarrow (C_6H_5)_3C-\dot{C}{=}O \longrightarrow (C_6H_5)_3C^{\cdot} + CO \qquad (52)$$

formation of carbon monoxide and of triphenyl carbinol as the only products has also been observed when a typical one-electron oxidant like Ce^{IV} was employed. On the other hand, permanganate oxidation yielded only triphenylacetic acid without any detectable formation of triphenyl carbinol.

V. MANGANIC SALTS

Because the oxidation by permanganate necessarily proceeds through several intermediates containing manganese in different oxidation stages, the role of the latter as oxidizing agents is of considerable interest. Drummond and Waters[69] initiated the investigation of this problem by a study using Mn^{III} in the form of its pyrophosphate as the oxidant. Unlike other forms of trivalent manganese, the pyrophosphate is stable enough to allow a kinetic investigation of the oxidation reactions.

Drummond and Waters[69] found that the manganic pyrophosphate oxidations of both propionaldehyde and n-butyraldehyde are fairly rapid reactions and follow the rate law (53). The rate of oxidation is

$$v = k[\text{aldehyde}][H^+] \qquad (53)$$

thus proportional to the concentration of both the aldehyde and the hydrogen ion, but does not depend upon the concentration of the oxidant as long as enough of it is present. The finding that the oxidation of the aldehydes is of zero order in manganic pyrophosphate clearly indicates that the rate-limiting step is not the oxidation itself

but another reaction which precedes it. On this basis Drummond and Waters suggested the mechanism (54) to (56) in which the rate-

$$RCH_2{-}CH{=}O + H^+ \rightleftharpoons RCH_2{-}CH{=}\overset{+}{O}H \quad (54)$$

$$RCH_2{-}CH{=}\overset{+}{O}H \xrightarrow{\text{Rate-limiting}} RCH{=}CHOH \quad (55)$$

$$RCH{=}CHOH + Mn(H_3P_2O_7)_3 \longrightarrow \text{Products} \quad (56)$$

limiting step is the enolization of the aldehyde. The reaction products have not been investigated, but the formation of α-hydroxy aldehydes is assumed.

Manganic pyrophosphate reacts also with α,β-unsaturated aldehydes[70]. Both acrolein and methacrylaldehyde undergo a fairly rapid oxidation. The reaction is again zero order in the oxidant and the rate-limiting step of the oxidation must therefore be a slow reaction of the aldehyde itself, without participation of the oxidant.

This situation is precisely analogous to that found in the oxidation of saturated aldehydes, where enolization constitutes the rate-limiting step. However, to assume that a simple enolization would play the same role in the oxidation of unsaturated alcohols would appear untenable. First, acrolein would, by enolization, yield hydroxy-allene (equation 57), the formation of which is rather improbable.

$$CH_2{=}CH{-}CH{=}O \rightleftharpoons CH_2{=}C{=}CH{-}OH \quad (57)$$

Moreover, methacrylaldehyde reacts readily although it has no enolizable hydrogen atom at all.

Another reaction which an unsaturated aldehyde could undergo prior to oxidation is the hydration of the double bond to form a β-hydroxy aldehyde (equation 58). This possibility is ruled out by

$$CH_2{=}CH{-}CH{=}O \xrightarrow{H_2O} HO{-}CH_2{-}CH_2{-}CH{=}O \quad (58)$$

the finding that the rate of hydration[71] is much slower than that of oxidation. To solve this dilemma, Land and Waters suggested that the rate-limiting step is the formation of the enol of the hydroxy aldehyde, which is an intermediate in the acid-catalyzed hydration of acrolein (equations 59, 60).

$$CH_2{=}CH{-}CH{=}O \overset{H^+}{\rightleftharpoons} CH_2{=}CH{-}CH{=}\overset{+}{O}H \longleftrightarrow \overset{+}{C}H_2{-}CH{=}CH{-}OH \quad (59)$$

$$\overset{+}{C}H_2{-}CH{=}CH{-}OH \xrightarrow[-H^+]{H_2O} HO{-}CH_2{-}CH{=}CH{-}OH \xrightarrow{Mn^{III}} \text{Products} \quad (60)$$

Rate-determining

This very plausible interpretation requires, however, that the

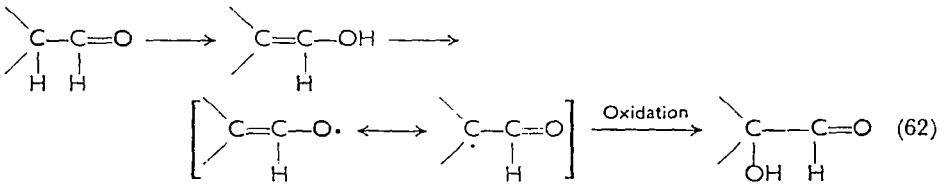
mechanism[71] of the hydration of acrolein be modified. The rate-limiting step for the hydration, which is much slower than the oxidation, then evidently must come later and must therefore consist in the addition of a proton to the hydroxy enol. This means that the ketonization of the enol and not the addition of the water molecule, as has been assumed previously, governs the overall rate of hydration. As an interesting consequence of the principle of microscopic reversibility, it follows that the enolization should be the rate-limiting step in the dehydration of a β-hydroxy aldehyde (equation 61).

$$HO{-}CH_2{-}CH_2{-}CH{=}O \overset{\text{Slow}}{\rightleftharpoons} HO{-}CH_2{-}CH{=}CH{-}OH \overset{\text{Fast}}{\rightleftharpoons} CH_2{=}CH{-}CH{=}O \quad (61)$$

The oxidation of crotonaldehyde[70] is faster than that of acrolein and becomes zero order in manganic pyrophosphate only at higher concentrations of the oxidant. The implication is that the mechanism of the reaction is the same, but the relative rate of oxidation to other reactions of the hydroxy enol intermediate is less favorable.

It follows from the above discussion that the manganic pyrophosphate oxidations of both saturated and unsaturated aldehydes proceed basically by the same mechanism—by a rapid oxidation of an enol which is formed in a slow step. The correctness of this mechanism is strongly supported by the unreactivity of nonenolizable aldehydes, formaldehyde and chloral, towards manganic pyrophosphate oxidation.

The exact fate of the enol intermediate in the oxidation is not known. Drummond and Waters[72] have expressed the opinion that the oxidation of aldehydes proceeds by the mechanism (62). Here a



(62)

hydrogen atom is lost from the hydroxy group of the enol to give a mesomeric radical. The free radical subsequently undergoes further oxidation. Supporting this interpretation is the fact that the oxidation of aldehydes via enol intermediates is found frequently with typical one-electron oxidants.

There is, on the other hand, a very serious objection to the above

mechanism. The free radical formed in the reaction is certainly a very reactive, unstable species despite its resonance stabilization. It is therefore to be expected that the transition state of the reaction will resemble this free radical very closely. Now, the very same mesomeric radical can be formed directly from the aldehyde by breaking

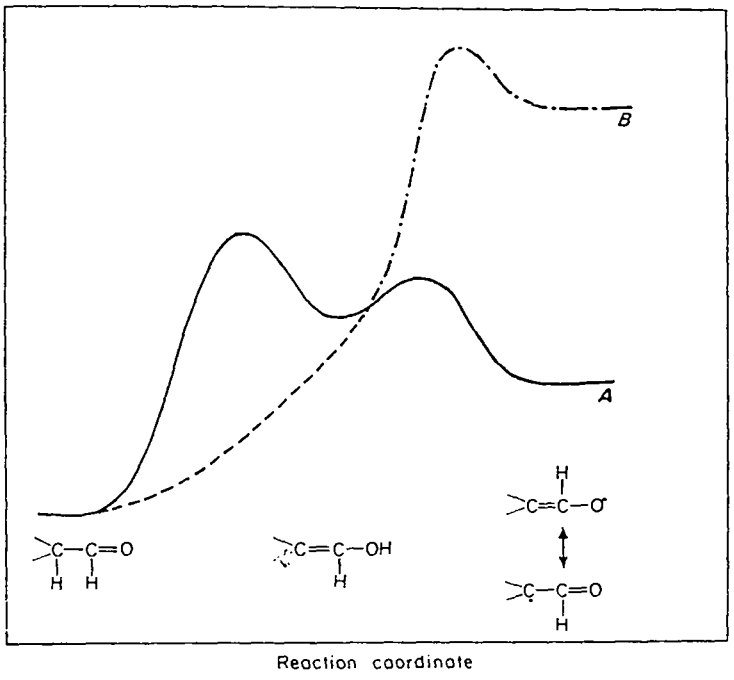


FIGURE 2. Different types of energy profiles for the oxidation of aldehyde R_2CHCHO to radical $R_2\dot{C}CHO$.

———— oxidation via enol with rate-limiting enolization to give radical of low energy as required by Drummond and Waters
– – – – – and ———— direct oxidation to form the same radical
———— and —·—·— formation of radical of high energy via enol

exactly the same C—H bond which has to be broken in the enolization step. If the energy of the free radical (and hence the energy of the transition states leading to it) is indeed lower than the energy of the enol (Figure 2, curve *A*)—and this is exactly the situation required for a rate-limiting enolization—then a direct hydrogen atom abstraction from the aldehyde should have a lower activation energy than the enolization and represent therefore the preferred route. If, on the other hand, the energy of the free radical is higher than that

of the enol (curve *B*), then the reaction might well proceed via the enol, but the actual oxidation step would be rate-limiting. The argument remains unchanged if the oxidation of the enol is assumed to proceed not directly but through an enolate anion with which the enol is in rapid equilibrium[73,74].

In the light of this analysis it seems much more likely to the present author that the oxidation of aldehydes takes place by an (probably electrophilic) attack at the double bond of the enol. It seems probable that this reaction consists of an addition of an oxygen atom in some form. Unfortunately the data which are available at present are insufficient for a detailed discussion.

Formaldehyde, which cannot form an enol, is unreactive towards manganic pyrophosphate. Kemp and Waters[75] showed, however, that the oxidation of formaldehyde can be achieved with manganic sulfate, a much more powerful oxidant which is stable only in rather acidic solutions. Measurements carried out in 0·3 to 3·5 molar sulfuric acid showed that the reaction rate is first-order in formaldehyde, slightly more than first-order in manganic sulfate, and does not depend upon the acidity of the solution. The oxidation of formaldehyde is slow and resembles that of alcohols. No details about the reaction mechanism are known.

No studies of oxidation of enolizable aldehydes with manganic sulfates have been published. It has been demonstrated, however, that manganic sulfate is able to oxidize ketones much faster than they undergo enolization[76]. It is therefore only natural to assume that the same should hold for the oxidation of aliphatic aldehydes. This leads to an interesting conclusion. It seems that the mechanism of oxidation may depend more on other properties of the oxidant than on its tendency to act as a one-electron or two-electron acceptor. In the case of aldehydes (and ketones) the less effective oxidant (e.g. manganic pyrophosphate) is able to react only with the enol, whereas the more powerful oxidant can react directly with the aldehyde. The important difference between the two species may be either their oxidative power (oxidation potential) or their availability for complex formation with the aldehyde.

VI. VANADIUM(V)

Vanadium(v) as an oxidant has been widely investigated by Waters[77,78] and his school. He and his coworkers have shown that the oxidation generally proceeds to the tetravalent vanadium stage

and generates free radicals which are able to initiate polymerization reactions or reduce mercuric ions. From all the amassed evidence it seems very likely that the oxidations proceed as one-electron transfer reactions.

The reactivity of aldehydes depends greatly upon their structure. The simplest situation was found for isobutyraldehyde, which undergoes a rapid oxidation which is zero-order in the oxidant[79]. The rate of oxidation is identical to the rate of enolization as determined, for example, by bromination. This situation is analogous to the previously discussed oxidation of aliphatic aldehydes by manganic pyrophosphate.

$$(CH_3)_2CH{-}CHO \xrightarrow{\text{Slow}} (CH_3)_2C{=}CHOH \tag{63}$$

$$(CH_3)_2C{=}CHOH \xrightarrow{VO_2^+} \text{Products} \tag{64}$$

For the straight-chain aldehydes[79], propionaldehyde and n-butyraldehyde, the oxidation is approximately first order in the pervanadyl ion, VO_2^+. The oxidation is slower than the rate of enolization and the available kinetic data do not permit one to decide whether the oxidation proceeds by way of the enol or by direct oxidation of the aldehyde. It seems, however, reasonable to assume that the mechanism of oxidation of all enolizable aliphatic aldehydes is the same. This is probably true also for acetaldehyde, which exhibits a much lower reactivity than its homologs.

The oxidation through the enol is, of course, impossible for chloral and formaldehyde. Consequently, both are very unreactive[77]. Formaldehyde, however, can be oxidized under rather drastic conditions. Bobtelsky and Glasner[80] studied its oxidation in sulfuric acid (1·8 to 9·0 M) and in hydrochloric acid (5·1 to 6·9 M); Kemp and Waters[33] investigated the range between 0·9 to 4·9 M perchloric acid.

In 4·9 M perchloric acid the oxidation of formaldehyde has a primary kinetic isotope effect of about 4·6, indicating that the C—H bond is broken in the rate-limiting step. The reaction is clearly acid-catalyzed, but the nature of acid catalysis is complicated and no simple rate equation properly describing the whole investigated area has been suggested. The order in vanadium seems to rise from one to two. The oxidation is first-order in formaldehyde at lower acid concentrations, but at very high acidities the rate becomes independent of the formaldehyde concentration.

The very complex chemistry of vanadium makes a definite interpretation of the data difficult. It seems, however, clear that VO_2^+ itself is not a sufficiently strong oxidant to bring about the oxidation of formaldehyde and that the formation of a more reactive species like $V(OH)_3^{2+}$ is required. Moreover, the second-order dependence upon vanadium concentration indicates either the combination of two vanadium atoms with the two hydroxyl groups of formaldehyde hydrate or, more likely, the oxidation by a more active dimer. Finally, the zero-order dependence upon substrate concentration at high acidities indicates intervention of still another oxidizing species which is formed in a rate-limiting step.

VII. CERIUM(IV)

Cerium(IV) is a one-electron oxidant. Its oxidative power depends very largely upon its state in solution. In perchloric acid the Ce^{4+} ion is present more or less free[81], associated only with water to some extent. On the other hand cerium(IV) sulfate is very highly complexed with the sulfate anion. The equilibrium constant for reaction (65)[82]

$$Ce^{4+} + HSO_4^- \rightleftharpoons CeSO_4^{2+} + H^+ \qquad (65)$$

is 3500; free Ce^{4+} is therefore practically absent in the presence of sulfate anions. Moreover, even the complex formed from the Ce^{4+} ion and one sulfate anion undergoes further complexations with sulfuric acid according to the equations (66) and (67), the equilibrium constants of which are 200 and 20, respectively.

$$CeSO_4^{2+} + HSO_4^- \rightleftharpoons Ce(SO_4)_2 + H^+ \qquad (66)$$

$$Ce(SO_4)_2 + HSO_4^- \rightleftharpoons Ce(SO_4)_3^{2-} + H^+ \qquad (67)$$

In agreement with the different nature of the cerium ions in solutions of different acids the oxidative properties of cerium vary greatly. In the oxidation of formaldehyde[83], the only aldehyde for which the oxidation has been investigated in some detail, the reaction proceeds about 10^4 to 10^5 times faster in perchloric acid than in sulfuric acid. Moreover, even the nature of the rate equation for the two systems varies considerably: the reaction is almost independent of acid concentration if cerium perchlorate is used, but increases very rapidly with the concentration of sulfuric acid if ceric sulfate has been employed as the oxidant. Actually, the acidity dependence is so strong that a third-order dependence on sulfuric

acid concentration has been postulated. It is well possible that acid catalysis is only apparent and does not indicate a transition state containing a proton, but reflects only changes in the concentration of the various cerium species present in the solution.

Only a few isolated data are available concerning the oxidation of higher aldehydes. Conant, Aston, and Tongsberg[84] observed that isobutyraldehyde is oxidized at the α-position to the carbonyl rather than at the carbonyl group itself (equation 68). This seems to

$$(CH_3)_2CH{-}CHO \longrightarrow (CH_3)_2\underset{\displaystyle OH}{\underset{|}{C}}{-}CHO \qquad (68)$$

indicate that the reaction proceeds through an enol intermediate. This finding is in agreement with the work of Shorter[85] who investigated the oxidation rates of acetaldehyde and of several ketones with ceric sulfate. The oxidation rate of acetaldehyde is only slightly faster than that of simple aliphatic ketones, making the assumption that both groups of carbonyl compounds are oxidized by the same mechanism well acceptable.

Wiberg and Richardson[47] used cerium sulfate in the oxidation of triphenylacetaldehyde, an aldehyde which cannot undergo enolization. They found that the only reaction products were triphenylcarbinol and carbon monoxide, a reaction which indicates a free-radical mechanism.

$$(C_6H_5)_3C{-}CH{=}O \xrightarrow{Ce^{IV}} (C_6H_5)_3C{-}\dot{C}{=}O \longrightarrow (C_6H_5)_3C^{\cdot} + CO \qquad (69)$$

$$(C_6H_5)_3C^{\cdot} \xrightarrow{Ce^{IV}} (C_6H_5)_3COH \qquad (70)$$

VIII. COBALTIC SALTS

Cobaltic salts are very strong oxidizing agents (cf. Table 5). The

TABLE 5. Oxidation–reduction potentials in acid solutions[86].

Couple	E^0
V^{IV}/V^{V}	−1·00
Mn^{II}/Mn^{III}	−1·51
Ce^{III}/Ce^{IV}	−1·61
Co^{II}/Co^{III}	−1·82

hexaaquo ion $Co(H_2O)_6^{3+}$, which is the predominant form of Co^{III} in solutions of strong noncomplexing acids, is unstable and oxidizes not only a large variety of organic compounds[87] but even water[88]. The instability of aqueous solutions increases with an increase in the pH of the solution. Studies of oxidations by cobaltic salts have therefore generally been carried out in very strongly acidic solutions.

Cobaltic ions are prone to complex formation and will form a complex even with sulfate ions[89]. Oxidation rates are therefore generally lower in sulfuric acid than in perchloric acid[90], but the effect is not very large and by far not as dramatic as in the previously discussed oxidations with ceric salts.

The oxidation of formaldehyde has been studied by several groups of investigators. The reaction product[91] is formic acid; the oxidation of formic acid is about 100 times slower[92] than that of the aldehyde. Bawn and White[93], who studied the oxidation in sulfuric acid, found the reaction to be of complex order in the oxidant and suggested the rate equation (71).

$$v = \frac{k_1[Co^{3+}]^2\,[CH_2O]}{A + k[Co^{3+}]} \tag{71}$$

Hargreaves and Sutcliffe[91] found that in perchloric acid the reaction is first-order in both the substrate and the oxidant, but that the reaction rate decreased markedly with increasing acidity of the solution even though constant ionic strength was maintained.

The decrease in the rate of oxidation with increasing acidity makes the oxidation with cobaltic salts different from all the other oxidation reactions discussed in this chapter until now. It is, however, a phenomenon very typical for this oxidant. We have mentioned before that the rate of oxidation of water by cobaltic ions is diminished if the acidity is decreased. The rate of decomposition of cobaltic perchlorate in aqueous solutions is actually about 30 times higher[88] at pH 1·0 than at pH 0·1. The well-investigated oxidation of alcohols shows a similar effect. Cyclohexanol[94] reacts with cobaltic perchlorate 14 times faster in 0·325 than in 3·4 M $HClO_4$ (at constant ionic strength). A similar effect is observed in the oxidation of diethyl ketone[95] which is oxidized 13 times faster in 0·325 than in 5·3 M $HClO_4$. Very much the same pattern is repeated in the oxidation of formic acid[92] and even in the oxidation of inorganic ions such as[96] Cr^{2+}. Actually, a decrease in reaction rate with increasing acidity is typical for many inorganic redox reactions[97].

In the cobaltic perchlorate oxidation of formaldehyde the reaction

rate decreases by a factor of less than three[91] when the acid concentration is raised from 1·0 to 6·0 M. It is well to keep in mind that this actually represents an increase of acidity by a factor of more than 30 if expressed in h_0 units[20,98].

Even though there is little doubt that a decrease in the rate of oxidation with increasing acid concentration exists, its exact nature is less clear. Hargreaves and Sutcliffe[91] propose the relationship (72)

$$1/k = a + b[H^+] \tag{72}$$

for describing the variations of rate with acidity. Hoare and Waters express their results in the closely related oxidation of alcohols[94] in two different forms, (73) and (74), whereas the same group of

$$k = a/[H^+] + b/[H^+]^2 \tag{73}$$

$$k = a + b/h_0 \tag{74}$$

authors uses the relation (75) for the cobaltic perchlorate oxidation

$$k = a + b/[H^+] \tag{75}$$

of diethyl ketone[95]. Bawn and White[88] use for the oxidation of water the expression (76).

$$k = a/[H^+]^n \tag{76}$$

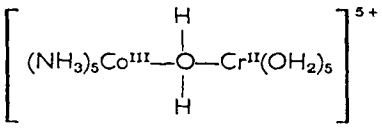
The very carefully investigated inorganic oxidation reactions by cobaltic ions seem to obey uniformly the expression (77). A similar

$$\text{Rate} = k_1[S][Co^{3+}] + k_2[S][Co^{3+}]/[H^+] \tag{77}$$

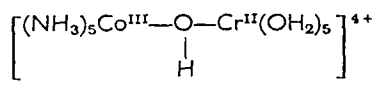
type of acidity dependence is also observed for many other oxidations by transition metal cations and is, indeed, typical and probably diagnostic for a group of reactions which proceed by way of a bridged activated complex[97]; e.g. the oxidation of chromous salts by $(NH_3)_5Co(OH_2)^{3+}$ follows the rate law (78), the two terms of

$$\text{Rate} = [Cr^{2+}][(NH_3)_5Co(OH_2)^{3+}]\left(k_1 + \frac{k_2}{[H^+]}\right) \tag{78}$$

which represent the two bridged intermediates **10** and **11**. In a 2 M solution of perchloric acid the two terms of the rate equation are of



(10)



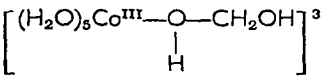
(11)

about the same magnitude[99]. Because the cobaltic ion is a very weak acid the concentration of the intermediate **11** will be very small and its reactivity therefore must be extremely high to be observable; it is estimated that the oxidation process through intermediate **11** is about 10^8 times faster than through its conjugated acid **10**. It is significant to realize at this point that the oxygen of the bridge stays with the chromium ion; hence the Co—O bond is broken in the transition state[96].

It seems most unlikely that oxidation reaction involving one oxidant in the same or in closely related forms could be governed by as many rate laws as indicated above. It is much more probable that all of them represent different approaches and approximations to describe the same basic type of behavior, namely that of a reaction where the rate decreases in a not-quite-straightforward way with increasing acidity. In the present author's opinion it seems likely that the expression derived for the carefully studied oxidations of inorganic salts represents most probably the best description of the acidity dependence. It can be shown, for example, that Hargreaves and Sutcliffe's data for formaldehyde give a fairly good straight line if replotted to fit equation (75), which has the same form as (78).

The observed decrease in rate with increasing acidity was interpreted by Hargreaves and Sutcliffe[91] as due to the protonation of formaldehyde to give an unreactive cation, whereas Hoare and Waters[90] prefer to assume that $(H_2O)_5Co(OH)^{2+}$ is a stronger oxidant than $Co(OH_2)_6^{3+}$. The first explanation would require formaldehyde to be a rather strong base which would be extensively protonated in 1 M perchloric acid. Even though the basicity of formaldehyde is not known, it seems unlikely that it should be a much stronger base than simple aliphatic alcohols which under comparable conditions are protonated only to a very small extent[100].

The second explanation, even though formally in full agreement with the rate equation, seems to contradict, at least formally, the general experience that of two similar species the one having the higher positive charge is the stronger oxidant. It can, however, be reformulated to represent the reaction as proceeding through two bridged intermediates analogous to those proposed for oxidation of inorganic ions (**12** and **13**).



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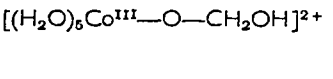


(13)

It is fully justified to assume that the Co—O bond rather than the O—C bond is broken in the transition state of the reaction. The two transition states will therefore differ by a proton in the *substrate part.* Visualized in this way the reaction then follows the usual pattern in which the substrate with the lower positive or higher negative charge is the more reactive one.

The first reaction product formed in the rate-limiting decomposition of the bridged intermediate then should be a free radical $HOCH_2O\cdot$ or its conjugate acid (equation 80). This radical will then undergo a rapid reaction and reduce another cobaltic ion (equation 81). This mechanism would not involve the breaking of a

$$Co(OH_2)_6^{3+} + CH_2(OH)_2 \rightleftharpoons [(H_2O)_5Co{-}O{-}CH_2OH]^{3+} \quad (79)$$

$$\left.\begin{array}{l} \left[(H_2O)_5Co^{III}{-}O{-}\underset{\displaystyle H}{\underset{|}{C}}H{-}OH\right]^{3+} \rightleftharpoons [(H_2O)_5Co^{III}{-}O{-}CH_2OH]^{2+} + H^+ \\ \downarrow \qquad\qquad\qquad \downarrow \\ Co^{II} + \cdot\overset{+}{O}{-}\underset{\displaystyle H}{\underset{|}{C}}H{-}OH \qquad Co^{II} + \cdot O{-}CH_2OH \\ \cdot\overset{+}{O}{-}\underset{\displaystyle H}{\underset{|}{C}}H{-}OH \rightleftharpoons H^+ + \cdot O{-}CH_2OH \end{array}\right\} \quad (80)$$

$$Co^{III} + \cdot O{-}CH_2OH \longrightarrow Co^{II} + HCO_2H + H^+ \quad (81)$$

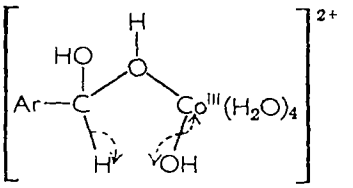
C—H bond in the rate-limiting step and only a small secondary kinetic isotope effect should be expected in the oxidation of deuteroformaldehyde. This was actually confirmed by Kemp and Waters[33] who found k_H/k_D to be only 1·54 for dideuteroformaldehyde. The isotope effect corresponding to the replacement of only one C—H bond by a C—D bond then is $(1{\cdot}54)^{\frac{1}{2}}$ or 1·24 which is in the range of values observed for secondary isotope effects[101].

There is, however, one fact which indicates that the mechanism must be more complicated than outlined. Formaldehyde is oxidized about 17 times faster than ethanol[102]. This is hard to interpret in terms of changes in stability of the R—O· radical and other effects have therefore to be taken into consideration. One reason for the high reactivity of formaldehyde could be that a C—H bond is partially broken despite the small isotope effect. Another explanation could be sought in a change in the equilibrium constant of reaction (82). Because the overall oxidation rate depends upon both the

$$Co(OH_2)_6^{3+} + ROH \rightleftharpoons (H_2O)_5Co(ROH)^{3+} + H_2O \quad (82)$$

equilibrium concentration as well as on the rate of decomposition of the substrate–oxidant complex, a shift to the right in equilibrium (82) would lead to an increase in rate of oxidation. A higher degree of complex formation is a fair possibility for formaldehyde hydrate which, owing to its two hydroxy groups, could actually replace two water molecules in the solvation shell and form thus a tighter complex with the cobaltic cation.

The oxidation of several aromatic aldehydes was investigated recently by Cooper and Waters[103]. The oxidation is considerably faster than the oxidation of formaldehyde and probably involves the formation of a ArĊ=O radical. In accordance with that, an isotope effect $k_H/k_D = 2{\cdot}3$ has been found for the oxidation of *m*-nitrobenzaldehyde. The rather surprising feature in this reaction is that aldehydes with electronegative substituents, such as nitro groups, are more reactive than benzaldehyde itself. To accommodate these results Cooper and Waters suggested several possible structures of the transition state, one of which (**14**), being derived from a hydrated



(**14**)

form of the aldehyde, seems particularly attractive. This transition state not only is able to explain the greater rates for those aldehydes which form more stable hydrates, but retains also the type of the oxygen-bridged intermediate which allows one to understand the increase of reaction rate with decreasing acidity of the same type as has been discussed in detail for formaldehyde.

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The Chemistry of the Carbonyl Group
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CHAPTER 11

Reduction of carbonyl groups

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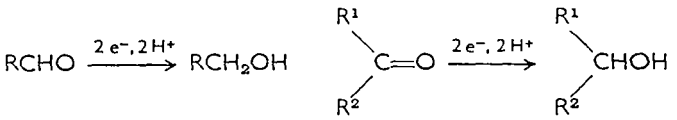
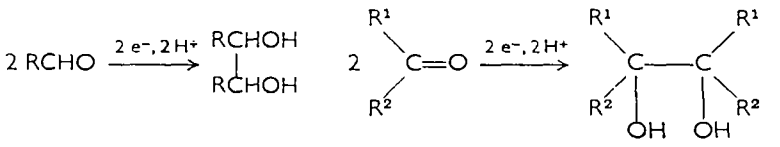
I. INTRODUCTION

The reduction of the carbonyl group in an aldehyde or ketone by a process involving two electrons (and two protons) per molecule results in the formation of a primary or secondary alcohol. These *unimolecular reductions* can be carried out by catalytic reduction (section II) or reduction accompanying the dissolution of a metal (section III), in either acid or basic solution.

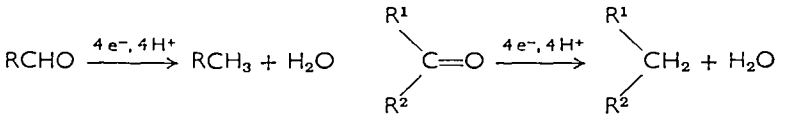


The addition of one electron (and one proton) per molecule of carbonyl compound, accompanied or followed by dimerization (*bimolecular reduction*), leads to a pinacol. This occurs under certain

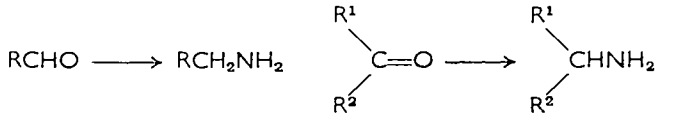
conditions in *dissolving metal* reductions (section III) or in *electrochemical* reduction (section IV).



A saturated hydrocarbon is formed by the addition of four electrons (and protons) per molecule with elimination of the carbonyl oxygen atom. Such a reaction can be brought about by dissolving metals (*Clemmensen reduction*, section III) or in electrochemical reduction at high overvoltage (section IV).

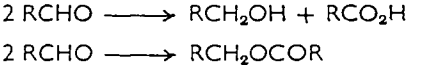


The oxygen atom of the carbonyl group can also be replaced by nitrogen in a unimolecular reaction forming primary amines (section

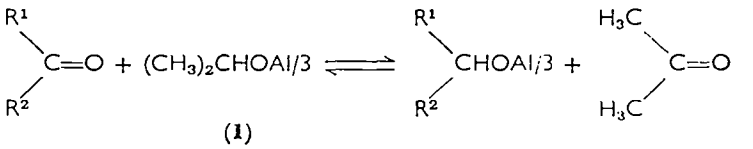


V). The reaction can be carried out by catalytic reduction in the presence of ammonia, or chemically in the *Leuckart* reaction, including the *Eschweiler–Clarke* modification.

A number of reactions are known in which a carbonyl group is reduced by an *organic compound*, the latter being itself oxidized (section VI). The organic reagent can be a second molecule of the carbonyl compound, as in the *Cannizzaro* reaction, which results in the formation of an aldehyde and acid. In the related *Tishchenko*

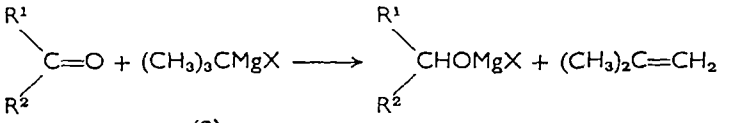


reaction the product is an ester. More commonly, the reducing reagent is an organometallic compound, such as aluminum isopropoxide (**1**) used in *Ponndorf–Meerwein–Verley* reductions. The



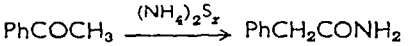
(**1**)

reaction of a sterically hindered *Grignard reagent* (e.g. **2**) with a carbonyl group can also lead to reduction of this group, accompanied by the formation of an olefin from the Grignard reagent. The



(2)

Willgerodt reaction is also treated in this section, since it formally involves the reduction of a carbonyl to a methylene group with simultaneous oxidation of a terminal methyl group to an amide (**3**).

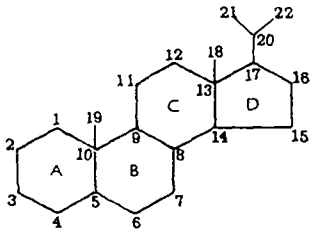


(3)

Within the last twenty years, a number of *metal hydrides* have been introduced (section VII) for the reduction of a carbonyl group to a carbinol, and in certain cases to a hydrocarbon. The last section (VIII) covers miscellaneous methods for reducing carbonyl groups by *biochemical* or *photochemical* means, or under the effect of ionizing radiation (x- or γ-rays); also included are a number of reductions of simple derivatives of a carbonyl group, such as the *desulfurization* of thioacetals and thioketals, the *Wolff–Kishner reduction* of hydrazones and similar compounds, and the *Bamford–Stevens reaction* of hydrazine tosylates.

During the reduction of a carbonyl group, other adjacent groups may suffer reaction. Thus α,β-unsaturated carbonyl compounds are often reduced at the carbon–carbon double bond in addition to, or instead of, reduction of the carbonyl group. A labile group, such as bromo or acetoxy, α to the carbonyl group, may also be eliminated. These various possibilities are considered in relation to each of the general methods of reduction.

The recent advances in the field of carbonyl reductions have been



(4)

in connection with the development of new and often selective methods of reduction, and the study of the *stereochemistry* (section VII) and mechanism of these reactions. Many of these studies have been carried out with steroid ketones. The lettering of the steroid rings and the numbering of the carbon atoms are given in **4** for reference, as partial formulas are often used in this chapter. The literature has been covered, as far as possible, up to May 1964.

II. CATALYTIC REDUCTION

The simplest method of reducing a carbonyl group is with gaseous hydrogen in the presence of a metal catalyst. Reduction occurs by means of the hydrogen chemisorbed on the metal surface.

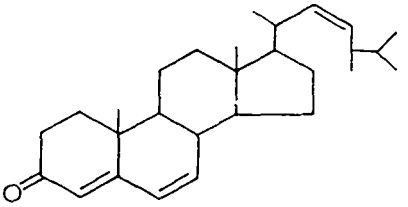
Active catalysts such as Adams' platinum oxide may result in the reduction of an aromatic ring conjugated to a carbonyl group, acetophenone giving ethylbenzene (30%) as well as phenyl methyl carbinol. Rhenium black, however, is less reactive and more selective, affording only the carbinol even at high pressure (> 150 atm) and temperature (100°)[1]. Dimerization does not usually occur in catalytic hydrogenation, although benzaldehyde is reduced by a tungsten sulfide (WS_2) catalyst (at 320° and 100 atm) to dibenzyl ($PhCH_2CH_2Ph$) (58%) as well as to toluene (25%)[2].

A comparative study[3] of the reduction of α,β-unsaturated ketones using the platinum-group metals supported on a carbon surface has shown that a palladium catalyst is ineffective, that platinum is effective in acid but not in basic solution, while ruthenium and rhodium catalysts give rapid reduction in neutral or basic solution and slow reduction in the presence of acid; in all cases the carbon–carbon double bond is preferentially reduced. For aromatic ketones, palladium is more selective in reducing the carbonyl group of acetophenone, whereas rhodium is most effective in also reducing the ring to give cyclohexyl methyl carbinol. Palladium is ineffective in reducing saturated ketones, probably due to their strong adsorption on the catalyst. Such ketones are readily reduced with platinum in aqueous acid, although this catalyst is easily poisoned in basic or neutral solution.

The nature of the catalyst support can affect its ability for reduction. Palladium on strontium carbonate reduces benzylideneacetone ($PhCH{=}CHCOCH_3$) to 4-phenyl-2-butanone ($Ph(CH_2)_2COCH_3$), whereas palladium on charcoal gives styryl methyl carbinol ($PhCH{=}CHCHOHCH_3$)[4]. A recent study[5] has shown that sub-

stances present in the solvent can modify a palladium–charcoal catalyst. The rate of reduction of the carbon–carbon double bond of mesityl oxide in ethanol is decreased to 70% by small amounts of potassium hydroxide. Triphenylphosphine and its oxide inhibit reduction, whereas amines decrease the rate to one-third. Chloride ion produces no change in rate, but bromide and iodide ion reduce the rate to two-thirds and one-fiftieth, respectively. The effectiveness of inhibition of reduction is in the order of the relative affinities of the additives as ligands for palladium.

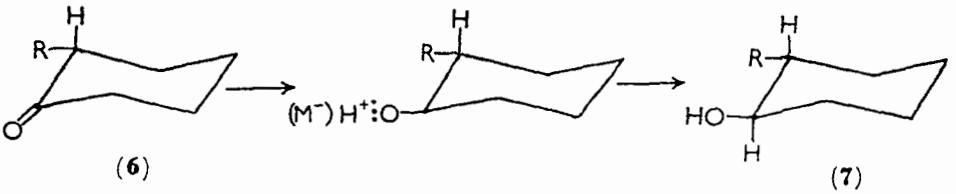
In the steroid field palladium in a neutral solvent, such as ethanol or dioxane, reduces isolated double or triple bonds before the double bond[6] of a conjugate Δ^4-3-keto system. However, a kinetic study[7] of the reduction of 4,6,22-ergostatrien-3-one (**5**) in methanol showed



(**5**)

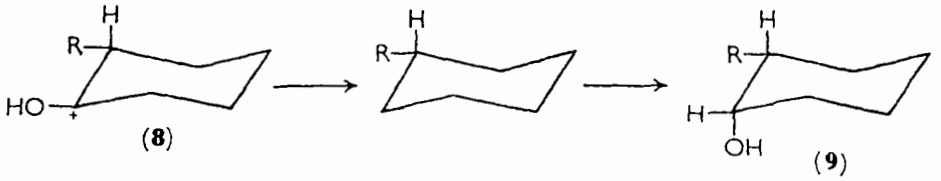
that the reaction is zero order at constant hydrogen pressure and appears to be controlled by the diffusion of the steroid to the catalyst surface. The 6,7-double bond is reduced first followed by the 4,5-double bond, and the addition of alkali favored the formation of the 4,22-dienone. Although conjugated ketones are less readily reduced, carbonyl groups can generally be protected from catalytic reduction in neutral solution by converting them into their ketals[8].

In the case of a cyclic ketone, the addition of hydrogen can occur from either side of the ring to give two isomeric alcohols[9]. Generally, catalytic reduction in neutral (or alkaline) solution affords largely the more stable (equatorial) carbinol, whereas in acid solution the less stable (axial) carbinol predominates[9]. This difference has been rationalized by Brewster[10] as due to 'direct' reduction in neutral solution by the transfer of electrons directly from the metal surface accompanied by protonation. Thus a 2-alkylcyclohexanone (**6**) is reduced to a *trans*-2-alkylcyclohexanol (**7**) (hydroxyl equatorial), the bulky metal surface being coordinated in an equatorial conformation with the oxygen atom in the intermediate. In acid solution the



(6) (7)

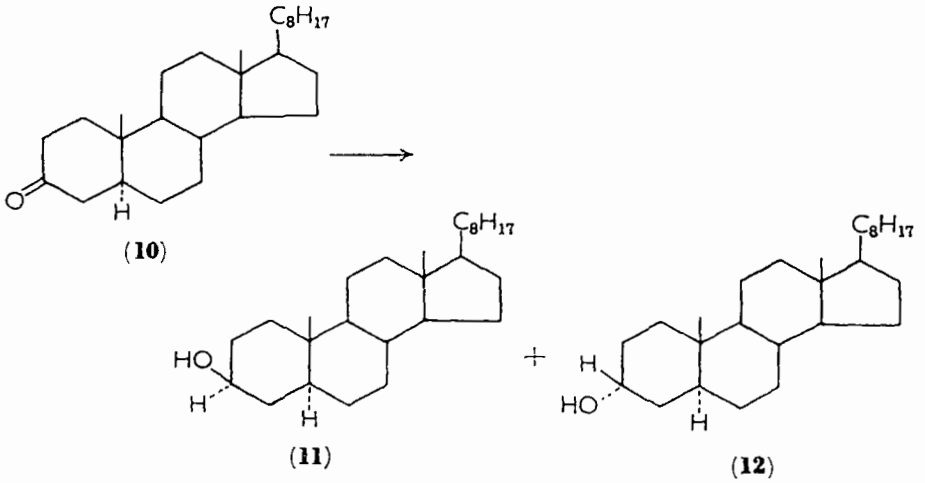
ketone group is protonated (**8**) and the metal surface with its chemisorbed hydrogen can now only coordinate with the carbon atom of the carbonyl group giving the *cis*-2-alkylcyclohexanol (hydroxyl axial) (**9**). In accord with this, 3-cholestanone (**10**) is



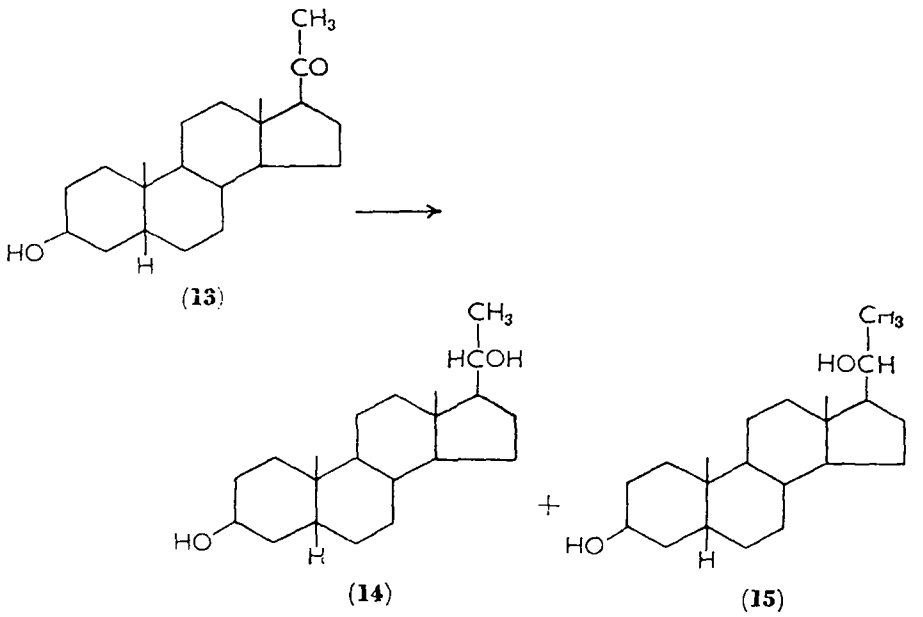
(8) (9)

reduced in alkaline or neutral solution mainly to 3β-cholestanol (**11**), whereas epi-(3α)-cholestanol (**12**) is predominately formed in acid solution[9]. Also, 3α-hydroxypregnan-20-one (**13**) with a nickel catalyst in alkaline or neutral solution affords 3α,20α- (**14**) and 3α,20β- (**15**) pregnanediols in the proportion of 2:1, and the same diols with platinum in acetic acid, but in the proportion of 1:2[11].

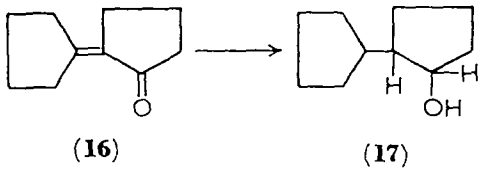
The hydrogenation of cyclopentylidenecyclopentanone (**16**) in the



(10) (11) (12)

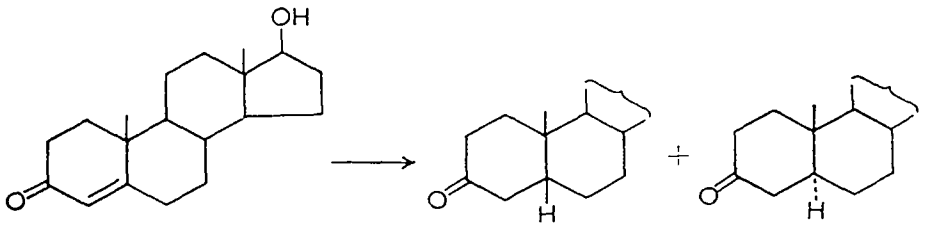


presence of Raney nickel gives a 71% yield of *cis*-2-cyclopentylcyclopentanol (**17**), while reduction with a platinum catalyst in acetic and hydrochloric acid gives a larger proportion of *trans*-carbinol (60% *cis*)[12]. With a calcium carbonate-supported palladium catalyst, only the carbon–carbon double bond is reduced to give 2-cyclopentylcyclopentanone.



The relative amounts of 5β (**19**) and 5α (**20**) derivatives formed on reducing the Δ^4-double bond in cholest-4-en-3-one and testosterone (**18**) have been studied in detail[5]. In methanol the ratios are 8 and 1·7 for the two ketones, increasing to 10 and 3·1 on addition of 1% potassium hydroxide and decreasing to 3·8 and 1·5 with 1% sulfuric acid. In acetic acid the ratios are 5·7 and 1·2, respectively, 2·9 and 1·0 in dioxane, and 2·4 and 0·7 in hexane. A basic catalyst such as

palladium on Dowex-1 (a quaternary ammonium hydroxide resin) gives ratios of 3·8 and 1·5, whereas an acidic catalyst such as palladium on Dowex-50 (a sulfonated resin) gives ratios of the saturated ketones of 0·8 and 0·6. The fact that a 5β compound is formed preferentially in basic hydroxylic media whereas the 5α isomer is formed in increasing amounts in acid or less polar media was explained as being due to effects in the polarization of the conjugated carbonyl system. In less polar solvents or in acid solution the



(18) (19) (20)

'decoupling' of the double bond (C=C—C=O) reduces the rigidity of the molecule and allows it to assume the more stable *trans* configuration on the catalyst surface, resulting in the formation of the more stable 5β compound. This decoupling is not possible in basic or polar solvents so that absorption and subsequent reduction can occur from either side of the molecule.

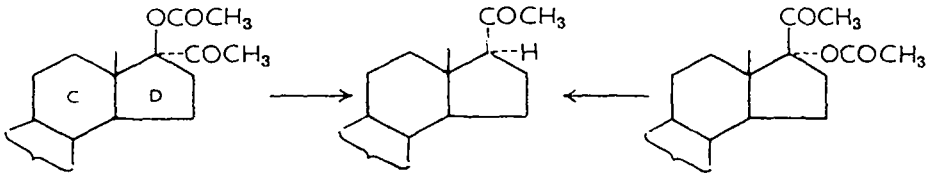
The *transfer of hydrogen* from cyclohexene catalyzed by palladium does not normally reduce a carbonyl group[13], and the carbon–carbon double bond of an α,β-unsaturated carbonyl compound, unlike that of an α,β-unsaturated acid, is not reduced. However, benzil (PhCOCOPh) is slowly reduced to benzoin (PhCOCHOHPh).

Catalytic reductive methylation has been reported[14]. Cholestanone on hydrogenation in methanol with platinum oxide in the presence of hydrobromic acid forms cholestanyl methyl ether (β-configuration). However, reduction in ether with hydrogen bromide gives epi-(α)-cholestanol. This reaction has recently been shown to apply generally for ketones in alcoholic solution[15]. Acetone is reduced to diisopropyl ether in isopropanol, and cyclohexanone to cyclohexyl methyl ether in methanol solution, in yields of 95 and 46%, respectively. Alcohols and alkanes are formed as by-products. The reaction may proceed through a hemiketal or ketal, since ketals are known to be reduced to ethers and alcohols.

III. REDUCTION BY DISSOLVING METALS

The electrons released when a metal dissolves in acid, neutral, or basic solution can reduce a carbonyl group to a variety of products.

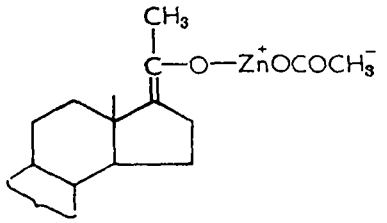
The dissolution of *zinc* in *acetic acid* does not generally reduce a ketone group, but will cause reductive elimination of an α-acetoxy or bromo group. 3β,17β-Diacetoxyallopregnan-20-one (**21**) gives 3β-acetoxyallopregnanone (**22**), and this same compound is formed from the isomeric 3β,17α-diacetoxylallopregnan-20-one (**23**)[16]. Both



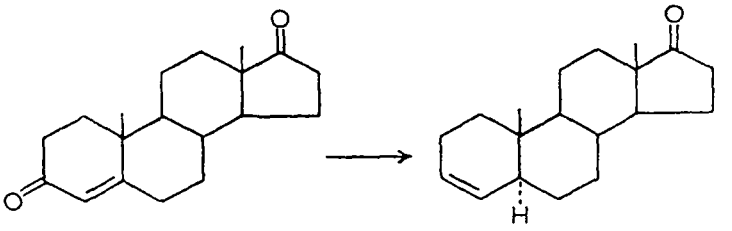
(**21**) (**22**) (**23**)

reactions must proceed through a common intermediate and it has been suggested that the acetyl group, after elimination of the acetoxyl group, exists in both cases in solution as a zinc enolate (**24**) which is then protonated from the more accessible axial direction to form **22**.

Δ⁴-3-Keto steroids are reduced by a large excess of zinc dust in acetic acid at room temperature[17] to the Δ³-unsaturated steroids. Thus androst-4-ene-3,17-dione (**25**) affords 5α-androst-3-en-17-one (**26**), the addition of hydrogen at position 5 occurring from the 'underside' of the molecule. The 17-ketone remains intact.



(**24**)

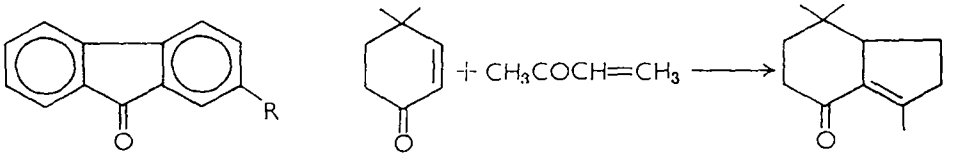


(**25**) (**26**)

Fluorenone (**27**, R = H) is easily reduced by zinc dust and calcium chloride in ethanol[18] to fluorenol. Phosphorus and hydroiodic acid has been recommended[19] for the reduction of fluorenone-2-carboxylic acid (**27**, R = CO_2H) to fluorene-2-carboxylic acid.

Acyloins (cyclic —CHOHCO) are reduced by zinc dust and hydrochloric acid to cyclic ketones (—CH_2CO—)[20].

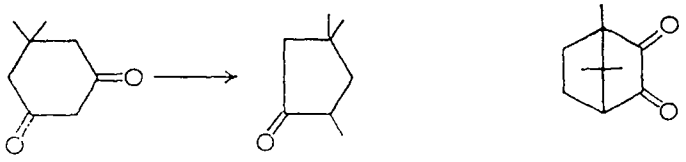
An interesting reductive coupling has been reported[21]. A mixture of 4,4-dimethylcyclohexenone (**28**) and methyl vinyl ketone is reduced by magnesium in acetic acid or by sodium amalgam to 1,4,4-trimethyl-1,8-perhydroinden-7-one (**29**). Reduction with Raney nickel affords the saturated bicyclic ketone.



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

The *Clemmensen reduction* of carbonyl groups with zinc and hydrochloric acid is usually carried out using amalgamated granulated zinc[22], and results in the formation of a hydrocarbon. An alternative general method is to use the Wolff–Kishner reaction (see section VIII). The Clemmensen reaction is general for ketones, but of limited use with aliphatic and aromatic aldehydes since polymeric products are also formed. Toluene or xylene is usually added, but ketones of high molecular weight require the addition of a more polar solvent, such as dioxane or acetic acid, to render them more miscible.

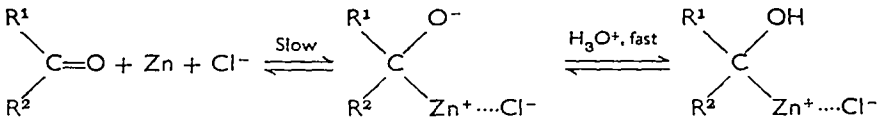
α,β-Unsaturated ketones can suffer reduction of the carbon–carbon double bond. An α-halo group is often eliminated to form a double bond. α-Diketones react normally, benzil (PhCOCOPh) giving dibenzyl ($PhCH_2CH_2Ph$), although stilbene (PhCH=CHPh) is formed in the presence of ethanol. However, dimedone (**30**) affords



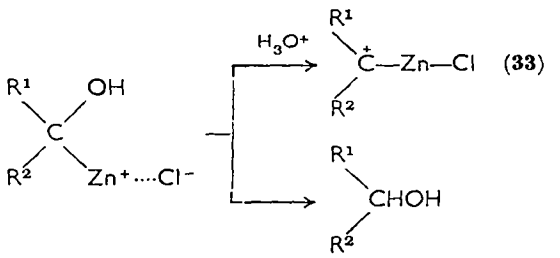
(**30**) (**31**) (**32**)

2,4,4-trimethylcyclopentanone (**31**). The reduction of aliphatic α-diketones can proceed at either carbonyl group[23]. 2,3-Pentanedione (MeCOCOEt) gives both diethyl ketone (EtCOEt) and methyl n-propyl ketone (MeCOPr-n), while camphorquinone (**32**) forms the two possible ketols (3-hydroxycamphor and 2-hydroxyepicamphor).

A kinetic study[24] of the rate of reduction of the soluble *p*-hydroxyacetophenone with liquid zinc amalgam at 60° has shown that the reaction is first-order in ketone with an energy of activation of 5·1 kcal/mole. The rate also depends upon the concentration of chloride ion and of zinc in the amalgam. However, the effects of the concentration of hydrogen ion and of the potential of the amalgam are small. This last fact suggests that electron transfer is not rate-determining. Moreover, in the presence of sufficient hydrochloric acid, the rate is independent of the proton concentration. Thus hydrogen ions (or atoms) cannot be the effective reducing agent. A reasonable mechanism involves a slow, reversible addition of zinc to the carbonyl group followed by a rapid (reversible) protonation. The protonated



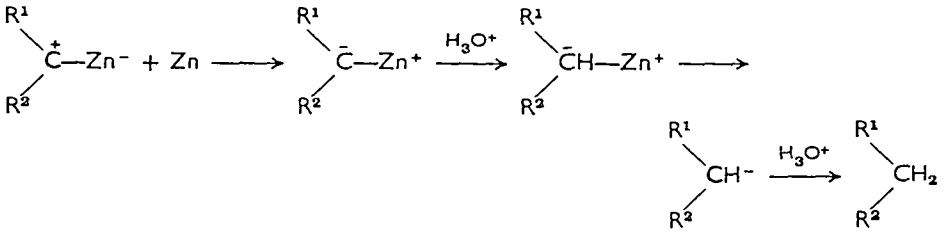
species can then either eliminate a hydroxyl group giving a zinc-coordinated carbonium ion (**33**), which can lead to olefins or rearranged products, or it can form a carbinol. Such by-products are



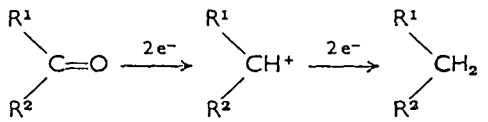
(**33**)

often found, but their formation will be slow at low acid concentration. Consistent with this mechanism is the fact that alcohols, chlorides, and olefins are not reduced to saturated hydrocarbons under the conditions of Clemmensen reduction[25,26]. They therefore cannot be intermediates in this reaction, but are rather by-products. The principal reaction must involve the coordinated carbonium ion and

a second equivalent of zinc, with subsequent protonation and elimination of zinc followed by a further protonation to generate the



methylene group. This mechanism differs from a previous, but similar, scheme[10,25] which postulated a bond between carbon and the massive metal surface, with electron transfer accompanying the dissolution of the metal. In the present mechanism the reaction is with zinc atoms and the electrons are transferred in pairs. The observation that cyclohexanone is reduced faster than cyclopentanone[25] is consistent with a slow step for the coordination of zinc with



the carbonyl group, due to *I* strain. This coordination also explains the slow rate of reduction of sterically hindered ketones[27].

In the Clemmensen reduction of acetophenone, while the major product is ethylbenzene, small amounts of styrene and phenyl methyl carbinol are formed by the alternate reaction paths of the protonated zinc coordinated compounds. However, minor quantities of pinacol are also formed[28]. The amount of pinacol increases with decreasing potential of the zinc amalgam. Since electrolytic reduction of acetophenone affords the pinacol (section IV), this must be formed during Clemmensen reduction by a separate one-electron reduction process.

Sterically hindered ketones often rearrange on reduction. Thus, pivalophenone ($PhCOC(CH_3)_3$) gives neopentylbenzene ($PhCH_2C(CH_3)_3$) and 2-methyl-3-phenyl-2-butene ($CH_3CH(Ph)=C(CH_3)_2$); elimination and rearrangement[27]. No 2-methyl-3-phenylbutane is formed in this reaction.

Reductions are usually not effected by the dissolution of metals in aqueous base. However, it has been recently reported[29] that the solution of Raney nickel alloy (Ni–Al) in aqueous alkali at 10–20°

reduces aliphatic aldehydes and ketones and aryl alkyl ketones (ArCOR) to the corresponding carbinols. Aryl alkyl ketones are also reduced at 80–90° to the corresponding hydrocarbons ($ArCH_2R$).

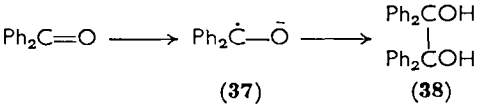
Simple aldehydes and ketones undergo reduction to pinacols with aluminum amalgam and wet ether. These can arise[10] either through dimerization of the intermediate carbanion (**34**) or by its reaction with another molecule of ketone. The reduction of α-diketones, such as benzil (PhCOCOPh), with this and similar reagents[30] terminates at the stage of the ketol (e.g. benzoin, PhCOCHOHPh). The reaction probably involves 1,4-addition, the ketol remaining in solution as the salt of its enol (**35**).

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

The reduction of organic compounds accompanying the dissolution of *sodium in liquid ammonia* has been widely used[31,32]. The addition of one electron to a carbonyl group results in an anion radical, whereas the addition of two electrons either in one or in two separate stages affords a dianion (**36**). An aromatic or nonenolizable aliphatic ketone reacts with sodium in liquid ammonia (and in ether or other

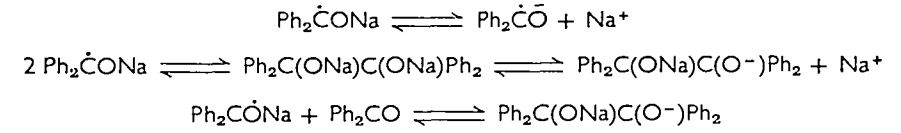
(**36**)

inert solvent) to give a ketyl ($R_2\dot{C}O^-$), which is a radical ion. The solution is paramagnetic (i.e. contains unpaired electrons). The electrical conductivity of a solution of benzophenoneketyl (**37**) shows



(**37**) (**38**)

that a series of complex equilibria exists between the ketyl and sodium cations. Possible reactions with benzophenone are as follows



The anion radical appears to be about 85% monomeric, and on the addition of acid forms benzopinacol (**38**) through either of the last

two equilibria. The equilibrium below does not occur in liquid ammonia, since no benzyl alcohol ($PhCH_2OH$) is formed. However,

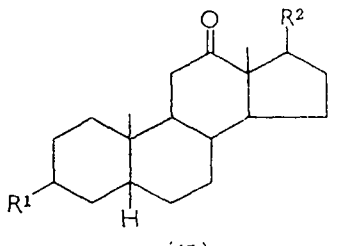
$$2\ Ph_2\dot{C}ONa \rightleftharpoons Ph_2C(Na)ONa + Ph_2C{=}O$$
(39)

the dianion of **39** is formed with a second equivalent of sodium and can react with more benzophenone to give the ketyl in the reverse of this last reaction. Benzophenoneketyl (**37**) can also exchange with another ketone forming its ketyl (**40**).

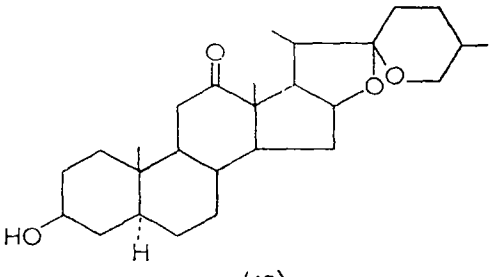
$$\underset{\textbf{(37)}}{Ph_2\dot{C}ONa} + R_2C{=}O \rightleftharpoons Ph_2C{=}O + \underset{\textbf{(40)}}{R_2\dot{C}ONa}$$

The addition of two protons to a dianion (**36**) results in the formation of a carbinol. Cyclic ketones are usually reduced to the more stable (equatorial) carbinol by an alkali metal and liquid ammonia followed by a proton donor. However, a recent communication[33] reports that the metal used affects the course of reduction. Camphor in ether was reduced with a series of metals in liquid ammonia and ethanol then added. The percentages of isoborneol (the *exo*, less-stable isomer) formed were: with lithium, 20; with sodium, 40; with potassium, 70; and with calcium 28.

Saturated ketones are also reduced to the corresponding carbinols by sodium in an alcohol, such as ethanol or n-amyl alcohol, or by sodium (or lithium) in liquid ammonia in the presence of a proton source, such as n-propanol. The more stable carbinol is also formed predominately. However, a 20-ketone gives a 20α-alcohol with sodium in ethanol[34]. It has been shown recently[35] that the direction of reduction of a 12-ketone is influenced by the nature of the side-chain substituent, and by the fusion of rings A and B. Thus, 12-cholanone (**41**; $R^1 = H$, $R^2 = C_5H_{11}$) or 12-ketocholanic acid (**41**; $R^1 = H$, $R^2 = C_4H_8CO_2H$) give predominantly the 12α-carbinol with either sodium and n-propanol or lithium, liquid ammonia and n-propanol; on the other hand, hecogenin (**42**) gives



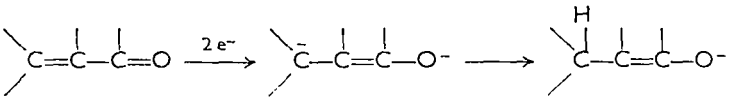
(41)



(42)

the 12β-ol with lithium in liquid ammonia and 80% of this isomer with sodium in ethanol. 3α-Hydroxy-12-ketoetianic acid (**41**; $R^1 = OH$, $R^2 = CO_2H$) gives, respectively, 60% and 64% 12β-ol with lithium and ammonia, and with sodium in n-propanol. Thus the *cis* configuration of rings A–B and the shielding of the 21-methyl group in 12-ketocholanic acid and 12-cholanone result in non-thermodynamically controlled reduction, while hecogenin (**42**) which possesses rings A and B in the *trans* configuration and the side-chain held in a rigid conformation undergoes normal reduction.

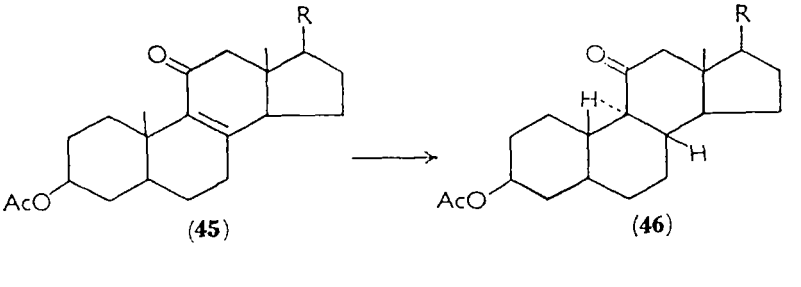
An α,β-unsaturated ketone adds two electrons to form a dianion (**43**) by 1,4-addition[32]. The addition of a proton donor such as ammonium ion (NH_4^+) or *t*-butanol yields a saturated ketone,



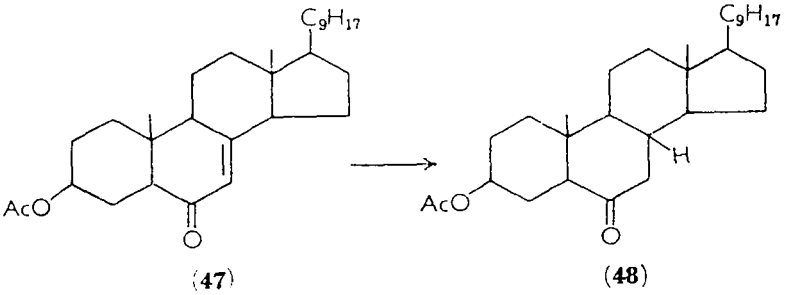
(**43**)

although the use of methanol often affords the saturated carbinol. The dianion is stable in solution and can be alkylated in the α-position[36].

Proton addition usually results in the formation of the more stable product[37]. Thus a Δ^8-11-ketone (**45**) leads to a 8β,9α-dihydro-11-ketone (**46**)[38], and a Δ^7-6-ketone (**47**) forms the 8β-derivative (**48**)[37].

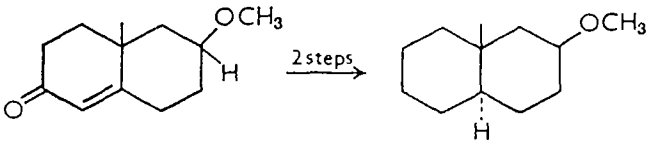


(**45**) (**46**)



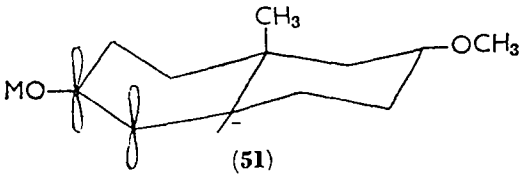
(**47**) (**48**)

The lithium, liquid ammonia, and ethanol reduction of the decalone derivative **49** gave, after Wolff–Kishner reduction of the ketone group, two *trans*-decalins (**50**) differing only in configuration at the methoxy group[39].



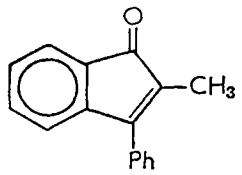
(**49**) (**50**)

The β-carbon atom will have considerable tetrahedral character in the transition state for protonation. However, the developing p orbital at this carbon atom must overlap continually with the π orbitals of the enol system and must remain perpendicular (**51**). The proton then enters from the axial direction to ring A. As a general rule the 'product will be the more stable of the two isomers (*cis* or *trans*) having the newly introduced hydrogen axial to the ketone

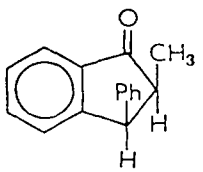


(**51**)

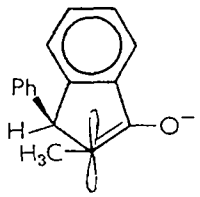
ring'[39,39a]. The addition of the α-hydrogen atom, which occurs during ketonization of the enol anion, does not necessarily give the more stable ketone. Thus the reduction[40] of 2-methyl-3-phenylindone (**52**) with lithium in ammonia, with subsequent addition of ammonium chloride, results in the formation of *cis*-2-methyl-3-phenyl-



(**52**)



(**53**)

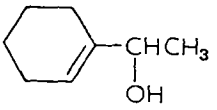


(**54**)

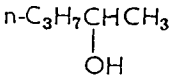
indanone (**53**). The proton addition to the 'top-side' of the anion (**54**) is hindered by the phenyl group and occurs from the underside.

The addition of a strong proton donor such as ammonium sulfate

to the liquid ammonia solution can lead to the reduction of other groups. Thus, acetophenone is reduced to cyclohexenyl methyl carbinol (**55**) by lithium in liquid ammonia, and sodium reduction

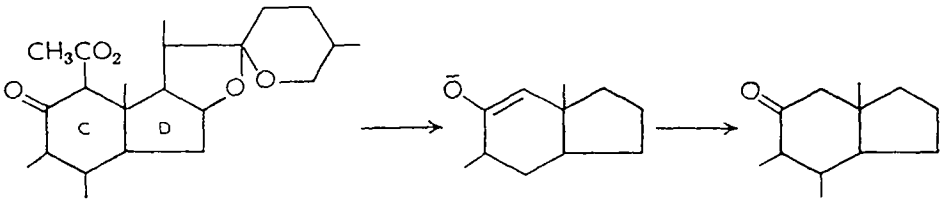


(**55**)



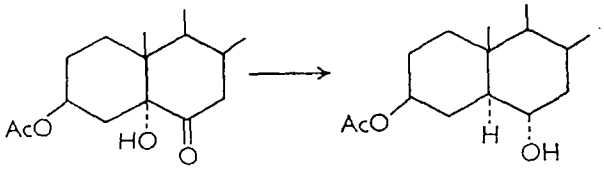
(**56**)

of cyclopropyl methyl ketone gives both n-propyl methyl ketone and its corresponding carbinol (**56**)[31]. Calcium in liquid ammonia appears to be a weaker reducing system. α-Acetoxy groups are eliminated with this reagent and a 12-acetoxy-11-ketone (**57**) is converted into the 11-ketone (**59**)[41]. This reaction probably involves



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

the enolate anion **58**, thus protecting the ketone from further reduction in solution. However, in the case of a 5-hydroxy-6-ketone (**60**), reduction of the carbonyl group occurs as well as elimination of the tertiary hydroxyl[42].



(**60**)

IV. ELECTROCHEMICAL REDUCTION

Cathodic reduction of a carbonyl group can proceed by either a unimolecular or bimolecular process. The particular reaction occurring depends on the nature of the solution surrounding the cathode

(catholyte) and the voltage applied (the overvoltage of the cathode material)[43,44].

The mechanism of electrochemical reduction may involve active hydrogen discharged at the cathode. However, organometallic com-

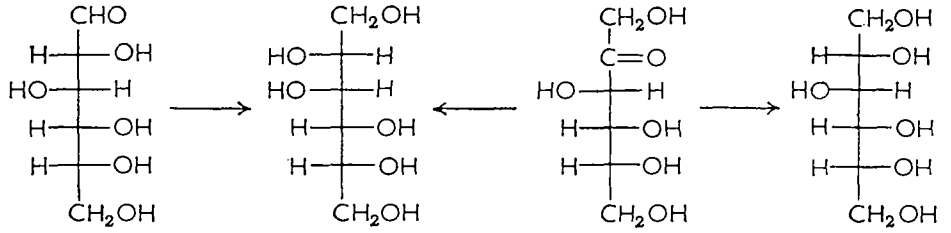
$$H^+ + e^- \longrightarrow H\cdot \qquad R + 2\,H\cdot \longrightarrow RH_2$$

pounds are often formed, particularly at mercury electrodes[45], suggesting that reduction occurs directly at the cathode surface. Moreover, the product formed depends upon the hydrogen overvoltage of the electrode. Tungsten and platinum have low overvoltages, followed by carbon and copper and then by mercury and lead. Preparatively, electrolytic reductions are slow, and although increasing the current density increases the rate of reduction it also decreases the overvoltage. Since oxidation can occur at the anode, accompanying the dissolution of the anode material, the anode and cathode compartments should be separated by a semipermeable membrane such as a porous pot. However, use of a graphite anode avoids this.

Aliphatic aldehydes undergo unimolecular reduction in acid solution and generally form alcohols at lead or mercury cathodes and hydrocarbons with cadmium at high overvoltage. Acrolein is

$$RCHO \xrightarrow[2\,e^-,\,2\,H^+]{} RCH_2OH \qquad RCHO \xrightarrow[3\,e^-,\,4\,H^+]{} RCH_3 + H_2O$$

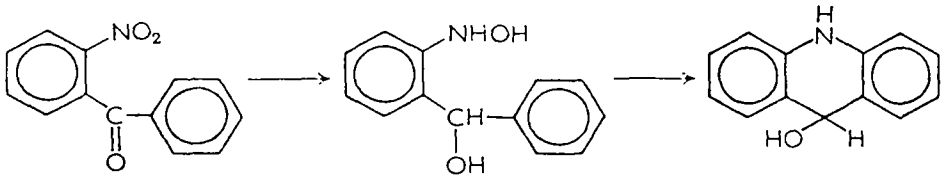
reduced to allyl alcohol without effecting the carbon–carbon double bond. D-Glucose (**61**) affords D-mannitol (**62**) in alkaline solution, presumably due to inversion at $C_{(2)}$ to give D-mannose. Fructose (**63**) forms both sorbitol (**64**) and mannitol (**62**). The catalytic and sodium-amalgam reduction of D-glucose (**61**) affords only sorbitol (**64**).



(**61**) (**62**) (**63**) (**64**)

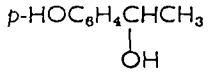
Aromatic aldehydes can be reduced to a variety of products; benzaldehyde, for example, can form benzyl alcohol, toluene,

benzopinacol (PhCHOHCHOHPh), and stilbene (PhCH=CHPh). The highest yields of the latter are obtained with an acid catholyte at high overvoltage, whereas reduction at lower overvoltage with a copper cathode affords predominately benzopinacol. Aliphatic ketones also give a variety of products, although pinacols are principally formed. Aromatic ketones give secondary alcohols in high yields at lead cathodes in basic solution, whereas the use of an acid catholyte results in the formation of a mixture of pinacol and monomeric alcohol[46]. In strongly acid solution the pinacol can subsequently rearrange to the corresponding pinacolone. *o*-Nitrobenzophenone (**65**) undergoes an interesting reduction with a lead cathode in alkaline medium yielding 1,2-dihydroanthranil (**67**), formed by

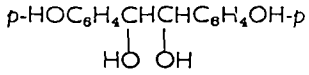


(**65**) (**66**) (**67**)

additional reduction of the nitro group and subsequent cyclization of the intermediate hydroxyliminobenzhydrol (**66**). *p*-Hydroxyacetophenone affords the carbinol **68** at −1·1 v and the hydrobenzoin **69** pinacol at −1·5 v, both with a mercury cathode and in acid solution.



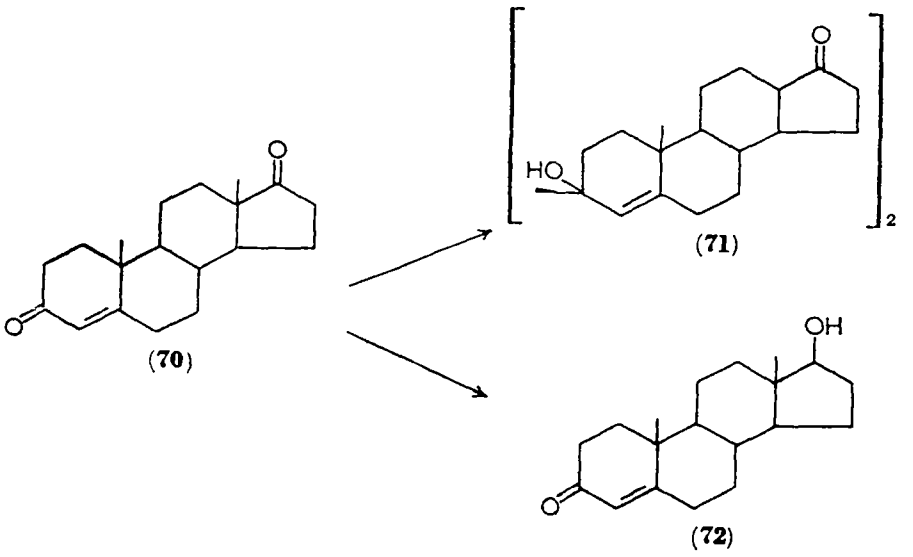
(**68**)



(**69**)

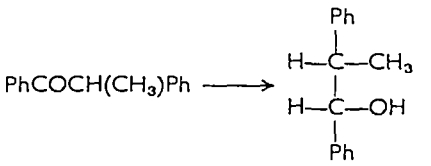
The stereochemistry of reduction also depends upon the overvoltage. Thus 2-methylcyclohexanone forms *trans*-2-methylcyclohexanol at lead and mercury cathodes, the *cis*-carbinol at copper, and a mixture of *cis* and *trans* with a nickel electrode. No reduction occurs at a platinum electrode.

α,β-Unsaturated ketones are more readily reduced. Androst-4-ene-3,17-dione (**70**) and progesterone both give the 3-pinacol (**71**) at a mercury cathode, whereas testosterone (**72**) and pregn-4-en-20α-ol-3-one are formed at lead, nickel, copper, platinum or graphite electrodes. Similarly, cholest-4-en-3-one forms its pinacol[47] with mercury cathode and graphite anode. In the case of saturated steroid ketones the more stable equatorial alcohol results, androstan-17β-ol-3-one



(70) (71) (72)

forming androstane-3β,17β-diol, and androstane-3β-16α-diol-17-one diacetate giving androstane-3β,17β-diol with elimination of the 16α-acetoxy group[48]. α-Methyldesoxybenzoin (**73**) is also reduced to the more stable *erythro*-1,2-diphenylpropan-1-ol (**74**)[49].



(73) (74)

In *polarographic reduction*[50] at a dropping mercury electrode pinacols are generally formed. At low pH the protonated ketone (or aldehyde) is most likely to be the species reduced, and the half-wave

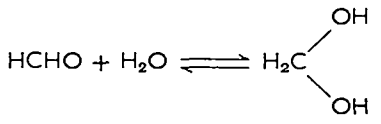
$$R_2C{=}O + H^+ \rightleftharpoons R_2\dot{C}OH \qquad R_2\dot{C}OH + e^- \rightleftharpoons R_2\dot{C}OH$$

reduction potential ($E_{\frac{1}{2}}$) becomes more negative with increasing pH, since the protonated ion will be more easily reduced at lower pH. In neutral or alkaline medium the carbonyl group is probably reduced directly. Saturated aldehydes are reduced at about $-1{\cdot}9$ v. The reduction of formaldehyde is abnormal, since the $E_{\frac{1}{2}}$ depends

$$R_2C{=}O + e^- \longrightarrow R_2\dot{C}\bar{O} \xrightarrow{H_2O} R_2\dot{C}OH + OH^-$$

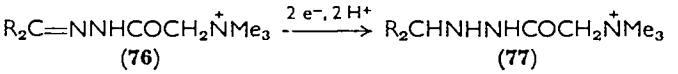
upon the pH, temperature, and solvent. Moreover, the height of the

reduction wave is kinetically and not diffusion controlled. This appears to be due to solvation of the aldehyde **75**. Saturated ketones



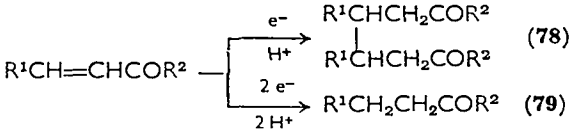
(**75**)

are only reduced at $-2{\cdot}2$ v. They are better determined polarographically as their Girard-T (trimethylammonium acethydrazine) derivatives (**76**) which are reduced unimolecularly to the corresponding hydrazines (**77**)[51].



(**76**) (**77**)

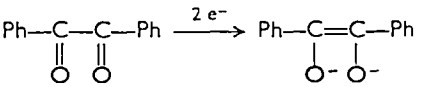
Unsaturated aliphatic ketones undergo polarographic 1,4-reduction to give a dimeric product (**78**) in acid solution and the



(**78**)

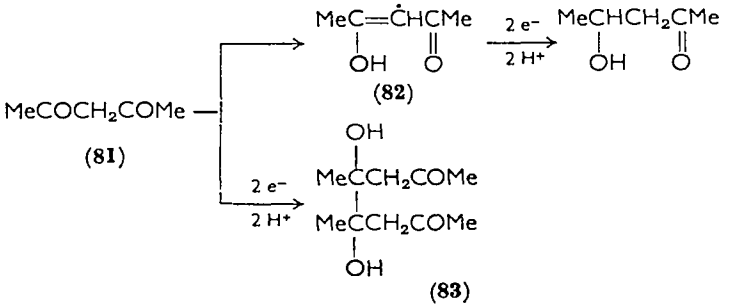
(**79**)

saturated monomeric ketone (**79**) in base. Similarly benzophenone gives benzopinacol in acidic and benzhydrol in basic media. The reduction of benzil affords benzoin, and presumably proceeds via the dienolate anion **80**. In the case of acetylacetone (**81**) two



(**80**)

reduction waves are given ($E_{\frac{1}{2}} = -1{\cdot}07$ and $-1{\cdot}37$ v in 0·1 N hydrochloric acid). The first reduction wave seems to involve the reduction of the enol **82**, whereas the second wave results in the



(**81**)

(**82**)

(**83**)

formation of a pinacol (**83**). The polarographic reduction of benzaldehydes shows two one-electron waves[52]. The first wave corresponds to a reversible electron addition to the carbonyl carbon atom, followed by irreversible dimerization to a pinacol (**84**). At pH below

$$ArCHO + e^- + H^+ \rightleftharpoons ArC\dot{H}OH \longrightarrow \underset{\text{(84)}}{\begin{matrix} ArCHOH \\ | \\ ArCHOH \end{matrix}}$$

5 a second wave, independent of the pH, is shown. Here the electron probably enters first, followed by protonation to give a benzyl alcohol. At pH above 5, only one irreversible wave is shown and this is approximately twice the height of the two waves formed below this pH. Here the reduction involves a two-electron and two-proton reaction and produces benzyl alcohol directly.

$$ArCHO + 2\,e^- + 2\,H^+ \longrightarrow ArCH_2OH$$

Reduction with *magnesium anodes* in nonaqueous solution involves unipositive magnesium cations ($Mg \rightarrow Mg^+ + e^-$)[53], since the same products are formed using magnesium and iodine or bromine ($Mg + X_2 \rightarrow MgX_2(+Mg) \rightleftharpoons 2\,MgX$). Aromatic ketones in ether or benzene afford pinacols (via **85**). The solutions are highly colored due to the radical salt **85**. In the case of benzaldehyde the pinacol

$$Ph_2CO + \dot{M}gX \rightleftharpoons \underset{\text{(85)}}{Ph_2\dot{C}OMgX} \rightleftharpoons \begin{matrix} Ph_2COMgX \\ | \\ Ph_2COMgX \end{matrix}$$

derivative (**86**) can react further to form a radical (**87**), which dimerizes to tetraphenylerythritol (**88**). The reduction of aromatic

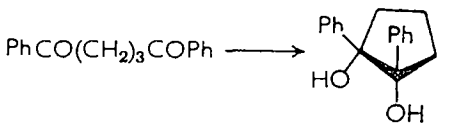
$$\underset{\text{(86)}}{\begin{matrix} C_6H_5CHOMgI \\ | \\ C_6H_5CHOMgI \end{matrix}} + C_6H_5CHO \longrightarrow \underset{\text{(87)}}{\begin{matrix} C_6H_5C{=}O \\ | \\ C_6H_5CHOMgI \end{matrix}} (+ C_6H_5CH_2OMgI) \longrightarrow$$

$$\underset{\text{(88)}}{C_6H_5CHOHCC_6H_4OHCC_6H_4OHCHC_6H_4OH}$$

diketones (**89**) at magnesium electrodes with sodium iodide in pyridine leads to the formation of a cyclic pinacol (**90**)[54] by the

$$\underset{\text{(89)}}{PhCO(CH_2)_nCOPh} \longrightarrow PhC(CH_2)_nCPh \longrightarrow \underset{Mg^{2+}}{\overset{(CH_2)_n}{PhC\!\!-\!\!\!-\!\!CPh}} \longrightarrow$$

$$\underset{\text{(90)}}{\overset{(CH_2)_n}{PhC\!\!-\!\!\!-\!\!CPh}}$$

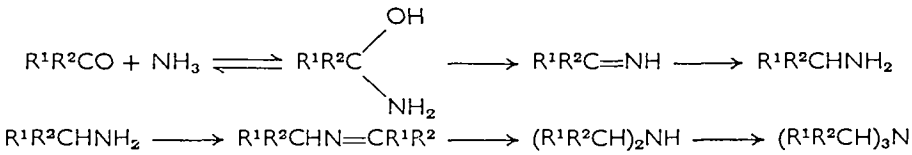


(91) (92)

mechanism indicated. 1,5-Diphenylpentane-1,5-dione (**91**) forms *cis*-1,2-diphenylcyclopentane-1,2-diol (**92**). The ease of reduction and cyclization depends on the number of methylene groups in the diketone **89**. A relation exists between the 'initial mean valence number' of the magnesium ions entering solution (i.e. the ratio of electrochemical equivalents consumed to equivalents of magnesium dissolved) and the stability of the ring 1,2-diol, the valence being lowest for the formation of the more stable 5- and 6-ring diols.

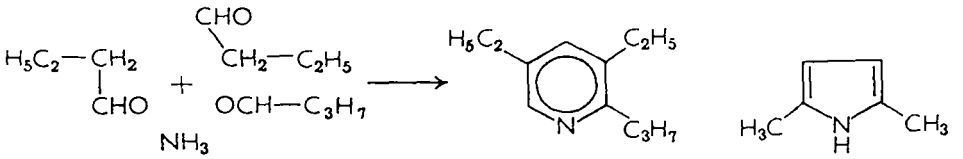
V. REDUCTIVE AMINATION

The catalytic hydrogenation of a carbonyl compound in the presence of ammonia results in the formation of amines[55]. The initial product is the primary amine which is probably formed via the imine, since this can be separately prepared and reduced, although the equilib-



rium for formation of the ketone–ammonia adduct is unfavorable. The primary amine, however, can condense with a second molecule of carbonyl compound to form a secondary amine, which can react further to a tertiary amine. This method of preparing a primary amine from the aldehyde or ketone is an alternative to reduction of the oxime, either catalytically, or with sodium and alcohol, or lithium aluminum hydride. These other methods do not lead to the formation of a secondary and tertiary amines.

The lower aldehydes are very reactive in the amination reaction and often react further to afford heterocyclic amines. Thus n-butyraldehyde gives the expected products, n-butylamine and di-n-butylamine, as well as 2-n-propyl-3,5-diethylpyridine (**93**). Acetonylacetone ($CH_3COCH_2CH_2COCH_3$) similarly gives 2,5-dimethylpyrrole (**94**) with hydrogen, ammonia and Raney nickel catalyst,



(93) (94)

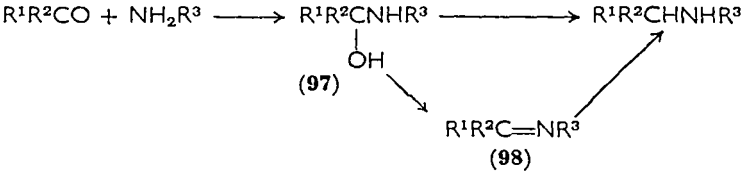
although acetylacetone ($CH_3COCH_2COCH_3$) suffers hydrogenolysis to acetamide (CH_3CONH_2). Carbon–carbon double bonds are naturally reduced under these conditions and mesityl oxide yields a saturated amine.

A more general method of converting an aldehyde or ketone into an amine is by the *Leuckart reaction*[56], which involves the reductive alkylation of ammonia or of an amine by the carbonyl compound and formic acid or its derivative. Thus, a ketone reacts with ammonium formate to give the formyl derivative of an amine (**95**), which can be hydrolyzed to the amine itself (**96**).

$$R^1R^2CO + HCO_2NH_4 \longrightarrow \underset{\textbf{(95)}}{R^1R^2CHNHCHO} \; (+2\,H_2O + NH_3 + CO_2) \longrightarrow \underset{\textbf{(96)}}{R^1R^2CHNH_2}$$

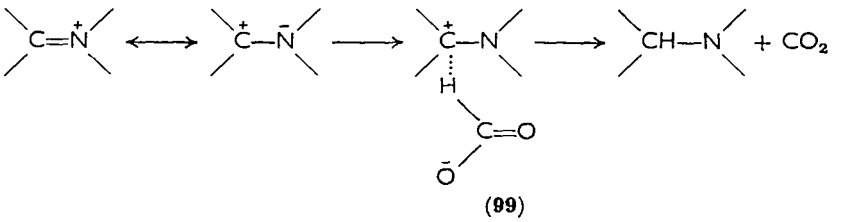
The use of nickel and cobalt salts as catalysts in this reaction has been recommended[57], and a statistical analysis presented[58] of the yields of *t*-butylmethylamine and *t*-butyldimethylamine formed in the reductive methylation of *t*-butylamine with formic acid.

The Leuckart reaction is generally considered to involve the reduction of the carbinolamine (**97**) or imine (**98**) with formic acid.



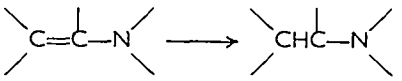
(97) (98)

In the case of secondary amines (R_2NH) only the carbinol amine ($R^1R^2C(OH)NR^3$) can be involved. The carbimine **98** probably forms an active complex (**99**) with formic acid which decomposes



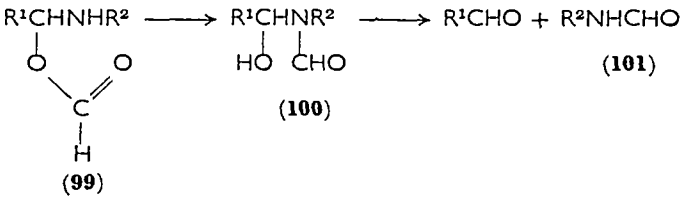
(99)

to the amine and carbon dioxide[59]. In support of this, enamines are



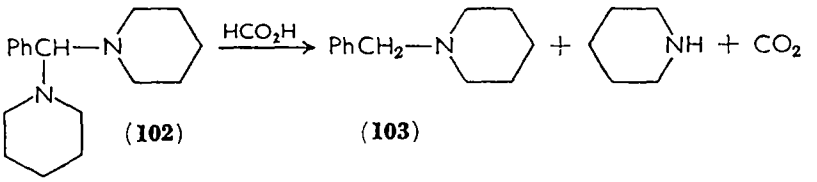
reduced by deuterium-labeled formic acid (DCO_2H) to an α-deuterated amine[60].

The resulting amine can also be decomposed to an aldehyde and the *N*-formyl derivative (**101**) of the amine, probably though the



(**99**) (**100**) (**101**)

N-formyl-α-amino alcohol (**100**). A related reaction is the reductive cleavage of benzylidenebispiperidine (**102**) with formic acid to benzylpiperidine (**103**), piperidine and carbon dioxide. Recently it



(**102**) (**103**)

has been shown that the reaction involves a chain mechanism[61] which depends upon the nature of the solvent. The rate is decreased by the addition of hydroquinone and accelerated by diphenylamine, indicating a radical mechanism is involved. Because of the similarity to the Leuckart reaction, it is suggested that the decarboxylation of the intermediate formate (**99**) of the α-amino alcohol also involves a radical.

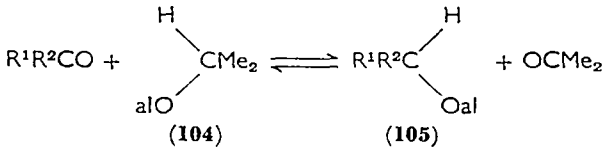
The *Eshweiler–Clarke* modification[56] represents a general method of methylating primary and secondary amines with formaldehyde and formic acid. Although the amine exists as the formic acid salt, the reaction must proceed via the carbinol amine, which is reduced by formic acid to the amine as in the Leuckart method. The reaction of a primary amine may also involve the imine, and benzalaniline ($PhCH{=}NPh$) is reduced by triethylamine formate to benzylaniline ($PhCH_2NHPh$). In this reaction primary amines are converted into

the tertiary dimethylamines ($RNMe_2$) and secondary amines to the tertiary methylamines (R_2NMe).

VI. REDUCTION BY ORGANIC REAGENTS

In this category are classed a number of different reactions in which the hydrogen atom transferred is originally attached to a carbon atom.

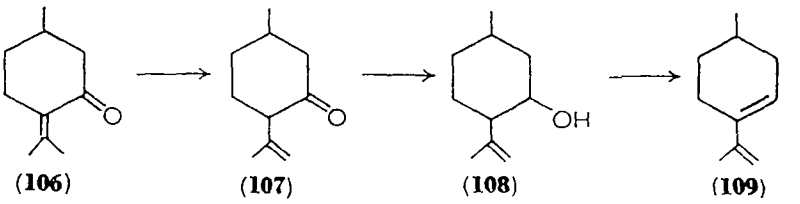
The most general reaction of this class is the *Meerwein–Pondorf–Verley* reduction[62]. Verley and Meerwein originally discovered that aldehydes are reduced to primary alcohols by aluminum ethoxide ($Al(OEt)_3$) in ethanol. However, Pondorf introduced the more general use of aluminum derivatives of secondary alcohols, and in particular aluminum isopropoxide in isopropanol. Magnesium and sodium alkoxides can be used but are inferior. An equilibrium (al = Al/3) is reached between the ketone and isopropoxide (**104**) and the aluminum derivative (**105**) of the carbinol and acetone.



Distillation of the acetone displaces the equilibrium in favor of the carbinol. One equivalent of aluminum isopropoxide is sufficient, since it is regenerated by reaction of the aluminum derivative of the product with isopropanol. However, an excess is usually employed to increase the rate of reaction, and to reduce side-reactions. The reverse reaction, the Oppenauer oxidation, is affected by treating the carbinol with an excess of ketone, such as acetone or cyclohexanone, in the presence of aluminum *t*-butoxide.

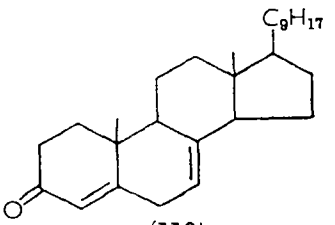
Cyclohexanone is reduced rapidly in the Meerwein–Pondorf–Verley reaction, but sterically hindered ketones such as camphor require 12–24 hours; the reaction produces no pinacol and does not reduce double bonds. Enolizable β-diketones and β-keto esters do not react, since they form the aluminum salts of their enols. Phenolic ketones and keto acids are also not reduced. Keto esters often undergo transesterification to give their isopropyl esters. Sensitive alcohols may also suffer dehydration under the conditions of the reaction. Thus *d*-pulegone (**106**) yields 10% *d*-neoisopulegol (**108**) and 40% menthene (**109**). The unreacted ketone contains isopulegone

(**107**) and the double-bond isomerization may occur before reduction. Ergosta-4,7,20-trien-3-one (**110**) similarly gives the normal product,

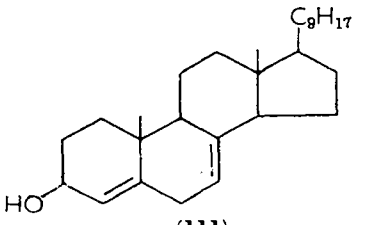


(**106**) (**107**) (**108**) (**109**)

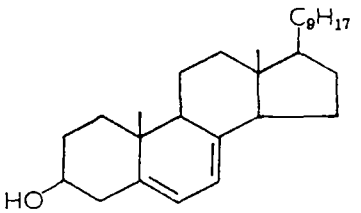
ergosta-4,7,20-trien-3β-ol (**111**) (80%), and the isomerized carbinol, ergosta-5,7,20-trien-3β-ol (**112**) (20%). The originally employed



(**110**)



(**111**)

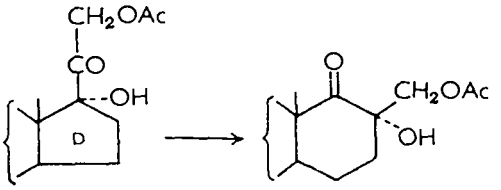


(**112**)

aluminum ethoxide seems a more powerful reducing agent, since benzophenone yields 7% diphenylmethane with this reagent, and the presumably intermediate benzhydrol gives 28% of the same hydrocarbon.

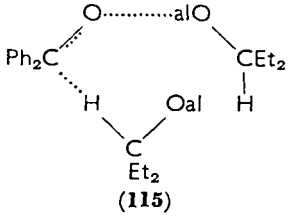
A rearrangement has been observed in the reduction of cortisone (**113**) with aluminum isopropoxide in cyclohexanone[63], when the product is a D-homosteroid (**114**).

The mechanism of the Meerwein–Pondorf–Verley reduction has been the subject of numerous studies. The use of deuterium-labeled isopropanol has shown[64] that the hydrogen atom transferred is that



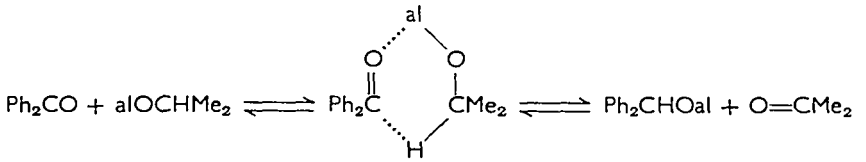
(113) (114)

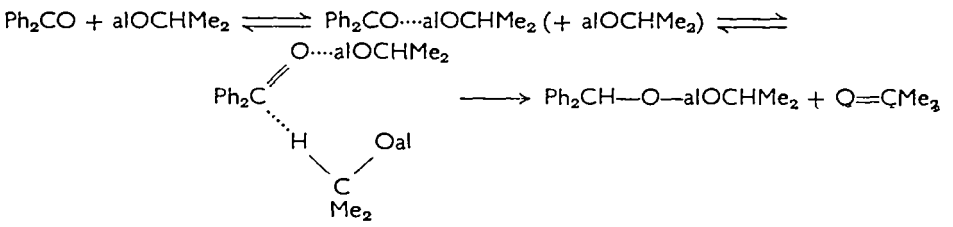
attached to the carbinol carbon atom. The reduction of a series of substituted benzophenones[65] with diethyl carbinol gave a Hammett reaction constant (ρ) of 1·296, indicating that the increased positive character of the group greatly facilitates hydrogen ion transfer. The mechanism was interpreted as involving two molecules of alkoxide (**115**), one complexing with the carbonyl oxygen while the other transfers hydrogen to the carbonyl carbon atom. The energy and



(115)

entropy of activation varied over the temperature range studied, being 17 kcal/mole and −20 e.u., respectively, at 25°. This variation suggests that more than one reaction may be involved, with the proportion of each reaction varying with the temperature. A more detailed kinetic study[66] showed that the rate of reduction of benzophenone by aluminum isopropoxide in isopropanol is first order in the ketone, but has an order of about 1·5 in the alkoxide. Two mechanisms were suggested, the classic reduction by one mole of alkoxide via a cyclic transition state[62] and a noncyclic process

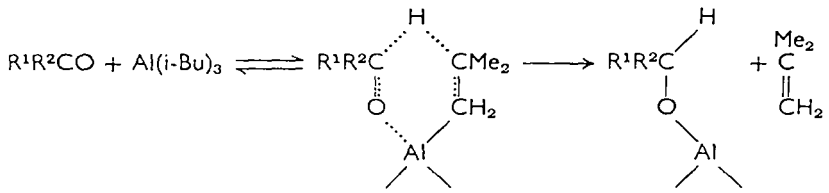




involving two moles of alkoxide as outlined above. A recent study[67] has shown that the tetramer of aluminum isopropoxide reduces acetophenone at a slower rate than its trimer. Moreover, the rate of formation of α-phenylethanol is lower than that of the formation of acetone, and the rate-determining step is probably the alcoholysis of the mixed alkoxide and not hydrogen transfer. The reacting ketone must first coordinate with the alkoxide trimer or tetramer. The reaction sequence is thus[66] the coordination of the ketone with alkoxide (as in **115**), hydride transfer, separation of acetone from the complex and alcoholysis of the mixed alkoxide.

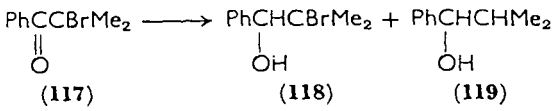
Reduction with optically active alkoxide has been reported to lead to asymmetric reduction[68,69]. Thus the reduction of 6-methyl-2-heptanone ($Me_2CH(CH_2)_3COMe$) with *dl*-aluminum-*s*-amyloxide in (−)-*s*-amyl alcohol (EtCHOHMe) gave (+)-6-methyl-2-heptanol with 5·9% activity. However, in view of the complexity of the reaction, the interpretation of these results is uncertain.

An allied reduction of 3,3,5-trimethylcyclohexanone with triisobutylaluminum ($(Me_2CHCH_2)_3Al$) in benzene[70] gives the *trans*-carbinol, the product of kinetic control (see section VII). However, in the presence of excess ketone the product epimerizes to the more stable *cis*- (equatorial) carbinol. The reaction probably involves a cyclic intermediate (**116**). If cyclohexanone is added at the end of the reaction, the 3,3,5-trimethylcyclohexanol (as its aluminum salt) is oxidized back to the ketone, in what must be essentially an Oppenauer oxidation. The cyclohexanone, however, is converted into side-products.



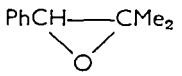
(116)

The aluminum isopropoxide reduction of α-bromoisobutyrophenone (**117**)[62] produced only a small amount of 1-phenyl-2-bromo-2-methylpropanol (**118**). The main product was 1-phenyl-2-methylpropanol (**119**) formed by reductive elimination of the bromine atom, although this product may have also arisen from

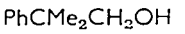


(117) (118) (119)

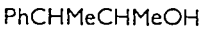
reductive cleavage of 1-phenyl-2-methylpropylene oxide (**120**), itself formed by elimination of hydrogen bromide from the bromohydrin



(**120**)

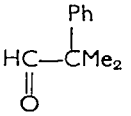


(**121**)

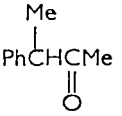


(**122**)

118. Two other products were 2-phenyl-2-methylpropanol (**121**) and 2-phenyl-1-methylpropanol (**122**). These compounds can also be derived from the oxide (**120**), by rearrangement and subsequent reduction. The first (**121**) via phenyl migration through 2-phenyl-2-methylpropanal (**123**) and the other (**122**) via 3-phenyl-2-butanone (**124**) formed by methyl migration.



(**123**)



(**124**)

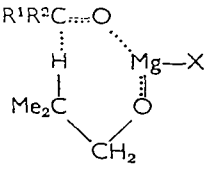
The use of aluminum chloroisopropoxide has been recommended for the reduction of α-bromo ketones[71] to bromohydrins, since the reaction proceeds at a lower temperature with fewer side-reactions.

Alkyl borates have been employed[72] to reduce aldehydes to primary alcohols at 150–175°. Aromatic aldehydes give good yields, but only poor results are obtained with aliphatic aldehydes. Ketones are not reduced with isopropyl borate at 160°, although cyclohexanone underwent 6% reduction with allyl borate. No esters (the Tischtschenko reaction, see below) were formed in these reactions.

The *Grignard reagent*[73] from a bulkly aliphatic halide, possessing a hydrogen atom on its β-carbon atom (**125**), reduces a carbonyl group rather than adding to it. In the reaction of benzophenone with

(**125**)

isobutylmagnesium bromides (Me_2CHCH_2MgBr) labeled with deuterium individually on the α-, β-, and γ-carbon atoms, only the β-hydrogen (or deuterium) is transferred[74]. The kinetic isotope effect is about 2, indicating that the β-hydrogen atom is involved in the transition state, which is usually considered to be cyclic (**126**). However, in the reaction of methyl *t*-butyl ketone with the Grignard



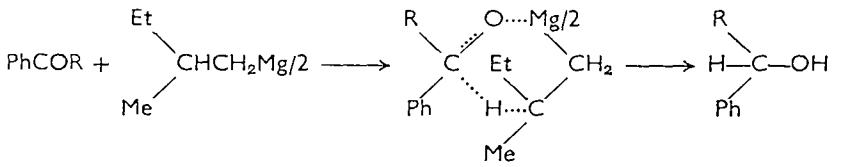
(126)

reagent from (+)-1-chloro-2-methylbutane and the dialkylmagnesium derivative (R_2Mg) of the same halide, the same product is formed with either reagent and there is no difference between the product formed at the beginning and end of the reaction[75]. The same reducing species must be present in all cases[76], and must be the dialkyl magnesium (R^1_2Mg) ($2\,R^1Mg \rightarrow R^1_2Mg + MgX_2$), which is regenerated by the reaction

$$2\,R^1MgOR^2 \rightleftharpoons R^1_2Mg + (R^2O)_2Mg$$

At the beginning of the reduction the reducing species is $R^1_2MgMgX_2$ and at the end $R^1MgOR^2MgX_2$.

The stereospecificity of reduction of a series of alkyl phenyl ketones with the Grignard reagent from (+)-1-chloro-2-methylbutane (**127**) increases with the increasing length of the alkyl chain[77].



(127) (128)

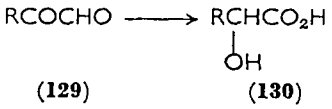
Similar results are obtained with alkyl cyclohexyl ketones[78]. This has been attributed to increased steric hindrance in the cyclic reaction intermediate (**128**), favoring attack from one side. The use of (+)-1-chloro-2-phenylbutane gave similar, although more stereospecific, results[79].

Two molecules of an aldehyde can undergo self-oxidation and reduction in the *Cannizzaro* reaction[80], giving an alcohol and acid.

$$2\,RCHO \longrightarrow RCH_2OH + RCO_2H$$

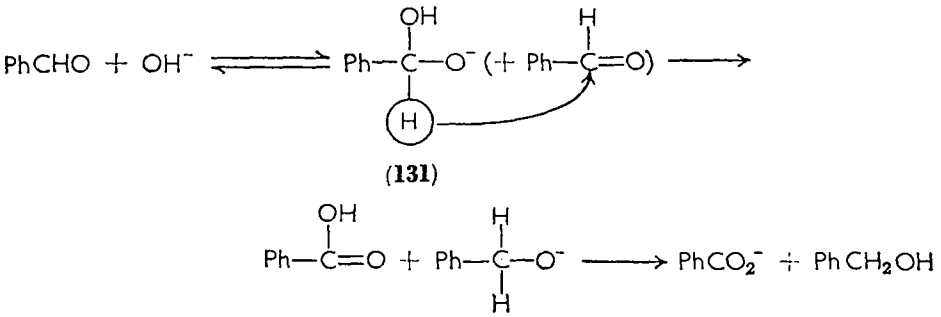
The reaction is usually carried out in strong aqueous or alcoholic alkali, but can also be effected with sodium ethoxide in ethanol or sodamide in liquid ammonia. Ketones cannot undergo this reaction, since they do not possess a hydrogen atom on the carbonyl carbon atom. α,β-Unsaturated aldehydes do not react, although aromatic aldehydes give good yields of product. Benzaldehydes are reduced in

good yield to benzyl alcohols by carrying out a mixed Cannizzaro reaction with formaldehyde. An α-keto aldehyde (**129**) can also under-



(**129**) (**130**)

go an internal Cannizzaro reaction giving an α-hydroxy acid (**130**). Electron-attracting groups in an aldehyde increase the rate of reaction, while electron-repelling groups decrease the rate. The reaction is characteristic of aldehydes not possessing hydrogen atoms on the α-carbon atom. Those having free α-hydrogens undergo aldol condensation. The carbinol resulting from a Cannizzaro reaction in heavy water contains no deuterium on the first carbon atom[81], and the hydrogen must arise from a second molecule of aldehyde and not from the solvent. The reaction is second order in aldehyde, but can be from first to second order in hydroxide ion. These results are consistent (for the first-order reaction in base) with a slow transfer of hydride ion ($H:^-$) from an aldehyde–hydroxide ion adduct (**131**)

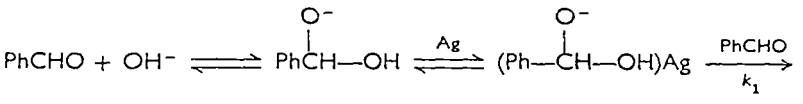


(**131**)

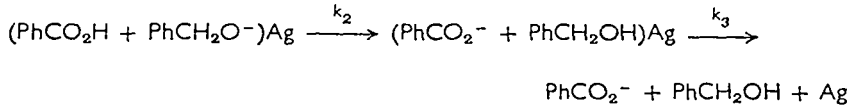
to a second aldehyde molecule, followed by a fast transfer of protons giving benzoate ion and benzyl alcohol[82].

Recently it has been shown that the Cannizzaro reaction of benzaldehyde with sodium hydroxide in 50% ethanol can be catalyzed by silver metal[83]. The reaction is initially first order in benzaldehyde but becomes zero order in this reactant at later stages of the reaction. The rate also depends directly upon the amount of silver-metal catalyst, but is zero order in sodium hydroxide. The reaction must thus take place on the catalyst surface. No benzyl benzoate was detected in the products, and it cannot be an intermediate in the reaction since it is hydrolyzed in the medium slower than the formation of benzyl alcohol. *o*-Hydroxy- and *p*-hydroxybenzaldehyde,

which do not undergo the usual Cannizzaro reaction, react in the presence of silver. The kinetic hydrogen isotope effect (k_H/k_D) in the silver-catalyzed reaction is 6·8, and this high value indicates that the carbonyl carbon–hydrogen bond is broken in the rate-determining step. The k_H/k_D ratio for the uncatalyzed reaction is 1·8[84]. The proposed mechanism involves the adsorption of the hydroxylated aldehyde (**132**) on the silver surface (**133**), where it reacts with another equivalent of benzaldehyde. The rate of desorption of the



(**132**) (**133**)



products (k_3) must be lower than that of the rate of reaction (k_1) on the silver, since little catalyst is available at the end of the reaction, which becomes first order in the catalyst and independent of the concentration of benzaldehyde (i.e. depends upon the rate of liberation, k_3, of the catalyst).

Aliphatic aldehydes, while not undergoing the Cannizzaro reaction, undergo an allied reaction—the *Tishchenko* reaction—with aluminum alkoxides in a nonpolar solvent. The mixed reaction of n-butyraldehyde with aliphatic and aromatic aldehydes has been studied in detail[85]. The mixed ester formed is that of the acid resulting from the more reactive aldehyde. The highest yields are formed by adding n-butyraldehyde to a solution of the other aldehyde and aluminum isopropoxide in carbon tetrachloride. Benzaldehyde and n-butyraldehyde give benzyl butyrate and butyl benzoate in the ratio of 1 to 0·07, and cinnamaldehyde gives only cinnamyl butyrate. Benzaldehyde and acetaldehyde react to give benzyl acetate and methyl benzoate (1:0·02). Although ketones cannot react, reactive ketones such as α,α-dichloroacetone are reduced by n-butyraldehyde. Acetone, cyclohexanone, and dibenzyl ketone, however, are not reduced.

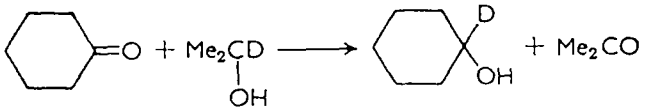
Tishchenko-type reactions can be achieved under other reaction conditions. Hydroxypivaldehyde (**134**) on heating with water without a catalyst gives 3-hydroxy-2,2-dimethylpropanyl 3-hydroxy-2,2-

dimethylpropionate (**135**). Heating a ketone in ethanol with Raney

$$2\ Me_3CCH(OH)CHO \longrightarrow Me_3CCH(OH)CH_2OCOCH(OH)CMe_3$$

(**134**) (**135**)

nickel produces the corresponding carbinol and ethyl acetate[86]. It has been suggested that the reaction involves nickel ethoxide. Similarly, a ketone and primary alcohol heated with aqueous base to 240° yield[87,88] a secondary alcohol and aldehyde. Diisopropyl ketone is reduced by sodium hydroxide in ethanol in 52% yield. α,β-Unsaturated aldehydes and ketones are also selectively reduced at the carbonyl group by passing their vapor over magnesia[89] with a saturated primary or secondary alcohol. The mechanism also involves direct transfer of the hydrogen atom attached to the carbon of the carbinol to the carbonyl group, since 2-deuteroisopropanol (**136**) reduced cyclohexanone to the deuterated carbinol (**137**).



(**136**) (**137**)

The *Willgerodt reaction*[90,91] involves heating an aryl methyl ketone with ammonium polysulfide, and results in the formation of an amide (**138**) with the same number of carbon atoms. A small amount

$$ArCOCH_3 \longrightarrow \underset{(\mathbf{138})}{ArCH_2CONH_2} + \underset{(\mathbf{139})}{ArCH_2CO_2NH_4}$$

of ammonium salt of the corresponding acid (**139**) is also formed. The reaction is best carried out in dioxane and the net result is the reduction of the carbonyl group to a methylene group, with the oxidation of the terminal methyl to an amide. A terminal methyl is always oxidized, and phenyl n-butyl ketone (**140**) gives 4-phenylbutyramide (**141**). Moreover, no rearrangement of the carbon skeleton occurs since acetophenone labeled with carbon-14 on the

$$\underset{(\mathbf{140})}{PhCO(CH_2)_3CH_3} \longrightarrow \underset{(\mathbf{141})}{Ph(CH_2)_3CONH_2}$$

carbonyl group (**142**) forms phenylacetamide (**143**) and phenylacetic acid (**144**) labeled on the methylene groups[92]. The *Kindler*

$$\underset{(\mathbf{142})}{Ph^{14}COCH_3} \longrightarrow \underset{(\mathbf{143})}{Ph^{14}CH_2CONH_2} + \underset{(\mathbf{144})}{Ph^{14}CH_2CO_2H}$$

modification[90,92a] of this reaction involves heating the ketone with equimolar amounts of sulfur and an anhydrous amine, and results in the formation of a thioamide (**145**) which can be hydrolyzed to the

$$ArCOCH_3 \xrightarrow{Me_2NH/S} \underset{(145)}{ArCH_2CSNMe_2} \longrightarrow ArCH_2CO_2H$$

acid. Secondary amines, particularly morphiline, give the best results. Aliphatic ketones often react well, and pinacolone (**146**)

$$\underset{(146)}{Me_3COMe} \longrightarrow \underset{(147)}{Me_3CCH_2CONH_2}$$

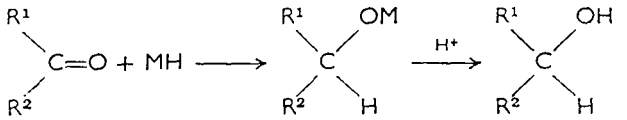
yields *t*-butylacetamide (**147**). However, aliphatic aldehydes give only poor yields. Phenyl ethyl ketone ($PhCOCH_2CH_3$), benzyl methyl ketone ($PhCH_2COCH_3$) and also dihydrocinnamaldehyde ($PhCH_2CH_2CHO$) all form 3-phenylpropionamide ($Ph(CH_2)_2CONH_2$).

The reaction of benzophenone with morpholine and sulfur gives diphenylmethane and some bisdiphenylmethyl disulfide (**150**)[93]. The reaction may proceed via thiobenzophenone (**148**). This compound could be partially reduced to **149** which dimerizes to the disulfide (**150**). The disulfide on heating decomposes to diphenylmethane, thiobenzophenones and sulfur.

$$Ph_2CO \longrightarrow \underset{(148)}{Ph_2CS} \longrightarrow \underset{(149)}{(Ph_2CHS)} \longrightarrow \underset{(150)}{(Ph_2CH)_2S_2} \longrightarrow Ph_2CH_2$$

VII. METAL HYDRIDE REDUCTION

During the last fifteen years, a number of metal hydrides[94,95,96] have been introduced for the reduction of carbonyl compounds to the corresponding carbinols. The reactions involve the transfer of hydrogen originally attached to a metal atom, as a hydride ion. The carbinol is generally present in the form of a metal alkoxide and is liberated on acidifying the solution.



The first of this class of reagents to be introduced was lithium aluminum hydride ($LiAlH_4$). The reductions with this reagent are carried out in diethyl ether or other higher boiling ether, and are usually very rapid and free from side-reactions. The use of deuterated

($LiAlD_4$) or tritiated ($LiAlTH_3$) lithium aluminum hydride results in the formation of primary or secondary carbinols with deuterium or tritium attached to the carbon atom of the original carbonyl group[97,98].

Although no kinetic measurements have been carried out on the reduction with lithium aluminum hydride, the four atoms of hydrogen in the hydride probably reduce four molecules of carbonyl compound in what must be four consecutive stages. The intermediate hydride species has usually been assumed to be aluminum alkoxyhydrides (e.g. $[Al(OR)H_3]^-$). However, it has recently been shown[99] that the reduction of 3,3,5-trimethylcyclohexanone affords 55% axial (*trans*) carbinol and that the percentage of isomer is independent of the proportion of the reagents or the order of mixing them. Moreover, reduction with an alkoxyhydride such as lithium aluminum tri-*t*-butoxyhydride ($LiAl(t\text{-}BuO)_3H$) gives a higher proportion (70%) of *trans* isomer (see below). Thus the intermediate alkoxyhydride must disproportionate in solution to liberate the original hydride and precipitate the tetraalkoxyaluminum ion, in reactions which involve steps such as

$$2\,ROAlH_3^- \longrightarrow AlH_4^- + (RO)_2AlH_2^-$$

$$2\,(RO)_2AlH_2^- \longrightarrow AlH_4^- + (RO)_4Al^-$$

Quaternary ammonium borohydrides, such as cetyltrimethylammonium and tricaprylmethylammonium borohydrides are available ('Hydriquats'), and are soluble in nonpolar solvents. However, they do not appear to have been used in synthetic reductions.

Sodium borohydride ($NaBH_4$) is stable in polar solvents in the presence of small amounts of base. The rate of reduction of simple aldehydes and ketones in isopropanol[100] is first order in the concentration of borohydride and first order in the carbonyl compound, although one borohydride ion reduces four molecules of carbonyl compound. This is consistent with an initial slow reaction between the borohydride ion and carbonyl group, followed by three con-

$$R^1R^2CO + BH_4^- \longrightarrow R^1R^2CHOBH_3^-$$

$$R^1R^2CO + R^1R^2CHOBH_3^- \longrightarrow (R^1R^2CHO)_2BH_2^-$$

$$R^1R^2CO + (R^1R^2CHO)_2BH_2^- \longrightarrow (R^1R^2CHO)_3BH^-$$

$$R^1R^2CO + (R^1R^2CHO)_3BH^- \longrightarrow (R^1R^2CHO)_4B^-$$

secutive rapid reactions involving the other three equivalents of hydride ion. The intermediate ions (e.g. $(R^1R^2CHO)_2BH_2^-$) can exchange their alkoxy substituents with the solvent. The reduction of

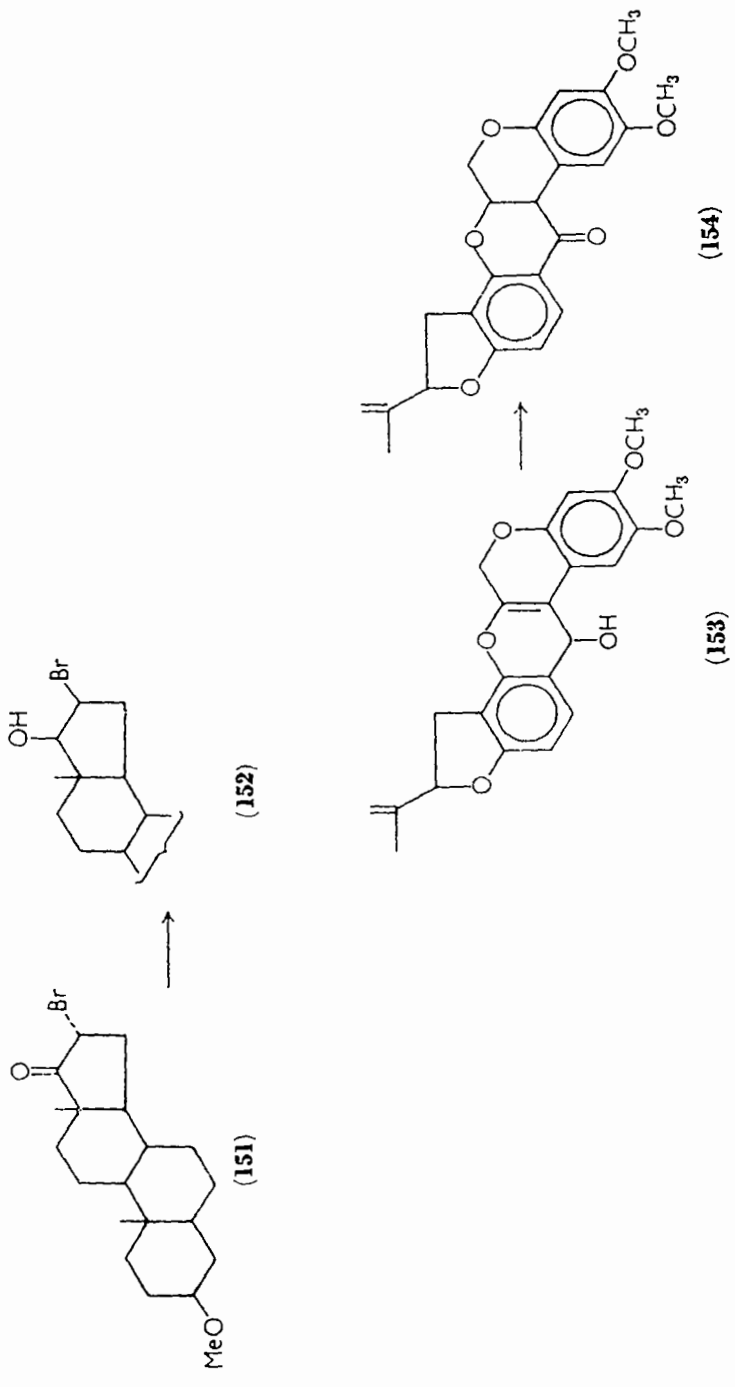
benzaldehyde is about 400 times more rapid than that of acetophenone and benzophenone, reflecting the greater reactivity of an aldehydic carbonyl group to attack by a nucleophilic reagent (BH_4^-).

The rate of reduction of acetone by sodium borohydride at 0°[101] is 93, 97, and 15·1 (10^4 l/mole sec) in water, ethanol and isopropanol, respectively. The addition of lithium chloride does not affect the rate of reduction in water, but the rate in isopropanol is increased to $50{\cdot}3 \times 10^{-4}$ l/mole sec (0·05 M LiCl), and the rate coefficient increases proportionally with the concentration of lithium chloride. The reduction in aqueous solution must involve the borohydride ion (BH_4^-). In isopropanol it is probably due to an ion pair ($M^+BH_4^-$) and the lithium ion pair ($Li^+BH_4^-$) is more reactive than that with sodium. Of interest in this connection is the fact that acetone is not reduced by sodium borohydride at 0° in solvents of low ionizing power, such as acetonitrile, pyridine and dimethylformamide.

The rates of reduction of a series of cyclanones with sodium borohydride in isopropanol[102] established an order of dependence on ring size of $4 > 6 \gg 5 > 7 > 17 > 15 > 12 \sim 13 > 8 > 9 > 10$. This is as anticipated on the basis of the *I* (internal) strain in these rings and is in agreement with the values of the dissociation constants of their cyanohydrins. The order of the rates of reduction of a number of steroid ketones, also in isopropanol, has been shown[103,104] to be Δ^5-3 > 3(A/B *cis*) > 3(A/B *trans*) > 6 > 7 > Δ^4-3 > 12 > 17 > 20 > 11, with an overall difference in rate of 1000. The differences between 3- and 17-, and 3- and 20-ketones are 100:6 and 100:1·5, respectively, explaining the fact that 3-ketones can be reduced selectively in the presence of 17- and 20-keto groups. Although the difference between the rates of reduction of Δ^4-3- and 20-keto groups is not sufficiently large to reduce the former selectively, a 20-ketone can be selectively protected[105] as its Girard-T derivative. These results are in agreement with the observations[106] that cortisone acetate is reduced with 1·4 equivalents of hydride undergoing 80% reduction at $C_{(20)}$ and 8% reduction at $C_{(3)}$.

Sodium borohydride in dimethylformamide seems to be more selective since a 20-carbonyl (17α) compound is reduced[107] in the presence of a Δ^4-3- and 11-keto groups and a 21-acetate. In the case of 3β-methoxy-16α-bromoandrost-17-one (**151**) reduction with sodium borohydride occurs with inversion of configuration of the bromide giving the 16β-bromo-17β-ol (**152**), whereas lithium aluminum hydride reduction affords the uninverted 16α-bromo-17β-ol.

Some differences have been noted between the courses of reaction


Br
O
MeO
(151)
Br
OH
(152)
OCH3
OCH3
OH
(153)
OCH3
OCH3
O
(154)

with various hydrides. Thus 21-benzylidenepregnan-3α-ol-11,20-dione is reduced by potassium borohydride at the 20-carbonyl[108], lithium borohydride reduces both the 11- and 20-keto groups, whereas lithium aluminum hydride reduces the 11- and 20-carbonyls and the benzylidine side-chain double bond (to $PhCH_2CH_2$). However, in the case of dehydrorotenone (**153**)[109] sodium borohydride reduces both the carbonyl group and its adjacent double bond forming rotenol (**154**), whereas lithium aluminum hydride only reduces the carbonyl group.

Acetylacetone is reduced by lithium aluminum hydride to pent-3-en-2-ol ($CH_3CH{=}CHCHOHCH_3$) (70·5%), with some pentane-2,4-diol (2·5%) and unchanged diketone (19%)[110]. Benzoin affords mesohydrobenzoin at 0° in ether and mixtures of mesohydrobenzoin and isohydrobenzoin in the ratios of 3:1 and 1·5:1 in tetrahydrofuran and dioxan, respectively[110].

An 11-keto-12α-bromo steroid (the 3,20-disemicarbazone of 12α-bromocortisone) can be reduced with lithium aluminum hydride in tetrahydrofuran at 0° with little loss of bromine[111]. This reagent often causes reduction of the conjugate double bond in α,β-unsaturated carbonyl compounds, and a complex between cinnamaldehyde and lithium aluminum hydride[112] has been isolated. Sodium borohydride also reduces aliphatic nitroketones to nitrocarbinols[113]. The problem of the formation of borate complexes in the reduction of sugars by sodium borohydride is best overcome[114] by acetylating the crude reduction product.

Sodium borohydride and lithium borohydride both reduce 4,4′-dichlorobenzophenone faster than cyclohexanone (ratios 4:1 and 3:1, respectively) in pyridine[115]. However, although sodium borohydride in diglyme reduces the benzophenone faster (ratio 1·3:1), lithium borohydride in this solvent reduces cyclohexanone at a faster rate (1:3). This difference was attributed to the coordination of the ketone with lithium cations in diglyme and electrophilic reduction of this complex. It has been shown recently[116] that the reduction of ketones with lithium borohydride in pyridine occurs nearly instantaneously on adding water to the mixture during working-up, and neither cyclohexanone or 3,3,5-trimethylcyclohexanone are reduced in pyridine even on the addition of water. The reaction with lithium borohydride apparently produces pyridine–borane ($C_5H_5N{:}B_2H_6$) via the reaction below. The reaction of both ketones is first order in

$$C_6H_{10}O + LiBH_4 + C_5H_5N \longrightarrow C_6H_{11}OLi + C_5H_5\overset{+}{N}\overset{-}{B}H_3$$

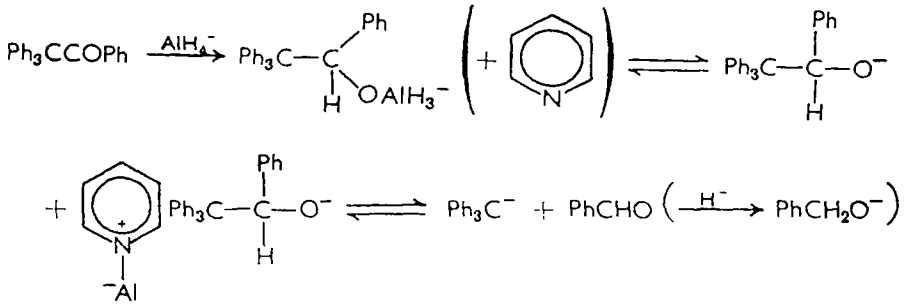
18+c.c.g.

both the ketone and hydride and the differences in rates of reduction are of the same order as the differences in their cyanohydrin dissociation constants, suggesting that the slower rate of reduction of the methyl-substituted ketone is due to steric hindrance.

Lithium aluminum hydride in pyridine has been shown to cleave carbon bonds in benzopinacolone (**155**) giving triphenylmethane and benzyl alcohol[117]. The four hydride ions seem to be available and the suggestion is that pyridine acts as a Lewis base coordinating the aluminohydride ion and allows the participation of undissociated

$$\underset{\textbf{(155)}}{Ph_3CCOPh} \longrightarrow Ph_3CH + PhCH_2OH$$

alkoxide ion. Diaryl ketones are also more reactive to this reagent[118]

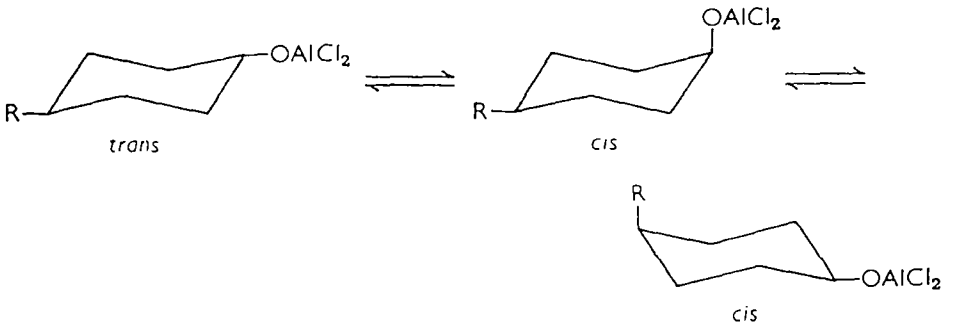


than dialkyl or aryl alkyl ketones. Thus 4-*p*-benzoylphenyl-2-butanone (**156**) is reduced by lithium aluminum hydride in pyridine

$$\underset{\textbf{(156)}}{PhCOPhCH_2CH_2COCH_3} \longrightarrow PhCHOHPhCH_2CH_2COCH_3$$

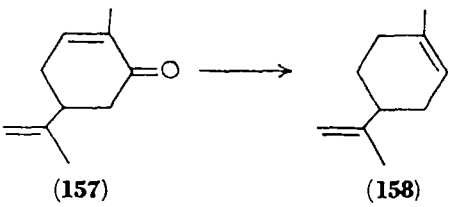
at the aroyl keto group, whereas use of ether as solvent causes reduction at both ketone groups. Sodium borohydride, however, only reduces the acetyl carbonyl group.

The addition of aluminum chloride to an ether solution of lithium aluminum hydride modifies its reducing power. Diaryl and alkyl aryl ketones are readily reduced by these reagents in equal molecular ratios to hydrocarbons[119], although dialkyl ketones are reduced normally to carbinols. These reagents in the proportion of 4:1 reduce 4-*t*-butylcyclohexanone to 80% *trans*-carbinol[120]. However, if more ketone is added at the end of the reduction, the carbinol product is 99% *trans*, formed in less than 15 minutes. It appears that a bulky aluminum complex (e.g. $ROAlCl_2$) is formed and any *cis*-carbinol is

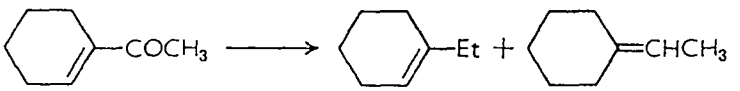


isomerized via the indicated equilibria in the presence of the ketone. In fact acetone will accomplish the same transformation. Lithium aluminum hydride and aluminum chloride in the ratio of 1:3 also effect this equilibration (probably via $AlHCl_2^-$, e.g. $LiAlH_4 + 3\ AlCl_3 \rightarrow Li^+ + 4\ AlHCl_2^-$), but not in the ratio of 3:1 (when AlH_3 may be formed).

The use of three parts of aluminum chloride to one part of lithium aluminum hydride reduces[121] benzalacetone ($PhCH{=}CHCOCH_3$) to 64% of hydrocarbon, of which 76% is *trans*-1-phenyl-1-butene and 33% is *trans*-1-phenyl-2-butene. No 1-phenylbutane was detected. (+)-Carvone (**157**) is reduced to nearly racemic dipentene



(**157**) (**158**)



(**159**) (**160**) (**161**)

(**158**), and 1-acetylcyclohexene (**159**) is converted into 1-ethylcyclohexene (**160**) (49%) and ethylidenecyclohexane (**161**) (34%).

Lithium cyanoborohydride ($LiBH_3(CN)$) reduces aromatic and aliphatic aldehydes in aqueous dioxan[122]. Ketones are not reduced, although α-ketols are. Calcium borohydride, prepared by mixing sodium borohydride and calcium chloride in ethanol, reduces

pregnane-3,20-dione to 77% pregnan-3α-ol-20-one[123] and is more specific than the sodium derivative.

Lithium aluminum alkoxyhydrides ($LiAlH_n(OR)_{4-n}$) prepared with optically active carbinols, such as (−)-menthol or with quinine, appear[124] to reduce ketones to slightly optically active carbinols.

A complex hydride synthesized by reacting calcium hydride with methyl borate[125] also reduces carbonyl compounds to carbinols, and sodium aluminum triethoxy hydride ($NaAl(OEt)_3H$), formed from sodium hydride and aluminum ethoxide, reduces simple carbonyl compounds[126].

A number of organotin hydrides have been investigated[127] as reducing agents for carbonyl compounds. The hydrides were prepared by reducing the corresponding organotin chlorides with lithium aluminum hydride, and are unique in that the carbinols are formed directly without the necessity of hydrolyzing an alkoxide, since no tin–oxygen bonds are formed. Thus diphenyltin dihydride (Ph_2SnH_2) reduces methyl vinyl ketone directly to methyl vinyl carbinol, forming diphenyltin with the direct transfer of two atoms of

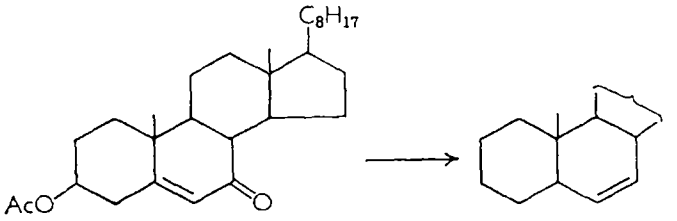
$$Ph_2SnH_2 + CH_2{=}CHCOCH_3 \longrightarrow Ph_2Sn + CH_2{=}CHCHOHCH_3$$

hydrogen. This hydride readily reduces simple aldehydes and ketones, as does the related butyl derivative (Bu_2SnH_2). However, camphor is only reduced slowly, forming similar proportions of *cis*- and *trans*-carbinols as does lithium aluminum hydride. This reagent also reduces a nitro group in preference to the carbonyl group in nitrobenzaldehydes. Triphenyltin hydride (Ph_3SnH) reduces benzaldehyde to benzyl alcohol, but does not reduce cyclohexanone. Phenyltin trihydride ($PhSnH_3$) is unstable and gives slow reduction, while butyltin trihydride ($BuSnH_3$) is more stable and causes reductions when used in large excess.

Diisobutylaluminum hydride ($(i\text{-}Bu)_2AlH$) and diethylaluminum hydride (Et_2AlH) are reported[128] to reduce cyclohexanone to cyclohexanol in 83% yield. The former hydride reacts with sodium hydride in benzene or toluene to form a complex hydride (probably $NaAl(i\text{-}Bu)_2H$) which reduces acetophenone and cyclohexanone to their carbinols, and cinnamaldehyde to cinnamyl alcohol.

Diphenylsilane (Ph_2SiH_2) reduces certain ketones[129] at high temperatures, and siloxane ($H_6Si_6O_3$) reduces aldehydes and ketones[130] via colored alkoxy- or aryloxysiloxanes. Cobalt hydrocarbonyl ($HCo(CO)_4$) has also been shown[131] to reduce α,β-unsaturated aldehydes and ketones to the saturated carbonyl compound through π-oxapropenyltricarbonyl complexes.

One of the simplest hydrides, diborane (B_2H_6), has recently been shown[132] to reduce aldehydes and ketones to carbinols in tetrahydrofuran or diglyme, although double bonds and carboxylic acids are also reduced[133]. The hydride is either generated externally or *in situ* by reaction of sodium borohydride with boron trifluoride (as its etherate). Diborane behaves as a Lewis acid and preferentially reduces groups of high electron density. Chloral is not reduced by this reagent ($Cl_3C\leftarrow\overset{\delta+}{C}H{=}O$), although it is readily reduced by sodium borohydride (BH_4^- is a nucleophile). 3β-Acetoxycholest-5-en-7-one (**162**) is reduced by diborane to 6-cholestene (**163**)[134].



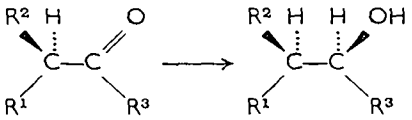
(162) **(163)**

Pyridineborane, prepared from pyridine hydrochloride and sodium borohydride, reduces carbonyl compounds to alcohols[135], although its reducing power is less than that of other hydrides. Ethylene-1,2-diamineborane ($(CH_2NH_2BH_3)_2$) reduces acetone to isopropanol and acrolein to allyl alcohol[136]. The reduction of 4-*t*-butylcyclohexanone with trimethylaminediborane ($Me_3N\cdot B_2H_6$) and diborane both give 16% *cis*-carbinol[137] suggesting that they are formed through a similar intermediate. However, trimethylaminediborane in the presence of boron trifluoride gives 50% *cis*-alcohol, whereas boron trifluoride has no effect on the stereochemistry of reduction by diborane. In the first case boron trifluoride undoubtedly adds to the carbonyl group. The borane complexes with ethylamine, *t*-butylamine, and dimethylamine ($EtNH_2\cdot BH_3$, t-$BuNH_2\cdot BH_3$, and $Me_2NH\cdot BH_3$) have also been shown[138] to reduce aldehydes and ketones.

Diisoamylborane (bis-(3-methyl-2-butyl)borane) is formed by the addition of borane to isobutene[139] and reduces carbonyl compounds to carbinols. n-Heptaldehyde and benzaldehyde are reduced very rapidly at 0°, cyclohexanone rapidly, and acetophenone and 2-heptanone at a slower rate; the reduction of benzophenone is very slow. The relative rate of reduction of 2-heptanone and pinacolone in dioxane is 12·9:1, while this ratio is 1·7:1 for diborane. Oximes are

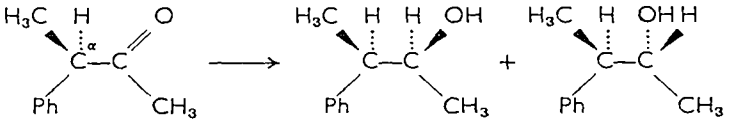
not reduced by this reagent and therefore offer the possibility of protecting a carbonyl group.

The *stereochemistry of the reduction* of carbonyl compounds by metal hydrides and other reducing reagents has been the subject of numerous studies[140], particularly in the case of cyclic ketones[141–143]. For acyclic compounds Cram[140] has enunciated a rule that in non-catalytic reductions 'the diastereomer will predominate which would be formed by the approach of the entering group from the least hindered side of the double bond when the rotational conformation of the carbon–carbon bond is such that the double bond is flanked by the two least bulky groups attached to the adjacent asymmetric center'. Thus the reduction of compound (**164**) should proceed as indicated, if the order of size of the substituents is $R^1 > R^2 > H$.



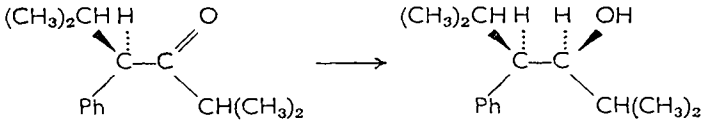
(**164**)

In support of this[140] 3-phenylbutan-2-one (**165**) is reduced by lithium aluminum hydride to *threo*- (**166**) and *erythro*-(**167**) 3-phenyl-



(**165**) (**166**) (**167**)

butan-2-ol in the ratio of 3:1. With a larger alkyl (e.g. ethyl) substituent on the α-carbon atom the ratio is reduced to 2:1. However, for a bulkier substituent on the other side of the carbonyl group, as in 2,5-dimethyl-4-phenylhexan-3-one (**168**)[144] the reaction is more stereospecific (90% *threo*-carbinol, **169**), the hydride approaching from the less-hindered side.

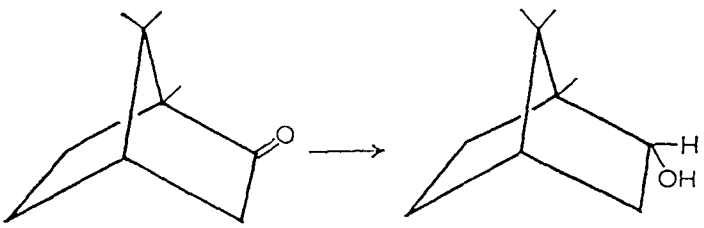


(**168**) (**169**)

A cyclic ketone can be reduced to two stereoisomeric alcohols, of which the equatorial isomer is the more stable. However, steric effects may often lead to the formation of more of the less stable (axial) isomer. These two factors are embodied in the effects[141] of

'product-development control' leading to the product of greater thermodynamic stability, and 'steric-approach control', in which the transition state for the formation of one of the products may be less favorable due to steric hindrance to approach of the attacking reagent from one side. Lithium aluminum hydride generally affords the carbinol resulting from 'product-development control', and 3-cholestanone is reduced to 90% 3β-cholestanol[145]. However, reductions with sodium borohydride begin to show the effect of 'steric-approach control' since 3-cholestanone forms 85% 3β-cholestanol with this reagent[103].

In the case of a bulkier hydride, such as lithium tri-*t*-butoxyaluminum hydride ($Li(t\text{-}BuO)_3AlH$), the bulky transition state will be more stable when occupying the equatorial position, if there is no large steric hindrance in the ketone. Accordingly, unhindered ketones such as 3-cholestanone and cholest-4-en-3-one afford essentially the equatorial alcohol[146]. However, although camphor (**170**) is hindered to attack from the *exo* direction, reduction with this complex hydride gives predominately borneol (**171**, 75%), the product of the less-



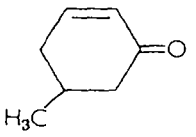
(170) (171)

hindered transition state. Lithium aluminum hydride forms 90% iso-(*exo*-)borneol.

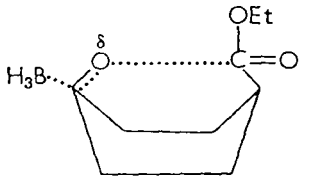
Other factors besides the hydride may also effect the proportion of isomer formed[147]. Varying the hydride from lithium aluminum hydride to sodium borohydride, lithium borohydride, and sodium trimethoxyborohydride ($NaB(OMe)_3H$), or changing the solvent and increasing the temperature produces little variation in the proportion of isomers formed in the reduction of 3-cholestanone. With sodium borohydride a small increase in axial product is noted on varying the solvent from isopropanol to ethanol and methanol (6·8 to 12·3 to 13·7%) and this probably results from reaction of the hydride with the solvent in the last two cases, or to a difference in ionization. Sodium borohydride appears to be more selective than lithium borohydride due to the increased ionic character and the

increased importance of hydrogen transfer in the transition state. The maximum amount of equatorial alcohol is formed with sodium borohydride in pyridine (94·4%), or with lithium borohydride in either tetrahydrofuran (91·5%) or diglyme (diethylene glycol dimethyl ether, 93·8%). The effect of temperature on the stereochemistry of reduction of 3,3,5-trimethylcyclohexanone and of 4-*t*-butylcyclohexanone has also been studied[148]. The effect is small in the second case, but in the case of the hindered trimethyl ketone the amount of axial product is favored by using solvents of good solvating power at low temperatures. Lithium aluminum hydride in ether gives 55% axial at 30° and 61·5% axial at −40°, whereas in pyridine and tetrahydrofuran 83 and 87·5% axial are formed at the same temperatures. Sodium borohydride reduction gives 80·5% axial at 27° and 98% at −40° in methanol and 57·5 and 62% in isopropanol at 27° and 0°, respectively.

The reduction of 4-methylcyclohexanone with lithium aluminum hydride in ether and potassium borohydride in ethanol gives 75 and 65% *trans*-4-methylcyclohexanol[149]. However, the reduction of 4-cyclohexylcyclohexanone with these reagents affords only 43 and 47%, respectively, of the *trans*-carbinol. The reduction of dihydroisophorone (3,3,5-trimethylcyclohexanone) also forms nearly equal amounts (50 and 47%) of the more stable (in this case *cis*) alcohol. The reduction of 2-methylcyclopentanone with lithium aluminum hydride and sodium borohydride forms, respectively, 75 and 73% of *trans*-2-methylcyclopentanol[150]. Sodium and ethanol reduction gives 87% *trans*-carbinol, although the equilibrium proportion is 58%. 5-Methylcyclohex-2-enone (**172**) is reduced by lithium aluminum



(**172**)



(**173**)

hydride to 93% of the *cis* unsaturated carbinol[151]. The electronic effect of a substituent in a cyclohexanone ring can effect the course of reduction of the keto group[152]. While 4-methoxycyclohexanone yields 41·4% *cis* (axial) carbinol, the 4-carbethoxy and 4-chloro derivatives give 73·8 and 66·0%, respectively, of this carbinol. This increased proportion of *cis* product induced by electronegative sub-

stituents was attributed to electrostatic interaction over the shorter distance possible for the *cis* transition state (**173**).

The stereochemistry of reduction of metal hydrides has often been compared to that of the Ponndorf–Meerwein–Verley reaction or of the Grignard reduction (see section VI). However, since these reactions are complex and their mechanism is still uncertain, no definite conclusions should be drawn. Reduction with aluminum alkoxides generally yields a larger proportion of the less-stable epimer[143] and this increases with the increasing size of the alkoxide. Thus 2-methylcyclohexanone gives 78% *trans*-2-methylcyclohexanol with aluminum isopropoxide[153] (82% is formed with lithium aluminum hydride[142]), and 99 and 98%, respectively, of this isomer with aluminum isobutoxide and aluminum *s*-butoxide.

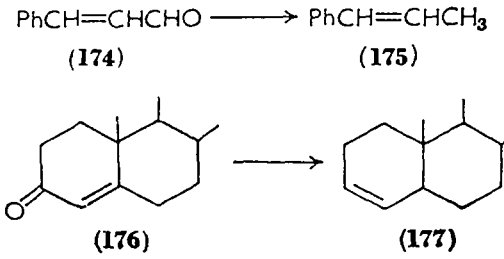
Whereas diborane forms 69% *trans*-2-methylcyclopentanol and 65% *trans*-2-methylcyclohexanol on reduction of the corresponding ketones[140], diisoamylborane affords 22 and 23%, respectively, of these carbinols. The related diisopinocamphenylborane, prepared from α-pinene and diborane, gives even less *trans*-carbinols (6 and 8%, respectively). This same reagent reduces methyl alkyl ketones ($RCOCH_3$) to optically active carbinols. The optical purities are 11% for ethyl, 17% for isopropyl, 30% for *t*-butyl, and 14% for phenyl.

VIII. MISCELLANEOUS REDUCTIONS

An alternate method to the Clemmensen reduction for converting a carbonyl compound into the corresponding hydrocarbon is through the *Wolff–Kishner reduction*[154] of the hydrazone or semicarbazone. The carbonyl derivative is heated to a high temperature (about 200°) with a base, usually sodium ethoxide. The reaction is conveniently carried out in a high boiling solvent, such as ethylene or diethylene glycol, and the hydrazone may be prepared *in situ* from the carbonyl compound and hydrazine hydrate. Sterically hindered ketones can be reduced by using completely anhydrous conditions[155]. It has recently been shown that the reaction can be carried out at lower temperatures[156] by using potassium *t*-butoxide in boiling toluene or in dimethylsulfoxide at room temperature. Wolff–Kishner reduction can be used in cases where Clemmensen reduction would destroy a ring system, as in pyrroles and furans, and also gives higher yields with insoluble high molecular weight ketones.

α,β-Unsaturated carbonyl compounds undergo rearrangement in

the normal Wolff–Kishner reaction[157], cinnamaldehyde (**174**) yielding 1-phenylpropene (**175**), and cholest-4-en-3-one (**176**) forming

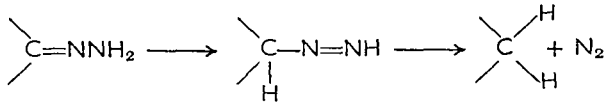


(**174**) (**175**)

(**176**) (**177**)

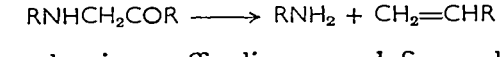
cholest-3-ene (**177**). However, with potassium *t*-butoxide in toluene **176** forms cholest-4-ene in 65% yield[156].

The reaction apparently proceeds via a diazo intermediate which

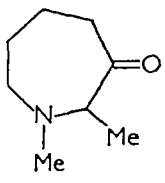


eliminates nitrogen. A kinetic study of the reduction of diaryl ketone hydrazones[158,159] has shown that the reaction is first order in ketone and base. The reaction is thought to involve the formation of the diazo anion $>CHN{=}N^-$, with the rate-determining step being the transfer of hydrogen in this anion. However, the values of energy and entropy of activation covered a large range and the hydrogen shift may occur in several ways.

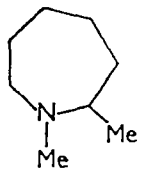
Tertiary α-amino ketones suffer a Hofmann-type elimination on



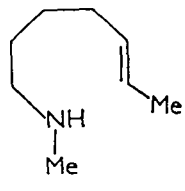
Wolff–Kishner reduction, affording an olefin and an amine. For cyclic α-amino ketones the extent of elimination varies with ring size ($8 > 7 \gg 6$)[159]. 1,2-Dimethyl-1-azacycloheptan-3-one (**178**) gives the normal product, 1,2-dimethylazacycloheptane (**179**) in 45% yield, and *N*-methylhept-6-enylamine (**180**) in 37% yield. The eight-



(**178**)



(**179**)



(**180**)

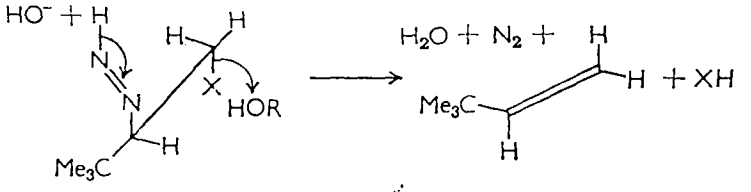
membered ring compound gives 65% octenylamine, but the β-pyrrolidone does not undergo ring opening. 1-Phenyl-3-*N*-piperidyl-2-propanone (**181**) forms 14% propenylbenzene (**182**) as well as 75% *N*-(-γ-phenylpropyl)piperidine (**183**). The reductive elimination

$$\underset{(181)}{PhCH_2COCH_2NC_5H_{10}} \longrightarrow \underset{(182)}{PhCH_2CH{=}CH_2} + \underset{(183)}{Ph(CH_2)_3NC_5H_{10}}$$

seems general for α-substituted pinacolones (**184**) [160]. If the substituent (X) is a saturated cyclic amine, the amount of olefin increases

$$\underset{(184)}{Me_3CCOCH_2X} \longrightarrow \begin{cases} Me_3CCH_2CH_2X \\ Me_3CCH{=}CH_2 \end{cases}$$

with ring size, and also with the anionic character in the order $Me_3CCO_2 < PhCO_2 < PhS < PhO$. A *trans* elimination (**185**) seems the most probable.



(**185**)

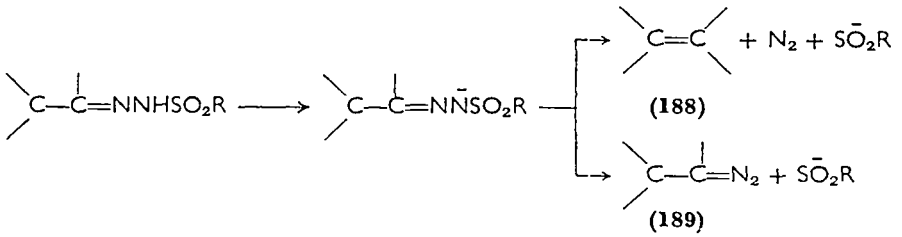
Recently Bamford and Stevens[161] have found that benzenesulfonylhydrazones (e.g. **186**) react with sodium in ethylene glycol to give olefins, if the ketone possesses an α-methylene group, and a

$$\underset{(186)}{PhCH_2\overset{\displaystyle CH_3}{\overset{|}{C}}{=}NNHSO_2Ph} \longrightarrow PhCH{=}CHCH_3 + PhSO_2H + N_2$$

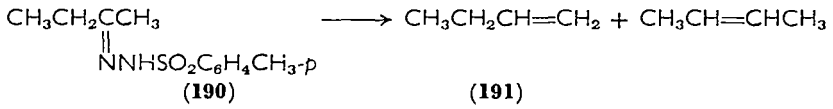
$$\underset{(187)}{PhC(CH_3){=}NNHSO_2Ph} \longrightarrow Ph{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}N_2 + PhSO_2H$$

diazo compound in other cases (e.g. **187**). Cyclohexanone gives a quantitative yield of cyclohexene, and dibenzil (PhCOCOPh) forms tolane (PhC≡CPh). The diazo compound cannot be the primary product in olefin formation, since camphor benzenesulfonylhydrazone gives camphene, whereas diazocamphane rearranges on treatment with base to tricyclene. The suggested mechanism involves the

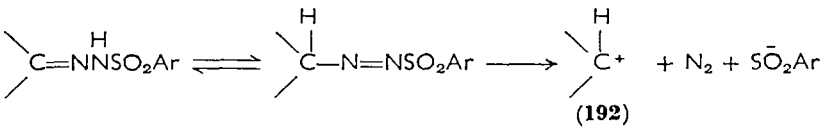
removal of a proton, followed by release of the sulfinate anion, either with loss of nitrogen and migration of a proton to yield an olefin



(188), or retention of nitrogen giving the diazo compound **189**. The formation of the olefin follows the Saytzeff rule, affording predominantly the most highly substituted olefin[162]. Thus the hydrazinyl derivative of ethyl methyl ketone (**190**) gives 28% 1-butene (**191**), 37% *trans*-2-butene, 30% *cis*-2-butene, and 5% n-butane. The



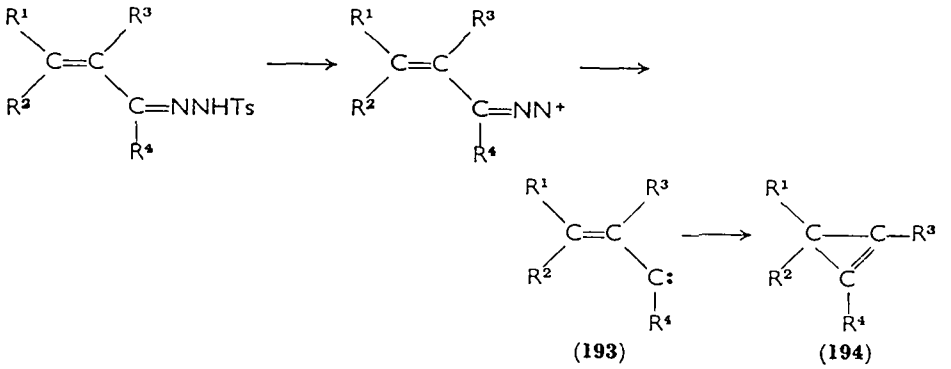
direction of elimination and the low *trans/cis* ratio indicate an *E*1 mechanism (unimolecular elimination) via a carbonium ion (**192**). The carbonium ion can then either eliminate a β-proton to form the



olefin, or rearrange and subsequently eliminate a proton, or react with the solvent (ethylene glycol) to yield an ether. Aryldiazoalkanes ($ArCHN_2$) are predominantly formed with exactly one equivalent of powdered sodium methoxide in pyridine in yields of 65–70%[163]. α,β-Unsaturated ketones undergo an interesting reaction[164] giving cyclopropenes (**194**) which must arise by internal addition to the double bond in the intermediate alkenyl carbene (**193**). The yields are good, except in the cases with one hydrogen atom in the β-position (R^2 = H).

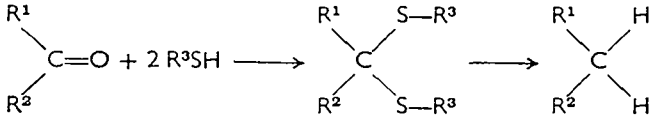
Simple tosylhydrazones are reduced[165] by sodium borohydride in methanol or dioxan to saturated hydrocarbons, and cyclohexanone and cholestan-3-one afford only cyclohexane and cholestane, respectively, in 80% yield.

Another indirect method of converting a ketone into the saturated hydrocarbon is by *desulfurization* of a *thioketal*[166] with Raney nickel,

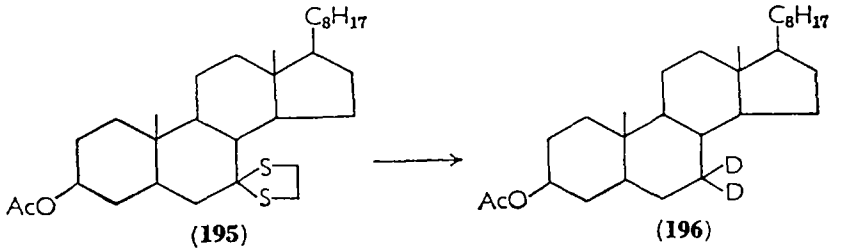


(193) (194)

The reaction is probably a free-radical one, and whereas benzaldehyde diethyl dithioketal ($PhCH(SEt)_2$) forms toluene with Raney nickel, the use of degassed Raney nickel gives stilbene

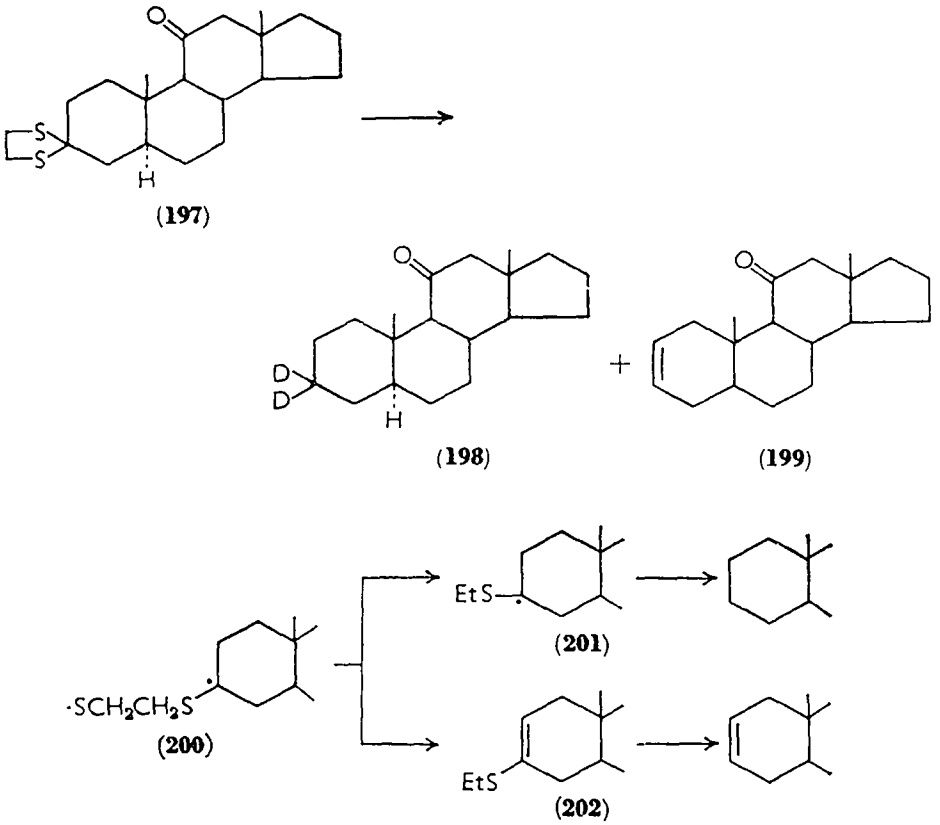


(PhCH=CHPh) [167]. If the Raney nickel is deuterized, a deuterated compound is formed and the ethylene dithioketal of 3-acetoxycholest-5-en-7-one (**195**) yields 7,7-dideuterocholesteryl acetate (**196**) [168].



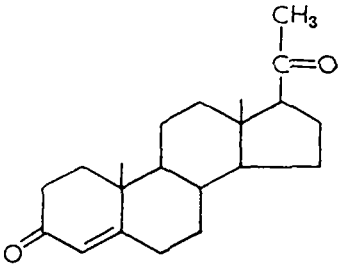
(195) (196)

The product of reduction can also depend upon the amount and type of Raney nickel used [169]. Androsta-3,11-dione 3-ethylene dithioketal (**197**) is reduced with fourteen times its weight of W-7 Raney nickel to 3,3-dideuteroandrostan-11-one (**198**). Using only an eight-fold amount of this catalyst, one-third of the product is 5α-androst-2-en-11-one (**199**). Cholestan-3-one ethylene dithioketal with fresh W-7 Raney nickel gives cholestane, whereas an aged sample of nickel catalyst gave cholest-2-ene, with some 3-ethylthiocholest-2-ene. The suggested mechanism involves the reduction of the diradical **200** to the saturated hydrocarbon via the thioethyl



radical **201** at high concentration of hydrogen radicals, and via the thioenol ether **202** at low concentration to the olefin. The benzylthio derivative (**204**) of the enol of androst-4-ene-3,20-dione (**203**) (which is formed selectively at position 3) is desulfurized to androsta-3,5-dien-20-one (**205**)[170]. Ethylene monothioketals (**206**) regenerate the ketone on treatment with Raney nickel in acetone[171], although the ketone may be subsequently reduced to the carbinol. Desulfurization can also be effected with hydrazine, with or without alkali in diethylene or triethylene glycol[172].

The *irradiation* of carbonyl compounds with ultraviolet light (see Chapter 16) can cause reduction[173]. The products in alcoholic solution are pinacols, as well as the monohydric carbinols[174]. The spectroscopic triplet state seems to be involved[175]. In nonpolar solvents hydrogen abstraction can take place within the same molecule from a γ-carbon atom, giving a cyclobutanol. The reaction probably involves the diradical, and optically active cyclic ketones



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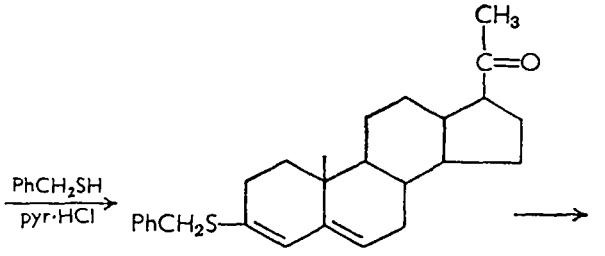
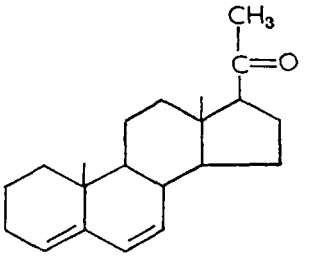


(204)



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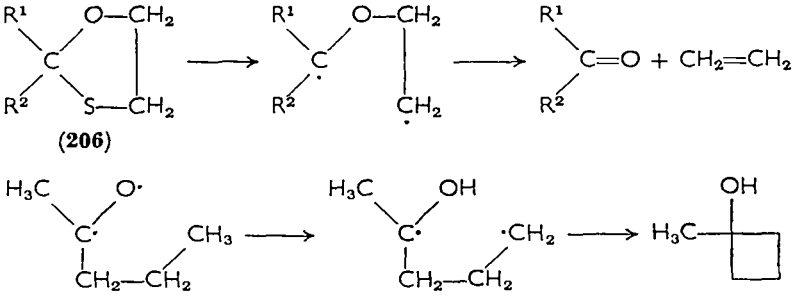
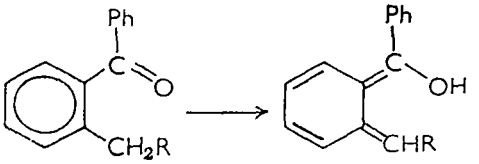


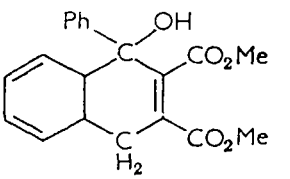
(206)

are converted into cyclobutanols with partial retention of configuration[176]. The intermediate diradical[177] is probably short-lived with comparable rates of racemization and cyclization.

o-Benzylbenzophenone (**207**, R = Ph) does not undergo photolysis in methanol solution[178], and appears to exist as its enol (**208**,



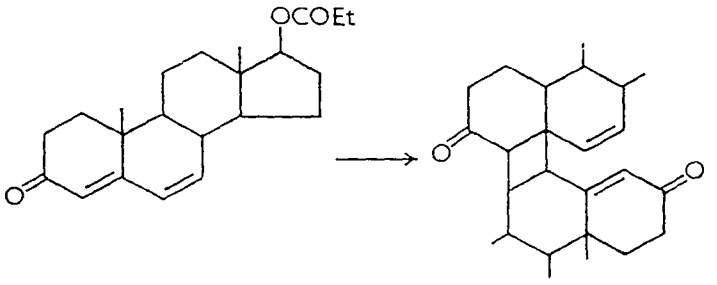
(207) (208)



(209)

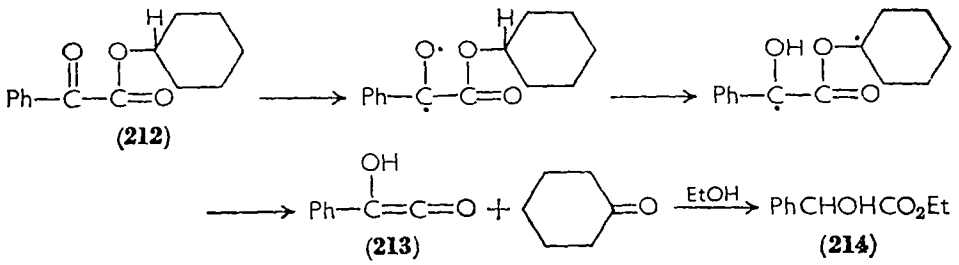
R = Ph). Irradiation in deuteromethanol results in the uptake of one atom of deuterium and the enolic form (**208**, R = H) of *o*-methylbenzophenone can be trapped as its diene adduct (**209**) with dimethyl acetylenecarboxylate ($MeO_2CC{\equiv}CCO_2Me$).

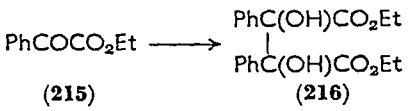
In the case of α,β-unsaturated ketones, photodimerization can occur, and androsta-4,6-dien-3-on-17β-ol propionate (**210**) gives only one product, probably **211**[179].



(**210**) (**211**)

An interesting photochemical reduction of benzoylformates has been reported recently[180]. Cyclohexyl benzoyl formate (**212**) yields ethyl phenylglycollate (**214**) and cyclohexanone (as well as 16% dimer) in ethanol. The reaction probably involves the transference of a hydrogen atom in the diradical, which splits off cyclohexanone giving **213**. Ethyl benzoylformate (**215**) in isobutanol affords only the dimer, diethyl α,α'-diphenyltartarate (**216**) and 2-butanone.

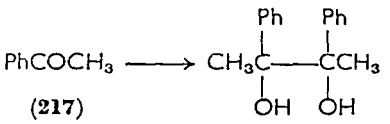




The action of *ionizing radiation* (x- or γ-rays) in aqueous solution usually results in oxidation or hydroxylation by hydroxyl radicals[181].

However, in the absence of oxygen, reduction can occur (probably by H·), and the x-ray irradiation of an air-free aqueous solution of cortisone gave dihydrocortisone[182].

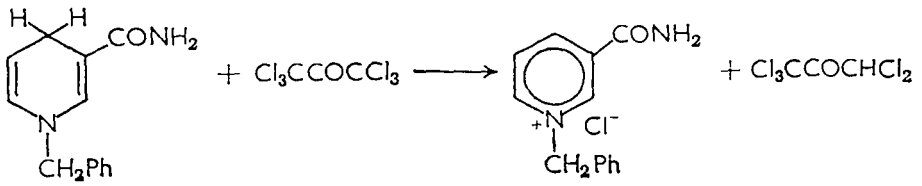
A *free-radical reduction* of aromatic ketones in 2-butanol at 130°, initiated by di-*t*-butyl peroxide, has been reported[183]. Benzophenone is reduced to benzhydrol, whereas acetophenone (**217**) gives *meso*- and racemic-2,3-diphenyl-2,3-butanediol (**218**) (2-butanone is also



(**217**) (**218**)

formed). The Hammett reaction constant (ρ) for the reduction of *m*- and *p*-substituted acetophenones is +1·59, and the reaction probably involves reaction of the 1-hydroxyalkyl radical with the ketone group.

Ketones can also undergo *biochemical reduction* (see Chapter 7), although an equilibrium is usually reached with the carbinol[184]. 1-Benzyl-1,4-dihydronicotinamide (**219**), a model for a coenzyme, reduces hexachloroacetone in formamide to the corresponding alcohol rapidly and nearly quantitatively at room temperature[185]. In cyclohexene in the presence of peroxide or ultraviolet light, pentachloroacetone and 1-benzyl-3-carbamoylpyridinium chloride



(**219**) (**220**)

(**220**) are formed, whereas in nitromethane a mixture of *sym*- and *unsym*-tetrachloroacetone results. The $C_{(4)}$ hydrogen atom is transferred in reduction, and 40% of the deuterium is available in the 4-deuterated compound.

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The Chemistry of the Carbonyl Group
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CHAPTER 12

Condensations leading to double bonds

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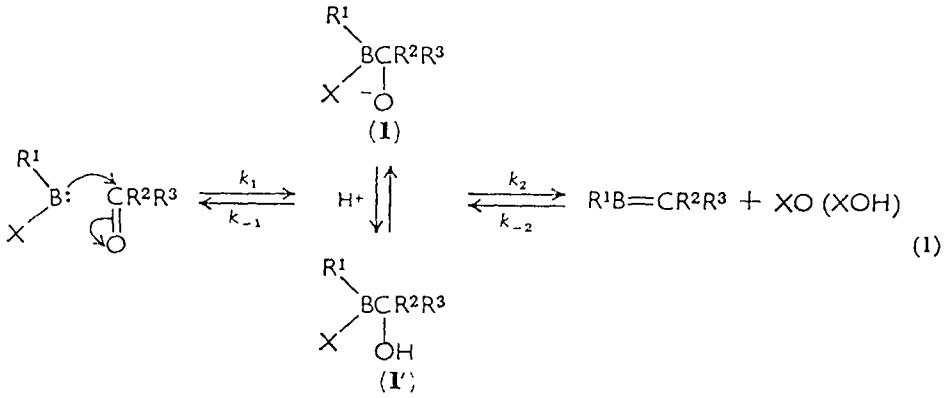
I. INTRODUCTION

The reactions to be considered in this chapter are those leading to formation of carbon–carbon double bonds such as the aldol,

Knoevenagel, and Wittig reactions, and those leading to compounds containing carbon–nitrogen double bonds such as imines, oximes, hydrazones, and semicarbazides. Much of the descriptive organic chemistry of these reactions is found in textbooks and reference books. The emphasis here will be on principles arising from more recent studies of the mechanisms of the reactions. With these principles in mind, the vast number of reported applications can be generalized, and factors of interest to the synthetic chemist such as yields, reaction conditions, side-reactions, and rates can be better appreciated. The discussion of the scope of the various reactions will serve to give the reader a feeling for the breadth of application but will not be comprehensive.

All the condensations to be covered have certain features in



(1)

common. These can be discussed in general terms initially so that when the reactions are considered individually later on, apparent differences may be seen to be special cases of a general scheme.

The condensations involve at least two steps. A nucleophilic reagent first adds to the carbonyl group to form an intermediate **1.** In most cases X is hydrogen, but in the Wittig reaction it is a phosphine moiety. The nucleophilic atom B is carbon or nitrogen. The second step is an elimination in which XO or XOH is split out. In those cases where B is carbon the addition step must be preceded by an ionization reaction in order to convert an inert reactant into a reactive nucleophile. In almost all cases the overall reaction is reversible. Because of this, the reaction mechanisms may be studied from either direction and the conclusions will be valid for the opposite direction since, by the principle of microscopic reversibility, each step proceeds in either direction through the same transition

state. In practice the chemist can often control the position of the overall equilibrium to suit his needs by changing solvent, acidity, or other reaction conditions, or by removing one of the products. Often the water is removed by azeotropic distillation, in other cases the condensation product will precipitate (phenylhydrazones, etc.). With some condensations, k_{-2} is negligibly small under most conditions so the overall condensation may be considered as irreversible. In general the product that is obtained, the ease of its formation, and the yield will depend upon the relative magnitudes of the four rate coefficients involved in the overall reaction. Since different types of bonds are formed and broken in the separate steps, the rates of these steps may be affected in different ways by changes in structure of the reactants or in reaction conditions. This differential response can modify the course of the reaction as well as the overall rate. Several important cases can be considered in a general way.

If the elimination is slow compared to the rate at which the addition equilibrium is attained, the addition compound **1′** will be the isolated product under a given reaction condition. As will be shown later in this chapter, the rate of the elimination step can be more responsive to a change in reaction conditions than the rate of the addition step so that under one set of conditions the intermediate is the isolated product while under other conditions the dehydration product is isolated. If the addition and elimination proceed at comparable rates, the intermediate **1** will accumulate to a measurable extent, reach a maximum concentration, and then diminish to zero or to an equilibrium concentration. The products that are isolated and their yields will depend upon whether overall equilibrium has been achieved or whether the products were isolated before complete equilibration. In both of these cases kinetic studies permit the evaluation of the rate coefficients in the general scheme, and the effect of changing structure or conditions on the individual constants can be determined.

A second important case exhibited by many of the reactions to be discussed is that in which the intermediate **1** never accumulates to a measurable extent. Under these conditions the measured rate coefficient for condensation may not be identifiable with any of the individual rate coefficients of equation (1) but may be a composite of several of the individual k values. In these cases interpretation of reactivity data can be difficult.

The condensations are almost invariably catalyzed by acids and/or bases. The nature of the catalysis may vary with different reactions

and is not completely understood in many instances. The difficulty arises from the fact that in most cases one or both of the reactants are weak acids or bases and often of quite different acidity or basicity. The carbonyl compound is rendered reactive by conversion into its conjugate acid ($R_2C{=}\overset{+}{O}H \leftrightarrow R_2\overset{+}{C}{-}OH$) or by hydrogen bonding with an undissociated acid. Carbonyl compounds are very weak bases, so the rate coefficients for addition to the conjugate acids must be much greater than those for the unprotonated carbonyls, since acid catalysis is observed at acidities where extremely low concentrations of the conjugate acids are present. In addition to rendering the carbonyl more electrophilic, acid catalysis can also operate in cases where the nucleophile is also a carbonyl compound (aldol condensation, etc.) by converting it into the more nucleophilic enol, as in (2). A third mechanism for acid catalysis arises from the fact that the

$$R^1CH{=}CR^2 \longleftrightarrow R^1\bar{C}HCR^2 \quad (2)$$
$$\quad\quad |\quad\quad\quad\quad\quad\quad ||$$
$$\quad\quad OH\quad\quad\quad\quad\quad\quad {}^+OH$$

dehydration step is subject to acid catalysis. In those condensations in which the nucleophilic atom B is nitrogen, an additional difficulty arises. Here the nucleophile is a base that loses its efficacy by conversion into its conjugate acid. In these cases an optimum acidity is often found for greatest reactivity where opposing effects of the acid are most favorably balanced.

Base catalysis is usually found in those condensations where the nucleophile is an 'active methylene' compound. The base serves to convert the reactant into a reactive anion, as in (3). In some cases

$$R^1\bar{C}HCOR^2 \longleftrightarrow R^1CH{=}CR^2 \quad (3)$$
$$\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad |$$
$$\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad O^-$$

the dehydration may be base-catalyzed. The nature of the catalysis mechanisms will be discussed in more detail for the individual condensations.

II. FORMATION OF CARBON–CARBON DOUBLE BONDS

A. The Wittig Reaction

The formation of an ethylenic bond by condensation of an alkylidene- or aralkylidenephosphorane (**3**) with a carbonyl group is known as the Wittig olefin synthesis or simply the Wittig reaction. The good yields of olefin and the unambiguous position of the double

bond has made the reaction increasingly attractive as a synthetic tool. In practice the quaternary phosphonium salts (**2**) are first

$$\underset{(2)}{R_3^1\overset{+}{P}CHR^2R^3}\ X^- \xrightarrow{\text{Base}} \underset{(3)}{R_3^1P{=}CR^2R^3} \xrightarrow{R^4R^5C=O} \underset{(4)}{R_3^1PO} + \underset{(5)}{R^2R^3C{=}CR^4R^5}$$

formed by reaction of the phosphine R_3^1P with a suitable alkyl halide R^2R^3CHX. As with other nucleophilic displacements, the order of reactivity[1] of the alkyl halides is I > Br > Cl. The lower alkyl halides and allylic halides form phosphonium salts readily at room temperature or by gentle warming in a solvent such as benzene. With larger alkyl groups, the reactants are heated without solvent or in a polar solvent such as nitromethane[2]. The salts are usually hygroscopic crystalline solids; they must be pure and dry before use.

The phosphoranes are resonance hybrids with contributions from ylene (**3a**) and ylide (**3b**) structures. Although the reagents are

$$\underset{(3a)}{R_3^1P{=}CR^2R^3} \longleftrightarrow \underset{(3b)}{R_3^1\overset{+}{P}{-}\bar{C}R^2R^3}$$

frequently referred to as ylides, we will refer to the class of compounds as phosphoranes (phosphorane = PH_5) and reserve the term 'ylide' for a particular contributing structure of the resonance hybrid. The phosphoranes are formed by removal of a proton from the corresponding phosphonium salt with a suitable base. Phenyllithium in an ether suspension was used originally[3]; other bases include n-butyllithium, sodium hydride, sodium triphenylmethide, sodium and potassium metal, sodamide, and alkoxides. Alkoxides are finding increasing favor despite the fact that they are similar in base strength to the phosphoranes so that an equilibrium mixture results (reaction 4). Since the overall condensation of the phosphorane with the

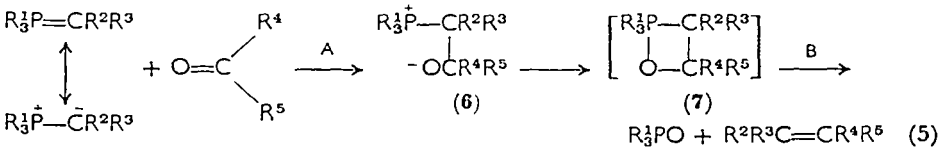
$$R_3^1\overset{+}{P}CHR^2R^3 + OEt^- \rightleftharpoons R_3^1P{=}CR^2R^3 + EtOH \qquad (4)$$

carbonyl compound is irreversible, the existence of this equilibrium has no adverse effect on the olefin synthesis. The phosphoranes can be isolated as stable compounds, but it is just as convenient to carry out the condensation by treatment of the phosphonium salt with base in the presence of the carbonyl compound. The acidity of the phosphonium salts is attributed both to the inductive effect of the positively charged phosphorus atom in the salt and to stabilization of the conjugate base by the mesomerism **3a** ↔ **3b**. This mesomerism arises from the ability of the phosphorus atom to expand its valence

shell to a decet by *d*-orbital resonance[1]. If R^2 or R^3 also possess electronegative groups such as —CN or —COR, the conjugate base is further stabilized by additional resonance, and good yields of phosphorane can be obtained with relatively weak bases. Thus, treatment of $Ph_3\overset{+}{P}CH_2CN\ Cl^-$ with 5% aqueous sodium hydroxide for an hour gives[4] an 85% yield of $Ph_3P{=}CHCN$.

I. Mechanism

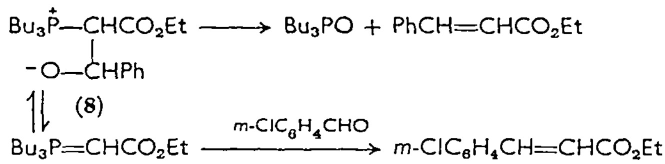
As with other double-bond forming condensations, the Wittig reaction involves nucleophilic addition to the carbonyl (equation 5, step A) followed by elimination (step B) to give the olefin. The



phosphorane derives its nucleophilic character from the ylide contribution **3b**. The existence of **7** as a true intermediate has not been demonstrated. It is more likely a representation of the configuration of the transition state for the elimination step. The important aspect of the elimination step is a four-centered transition state by which the olefinic bond arises in a fixed and unambiguous position. The existence of such a transition state is inferred from the fact that optically active phosphonium salts undergo Wittig reactions to give active phosphine oxides with overall retention of configuration[5,6]. Since the elimination step is the only one involving displacement at the optically active phosphorus, it must proceed with retention. The intermediacy of the betaine **6** has been demonstrated in at least one case. Condensation of $Ph_3P{=}CH_2$ with benzaldehyde in ether gives the stable betaine as a precipitate. Warming the betaine in ether gives phosphine oxide and styrene in 91% and 67% yields, respectively. Decomposition of the betaine in the presence of benzophenone, which forms olefin more readily than benzaldehyde, gives only a trace of 1,1-diphenylethylene. The benzophenone is recovered quantitatively[7]. Thus the addition step is almost completely irreversible, and the betaine must be a true intermediate and not just an inert side-product.

Direct evidence for reversible betaine formation has been obtained in at least one case. The phosphorane arising from dissociation of the

betaine **8** has been trapped by reaction with *m*-chlorobenzaldehyde (equation 6).



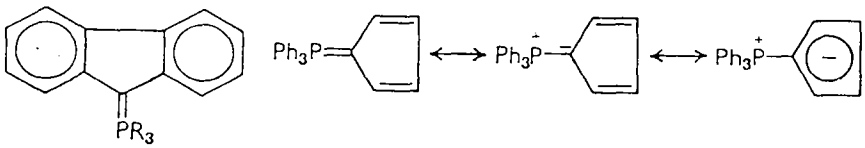
(6)

Few kinetic studies of this reaction have been made. It has been shown that the condensation of $Ph_3P{=}CHCOOR$ with benzaldehyde is subject to acid catalysis[9]. Traces of benzoic acid in the aldehyde give very poorly reproducible results. Many of the conclusions regarding the effect of structure on reactivity have been drawn from studies of product yields under standardized conditions. The interpretation of the results depends upon whether addition (step A) or elimination (step B) is rate-determining. In most cases the nature of the rate-determining step has been deduced intuitively from the effect of systematic structural changes in the carbonyl compound and phosphorane on the yield of products, and from whether betaine accumulates during the reaction. By analogy with other carbonyl condensations, the addition step should occur most readily with those carbonyl compounds in which the carbonyl carbon is rendered more electrophilic by a high degree of polarization. Electron-withdrawing substituents should facilitate addition and electron-donating groups should retard it. This has been confirmed in a study of the kinetics of reaction of carbomethoxymethylenetriphenylphosphorane with a series of *m*- and *p*-substituted benzaldehydes[8]. The addition step is rate-determining, and a linear Hammett correlation is obtained with $\rho = +2{\cdot}7$. In the reaction of fluorenylidenetriphenylphosphorane (**9**, R = Ph) with a series of *p*-substituted benzaldehydes, no betaine intermediates could be detected; the addition step is probably rate-determining. Under a standard set of conditions, the yields of olefin varied from 96% with *p*-nitrobenzaldehyde to 0% with the *p*-dimethylamino derivative[10].

The nucleophilic character of the phosphorane also influences the ease of addition to a given carbonyl compound. Electron-withdrawing R^2 and R^3 groups decrease the reactivity of the phosphorane in the addition step by delocalizing the negative charge and lowering the carbanion character of the ylide carbon. Methylenetriphenylphosphorane ($R^2 = R^3 = H$) reacts with almost all aldehydes and ketones[11] while cyclopentadienylidenetriphenylphosphorane is

unreactive[12]. The stability of the latter is attributed to a large contribution of **10c** to the resonance hybrid. This same type of charge delocalization is responsible for the low nucleophilicity of **9**, R = Ph or alkyl, and explains why the addition step with these reagents is slow and rate-determining.

The nucleophilic character of the phosphorane is also altered by phosphorus substituents that can change the relative contributions of the ylide and ylene to the resonance hybrid. Increased *d*-orbital resonance (ylene form) lowers the nucleophilic reactivity. The extent of *d*-orbital resonance between the partially negative carbon and partially positive phosphorus atom increases with the degree of positive charge on the latter[13]. Phosphorus substituents that withdraw electrons by an inductive effect increase the contribution of the ylene form and decrease the ease of addition to the carbonyl. Thus, ylidenetrialkylphosphoranes are more reactive than similar triphenyl analogs because the latter derivatives decrease the ylide contribution to the



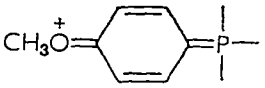
(**9**) (**10a**) (**10b**) (**10c**)

hybrid. In a series of reactions where addition is rate-determining, **9**, R = butyl, gives 94% yields of olefin with *p*-methoxy- and *p*-dimethylaminobenzaldehyde under the same conditions that the triphenyl analog gives 37% and 0% yields[10].

In those cases where decomposition of the betaine is rate-determining intuitive prediction of the effect of substituents is less straightforward. If addition is rapid and irreversible, betaine will accumulate and the effect of structural variations will be to alter the specific rate coefficient for elimination. If, on the other hand, addition is rapid and reversible, the overall rate will depend upon the product of the specific rate coefficient for elimination and the equilibrium concentration of betaine, which could be immeasurably small. Phosphorus substituents that decrease the formal positive charge in the betaine decrease the electrostatic attraction for the negative oxygen and decrease the ease of elimination. This same type of substitution facilitates addition, as pointed out above, so that in certain cases opposing R^1 substituent effects result. The net effect might be small and of unpredictable direction. The rate of elimination should be

accelerated by R^2–R^5 groups that can conjugate with the incipient double bond in the transition state.

Few structure–reactivity studies have been made of cases where decomposition of the betaine to olefin is clearly the rate-determining step. The reactions of benzaldehyde and of benzophenone with methylenetriarylphosphoranes appears to fall into this case, since the rapid accumulation of betaine followed by a slow elimination to products has been demonstrated[7]. The rates of elimination are slower when R^1 = *p*-tolyl or *p*-anisyl than when R^1 = phenyl. This has been attributed to a reduction of the formal positive charge on the phosphorus atom of the betaine through a significant contribution from



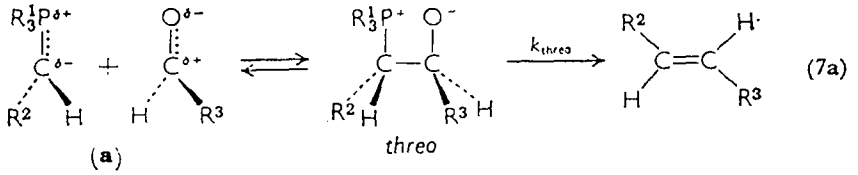
There is a question, however, whether resonance interactions between phenyl rings and tetracovalent phosphorus occur[13–16].

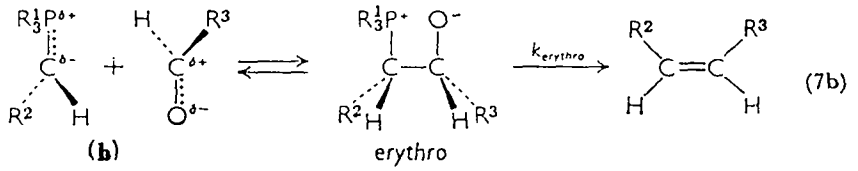
2. Stereochemistry

The ratio of geometric isomers in the olefinic product appears to be controlled by a combination of steric factors in the reactants and by environmental factors. In nonpolar solvents, such as ether and benzene, the thermodynamically more stable *trans* isomer predominates; increasing the polarity of the solvent increases the proportion of *cis* olefin. Benzylidenetriphenylphosphorane (**11**) reacts with benzaldehyde to give 30% *cis*-stilbene in ether and benzene[3,17], 53% in ethanol[17], and 75% in dimethylformamide[18]. The addition of nucleophilic substances to nonpolar solvents also increases the proportion of *cis* olefin. Reaction of **11** with propionaldehyde in benzene containing the following additives gives the indicated fraction of *cis* olefin: none (0·26), piperidine (0·33), n-butylamine (0·36), aniline (0·40), lithium bromide (0·91), and lithium iodide (0·93). Lithium iodide in dimethylformamide gives nearly pure *cis* olefin[19].

The stereochemical course of the reaction is determined during the addition step, since once the point represented by **6** is reached, the configuration of the R groups is fixed. The phosphorane can approach the carbonyl to give betaine having either the *threo* or the *erythro* configuration. The *threo*-betaine will decompose to *trans* olefin

while the *erythro* will give *cis* product (equations 7). The stereoselectivity of the overall reaction will depend in part upon whether the addition is reversible. If it is not, the diastereomeric betaine that forms fastest will predominate. If addition is completely reversible, the isomer ratio in the olefinic product will be determined by the equilibrium ratio of diastereomers and/or the ratio $k_{threo}/k_{erythro}$. In nonpolar solvents the reactants probably approach as in **a** to give the *threo* form with maximum electrostatic attraction and minimum nonbonded interaction between the eclipsed substituents. If addition is essentially irreversible, *trans* olefin will predominate. In nucleophilic solvents or in nonpolar solvents containing added nucleophiles solvation or interaction with the ylide phosphorus would decrease





the positive charge on phosphorus so that electrostatic attraction between ylide phosphorus and carbonyl oxygen would become less important in the addition transition state. In these media the approach via configuration **b** might become more probable. The decreased electrostatic attraction is compensated in part by going from an eclipsed conformation to a more favored staggered conformation. Support for this interpretation comes from the fact that the yield of *cis* olefin increases with the concentration and basicity of the added nucleophile, suggesting a preequilibrium between the reagent and nucleophile[19]. The nucleophilic addenda decrease the rate of the overall reaction which also supports the idea of a decreased charge on phosphorus through prereaction complex formation.

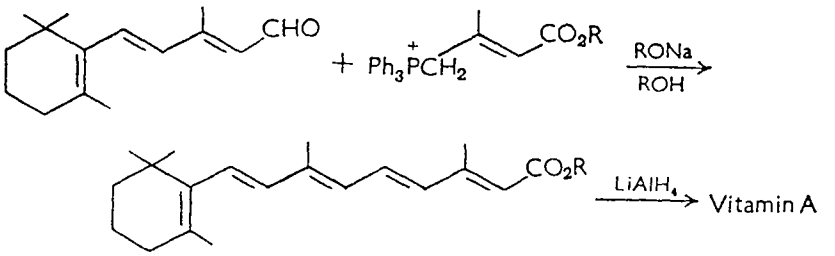
The ability to control the stereochemical course of the olefin synthesis by choice of solvent or environmental factors has led to the preparation of natural products not readily accessible by other means. *cis* Ethylenic fatty acids from C_{16} to C_{22} have been prepared by the Wittig reaction in overall yields of 54–73% in dimethylformamide[20].

Condensation with ketones in this solvent leads to stereoselective synthesis of branched-chain unsaturated fatty acids[21].

3. Scope

Several excellent reviews have covered the applications of the Wittig reaction[1,2,11,22]. For the sake of completeness some of these applications will be summarized in order that the reader may gain a feeling for the breadth of the reaction. It was pointed out in section II.A.1 that the phenyl groups of fluorenylidenetriphenylphosphorane (**9**, R = Ph) could be replaced with alkyl groups (**9**, R = Me or n-Bu) to give increased reactivity. It has been shown that the phosphorus substituents can be phenyl or methyl or any combination and the resulting phosphorane will give satisfactory yields of olefins with several aldehydes and ketones[23].

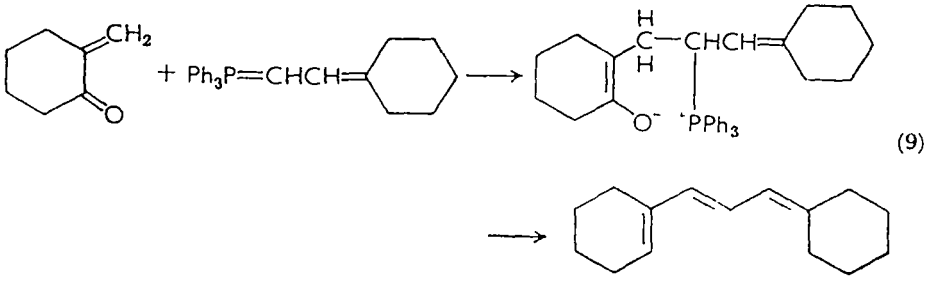
In general the condensations proceed more readily with aldehydes than with ketones. Sterically hindered ketones show very low



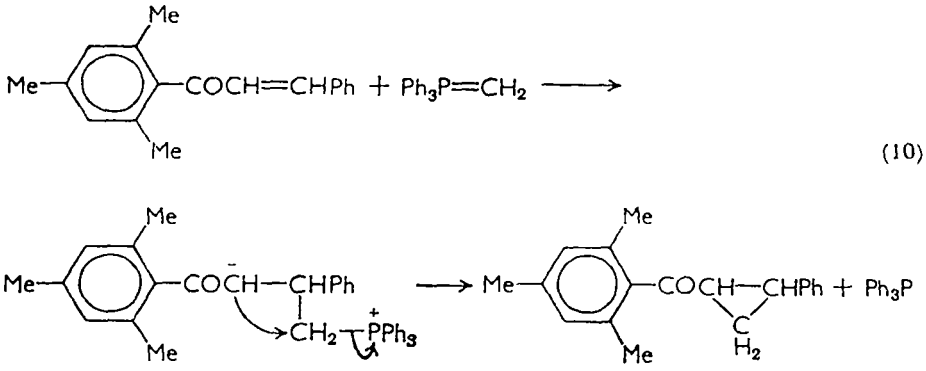
(8)

reactivity. The phosphorane $Ph_3P{=}CHCO_2R$ (**12**, R = Et) condenses with a variety of aldehydes in benzene to give 80–100% yields of unsaturated esters[24] while reaction with cyclohexanone in the same solvent gives cyclohexylideneethyl acetate in only 25% yield[25]. It does not condense with 2-methylcyclohexanone, 3-pentanone, acetophenone, or benzophenone. A 30% yield of unsaturated ester can be obtained when **12**, R = Me, is condensed with 2-methylcyclohexanone at 150° in the absence of solvent[26]. The condensation with aldehydes, α,β-unsaturated aldehydes, and polyene aldehydes occurs without complication and with good yields. No instances of conjugate addition have been reported for unsaturated aldehydes; addition is always at the carbonyl group, giving olefins in which the position of the new double bond is unambiguous. The synthesis of vitamin A is but one of a large number of examples (equation 8)[27].

Cases of conjugate addition have been reported with sterically hindered α,β-unsaturated ketones (equation 9[28], 10[29]).

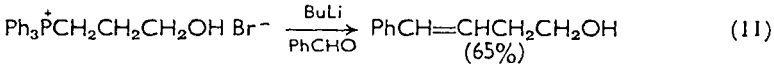


(9)



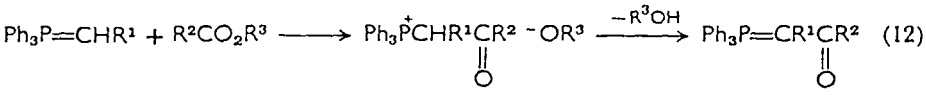
(10)

The carbonyl compound may contain other functional groups including halogen, dimethylamino, ester, ether, and hydroxyl. Since phosphoranes react reversibly with alcohols to give phosphonium alkoxides, an OH group in the carbonyl compound may conveniently be protected as the tetrahydropyranyl ether[30]. Phosphoranes containing an OH group are condensed successfully (equation 11)[2].



(11)

Methylenetriphenylphosphorane adds to the carbonyl function of esters to give a stable adduct that does not give olefin on heating. Instead, ROH is eliminated and the β-oxoalkylidenephosphorane is formed (equation 12)[3].



(12)

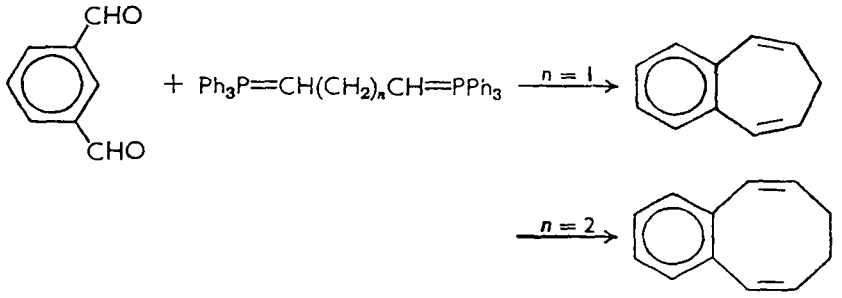
Bifunctional phosphoranes and carbonyl compounds have been

employed in the Wittig reaction to give bisarylpolyenes (equations 13a[31], 13b[32]). Condensation of bifunctional phosphoranes with

$$Ph_3\overset{+}{P}CH_2CH{=}CHCH_2\overset{+}{P}Ph_3\ 2Br^- \xrightarrow[PhCHO]{LiOR} PhCH{=}CHCH{=}CHCH{=}CHPh \quad (13a)$$

$$Ph_3\overset{+}{P}CH_2CH{=}CHPh\ Cl^- + OHC{-}C_6H_4{-}CHO \xrightarrow{LiOEt} PhCH{=}CHCH{=}CH{-}C_6H_4{-}CH{=}CHCH{=}CHPh \quad (13b)$$

bifunctional aldehydes has given fused-ring hydrocarbons (equation 14)[33].

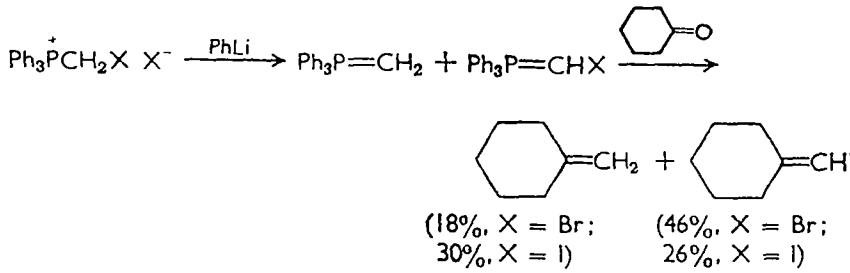


(14)

2-Bromo-1,1-diphenylethylene reacts with triphenylphosphine to form a phosphonium salt which condenses with benzophenone in the presence of phenyllithium to give a 54% yield of tetraphenylallene (equation 15)[34].

$$Ph_2C{=}CH\overset{+}{P}Ph_3\ Br^- + Ph_2CO \xrightarrow{PhLi} Ph_2C{=}C{=}CPh_2 \quad (15)$$

Halomethylenephosphonium salts react with phenyllithium to form two phosphoranes (equation 16)[35]. With cyclocitral, the salt



(16)

with X = Br gives the corresponding ethylene and vinyl bromide in the ratio 3:2 when the base is phenyllithium. When butyllithium is used, only the ethylene is found[36].

Phosphoranes can be condensed with a single carbonyl group of

α-diketones to give the corresponding α,β-unsaturated ketone (equation 17)[37].

$$\underset{\text{2 moles}}{Ph_3P{=}CHPh} + \underset{\text{1 mole}}{PhCOCOPh} \xrightarrow[6h]{\text{Reflux}} \underset{(32\%)}{PhC({=}CHPh)COPh} \qquad (17)$$

4. Modifications of the Wittig reaction

The Horner modification involves the addition of the anions of phosphine oxides (**13**, R^1 = alkyl, Ph) or of phosphonates (**13**, R^1 = OEt) to carbonyl compounds[38,39]. The intermediates eliminate phosphinate or phosphate anions to form olefins. Strong bases such

$$\underset{(\mathbf{13})}{R^1_2PO\bar{C}R^2R^3} + R^4R^5C{=}O \longrightarrow R^1_2POCR^2R^3CR^4R^5(O^-) \longrightarrow R^1_2POO^- + R^2R^3C{=}CR^4R^5$$

as sodamide or potassium *t*-butoxide are needed to form the anions. Only those phosphonates in which R^2 and R^3 are capable of stabilizing the carbanion (Ph, RCO, CN) are suitable. The modified reaction has the advantages that the alkylphosphonates are obtained more cheaply than the alkylphosphonium salts, the separation of products is easier because of the water solubility of the phosphate salt, and the phosphonate anions are stronger nucleophiles than the corresponding ylidenephosphoranes and condense with ketones that react with difficulty with the standard Wittig reagents.

Triethyl phosphonoacetate (**14**) has been condensed with benzaldehyde in a reaction that is analagous to a Knoevenagel reaction[40].

$$\underset{(\mathbf{14})}{EtO_2CCH_2PO(OEt)_2} + PhCHO \longrightarrow PhCH{=}C(CO_2Et)(PO(OEt)_2) \longrightarrow PhCH{=}CHCO_2Et + HOPO(OEt)_2$$

When piperidine is used as catalyst, 22–40% yields are obtained; addition of one-half equivalent of acetic acid increases the yield to 70%.

B. Aldol Condensations

A separate discussion of aldol and Knoevenagel condensations is based on differences in reactants and reaction conditions rather than any fundamental difference in mechanism. Because it is more convenient to discuss certain aspects of these condensations separately,

the classical approach will be followed. The aldol condensations treated in this section will involve only aldehydes and ketones as reactants; condensations of all other 'active methylene' compounds with carbonyl compounds will be classed as Knoevenagel condensations.

I. Conditions

Aldehydes and ketones do not condense readily without catalysts because they are not in themselves sufficiently strong electrophiles or nucleophiles. The acids and bases used to catalyze the condensations serve to convert the inherently unreactive compounds into reactive nucleophilic anions or enols or to electrophilic cations. Thus, while the general addition–elimination mechanism still applies to the aldol condensation, the addition step is preceded by a reversible acid–base reaction (equations 18, 19). Writing these acid–base reactions as

$$R^1CH_2COR^2 + B: \rightleftharpoons R^1\bar{C}HCOR^2 + B{:}H^+ \tag{18}$$

$$R^1CH_2COR^2 + HA \rightleftharpoons \left[\begin{array}{l} R^1CH_2CR^2 \\ \quad\| \\ \quad {}^+OH \\ \quad\uparrow\downarrow \\ R^1CH_2\dot{C}R^2 \\ \quad\quad| \\ \quad\quad OH \end{array}\right] + A^- \rightleftharpoons \left[\begin{array}{l} R^1\bar{C}HCR^2 \\ \quad\| \\ \quad {}^+OH \\ \quad\uparrow\downarrow \\ R^1CH{=}CR^2 \\ \quad\quad| \\ \quad\quad OH \end{array}\right] \tag{19}$$

reversible reactions is not to imply that equilibrium is always rapidly established. Removal of a proton from a carbon atom is often a relatively slow process, and may even become the rate-determining step in the overall condensation reaction. In this case the equilibrium is not established, and neither the base strength of the catalyst nor the acidity of the methyl or methylene group (in the thermodynamic sense) may be as important as the rate at which enolization is accomplished.

With certain carbonyl compounds, the rate of addition to form the aldol or ketol is much more rapid than the rate at which the aldol or ketol dehydrates, so that the intermediate can be isolated as a reaction product. This is true of the acid- and base-catalyzed condensation of acetaldehyde (equation 20) and the base-catalyzed condensation of acetone (equation 21). The self-condensation of acetone illustrates two practical examples of how control of the overall course of the condensation can be exerted by manipulation of the various rates. (*a*) The addition equilibrium does not favor the

diacetone alcohol; equilibration is avoided and the alcohol is formed in 71% yield by placing the catalyst in a Soxhlet extractor and removing the alcohol from contact with the catalyst as it forms. (*b*) The dehydration of the aldol is promoted by acids. When acetone is condensed in the presence of hydrochloric acid, the diacetone alcohol dehydrates as rapidly as it forms. Thus, k_2/k_1 is greater in

$$2\ MeCHO \rightleftharpoons MeCHOHCH_2CHO \xrightleftharpoons{Heat} MeCH{=}CHCHO \qquad (20)$$

$$2\ MeCOMe \underset{Reflux}{\overset{Ba(OH)_2}{\rightleftharpoons}} \underset{\text{diacetone alcohol}}{Me_2COHCH_2COMe} \xrightleftharpoons{H^+} \underset{\text{mesityl oxide}}{Me_2C{=}CHCOMe} \qquad (21)$$

acid than in basic solutions, and the course of the condensation is controlled by taking advantage of this differential response of the rates of the two steps to the acidity of the medium.

In most preparations the α,β-unsaturated carbonyl compound is the desired product. The dehydration either occurs rapidly under the conditions of the preparation, as in the formation of benzylideneacetophenone (equation 22)[41], or is effected by altering reaction

$$PhCHO + PhCOMe \xrightarrow[15\text{–}30°]{NaOH} \underset{(97\%)}{PhCH{=}CHCOPh} \qquad (22)$$

conditions prior to isolating the final products, as in the preparation of benzylideneacetone (equation 23)[42].

$$PhCHO + Me_2CO \xrightarrow[25\text{–}31°]{1.\ NaOH} \xrightarrow[distil]{2.\ HCl} \underset{(65\text{–}78\%)}{PhCH{=}CHCOMe} \qquad (23)$$

Aldol condensations are carried out under as mild conditions as possible—usually at or near room temperature with as weak a base as will promote the reaction. More drastic conditions favor further condensation of products. As the intermediates are subject to air oxidation, the reactions are usually carried out in an inert atmosphere.

Most acid-catalyzed condensations involve use of strong mineral acids. Amine salts have been used in the condensation of aldehydes[43] and a number of condensations are successfully catalyzed by ion-exchange resins[44–48]. These include strongly acidic sulfonic acid cation-exchange resins and strongly basic quaternary ammonium and weakly basic amine anion-exchange resins. In the condensation of aldehydes with β-diketones the reactions are more complete with

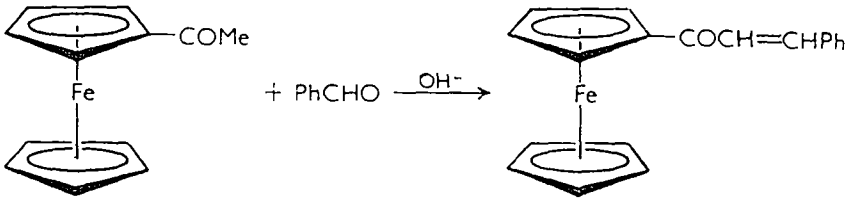
the weakly basic resins than when the quaternary ammonium type is used[48]. Use of resins facilitates isolation of the condensation product since the catalyst can be removed simply by decanting.

2. Scope

Aliphatic aldehydes and simple aliphatic ketones will usually undergo self-condensation. Condensations between two different aldehydes or two different ketones give the two products from self-condensation as well as the two crossed products. When a mixture of an aliphatic aldehyde and ketone is condensed under basic conditions the major product is the one in which the carbanion of the ketone appears to add to the carbonyl of the aldehyde. This could be due either to the fact that the aldehyde carbonyl is less hindered, or that the ketone is more acidic, or merely that both aldols are formed easily but one undergoes dehydration more rapidly than the other. Wittig and coworkers have recently reported a novel method for reversing this normal course of condensation[49]. The aldehyde is first converted into an imine and the lithium salt of the latter is condensed with the ketone (equation 24). Either the addition product or the unsaturated aldehyde may be isolated.

$$[\bar{C}H_2CH{=}NR]Li^+ + Ph_2CO \longrightarrow Ph_2CCH_2CH{=}NR \xrightarrow{H^+} \underset{OLi}{|} \qquad Ph_2C{=}CHCHO + H_2NR \quad (24)$$
$$(81\%)$$

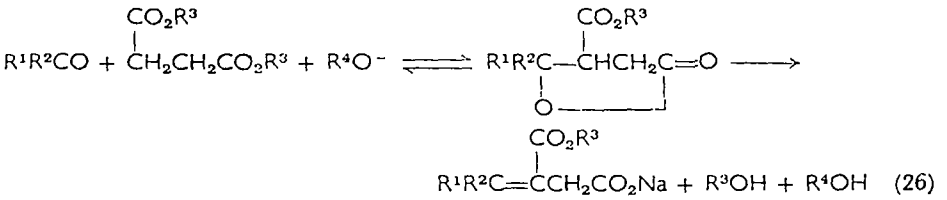
Aromatic aldehydes condense readily with alkyl and aralkyl ketones, including acetyl metallocenes (equation 25)[50].



(25)

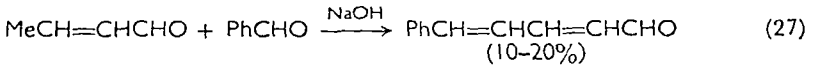
The α-methylene groups of simple esters will not usually undergo aldol condensation with carbonyl compounds. The condensation of aromatic aldehydes with γ-butyrolactone does take place, however[51,52]. Succinic esters also react with aliphatic and aromatic aldehydes and ketones under catalysis by strong bases in the Stobbe

condensation (equation 26). The specificity of succinic esters in this condensation is attributed to a second carbalkoxyl group suitably situated for formation of the intermediate paraconic ester[53].



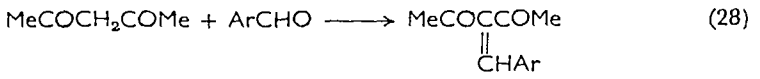
(26)

Vinylogous aldol condensations occur but usually in lower yields (e.g. equation 27).



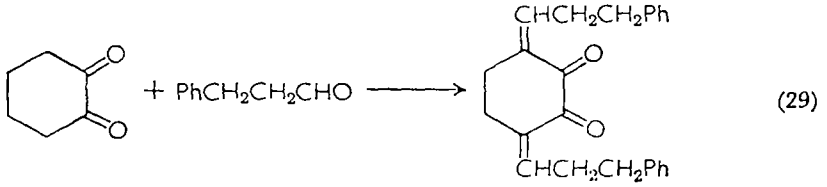
(27)

Diketones undergo aldol condensation, the nature of the product depending upon the number of carbon atoms separating the carbonyls. β-Diketones are condensed easily with aldehydes to give a normal product (equation 28). Relatively weak bases such as pyridine



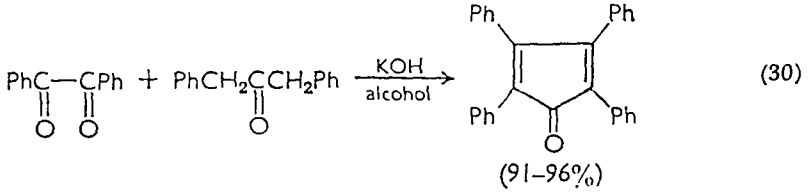
(28)

and ion-exchange resins will promote the condensation[54]. α-Diketones will condense normally with two moles of aldehyde if both adjacent methylene groups are free (equation 29)[55].



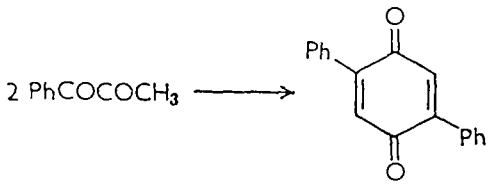
(29)

A ketone having two free α-methylene groups will condense with an α-diketone having no free methylenes to give intermolecular ring closure, as in the formation of tetraphenylcyclopentadienone from benzil and dibenzyl ketone (equation 30)[56]. Self-condensation of an



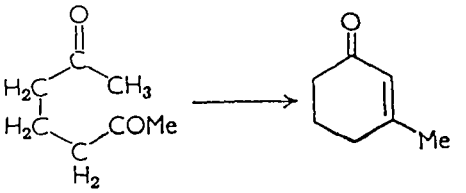
(30)

α-diketone having an unsubstituted methyl group can give ring closure to a substituted benzoquinone[57], as in equation (31).



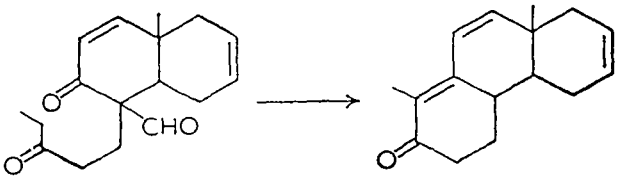
(31)

Intramolecular aldol condensations of 1,5-diketones to six-membered rings constitute one of the more important synthetic uses of the reaction. A simple case (equation 32) is the formation of 1-methyl-1-cyclohexen-3-one[58].

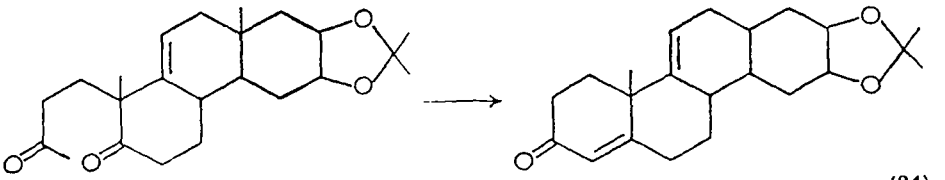


(32)

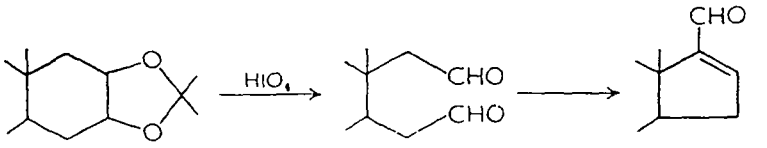
The greatest use of this ring closure in recent years has been in the synthesis of natural products. The successive formation of rings B, A, and D of a steroid by Woodward and coworkers illustrates the usefulness of the condensation (equations 33–35)[59].



(33)

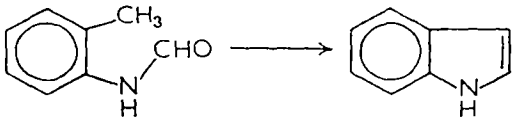


(34)



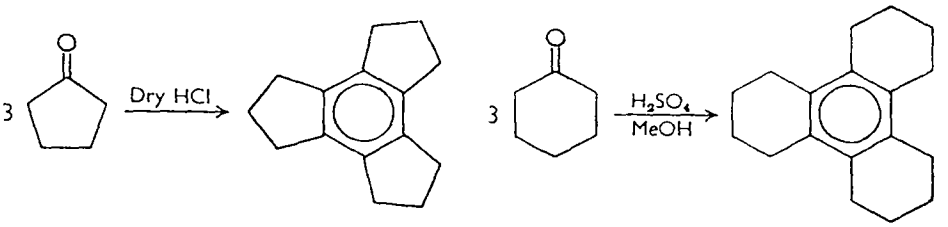
(35)

Intramolecular aldol condensations can also form rings containing heteroatoms, as in the synthesis of indole (equation 36)[60].



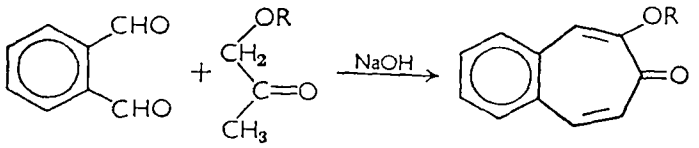
(79%) (36)

When simple aliphatic ketones are condensed in the presence of acids, the initial product can condense further to give either polymeric materials or cyclic products. The most familiar example is the formation of mesitylene from acetone in the presence of HCl. Alicyclic ketones such as cyclopentanone[61] and cyclohexanone[62] form similar cyclic trimers (equation 37).



(37)

Benzotropolones are formed by ring closure of phthalaldehyde with α-hydroxyacetone or its ether (equation 38)[63,64].

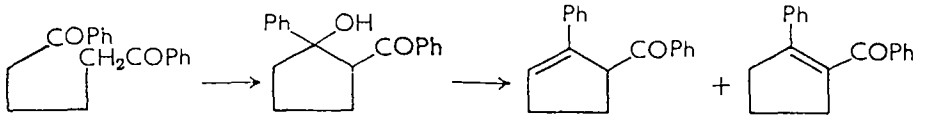


(38)

3. Limitations

The aldol condensation is not as free from complications and side-reactions as the Wittig reaction. Mixtures of products can arise either through competitive paths in the addition or dehydration stage leading to primary product, or by way of consecutive reactions of the primary product with itself or with unused reactant. Among the reactions that occur during the primary condensation to give different products are the competitive self-condensation and crossed-condensations between two different aliphatic aldehydes or ketones. The dehydration step can lead to a mixture of the α,β- and β,γ-unsaturated

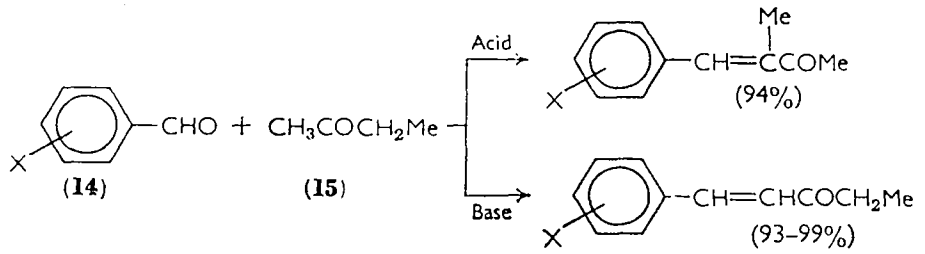
product by competitive loss of protons from either an α- or α′-position (equation 39)[65]. The ratio of isomers will be determined by their



(39)

relative stabilities if the dehydration–hydration equilibrium is rapidly established relative to the rate of formation of the intermediate, or by the relative rates of dehydration in the two directions if this step is essentially irreversible.

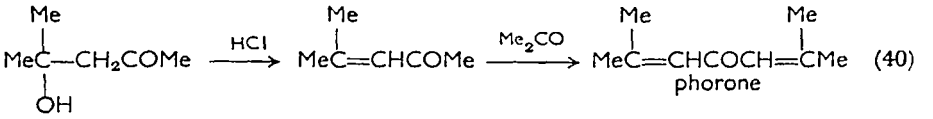
Unsymmetrical methyl ketones can undergo competitive condensation at either the methyl or methylene carbon, depending upon whether the reaction is carried out in acid or base. Acid-catalyzed reactions give condensation at the methylene carbon, while base catalysis usually gives the product with the double bond at the original methyl carbon. Gettler and Hammett showed that the condensation of benzaldehyde (**15**, X = H) with butanone (**16**) proceeds in a highly selective way under either condition[66]. In the aliphatic



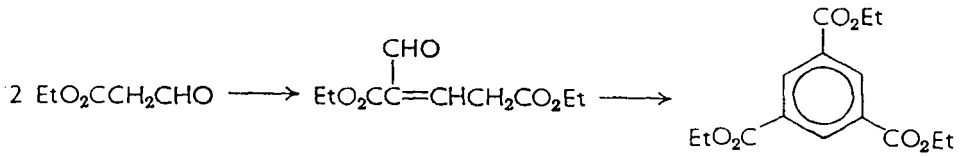
series **16** undergoes self-condensation in acid to give 80% methylene condensation and in base predominantly methyl condensation. Methyl ketones having alkyl groups larger than ethyl give both products regardless of the catalyst[67]. In a systematic study it has been shown that under basic conditions aromatic aldehydes and aliphatic aldehydes possessing an α-methylene substituent react with **16** to give methyl condensation while aliphatic aldehydes having two α-methylene hydrogens give methylene condensation. Under acid conditions, methylene condensation occurs in all cases[68]. Methyl benzyl ketone reacts with **15**, X = H or *m*-NO_2, to give methylene condensation when the catalyst is piperidine–heptanoic acid. The nature of the condensation product is determined by the relative

rates of the two stages in the condensation and will be considered in more detail in section II.B.4.

Examples of consecutive condensations involving the initial condensation product and unreacted carbonyl compound are found in the acid-catalyzed condensation of acetone to mesityl oxide and then phorone (equation 40), and in the condensation of ethyl formylacetate to ethyl α-formylglutaconate and finally ethyl trimesate (equation 41)[69].

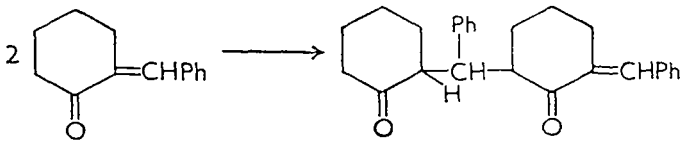


(40)



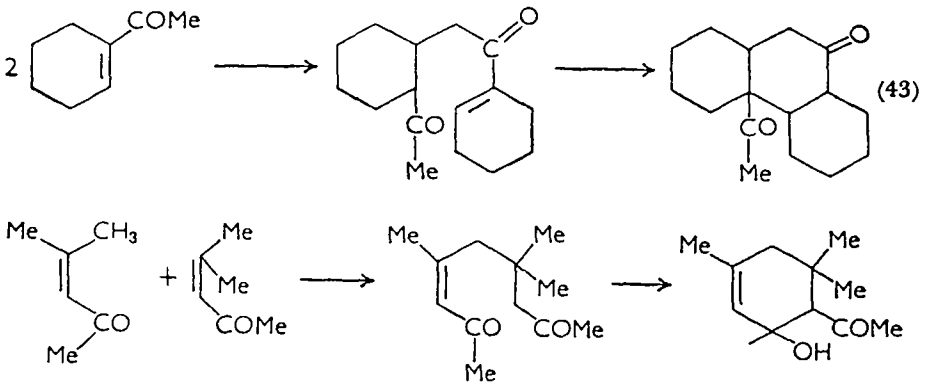
(41)

Condensation of an aldehyde with a ketone gives one predominant product unless the ketone is particularly unreactive; in such a case self-condensation of the aldehyde will occur if it has two α-hydrogens. The α,β-unsaturated ketone formed by condensation of an aliphatic aldehyde with an aliphatic ketone has active α-, α′- and (by vinylogy) γ-carbons ($R^1\dot{C}H_2CO\dot{C}H{=}CH\dot{C}H_2R^2$). These products may dimerize via Michael reactions to form monoolefinic 1,5- or 1,7-diketones. The latter may react still further via intramolecular aldol or Michael reactions. Thus, the condensation product from benzaldehyde and cyclohexanone dimerizes via a Michael reaction (equation 42)[70].



(42)

1-Acetyl-1-cyclohexene undergoes two consecutive Michael reactions to give a tricyclic diketone (equation 43)[71]. Mesityl oxide can react with itself, first by a Michael reaction and then by an intramolecular aldol condensation (equation 44)[72].



(43)

(44)

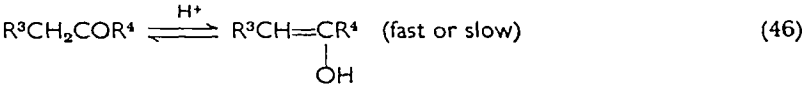
4. Kinetics and mechanism

The general scheme for carbonyl condensations given in section I (equation 1) can be made specific and expanded into accepted mechanisms for the acid- and base-catalyzed aldol condensation.

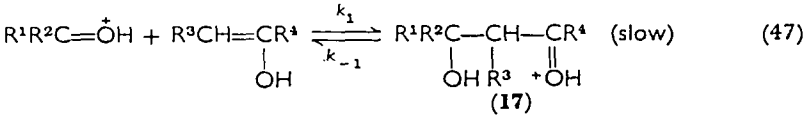
Acid catalysis

Addition step

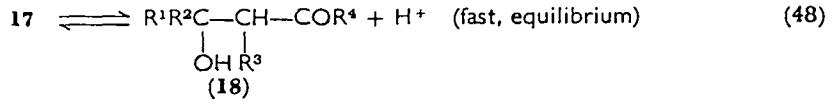
(45)



(46)



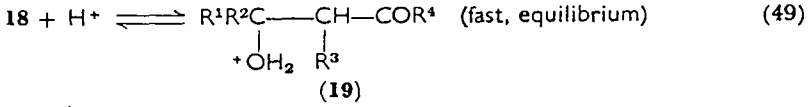
(47)



(48)

Dehydration step

i. Carbonium ion mechanism



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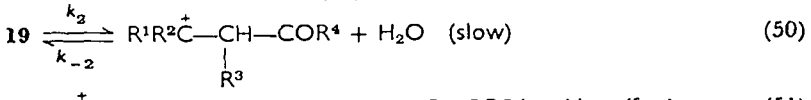

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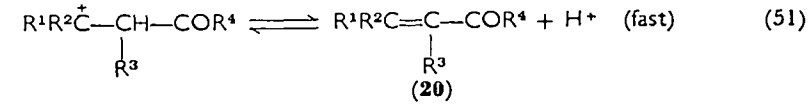


(51)

ii. Enolization mechanism

$$\mathbf{18} + H^+ \rightleftharpoons \mathbf{17} \quad \text{(fast, equilibrium)} \tag{48}$$

$$\mathbf{17} \rightleftharpoons R^1R^2C(OH)-C(R^3)=CR^4(OH) + H^+ \quad \text{(fast or slow)} \tag{52}$$

$$R^1R^2C(OH)-C(R^3)=CR^4(OH) \overset{H^+}{\rightleftharpoons} \mathbf{20} + H_2O + H^+ \quad \text{(fast or slow)} \tag{53}$$

Base catalysis

Addition

$$R^3CH_2COR^4 + B \rightleftharpoons R^3\bar{C}HCOR^4 + BH^+ \quad \text{(fast or slow)} \tag{54}$$

$$R^1R^2CO + R^3\bar{C}HCOR^4 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R^1R^2C(O^-)-CR^3HCOR^4 \quad \text{(slow)} \tag{55}$$

$$R^1R^2C(O^-)-CR^3HCOR^4 + BH^+ \rightleftharpoons \mathbf{18} + B \quad \text{(fast, equilibrium)} \tag{56}$$

Dehydration

$$\mathbf{18} + B: \rightleftharpoons R^1R^2C(OH)-\bar{C}R^3COR^4 + BH^+ \quad \text{(fast or slow)} \tag{57}$$

(**21**)

$$\mathbf{21} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathbf{20} + OH^- \quad \text{(slow)} \tag{58}$$

In these mechanisms all equilibria involving proton addition or removal from oxygen are regarded as being very rapidly established. Proton removal from carbon may or may not be rapid compared to the rates of the other reactions. The reactions designated as 'slow' are possible rate-determining steps in a particular overall condensation or in either of the two isolated steps. Evidence for two mechanisms for the acid-catalyzed dehydration step has been obtained. The two corresponding ketol conjugate acids, **17** and **19**, would be present in a mobile equilibrium and the exact mechanism for dehydration in a specific case could depend on the position of this tautomeric equilibrium as well as the magnitudes of the rate coefficients involved.

The base-catalyzed condensation of acetaldehyde to aldol is more rapid than the dehydration to crotonaldehyde, so the kinetics of the addition can be studied with only minor complication from succeeding reactions. Bell and coworkers[73,74] found that the order with

respect to acetaldehyde varies from approximately first to nearly second, depending upon the initial concentration of the aldehyde. The rate shows a nonlinear dependence on hydroxide ion concentration, with a minimum between 0·5 and 1·0 M. The results indicate that proton removal (equation 54) and carbonyl addition (equation 55) proceed at comparable rates. Further evidence for slow anion formation is that the reaction shows general base catalysis[74] and condensation of concentrated solutions of acetaldehyde in deuterium oxide gives no incorporation of deuterium into the aldol[75].

In acid solution the dehydration of aldol is greatly accelerated to where the carbonyl addition becomes the slowest step in the overall condensation. Since the dehydration–hydration equilibrium between aldol and crotonaldehyde is so rapidly established in acid solution relative to the rate at which aldol reverts to acetaldehyde, the approach to this equilibrium can be studied separately and from both directions[76]. The equilibrium ratio of aldol to crotonaldehyde is nearly unity, and the rates of hydration and dehydration both show a first-order dependence upon acid concentration.

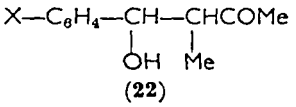
A kinetic study of the acid-catalyzed condensation of substituted benzaldehydes (**15**) with acetone and butanone by Noyce and coworkers[77–80] has shed considerable light on the relative rates of the various steps and the way in which the corresponding rates respond to changes in structure. In acid the rates of dehydration of the intermediate ketols are relatively rapid so that the ketols do not accumulate. They could be prepared and studied independently. The structure of the aldehyde has but a small effect on the rate of addition; *p*-methoxybenzaldehyde is three times as fast as the *p*-nitro derivative. This small rate difference is undoubtedly due to opposing substituent effects on the basicity of the aldehydes and on the stabilization of the transition state for addition since *p*-methoxybenzaldehyde is a thousand times more basic than *p*-nitrobenzaldehyde[81]. The rate of regression of the ketol to reactants (k_{-1} in equation 47) is very sensitive to the nature of the substituent in the aromatic ring with *p*-OMe $\gg$ H $\gg$ *p*-NO_2. The dehydration rate is rather insensitive to the substituent. In aqueous sulfuric acid the dehydration rates of the three ketols formed from acetone and **15** (X = *p*-OMe, H, and *p*-NO_2) gave only a three-fold variation, tending to rule out a mechanism involving rate-determining formation of a benzyl carbonium ion (equation 50) for the whole series. The fact that the rate of dehydration of the *p*-methoxy ketol shows a linear dependence on the Hammett acidity function, H_0, while the

other two ketols do not, suggests a carbonium ion mechanism for the former and the enolization mechanism for the others (equations 52 and 53).

The addition step is the rate-determining process in the acid-catalyzed condensation of *p*-substituted benzaldehydes with acetophenone[82]. The addition is again quite insensitive to substituent ($\rho = -0{\cdot}25$), reflecting a balancing of substituent effects on the equilibrium (equation 45) and on the rate (equation 47).

The base-catalyzed condensation of *p*-substituted benzaldehydes with *p*-substituted acetophenones in 90% ethanol proceeds by a rate-determining addition step[83]. The rate law (rate = k[aldehyde][ketone][base]) indicates that the initial ionization equilibrium (equation 54) is rapidly established and that addition is the only slow step. In contrast to the acid-catalyzed condensation the methoxy group in both the aldehyde and ketone decreases the rate. The rate decrease involves an increase in Arrhenius activation energy with little change in the PZ factor when the substitution is in the aldehyde ring, and a change in the PZ factor with little change in activation energy when substitution is in the ketone.

The base-catalyzed condensation of benzaldehyde with butanone in 70% dioxane–water proceeds to completion with no accumulation of ketol intermediate[66]. In this medium the rate law is rate = k[aldehyde][ketone][OH^-]^2, and the addition step appears to be rate-determining. In aqueous sodium hydroxide solution the rate of condensation of benzaldehyde with acetone shows a first-order dependence upon hydroxide ion concentration[84]. The condensation proceeds to an equilibrium with no accumulation of ketol. Separate study of the decomposition of this ketol showed that it undergoes competitive dehydration and cleavage to reactants at nearly equal rates, the partitioning coefficient k_{-1}/k_2 (equations 55 and 58) being equal to 1·5. The corresponding *p*-methoxy ketol behaves similarly with a value of k_{-1}/k_2 equal to 1·2. In sharp contrast the ketol **22**, X = OMe, obtained by methylene condensation of butanone with *p*-methoxybenzaldehyde reverts rapidly to reactants with negligible dehydration to the unsaturated ketone. Noyce and Reed



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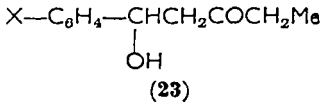


(23)

conclude that the structure of the final product obtained from base-catalyzed condensation of unsymmetrical ketones is governed by the

fact that the ketol formed by methyl condensation (**23**) can dehydrate with ease while the ketol from methylene condensation dehydrates with difficulty. It has been shown that both ketols (**22** and **23**, X = H) are formed in the condensation of benzaldehyde with butanone but while **23** undergoes simultaneous dehydration and regression to reactants, **22** gives only reactants[85]. The product of methyl condensation is the final product. These studies show that the product from base-catalyzed condensation of unsymmetrical ketones is governed by the ratio k_{-1}/k_2 for the intermediate, while the product from acid-catalyzed condensation is determined by the addition step, since dehydration in acid solution is very rapid. The acid-catalyzed rate of formation of **22** is greater than the rate of formation of **23** because of the difference in stability (and hence equilibrium concentration) of the reactants (enols) and of the transition states for formation of the two ketols.

C. Knoevenagel Condensations

1. Scope and limitations

Condensations of 'active methylene' nucleophiles other than aldehydes and ketones with carbonyl compounds are classed as Knoevenagel condensations. The nucleophiles are usually compounds distinguished by the possession of relatively acidic methylene groups, this acidity being the result of stabilization of the anionic conjugate bases by resonance. Many of the commonly used nucleophiles possess two activating groups as with the malonic acid derivatives, but compounds rendered acidic by single strongly electron-withdrawing groups such as —CN or $—NO_2$ are reactive.

Because the methylene compounds are more acidic than aldehydes and ketones, the bases used as catalysts in the Knoevenagel condensations are weaker than those needed to effect aldol condensations. Primary, secondary, and tertiary amines, as the free bases or their salts, and ion-exchange resins of the weakly basic amine types[86,87] are effective. Piperidine and diethylamine are particularly popular catalysts. The Doebner modification involves use of piperidine in pyridine as the reaction medium. Besides amine salts, Lewis acids such as BF_3[88], $AlCl_3$[88], and KI[89] have been used as catalysts. The condensation is similar in principle to the aldol condensation, having the same two-step addition–elimination mechanism, with the acid and basic catalysts playing similar roles in both condensations.

Aliphatic aldehydes condense readily with malonic acid or the half- or diester derivatives. The diester gives the alkylidenemalonate;

the initial product from the acid or acid ester usually undergoes decarboxylation to give the unbranched α,β-unsaturated acid or ester (equation 59). α,β-Unsaturated aldehydes condense in lower

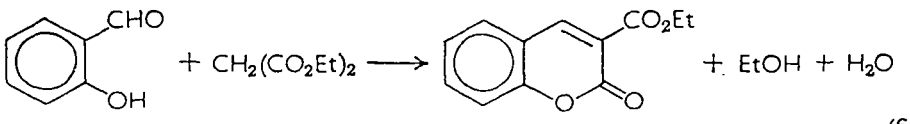
$$RCHO + CH_2(CO_2H)_2 \longrightarrow RCH{=}CHCO_2H + CO_2 + H_2O \quad (59)$$

$$MeCH{=}CHCHO + CH_2(CO_2H)_2 \xrightarrow[\text{heat}]{C_5H_5N} \underset{(28\text{–}32\%)}{MeCH{=}CHCH{=}CHCO_2H} \quad (60)$$

yields (equation 60). Use of acetic acid as solvent instead of pyridine in the crotonaldehyde condensation gives the alkylidenemalonic acid[90]. Pyridine has been found to promote decarboxylation[91].

Alkyl, aralkyl, and aryl ketones condense with ethyl cyanoacetate in satisfactory yields when catalyzed by piperidine, piperidinium acetate, or zinc chloride in acetic anhydride[92,93]. Ketones with unbranched carbon chains give 75–87% yields of alkylidene cyanoacetates with ammonium acetate in acetic acid; branching gives lower yields until pinacolone and camphor fail to condense. Cyclohexanone condenses with cyanoacetic acid to give 65–76% yields of the expected exocyclic α,β-unsaturated acid; heating to 165–175° results in isomerization to the endocyclic β,γ-isomer[94].

Aromatic aldehydes containing both electron-withdrawing and electron-donating substituents condense with malonic acid derivatives. The initial product from reaction of salicylaldehyde and ethyl malonate undergoes ring closure to 3-carbethoxycoumarin (equation 61)[95]. Aldehydes with aromatic rings containing heteroatoms such

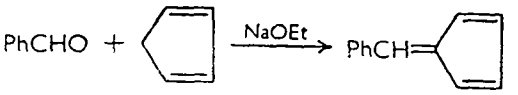


(61)

as the furan and thiophene system undergo satisfactory condensations. Base-catalyzed condensation of aromatic aldehydes with nitromethylene compounds gives a relatively rapid addition reaction. The subsequent dehydration is slower than the addition. Unless the intermediate nitro alcohol is desired as a product, the reaction mixture must usually be acidified to effect the dehydration to the β-nitrostyrene[96].

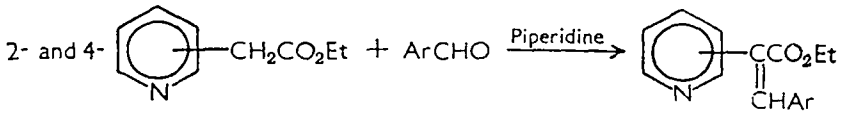
Cyclopentadiene is an effective nucleophile in Knoevenagel condensations by virtue of the resonance stabilization of the cyclopentadienyl anion (equation 62)[97]. The —CN group of benzyl cyanide provides sufficient activation of the methylene group that

condensation of this class of nucleophile with aromatic aldehydes proceeds in good yields[98,99]. The free or quaternized pyridine ring activates an adjacent methyl or methylene so that condensation with



(62)

aromatic aldehydes can be accomplished. Better yields are obtained when the aldehyde bears an electron-donating substituent (equation 63)[100].



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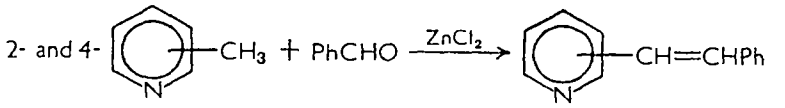

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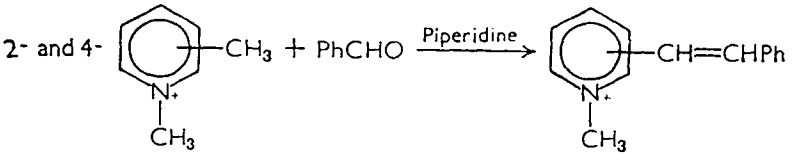
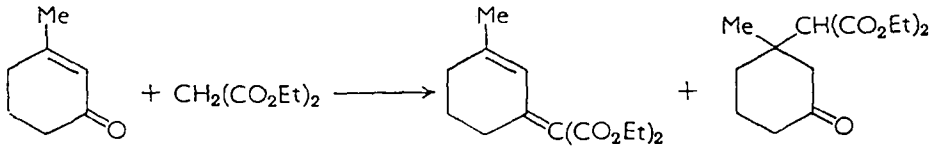


(63c)

The Knoevenagel condensation is less satisfactory with aryl alkyl or diaryl ketones than with aromatic aldehydes. If the ketone is first converted into the corresponding imine, satisfactory condensations can be effected (equation 64)[101].

$$Ar_2CO \longrightarrow Ar_2C{=}NH + CH_2(CN)CONH_2 \longrightarrow Ar_2C{=}C(CN)CONH_2 \quad (64)$$

The limitations and side-reactions in Knoevenagel condensations are similar to those for aldol condensations. Isomeric mixtures can be produced in the initial reaction and further condensation of the initial product can occur. Use of triethanolamine as catalyst is reported to promote formation of the β,γ-unsaturated isomer[102].



(65)

Condensation of an α,β-unsaturated carbonyl compound can give rise to a mixture of products by virtue of competitive Knoevenagel and Michael reactions (equation 65).

2. Kinetics and mechanism

The basic mechanism for Knoevenagel condensations is similar to the mechanisms for aldol condensations detailed in section II.B.4. In general, condensation proceeds through addition of a carbanion to a carbonyl group followed by a dehydration step. The central problem in the study of the mechanism has been to establish which of the three reactions (ionization, addition, and dehydration) is rate-determining.

The fact that the condensation may be acid- or base-catalyzed and that weak catalysts such as amines or their salts are effective has caused some confusion as to the particular species of the catalyst that is most effective. Sound evidence indicates that the amine free base is the effective catalyst in some cases while equally good evidence involves the conjugate acid in other cases. The uncatalyzed condensation of malononitrile with aromatic aldehydes in water and alcohol is inhibited by addition of strong acids[103,104]. The reaction is strongly catalyzed by piperidine but to a lesser extent if benzoic acid is added to neutralize partially the piperidine. Similarly, the rate of condensation of ethyl malonate with benzaldehyde in benzene is proportional to the concentration of piperidine and is decreased by addition of acid[105]. Piperidine is also a more effective catalyst than its salt in the condensation of *p*-nitrobenzyl cyanide with aromatic aldehydes[106]. On the other hand, numerous examples are reported in which the amine salt is a slightly better catalyst than the free base. Under standardized conditions, better yields of product are obtained in the piperidinium acetate-catalyzed condensation of methyl cyanoacetate with butanone than with piperidine[107]. In contrast to the results obtained in benzene, piperidinium acetate is a slightly better catalyst than piperidine in the condensation of ethyl malonate with benzaldehyde in alcohols[108]. It has been suggested[107] that the presence of both an acid and a base is more favorable than when a single catalyzing species is present. Following this reasoning, it was found that a number of 'bifunctional' amino acids are good catalysts[109–113], with some being superior to piperidinium acetate or piperidine[110]. The effectiveness of alanine is greatest at pH values near the isoelectric point[109].

The seemingly anomalous observations might become more com-

patible if more were known in each case regarding the rate-determining step under the conditions of the particular condensation. If ionization or addition were the slow step, base catalysis might be of greatest importance, while the reverse would probably be true if the dehydration step were rate-controlling. Partial support for this view is found in kinetic studies where the rate-determining step is indicated. The uncatalyzed rates of condensation of cyanoacetamide with *p*-substituted benzaldehydes are depressed by acids; the apparent rate-determining step is either ionization of the nucleophile or addition to the aldehyde, depending upon the particular aldehyde[114]. The rate-determining step in the condensation of malononitrile with *p*-substituted benzaldehydes in alcohol is addition of the carbanion to the aldehyde; piperidine is the effective catalyst and the rates are decreased by addition of acids[104]. In the condensation of aromatic aldehydes with *p*-nitrobenzyl cyanide the rates are first-order with respect to piperidine free-base concentration and are depressed by acids; the kinetics indicate that both ionization and addition are rate-controlling[106]. No kinetic studies appear to have been made on condensations in which dehydration is a slow step.

The exact role of the catalyzing amine is further clouded by the finding that some primary amines catalyze the condensation of nitromethane with aromatic aldehydes by first forming an imine with the aldehyde. The imine is more readily attacked by the nucleophile than the carbonyl compound[115,116]. In these cases the amine is acting as a nucleophilic catalyst rather than as a simple base.

An interpretation of the effect of structure on reactivity again requires some knowledge of the rate-determining step in the condensation. If ionization of the nucleophile is the only slow step, the overall rate will be independent of both the concentration and structure of the carbonyl compound. If, on the other hand, the ionization equilibrium is established and addition is the only slow step, the overall rate will depend upon the acidity of the nucleophile (equilibrium concentration of anion) and the specific rate coefficient for addition to the carbonyl group which should vary with the structure of the carbonyl compound. Both the rates of ionization and the acid dissociation constants for several malonic acid derivatives have been measured in water at 25°[117]. The ionization rates vary in the order

$$CH_2(CN)_2 > CH_2(CO_2H)_2 > CH(CN)CO_2Et > CH_2(CO_2Et)_2.$$

No clear-cut case has been reported where ionization is the slowest step in the overall condensation. The rates of the uncatalyzed condensation of malononitrile with a series of substituted benzaldehydes in water are independent of the aldehyde concentration, and a rate-controlling ionization step is suggested[103], but the rates do depend upon the structure of the aldehydes (p-NO_2 > p-Cl > H > p-OMe) and are considerably slower than the rates of ionization of malononitrile. In the uncatalyzed condensation of cyanoacetamide with substituted benzaldehydes in water and alcohol the kinetic order with respect to aldehyde concentration varies from first to less than first depending upon the reactivity of the aldehyde. This reflects a change in rate-determining step from addition (unreactive aldehydes) to both ionization and addition (reactive aldehydes). Raising the temperature increases the ionization rates relative to the addition rates. The uncatalyzed condensation of malononitrile with substituted benzaldehydes in ethanol appears to be a clear-cut case of a rapidly established ionization followed by a slow addition step[104]. Here the rates vary with aldehyde substituent in the order p-NO_2 > p-Cl > H > p-OMe > p-OH, which is the expected order of decreasing polarization of the carbonyl group. A good linear free-energy correlation with σ^+ values is obtained ($\rho^+ = 1{\cdot}45$). A similar order is observed in the condensation of malonic acid with aromatic aldehydes in pyridine, using piperidine as catalyst[118]. The rates of the acid-catalyzed condensation of ethyl cyanoacetate with a series of benzaldehydes in acetic acid follow the reverse order, and show only a slight sensitivity to aldehyde structure. Qualitatively, the rates vary as the basicity of the aldehydes. The low sensitivity of the overall rates to structure probably reflects opposing effects of structure on the equilibrium constants and on the rate coefficients for addition to the aldehyde conjugate acids.

3. The Perkin reaction

The condensation of an aromatic aldehyde with an aliphatic acid anhydride in the presence of the salt of the fatty acid gives rise to a cinnamic acid (equation 66)[119]. By our broad classification, this

$$ArCHO + (RCH_2CO)_2O + RCH_2CO_2^- \longrightarrow ArCH{=}\underset{\displaystyle R}{C}CO_2H \qquad (66)$$

reaction may be regarded as a type of Knoevenagel condensation, but because of the nature of the catalyst and the high temperatures

required to condense the aldehyde with the unreactive anhydride it has not usually been classed with other Knoevenagel-type condensations. There is no difference in principle, however. The reaction represents another special case of the general carbonyl addition–elimination reactions that have been discussed.

Because the nucleophiles in this condensation are so unreactive, the usefulness of the reaction is limited to the most reactive carbonyl compounds, e.g. the aromatic aldehydes. Aliphatic aldehydes usually undergo self-condensation at greater rates than they react with the anhydride.

When the anhydride and salt are derived from different aliphatic acids, a mixture of cinnamic acids can result under the conditions of the reaction. Thus a mixture of benzaldehyde, acetic anhydride, and sodium n-butyrate heated together at 150° gives α-ethylcinnamic acid and cinnamic acid in a 1:2 ratio. The ratio of products changes with the reaction temperature[120]. The formation of cinnamic acids corresponding to both the anhydride and the salt caused considerable controversy over whether the anhydride or the salt yielded the active nucleophile. This is because the equilibrium (67) is set up between the two at the temperature of the condensation (100–180°). Breslow

$$2\ R^1CO_2^- + (R^2CO)_2O \rightleftharpoons 2\ R^2CO_2^- + (R^1CO)_2O \qquad (67)$$

and Hauser[121] found that equilibrated mixtures of either acetic anhydride and sodium butyrate or butyric anhydride and sodium acetate gave the same ratio of cinnamic acid and α-ethylcinnamic acid with benzaldehyde. The proportion of acetic anhydride in the equilibrium mixture is greater at 180° than at 100°; there is a proportionate increase in the amount of cinnamic acid in the product mixture at the higher temperature. This fact was taken as evidence that the anhydride is ionized by the salt and is the active nucleophile. This rests on the unproved assumptions that the acidities of the α-hydrogens of the two anhydrides are similar at the two temperatures and that the specific rate coefficients for addition of the carbanions are similar and have nearly equal temperature coefficients. Additional evidence for involvement of the anhydride carbanion as the active species rests on the fact that benzaldehyde and acetic anhydride condense in the presence of a number of inorganic and organic bases[122,123], including sodium formate, borate, sulfite and carbonate, triethylamine, pyridine, and acetamide.

The conditions of the Perkin reaction (high temperature and the absence of an inert solvent) have made quantitative kinetic studies

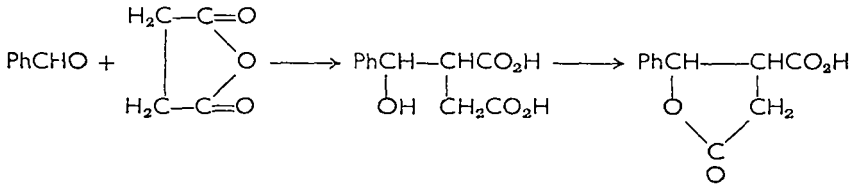
impractical. It has been shown, however, that electron-withdrawing substituents in the aldehyde increase yields of cinnamic acids while yields are lower with electron-donating substituents[124]. This would indicate that the addition step is rate-controlling.

The intermediate addition compound is rarely isolated in this condensation. It can be isolated as an acylated derivative in those cases where the elimination of water is prevented, as in the condensation of benzaldehyde with isobutyric anhydride (equation 68)[125,126].

$$PhCHO + (Me_2CHCO)_2O + Me_2CHCO_2^- \longrightarrow PhCHC(Me)_2CO_2H + PhCHC(Me)_2CO_2COPr\text{-}iso \quad (68)$$

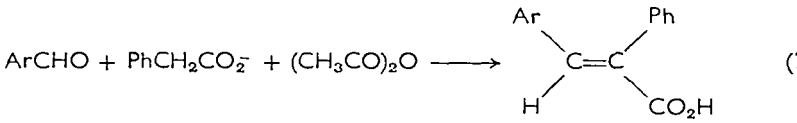
(OCOPr-iso) (OCOPr-iso)

Condensation with succinic anhydride at 100° permits the isolation of the intermediate as the lactone, γ-phenylparaconic acid (equation 69)[127].



(69)

The Oglialoro modification[128] of the Perkin reaction involves use of sodium phenylacetate and acetic anhydride. The resulting α-arylcinnamic acids correspond to the salt used rather than the anhydride (equation 70). The aryl groups in the α-phenylcinnamic acids have a *cis* configuration[129].



(70)

III. FORMATION OF CARBON–NITROGEN DOUBLE BONDS

A. General Considerations

The condensation reactions of carbonyl compounds with nitrogen bases such as amines, hydroxylamine, hydrazines, and semicarbazide are familiar to organic chemists. Application of fairly standard methods usually gives successful condensation. In a great number of cases the primary practical interest in condensations with these so-called 'carbonyl reagents' is in obtaining a derivative for characterizing the carbonyl compound. For this reason a discussion of reaction

conditions, scope and applications would seem to contribute little that is not already available in standard texts. In recent years, however, new contributions have been made that lead to greater understanding of the mechanisms of the condensations; this understanding now leads to a better appreciation of the procedures and empirical observations. In this section the primary emphasis will be on the condensation mechanism.

Similarities in the mechanisms of condensation of carbonyl compounds with all the nitrogen bases facilitate their discussion as a group. Apparent observed differences between reagents or different carbonyl compounds can usually be resolved into differences in the rates of the several steps in the condensation or in the position of equilibrium of one or all of the steps. From this frame of reference it will be seen that there are probably no fundamental differences in principle among the condensations with various nitrogen bases or indeed between the olefin-forming and imine-forming condensations.

The basic mechanism is a two-step addition–elimination mechanism, as in the case of condensation of carbanions. In the first step the nitrogen base adds to the carbonyl compound to give a carbinolamine intermediate, followed by elimination of water to form the carbon–nitrogen double bond in the second step (equation 71).

$$R^1R^2C{=}O + NH_2R^3 \rightleftharpoons \left\{ \begin{array}{c} R^1R^2C\overset{+}{N}H_2R^3 \\ | \\ O^- \\ \Updownarrow \\ R^1R^2CNHR^3 \\ | \\ OH \end{array} \right\} \rightleftharpoons R^1R^2C{=}NR^3 + H_2O \quad (71)$$

The similarities in the general mechanisms for carbon–carbon and carbon–nitrogen condensations are obvious. The important experimental differences that the chemist observes arise from the following facts. (*a*) The nitrogen bases are good nucleophiles in their own right; an ionization preceding the addition step is unnecessary. (*b*) The intermediate addition product is almost never isolable, and in some cases never accumulates in the reaction medium to a measurable extent. (*c*) The condensations are all acid-catalyzed. While oxime formation has also been shown to be catalyzed by hydroxide ion[130], this is not the customary experimental condition. Furthermore, the rates of condensation pass through a maximum with changing acidity, falling off on either side of an optimum pH. In practice some sort of buffering is often desirable to approach this pH optimum.

The main effort that has been made in the study of the mechanism of these condensations has been directed toward establishing the rate-determining steps, understanding the nature of the acid catalysis, and elucidating the structure–reactivity relationships in detail.

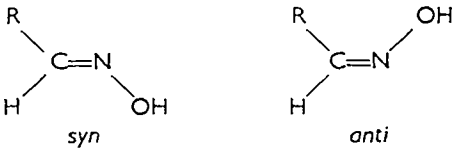
B. Oximes, Semicarbazones, and Hydrazones

1. The nature of the condensation

The condensations are usually carried out by warming the carbonyl compound and reagent together in a polar solvent. Reaction times seldom exceed an hour, and the reaction is often complete within minutes. The reagents are usually obtained as the salts since the free bases are subject to air oxidation. The salts are partially or completely neutralized by addition of a base. A weak acid–weak base combination provides a buffering action near the optimum pH for condensation.

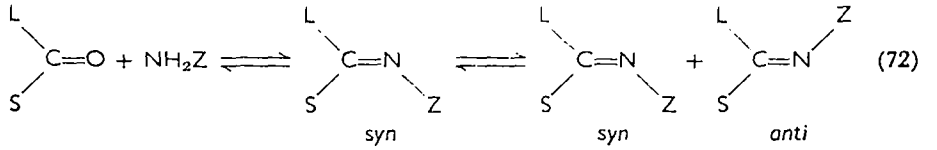
Although all the reactions with 'carbonyl reagents' are reversible, the equilibrium favors condensation under the usual experimental conditions. Removal of water from the reaction medium to force condensation is unnecessary. In general, semicarbazone formation is less complete for a given carbonyl compound under similar conditions than oxime or phenylhydrazone formation. The equilibrium constants for condensation with *d*-carvone in aqueous alcohol are[131]: phenylhydrazine, -6×10^2; hydroxylamine, -4×10^2; and semicarbazide, $-3{\cdot}6 \times 10^2$. Under similar conditions of pH and reagent concentration semicarbazone and thiosemicarbazone formation is reversible for a number of carbonyl compounds while oxime formation shows no measurable reverse reaction[132]. Reversal of 2,4-dinitrophenylhydrazone formation is quite difficult to accomplish. The reversibility of the reaction is demonstrated by the fact that ketone exchange occurs when a given hydrazone is heated in acid solution in the presence of a second ketone[133].

Discrete geometrical isomers are distinguishable in the products of condensation with the carbonyl reagents. These are usually designated as *syn* and *anti* according to the relative positions of the groups



adjacent to the double bond, as shown for the aldoximes. With ketone

derivatives, the designation is ambiguous, and one of the R groups must be specified in labeling the isomers. In solutions of acetaldehyde oxime the *anti* isomer is thermodynamically more stable[134]. Nuclear magnetic resonance studies of solutions of semicarbazones, phenylhydrazones, and 2,4-dinitrophenylhydrazones of aliphatic aldehydes and ketones show that condensation gives rise exclusively to the isomer in which the bulky Z group attached to the imino nitrogen bears a *syn* relationship to the smaller R group[135–137] (equation 72).



(72)

On standing or on acidification, equilibration of the isomers occurs. At equilibrium, the *syn* isomer predominates (bulkiest groups *trans*), the exact equilibrium mixture depending upon the solvent. The fact that the nature of the condensation product is kinetically controlled reflects the low rate of hydration of the product relative to the rate of dehydration of the carbinolamine.

Besides the hydrazone form, tautomeric azo- and ene-hydrazine forms of phenylhydrazones are possible (equation 73). The hydrazone

$$R^1R^2CH_2C{=}NNHPh \rightleftharpoons R^1R^2CH_2CHN{=}NPh \rightleftharpoons R^1R^2CH{=}CNHNHPh \quad (73)$$

form is the most stable, and examination of solutions of a large number of phenylhydrazones from aliphatic aldehydes and ketones by nuclear magnetic resonance shows only the hydrazone form[137]. Azo coupling with certain naphthols and active methylene compounds is thought to give predominantly the hydrazone tautomer. The infrared spectra of acetone and butanone phenylhydrazones show only C=N absorption in nonpolar solvents. In methanol a new band ascribed to a C=C bond is found[138].

2. Mechanism

Direct and indirect evidence supports the intuitive conclusion that the condensations involve an intermediate addition compound. The addition compound from chloral and hydroxylamine can be isolated. Addition of hydroxylamine and semicarbazide to neutral solutions of a variety of carbonyl compounds gives a rapid decrease in the typical ultraviolet and infrared carbonyl absorption followed by a slow increase in the oxime or semicarbazone absorption[139]. An interpretation involving a rapid addition reaction to form an intermediate

with a subsequent slow formation of product is required even though the structure of the intermediate is not established. The slow dehydration is acid-catalyzed. The acid catalysis of hydroxylamine and semicarbazide condensation in neutral solution involves catalysis of the dehydration step and not facilitation of the addition by conversion of the carbonyl compound into its conjugate acid.

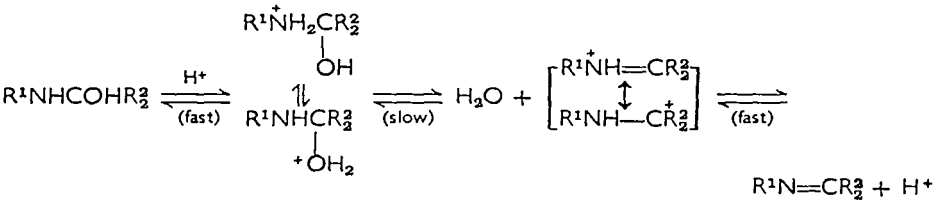
Since the addition equilibrium is rapidly established relative to the rate of dehydration in neutral and slightly basic solution, the overall rate of condensation at constant pH depends upon the product of the equilibrium concentration of carbinolamine and the specific rate coefficient for dehydration. At low concentrations of carbonyl reagent, only a small fraction of the carbonyl compound is present as carbinolamine and the overall rate will be second-order at constant pH. At high reagent concentration, most of the carbonyl compound is present as carbinolamine and the overall rate approaches first-order at a given pH. From these considerations it is seen that a series of carbonyl compounds having very different susceptibilities toward nucleophilic addition might show similar overall condensation rates because of compensating effects on the dehydration rates.

Hammett interpreted the maxima in the pH–rate profiles for oxime and semicarbazone formation as being due to opposing effects of general acid catalysis of the addition reaction and the decrease in the concentration of free nitrogen base by conversion to its conjugate acid[140]. The dehydration was thought to be rapid. Jencks attributes the rate maximum to a change in rate-determining step from acid-catalyzed dehydration of the carbinolamine on the basic side of the maximum to rate-limiting addition of the free base on the acid side of the maximum. Since the maximum occurs at a pH near the pK_a of the base, the decrease in observed rate is due to the decrease in concentration of the reactive nucleophile with increasing acid concentration. The change in rate-determining step corresponds to a change from a rate governed by the equilibrium concentration of intermediate (neutral solution) to a rate governed by a steady-state concentration of intermediate (acid solution). This change is brought about at acidities near the pK_a of the base through a simultaneous increase in dehydration rate by the acid-catalyzed reaction and a decrease in formation rate by conversion of the free base into its conjugate acid. At that pH where the carbinolamine is dehydrated as rapidly as it forms, a steady-state concentration of intermediate is established and the addition step becomes rate-determining. Jencks has shown that the observed pH–rate profile is reproduced fairly

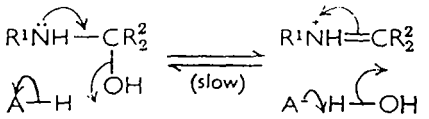
well by the combination of calculated pH–rate profiles for the two proposed rate-determining steps[139]. Additional evidence for this interpretation is found in the observation that different structure–reactivity relationships exist on either side of the pH–rate maximum for semicarbazone formation, suggesting different transition states in the two pH regions[141].

The dehydration of the carbinolamines and the addition of water to oximes and semicarbazones are subject to both specific and general acid catalysis. The following reactions can explain these phenomena.

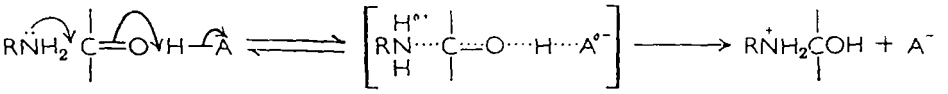
Specific acid catalysis



General acid catalysis



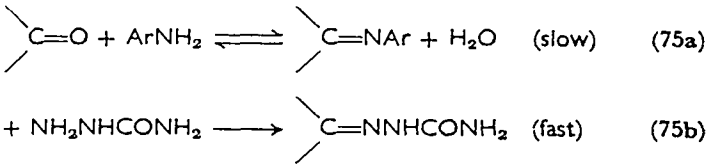
The addition of hydroxylamine to the carbonyl group shows slight specific acid catalysis; the addition of the weaker base, semicarbazide, is subject to both specific and general acid catalysis. The role of protonated carbonyl intermediates in the addition of semicarbazide to substituted benzaldehydes[142] has been ruled out on theoretical grounds. The preferred mechanism for the general acid catalysis involves concerted semicarbazide attack and transfer of a proton to the carbonyl group.



(74)

The formation of semicarbazones is also subject to nucleophilic catalysis by primary aromatic amines[143]. The mechanism for this catalysis involves a rate-determining reaction between the amine and carbonyl compound to form a Schiff base (equation 75a), followed

by rapid attack of semicarbazide on the Schiff base to give the semicarbazone (equation 75b). Other similar cases of transimination



of Schiff bases have been noted[144]. The rates of formation of osazones with phenylhydrazine is also accelerated by aniline but not by secondary or tertiary amines[145], and a similar mechanism may be involved.

The formation of phenylhydrazones from carbonyl compounds has not been studied as thoroughly as oxime and semicarbazone formation, but the existing data suggest similar mechanisms. Addition of phenylhydrazine to a solution of *m*-nitrobenzaldehyde gives a rapid decrease in phenylhydrazine concentration with a slower formation of the phenylhydrazone[146]. This indicates that dehydration of the intermediate is rate-controlling under certain conditions. The change from second-order kinetics at low phenylhydrazine concentration to first-order kinetics at high reagent concentration is also in accord with a rate-determining dehydration step. Evidence for a change in rate-determining step with changing acidity is lacking. Osazone formation from phenylhydrazine and several sugars is subject to general acid catalysis[147]. For a given buffer concentration, the rate increases with acidity to pH 5·4 and then is independent of pH at higher acidity. Extrapolation of the pH–rate profiles for a series of buffer concentrations to zero buffer concentration gives a very small catalysis by H_3O^+ alone. By analogy with the case of hydroxylamine, absence of pronounced specific acid catalysis at low pH may indicate that in acid solutions addition of the base to the carbonyl group is rate-determining.

3. Factors affecting reactivity

Where comparable rate data exist for a given carbonyl compound, the relative rates of condensation decrease in the order oximes > semicarbazones > thiosemicarbazones[132]. The temperature coefficients of condensation rate decrease in the same order, suggesting that some temperature exists where the relative reactivities, if measurable, would become interchanged. Excellent free-energy relationships are found between rates of formation of oximes, semi-

carbazones and thiosemicarbazones, implying similar transition states for the three condensations.

Rates of condensation of semicarbazide with a series of *p*-substituted acetophenones at a pH near the pK_a of semicarbazide are facilitated by electron-withdrawing substituents[148]. A linear correlation of log rate coefficient with the Hammett σ constant is obtained ($\rho = +0{\cdot}91$). The more reactive ketones actually have higher activation energies, but a large positive preexponential term more than compensates for the unfavorable activation energy. Condensation of a series of substituted benzaldehydes in 75% ethanol in neutral solution does not follow a simple ρ–σ relationship[149]. The rates are similar for aldehydes having substituents with as greatly different electronic effects as *p*-NO_2 and *p*-NEt_2. The rate-determining step under the conditions of the rate measurements is probably dehydration of the carbinolamine.

A detailed study of the effect of structure on the rates and equilibrium constants of the individual steps of the overall condensation of *p*-substituted benzaldehydes with semicarbazide has been carried out by Anderson and Jencks[141]. At neutral pH, where the dehydration step is rate-determining, the overall rate coefficient for condensation is the product of the equilibrium constant for carbinolamine formation and the specific rate coefficient for dehydration. Carbinolamine formation is facilitated by electron-withdrawing substituents in the aldehyde. The logarithms of the equilibrium constants give a linear correlation with Hammett σ values, with $\rho = 1{\cdot}81$. The rates of the acid-catalyzed dehydration of the carbinolamine, on the other hand, are promoted by electron-donation from the *p*-substituent. A Hammett correlation of these specific rate coefficients has $\rho = -1{\cdot}74$. Since the electronic effects of the substituents have nearly equal and opposite effects on the two individual coefficients comprising the observed rate coefficient for condensation in neutral solution, the effects essentially cancel and changing the structure of the aldehyde has practically no effect on the overall rate. In acid solution, where the addition step is rate-determining, the observed rate is increased by electron-withdrawing substituents ($\rho = 0{\cdot}91$). This is the direction expected for nucleophilic attack at a polarized carbonyl group. The markedly different effects of structure on the reactivity in the two regions of acidity provide powerful support for a change in rate-determining step with increasing acidity. A similar change in structural effects with acidity was noted earlier for semicarbazone formation in 60% methyl cellosolve–water[150].

The ring size of a series of alicyclic ketones has a pronounced effect on the condensation rates with semicarbazide. Cyclohexanone is more reactive than cyclopentanone or cycloheptanone at pH 7[151]. The difference is attributed to differences in internal strain of the ring in passing from the trigonal carbon of the reactants to the tetrahedral carbon of the intermediate. The entropies of activation for condensation of a series of aliphatic and alicyclic ketones with semicarbazide at pH 7·0 parallel presumed rigidities of the carbonyl compounds. The more rigid carbonyl compounds show the highest entropies of activation[152]. A similar correlation with the same carbonyl compounds was not observed in the condensation of thiosemicarbazides[132]. Since the temperature coefficients of the overall rate at pH 7·0 involves both the free energy of carbinolamine formation and the free energy of activation for dehydration of the carbinolamine, the temperature coefficients of each rate must be separated before a complete interpretation is possible.

Fewer studies have been made of the effect of structure on the rates of oxime formation. Strong electron-releasing substituents facilitate condensation of substituted benzophenones with hydroxylamine in acidic 70% methanol[153]. Dehydration of the carbinolamine would appear to be rate-determining under this condition. The relative rates of a series of carbonyl compounds are parallel for oxime and semicarbazone formation and decrease in the order cyclohexanone > acetone > cyclopentanone > furfural > butanone > pinacolone > acetophenone[154].

No detailed studies have been made of the mechanism of phenylhydrazone formation or of structure–reactivity relationships. Stroh has estimated the reactivities of a number of substituted phenylhydrazines in osazone formation with a wide variety of sugars by noting the time elapsing before appearance of a precipitate[155–158]. Since the results reflect the effect of structure on both chemical reactivity and the physical process of nucleation, they have more practical than theoretical value. The results show that a systematic variation of substituent in the phenylhydrazine does not give an ordered progression of reactivities, and the relative orders vary from sugar to sugar.

C. Schiff Bases

1. Scope and limitations

The condensation of aldehydes and ketones with primary amines to give imines was first discovered by Schiff in 1864 and the resulting

bases bear his name. The chemistry of these compounds has been reviewed[159,160]. In contrast to the condensations with semicarbazide, hydroxylamine, or phenylhydrazine the overall equilibrium in the reaction with amines greatly favors hydrolysis in aqueous or partially aqueous solvents. The condensations are usually carried out in solvents in which the water can be removed as it forms by azeotropic distillation. This not only forces the condensation to completion but provides a means of following the progress of a condensation on a preparative scale.

Aliphatic aldehydes having unsubstituted α-positions generally do not give successful condensations with most amines because the imines formed initially undergo further condensation to dimeric or polymeric materials. The properties of the >C=NR bond and >C=O bond are similar, so it is not surprising that certain imines show chemical behavior similar to carbonyl compounds. The imines from primary aliphatic aldehydes can undergo aldol condensations just as the aldehydes themselves. These aldehydes can be successfully condensed with amines containing tertiary alkyl groups[161], presumably because of steric inhibition of a subsequent aldol condensation. Condensation at low temperature retards further reaction of the imine and gives acceptable yields of the Schiff base[162,163].

Aliphatic aldehydes that are branched at the α-position condense readily with amines to form the imine in good yield. Imines having single α-hydrogens apparently do not undergo further condensation. Tertiary aliphatic aldehydes give nearly quantitative yields of imines at room temperature. Aromatic aldehydes condense very readily so that removal of the water formed in the reaction is often unnecessary.

Ketones are generally much less reactive than aldehydes in the formation of imines. By using acid catalysts, higher reaction temperatures, longer reaction times, and removing the water as it forms, respectable yields of Schiff bases are obtained. Sterically hindered ketones are particularly unreactive. Aromatic ketones are generally less reactive than aliphatic ketones. Condensation of acetophenone and benzophenone with ammonia requires a four-hour reaction time at 180° with aluminum chloride as catalyst[164]. Strong acids should be avoided in the condensation of methyl ketones since they facilitate aldol condensation. Good results are obtained with weak acids. Methylene ketones can be condensed in the presence of strong acids since they do not undergo aldol condensations as easily as the methyl ketones.

Any primary amine will condense with the carbonyl group, subject

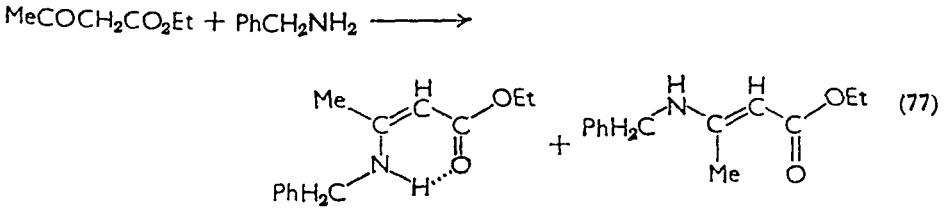
to the limitations outlined above. The reactivity of amines appears to parallel the base strengths[159] or, probably more correctly, the nucleophilicities. Amino acids form imines[165,166], and imine formation with free amino groups of proteins appears to be of importance in a number of biochemical mechanisms.

The formation of Schiff bases is reported to be accelerated by ultraviolet irradiation[167]. This phenomenon may involve light-promoted autoxidation of some of the aldehyde to the corresponding acid, which then catalyzes the condensation. A similar explanation was used to account for promotion of the Wittig reaction by light.

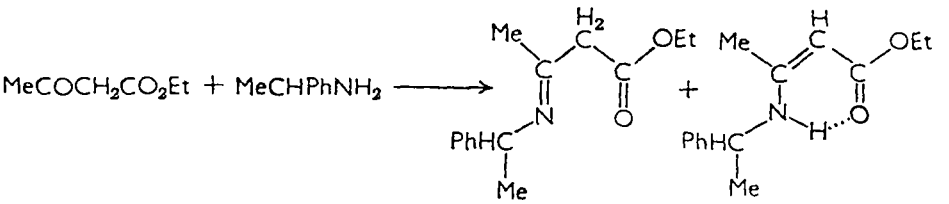
Formation of two imine tautomers is possible in the condensation with aliphatic amines having α-hydrogens (equation 76). In addition,

(76)

condensation with carbonyl compounds having active methylene groups can give isomeric enamine tautomers. Condensation of acetoacetic ester with benzylamine (equation 77)[168,169] and α-phenylethylamine (equation 78)[170] is illustrative. The energy barrier



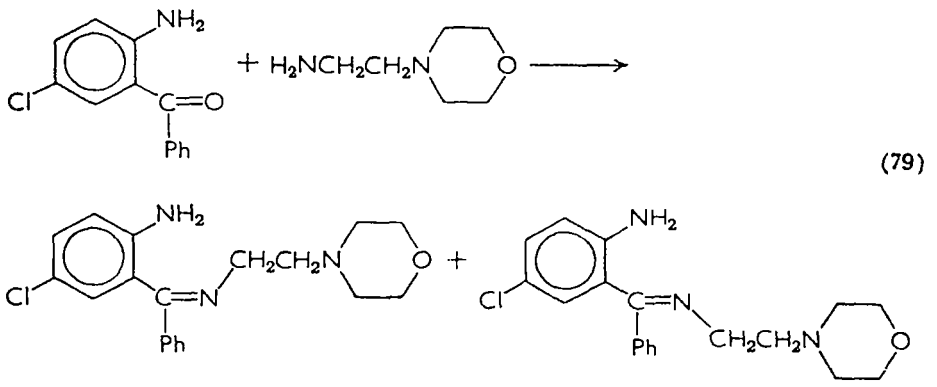
(77)



(78)

between *syn* and *anti* isomers of Schiff bases is low so that isolation of the discrete isomers is not usually possible. Most reports of isolation of geometric isomers have been disputed. Recent evidence for the isolation of the geometric isomers of the imine from 2-amino-5-chlorobenzophenone and β-morpholinoethylamine seems compelling (equation 79)[171]. Infrared and nuclear magnetic resonance

spectra support the assignments. The ultraviolet spectra are different and are quite similar to the spectra of the known *syn*- and *anti*-oximes.



(79)

2. Kinetics and mechanism

The mechanism of imine formation is very similar in principle to the mechanism of formation of oximes, semicarbazones, and hydrazones. Differences in detail arise mainly from differences in relative rate coefficients or equilibrium constants of the general addition–elimination mechanism. These differences have usually served to make kinetic study of imine formation more difficult to execute or the results more difficult to interpret. For instance, the carbinolamine intermediate in Schiff base formation is much less stable than the intermediate in oxime or semicarbazone formation; it reverts rapidly to reactants or is converted rapidly into product in competing reactions. It is usually present in low steady-state concentrations so that experimental rate coefficients for imine formation or hydrolysis are often composites of several rate and/or equilibrium constants and are sometimes difficult to interpret unambiguously. Fortunately, imine formation is sufficiently similar to oxime formation that mechanistic analogies and interpolations can be made.

Intermediates have been isolated when aromatic amines and aldehydes were condensed in the absence of solvent or in aqueous emulsions[172–176]. These substances were isolated either as the free bases or their salts and were characterized as the carbinolamine on the basis of elemental analyses. They decomposed readily in moist air to the amine and aldehyde. The only evidence for a measurable accumulation of intermediate in dilute aqueous solution is from a polarographic study of the hydrolysis of benzylideneaniline in 30%

methanol[177]. The absence of a measurable accumulation of intermediate has been demonstrated in the hydrolysis of a substituted benzylideneaniline in aqueous solution[178] and the formation of benzylideneanilines in nonpolar solvents[179]. In most other cases a low steady-state concentration of intermediate has been assumed in the analysis of kinetic results in aqueous or partially aqueous solution.

The only kinetic study made under the usual preparative conditions (refluxing benzene with removal of water) indicates that the rate-determining step in the condensation of aromatic amines with aromatic aldehydes is the addition of the amine to the carbonyl group[180]. The evidence is based on the fact that electron-withdrawing substituents in the aldehyde increase the rate while the same substituents in the aniline decrease the rate.

Much of the information on the mechanism has been derived from interpretations of the effect of acidity on the rates of condensation and of hydrolysis of the imine. In general, condensation and hydrolysis show a pH-independent ('uncatalyzed') reaction in mildly basic solution and an acid-catalyzed reaction in neutral and slightly acid solution. Both specific and general acid catalysis is observed. The hydrolysis of benzylideneaniline also shows specific base catalysis at very high pH[177]. In mildly basic solution the rate-determining step in the hydrolysis may be addition of water to the unprotonated imine[177,178,181] or the kinetically undistinguishable addition of hydroxide ion to the protonated imine[182]. In the reverse direction this would correspond to rate-determining elimination of water or hydroxide ion from the carbinolamine (equations 81 and 81′, Scheme 1). In mildly acid solutions, where both the hydrolysis rates and condensation rates increase with increasing acidity, an important rate-determining step is probably addition of water to the protonated imine in the hydrolysis reaction, or acid-catalyzed dehydration of the carbinolamine in the condensation reaction. It has been shown, however, that such a mechanism for acid catalysis does not completely fit the kinetic data for hydrolysis of imines [178,181–183] so that additional rate-determining steps must become important. A logical explanation involves a transition in rate-determining step at higher acidities to where addition of the amine to the carbonyl group becomes an important slow step in the condensation reaction and decomposition of the carbinolamine to amine and carbonyl compound becomes partially or wholly rate-determining in the hydrolysis reaction. The occurrence of a pH–rate maximum, a difference in structure–reactivity relationships on either side of the maximum, a difference in susceptibility

toward general acid catalysis on either side of the maximum[183], and a differential effect of solubilizing agents on the hydrolysis rates in the different pH regions[184] point to a change in rate-determining step in going from mildly acid to more strongly acid solution. The reactions involved in the mechanism are summarized in Scheme 1. It thus appears that the mechanism of condensation of amines agrees in major detail with the more readily demonstrable mechanism of oxime and semicarbazone formation.

Alkaline solution

$$R^1R^2C{=}O + NH_2R^3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R^1R^2COHNHR^3 \quad \text{(fast)} \qquad (80)$$

$$R^1R^2COHNHR^3 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R^1R^2C{=}NR^3 + H_2O \quad \text{(slow)} \qquad (81)$$

or

$$R^1R^2COHNHR^3 \rightleftharpoons R^1R^2C{=}\overset{+}{N}HR^3 + OH^- \quad \text{(slow)} \qquad (81')$$

Neutral and mildly acid solution

$$R^1R^2C{=}O + NH_2R^3 \rightleftharpoons R^1R^2COHNHR^3 \quad \text{(fast)} \qquad (82)$$

$$R^1R^2COHNHR^3 + H^+ \rightleftharpoons R^1R^2C(\overset{+}{O}H_2)NHR^3 \quad \text{(fast)} \qquad (83)$$

$$R^1R^2C(\overset{+}{O}H_2)NHR^3 \rightleftharpoons R^1R^2C{=}\overset{+}{N}HR^3 + H_2O \quad \text{(slow)} \qquad (84)$$

Acid solution

$$R^1R^2C{=}O + NH_2R^3 \rightleftharpoons R^1R^2COHNHR^3 \quad \text{(slow)} \qquad (85)$$

and possibly

$$R^1R^2C{=}\overset{+}{O}H + NH_2R^3 \rightleftharpoons R^1R^2COH\overset{+}{N}H_2R^3 \quad \text{(slow)} \qquad (86)$$

Scheme 1. Mechanism of formation of Schiff bases.

Changing the structure of one or both of the reactants has rarely been found to change the rate in a simple manner. An exception is found in the condensation of substituted anilines with substituted benzaldehydes in refluxing benzene[180]. The rates of reaction of *p*-substituted anilines with benzaldehydes gives a good Hammett ρ–σ correlation with $\rho = -2{\cdot}00$, while *p*-substituents in the benzaldehyde have the opposite effect on the rate of condensation with aniline ($\rho = 1{\cdot}54$). The uncatalyzed rates of condensation of substituted benzaldehydes with n-butylamine in methanol gives a nonlinear ρ–σ plot, with a maximum at benzaldehyde[185]. Rates of condensation of piperonal with a series of aliphatic amines give poor correlations with the basicities of the amines measured in water or alcohol, but do

correlate well with the free energies of dissociation of the corresponding amine–trimethylboron complexes[186]. Nonlinear Hammett correlations are also obtained for the hydrolysis of benzylideneanilines[187,186].

Failure of the rates to follow a simple structure–reactivity relationship is the result of the fact that the rates of the individual steps in the reaction cannot be studied separately, so that the measured rate coefficients (k_{obs}) are often composite. Consider the simplest case of the uncatalyzed condensation (equations 80 and 81) going to completion (k_{-2} can be neglected). Application of the steady-state approximation to the carbinolamine gives equation (87) for the

$$k_{obs} = k_1k_2/(k_{-1} + k_2) \tag{87}$$

general case. If $k_{-1} \ll k_2$, $k_{obs} = k_1$ and a linear correlation with σ or σ^+ would be expected. If $k_{-1} \gg k_2$, $k_{obs.} = k_1k_2/k_{-1}$ and a linear Hammett correlation would still be expected, although the observed ρ could be quite small if changing substituents had opposing effects on the equilibrium constant, k_1/k_{-1}, and the rate coefficient, k_2. If $k_{-1} \simeq k_2$, then nonlinear effects of changing substituents could result. The small amount of data available indicates that k_{-1} and k_2 are of comparable magnitude so that neither becomes negligibly small compared to the other for an entire series of substituted reactants. In neutral or mildly acid solution the interpretation of changes in structure on k_{obs} is further complicated by the fact that the rate coefficients for the individual steps have both uncatalyzed and acid-catalyzed components and the resulting composite constant is not a simple factorable product of constants that might give a linear Hammett correlation.

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The Chemistry of the Carbonyl Group
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CHAPTER 13

Reactions of carbonyl groups with organometallic compounds

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I. INTRODUCTION

The reaction of organometallic reagents with carbonyl compounds has been the subject of a considerable number of reviews[1-4] which mainly cover the preparative utility of reactions of carbonyl compounds with organoalkali reagents, Grignard reagents, and other organometallic derivatives of Group II elements, and also of aluminum.

Since within the last decade apparently no novel preparative reaction has appeared[5], this chapter will emphasize the mechanistic aspects developed during the past years; preparative aspects will be discussed only to a minor extent. A brief discussion of the present knowledge on the structure of the organometallic species will be added where necessary for the understanding of mechanisms under discussion, as is particularly necessary in the case of Grignard reagents.

Only reactions which imply the reaction of carbon–metal bonds with a carbonyl group[5] will be discussed. Condensation reactions of the Claisen, Michael or aldol type, however, are not treated, and the choice of carbonyl compounds is restricted to aldehydes and ketones.

As far as possible, the literature has been covered up to March 1965.

II. GROUP I ELEMENTS

A. General

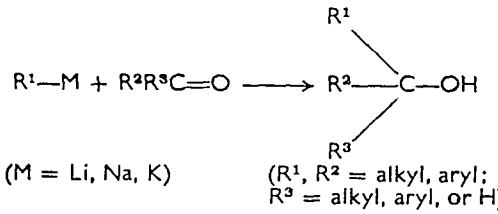
The use of organoalkali reagents in organic syntheses and their reactions with carbonyl compounds have been the subject of several comprehensive articles. Besides the detailed discussion by Runge[1], extensive reviews have been made by Wittig[6] (reactions of organolithium compounds), Braude[7] (reactions of lithium compounds with particular emphasis on the reactivity of alkenyllithiums), and by Schlosser[8] (reactivity of organosodium and -potassium compounds).

The different types of reaction occurring with aldehydes and ketones will be discussed by means of selected typical examples.

B. 1,2-Addition

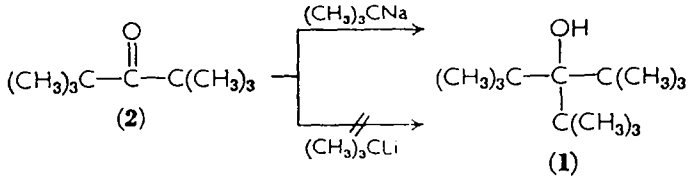
Saturated aldehydes and ketones react with organoalkali compounds in the normal 1,2-addition mode to give, respectively, secondary and tertiary carbinols (equation 1). The order of relative reactivity of alkali metal compounds in metalation reactions[9] seems

also to be observed in additions to the carbonyl group[8], i.e. K > Na > Li > e.g. Mg. This difference in reactivity may be

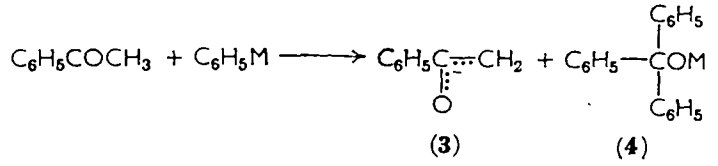


(1)

illustrated by the formation of tri-(*t*-butyl) carbinol (**1**) from the sterically hindered hexamethylacetone (**2**) and *t*-butylsodium, whereas *t*-butyllithium fails to undergo addition[10]. A similar difference occurs in the relative reactivities of lithium compounds toward Grignard reagents; for example, isopropylmagnesium halide does not add to diisopropyl ketone, but isopropyllithium does to a considerable extent[11].



Steric factors often affect the course of the reaction between organometallic compounds and enolizable aldehydes and ketones. With sterically hindered organometallic compounds[12], especially tritylsodium[13], enolate formation dominates over addition. The ratio of addition to enolization strongly depends upon the nature of the metal in the attacking species, as shown by Hauser and co-workers[14], who investigated the reaction of acetophenone with several arylmetals (equation 2). Their results, shown in the Table 1, were



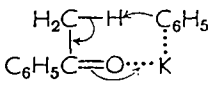
(2)

rationalized on the basis of the polarity of the phenyl–metal bond, which decreases in the order K > Na > Li > MgX. Thus potas-

TABLE 1.

Metal	Ratio of enolization to addition
K	10:1
Na	2:1
Li	1:23
MgX	1:∞

sium and sodium favor the arylmetal reacting like a base in a deprotonation reaction, as shown in **5**, to give **3**, while lithium and magnesium facilitate attack at the carbonyl group, leading to **4**, probably through a four-centered transition state like **6**.



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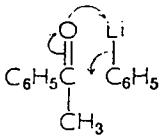
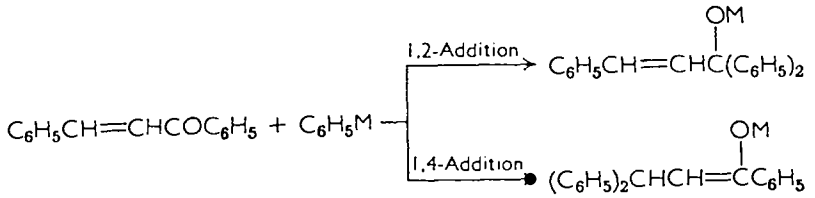


(6)

C. Conjugate Addition

With α,β-unsaturated ketones, organoalkali reagents generally tend to give 1,2-addition rather than 1,4- (or conjugate) addition. A comparative study by Gilman[15] on the reaction of benzalacetophenone with arylmetals (equation 3), which was later confirmed by



(3)

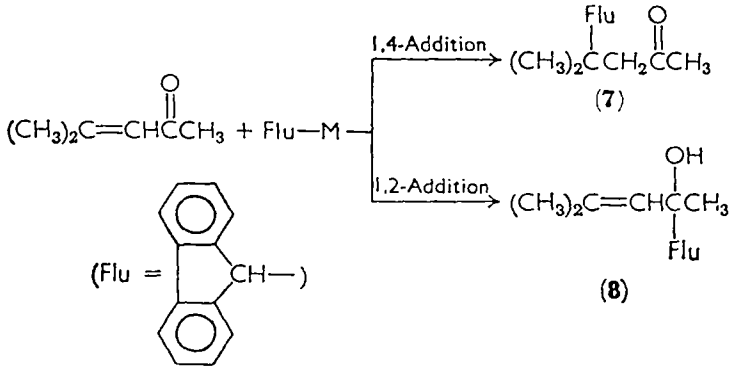
Hauser[14], again showed that the direction of addition depended upon the metal involved, as shown in Table 2[4].

The mechanistic interpretations discussed in the literature[8,16] for the exclusive formation of 1,4-adduct with RMgX may need some reevaluation in the light of recent findings discussed later (sections III.A.5 and B.2). Table 2 also indicates the superiority of organolithium compounds over Grignard reagents, when using 1,2-addition for preparative purposes. However, in some cases[17,18] the reactivity of

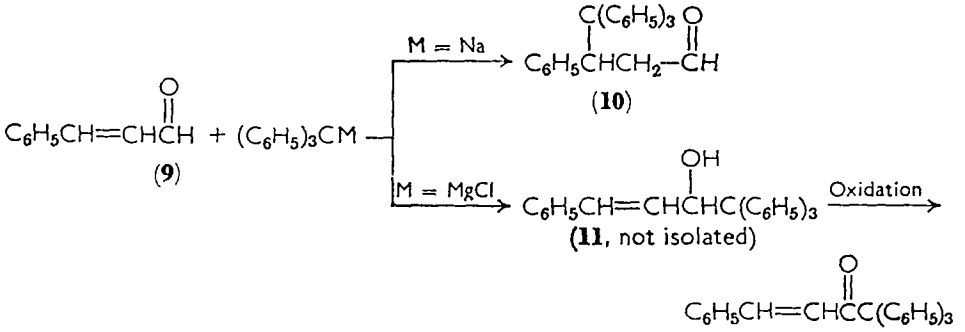
TABLE 2.

Cation	1,2-Addition (%)	1,4-Addition (%)
K	67	—
Na	60	14
Li	75	14
MgX	—	94

organolithiums and -magnesiums is reversed, and organoalkali compounds add preferentially in the 1,4-manner to conjugated systems. For example, fluorenyllithium, -sodium, and -potassium combine with mesityl oxide to form the product of conjugate addition (**7**),



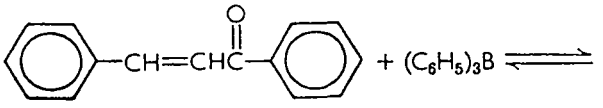
whereas fluorenylmagnesium bromide yields the allylic carbinol (**8**) by 1,2-addition. Similarly, tritylmagnesium chloride undergoes 1,2-addition in the reaction with cinnamic aldehyde[19], but with tritylsodium the 1,4-pattern is observed[20]. If in **9** a β-hydrogen is replaced by a phenyl group, the reaction with tritylsodium changes



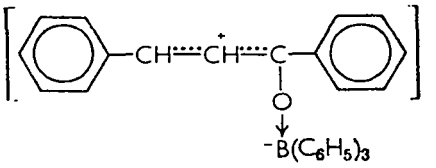
to 1,2-addition, probably for steric reasons[20] (equation 4) and **12**, an allylic alcohol analogous to **11** is obtained. Interestingly, benzalacetophenone fails to react with tritylsodium alone, but in the presence of triphenylboron 1,4-addition occurs quantitatively[20]. Activation of

$$(C_6H_5)_2C{=}CHCH + (C_6H_5)_3CNa \longrightarrow \underset{\textbf{(12)}}{(C_6H_5)C{=}CHCHC(C_6H_5)_3} \qquad (4)$$

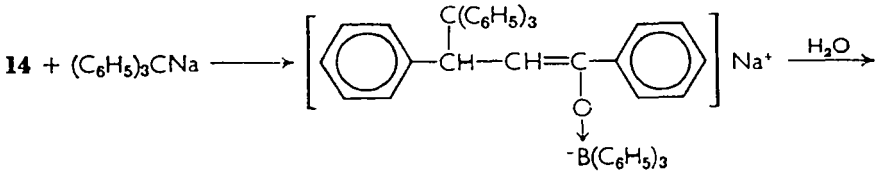
the α,β-unsaturated system via 'at-complex' formation[21] at the carbonyl group seems probable, thus leading to the proposed

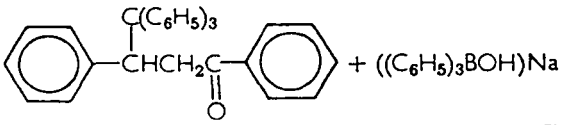


(13)



(14)





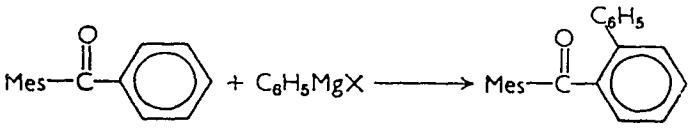
(5)

mechanism (5). (The advantage of applying the concept of 'at-complex' formation, developed by Wittig[21]*, to mechanisms of organometallic reactions will be discussed later.) Nucleophilic attack on a primarily formed 'at-complex' (**14**) by a trityl anion is analogous to a mechanism postulated by Wittig and coworkers for the

* An 'at-complex' is formed when a Lewis acid combines with a nucleophilic center.

reaction of unsaturated hydrocarbons with tritylsodium in the presence of complex-forming reagents[22].

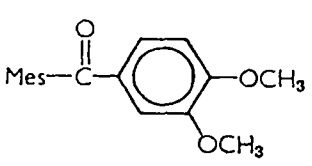
Sterically hindered aromatic ketones of the benzophenone type, which undergo almost exclusively conjugate addition with Grignard reagents[23,24], may still give 1,2-addition with the more reactive organolithium compounds. For example, mesityl phenyl ketone (**15**) is *o*-phenylated by phenylmagnesium bromide[25] (equation 6) while



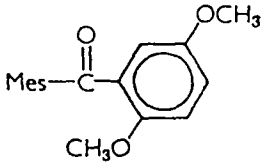
(6)

(**15**)

the mesityl phenyl ketones **16** and **17** give the corresponding triaryl carbinols resulting from 1,2-addition with phenyllithium[26]. But

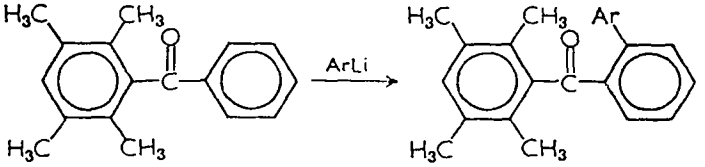


(**16**)



(**17**)

even the slight steric change caused in the environment of the carbonyl group on going from **15** to duryl phenyl ketone (**18**) makes 1,2-addition impossible even for phenyllithium; thus conjugate addition (equation 7) is observed.

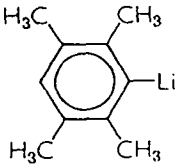


(7)

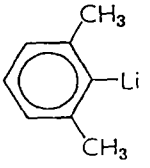
(**18**)

(**19**. Ar = C_6H_5; **20**, Ar = duryl)

Sterically hindered duryllithium (**21**) and 2,6-dimethylphenyllithium (**22**) provide further examples of the influence of steric hindrance on the course of interaction with ketones. Duryllithium (**21**), which is capable of 1,2-addition to benzophenone, effects *o*-phenylation of **18**, yielding **20**. In the reaction of **22** with 2,2′,6,6′-tetramethylbenzophenone (**23**) the extreme steric hindrance at

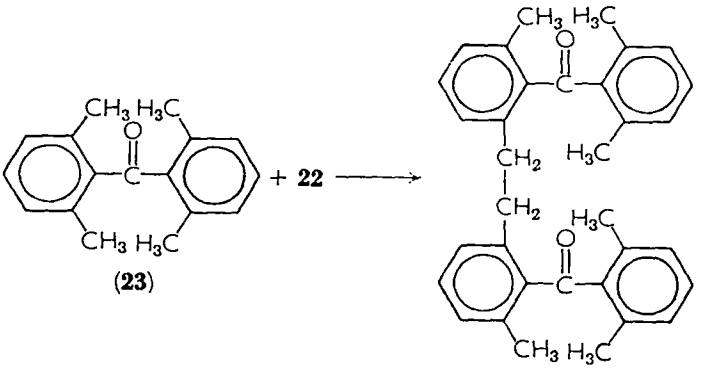


(21)



(22)

the carbonyl group as well as at the ring positions *ortho* to the carbonyl group is responsible for the rarely observed type of reaction which occurs (equation 8)[27]. **24** is only obtained in the cold; at

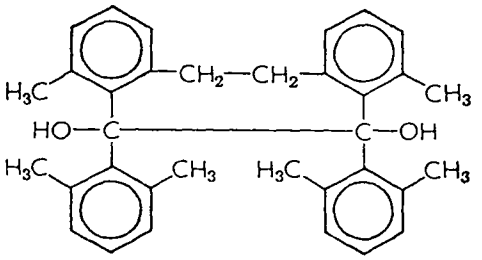


(23)

(24)

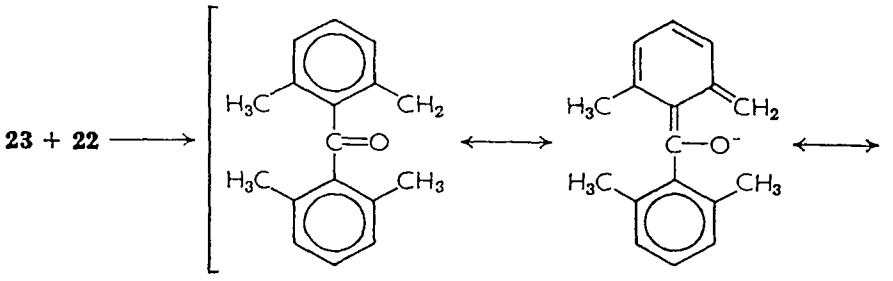
(8)

higher temperatures a different product is obtained, for which the structure **25** was proposed since chromic acid gave **24**, and Bachmann–Gomberg reduction[28] of **24** gave **25**. The structure of **24** was proved

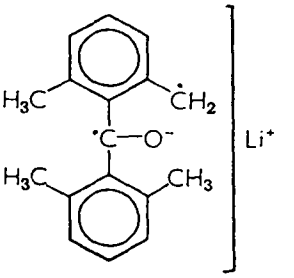


(25)

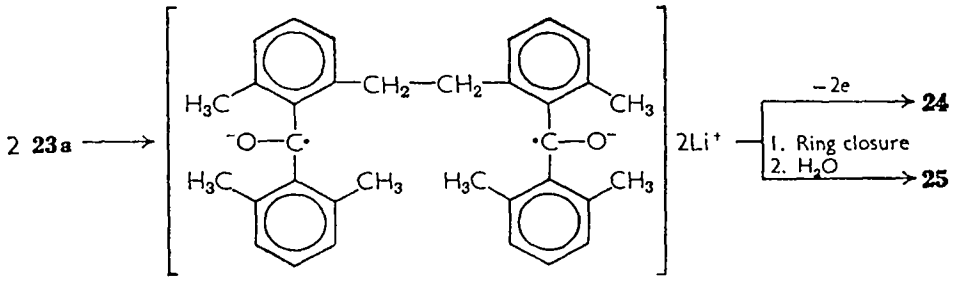
by independent synthesis. Using phenyllithium instead of **22** also led to the same products, **24** and **25**, and carboxylation at an early stage of the reaction yielded a carboxylic acid derived from metalation of one of the methyl groups of **23**. Hence the mechanism (9)



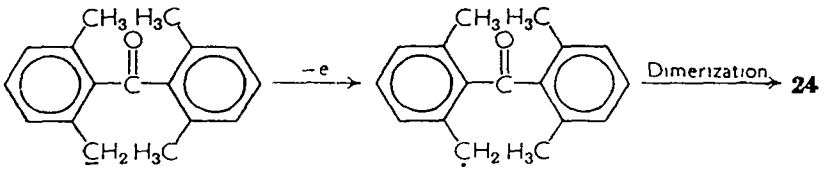
(23a)



(9a)



(9b)

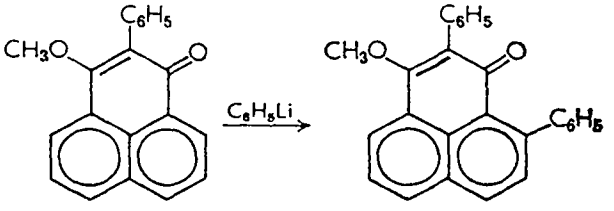


(23a)

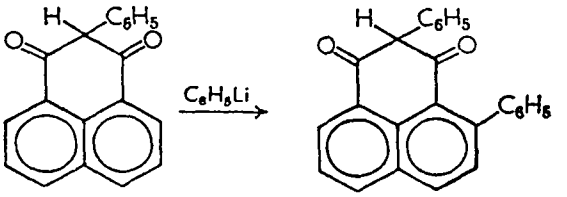
(10)

seems most likely. Whether the oxidation step takes place after dimerization or by an alternative route (10) of oxidative dimerization of the primarily formed carbanion (**23a**) cannot be decided from the data available.

Other examples of conjugate addition of organolithium compounds to aromatic ketones have been provided by Koelsch[29,30] who found that the phenylperinaphthindanedione derivatives **26** and **27** are phenylated in the naphthalene nucleus by phenyllithium.

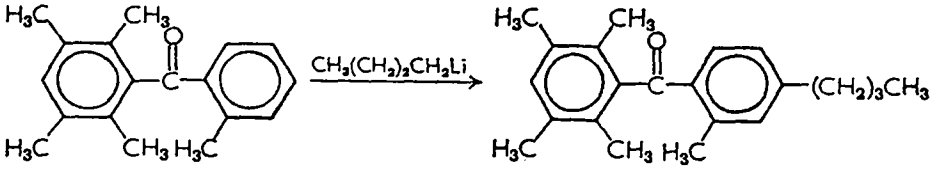


(**26**)



(**27**)

Besides 1,4-conjugate addition to sterically hindered diaryl ketones, 1,6-addition is also observed[23]. The reaction of n-butyllithium with duryl *o*-tolyl ketone leads to the product of 1,6-addition across the aromatic system (reaction 11)[31] along with metalation of

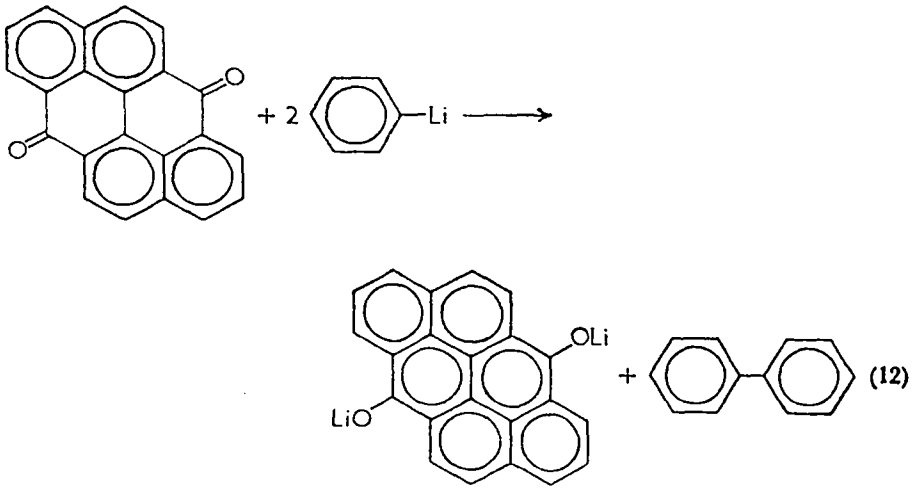


(11)

the *o*-methyl group. The preferential 1,6-attack of n-butyllithium parallels the reactivity of certain secondary and tertiary Grignard reagents towards duryl phenyl ketones[32].

D. Reduction

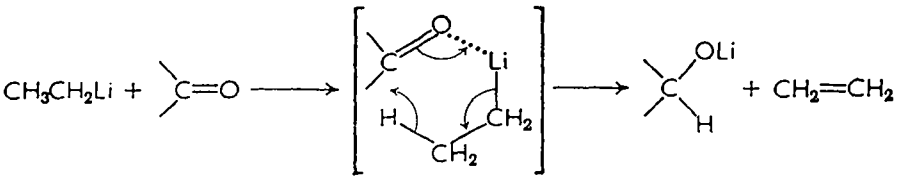
Another advantage of organolithium compounds over Grignard reagents is that with sterically hindered ketones (e.g. diisopropyl ketone), the latter give reduction to a large extent, while the former tend rather to addition than to reduction. Similarly, 17-oxo steroids are reported to undergo mainly reduction with alkylmagnesium halides, whereas tertiary carbinols are obtained with alkyllithiums, although some reduction also seems to occur[33]. Only very few carbonyl compounds are known which give reduction exclusively with organolithiums. Thus, anthanthrone is reduced by phenyllithium[34] forming **28** and biphenyl (reaction 12).



(12)

(**28**)

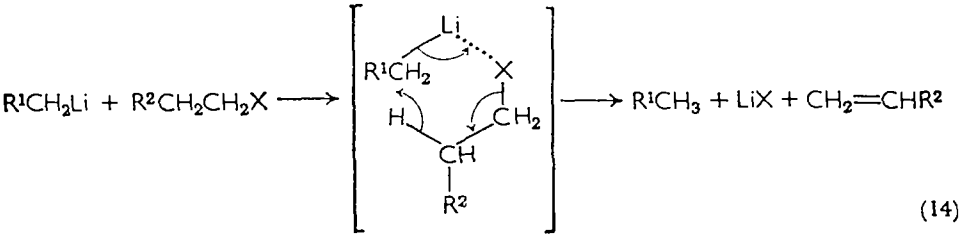
In analogy to the mechanism of reduction performed by organometallics of Group II elements a mechanism of direct reduction



(13)

(without preceding elimination of lithium hydride) may occur (equation 13). A related mechanism (14) is very likely for the direct

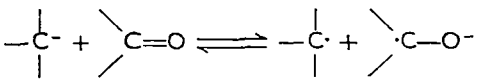
reduction of alkyl halides with alkyllithiums[34a] facilitated by non-polar solvents.



(14)

E. Ion-Radical Transfer; Ketyl Formation

The reaction of an aromatic ketone with a sterically hindered organoalkali compound unable to act as a nucleophile is generally accepted as involving a one-electron transfer from the anion to the carbonyl group leading to the corresponding radical and a ketyl, according to the reaction scheme (15) developed by Schlenk[35]. For



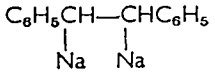
(15)

example, with tritylsodium and benzophenone in ether solution, the observed green color was attributed to the equilibrium (16) being shifted to the right at room temperature[36]. A similar behavior was

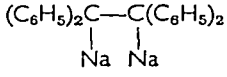
$$(C_6H_5)_3CNa + (C_6H_5)_2C{=}O \rightleftharpoons (C_6H_5)_3C\cdot + (C_6H_5)_2\dot{C}ONa \qquad (16)$$

yellow + blue = green

found in the reactivity of stilbenedialkali adducts[37] (**29**) and the corresponding dianion derived from tetraphenylethylene (**30**)[38]

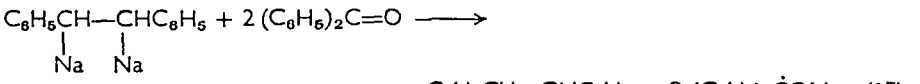


(29)



(30)

towards benzophenone, which regenerated the olefin and gave two moles of ketyl, e.g. equation (17), via an intermolecular redox



(17)

process; formaldehyde and acetone, however, exhibited normal bifunctional 1,2-addition to the dicarbanions **29** and **30.**

Issleib[39] recently found another type of ion–radical transfer in

the interaction of aromatic ketones with alkali phosphorus compounds, e.g. reaction (18). This reaction only occurred with the

$$2\,Ar_2C{=}O + 2\,MPR_2 \longrightarrow 2\,Ar_2\dot{C}OM + R_2PPR_2 \qquad (18)$$

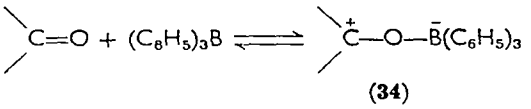
(**31**, R = C_6H_5; **32**, R = C_2H_5; M = Li, Na)

alkali diphenylphosphine **31**; the aliphatic **32** prevented ketyl formation by giving a stable 1:1 adduct (**33**). It is assumed that with

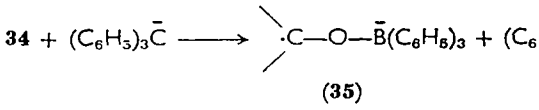
$$2\,[Ar_2C{=}O{\cdot}MPR_2] \rightleftharpoons 2\,Ar\dot{C}OM + R_2PPR_2$$

(**33**)

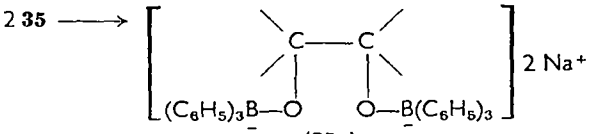
aromatic residues at the phosphorus atom the equilibrium lies preferentially on the right, whereas with aliphatic residues it is shifted to the left owing to the stability of **33**. The 1:1 complex **33** provides an analogy to the 1:1 adducts discussed for ketones and other organometallic Lewis acids (see section III.A.4 below). Some results of Wittig and coworkers, in particular those from the reaction of benzophenone[40] and fluorenone[41] with tritylsodium, do not support the formulation of the equilibrium in the form given by Schlenk. Under certain conditions, tritylsodium and benzophenone formed a colored 1:1 adduct, which hydrolyzed to triphenylmethane and benzophenone in equal amounts. Products indicating the presence of a trityl radical in the complex or in solution were not



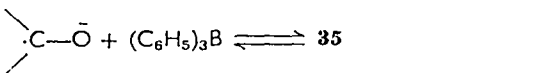
(**34**)



(**35**)

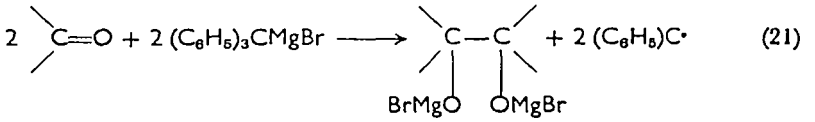


(**35a**) (19)



$$2\,\mathbf{35} \longrightarrow \mathbf{35a} \qquad (20)$$

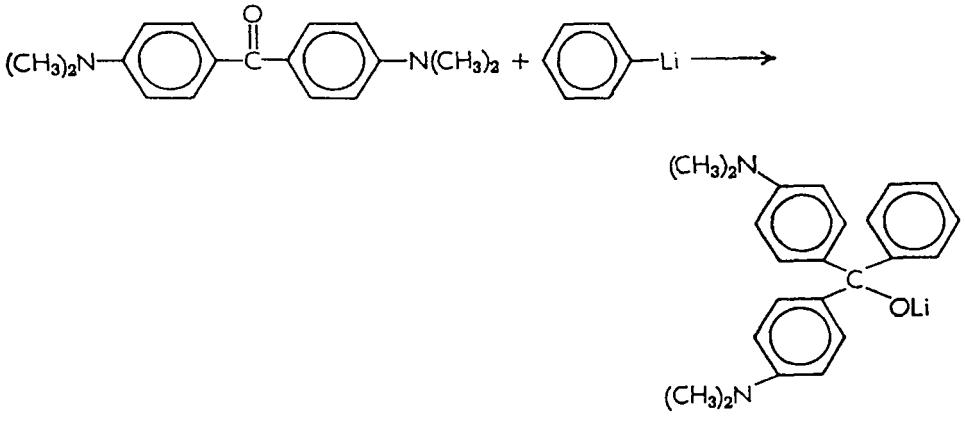
obtained here, nor in the reaction with fluorenone. The hypothesis of a charge-transfer complex for the 1:1 adduct seems reasonable. In the presence of triphenylboron, however, tritylsodium reduced ketones to the corresponding pinacols; in addition one equivalent of trityl radical was formed. Two reaction patterns (19 and 20) seem possible. With fluorenone, the bisboranate complex (**35a**) was isolated and characterized by further reactions. Probably triphenylboron activates the ketyl, present in low equilibrium concentration (a possibility not excluded by the results obtained) by formation of an 'at-complex' (**35**), which then undergoes the dimerizing reduction not observed without triphenylboron. A similar complexing of an intermediate ketyl may be responsible for the exclusive pinacol reduction of aromatic ketones by tritylmagnesium bromide (in contrast to tritylsodium) (equation 21)[42]. This might be due to the Lewis-acid activity exhibited by RMgX, but not by RNa.



(21)

F. Mechanism

In contrast to the metalation reaction[43] and the halogen–metal interconversion[44] there are few reports in the literature on the detailed mechanism of 1,2-additions and other reactions of organoalkali compounds with carbonyl groups, probably because the addition is extremely fast. The reaction of phenyllithium with carbonyl groups was compared to a titration process by Wittig[6] who stated



(22)

that 'the extraordinary reactivity leads to instantaneous and complete reaction in the majority of cases investigated'.

In the kinetic investigation of the reaction of Michler's ketone (4,4'-bis-(*p*-dimethylamino)benzophenone) with phenyllithium by Swain and Kent[45], reaction (22) was followed by means of a flow technique and was found to be homogeneous and first-order in each reactant, with a rate coefficient of approximately 5×10^3 (l/mole sec), i.e. a half-life of 0·002 sec (0·1 M at 25°).

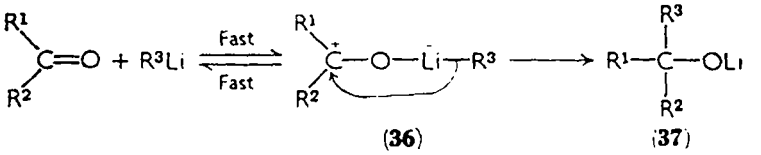
In competition experiments the relative reactivity of several organolithium compounds was found to fall in the sequence[46]

$$p\text{-}CH_3C_6H_4Li > C_6H_5Li > C_2H_5Li > (CH_3)_2CHLi$$

On the other hand, the relative reactivity of diaryl ketones decreased in the series

4,4'-dichlorobenzophenone > benzophenone > Michler's ketone.

The usual order of reactivity of aliphatic and aromatic organolithium compounds is reversed (as a rule, only aliphatic RLi compounds cleave ethers and metalate benzenes readily) and, moreover, the least basic, i.e. the poorest complex-forming ketone, reacted most rapidly. Therefore, the mechanism (23) was proposed, the key part of which was believed to be a 1 : 1 coordination complex (**36**) between the ketone and the lithium reagent. The combination



(36) (37) (23)

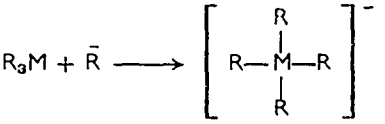
of the ketone and R^3Li in the first step of (23) was assumed to be fast and reversible, and the rearrangement of the 1 : 1 adduct **36** to **37** to be the rate-determining step. Indeed, the order of reactivity of the R^3Li compounds tested corresponds characteristically to the order of migration aptitudes of the R^3 groups in ionic Wagner–Meerwein-like rearrangements (i.e. aryl > alkyl)[47]. The stability of **36** as a function of the complexing power of the ketones involved might also explain their relative reactivity.

An important assumption for the above mechanism is the ability of organolithium compounds to act as complexing agents. This was established by Wittig[48], who prepared stable complexes (38) of

$[C_6H_5\ Li\ C_6H_5]M$
(**38**, M = Na, K, Cs)

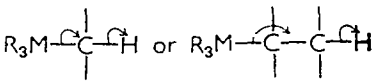
phenyllithium with organosodium, -potassium, and -cesium reagents. Phenyllithium itself, reported to be dimeric in diethyl ether[49], can similarly be formulated as an autocomplexing ion pair (**38**, M = Li), in which one lithium atom functions as center of coordination and the other is attached as a cation to the complex anion. However, the attack of a monomeric R^3Li species in equation (23) seems most probable, since the monomer should be more reactive than the higher associated entities present in equilibrium[50]. It has been demonstrated that deassociation processes often complicate the kinetic picture of metalation and polymerization reactions investigated in nonpolar solvents[51].

The formulation of a coordination complex (**36**) involves another important principle, which Wittig[21] recognized to be of general value for the understanding of organometallic reactivity. By combination of a nucleophilic center with a Lewis acid an 'at-complex' is formed, e.g. equation (24), which shows increased anionic mobility

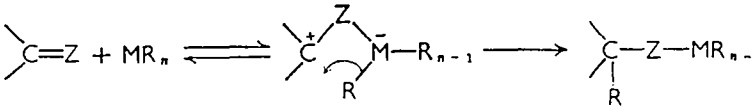


(24)

of the ligands R as well as enhanced aptitude for hydride ion abstraction, if R is a hydrocarbon residue with α- or β-C—H bonds:



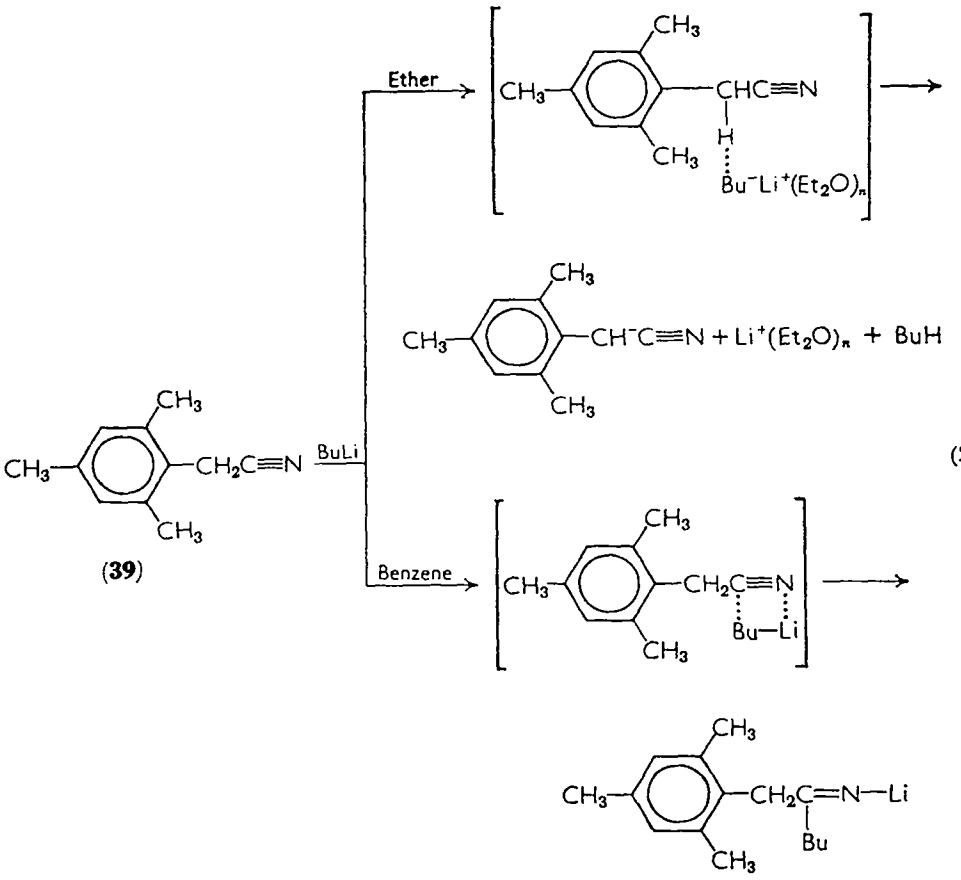
Thus an organometallic reagent can, by 'at-complex' formation, provide a carbanion for attack by a nucleophilic center. When organometallic compounds add to multiple bonds containing a heteroatom (e.g. >C=O, >C=N—, —C≡N) coordination of the metal with the nucleophilic heteroatom assists the subsequent anionic attack on the neighboring positively charged carbon, leading to formation of a new carbon–carbon bond (reaction 25, Z = heteroatom). According to Dessy and Paulik[52], the addition of



(25)

organometallic compounds to multiple bonds containing a heteroatom takes place through an 'assisted four-center mechanism'. These authors stated that in a large number of reactions electrophilic

or nucleophilic assistance occurs, which is due to the coordination of one of the reactants with the second one at a site neighboring to the reaction center, resulting in an increase of reactivity. This terminology resembles very closely the concept of 'at-complex' formation[21]. Coordinative assistance of reactivity may also be due to the solvent, as shown by the different behavior of n-butyllithium in ether and in benzene. In benzene the organometallic compound is added as a polarized covalent species, whereas in ether the solvation of the lithium cation causes some mobility of the butyl anion within the ion pair and thus preferentially brings about metalation (i.e. deprotonation) of the nitrile **39** (reaction 26)[14,52].



(39)

(26)

III. GROUP II ELEMENTS

A. *Organomagnesium Compounds*

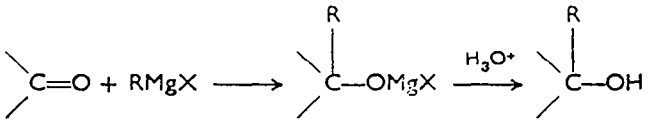
1. General

The various reactions of Grignard compounds with aldehydes and ketones have been reviewed up to 1954 by Kharasch and Reinmuth[2].

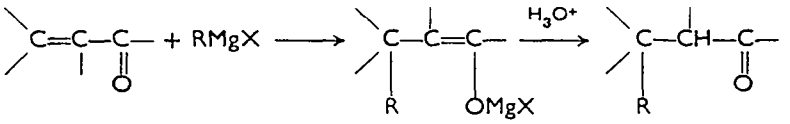
Apart from the development of the chemistry of the alkenylmagnesium halides, reviewed by Normant[53], no completely new aspects or types of reaction seem to have appeared in the literature of the last decade. On the other hand, the mechanistic understanding of the reactivity of Grignard compounds towards the carbonyl group and the establishment of their structure have been the subject of vivid controversies in the last decade with a remarkably large number of questions still remaining open. Thus a brief discussion of the problems connected with the structure of Grignard reagents seems to be justified in this chapter.

The following types of reaction can occur between Grignard compounds and aldehydes or ketones:

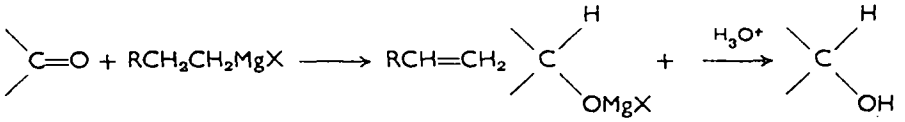
a. Normal or 1,2-addition.



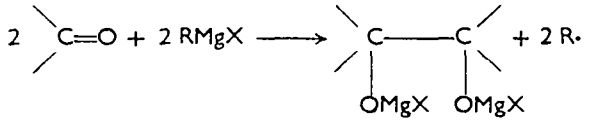
b. Conjugate (or 1,4) addition to unsaturated systems.



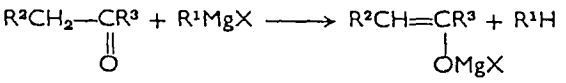
c. Two-electron reduction of the carbonyl group.



d. One-electron reduction of the carbonyl group leading to pinacol formation.



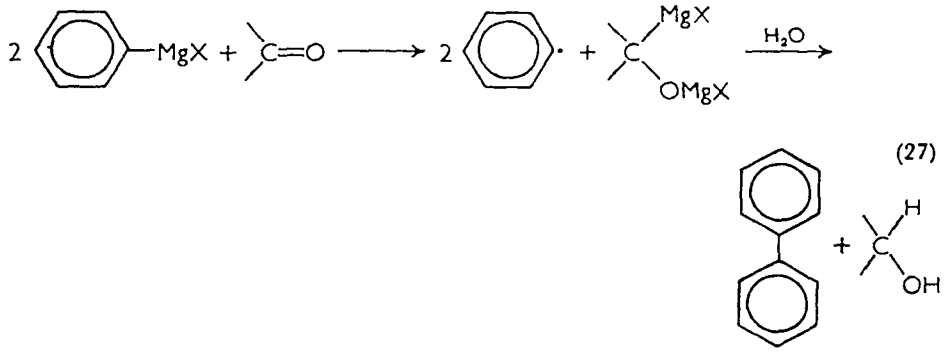
e. Enolization (deprotonation) of the carbonyl compound.



Reduction and enolization will be treated before addition since their mechanisms are easier to survey and are often used in the discussion of addition mechanisms. RMgX and R_2Mg compounds are generally treated together because of the development of the structure problem discussed later.

2. Reduction and enolization

Reduction of a ketone by a Grignard reagent results in a carbinol, as shown above under (*c*). With aliphatic Grignard reagents, the hydrocarbon residue is dehydrogenated to an olefin, whereas with aromatic Grignard compounds a rather complicated sequence not yet completely elucidated (formally the oxidation of the aryl anion to the radical) leads finally to biphenyl derivatives (equation 27)[54].

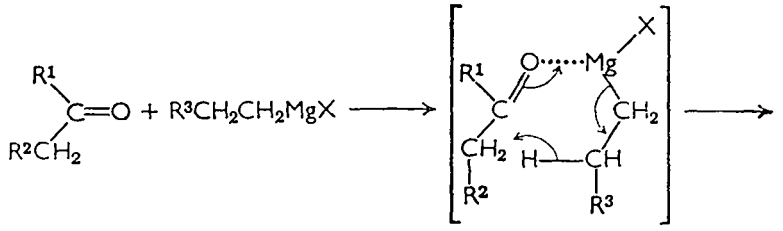


(27)

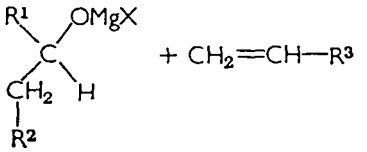
In the aliphatic series reduction and enolization are always observed if the Grignard reagent is branched in the α-position to the metal or generally if it is sterically crowded. Qualitative relationships between the structure of the Grignard reagent and the ratio of addition *versus* reduction and enolization were discussed by Whitmore[55]. Table 3 contains results obtained in the reaction of diisopropyl ketone and several Grignard reagents. As expected, increasing the bulk of the alkyl group results in an increase of reduction and enolization, and a decrease of addition. The complete absence of reduction in the case of the neopentyl Grignard reagent led to the conclusion that β-hydrogen atoms were necessary for reduction.

TABLE 3.

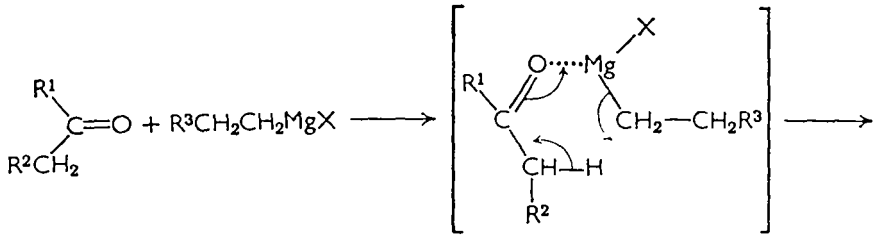
R in RMgBr	Enolization (%)	Reduction (%)	Addition (%)
Methyl	0	0	95
Ethyl	2	21	77
n-Propyl	2	60	36
Isopropyl	29	65	0 (!)
Isobutyl	11	78	8
Neopentyl	90	0 (!)	4



(40) (28)



Thus, a mechanism involving the transfer of a hydride ion in a cyclic six-membered transition state (**40**) was proposed (reaction



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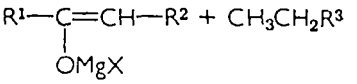
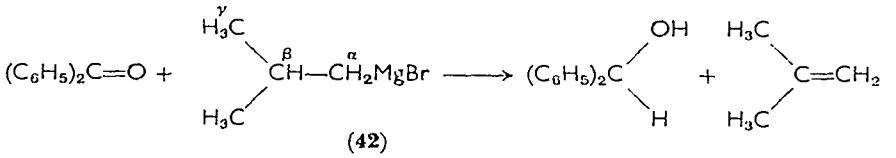


(29)

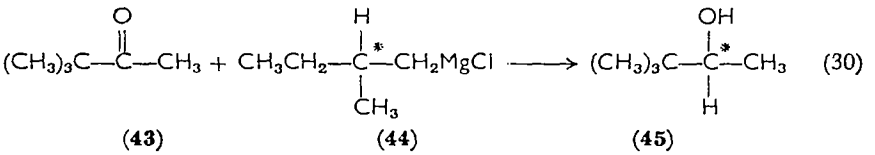
28)[56]. A similar mechanism had been suggested earlier by Lutz and Kibler[57] for the enolization process (29). The possibility of a cyclic transition state like **41** was indicated by later results on the competition of enolization with reduction and addition (see below).

Dunn and Warkentin[58] investigated the reduction of benzophenone by isobutyl Grignard reagents (**42**) labeled with deuterium alternatively at the α-, β-, and γ-carbon atoms. Only in the case of β-deuterated **42** did the deuterium appear in the product of reduction



(**42**)

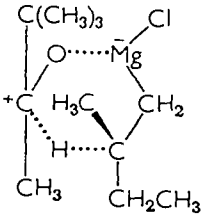
benzhydrol, at the carbon bearing the hydroxyl group. This was clear proof that β-hydrogen atoms participated in the transition state of the reduction, in support of the mechanism postulated above. Furthermore, if a cyclic transition state like **40** is involved, one would expect stereospecificity for the reduction of a sterically suitable ketone resulting, at least to a certain extent, in asymmetric induction if a center of optical activity is introduced at the β-position of the Grignard reagent. Indeed, Mosher[59,60] was able to show that the reaction of *t*-butyl methyl ketone with optically active (+)-2-methylbutylmagnesium chloride resulted in the formation of a partially optically active carbinol (reaction 30). The partial asymmetric



(30)

(**43**) (**44**) (**45**)

reduction 'furnishes conclusive evidence for some closely associated complex in which the reduction of the ketone takes place simultaneously with the destruction of asymmetry of the Grignard reagent in a stereospecific manner'[59]. The preponderance of one of the optical isomers **45** is accounted for by the fact that one (**46**) of the two possible transition states is energetically favored: the greater sterical interference of two bulky groups on the same side of the ring destabilizes **47** compared to **46**. The importance of the β-position of the Grignard reagent participating in the transition state is further indicated by the reduction of **43** with (+)-3-methylpentylmagnesium bromide possessing its center of optical activity in the γ-position,



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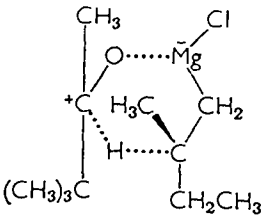
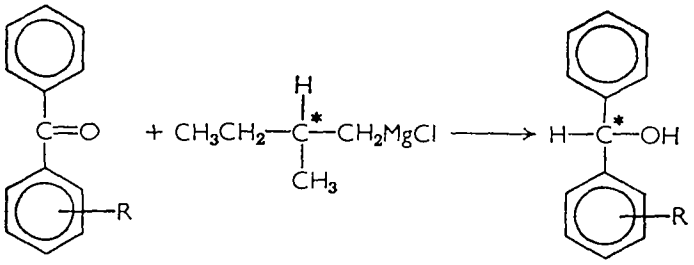


(47)

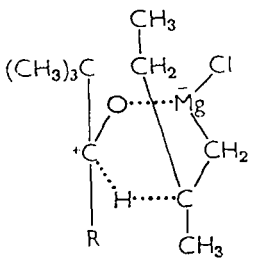
which gave an amount of asymmetric induction smaller than 0·01%[61]. The corresponding dialkylmagnesium compound (di-((+)-2-methylbutyl)magnesium)[62] gave an amount of asymmetric reduction (as well as addition and enolization) very similar to the Grignard compound **44**. The same species was thought responsible for the reaction observed in both cases, namely the dialkylmagnesium compound **48**.

The energetically determined preference of one of two possible transition states caused by less steric crowding was confirmed by further investigations. Thus, asymmetric reduction of substituted benzophenones **49** with **44** was observed with *o*-substitution in **49**, while *p*-substituted **49** did not give optically active benzhydrol (equation 31)[63]. The amount of asymmetric reduction was found to



(49) (31)

decrease with increasing chain-length and branching at the α-carbon of R in the series of alkyl *t*-butyl ketones $(CH_3)_3CCOR$ undergoing reaction (30)[64], since increasing steric requirements by R will lead to smaller differences in the transition states **50** and **51**. In the series of phenyl ketones C_6H_5COR, however, the effect of varying R was opposite to that in the *t*-butyl series: asymmetric induction increased with increasing bulk of R[65]. Since in cyclohexyl ketones ($C_6H_{11}COR$) the change of asymmetric induction observed on change of R[66] did not obey any simple relation connected to the bulk of the substituents, it was assumed that the transition state of the



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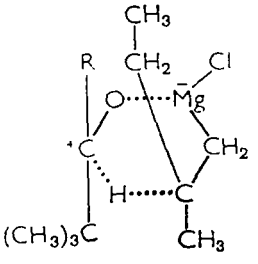
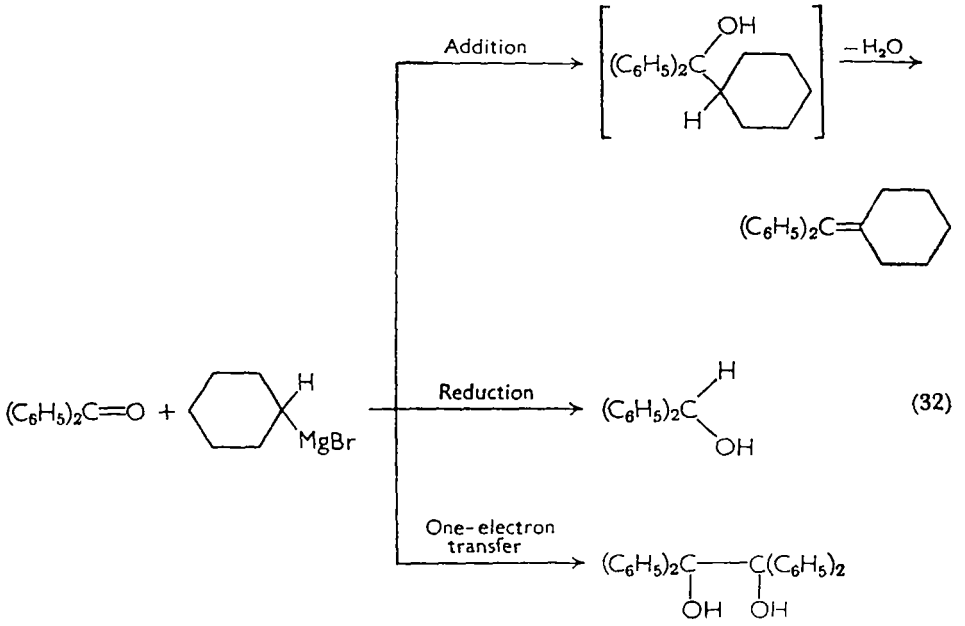


(51)

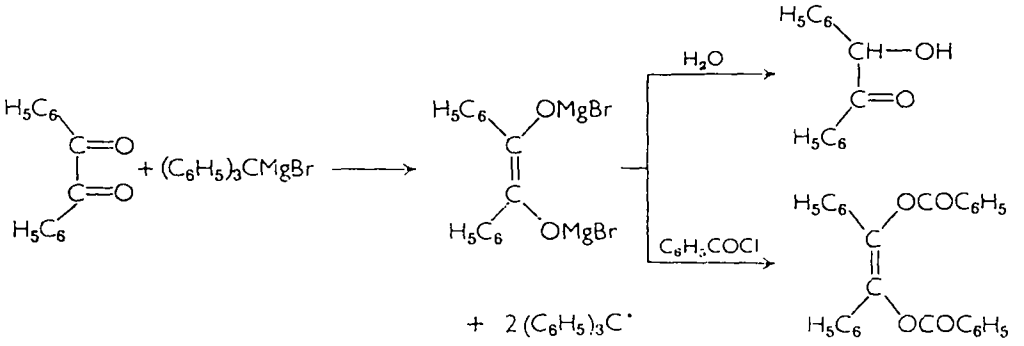
reduction is also influenced by inductive and electronic factors not yet completely known.

A small measure of optical activity may also be induced by a Grignard reaction carried out in an optically active solvent. Cohen and Wright[67] obtained optically active carbinols from 2-butylmagnesium chloride and several carbonyl compounds in optically active dimethoxybutane. Similarly, the reaction of certain optically active amino ketones with Grignard reagents[68] led to the preferential formation of one of the enantiomers, indicating the possibility of asymmetric induction in Grignard reactions by an optically active carbonyl substrate.



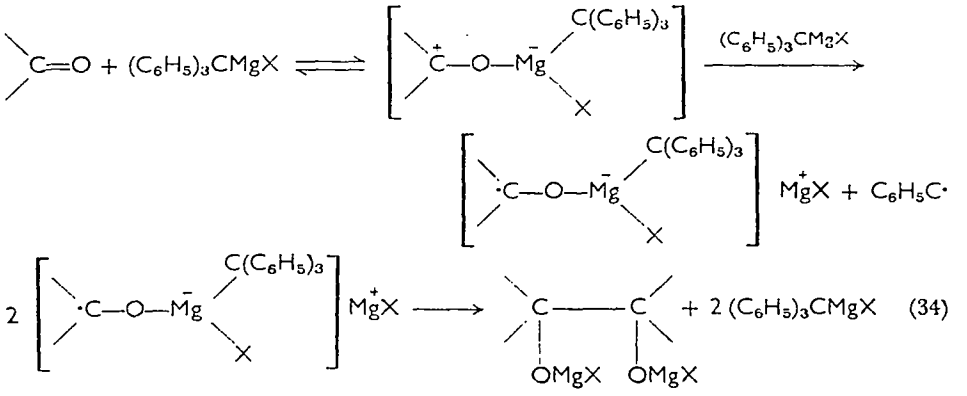
(32)

The pinacone reduction, which takes place nearly quantitatively with triphenylmethylmagnesium halides and aromatic ketones[42], sometimes also occurs with aliphatic Grignard reagents. For example, cyclohexylmagnesium bromide reacts with benzophenone to yield not only the 'normal' products of addition and reduction, but also a considerable amount of benzopinacol (equation 32)[69]. Interestingly, diketones also undergo one-electron transfer reaction with triphenylmagnesium bromide: benzil[42] gives stilbene dienolate with consumption of two moles of Grignard reagent (reaction 33) which was further characterized by reaction with water or with benzoyl chloride.



(33)

No conclusive studies have been reported on the precise mechanism of the Bachmann reaction. Since triphenylmethylsodium alone does not give pinacone reduction[40,41], but does in the presence of triphenylboron might mean that complex formation has to be an attribute of the organometallic reagent. As this is true for triphenylmethylmagnesium bromide but not for triphenylmethylsodium, (34) probably depicts the mechanism of pinacone reduction.



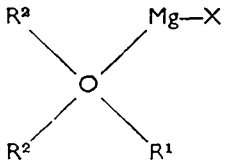
(34)

3. Structure of the Grignard reagent

The large amount of diverse and partially conflicting data reported in the literature on the structure of Grignard reagents and on the mechanism of Grignard reactions represents a classical case of the principal problems of structure–reactivity relation: physical methods may well reveal the composition of a given substrate, but may contribute little or no compelling information about the species responsible for the observed reactivity, if these are involved in equilibria systems.

The investigation of the composition of Grignard solutions by physical methods has been reviewed by Kharasch and Reinmuth[2], Ashby and Smith[70], and Salinger[71]. Some aspects of the structural problems studied very recently will be introduced, since they are of importance for the discussion of mechanism presented in the subsequent section.

The first suggestion made by Grignard[72] (**52**) and later supported by Meisenheimer[73] (**53**) was that Grignard compounds are best represented by RMgX coordinated with the solvent ether. These



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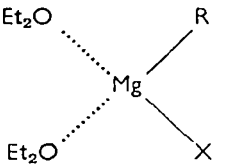
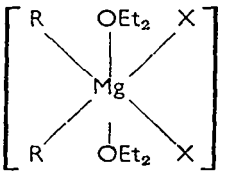


(53)

proposals were questioned by Jolibois[74] and by Terentiew[75] who interpreted their findings from chemical behavior[74] and ebullioscopy[75] by means of the dimeric formulations **54** and **55**. The di-

$R_2Mg{\cdot}MgX_2$

(54)



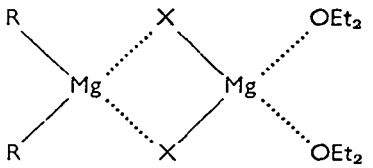
(55)

meric species **54** was conceived in order to explain the phenomena observed in physical measurements of Grignard solutions, for example measurements of specific conductance[76], transference studies[77], and behavior on electrolysis[78]. Convincing evidence permitting a clear-cut choice between monomeric and dimeric formulations was presented by Dessy and coworkers[79]. When $^{28}MgBr_2$ and diethylmagnesium

were equilibrated in diethyl ether, essentially *no* exchange of radioactive magnesium was obtained. If an equilibrium of the type (35)

$$2\,RMgX \rightleftharpoons R_2Mg + MgX_2 \tag{35}$$

occurred in Grignard solutions, as proposed by Schlenk and Schlenk[80], statistical exchange of radioactivity should take place. Although Dessy had reported one experiment with ^{25}Mg as a tracer leading to statistical exchange, his negative exchange experiments with ^{28}Mg proved to be decisive for the conclusions soon accepted generally, namely that exchange of residues R does not take place in Grignard reagents, and that these are best represented by the $R_2Mg \cdot MgX_2$ structure (**56**), as first suggested by Jolibois (**54**), or by



(**56**)

an equilibrium (36). Comparison of data obtained from measure-

$$R_2Mg \cdot MgX_2 \rightleftharpoons R_2Mg + MgX_2 \tag{36}$$

ments of conductivity[81] and dielectric constants[82] of equimolar mixtures of R_2Mg and MgX_2 as well as the Grignard reagent from RX and Mg seemed to indicate the presence of the same entity in both cases, namely $R_2Mg \cdot MgX_2$.

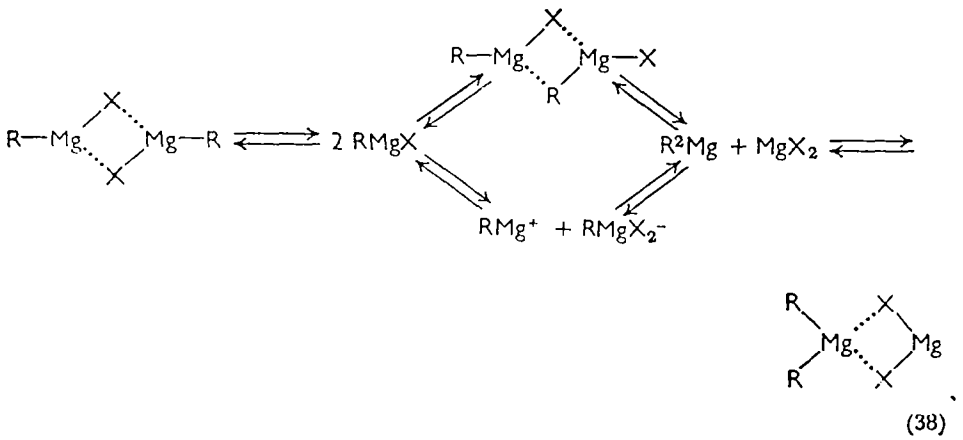
However, in a reinvestigation of his former experiments Dessy[83] found statistical exchange of radioactivity *also* with ^{28}Mg when another commercial sample was used as carrier. Since an exchange of magnesium, i.e. an exchange of R groups, necessarily implies the (at least intermediate) formation of RMgX entities, a system of equilibria (37) seems to be an appropriate description of the situation in Grignard solutions.

$$\begin{array}{ccc} R_2Mg \cdot MgX_2 & \rightleftharpoons & R_2Mg + MgX_2 \\ \downarrow\uparrow & \times & \downarrow\uparrow \\ (RMgX)_2 & \rightleftharpoons & 2RMgX \end{array} \tag{37}$$

Recently, findings based on molecular weight determinations[70,84–86], x-ray analyses of crystalline Grignard compounds[87,88], and infrared spectroscopy[89] gave further evidence that the existence of monomeric RMgX has to be taken into consideration. Ebullioscopic measurements by Ashby[70,84] showed a marked dependence

of association upon the concentration, upon the nature of the R group, upon the halogen, and upon the solvent, as earlier results[86] had already indicated. In diethyl ether[70] bromides and iodides between 0·05 and 0·1 M were monomeric, between 0·3 and 1 M increasing association to dimers took place, while chlorides proved to be dimeric over the whole range of concentrations investigated. In tetrahydrofuran[84] only molecular weights corresponding to monomers were found, regardless of the nature of halogen involved.

A somewhat modified array of equilibria (38) was stated by



(38)

Ashby[70] to represent the composition of Grignard solutions; amplification of the system by ionic species had been supposed earlier[76,90]. Additionally, Vreugdenhil[85] had reported that dilute solutions of ethylmagnesium in diethyl ether or tetrahydrofuran (0·01 M) contained only monomeric species. Stucky and Rundle[87,88] isolated the well-defined dietherates $C_6H_5MgBr \cdot 2(C_2H_5)_2O$ and $C_2H_5MgBr \cdot 2(C_2H_5)_2O$[88]. X-ray analysis of these showed monomeric entities with the unit cell consisting of Mg tetrahedrally surrounded by phenyl (ethyl), bromine, and two molecules of ether. Although structures proved to exist in the solid state do not necessarily describe the situation in solution, they at least show the necessity of taking into account the existence of monomeric RMgX coordinated with the solvent, as Meisenheimer[73] (**53**) already had postulated.

Infrared investigation of Grignard reagents were undertaken by several authors[89–92], but the reported[90] band assignments were not always accepted, since coordination effects of the solvent (ether) had not been taken into account[92]. In a comparative study of dialkyl- and diarylmagnesiums and the corresponding Grignard compounds

Salinger and Mosher[89] accumulated evidence that in tetrahydrofuran the Grignard solutions were best represented as mixtures of RMgX, R_2Mg, and MgX_2, perhaps with some contribution of ionic counterparts according to the modified Schlenk equilibrium (39). In ether all the Grignard reagents studied, except phenyl-

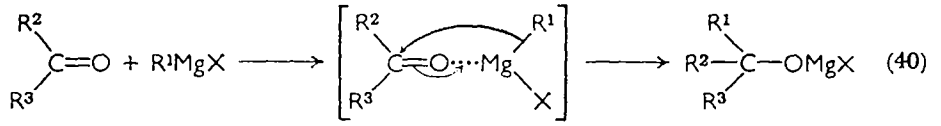
$$2\ RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons RMg^+ + RMgX_2^- \qquad (39)$$

magnesium iodide, showed small differences in spectra from those of the corresponding R_2Mg compounds so that no definite conclusion could be drawn. Only for phenylmagnesium iodide did it appear likely that the equilibrium (39) lies far to the left. It should be noted that nuclear magnetic resonance studies[93-96] have not been definitive so far concerning differentiation between RMgX *versus* $R_2Mg \cdot MgX_2$ and R_2Mg, respectively. Little if any difference is reported on n.m.r. spectral properties of organometallic derivatives of different metals, e.g. CH_3MgI and CH_3Li[96], indicating the inability of n.m.r. in certain cases to differentiate between two different chemical species.

4. The mechanism of 1,2-addition

The development of mechanistic ideas about 1,2-addition of organomagnesium reagents to saturated ketones very closely parallels the controversy over Grignard reagents discussed in the previous section. The mechanistic interpretations of 1,2-addition, which more or less tacitly assumed that the Grignard reagent is exclusively dimeric, probably need to be reinterpreted or at least handled only *cum grano salis*.

Two proposals for the mechanism of such addition have received serious consideration in the earlier literature. The first of these, advanced by Meisenheimer[97], considered the addition as occurring by rearrangement of an association complex **59** between the Grignard reagent and the carbonyl compound (reaction 40). A mechanism of

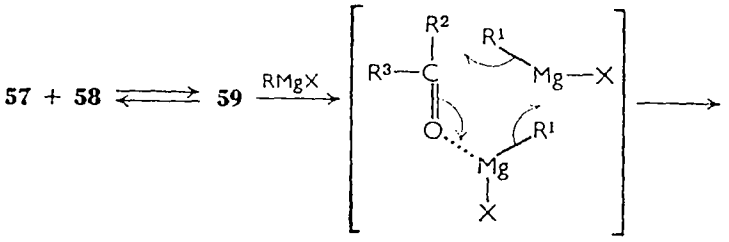


(40)

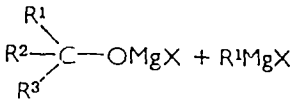
(57) (58) (59)

this kind would now be considered a four-center process, as discussed later. The second proposal, advanced by Swain[98], involves attack of a *second* Grignard entity upon the complex primarily formed between

57 and **58** (reaction 41). The nature of attack was pictured (**60**) via a six-membered cyclic transition state. As written, mechanism (40) requires second-order overall kinetics, whereas according to (41) the



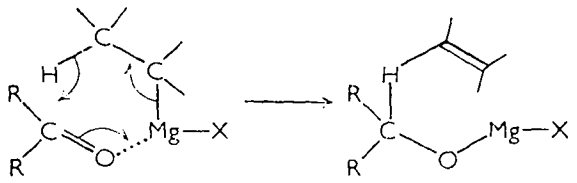
(**60**)



(41)

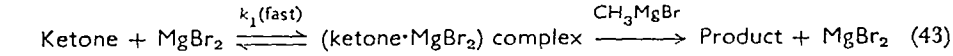
addition reaction should be second-order in RMgX and third-order overall.

A kinetic investigation of the reaction of benzophenone and pinacolone with CH_3MgX (X = Br, I) by Anteunis[99] showed that the reaction apparently followed, on the basis of the steady-state treatment, a third-order kinetic expression $v = k_3[\text{ketone}][\text{RMgX}]^2$ thus supporting mechanism (41). Another investigation by Anteunis[100] seemed to support an observation made by Swain[98]. In the reaction of diisopropyl ketone with n-propylmagnesium bromide[101], the ratio of addition to reduction was found to change considerably in favor of addition when $MgBr_2$ was added; it was concluded that, in agreement with mechanism (41) and the mechanism (42) suggested for



(42)

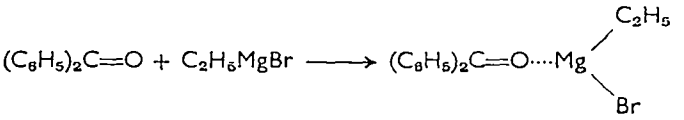
reduction[56], the complex with $MgBr_2$, which is a stronger Lewis acid than RMgX, seems to be more susceptible to addition than to reduction. Indeed, the reaction of pinacolone with methylmagnesium bromide, which had been of third-order without $MgBr_2$[99], followed



(43)

second-order kinetics in the presence of magnesium bromide[100], supporting the above conclusions (reaction 43).

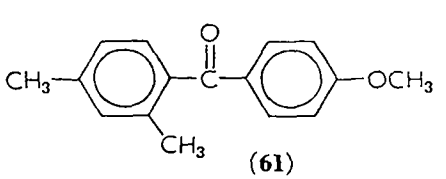
It should be added here that a large number of observations and speculations[102] on 1:1 addition complexes of ketones and aldehydes with organomagnesium compounds (as well as magnesium halides) is found in the earlier literature. Mechanism (41) was based on the findings of Pfeiffer and Blank[103], who reported on a 1:1 complex between benzophenone and ethylmagnesium bromide (equation 44).



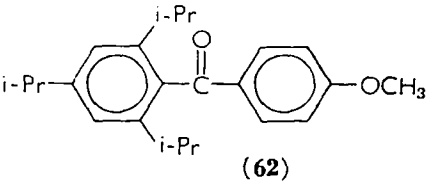
(44)

Although they could not isolate a defined product, they attributed the fact that only unchanged benzophenone (and *no* addition product!) was found after quenching the reaction mixture to the existence of a stable 1:1 adduct. Later, Nesmeyanov[104] found that the results of Pfeiffer were not reproducible; instead, he obtained a 79% yield of the carbinol resulting from normal addition under the given conditions[103]. Despite the fact that other 1:1 complexes reported by Pfeiffer and Blank could be confirmed, e.g. the adduct of Michler's ketone and ethylmagnesium bromide[105], later authors did not give credit to the concept of a stable 1:1 complex preceding the addition step[109,110].

Recently, Smith[106] offered convincing evidence for the existence of 1:1 adducts from an ultraviolet spectroscopic study of the interchange of sterically hindered ketones **61** and **62** and organomagne-

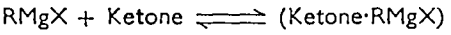


(61)



(62)

sium compounds (RMgX, R_2Mg) as well as $MgBr_2$. From the change of the ultraviolet spectrum compared to that of the uncomplexed ketone, the constants for the equilibrium (45a) were estimated (e.g. 25% of **62** was complexed with ethylmagnesium bromide in 0·1 M solution).



(45a)

The subsequent interpretations of other authors differed markedly from the implications of mechanisms (40) and (41). First, Swain's experiments with added $MgBr_2$, considered to support mechanism

(40), were given a different interpretation[107]. No detectable amount of a complex between $MgBr_2$ and fluorinated carbonyl compounds was found, yet the presence of $MgBr_2$ in ethylmagnesium iodide favored addition, an effect which Swain had ascribed to preferential complexing of $MgBr_2$ at the carbonyl group. Addition was favored also in the absence of $MgBr_2$ when pyridine was used as solvent, indicating that changes in the polarity of the reaction medium may be an important factor for the effects observed[107]. A suggestion by Cram[108] pointed out that the Schlenk equilibrium (45b) on addi-

$$R_2Mg + MgBr_2 \rightleftharpoons 2\,RMgX \qquad (45b)$$

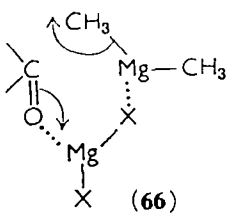
tion of $MgBr_2$ would be shifted toward RMgX and that the results[98,107] might be rationalized by assuming that R_2Mg is a better reducing agent than RMgX. Becker[109] observed spectral evidence for a complex of $MgBr_2$ with benzophenone, but the addition of methylmagnesium bromide regenerated the ketone spectrum. The assumption that no complexing of the ketone should occur in the presence of methylmagnesium bromide is not fully understood in the light of the findings of Smith[106], and Becker's observations are not in agreement with the spectroscopical results of other authors[89]. Kinetic results differing from prior investigation[99] were obtained by Becker and Bikales[109,110] in the reaction of benzophenone with methylmagnesium bromide in tetrahydrofuran. The overall reaction (giving 96% addition) was found to be complex, but the initial period (about the first 40% of reaction) obeyed second-order kinetics, first-order in benzophenone and first-order in methylmagnesium bromide. There was a well-marked decrease of rate after consumption of 50% of the alkyl groups in the Grignard reagent.

It was recognized[111] that regardless of whether the 'normal' (ketone to Grignard) or the 'inverse' addition technique was used, about 86% addition product was obtained from the reaction of

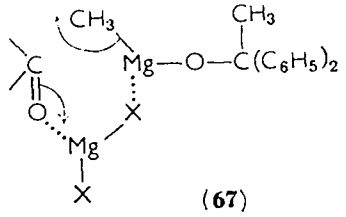
$$(C_6H_5)_2C{=}O + (CH_3)_2Mg{\cdot}MgBr_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\textbf{(63)}}{\text{complex I}} \xrightarrow{k_2} \underset{\textbf{(64)}}{(C_6H_5)_2\overset{CH_3}{\overset{|}{C}}-O-Mg_2Br_2CH_3}$$

$$\textbf{64} + (C_6H_5)_2C{=}O \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \text{complex II} \xrightarrow{k_4} \underset{\textbf{(65)}}{\left[(C_6H_5)_2\overset{CH_3}{\overset{|}{C}}-O\right]_2-Mg{\cdot}MgBr_2} \qquad (46)$$

benzophenone and methylmagnesium bromide. According to Swain's mechanism only the complex should have been primarily formed if the inverse addition was employed. Thus, the mechanism (46) was suggested[109]. If **63** and **64** are assumed to be of different reactivity toward the ketone, this accounts for the decrease of the rate after 50% conversion. The transition states for the rate-determining steps with k_2 and k_4 were visualized as **66** and **67** using Dessy's[79] structure.



(66)



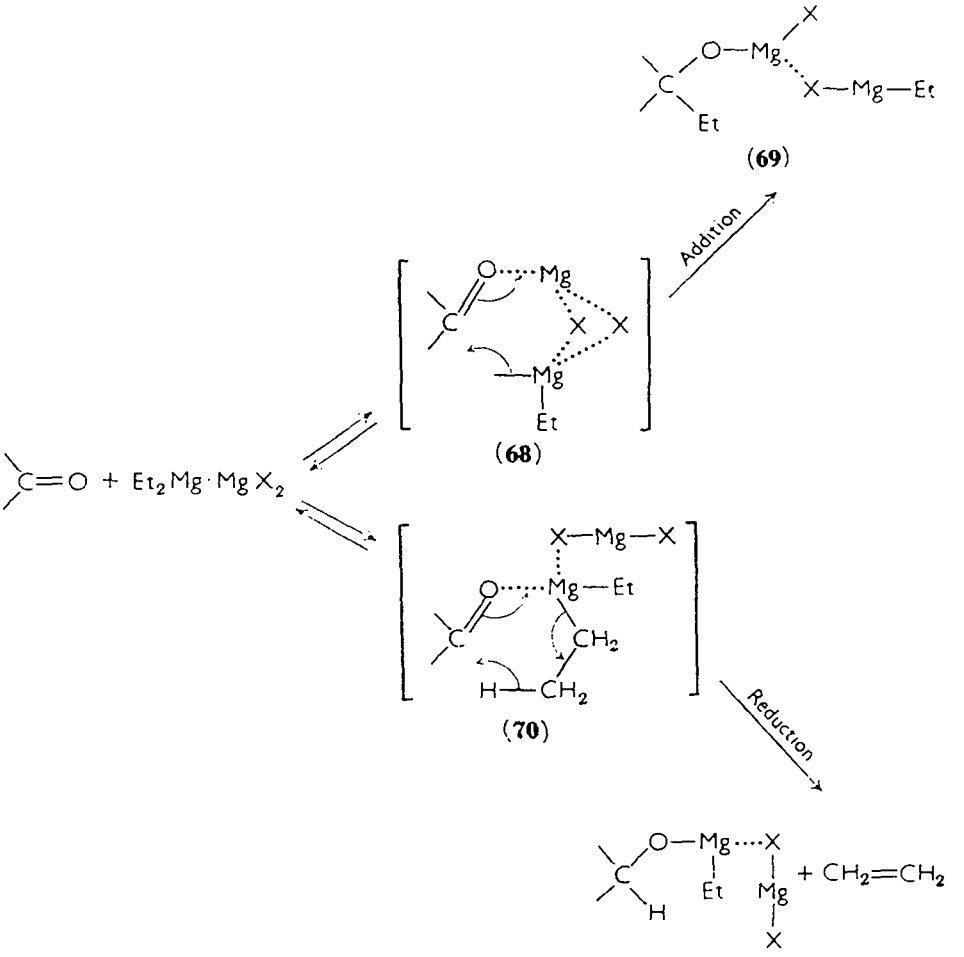
(67)

It is worth noting the opinion expressed by Becker[109] that 'from a kinetic point of view the order in Grignard reagent does not depend upon the fact that the Grignard reagent is $R_2Mg \cdot MgX_2$ rather than RMgX', since Ashby[84] demonstrated that methylmagnesium bromide is essentially monomeric in tetrahydrofuran under the conditions employed in the kinetic investigation[109]. Deviations from simple second-order kinetics were also found in the reaction of Grignard reagents with alkynes[112] and with benzonitrile[113], and in both cases competitive, consecutive second-order reactions were assumed responsible. Utilization of only 50% of alkyl groups present was similarly observed in the reaction of phenyl cyanide with R_2Mg and RMgX[113], of RMgX with Schiff bases[114], of RMgX with 1-hexyne[112], and of dimethylmagnesium with benzophenone[100].

Similar results were obtained by Mosher and coworkers[115] who studied the relative rates of addition to reduction and the relationship between product distribution and the ratio of the concentration of reactants in the system diisopropyl ketone/ethylmagnesium bromide. The ratio of addition to reduction was found to be invariant with concentration and ratio of reactants when ketone was in excess (case A); when Grignard was in excess (case B) the addition to reduction ratio was found to be a function of the ratio of reactants, but not of their concentration. Mechanisms (40) and (41) do not explain these data: with (40) the ratio should be invariant in (A) and (B), while with (41) one would expect a decrease of the addition to reduction ratio with concentration.

The explanation of these data seems to require an associated

(dimeric) Grignard entity, involved in a sequence of consecutive competitive reactions. The mechanism (47) appears to be reasonable. Complexes **68** and **70** differ only in the site of the Mg coordination and are essentially identical. The assumption of the complex may account for addition or reduction via a six-membered transition state

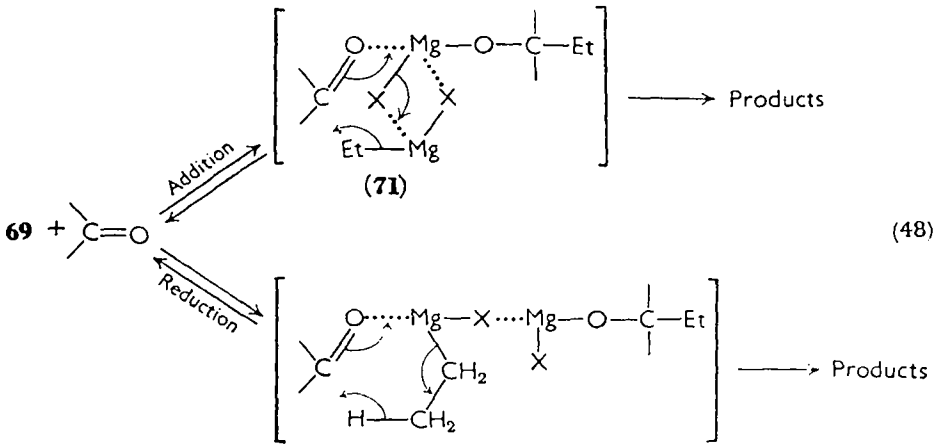


(47)

in a concerted mechanism under the conditions of (B). For case (A) a second reaction stage (48) is required in amplification of (47), in order to explain why the addition:reduction ratio is not the same as in (B).

A mechanism in principle identical to (47) and (48) was proposed independently by Hamelin[116], who investigated the reaction of

several ketones with ethylmagnesium bromide and diethylmagnesium. He also reached the conclusion that the reactive behavior of

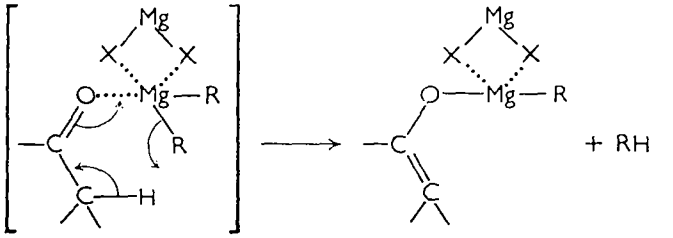


(71)

(72)

(48)

Grignard compounds could be satisfactorily understood only if $R_2Mg \cdot MgX_2$ was the reactive species in ether. These interpretations[117] tried to substantiate *chemically* the dimeric structure earlier believed to be established by physical means[79]. From the transition states **68** and **70** and the transition state **73** proposed for enolization[57,118] (reaction 49), it was expected that changing the



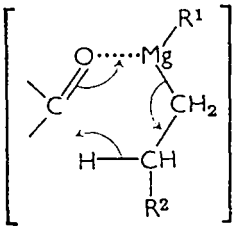
(73)

(49)

halogen of the Grignard reagent would affect the course of addition to a much larger extent than that of reduction and enolization. Shine[119] demonstrated that the amount of 'normal' addition and the decrease of 'anomalous' reactions (i.e. reduction and enolization) with a series of Grignard reagents differing only in halogen (Cl, Br, I) was directly dependent on the size of the halogen involved. Cowan and Mosher[118] found that the ratio of addition to reduction and enolization in Grignard reactions of diisopropyl ketone was considerably affected by the halogen, and that addition was altered much

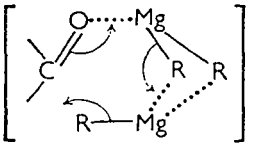
more than the other reactions; when a Grignard reagent not capable of addition (isopropylmagnesium halide) was employed, the ratio of reduction to enolization was invariant with the halogen involved. These effects reflect the participation of the halogen bridges in the transition state **68** for addition, where the steric requirements and the inductive effect of the halogen will be crucial in determining the rate of reaction, while in **70** and **73** the nature of the halogen should display no significant influence.

Further evidence for the reaction scheme proposed by Mosher and by Hamelin was afforded by the use of dialkylmagnesium compounds instead of Grignard reagents. The reaction of two moles of diisopropyl ketone with an equivalent quantity (one mole) of diethylmagnesium resulted in an increase of reduction and enolization at the expense of addition[118], compared to the reaction of ethylmagnesium bromide. However, when a 100% excess of diethylmagnesium (i.e. 1:1 ratio of R_2Mg/ketone) was used, the product distribution resembled very closely the reaction with the Grignard reagent itself. A possible explanation for these results was given by Salinger[71]. A modification of **70** should account for the reduction process, namely **74**, which would be favored by an excess of ketone.



(74)

Increasing amounts of R_2Mg should favor the formation of a transition state (**75**) for addition in which an additional molecule of



(75)

R_2Mg takes the place of the MgX_2 in **68**. Several other authors[100,120] observed utilization of only 50% of the alkyl groups in R_2Mg compounds on reaction with equimolecular amounts of ketones. This behavior is analogous to that of the R_3Al series, where Grignard-like

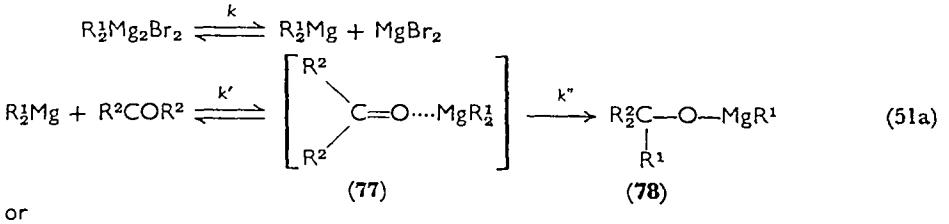
additions often take place only with the first R group, and the resulting $R^1_2AlOR^2$ compounds are nearly inert to further addition[121].

House and Traficante[122] investigated the product composition and the rate of reaction of diethyl ketone and diisopropyl ketone with diethylmagnesium, ethylmagnesium bromide, and ethylmagnesium alkoxides. Alkylmagnesium alkoxides are the products of addition of R_2Mg to ketones (reaction 50). Their influence on the addition

$$R^1_2Mg + R^2_2C{=}O \longrightarrow \underset{\textbf{(76)}}{R^2_2\overset{R^1}{\overset{|}{C}}{-}OMgR^1} \qquad (50)$$

reaction of Grignard and R_2Mg compounds and their reactivity toward ketones was also investigated by Hamelin[116]. The tendency of **76** towards reduction and enolization was recognized by several other authors[100,109,113] and was ascribed to a markedly retarded rate of addition through the presence of the —MgOR grouping as well as to steric factors[116,122a]. In the investigation of House special attention was paid to the influence of $MgBr_2$, which has been reported to affect the course or the rate of a variety of reactions. For instance, compared to Grignard reactions a rate enhancement is observed in the absence of $MgBr_2$ for the reaction of diethylmagnesium with 1-hexyne[123] and of dimethylmagnesium with acetone[120] and with benzophenone[100,109,120a]; while the rate of addition of R_2Mg compounds to nitriles in the absence of $MgBr_2$ or MgI_2 is decreased[113,124]. The amount of enolization and reduction as side-reactions in the addition of n-propylmagnesium bromide to diisopropyl ketone is decreased by an excess of $MgBr_2$[98], and an increased amount of enolization was observed in the reaction of acetomesitylene with dimethylmagnesium in the absence of $MgBr_2$[125] and a decreased amount of enolization and reduction in the presence of $MgBr_2$[115,118]. In accord with other studies[100,109,120] it was shown by House and Traficante[122] that $MgBr_2$ markedly retards the interaction of ketones with dialkylmagnesium compounds. Furthermore, the effect of $MgBr_2$ in favoring addition rather than reduction and enolization was established as resulting not from catalyzing the addition of R_2Mg to the carbonyl group (as suggested earlier[98]) but from suppressing the tendency of the intermediately formed alkylmagnesium alkoxides to give enolization and reduction rather than addition. In the opinion of the authors[122] these results remove the need[98,107] for including $MgBr_2$ in the transition state of the addition mechanism. Consequently, and since the reaction rate depends upon ketone concentration for ketones of low[99,109] and moderate

reactivity but becomes *independent* from ketone concentration for very reactive ketones, e.g. acetone[126], the reaction scheme (51) depicting R_2Mg as the reactive species is suggested for the Grignard reaction. The observed kinetic dependence on both ketone and

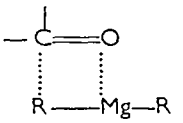


(51a)

or

(51b)

$R_2Mg_2Br_2$ or R_2Mg concentration would be expected for relatively unreactive ketones with $k > k''$; inversion of reactivity order ($k'' > k$) would result in dependence only on Grignard concentration, as observed for acetone[126]. Evidence for the possible intervention of a complex **77**—which could be termed an 'at-complex'[21]—was indicated by a transient yellow color in the reaction of diethylmagnesium and diisopropyl ketone, but spectroscopic measurements of the colored species were unsuccessful. Although there was no compelling evidence, the authors[122] felt that their data were compatible with a four-center transition state (**79**). A four-centered trans-



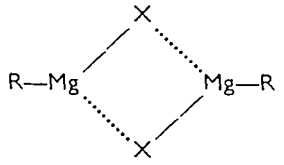
(79)

sition was also suggested for the addition of Grignard reagents to ketones and esters by Tuulmets[127] and for the addition of ethylmagnesium bromide to Schiff bases by Dessy and Salinger[114].

The results of Dessy[79] presented striking evidence that monomeric RMgX is *not* present in Grignard solutions; this was generally accepted, and was supported by the opinions that dimers are needed directly (Becker, Mosher) or as precursors (House) for describing the reactive entity in Grignard reactions.

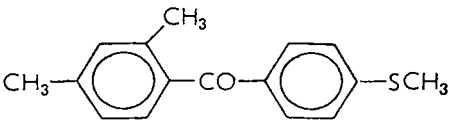
According to recent developments[70,83–89] alternative mechanistic interpretations using RMgX or a symmetrical dimer (**80**) derived from it deserve serious consideration. Smith and Su[128] investigated the kinetics of the addition of methylmagnesium bromide to 2,4-dimethyl-4'-methylmercaptobenzophenone (**81**) by an ultraviolet

spectroscopic method. The rate of disappearance of both the ketone band and the longer wavelength absorption ascribed to a 1:1 ketone/CH_3MgBr complex[106] obeyed good first-order kinetics in the range of 0·01 to 0·4 M. Ketone and complex disappeared at the



(80)

same rate and below 0·1 M the reaction was approximately first-order in methylmagnesium bromide. The results fit the scheme (52) or (53), where K is the equilibrium constant and k is the observed first-order rate coefficient. The reaction was believed to imply a monomeric Grignard species at the concentration range employed on the



(81)

basis of earlier physical data[85,87]. However, a differentiation between schemes (52) and (53) is not possible on the basis of the data pre-

$$\text{Ketone} + \text{Grignard} \overset{K}{\rightleftharpoons} \text{Complex} \xrightarrow{k} \text{Product} \qquad (52)$$

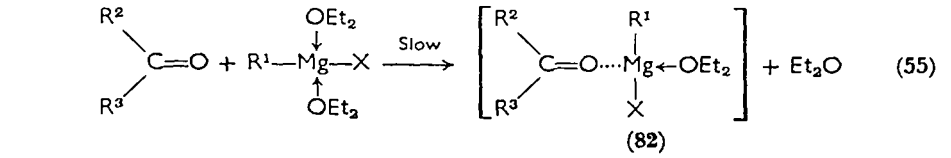
$$\text{Complex} \overset{K}{\rightleftharpoons} \text{Ketone} + \text{Grignard} \xrightarrow{k} \text{Product} \qquad (53)$$

sented; the same basic difficulty was already mentioned by House[122].

Finally, the ebullioscopic molecular-weight measurements of Ashby and Smith[70] showed that even in cases where the authors were sure of an attacking dimeric species[109,115,118], the Grignard reagents used were in fact essentially monomeric at the concentrations employed in these studies. As already indicated by Becker[109], but doubted by others[115,116], the published kinetic data do not exclude the possibility that monomer is the attacking entity.

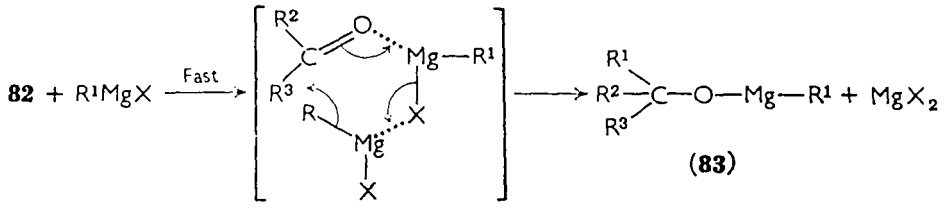
According to Ashby[70], a mechanism involving RMgX as the reactive entity would be consistent with all data available for Grignard addition in diethyl ether (reaction 54 to 56). In this mechanism the

$$(R^1MgX)_2 \rightleftharpoons 2\ R^1MgX \qquad (54)$$



(55)

(82)

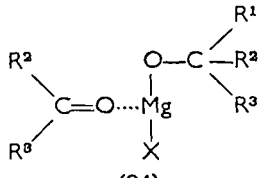


(83)

(56)

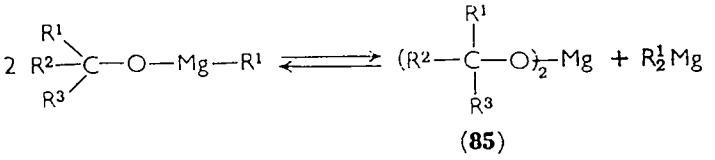
rate-determining process consists of the displacement by the ketone of one of the solvent molecules attached to magnesium.

The basicity of solvent, i.e. association processes at the Mg center, may exhibit significant effects on the course and the rate of Grignard reactions, as earlier findings[129-131] already indicated. Generally, the rate of reaction between Grignard reagent and ketone decreases as the basicity of the solvent increases[132]. The retardation of Grignard reactions in pyridine[129,130] was explained[129] by a mechanism which differed only slightly from equations (55) and (56). Thus, in a more basic solvent the displacement of the associated solvent molecule by a ketone will become more difficult. This mechanism explains several facts not fully understood in earlier interpretations. Firstly, the enhancement of reaction rate of R_2Mg compared to RMgX may simply be due to the fact that the solvating ether molecules will be displaced at a slower rate from the stronger Lewis acid, RMgX, according to equation (55). Secondly, an explanation for the large difference in reactivity after utilization of the first 50% of R groups in Grignard reagents might be well explained by the intermediate **83** which is expected to react with a second ketone molecule at a considerably lower rate than RMgX (as already indicated by earlier findings[122,116]) and through different mechanisms owing to the differences in its steric and electronic environment compared



(84)

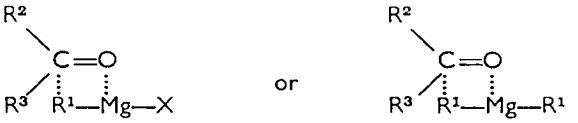
to RMgX (or R_2Mg). Thus, **83** may react with another ketone giving **84** or slowly disproportionate to a more reactive species, probably R_2Mg and **85** equation (57). Thirdly, if the monomer



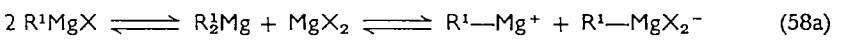
(57)

(85)

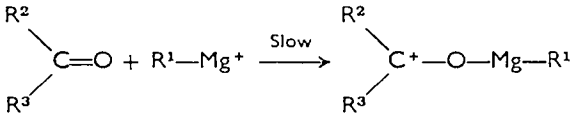
formation in the equilibrium (54) becomes rate-determining, the reaction rate would become dependent only on the concentration of the Grignard reagent as in the case of acetone[126]. According to Ashby attack by RMgX or R_2Mg on a ketone through a 'four-center' transition state[122]



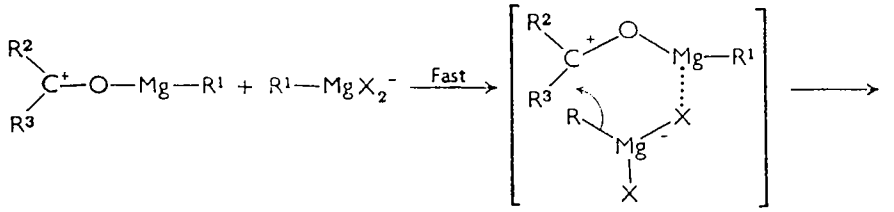
is not likely, since these do not account for the substantial decrease of reaction rate after 50% reaction and would probably imply that



(58a)



(58b)

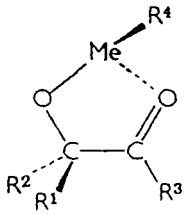


83 + MgX_2

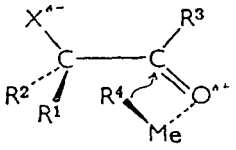
(58c)

RMgX and R_2Mg addition should proceed at similar rates, which is not the case[100,120,122]. Finally, the interference of ionic species has to be considered (reaction 58). Attack by a cationic species has to be taken into account, since, even if present at low concentration in the solution, its reactivity might be assumed to be high. The arguments justifying the addition of monomeric RMgX are believed to hold also for an attack by an ionic entity.

Interesting stereochemical results were obtained by Cram and Wilson[133] in the interaction of various Grignard reagents with α-hydroxy ketones, e.g. phenylmagnesium halides and *dl*-3-hydroxy-3-phenyl-2-butanone. Using the chloride or bromide instead of the iodide resulted in a reversal in stereoselectivity (i.e. preponderance of one diastereomer in the ratio *meso*/*dl*). The stereoselectivity of this reaction was interpreted in terms of relative energies of cyclic and dipolar models for the transition states **86** and **87** involved. It was



(**86**, cyclic model)



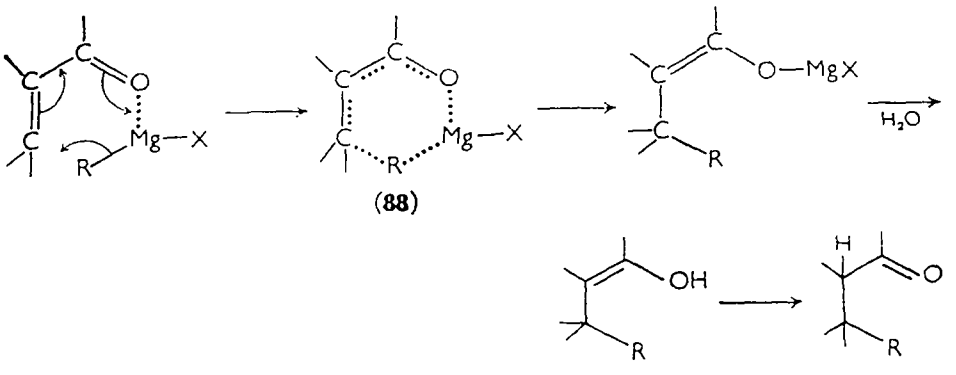
(**87**, dipolar model)

postulated that the cyclic transition state was favored (as in the case of organolithium compounds[133]) with the less-hindered attacking reagent. Since phenylmagnesium iodide might be regarded as being monomeric in ether[89], it should favor the cyclic transition state **86**, whereas reaction via dipolar transition states less subject to steric effects is preferred by the chloride and the bromide which are supposed to be represented to a considerable extent by symmetrical[70] or unsymmetrical[89] dimeric structures, and are therefore certainly more sterically hindered.

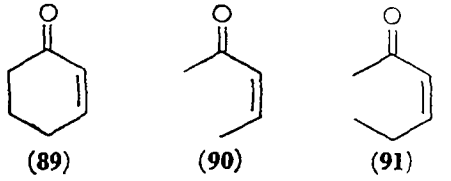
Stocker and coworkers[134], studying Grignard addition to benzil, diacetyl, methylbenzoin, and phenylacetoin, also found that the stereochemical outcome of the reaction of phenylmagnesium iodide in ether was different from that of the bromide and the chloride as well as from ethylmagnesium halides, as was established by other authors[135]. The results point to a difference in the nature of the reactive species between phenylmagnesium iodide and the other Grignard reagents in ether, as indicated above.

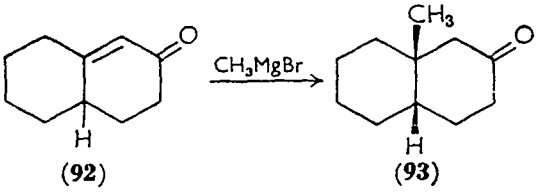
5. Conjugate addition

a. 1,4-Addition. A mechanism for the conjugate addition of Grignard reagents to α,β-unsaturated ketones was first suggested by Lutz and Revely[136], which involved the formation of a six-membered cyclic transition state **88**. This mechanism seemed to account for the



initial formation of an enol, which had been observed in some instances[137], and furthermore seemed to provide an explanation for the fact that Grignard reagents favor 1,4-addition, unlike organolithium compounds[138], for which another type of mechanism is assumed[45].

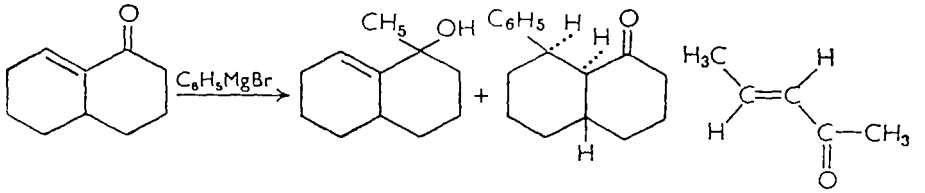




From the point of view of the above cyclic process, it was surprising that 2-cyclohexenone (**89**) underwent conjugate addition with Grignard reagents[139]. Likewise, a comparison of the reactivity of **89** and some of its open-chain analogs (e.g. 3-penten-2-one (**90**), 3-hexen-2-one (**91**)) toward Grignard reagents[140] showed that the amount of

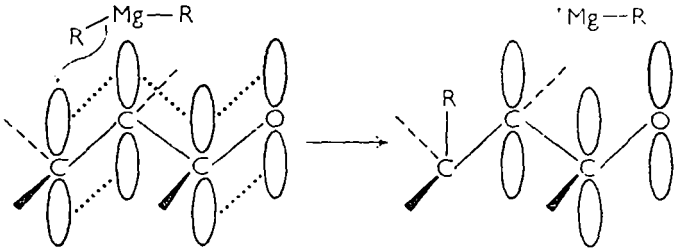
conjugate addition to **89** was in the same range as the amount of conjugate addition of the open-chain unsaturated ketones **90** and **91**. Together with the observed addition of methylmagnesium bromide to the $\Delta^{1,9}$-octal-2-one (**92**)[141] these findings cast some doubt on the cyclic formulation (59) of 1,4-addition in the systems investigated, since the necessarily *trans*-oid system of double bonds in **89** and **92** offers for steric reasons the worst possible geometry for attaining a cyclic transition state **88**.

The stereochemistry of conjugate addition was investigated by House[142] using $\Delta^{8,9}$-octal-1-one (**94**) as the unsaturated system.



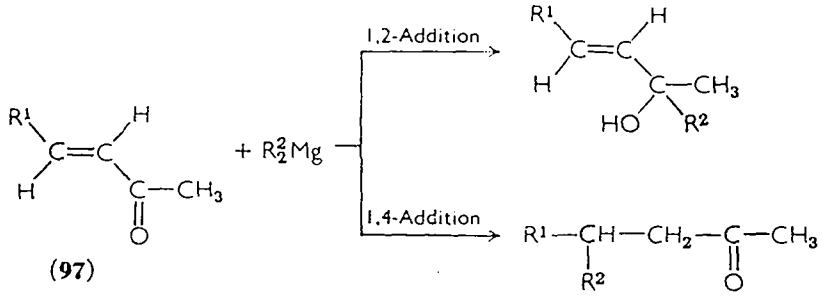
(**94**) (**95**) (**96**)

Here the *cis*-oid arrangement should provide ideal steric requirements for **88**. Additionally, the reactivity of **94** was compared to an open-chain analog, namely **96**. From the stereochemistry of the product of 1,4-addition (**95**) and from the result that the acylic ketone **96** gave an even higher amount of conjugate addition than **94**, the lack of sensitivity of conjugate addition to the geometry of the conjugated system was evident. This made a cyclic transition state like **88** appear most improbable for the system investigated (**94**). Instead, an attack of the organomagnesium species on the unsaturated ketone from a direction perpendicular to the plane of the conjugated system, i.e. from the sterically least-hindered side, was assumed to explain the stereochemistry observed in the reaction of **92** as well as in **94** (reaction 60). This proposal is a counterpart to the mechanism of the Michael addition except that the group being added has no discrete existence as a carbanion[143].



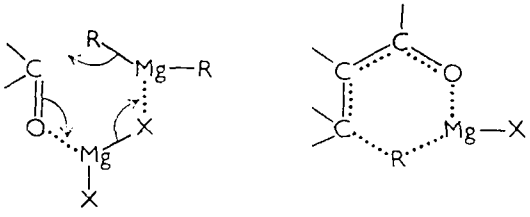
(60)

Further studies of House and coworkers[144] on the factors influencing the relative rates of normal (1,2-) and 1,4-addition revealed evidence for a relatively close mechanistic relationship between the two reaction types concerning the interaction of *trans*-3-pentenone (**97**, $R^1 = CH_3$) and *trans*-4-phenyl-3-buten-2-one (**97**, $R^1 = C_6H_5$)



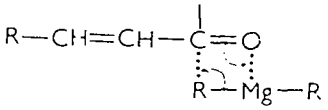
(**97**)

with dialkyl- and diarylmagnesium compounds and the corresponding Grignard reagents ($R^2 = CH_3$, C_2H_5, C_6H_5). It was found that the ratio of normal to conjugate addition is neither substantially affected by the concentration of organomagnesium compounds (R^2_2Mg)[145] nor by the addition of magnesium halide. Furthermore, it was found that the presence of MgBr only slightly enhances normal and conjugate addition. In the opinion of the authors[144] this implies that both reactions are of the same kinetic order and that the transition states for normal and conjugate addition are derived from the same reactants and are similar in character. Consequently, representations of the transition state for 1,2-addition requiring magnesium halide as a necessary component such as **98** do not seem to be

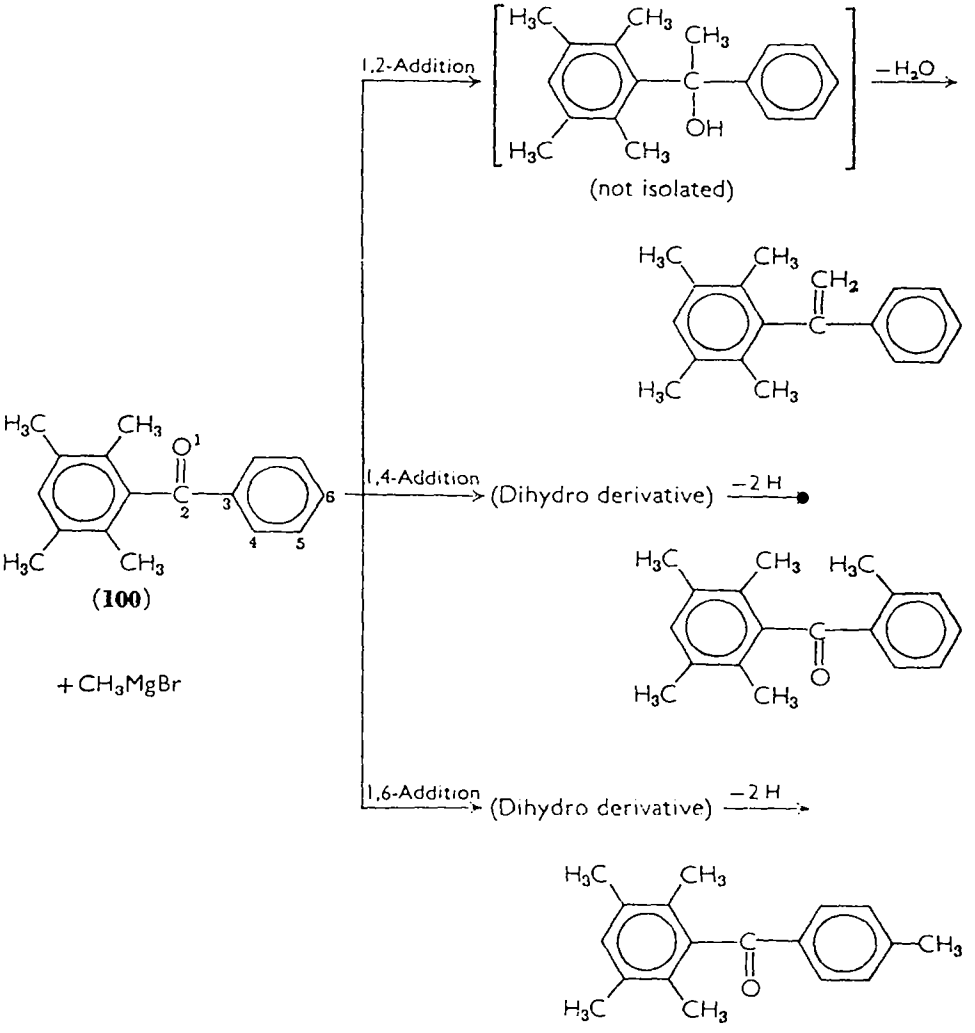


(**98**) (**99**)

very likely; the cyclic mechanism of 1,4-addition (**99**) is doubted for reasons already discussed. Although not conclusive, the data obtained are believed to be compatible with a four-center mechanism for 1,2-addition, along with the Michael-type mechanism for 1,4-addition.

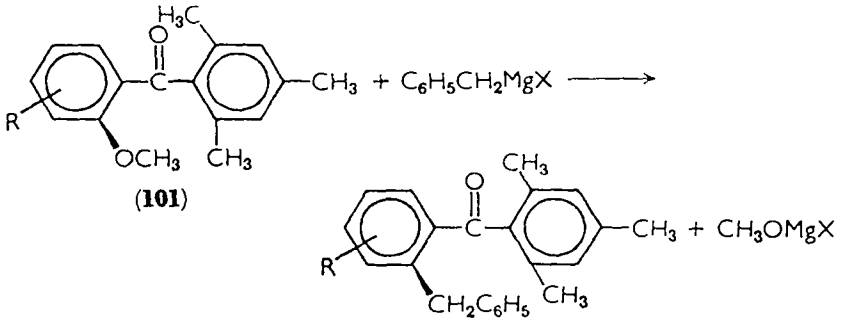


b. Reaction of sterically hindered aryl ketones with Grignard reagents. The subject of conjugate addition to sterically hindered multiple bonds has recently been reviewed by Fuson[24]. The principle of this type of reaction consists of participation of the aromatic system in the 1,4- or 1,6-addition process. Phenyl duryl ketone (**100**) may serve



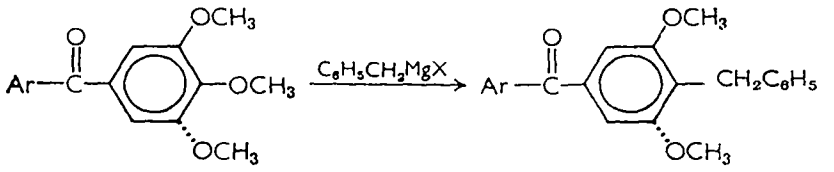
as an unique example[146] of the reaction of hindered ketones with organomagnesium compounds, where all possible modes of addition occur with methylmagnesium bromide.

Nucleophilic displacement is observed in the interaction of benzyl or, more often, *t*-butyl Grignard reagents with diaryl ketones



(101)

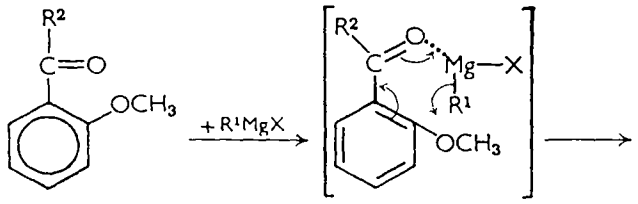
bearing groups of good leaving abilities. For example, in *o*-methoxyphenyl mesityl ketones (**101**)[147] when treated with benzyl Grignard reagents, the *o*-methoxy group was readily displaced by the Grignard



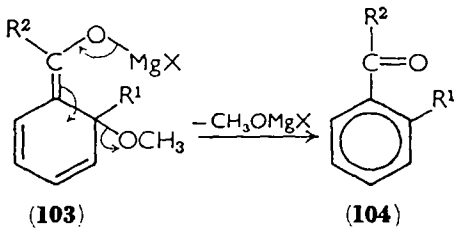
(61)

(Ar = duryl or mesityl)

residue, the same being true also for an *o*-bromo substituent. *p*-Methoxy groups were not displaced, unless they were flanked by one or two additional methoxy groups[148], e.g. reaction (61). These reactions were discussed in terms of attack of the Grignard species on



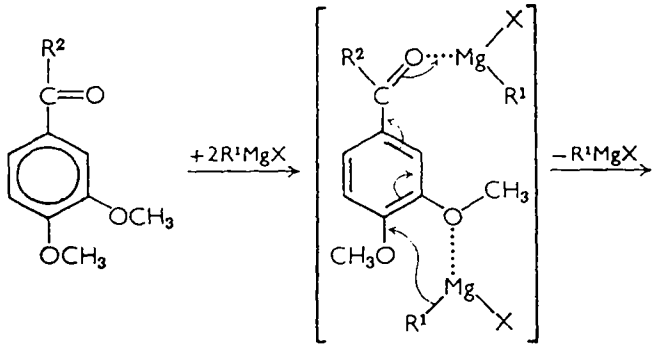
(**102**)



(**103**) (**104**)

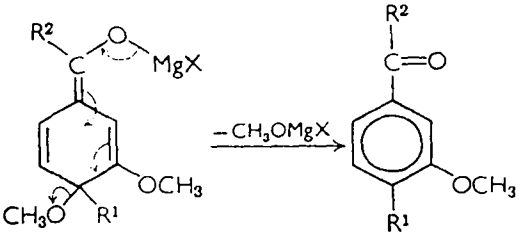
(62)

a system which is formally the vinylog of an ester grouping[23] with either the carbonyl group or an *o*-methoxy group serving as center of a primary Lewis base–acid interaction shown in (62) or (63). Neither here nor in the following examples is it decided whether a direct S_N2 displacement **102** → **104** or **105** → **107** takes place,



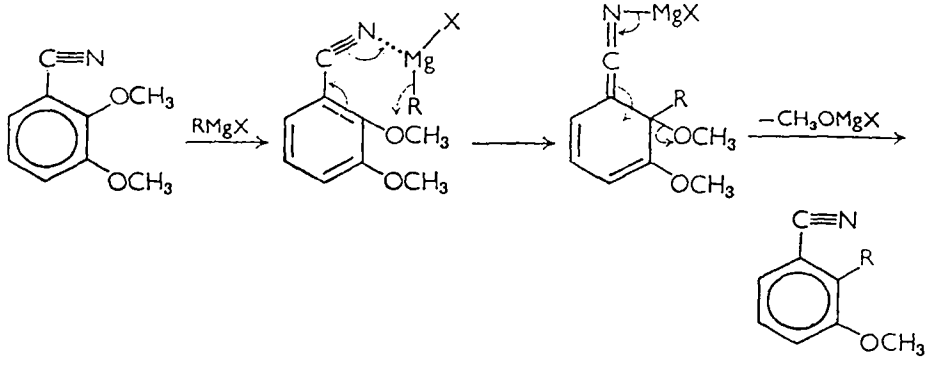
(**105**)

(63)

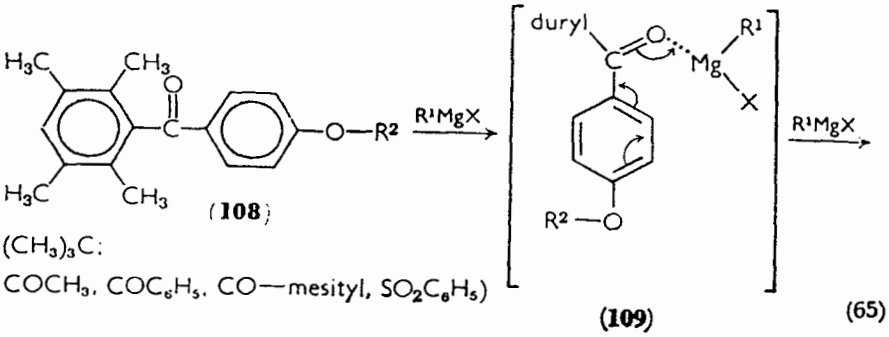


(**106**) (**107**)

assisted by complexing, in a concerted mechanism or the step-wise addition–elimination mechanism pictured in (62) and (63). A similar mechanistic concept should account for the easy displacement of methoxy groups *ortho* to cyano groups[23], e.g.



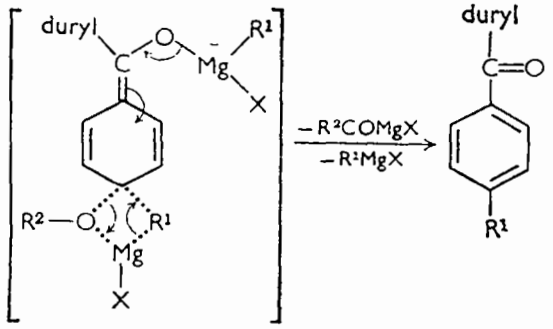
(64)



(108)

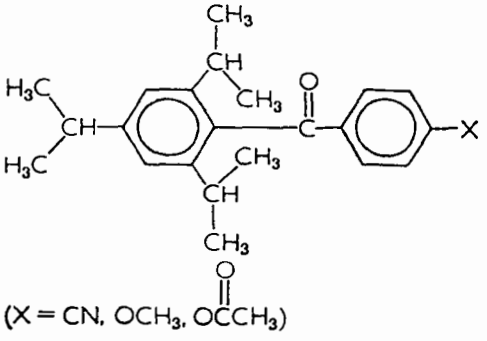
($R^1 = (CH_3)_3C$;
$R^2 = COCH_3$, COC_6H_5, CO—mesityl, $SO_2C_6H_5$)

(109) (65)



(110)

Duryl phenyl ketones (**108**) bearing an acetoxy, benzoyloxy, mesitoyloxy or benzenesulfonyloxy residue in the *para* position of the phenyl ring also gave nucleophilic displacement by *t*-butylmagnesium halide

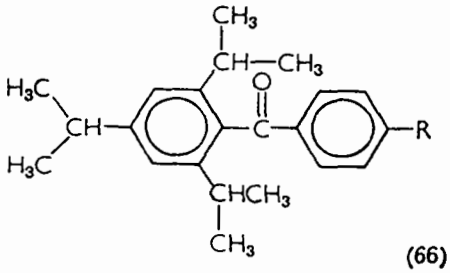


(X = CN, OCH_3, $OCCH_3$)

(111)

+ RMgX ⟶

(R = $(CH_3)_3C$, benzyl)



(66)

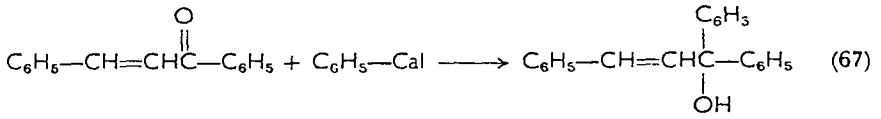
(reaction 65)[149]. This formulation involving attack of a second Grignard entity on the primarily formed adduct[106] or 'at-complex' (**109** or **110**, respectively) and consecutive displacement of the *para* substituent does not seem to be unlikely. Again, activation for nucleophilic displacement is due to the electron-withdrawing effect of the carbonyl group enhanced by complex formation. Similarly, derivatives of 2,4,6-triisopropylbenzophenone (**111**) gave nucleophilic displacement of X by *t*-butyl and (in the case of X = CN) with benzyl Grignard[150] reagents (reaction 66). The formation of addition complexes in equilibrium mixtures with Grignard reagents was established by Smith[106] in the case of **111**, X = OCH_3, indicating the possibility of a mechanism through attack by the nucleophile at a coordination complex analogous to (65).

B. Beryllium, Zinc, and Cadmium

1. Compounds of the type RMX and R_2M

Compared to organomagnesium compounds, knowledge of the reactivity toward C=X double bonds (X = O, S, N, N—R) of the other Group II elements is relatively poor. Apart from the investigations of Wittig[151] on the behavior of diphenylmetals, the data reported in the literature are qualitative in nature and may perhaps need a more careful reinvestigation in some cases.

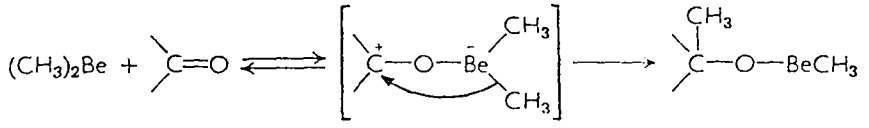
The dimethyl derivatives of the alkaline earth metals Ca, Sr, and Ba have been prepared[152] but no reactions with carbonyl compounds are reported. From the RMX compounds of calcium and barium prepared by Gilman[153], phenylcalcium iodide reacted with benzonitrile and benzophenone anil to give the corresponding addition products, and with benzalacetophenone to give the product of 1,2-addition, diphenyl styryl carbinol (**112**)[138] (reaction 67).



(67)

(**112**)

Gilman[154] found that organometallic compounds of beryllium undergo addition and reduction reactions with carbonyl compounds.



(68)

(**113**)

Thus, dimethylberyllium adds benzophenone to form diphenyl methyl carbinol, probably according to the sequence (68) analogous to prior examples. Similarly, diphenylberyllium gave tritanol on addition to benzophenone[151] and diphenylpropiophenone (**114**) in conjugate addition to benzalacetophenone (reaction 69)[138,151].

$$(C_6H_5)_2Be + C_6H_5CH{=}CHC(=O)C_6H_5 \xrightarrow[2.\ H_2O]{1.\ \text{Addition}} \underset{\textbf{(114)}}{(C_6H_5)_2CHCH_2C(=O)C_6H_5} \qquad (69)$$

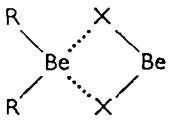
Diethylberyllium did not yield the product of addition with benzophenone[154], but reduction occurred to form benzhydrol. As in the case of diethylmagnesium[122] and in some aluminum species (see sections III.A.4 and IV.C) a transient orange-red color appeared at the junction of the two components, probably caused by the formation of an 'at-complex' (**113**, with C_2H_5 instead of CH_3). Some aryl- and alkylberyllium halides were obtained by Gilman[155] and Coates[156]; they were less reactive than the corresponding diethyl- and diarylberylliums[155]. In a recent investigation the structure RBeX postulated by Gilman is doubted by Dessy[157], since no exchange took place between diphenylberyllium and radioactive $^7BeBr_2$, indicating that no Schlenk equilibrium (70a) exists. Instead, an equilibrium

$$R_2Be + BeX_2 \rightleftharpoons 2\ RBeX \qquad (70a)$$

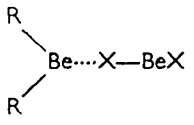
(70b) involving a complex species was proposed, and structures like

$$(C_6H_5)_2Be + BeBr_2 \rightleftharpoons \underset{\textbf{(115)}}{(C_6H_5)_2{\cdot}BeBr_2} \qquad (70b)$$

116 and **117** were suggested for **115**.



(116)



(117)

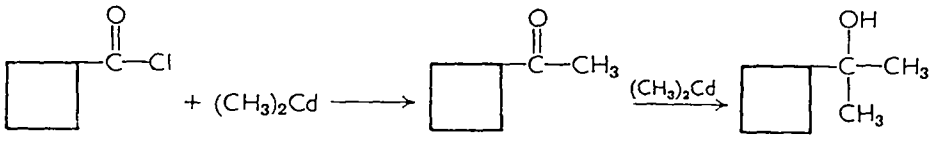
Similar results were obtained by Garrett[158] with organocadmium halides: there was no evidence for exchange between diethylcadmium and radioactive cadmium halide. The existence of a species $R_2Cd \cdot CdX_2$ received support from equilibrium constant measurements and molecular-weight determinations. Experiments with zinc compounds indicated that there was no corresponding RZnX entity[158].

The use of organometallic compounds of zinc in syntheses with carbonyl compounds is at present only of historical interest, having become almost entirely displaced by the use of more reactive and easier to handle organomagnesium compounds. In the reaction with Michler's ketone Gilman established[159] the order of reactivity $R_3Al > R_3B > R_2Zn$. The low rate of reaction with cyanides, isocyanates, esters, and ketones allows these groups to remain unaffected in reactions involving other functional groups. Thus, the rapid combination of organozinc compounds with acid chlorides has been applied in the synthesis of ketones (reaction 71)[160], but has

$$R^1COCl + R^2_2Zn \text{ (or } R^2ZnX) \longrightarrow R^1COR^2 \qquad (71)$$

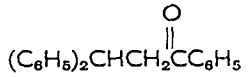
been completely superseded by the use of organocadmium derivatives.

Organocadmium compounds are very versatile reagents in the synthesis of ketones[161]. In most cases they react only very slowly with carbonyl groups, unless these are highly activated. For example, cyclobutanecarbonyl chloride (**118**) yields cyclobutyl dimethyl carbinol (**120**) on reaction with dimethylcadmium[162]. Further



(118) **(119)** **(120)**

addition of the reactive ketone **119** with the cadmium reagent can be prevented by carrying out the reaction at low temperatures. Furthermore, organocadmium derivatives may be forced to add to a less reactive carbonyl group by rigorous conditions; e.g. diphenylcadmium does not add to benzalacetophenone at room temperature, but at 100° and prolonged reaction time it gives the product of conjugate addition (**121**) in quantitative yield[151].

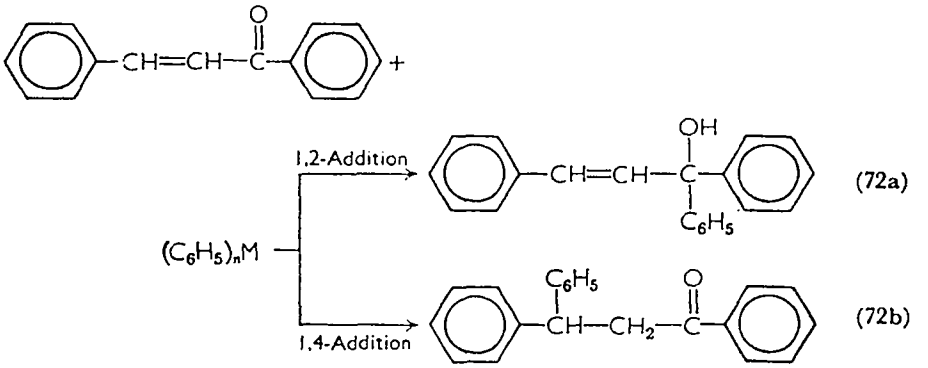


(121)

2. Reactivity in 1,2- *versus* 1,4-addition; comparison with other organometallic compounds

A comparative study of the reaction of a number of Group II phenylmetals and phenylalkali compounds with benzalacetophenone was undertaken by Gilman and Kirby[138], and was later confirmed

by Hauser[14]. The two possible reaction modes are shown in (72). The data obtained are compiled in Table 4. The reactions were run at room temperature in diethyl ether, except those with phenylsodium and -potassium, which were run in benzene. These results



demonstrate that the ratio of 1,2- to 1,4-addition is strongly dependent on the nature of the organometallic species, especially on the polarity of the carbon–metal bond and hence on the ability of the organometallic source to provide an anion for the reaction. Thus, the highly reactive (predominantly ionic) phenyl derivatives of

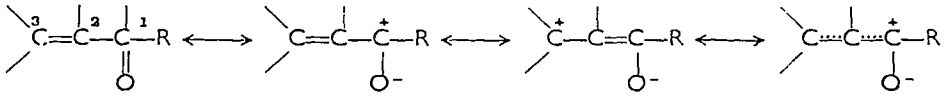
TABLE 4.

Organometallic species	1,2-Addition (%)	1,4-Addition (%)
C_6H_5Li	69	13 see also 163
C_6H_5Na	39	3·5
C_6H_5K	52	—
C_6H_5MgBr	—	94 see also 164
C_6H_5CaI	52	—
$(C_6H_5)_2Be$	—	90
$(C_6H_5)_2Zn$	—	91
$(C_6H_5)_2Cd$	—	100 [151]
$(C_6H_5)_3Al$	—	94

potassium, sodium, and calcium give little or no 1,4-addition, while the predominantly covalent phenyllithium already shows an increased amount of 1,4-addition. The less reactive phenyl derivatives of beryllium, zinc, cadmium, and aluminum give exclusively 1,4-addition. Another relevant factor is the nature of the α,β-unsaturated

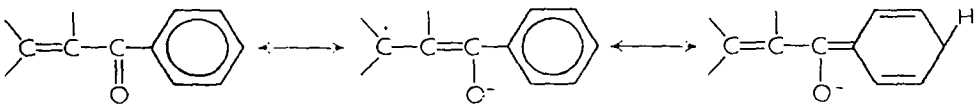
system, as already pointed out by Kohler[164,165] and later by Lüttringhaus[166] mainly on the basis of results obtained in Grignard reactions.

α,β-Unsaturated aldehydes add exclusively in the 1,2-position (case 1); alkyl-substituted unsaturated ketones show both 1,2- and 1,4-addition, often in a ratio of about 1 (case 2); and unsaturated ketones with a phenyl group at the carbonyl carbon give preferentially 1,4-addition (case 3). In a conjugated system including a carbonyl group (**122**), the reactivity toward a polarized carbon–



(122)

metal bond should be considered in terms of the electrophilicity of the system at $C_{(1)}$ and $C_{(3)}$ and of the sterical accessibility of these electrophilic centers. If, in a further simplification of system **122**, the substituents at $C_{(3)}$ are kept constant, to a first approximation the electrophilicity of the system should be controlled by the inductive and electronic effects of the substituent R at the carbonyl carbon $C_{(1)}$. These effects should be smallest in the case where R = H, when the steric accessibility of the carbonyl carbon allows unhindered attack at $C_{(1)}$ as in case (1). The inductive effect on the electron density at $C_{(1)}$ and the steric change when going from R = H to R = alkyl raises the relative electrophilicity at $C_{(3)}$ resulting in the appearance of 1,4-addition, which is increased in amount when R is enlarged (case 2). In the case of R = phenyl (case 3) an increase of electron density and a decrease of electrophilicity of $C_{(1)}$ compared to $C_{(3)}$ may result from conjugation. This effect, together with the



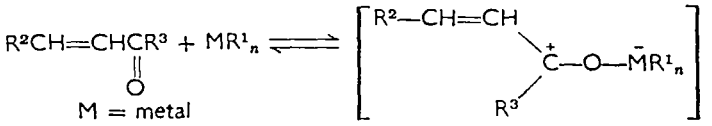
steric effect of the bulk of the phenyl group, leads to 1,4-addition exclusively in most cases investigated. These considerations present only a qualitative approximation for the Grignard case and cannot predict satisfactorily the course of addition for other carbon–metal bonds. Additional factors will decide the course of the reaction, such as Lewis-acid strength (or tendency for complex formation) and bulk of the attacking R—M species as well as steric requirements of the transition state arising from the stereochemistry of the unsaturated

system. In Table 5 the reaction modes of some unsaturated conjugated systems of type (**122**) are shown in the order of increasing bulk of R and in the order of cases (1) to (3). Likewise, organometallic reactants were selected with increasing steric requirements.

TABLE 5.

Conjugated system	Organometallic compound	1,2-Addition	1,4-Addition
$C_6H_5CH{=}CHCH{=}O$	CH_3MgI[168]	yes	none
	C_6H_5MgBr[164]	yes	none
	C_6H_5Li[167]	yes	none
	$(C_6H_5)_3Al$[167]	yes	none
$(C_6H_5)_2C{=}CHCH{=}O$	$(C_6H_5)_3CNa$[20]	yes	none
$C_6H_5CH{=}CHCOCH_3$	CH_3MgBr[169]	yes	none
	C_6H_5MgBr[164, 165]	ca. 90%	ca. 10%
	C_6H_5Li[167]	yes	none
	cyclohexyl-MgBr[170]	none	yes
	$(C_6H_5)_2CHNa$[171]	none	yes
	$(C_6H_5)_3Al$[167]	none	yes
$C_6H_5CH{=}CHCOC(CH_3)_3$	C_6H_5Li[167]	ca. 60%	ca. 10%
	C_6H_5MgBr[165]	none	yes
	$(C_6H_5)_3Al$[167]	none	yes
$C_6H_5CH{=}CHCOC_6H_5$	C_6H_5Li[163, 166]	ca. 75%	ca. 10%
	C_6H_5MgBr[164]	none	yes
	$(C_6H_5)_3Al$	none	yes
$(C_6H_5)_2C{=}CHCOC_6H_5$	C_6H_5MgBr[166]	yes	none
$C_6H_5CH{=}CHCOMes$	C_6H_5Li[167]	none	yes

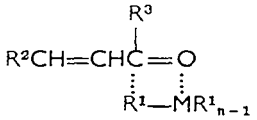
It should be emphasized that at present no unequivocal mechanistic interpretation exists for addition to unsaturated systems. It is likely that the primary interaction of carbonyl groups with organometallic compounds of polarized covalent carbon metal bonds (Li, Mg, Be, Zn, Al) in all cases consists of formation of an 'at-complex' (**123**),



(**123**)

in which the R^1 groups obtain additional anionic activation to undergo intramolecular transfer to the most electrophilic and sterically most accessible site of the complex. Further investigations will have to show why in the case of M = Li this transfer leads to 1,2-addition, while in the case of M = Mg the 1,4-addition mode is preferred; this is certainly not due only to different steric requirements in the complex **123** or to energetical implications of the transition states involved.

House[142,144] suggested that in 1,4-addition of Grignard compound a Michael-type mechanism is valid, which does *not* start with a reaction of the carbonyl oxygen with the Mg center. In 1,2-addition of compounds of Li[45] a four-center transition state like



has been assumed[122], but there are several reasons[70] for denying this assumption.

3. Reactions of 'at-complexes' of Group II elements

Wittig[151] showed that phenyl derivatives of Group II and also of Group III[172] metals combine with phenyllithium. For example, diphenylberyllium with phenyllithium in ether gives the stable lithium triphenylberyllate (**126**), which in solution shows practically

$$\underset{\textbf{(124)}}{(C_6H_5)_2Be} + \underset{\textbf{(125)}}{C_6H_5Li} \longrightarrow \underset{\textbf{(126)}}{[(C_6H_5)_3Be]Li}$$

no dissociation into the components **124** and **125**, does not give the color test characteristic for phenyl metal derivatives (Gilman test[173]), and is not capable of metalating fluorene. Phenyl derivatives of manganese, zinc and cadmium give similar at-complexes with phenyllithium. By studying the metalation of fluorene it could be demonstrated that in the series **126** to **129** the tendency of the

$$\underset{\textbf{(126)}}{[(C_6H_5)_3Be]Li} \quad \underset{\textbf{(127)}}{[(C_6H_5)_3Zn]Li} \quad \underset{\textbf{(128)}}{[(C_6H_5)_3Mg]Li} \quad \underset{\textbf{(129)}}{[(C_6H_5)_3Cd]Li}$$

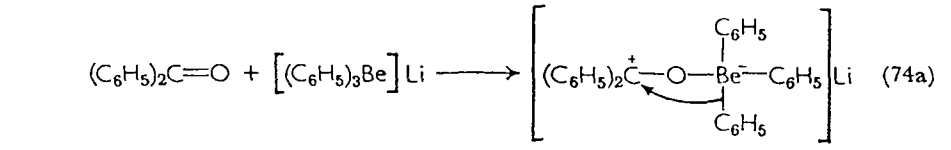
dissociation (73) increases, i.e. the stability of the aryl complexes

$$[(C_6H_5)_3M]Li \rightleftharpoons (C_6H_5)_2M + C_6H_5Li \qquad (73)$$

decreases with increasing radius of the central metal atom[174].

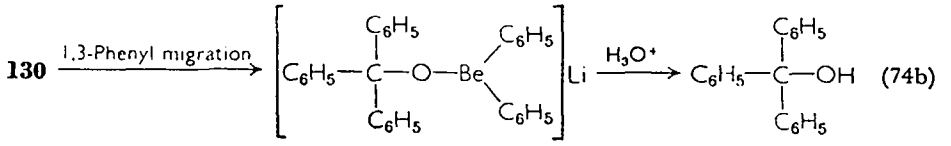
Nevertheless complex **126** yields the addition product with benzophenone. This can be understood by assuming a direct reaction of

the complex itself with the carbonyl compound. In contrast to $Li[B(C_6H_5)_4]$, **126** is still able to fill up its octet shell by addition to the carbonyl oxygen (reaction 74a) followed by phenyl migration (74b). The transient yellow color observed in the reaction is believed



(74a)

(**130**)

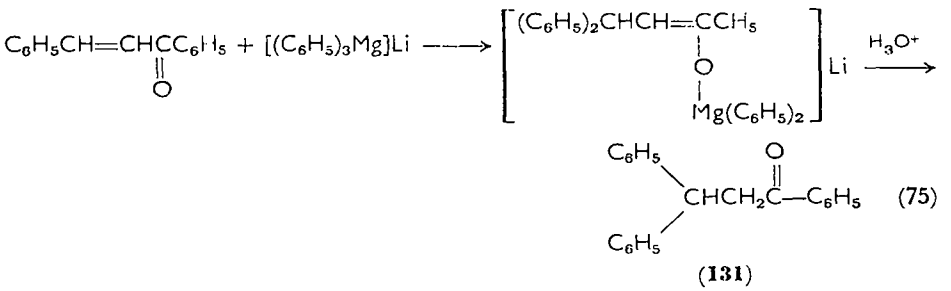


(74b)

to be due to the complex **130**. Benzalacetophenone is similarly attacked by **126** to give the product of 1,4-addition.

Unlike **126**, the phenyl complexes of zinc and cadmium are dissociated in solution to a considerable extent; they metalate fluorene and add to α,β-unsaturated ketones in a similar manner to phenyllithium. Thus, both 1,4- and 1,2-addition to benzalacetophenone takes place, and while the former might be affected by $(C_6H_5)_2M$ or the complex itself (see above), 1,2-addition can only be initiated by free phenyllithium. In the case of the cadmium complex **129** it was estimated that at room temperature in ether 20% of the components are present uncomplexed in the equilibrium mixture.

The magnesium complex **128**, although partially dissociated in solution, seems to react as a whole, since with benzalacetophenone diphenylpropiophenone (**131**) is formed nearly exclusively (reaction 75), whereas phenyllithium would only give 1,2-addition.



(75)

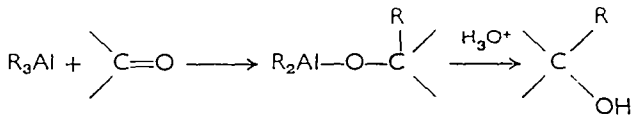
(**131**)

IV. GROUP III ELEMENTS

Of the derivatives of Group III metals, little is known about reactions of organoboron and organogallium compounds with carbonyl compounds. Consequently this section deals mainly with the chemistry of organoaluminum compounds, which has recently been revived through the extensive work of Ziegler[175]. Organoaluminum compounds react with the carbonyl group in a similar way to Grignard reagents. Condensation reactions[176] as well as 1,2- and 1,4-additions may occur as may reduction processes if a β-hydrogen is present in the organoaluminum reagent.

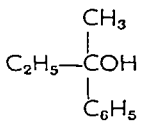
A. 1,2- and 1,4-Addition

Trialkyl- and triarylaluminums give 1,2-addition according to reaction (76), where only *one* of the three alkyl groups is involved in

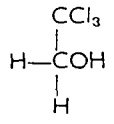


(76)

the reaction. Thus, trimethylaluminum is reported to undergo smooth and nearly quantitative reaction with propiophenone[177] forming ethyl methyl phenyl carbinol (132a) and with chloral[178] forming 1,1,1-trichloro-2-propanol (132b) as the sole products.

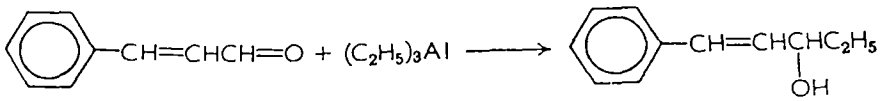


(132a)



(132b)

Triethylaluminum was found to add to benzaldehyde and substituted benzaldehydes to form, in good yields, the corresponding secondary carbinols, reduction being only a minor side-reaction[179]. Similarly, cinnamic aldehyde gave 1,2-addition in practically quantitative yield (reaction 77). Another example is the addition of triphenylaluminum to benzophenone, forming tritanol[180].



(77)

In addition reactions it is often observed that only one third of the available alkyl groups in R_3Al are utilized[121]. Generally, a

marked decrease in reactivity of the Al—R bond is induced when electronegative substituents are attached to aluminum. Thus, the reactivity towards carbonyl groups decreases in the series

$$R_3Al > R_2AlOR > RAl(OR)_2$$ [121]

as well as in the series of the corresponding halogen compounds

$$R_3Al > R_2AlCl > RAlCl_2$$ [177,181]

This decrease in reactivity is paralleled by a decrease in the mobility of the R groups, as shown by a nuclear magnetic resonance study by Hoffmann[182] who observed only slow exchange in the system $R^1_3Al/R^1_2AlOR^2$. Nevertheless, utilization of all three R groups in addition reactions to carbonyl groups seems possible. Gilman[159] showed on the basis of his 'color test'[173] that the reaction between triphenylaluminum and benzophenone or benzaldehyde was only complete when three moles of carbonyl compound per mole of R_3Al reacted. Interestingly, triphenylboron added to benzaldehyde in a similar way to form benzhydrol in moderate yield[159] utilizing only two of the three phenyl groups. Comparative studies with the corresponding zinc compounds indicated an order of relative reactivity (in the aliphatic as well as in the aromatic series) in the sequence $R_3Al > R_3B > R_2Zn$. Among the functional groups subjected to addition the order $-CH{=}O > -COC_6H_5 > -C{\equiv}N$ seemed to be valid in analogy to the relative reactivity toward RMgX compounds shown earlier[183].

The reaction of benzalacetophenone with triphenylaluminum may serve as an example of 1,4-addition of an organoaluminum compound to a conjugated system (reaction 78)[138,184]. In forced conditions the

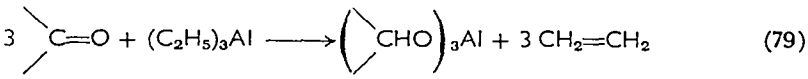
$$C_6H_5CH{=}CHCC_6H_5 + (C_6H_5)_3Al \longrightarrow (C_6H_5)_2CHCH{=}CC_6H_5 \xrightarrow{H_3O^+} \mathbf{131}\ (78)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad O{-}Al(C_6H_5)_2$$

less reactive triphenylboron could be induced to add to **133** giving the product of 1,4-addition in moderate yield[167].

B. Reduction

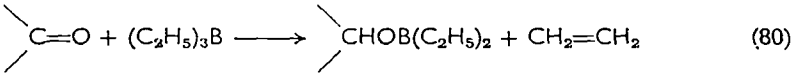
The property that trialkylaluminums and -borons can serve as potential reducing agents was discovered by Meerwein and coworkers[179]. As already mentioned, the interaction of triethylaluminum with benzaldehydes gave benzyl alcohols as side-products. With halogenated carbonyl compounds (chloral, bromal, halo-

acetones, etc.), which undergo addition with trimethylaluminum[178], the addition reaction was completely superseded by reduction and the corresponding alcohols were formed in excellent yields, ethylene being the second product of reaction. One-third mole of triethylaluminum was sufficient to reduce 1 mole of ketone (reaction 79).



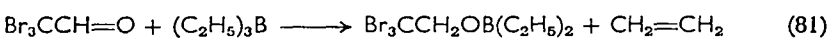
(79)

Similarly, triethylboron was capable of reducing benzaldehydes and halogenated carbonyl compounds. In contrast to triethylaluminum, however, triethylboron reacted with utilization of only *one* of the three ethyl groups (reaction 80). With bromal, the normal reduction

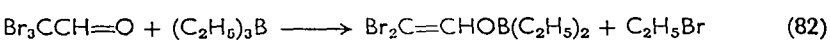


(80)

(81) was under certain conditions superseded by a reaction involving additional elimination of HBr according to reaction (82).

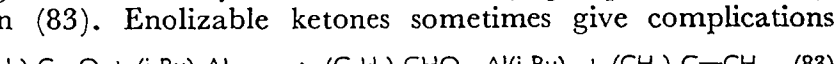


(81)



(82)

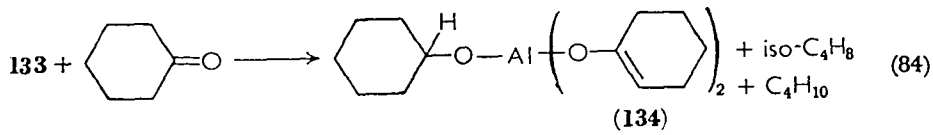
As Ziegler[185] showed later, the reduction of benzil[179], benzophenone, and trichloroacetophenone[179] with triethylaluminum consumed only *one* of the alkyl groups per mole of ketone. Additionally, triisobutylaluminum was introduced[185] as an excellent reducing agent for saturated and unsaturated aldehydes and ketones. This again reacted only with one of the alkyl groups available, e.g. reaction (83). Enolizable ketones sometimes give complications



(83)

(133)

when higher ratios than 1:1 (ketone/R_3Al) are employed. For example, cyclohexanone yielded only cyclohexanol on reaction with **133** in a 1:1 ratio. But when a 3:1 ratio was applied, a mixture of cyclohexanol and cyclohexanone was obtained, indicating that



(84)

(134)

after participation of the first alkyl group in the reduction the second and third alkyl group had effected enolization of the ketone, leading

to a mixed aluminum alcoholate–enolate **134** (reaction 84). Interestingly, in the reaction of cyclohexanone with triethylaluminum, the first alkyl group seems to bring about enolization, since no reduction product was obtained[185].

C. Mechanism

A mechanism for the reaction of carbonyl compounds with triarylaluminums was proposed by Wittig[184], which is shown in reaction (85) for the addition of triphenylaluminum to benzophenone:

$$(C_6H_5)_3Al + (C_6H_5)_2C{=}O \rightleftharpoons \underset{\textbf{(135)}}{(C_6H_5)_2\overset{+}{C}{-}O{-}\bar{A}l(C_6H_5)_3} \longrightarrow (C_6H_5)_3COAl(C_6H_5)_2 \quad (85)$$

It is assumed that attack of a monomeric triphenylaluminum species[186] leads to formation of an 'at-complex' (**135**) in a fast and possibly reversible step and that the following phenyl migration is slow and rate-determining. The formation of a complex like **135** is supported by the observation that in the reaction of unsaturated systems very intense transient colors were developed, which might be interpreted in terms of betains (**136**) stabilizing the positive charge by the resonance (86). Similar halochromic inner salts had already been

$$R^1CH{=}CHC(=O)R^2 + (C_6H_5)_3Al \rightleftharpoons \underset{\textbf{(136)}}{\left[R^1CH{=}CH{-}\overset{+}{C}(-O{-}Al(C_6H_5)_3){-}R^2 \longleftrightarrow R^2{-}\overset{+}{C}H{-}CH{=}C(-O{-}Al(C_6H_5)_3)R^2\right]} \quad (86)$$

observed by Meerwein[179] and Pfeiffer[187] in the reaction of alkylaluminums and aluminum halides[187] with aldehydes and ketones. These were similarly interpreted as molecular association complexes which in some cases could be isolated and chemically characterized ($AlBr_3$[187]). Furthermore, the formation of adducts with Lewis bases of all types (ethers and amines[188], carbanions[183]) is a general feature of R_3Al compounds thus supporting the idea of a 1:1 complex R_3Al/ketone.

Mechanism (85) closely resembles the mechanism proposed for the addition of phenyllithium to ketones[45]. Phenyllithium and triphenylaluminum give the same products with benzophenone, but with a pronounced difference in rate[183]. Apart from the higher

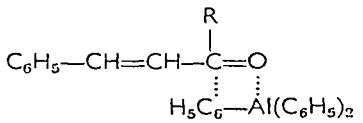
tendency of phenyllithium to provide an anion in etheral medium[52], the intermediate 1:1 complex with the ketone is probably more stable with triphenylaluminum than with phenyllithium, leading to a slower formation of the carbinolate in the case of the former.

A comparative study of Wittig and Schliesser[167] on the reactivity of phenyllithium and triphenylaluminum toward numerous unsaturated aldehydes and ketones revealed further aspects of the mechanism of 1,2- as well as 1,4-addition. The experimental results are collected in Table 6. These data support the conclusions given

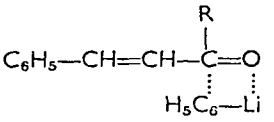
TABLE 6.

Unsaturated system	Triphenylaluminum		Phenyllithium	
	1,2-Addn. (%)	1,4-Addn. (%)	1,2-Addn. (%)	1,4-Addn. (%)
$C_6H_5CH{=}CHCH{=}O$ (**137**)	64	—	72	—
$C_6H_5CH{=}CHCOCH_3$ (**138**)	—	55	87	—
$C_6H_5CH{=}CHCOC(CH_3)_3$ (**139**)	—	94	60	12
$C_6H_5CH{=}CHCOC_6H_5$ (**140**)	—	88	69[138]	13[138]
$C_6H_5CH{=}CHCOMes$ (**141**)	—	77	—	77

in section III.B.2 for the dependence of the observed reactivity upon steric requirements of the unsaturated system and on those of the attacking organometallic species. If the carbonyl group is sterically accessible without any hindrance, as in **137**, both reagents add in the 1,2-manner probably via a four-center transition state like **142** and **143**. But if the aldehyde hydrogen is replaced by alkyl or aryl



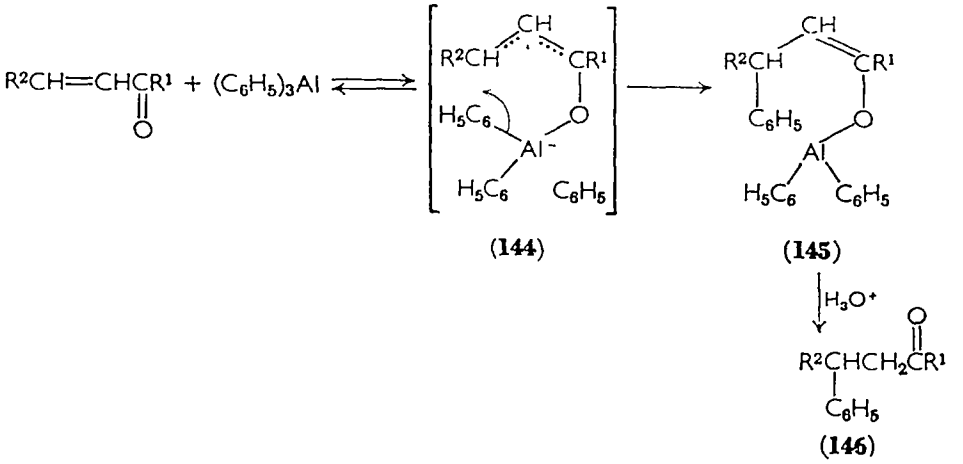
(**142**)



(**143**)

groups (**138–140**), phenyllithium is still able to give preferentially 1,2-addition, whereas the bulkier triphenylaluminum is added exclusively in the 1,4-manner. If blocking of the carbonyl group is further increased, as in benzalacetomesitylene (**141**), even phenyllithium is prevented from attacking at the carbonyl carbon: conjugate (1,4-) addition remains the only possible one for both reagents.

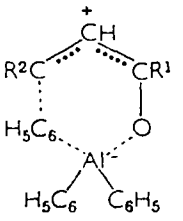
The scheme shown in (87) seems to fit the 1,4-addition of triarylaluminums to conjugated systems[167,183]. From considerations of



(144) (145) (146)

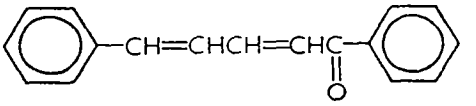
(87)

molecular models it is clearly evident that attack of triphenylaluminum on the carbonyl group for complex formation *and* the following phenyl transfer via **142** is sterically hindered in the



(147)

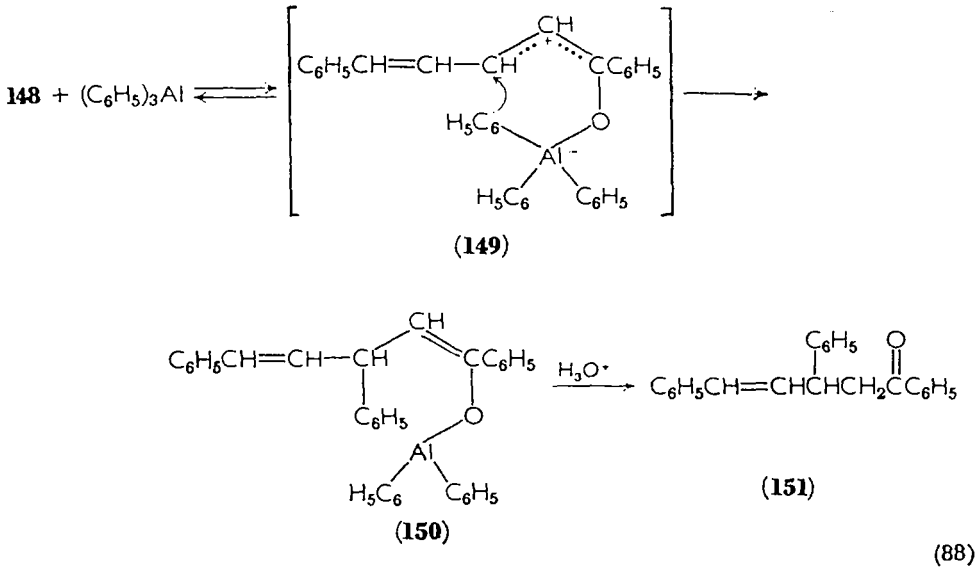
presence of bulky R groups. In these cases the transition **144** → **145** through a six-membered cyclic 'activated complex' (**147**) involving the β-carbon might be favored energetically. Cinnamalacetophenone



(148)

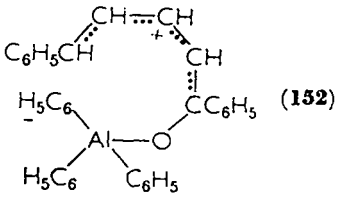
(**148**), which offers competitive reaction possibilities of 1,2- as well as of 1,6-addition, was used for testing the assumption of a six-membered transition state (**147**). With triphenylaluminum, **148** gave β-phenyl-

β-styrylpropiophenone (**151**) (reaction 88) as the sole product, indicating that only 1,4-addition had occurred. It might be argued that a transition state like **147** or **149** requires lower activation energy than the eight-membered one (**152**) required for 1,6-addition and that 1,2-addition does not take place owing to the severe sterical requirements of the reactants.



(88)

It was not possible to follow reaction (88) kinetically by the aid of the intermediately formed deeply colored complex (**149**). Thus, as in the addition of organomagnesium reagents[122], a rigorous proof for the formation of the products from primarily formed 1:1 adducts is still missing. In the 1,4-addition of organomagnesium reagents,

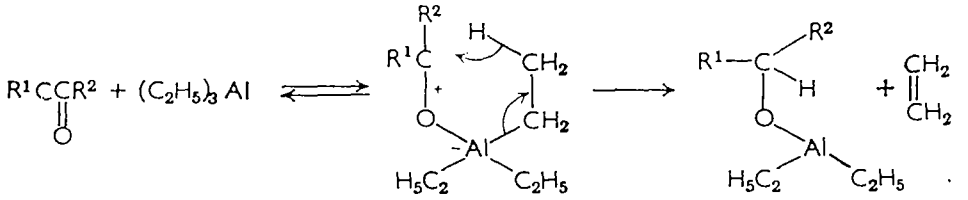


(**152**)

according to House[142,144], a six-membered cyclic mechanism seems unlikely, in contrast to the mechanism including **147** in the addition of triarylaluminums. Again in contrast to organomagnesium reagents[140] triphenylaluminum did *not* react in the 1,4-mode with the *trans*-oid conjugate system of 2-cyclohexenone[167]: besides a small amount of 1,2-addition product, only polymers were obtained. This

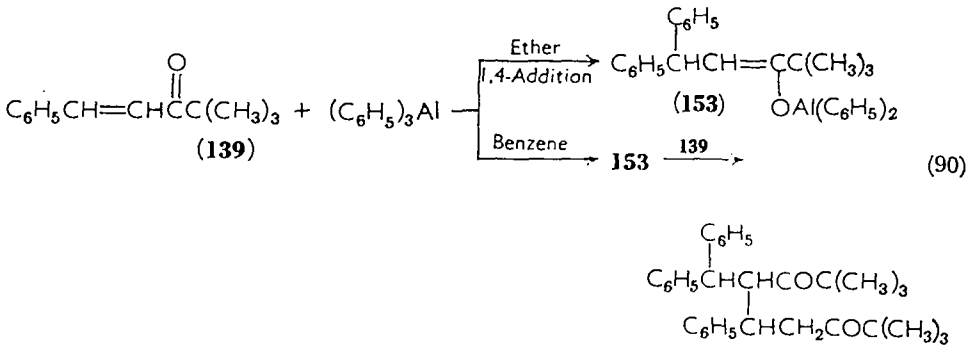
indicates that triphenylaluminum cannot be involved in a Michael-type mechanism suggested for conjugate addition in the magnesium series[142] and that the mechanism proposed by Wittig[184] has to be taken into account.

For the reduction by trialkylaluminums[179], a mechanism closely resembling that proposed for the Meerwein–Ponndorf–Verley reaction[189] and for the reduction by Grignard reagents[56] was suggested by Wittig (reaction 89)[183]. The polarity of the solvent seems



(89)

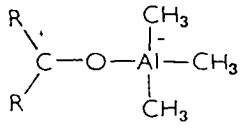
to play a certain role in the reactions of organoaluminum compounds, as also observed in the reactivity of organolithium derivatives[52]. For example, the unsaturated ketone **139** reacted with triphenylaluminum in ether to give exclusively the product of 1,4-addition, whereas in benzene the enolate **153** undergoes Michael addition with **139** to a considerable extent (reaction 90).[167]



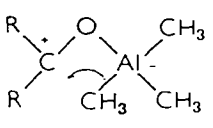
(90)

Mechanisms for the reaction of trialkylaluminums with ketones were recently proposed by Pasynkiewicz and coworkers[177,190]. The reaction of trimethylaluminum and propiophenone[177] gave the highest yield of addition when a 1:2 molar ratio of ketone/$(CH_3)_3Al$ was employed. The rearrangement of the primarily formed 1:1 complex (**154**) was believed to occur via a four-centered transition state (**155**), and for the reactant ratio 1:2 a six-membered transition

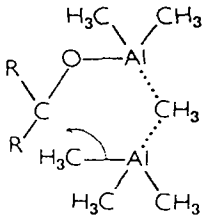
state (**156**) with participation of dimeric trimethylaluminum was assumed.



(**154**)



(**155**)



(**156**)

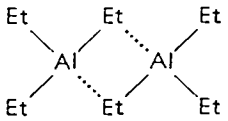
While attempts to isolate 1:1 adducts of R_3Al compounds with ketones were unsuccessful, in the gallium series a 1:1 adduct of trimethylgallium with acetone ($(CH_3)_3Ga \cdot (CH_3)_2C{=}O$) has been described[191] along with other complexes, justifying the hypothesis of a primary formation of **154**. Trimethylaluminum gives exclusively addition, but triethylaluminum with diethyl and diisopropyl ketone shows three competitive reaction modes of addition (91a), reduction

$$R_2C{=}O + Et_3Al \longrightarrow R_2COAlEt_2 \xrightarrow{H_2O} R_2COH \quad \text{(addition)} \quad (91a)$$

$$R_2C{=}O + Et_3Al \longrightarrow R_2CHOAlEt_2 \xrightarrow{H_2O} R_2CHOH \quad \text{(reduction)} \quad (91b)$$

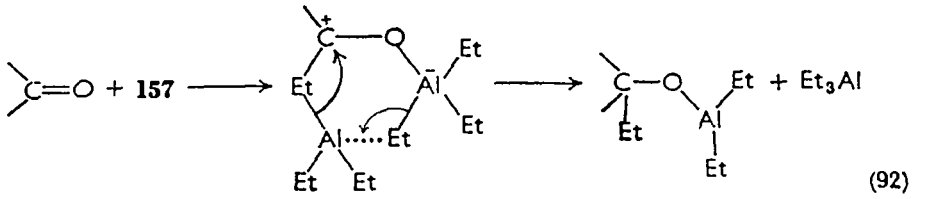
$$R^2CH_2COR^1 \underset{H_2O}{\overset{Et_3Al}{\rightleftharpoons}} R^2CH{=}COAlEt_2 \quad \text{(enolization)} \quad (91c)$$

(91b) and enolization (91c). With diethyl ketone increasing $(C_2H_5)_3Al$/ketone ratios enhanced addition, while an increase in temperature favored reduction. Enolization was only little affected by these variations of reaction conditions. At low temperatures, where addition was predominant, triethylaluminum exists exclusively as the dimeric species **157**[192], so that the addition probably involves



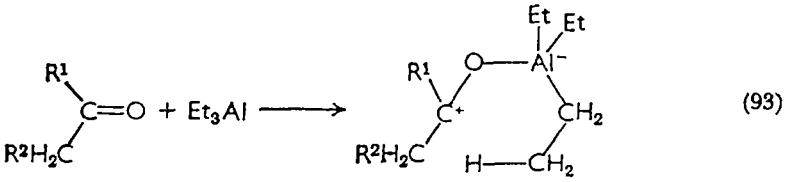
(**157**)

the sequence (92). The geometry of the transition state (**158**) is believed to permit close approach of the alkyl group to the carbonyl carbon thus facilitating transfer of an anion. With lower $(C_2H_5)_3Al$/



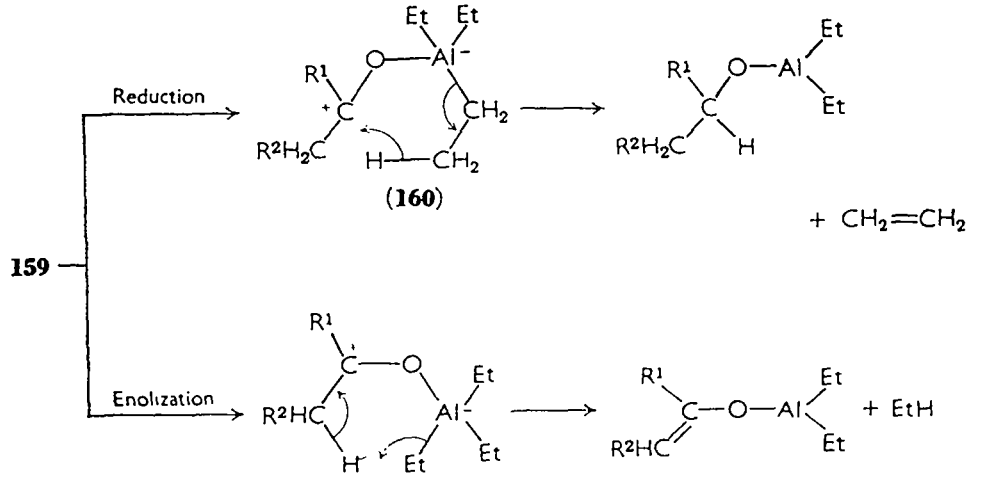
(158) (92)

ketone ratios, or when the ketone is in excess, a mechanism (93) involving attack of monomeric triethylaluminum (formed either by reaction (92) or by attack on the dimer) has been proposed. The



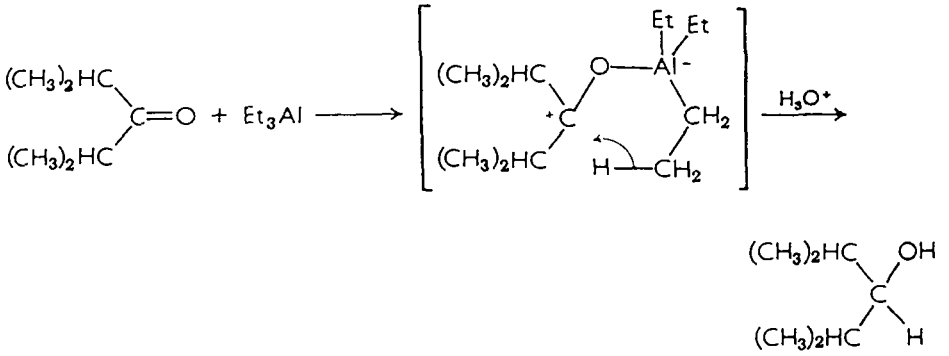
(159) (93)

structure **159** might show a larger distance between the ethyl groups and the carbonyl carbon, favoring other configurations than the one leading to addition (reaction 94).



(94)

Diisopropyl ketone reacts with more difficulty than diethyl ketone, and gives reduction in nearly quantitative yield (reaction 95) along with only a very small amount of enolization. The complete lack of addition, the overwhelming preference for reduction,



(95)

and the significant decrease in reactivity were explained on the basis of steric hindrance which prevents the formation of a transition state analogous to **158** with a molecule of dimeric triethylaluminum while interaction with an ethyl group in the transition state for reduction (**160**) seems to be sterically possible.

V. ACKNOWLEDGMENTS

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The Chemistry of the Carbonyl Group
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CHAPTER 14

Decarbonylation

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I. INTRODUCTION

The title of this chapter is considered to embrace not only reactions in which aldehydes and ketones yield carbon monoxide, but also reactions in which the formyl group of aldehydes is converted into formic acid or formate ion. Decarbonylation reactions that are initiated by irradiation of various sorts will not be discussed, as these are covered in Chapter 16. The decarbonylations of α-keto acids and esters, in which the carboxyl carbonyl is lost, are considered to be reactions of carboxylic acids and esters rather than carbonyl compounds and thus will be dealt with in a forthcoming volume of this series. However, a number of reactions of aldehydes and ketones not giving decarbonylation are included here for purposes of comparison or of delineating the structural requirements of certain decarbonylation reactions.

As can be seen in the above outline, an attempt has been made to categorize the decarbonylation reactions according to mechanistic type. However, section V on thermal decarbonylations includes both radical-chain and molecular processes, as well as some for which the mechanism is in doubt. Section VI on miscellaneous decarbonylations seemed inevitably necessary. This section includes decarbonylations that may proceed by more than one mechanism, e.g. Dakin-like reactions, which can be either base- or acid-catalyzed. Also included in this last section are reactions which have no firm mechanistic assignment.

Emphasis has been placed on recent work, although examples from the older literature are included. We cannot guarantee that all key work has received mention, despite our having made a thorough scrutiny of the literature, searching under all conceivable headings. Our worries stem from the fact that we stumbled across two important references quite by accident. We apologize to the authors of pertinent work that inadvertently may have been omitted, slighted, or misrepresented.

II. AROMATIC ELECTROPHILIC DEFORMYLATION

Aromatic aldehydes substituted in *ortho* or *para* positions with electron-releasing substituents undergo aromatic electrophilic substitution reactions in which the formyl group is displaced. Depending upon the structure of the aldehyde and upon the reaction conditions, the formyl group is converted either into formic acid or into carbon monoxide. Similar reactions are shown by corresponding aromatic acids, the carboxyl group being eliminated as carbon dioxide.

A. Acid-catalyzed Replacement of CHO by H

In the earliest investigations of this reaction Bistrzycki and coworkers treated various substituted benzaldehydes with concentrated sulfuric acid at temperatures around 150°[1]. Carbon monoxide was obtained as the principal gaseous product along with smaller amounts of sulfur dioxide and carbon dioxide. When benzaldehyde was treated in this manner, only a 12% yield of carbon monoxide was obtained. Carbon monoxide resulted in good yield when a hydroxyl, methoxyl, or methyl substituent was present in the *ortho* or *para* position, but in poor yield when these substituents were *meta*. With electron-withdrawing substituents, i.e. Cl, NO_2, or CHO, in any position, the yields of carbon monoxide also were poor. Oxidation and sulfonation of the aromatic compounds probably was extensive and the nongaseous products were not identified. There remains the question as to whether carbon monoxide is formed directly from the aldehyde or whether the formyl group is eliminated as formic acid, which subsequently is decarbonylated under the reaction conditions[1] (see below).

Zahler studied the deformylation of a number of aldehydes substituted in the 2-, 4-, and 6-positions by activating substituents such as methoxyl, hydroxyl, and alkyl[2]. The relative ease of deformylation in 60% perchloric or sulfuric acid was 2,4,6-trimethoxybenzaldehyde

> 2,4,6-trihydroxybenzaldehyde ≫ 2,4,6-triisopropylbenzaldehyde > 2,4,6-triethylbenzaldehyde > mesitaldehyde > 2-hydroxy-4,6-dimethylbenzaldehyde, 4-hydroxy-2,6-dimethylbenzaldehyde. For 2,4,6-trimethoxy- and 2,4,6-trihydroxybenzaldehyde, when the reaction was carried out with greater than about 10^{-2} M concentration of aldehyde, condensation between deformylated aromatic residues and aldehyde occurred, yielding diaryl carbinols and triarylmethanes[2,3].

Extensive kinetic studies of the quantitative deformylation of 2,4,6-trialkylbenzaldehydes in 60–100% sulfuric acid have been carried out[4–6]. It was demonstrated that carbon monoxide was a direct

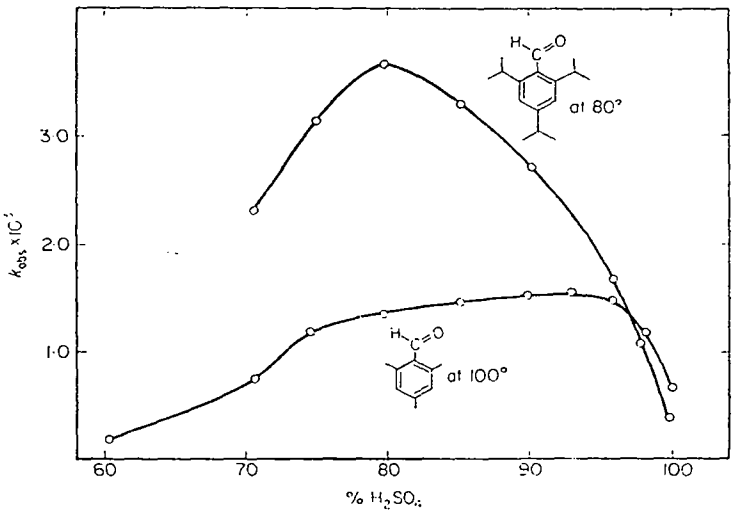


FIGURE 1. First-order rate coefficient for decarbonylation as a function of percentage H_2SO_4.

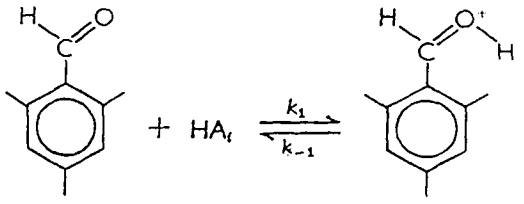
product of deformylation and did not arise via formic acid as an intermediate[4]. Rates were measured both gasometrically[4] and by the change in ultraviolet spectrum[4–6]. The effect of medium on the first-order rate coefficient k_{obs} is plotted in Figure 1. Deuterium isotope effects are given in Table 1. The assigned mechanism is given by equations (1), (2), and (3), in which HA_i refers to general acid (H_3O^+ and molecular H_2SO_4) and A_i refers to general base (H_2O and HSO_4^-). The rate equation (4) is obtained by application of the steady-state assumption to the carbon conjugate acid SH^{*+}, the concentration of which is indetectably low. Equation (5) gives the ratio of the velocity of step (2) reverse over that of step (3). In equations (4) and (5) the *a* symbols refer to activities, the *k* symbols

TABLE 1. Deuterium isotope effects in the decarbonylation of mesitaldehyde.

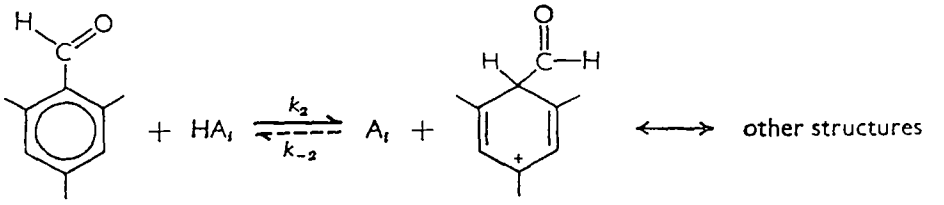
% acid	$k_{MesCHO}/k^{a}_{MesCDO}$	$k_{H_2SO_4}/k^{b}_{D_2SO_4}$	$[SH^+]/[SD^+]^c$
59·9	1·8	0·56	0·58
65·0	—	0·72	0·70
70·1	—	0·85	0·87
85·2	2·8	1·5	1·0
96·3	2·8	2·1	1·0
99·5	2·0	2·4	1·0

[a] Ratio of k_{obs} for mesitaldehyde over that for deuteriomesitaldehyde in H_2SO_4 solutions.
[b] Ratio of k_{obs} in H_2SO_4–H_2O over that in D_2SO_4–D_2O of the same percentage.
[c] Ratio of degree of oxygen protonation in H_2SO_4 *vs.* D_2SO_4.

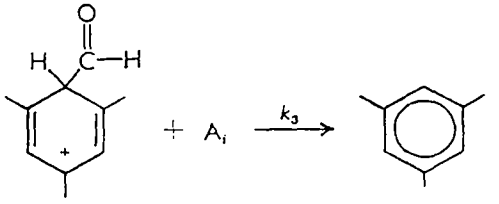
refer to catalytic constants, and the f symbols refer to activity coefficients.



(S) (SH$^+$) (1)



(SH^{*+}) (2)



(3)

$$k_{obs} = \frac{[S]}{[S] + [SH^+]} \frac{f_s[(k_2^{H_3O^+} a_{H_3O^+}/f_{tr_2}{}^+) + (k_2^{H_2SO_4} a_{H_2SO_4}/f_{tr_2}{}^0)]}{1 + v_{-2}/v_3} \quad (4)$$

$$v_{-2}/v_3 = \frac{(k_{-2}^{H_2O} a_{H_2O}/f_{tr_2}{}^+) + (k_{-2}^{HSO_4^-} a_{HSO_4^-}/f_{tr_2}{}^0)}{(k_3^{H_2O} a_{H_2O}/f_{tr_3}{}^+) + (k_3^{HSO_4^-} a_{HSO_4^-}/f_{tr_3}{}^0)} \quad (5)$$

Oxygen protonation (equilibrium 1) is extensive in the media used. For example, in 70% H_2SO_4 the degree of oxygen protonation is 85%, 82%, and 70% for 2,4,6-trimethyl-, 2,4,6-triethyl-, and 2,4,6-triisopropylbenzaldehyde, respectively. Extensive oxygen protonation accounts for the failure of k_{obs} to rise precipitously with increasing mineral acid strength. In other words once $[SH^+] \gg [S]$, the decrease in the concentration ratio of equation (4) more than counterbalances the increase in the remaining catalytic term.

Whether step (2) or (3) is rate-controlling, or whether both compete as rate-controlling steps, depends upon the structure of the aldehyde and the percentage of H_2SO_4. From the isotope effects of Table 1 the following conclusions for mesitaldehyde decarbonylation were made. (*a*) Step (3) is at least partially rate-controlling throughout the mineral acid range since k_{MesCHO}/k_{MesCDO} is greater than unity throughout. (*b*) Step (3) is practically completely rate-controlling in 59–70% H_2SO_4 ($v_{-2} \gg v_3$) since the reaction is slower in D_2SO_4–D_2O than in sulfuric acid of the same molarity; also $k_{H_2SO_4}/k_{D_2SO_4} = [SH^+]/[SD^+]$†. (*c*) Step (2) competes with step (3) for rate-control in 85–100% H_2SO_4 ($v_{-2} \sim v_3$) since $k_{H_2SO_4}/k_{D_2SO_4}$ increases considerably beyond unity in this region.

General base catalysis in steps (2) reverse and (3) was invoked to explain the required decrease in v_{-2}/v_3 in the higher mineral acid molarities. In 59–70% H_2SO_4, in which there is an appreciable concentration of unprotonated water, it can reasonably be assumed that catalysis by the weakly basic HSO_4^- is negligible, i.e. the first terms in both the numerator and denominator of equation (5) greatly exceed the second terms. Apparently $k_{-2}^{H_2O} \gg k_3^{H_2O}$ and hence, in 59–70% H_2SO_4, $v_{-2} \gg v_3$. In greater than 84·5% H_2SO_4 ('monohydrate' strength) a_{H_2O} decreases sharply since practically all of the water molecules are protonated. The concentration of HSO_4^- now greatly exceeds that of H_2O and catalysis by HSO_4^- becomes important, i.e. the second terms of equation (5) become important. If $k_{-2}^{HSO_4^-}$ is comparable to or less than $k_3^{HSO_4^-}$, v_{-2}/v_3 would suffer a decrease as the H_2SO_4 percentage is increased beyond 85%. The requirement that $k_{-2}^{HSO_4^-}/k_3^{HSO_4^-}$ be significantly less than $k_{-2}^{H_2O}/k_3^{H_2O}$ was rationalized on steric grounds. That is, the energy of the transition state of step (2) reverse would be raised relative to that of step (3) when the bulkier HSO_4^- is the participating base. In step (3) a peripheral proton is being removed. In step (2) reverse the

† The more pertinent ratio $[SH^{*+}]/[SD^{*+}]$ was experimentally inaccessible. However, it should have approximately the same values as $[SH^+]/SD^+]$[5].

transition state is subject to steric compression between the *o*-methyl groups and the participating base.

On the basis of the above steric argument it would be expected that in H_2SO_4 media in which HSO_4^- catalysis is important, step (2) reverse would be slowed even more relative to step (3) if the *o*-alkyl substituent were larger. This has been borne out by experiment for 2,4,6-triisopropylbenzaldehyde[6]. Thus in concentrations greater than 85% H_2SO_4 there was a negligible isotope effect in the decarbonylation of the deuterioaldehyde (ArCDO) and an appreciable solvent isotope effect ($k_{H_2SO_4}/k_{D_2SO_4}$ as large as 5·0). This indicates that step (2) forward is practically completely rate-controlling, i.e. $v_{-2} \ll v_3$. In lower percentages of H_2SO_4 the isotope effect in the decarbonylation of ArCDO is quite small and the solvent isotope effect is still large, though somewhat reduced; i.e. even in H_2SO_4 media, in which H_2O functions principally as the base, step (2) reverse has been slowed relative to step (3), enough to make step (2) forward largely rate-controlling.

The acidity profiles for the decarbonylations (Figure 1) also are consistent with the assigned mechanism. In particular the greater falloff in k_{obs} in high percentages of H_2SO_4 in the order triisopropylbenzaldehyde > triethylbenzaldehyde > mesitaldehyde is explained. In step (2) reverse, increased bulk of the *o*-substituents raises the free energy of the transition state in which HSO_4^- is the participating base more than that in which the smaller H_2O molecule is the participating base, i.e. $k_{-2}^{HSO_4^-}/k_2^{H_2O}$ is reduced. Since step (2) *forward* must proceed through the same transition states, it follows that $k_2^{H_2SO_4}/k_2^{H_3O^+}$ is less for triisopropylbenzaldehyde than for mesitaldehyde. Thus as H_2SO_4 percentage is increased, the catalytic term of equation (4) will not increase as greatly for the more hindered aldehyde. Since the increase in this term cannot keep up with the large decrease in the concentration ratio $[S]/[SH^+]$, the result is a steeper falloff in k_{obs} for the more hindered aldehyde.

The results establish that acid-catalyzed decarbonylation of aromatic aldehydes is an aromatic electrophilic substitution. The replacement of the formyl group by a proton is not as rapid as the exchange of the *meta* hydrogens, however[7]. Along with the work on certain coupling reactions carried out by Zollinger[8], the results of the decarbonylation studies are perhaps the best evidence that aromatic electrophilic substitution proceeds via a σ-complex intermediate. Further, they constitute the first evidence of general acid–base catalysis in strong mineral acid solution.

The decarbonylation of 2,4,6-trimethoxybenzaldehyde has also been extensively investigated[9,10]. The effect of mineral acid media on the first-order rate coefficient is shown graphically in Figure 2. The rate coefficients were obtained by an ultraviolet spectrophotometric method, allowing the use of aldehyde concentrations of the order of 10^{-4} M. Under these conditions, trimethoxybenzene and formic acid are obtained quantitatively, the former compound slowly undergoing subsequent ether cleavage in stronger acids[11]. At higher aldehyde concentrations, above 10^{-2} M, condensation reactions (dependent on a higher kinetic order of the aldehyde) take place[3],

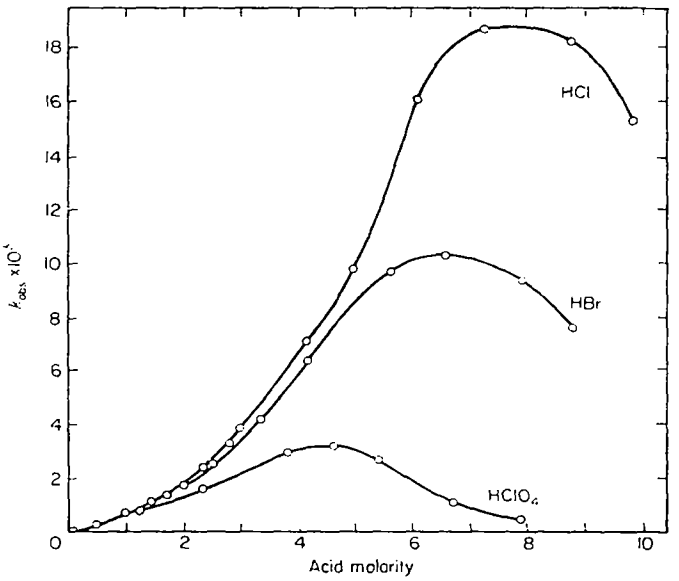
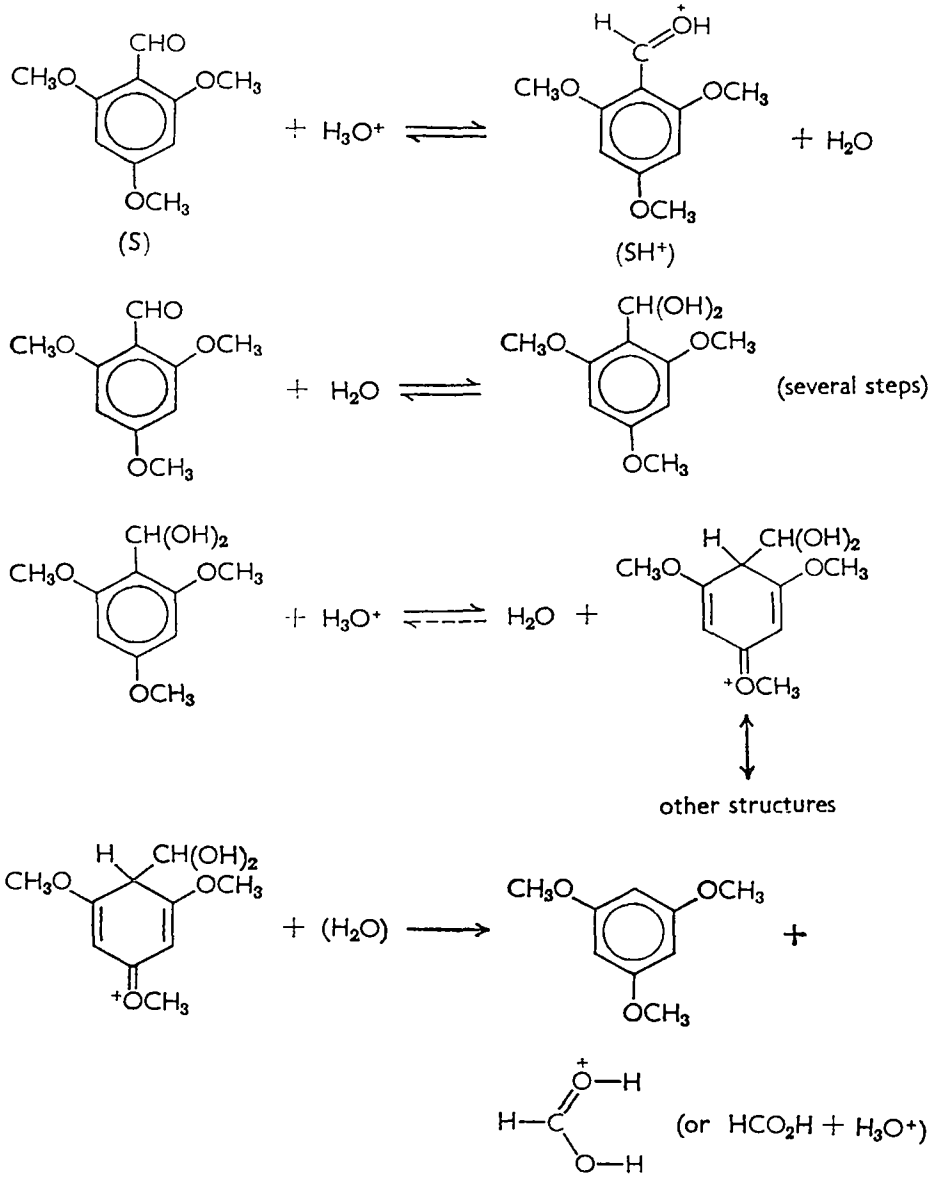


FIGURE 2. First-order rate coefficient for deformylation of 2,4,6-trimethoxybenzaldehyde at 80° as a function of molarity of mineral acid.

as mentioned earlier in this chapter. As is to be expected, the decarbonylation reaction of 2,4,6-trimethoxybenzaldehyde proceeds more facilely, i.e. at lower acid concentrations, than does that of 2,4,6-trialkylbenzaldehydes.

A mechanism consistent with the facts amassed to date is given in Scheme 1.

The aldehyde is a remarkably strong oxygen base ($pK_{SH^+} = -2{\cdot}1$), being about 50% protonated to the oxygen conjugate acid in 4·7 M $HClO_4$. The fact that k_{obs} reaches a maximum is due primarily to this fact. The further falloff of k_{obs} in higher acid molarities is



SCHEME 1.

indicative of the involvement of water molecules in the transition state, either in covalent bonding or in solvation[12,13]. The fact that the maximum rate has a larger value in hydrochloric acid than in perchloric acid may indicate chloride ion catalysis. On the other

hand, it may simply be a reflection of the greater availability of water in hydrochloric than in perchloric acid of the same molarity.

A mechanism proceeding via the aldehyde hydrate is consistent with the fact that formic acid and not carbon monoxide is directly formed. Although the hydrate concentration is too small to be measured, its presence is inferred from the rapid exchange of the carbonyl oxygen of the aldehyde with ^{18}O-enriched aqueous acid[10]. Finally, the mechanism also is consistent with the finding of a solvent isotope effect of 3 to 4 in all acid molarities[10].

It seems likely that formic acid is the 'normal' product of the acid-catalyzed deformylation of aromatic aldehydes. Carbon monoxide has been demonstrated to be the direct product of deformylation only in the case of 2,4,6-trialkylbenzaldehydes, where hydration of the aldehyde is quite hindered. In all other instances either carbon monoxide is not formed or, if formed, is obtained in mineral acid media strong enough to decarbonylate formic acid.

B. Other Electrophilic Aromatic Deformylations

Substitution of the formyl substituent of suitably activated aldehydes can be brought about by electrophiles other than proton sources. Salway and later workers showed that nitration of certain alkoxy aldehydes yields some of the product in which a nitro substituent has replaced the formyl substituent[14–16]. In the nitration of myristicinaldehyde (3-methoxy-4,5-methylenedioxybenzaldehyde) in nitric acid at 0°, nitromyristicinaldehyde constituted only 40% of the product, the remainder being 5-nitro-3-methoxy-1,2-methylenedioxybenzene. The proportion of replacement product to nitro aldehyde was less (30%) in the nitration of piperonal and still less (6%) in the nitration of vanillin methyl ether. Nitration of anisaldehyde in nitric acid gave only nitroanisaldehyde. Salway rejected the idea that the formyl group is oxidized before replacement, since no nitromyristicinic acid could be isolated on nitration of myristicinic aldehyde, whereas it *was* a product of the nitration of myristicinic acid. The formyl substituent evidently was converted into formic acid, and the small amount of carbon dioxide noted was attributed to the oxidation of formic acid[14].

Treatment of 2,4,5-trimethoxybenzaldehyde with absolute nitric acid in acetic anhydride yielded 2,4,5-trimethoxynitrobenzene and an unspecified amount of carbon monoxide[17]. It is possible that under these conditions formic acid is first formed and is then decarbonylated. Nitration of 2-methoxy-1-naphthaldehyde gave 'some'

1-nitro-2-methoxynaphthalene as well as 'normal' nitration product, the fate of the formyl group being unspecified[16,18].

Chlorination or bromination of piperonal in acetic acid yielded 4,5-dihalomethylenedioxybenzene as well as the major product of 6-halopiperonal[19]. Neither the 6-bromo- or 6-chloropiperonal could be converted readily into the corresponding 4,5-dihalomethylenedioxybenzene, indicating that the former is not an intermediate in the formation of the latter. No mention was made of the fate of the formyl group. More recently, Hazlett found that treatment of isovanillin acetate with bromine in acetic acid gave the bromination–deformylation product, 5-bromoguaicol acetate. In the bromination of isovanillin itself the directive influence of the hydroxyl group predominated, and the 'normal' products, 2- and 6-bromoisovanillin, were obtained[20].

Early observations regarding the action of excess bromine on *o*- or *p*-hydroxybenzaldehyde indicated that the formyl group is lost and 2,4,6-tribromophenol and 2,4,6,6-tetrabromocyclohexa-1,4-dien-3-one are obtained[21–23]. Competitive experiments by Francis and Hill, using bromine in water solution, indicated that the formyl group of *o*- and *p*-hydroxy- and *o*- and *p*-aminobenzaldehydes is not replaced by bromine as rapidly as a hydrogen atom in the same position. No visible gas evolution was noted, indicating that the formyl group was converted into formic acid. Oxidation of the formyl group before or after displacement was ruled out by the finding that only three equivalents of bromine were necessary to convert *o*- or *p*-hydroxybenzaldehyde into 2,4,6-tribromophenol in good yield[23].

Salicylaldehyde, treated with excess iodine–potassium iodide in dilute sodium hydroxide solution at room temperature, was reported to 'split off formate ion' (no proof given) and yield 2,4,6-triodophenol[24]. *p*-Hydroxybenzaldehyde also yielded 2,4,6-triodophenol, but *m*-hydroxybenzaldehyde was not deformylated. Other *o*-hydroxy aldehydes, including 1-formyl-2-naphthol and 2-hydroxy-5-methylbenzaldehyde, yielded deformylated iodinated phenols under the same conditions.

Displacement of the formyl substituent can also occur in the phenyl allyl ether rearrangement[25], a reaction which can be considered an example of aromatic electrophilic substitution. *o*-Formylphenyl allyl ether rearranged normally to give 2-formyl-6-allylphenol. On the other hand, when the other *ortho* position was blocked, the main product was the *o*-allylphenol resulting from displacement of

the formyl group. For example, 2,6-diallylphenol constituted 75% of the product arising from heating 2-formyl-6-allylphenyl allyl ether, the other product being 2-formyl-4,6-diallylphenol. Replacement of a *p*-formyl substituent occurred when both *ortho* positions were blocked. For example, 2,6-diallyl-4-formylphenyl allyl ether gave a good yield of 2,4,6-triallylphenol. The displaced formyl group appeared as carbon monoxide[25].

III. BASE-CATALYZED DEFORMYLATION

Discussion will be confined to the deformylations that occur when suitable negatively substituted aliphatic and aromatic aldehydes are treated with strong base. The base-catalyzed deformylation of β-keto aldehydes will not be covered, as this is an example of a reverse Claisen-type reaction.

A. Aliphatic Aldehydes

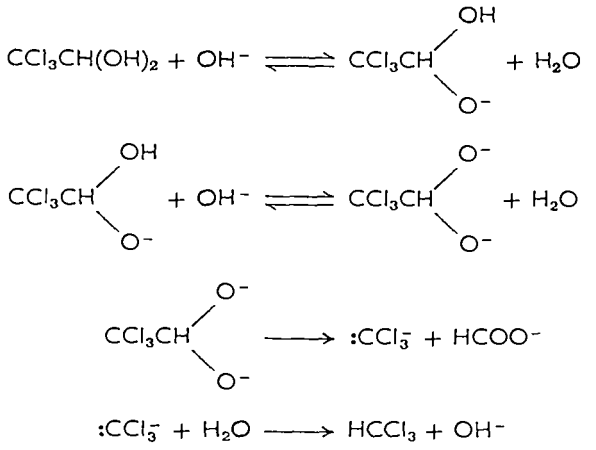
Alkaline treatment of aliphatic aldehydes having two or three electron-withdrawing substituents in the α-position leads to the replacement of the formyl group by hydrogen and the conversion of the formyl group into formate ion.

$$RCHO + OH^- \longrightarrow RH + HCOO^-$$

A similar reaction is shown by 2,3-alkynals. Ordinary aldehydes do not give this reaction, nor do any other aldehydes that readily undergo aldol condensations or the Cannizzaro reaction under deformylation conditions. Experimental details are sparse. The aldehyde is treated with dilute to strong aqueous alkali at temperatures ranging from room temperature to reflux temperature, depending upon the structure of the aldehyde. Specific yields are not given, although mention is made of 'nearly quantitative yields' in some instances. Aldehydes which have been reported to give the reaction include propynal[26], 2-butynal[27], 2-octynal[28], 3-phenylpropynal[26], 2,3,3-trichloropropenal[29], trichloroacetaldehyde[30], tribromoacetaldehyde[31], dichlorobromoacetaldehyde[32], dibromochloroacetaldehyde[32], diphenylcyclohexylacetaldehyde[33], 9-formylfluorene[34], and various α-sulfonated acetaldehydes[35–37].

The base-catalyzed deformylation of chloral hydrate occurs with particular ease and apparently quantitatively. The kinetics of the reaction in dilute aqueous sodium hydroxide have been studied by

Gustafson and Johanson[38], who assigned the mechanism shown in Scheme 2.



SCHEME 2.

Chloral hydrate has an acidity comparable to that of phenol, with $K_{HA} = 1{\cdot}7 \times 10^{-10}$ at 25° and at ionic strength 0·1. Consequently, in the presence of excess sodium hydroxide it is practically all in the form of the monoanion. In 0·0048 to 0·0139 M excess OH^- (with ionic strength maintained at 0·1 by addition of sodium chloride) the observed first-order rate coefficient was linearly dependent on the concentration of excess hydroxide ion; i.e. the rate law is $v = k_{OH^-}([OH^-]_{stoich} - [S]_{stoich})[S]_{stoich}$. The quantity $\Delta H^{\ddagger} =$ 19·6 kcal/mole, and $\Delta S^{\ddagger} = 8{\cdot}4$ e.u. The kinetics clearly indicate that the transition state contains the elements of the dianion. They do not answer the question of whether or not the transition state contains the elements of water (covalently involved)[39].

Upon running the reaction using chloral in excess of base, the authors reported obtaining terms for catalysis by the monoanion and by solvent[38]. This is in contradiction to their assigned mechanism, which is one of *specific* hydroxide ion catalysis (see ref. 39). However, the general catalysis experiments are in doubt in view of Pfeil's finding that hydrolysis of the α-chlorine atoms is a major side-reaction under these conditions[40]. Hydrolysis occurred to the extent of 21% when $[OH^-]_{stoich}/[S]_{stoich}$ was 0·50, and to 77% when this ratio was 0·056. The deformylation rate was influenced by the nature of the positive ion and was accelerated in dioxane–water solution. Pfeil, on dubious grounds, assigned a mechanism involving

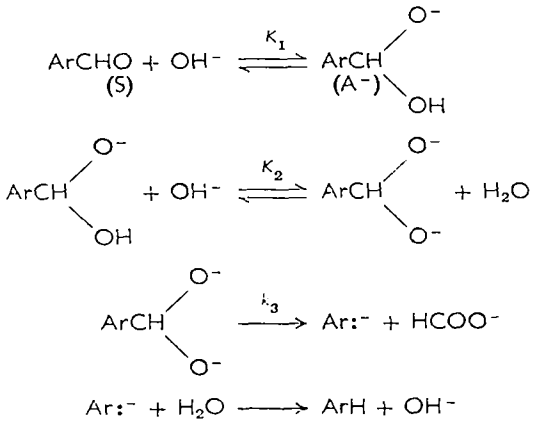
an intimate specific role for the positive ion[40]. Bromal deformylated more rapidly, and fluoral appreciably more slowly, than chloral.

In an isotope experiment Lauder and Wright found formate arising from chloral deformylation to have about 12% (average of 4 experiments) deuterium enrichment from solvent[41]. Neither unchanged chloral nor chloroform were examined for deuterium incorporation. The authors concluded, but without proof, that the small deuterium incorporation was the result of rapid aldehyde–solvent exchange.

B. Aromatic Aldehydes

In the 1930's Lock carried out extensive investigations of the action of strong alkali on nitro- and halo-substituted benzaldehydes[42–52]. Good yields (70–90%) of formate ion (isolated as the mercury salt) and the deformylated aromatic compound were obtained on treatment of 2,6-dinitro-[46], 2,4-dinitro-[46], 2,6-dihalo-[45,50,51], or 2-halo-6-nitrobenzaldehydes[50] with concentrated aqueous alkali at steam-bath temperature. The nitro substituent exerted a stronger activating effect than a halo substituent as indicated by the milder conditions required for the nitro aldehydes[37,46]. However, the yields of nitroaromatics were somewhat lower than those of the haloaromatics, evidently as the result of further reaction of the nitroaromatics with strong base.

The conditions are the same as those of the Cannizzaro reaction, and this was the main reaction with 2,3-dichloro-[52], 2,4-dichloro-[53], 2,5-dichloro-[45,54], and 3,5-dichlorobenzaldehyde[47], or the mononitro-[42] and monohalobenzaldehydes[42]. Neither reaction occurred



Scheme 3.

when 3-methoxy-4-hydroxy-2,6-dibromobenzaldehyde was used[50]. However, 3-hydroxy-2,6-dichlorobenzaldehyde[44] as well as 3,4-dimethoxy-2,6-dibromobenzaldehyde[48] were successfully decarbonylated.

Bunnett has recently studied the kinetics of the cleavage of a number of 2,6-dihalobenzaldehydes in aqueous solutions around 1 M in sodium hydroxide[55]. The assigned mechanism, based mainly upon extensive studies with 2,6-dichlorobenzaldehyde, is one in which a 2,6-dihalophenyl anion is formed in the rate-controlling step (Scheme 3). It is similar to that assigned to the decarbonylation of chloral hydrate (see above).

The rate expression for the Bunnett mechanism is given by equation (6), in which K_1 and K_2 are the thermodynamic equilibrium constants for the first and second steps, K_1^c is the concentration

$$k_{obs} = \frac{[S]}{[S] + [A^-]} \frac{k_3 K_2 K_1}{a_{H_2O}} [OH^-]^2 \frac{f_S f_{OH^-}^2}{f_{tr_3}}$$

$$= \frac{K_1^c}{1 + K_1^c[OH^-]} k_c[OH^-]^2 \qquad (6)$$

equilibrium constant for the first step, f_{tr_3} is the activity coefficient of the transition state of the rate-controlling step, and

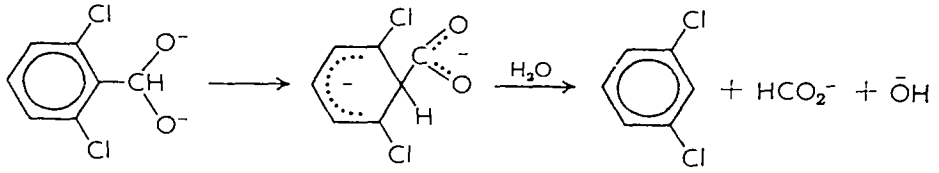
$$k_c = k_3 K_2 f_{A^-} f_{OH^-} / f_S f_{tr_3}$$

The concentration ratio $[S]/([S] + [A^-])$ was obtained by an ultraviolet spectrophotometric method. With 2,6-dichlorobenzaldehyde, for example, K_1^c had a value of 3·2 at 58·4°; i.e. the degree to which the substrate is present as A^- is appreciable in the media used for the kinetic measurements. Values of the first-order rate coefficient k_{obs} in the various media also were determined spectrophotometrically.

In experiments in which the ionic strength was held constant, equation (6) was obeyed reasonably well under the assumption that the activity coefficient ratio remains constant. The ionic strength, maintained at 1·0 by the addition of suitable amounts of sodium chloride, was of necessity somewhat high. In experiments in which the ionic strength was varied the salt effect was large and positive, but only above an ionic strength of 0·4. For the various 2,6-dihalo aldehydes the values of k_c in the order Br, Cl:F, F:Cl, F:Cl, Cl were 2·4:1·6:1·0:1. With the fluoro aldehydes, net replacement of fluorine by hydroxide ion was competitive with deformylation. The extent of

this side-reaction decreased with increasing base concentration from 66% in 0·102 M base to 16% in 1·04 M base for the difluoro aldehyde. This is because the fluorine replacement depends upon a lower power of the hydroxide concentration than does deformylation[55].

The Bunnett mechanism is nicely consistent with all the data. Another mechanism consistent with the facts is one in which the dianion undergoes intramolecular hydride transfer of the aldehydic



hydrogen. This step, a nucleophilic aromatic substitution reaction, also accounts for the necessary activation by electron-withdrawing substituents. It bears a resemblance to other intramolecular hydride transfer reactions, such as the one that occurs in the base-catalyzed conversion of phenylglyoxal into mandelic acid[56]. A choice between the two mechanisms could be made by determining whether deuterium is incorporated into the dihalobenzene product when D_2O is used as the solvent, or alternatively, when deuterioaldehyde (ArCDO) is used.

IV. RADICAL-INITIATED DECARBONYLATION

The decarbonylation of many aldehydes can be initiated by the addition of radical sources such as di-*t*-butyl peroxide. Attention will be confined here to decarbonylations carried out in the liquid phase. In the gas phase the action of radical sources has usually been examined in conjunction with thermal or photolysis studies. In the next section there is some discussion of the initiating effect of nitric oxide on the gas-phase thermal decompositions of carbonyl compounds. For the effect of numerous other initiators in the gas phase, the interested reader is referred to a review by Steacie[57] and Chapter 16 of this book.

A. Aliphatic Aldehydes

In most liquid-phase radical-initiated decarbonylations of aliphatic aldehydes, a major overall reaction is RCHO → RH + CO. This reaction proceeds by a radical-chain process (equations 7–10). Both steps (8) and (9) require appreciable activation and the chain length

is relatively short. Thus significant quantities of initiator (I·) and high temperatures (usually 130° or higher) must be used to obtain reasonable yields, and compounds resulting from chain-terminating steps often constitute a major portion of the reaction product. Lower

$$RCHO + I\cdot \longrightarrow R\dot{C}O + IH \quad (7)$$

$$R\dot{C}O \longrightarrow R\cdot + CO \quad (8)$$

$$R\cdot + RCHO \longrightarrow RH + R\dot{C}O \quad (9)$$

$$R\cdot + R\cdot \longrightarrow RR, \text{ and other chain-terminating steps} \quad (10)$$

reaction temperatures appear to favor the formation of products in which the carbonyl group is retained. Depending upon the structure of the aldehyde and the reaction conditions, competitive reactions of the intermediate acyl or alkyl radical occur to a greater or lesser extent.

The most widely used initiator has been di-*t*-butyl peroxide; di-*t*-amyl peroxide has been used with about the same effectiveness. The common procedure has been to heat the neat aldehyde with at least 10–20 mole per cent peroxide at temperatures ranging from 100 to 170° until carbon monoxide evolution ceases. Solvents such as chlorobenzene have also been used. Additional peroxide often is added during the heating period, and sometimes volatile products (*t*-butyl alcohol, acetone, hydrocarbons) are removed by distillation during the reaction. Initiation at lower temperatures by other radical sources, such as dimethyl α,α′-azobisisobutyrate, has given very low conversion of the aldehyde.

The impetus for the study of liquid-phase decarbonylations was given by Winstein and Seubold, who found that heating β-phenylisovaleraldehyde with 11 mole percent di-*t*-butyl peroxide at 130° gave a 90% yield of carbon monoxide and a 70% yield of hydrocarbon consisting of about equal amounts of *t*-butylbenzene and a rearrangement product, isobutylbenzene[58]. Thus rearrangement of the neophyl radical ($PhC(CH_3)_2CH_2\cdot \rightarrow (CH_3)_2\dot{C}CH_2Ph$) was competitive with the hydrogen abstraction step (equation 9). At 80° over an extensive period of time, mainly unchanged aldehyde was recovered. In the presence of carbon tetrachloride no carbon monoxide was obtained, but chloroform and β-phenylisovaleryl chloride were obtained, i.e. chlorine atom abstraction by the intermediate acyl radical ($R\dot{C}O + CCl_4 \rightarrow RCOCl + \cdot CCl_3$) took precedence over its loss of carbon monoxide (equation 8).

Much of the further work on aldehyde decarbonylation has been

concerned with the neophyl-type rearrangement and attempts to find alkyl or hydrogen migration. No instance of hydrogen or alkyl-substituent migration has yet been encountered, even in instances in which related carbonium ion type reactions show extensive rearrangement. Nor has anchimeric assistance been demonstrated. Evidently, the alkyl radicals produced are much less prone to rearrangement than are the corresponding carbonium ions; or at least, rearrangement of the radical $R^{\bullet}$ is not very competitive with its other reactions, such as hydrogen abstraction (equation 9). The reader is referred to the excellent review by Walling for a discussion of the rearrangement of radicals, both those generated by the decarbonylation reaction and those generated under other conditions[59].

I. Aryl migration

The postulated chain-initiation and chain-propagating steps for the decarbonylation of β-phenylisovaleraldehyde (**1**) are given by equations (11) to (15)[59–72]. There is ample evidence that the

$$t\text{-BuO}^{\bullet} + \underset{(1)}{\text{PhC(CH}_3)_2\text{CH}_2\text{CHO}} \longrightarrow t\text{-BuOH} + \underset{(2)}{\text{PhC(CH}_3)_2\text{CH}_2\dot{\text{C}}\text{O}} \qquad (11)$$

$$\text{PhC(CH}_3)_2\text{CH}_2\dot{\text{C}}\text{O} \longrightarrow \text{CO} + \underset{(3)}{\text{PhC(CH}_3)_2\text{CH}_2^{\bullet}} \qquad (12)$$

$$\underset{(3)}{\text{PhC(CH}_3)_2\text{CH}_2^{\bullet}} \xrightarrow{k_r} \underset{(4)}{\text{(CH}_3)_2\text{C}\!-\!\text{CH}_2} \longrightarrow \underset{(5)}{\text{(CH}_3)_2\dot{\text{C}}\text{CH}_2\text{Ph}} \qquad (13)$$

$$\text{PhC(CH}_3)_2\text{CH}_2^{\bullet} + \text{PhC(CH}_3)_2\text{CH}_2\text{CHO} \xrightarrow{k_a} \underset{(6)}{\text{PhC(CH}_3)_3} + \text{PhC(CH}_3)_2\text{CH}_2\dot{\text{C}}\text{O} \qquad (14)$$

$$\text{(CH}_3)_2\dot{\text{C}}\text{CH}_2\text{Ph} + \text{PhC(CH}_3)_2\text{CH}_2\text{CHO} \longrightarrow \underset{(7)}{\text{PhCH}_2\text{CH(CH}_3)_2} + \text{PhC(CH}_3)_2\text{CH}_2\dot{\text{C}}\text{O} \qquad (15)$$

primary radical **3** is a discrete intermediate, i.e. that the bridged radical **4** is not directly formed in the decarbonylation step (anchimeric assistance). The radical **4**, obtained from **3** by intramolecular radical aromatic substitution, is inferred as a logical intermediate in the practically irreversible rearrangement of **3** to **5**[59].

In agreement with the assigned mechanism Seubold observed that the ratio of rearranged to unrearranged hydrocarbon [**7**]/[**6**] increased from 1·3 when neat aldehyde (6·4 M) was used to 4·0 when a 1 M solution of aldehyde in chlorobenzene solvent was used[63]. The hydrogen-abstraction step (14) depends upon the aldehyde concentration whereas the rearrangement step (13) does not. If, further, the hydrogen-abstraction step (15) is faster than the rearrangement of **5** back to **3** (reversal of step 13), then $d[\mathbf{7}]/d[\mathbf{6}] = k_r/(k_a[RCHO])$ and the percentage rearrangement should increase as the concentration of the aldehyde is reduced. That the rearrangement step is practically irreversible is confirmed by the finding that 2,2-dimethyl-3-phenylpropanal decarbonylates without rearrangement[61]. It is interesting that hydrogen abstraction should be faster than rearrangement for the tertiary radical **5**, whereas such steps are competitive for the primary radical **3**.

That the increase in rearrangement with dilution of the aldehyde is not a solvation effect is confirmed by Rüchardt's observation that the percentage rearrangement is practically the same in anisole and benzonitrile as in chlorobenzene solvent[69]. Rüchardt determined the product ratio [**7**]/[**6**] (by vapor-phase chromatographic analysis) as a function of a number of initial concentrations of aldehyde in *o*-dichlorobenzene. Treating the data by a graphical method which takes into account the fact that the aldehyde concentration decreases during reaction, he obtained the rate coefficient ratio k_r/k_a. The value of this ratio was 2·76 at 130° and 3·25 at 145°. Although these numbers may only be approximate because the reaction is not quantitative (yields are as low as 70%), the conclusion that the activation energy is higher for the rearrangement step (13) than for the hydrogen abstraction of step (14) seems safe[68*].

Ratios of k_r/k_a at 129·7° also were determined for a number of ring-substituted aldehydes, the relative values being *p*-CH_3O, 0·35; *p*-F, 0·38; *p*-CH_3, 0·65; H, 1·00; *p*-Br, 1·79; *p*-Cl, 1·82; *p*-CN, 19·0; *m*-F, 1·45; *m*-Cl, 1·55; *m*-Br, 1·70; *o*-CH_3O, 1·10; and *o*-Cl, 0·90[69,74]. Earlier, Urry had found that the degree of rearrangement of neat aldehyde was little influenced by *p*-CH_3 substitution[61]. Assuming that the hydrogen-abstraction rate coefficient, k_a, is practically unchanged by a change in a remote ring substituent, these numbers represent relative rates of rearrangement of the 2-phenyl-2-methylpropyl radicals and give a ρ value of about +1 for this step. The

* The activation energy for the gas phase reaction $CH_3\cdot + CH_3CHO \rightarrow CH_4 + CH_3\dot{C}O$ has been determined to be 7·5 kcal/mole[73].

relative insensitivity to substituent is consistent with a radical rearrangement of the type of equation (13)[74].

Relief of steric strain and stability of the tertiary relative to the primary radical may be factors in promoting the neophyl rearrangement. However, Slaugh demonstrated that these are not necessary factors, finding that decarbonylation of a 1 M solution (*o*-dichlorobenzene solvent) of β-phenylpropionaldehyde labeled in the α-position with ^{14}C gave 3·3% rearranged ethylbenzene at 150–155° and 5·1% at 165–170° (equation 16)[65]. The rearrangement yield

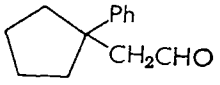
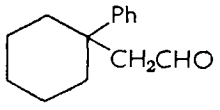
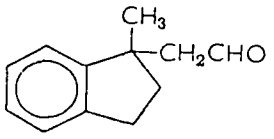
$$PhCH_2\dot{C}H_2CHO \xrightarrow{t\text{-}Bu_2O_2} PhCH_2CH_3 + Ph\dot{C}H_2CH_3 + CO \qquad (16)$$

was reduced somewhat by the addition of 2·4 mole percent of thiophenol. Thiophenol is a better hydrogen-transfer agent than the aldehyde, and thus the rate of conversion of initially formed β-phenylethyl radicals into unrearranged phenylethane is increased over the rate of their rearrangement. Slaugh also found little or no tritium incorporation in the α-position of the ethylbenzene product when decarbonylation was carried out with PhST. This indicates absence of hydrogen migration in the intermediate β-phenylethyl radical[65].

Gross structural changes in the neophyl system do not profoundly influence the extent of rearrangement, as seen in Table 2. Wilt and Phillip found that the behavior of the cyclopentyl aldehyde (**8**) was very similar to that of β-phenylisovaleraldehyde, both when decarbonylated neat and in 1 M solution[67]. A greater proportion of rearranged monomeric hydrocarbon was obtained from the corresponding cyclohexyl compound **9**, but the reaction was less facile[67]. The extent of rearrangement in possible residual dimeric products was not determined. The addition of a large amount of thiophenol lowered the percentage of rearranged hydrocarbon much more substantially for **8** than **9**, but also appreciably lowered the overall yield of monomeric products from **9**. A steric argument was advanced for the difference in behavior between **8** and **9**[67]. The percent of rearranged hydrocarbon obtained from the aldehyde **10** was 35% as compared to 53% from β-phenylisovaleraldehyde under roughly comparable conditions, perhaps because of additional steric strain in the transition state of rearrangement[70].

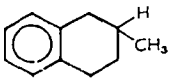
Work by Curtin on aldehydes having more than one β-aryl substituent is summarized in equations (17) to (22)[62,66]. The yields quoted are those obtained when about 20 mole percent di-*t*-butyl peroxide was used. Only rearranged hydrocarbons were isolable from the monomeric fraction obtained from β,β,β-triphenylpropion-

TABLE 2. Effect of gross structural changes on neophyl rearrangement.

Compound	Treatment[a]	% CO	% RH[b]	% rearr.	Ref.
$PhC(CH_3)_2CH_2CHO$	A, 130°	100	90	53	68
	B, 130°	98	71	83	
 (**8**)	A, 140°	87	74	63	67
	B, 132°	77	58	92	
	C, 160°	64	64	3	
 (**9**)	A, 140°	48	47	89	67
	B, 132°	43	42	94	
	C, 160°	22	21	50	
 (**10**)	A, 160°	85	76	35[c]	70

[a] Treatment A, neat aldehyde + 10–20 mole % t-Bu_2O_2; B, 1 M solution in PhCl; C, 20 mole % PhSH added, neat aldehyde.

[b] Percent yield of monomeric hydrocarbons.

[c] Rearrangement product is 

aldehyde (**11**)[62,66] and its α-methyl derivative (**12**)[62]. The indanone isolated in the decarbonylation of **11** evidently resulted from an internal attack of the acyl radical at the *ortho* position of the ring[66]. Further examples of this sort of reaction will be given later. In the decarbonylation of the nitro derivative **13** only a product of preferential migration of the *p*-nitrophenyl group was isolated, in very small yield (equation 19)[66]. It is interesting that the diaryl aldehyde **14** gave only *unrearranged* hydrocarbon, although 'it is possible that the rearranged hydrocarbon is present to the extent of as much as 15%[62].' By way of contrast, the β-methyl compound **16** gave only rearranged product, but it was entirely dimeric[62]. Evidently, chain-perpetuating hydrogen abstraction by rearranged radical $PhCH_2\dot{C}(CH_3)Ph$ was not competitive with its dimerization. That decarbonylation of **14** did not proceed with hydrogen migration was

evidenced by the results of equation (21), no detectable amount of deuterium migration having occurred[66].

$$\underset{(\mathbf{11})}{Ph_3CCH_2CHO} \xrightarrow{20\%\ t\text{-}Bu_2O_2,\ 140^\circ} \underset{(40\%)}{\mathbf{11}} + \underset{(32\%)}{CO} + \underset{(20\%)}{Ph_2CHCH_2Ph}$$

$$+ \underset{(4\%)}{Ph_2C{=}CHPh} + \underset{(3\%)}{\text{2,2-diphenylindanone}} \qquad (17)$$

$$Ph_3CCHCHO \longrightarrow \underset{(\mathbf{12})}{\mathbf{12}} + \underset{(44\%)}{CO} + \underset{(36\%)}{Ph_2CHCH(CH_3)Ph} + \underset{(17\%)}{Ph_2C{=}C(CH_3)Ph} \qquad (18)$$

$$\underset{(\mathbf{13})}{p\text{-}NO_2C_6H_4C(Ph)_2CH_2CHO} \longrightarrow \underset{(50\%)}{\mathbf{13}} + \underset{(11\%)}{CO} + \underset{(3{\cdot}3\%)}{Ph_2C{=}CHC_6H_4NO_2} \qquad (19)$$

$$\underset{(\mathbf{14})}{p\text{-}CH_3OC_6H_4CH(Ph)CH_2CHO} \longrightarrow \underset{(40\%)}{\mathbf{14}} + \underset{(40\%)}{CO} + \underset{(36\%)}{p\text{-}CH_3OC_6H_4CH(Ph)CH_3} \qquad (20)$$

$$\underset{(\mathbf{15})}{p\text{-}CH_3OC_6H_4CD(Ph)CH_2CHO} \longrightarrow \underset{(46\%)}{\mathbf{15}} + \underset{(38\%)}{CO} + \underset{(29\%)}{p\text{-}CH_3OC_6H_4CD(Ph)CH_3} \qquad (21)$$

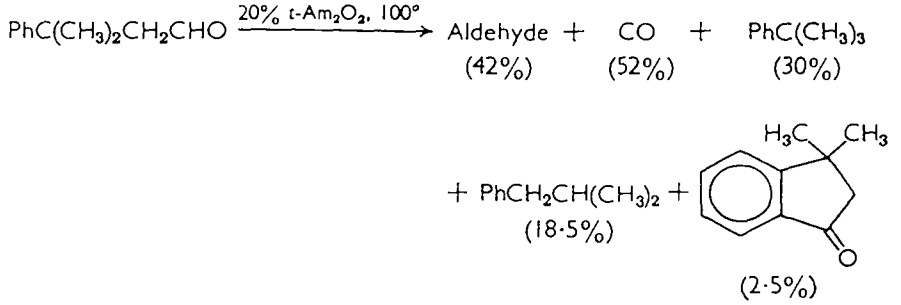
$$\underset{(\mathbf{16})}{Ph_2C(CH_3)CH_2CHO} \longrightarrow \underset{(66\%)}{\mathbf{16}} + \underset{(31\%)}{CO} + \underset{(34\%)}{PhCH_2C(CH_3)(Ph)C(CH_3)(Ph)CH_2Ph} \qquad (22)$$

Extensive dimer formation was encountered by Bonner and Mango in the decarbonylation of a 1 M solution of 2,3,3-triphenylpropanal[72]. The hydrocarbon product consisted of 85% dimer and 15% monomer, of which 5% was the disproportionation product, 1,1,2-triphenylethene. The results indicate that dimerization of the

$$Ph_2CH{-}CH(Ph)CHO \xrightarrow[o\text{-}Cl_2C_6H_4]{t\text{-}Bu_2O_2,\ 170^\circ} Ph_2CHCH_2Ph + Ph_2C{=}CHPh + (Ph_2CHCH(Ph))_2$$

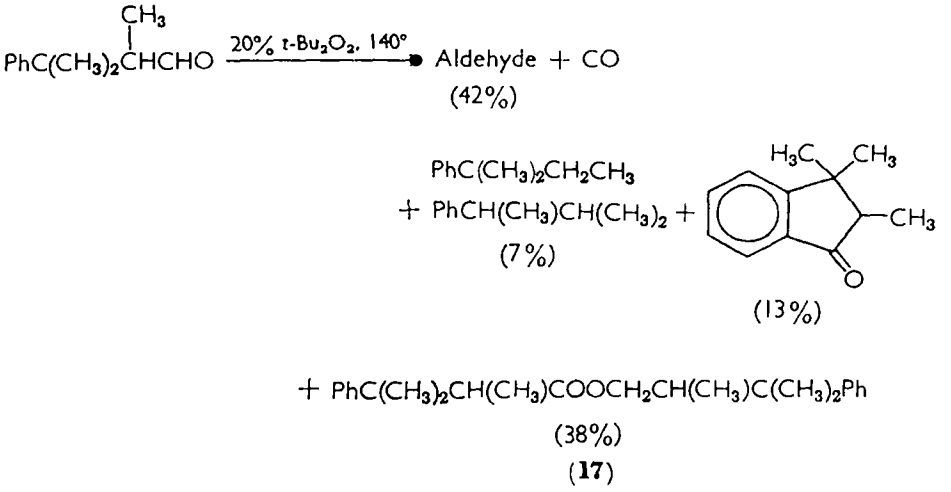
$Ph_2CH\dot{C}HPh$ radical takes precedence over its chain-propagating abstraction of hydrogen from the aldehyde. Hence abstraction of aldehydic hydrogen is largely by chain-initiating radicals, *t*-BuO· and CH_3·[72]. As expected, the yield of monomeric hydrocarbon was increased (to 37%) and that of dimer decreased (to less than 22%) on the addition of 5 mole percent of the more efficient hydrogen-transfer reagent, thiophenol. By using α-^{14}C-labeled aldehyde, the authors were able to establish the extent of phenyl migration, 4·9% at 155–165° and 13·9% at 176–184°, with 5 mole percent thiophenol present. This confirmed that radical stability and relief of steric strain are not uniquely important in promoting radical rearrangement[65].

The extensive formation of products in which the carbonyl group is retained accompanied a number of decarbonylations carried out by Urry, Trecker, and Hartzler[75]. Indanone formation occurred in 5% yield, based on aldehyde consumed, when β-phenylisovaleraldehyde was treated with 20 mole percent di-*t*-amyl peroxide at 100° (equation 23). This product had not been encountered in



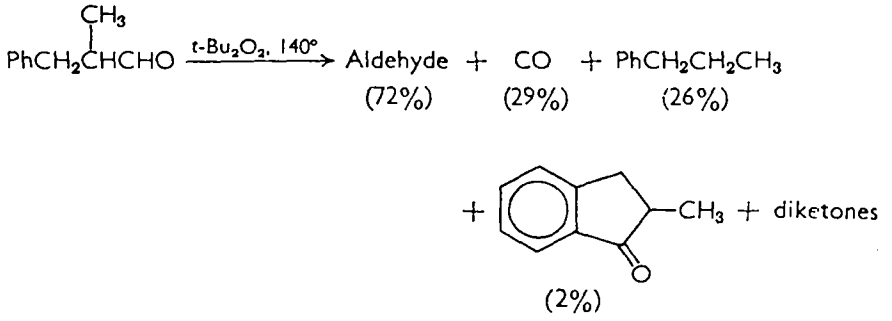
(23)

previous decarbonylations of the aldehyde at 130° or higher[60,63,68,70], although Curtin found concurrent indanone formation together with decarbonylation of β,β,β-triphenylpropionaldehyde[66]. The relative percentage of rearranged hydrocarbon, isobutylbenzene, was also less at the lower temperature (cf. refs. 68, 70). Indanone formation was extensive and the hydrocarbon yield very low in the treatment of α-methyl-β-phenylisovaleraldehyde with di-*t*-butyl peroxide (equation 24)[75]. The main product was the ester **17**. It was apparently formed via acyl radical attack on the oxygen atom of an aldehyde molecule: $R\dot{C}O + RCHO \rightarrow O{=}C(R)O\dot{C}HR$[75]. When the aldehyde was diluted to 1 M in chlorobenzene, the yield of bimolecularly formed ester was reduced somewhat (46%, based on aldehyde consumed) and that of the hydrocarbons was increased (27%, with 70%



(24)

rearrangement). The less highly substituted β-phenyl-α-methylpropionaldehyde gave a good yield of unrearranged hydrocarbon and only 2% indanone (equation 25)[75]. The γ-phenyl aldehyde **18**



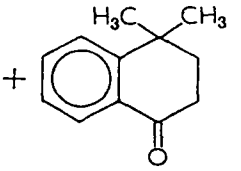
(25)

gave appreciable quantities of the tetralone **19** and the ketone **20**[75]. Apparently, the intermediate acyl radical underwent intramolecular acyl radical attack at both the 2- and 1-positions of the aromatic ring, the latter reaction leading to the ketone (equation 27). Of further interest is the fact that the intermediate γ-phenylpropyl radical failed to give any detectable 1,3-phenyl migration, only unrearranged hydrocarbon being found among the decarbonylation products. Slaugh also had found no 1,3-phenyl migration in the decarbonylation of α-^{14}C-labeled γ-phenylbutyraldehyde[76].

Although no 1,3-phenyl migrations in alkyl radicals have been

$$PhC(CH_3)_2CH_2CH_2CHO \xrightarrow{t\text{-}Am_2O_2,\ 100^\circ} \underset{(42\%)}{\text{Aldehyde}} + \underset{(18\%)}{CO} + PhC(CH_3)_2CH_2CH_3\ (17\%)$$

(18)



(18%)

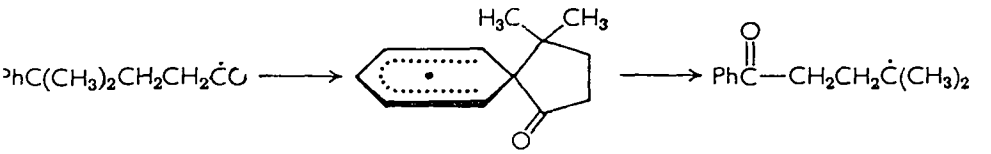
(19)

$$+\ PhCOCH_2CH_2CH(CH_3)_2$$

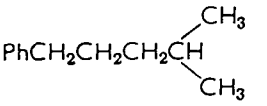
(18%)

(20)

(26)



(27)



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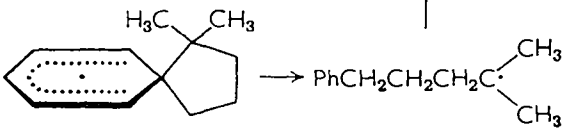
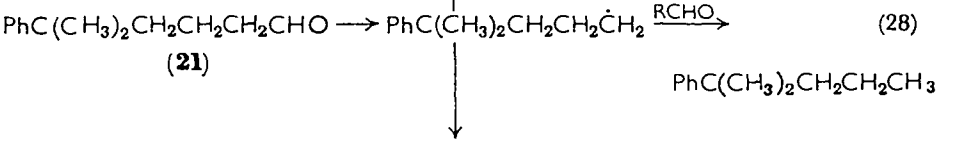
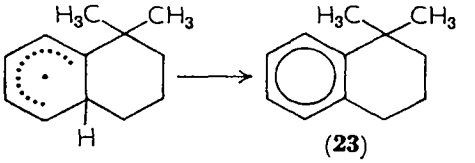




(21)

$$\xrightarrow{RCHO} PhC(CH_3)_2CH_2CH_2CH_3$$

(28)



(23)

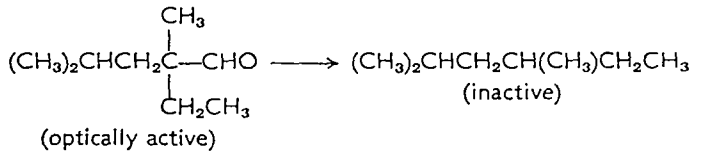
reported, an instance of 1,4-phenyl migration was found by Winstein[64]. Decarbonylation of the δ-phenyl aldehyde **21** led to the mixture of products shown in equation (28). Apparently, intramolecular radical attack at the 1-position (Ar_1–5 involvement) led to the rearranged hydrocarbon **22**, and attack at the 2-position (Ar_2–6 involvement) led to the tetralin **23**[64].

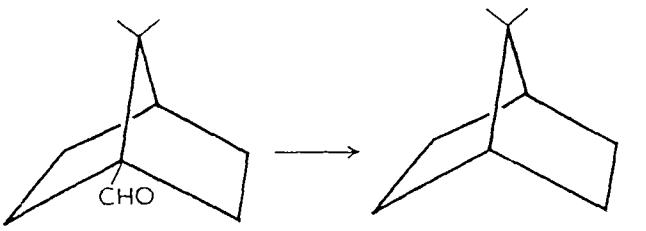
Wilt has recently made an attempt to detect 1,2-phenyl migration from silicon to carbon. However, treatment of Ph_3SiCH_2CHO with di-*t*-butyl peroxide at 150° yielded only the unrearranged product, methyltriphenylsilane, in 48% yield[83b]. This contrasts with the decarbonylation of the carbon analog, Ph_3CCH_2CHO, which yielded only rearranged hydrocarbon[62,66]. Wilt also found no oxygen-to-carbon migration in the decarbonylation of phenoxyacetaldehyde, the only monomeric product being anisole[83c].

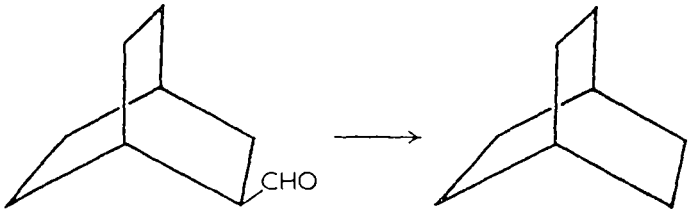
2. Nonphenylated aldehydes

Decarbonylations of nonphenylated aldehydes have been carried out almost exclusively with di-*t*-butyl peroxide. When the initiators dimethyl α,α′-azobisisobutyrate and α,α′-azobisisobutyronitrile were used with a number of aliphatic aldehydes at 80–110°, only very low yields of carbon monoxide and alkane (3–8%) were obtained[77]. When benzyl mercaptan (optimum amount, ca. 5 mole percent) was also added, the carbon monoxide yields increased to 33–80%, but no mention was made of the hydrocarbon yields[78]. Carbon tetrachloride effectively stopped the decarbonylation chain by reacting with the acyl radical to yield the acid chloride[77], confirming the observation of Winstein and Seubold[60].

In 1952 Doering, Faber, Sprecher, and Wiberg carried out the following decarbonylations, using neat aldehyde and di-*t*-butyl peroxide at reflux temperature[79]:







The first reaction confirmed that an intermediate alkyl radical, unable to maintain an asymmetric configuration, is formed. The second showed that there is no particular inhibition to the formation of a bridgehead radical, as there is to the formation of a bridgehead carbonium ion. The third indicated that rearrangement of the 2-bicyclo[2.2.2]octanyl radical is not competitive with its abstraction of a hydrogen atom from a molecule of the aldehyde. This contrasts with the extensive rearrangement occurring in carbonium ion reactions at the same center[79]. Indeed, no instance of a 1,2-alkyl migration has yet been encountered in aldehyde decarbonylation, including neopentyl and bicyclic systems of the type particularly prone to rearrangement in heterolytic carbonium ion type processes*. In all cases the unrearranged hydrocarbon was the principal monomeric product. Side-products resulting from competitive intra- or intermolecular reactions of the generated alkyl radical were noted in some instances.

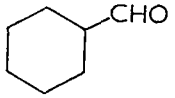
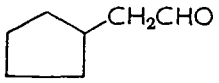
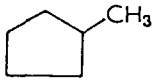
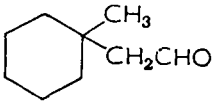
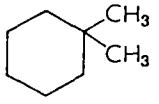
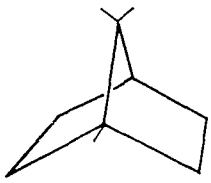
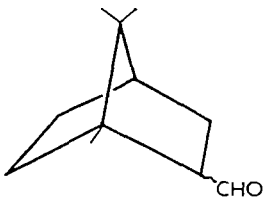
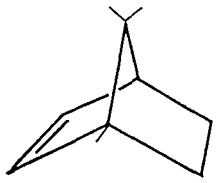
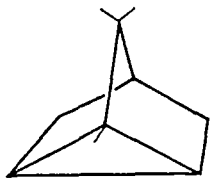
The neopentyl-type aldehydes, examples 6 to 8 of Table 3, decarbonylated without any particular difficulty to yield the unrearranged hydrocarbon as the sole isolable monomeric product. Similarly, the bicyclic aldehyde (example 9) gave mainly bornane and no detectable amount of rearranged product such as isocamphane or isocamphene[71]. Bornene, a disproportionation product, was found in small yields and a trace of a tricyclene was also obtained. Increasing the mole percentage of di-*t*-butyl peroxide decreased the chain length, leading to an increase in the yield of bornene and tricyclene as well as of products resulting from radical–radical combinations.

Unsaturated bicyclo aldehydes (examples 11 to 13) also failed to yield rearranged monomeric products[83a]. The unsaturated aldehydes (examples 10 to 12) in general gave low yields of carbon monoxide

* For an explanation, in molecular-orbital terms, of the stability toward rearrangement of alkyl radicals as compared to carbonium ions, see C. Walling in *Molecular Rearrangements*, Part I (Ed. P. de Mayo), Interscience Publishers, New York, 1963, pp. 427–431.

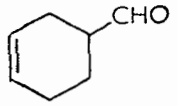
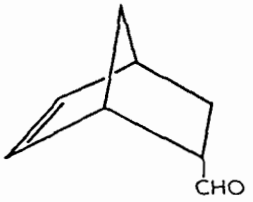
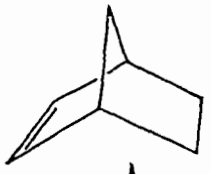
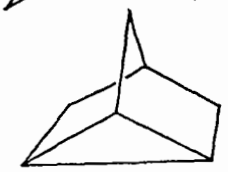
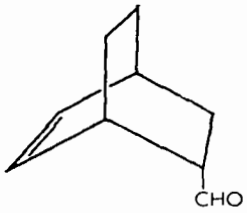
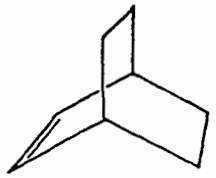
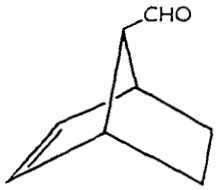
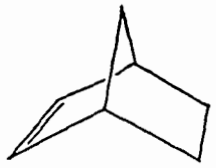
Examples that have been investigated include those listed in Table 3.

TABLE 3. Decarbonylation of nonphenylated aldehydes[a].

Example	RCHO	Temp. (°C)	CO (%)	Monomeric products[b]	Ref.
1[c]	n-C_3H_7CHO	115°	70	$CH_3CH_2CH_3$(70), $(C_3H_7)_2CHOH$ (9)	91
2	n-$C_6H_{13}CHO$	130°	35	n-C_6H_{14} (34), (n-C_6H_{14})$_2$CHOH	91
3[d]	$(PhCH_2)_2CHCH_2CHO$	160°	78	$(PhCH_2)_2CHCH_3$ (59)	76
4[e]		135°	90	 (52)	80
5		135°	76	 (43)	80
6	$CH_3CH_2C(CH_3)_2CH_2CHO$	135°	76	$CH_3CH_2C(CH_3)_3$	80, 81
7	$(CH_3)_3CCHCHO$ $\vert$ CH_3	130°	80	$(CH_3)_3CCH_2CH_3$ (83)	75
8		140°	95	 (76)	82
				 (57)	
9		138°	74	 (4·3)	71
				 (0·3)	

(*Table continued*)

TABLE 3—*continued*

Example	RCHO	Temp. (°C)	CO (%)	Monomeric products[b]		Ref.
10[e]		170°	30		(27)	83a
11[e]		170°	14		(3·6)	83a
					(5·0)	
12[e]		170°	20		(5·1)	83a
13		170°	80		(2·3)	83a

[a] Except where noted, at least 20 mole percent di-*t*-butyl peroxide was used.
[b] Percent yields, where reported, are given in parentheses.
[c] 10 mole percent of di-*t*-butyl peroxide used.
[d] 1 M solution in *o*-dichlorobenzene.
[e] Substantially the same results were also obtained in chlorobenzene solvent.

and unrearranged hydrocarbon. The formation of residual dimeric and polymeric products was extensive. In examples 10 to 12 these

were carbonyl compounds, evidently the result of addition of generated acyl radicals to the olefinic bond of starting material[83a]. This is not surprising in view of the fact that acyl addition to the carbon–carbon double bond is carried out by di-*t*-butyl peroxide treatment of aldehydes in the presence of olefins (equation 29)[84–87].

$$R^1CHO + R^2CH{=}CH_2 \xrightarrow{t\text{-}Bu_2O_2,\ \Delta} R^2CH_2CH_2COR^1 + \text{some decarbonylation and polymerization product} \quad (29)$$

Cyclohexene is noted as failing in this reaction, however, and the best yields are obtained from long-chain aldehydes and long-chain terminal olefins[84]. Anchimeric assistance was suggested as a cause of the large yield of carbon monoxide obtained in example 13 as compared to examples 10 to 12[83a]. The yield of monomeric hydrocarbon, norbornene, was very low however. The resinous reaction residue contained oxygen but had only weak carbonyl absorption in the infrared[83a].

Examples 1 and 2 are of interest because carbinols were formed as secondary products. Their formation indicates that the chain-carrying alkyl radicals in part added to the carbon of the carbonyl group: $R\cdot + RCHO \rightarrow R_2CHO\cdot$. By way of contrast, the acyl radical obtained from $PhC(CH_3)_2CH(CH_3)CHO$[75] (discussed previously) and that obtained from benzaldehyde[88,89] preferentially attack the oxygen of the carbonyl group: $R\dot{C}O + RCHO \rightarrow RC(O)O\dot{C}HR$. Apparently, ester-type stabilization in the transition state is a factor in the latter instances.

Instances of vinyl group migration have been encountered. Treatment of 3-methyl-4-pentenal with di-*t*-butyl peroxide at 130° yielded carbon monoxide (40%) and a mixture of 1-pentene and 3-methyl-1-butene (yields unspecified). The ratio of rearranged to unrearranged hydrocarbon was 10·8. Similar behavior was shown by 3-methyl-4-hexenal[209].

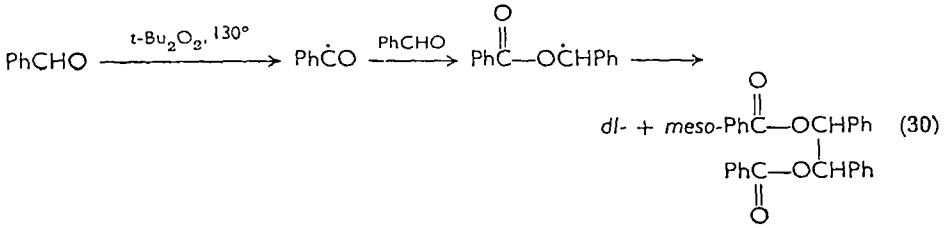
The behavior of a few cyclopropyl aldehydes has been examined. Formylcyclopropane on treatment with di-*t*-butyl peroxide in diphenyl ether at 135° gave cyclopropanecarboxylic acid (50% yield), but only a trace of carbon monoxide and no cyclopropane or propylene[90]. The high energy of the transition state for decarbonylation relative to that for carboxylic acid formation may be a reflection of the cyclopropyl-radical character of the former. The cyclopropyl radical has a high energy relative to acyclic alkyl radicals[90]. The 1-methyl and 1-phenyl derivatives decarbonylated normally (the

former giving 40% methylcyclopropane and 15% of the carboxylic acid and the latter, 55% phenylcyclopropane and 9% of the acid) evidently due to the stabilizing influence of the substituent on the cyclopropyl radical[90]. Although ring opening of the cyclopropyl radicals would appear to be energetically favored[90], no ring-opened products were found.

The ring-opened product, 1-butene, was the only four-carbon compound found in the decarbonylation of cyclopropylacetaldehyde[75]. Similarly, dimethylcyclopropylacetaldehyde yielded 2-methyl-2-pentene[92]. When benzyl mercaptan was added as a hydrogen-transfer agent to divert the initially formed dimethylcyclopropylmethyl radical, some isopropylcyclopropane was obtained as well.

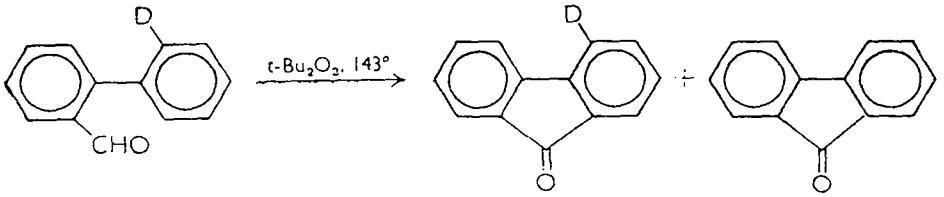
B. Aromatic Aldehydes

Aromatic aldehydes fail to decarbonylate when treated with various radical initiators[88,89]. Products in which the carbonyl group is retained are isolated however, indicating that the acyl radical is initially formed but that the activation energy for its decarbonylation ($ArC\dot{O} \rightarrow Ar^{\bullet} + CO$) is relatively high. This is comparable to the situation encountered with formylcyclopropane[90] (see above). Thus, benzaldehyde and excess di-*t*-butyl peroxide gave *sym*-diphenylethyleneglycol dibenzoate, in 85% yield based on peroxide consumed, presumably by the path of equation (30)[88]. The attack of acyl radical on the oxygen of an aldehyde molecule has been encountered in one instance of an aliphatic aldehyde, α-methyl-β-



phenylisovaleraldehyde[75] (see equation 24 above).

Intramolecular acylation occurred when 2-phenylbenzaldehyde



was heated with di-*t*-butyl peroxide, resulting in a 40% yield of fluorenone, based on aldehyde consumed[93]. The deuterium isotope effect in the ring closure (k_H/k_D) was 1·38.

V. THERMAL DECARBONYLATION

A variety of procedures have been employed in the thermal decomposition of aldehydes and ketones. Flow techniques were widely employed in early work. With involatile compounds, condensed phase decompositions have been carried out. Most of the recent work has dealt with gas-phase mechanistic studies. The reaction bulb kept at constant temperature is part of a vacuum-line system that enables measurements of pressure change and the periodic bleeding off of samples of the reaction mixture. With the development of mass spectrometric and gas chromatographic methods of analysis, the variations in concentration of one to several volatile components have been followed.

A. Aldehydes

Most of the discussion here deals with the gas-phase kinetics of the decarbonylation of aliphatic aldehydes. A major overall reaction in most instances is: $RCHO \rightarrow CO + RH$. However, the decompositions are usually complex and other products are found in growing number as the size of the aldehyde increases. Steacie has written, 'The acetaldehyde decomposition is remarkable for lack of agreement on both mechanism and experimental fact, and for the complications involved'[57]. This fairly well characterizes the entire area of gas-phase aldehyde decarbonylations.

The decarbonylations are usually carried out at temperatures around 500° with aldehyde pressures ranging from about 50 to 300 mm. The course of events is often influenced by the products formed and by the change in aldehyde pressure as reaction proceeds. As a consequence, kinetic studies have involved product analyses and pressure-change measurements only over the initial portion of the reaction. The dependence of the reaction on aldehyde concentration has been determined by measuring initial rates at a number of different initial pressures of aldehyde. The kinetic order thus determined varies with the nature of the aldehyde and can also depend upon the pressure and upon the temperature. The effect of adding various substances, particularly nitric oxide, propylene, and inert gases, has been studied extensively. Nitric oxide in small amounts

generally has an inhibitory effect and when added in substantially larger amounts an accelerating effect. Propylene in relatively large amounts has an inhibitory effect. There is some disagreement as to whether the maximally inhibited reaction is largely molecular or radical-chain in nature. However, there appears to be general agreement that the uninhibited reaction is largely a fairly long chain radical process. As a basis mechanism, all recent authors use the Rice–Herzfeld scheme shown below[57,94]. This mechanism must be regarded as a gross oversimplification. For one thing, larger alkyl radicals formed in the initiation step can undergo splitting reactions as well as the chain-propagating hydrogen abstraction of equation (34)[95]. Also, different initiation and terminating steps have been proposed. In other words the relatively simple Rice–Herzfeld scheme has been added to and modified in various ways, depending upon the investigator and the structure of the aldehyde.

Initiation

$$RCHO \longrightarrow R\cdot + \cdot CHO \tag{31}$$

$$\cdot CHO + X \longrightarrow CO + H\cdot \tag{32}$$
(X = second body or wall)

$$H\cdot + RCHO \longrightarrow H_2 + R\dot{C}O \tag{33}$$

Propagation

$$R\cdot + RCHO \longrightarrow RH + R\dot{C}O \tag{34}$$

$$R\dot{C}O + X \longrightarrow R\cdot + CO \tag{35}$$

Termination

$$R\cdot + R\cdot \longrightarrow RR \text{ (or } RH + R_{(-H)}) \tag{36}$$

$$R\cdot + R\dot{C}O \longrightarrow RCOR \tag{37}$$

$$R\dot{C}O + R\dot{C}O \longrightarrow RCOCOR \tag{38}$$

I. Acetaldehyde

The thermal decomposition of acetaldehyde yields carbon monoxide and methane in nearly quantitative yield. Evidently the intermediate methyl radicals largely undergo chain-propagating hydrogen abstraction (equation 34). As predicted by a Rice–Herzfeld-type reaction scheme, very small amounts of hydrogen and ethane also should arise, and these have recently been estimated[96–99]. Other products obtained in very small amount include acetone, ethylene, and carbon dioxide[98]. The initial overall reaction order at a number of acetaldehyde pressures appears to be fairly cleanly 1·5 with an overall activation energy of about 47 kcal/mole[57,97,99,100]. The unadulterated Rice–Herzfeld mechanism is consistent with the reaction

order, provided the second-order radical-coupling step (equation 36) is the main terminating step.

Trenwith found that hydrogen production, after an initial induction period, was second-order in concentration of acetaldehyde[97]. On this basis he concluded that the initiation step is second-order in acetaldehyde (the second aldehyde molecule acting merely as a necessary second body), rather than the simple first-order reaction in the Rice–Herzfeld scheme:

$$CH_3CHO + X \longrightarrow CH_3\cdot + \cdot CHO + X$$
(X can be CH_3CHO)

Laidler found that ethane production is second-order in acetaldehyde and also concluded that initiation is second-order in acetaldehyde[99]. However, he postulated a specific role for the second aldehyde molecule, that of a hydrogen-atom transfer agent (equation 39).

$$\begin{array}{ccccc} CH_3CHO + CH_3CHO & \longrightarrow & CH_3\dot{C}O & + & CH_3\dot{C}HOH \\ & & \downarrow & & \downarrow \\ & & CH_3\cdot + CO & & CH_3CHO + H\cdot \end{array} \qquad (39)$$

To preserve the overall 1·5 kinetic order, Laidler postulated that termination is largely by alkyl radical combination but that it requires a third body (equation 40). Trenwith included this third-order termination process in his scheme[97,98], but noting that acetone

$$CH_3\cdot + CH_3\cdot + X \longrightarrow CH_3CH_3 + X \qquad (40)$$
(X can be CH_3CHO)

$$CH_3\dot{C}O + CH_3\cdot \longrightarrow CH_3COCH_3 \qquad (41)$$

production is appreciably greater than ethane production, postulated that equation (41) represents the main chain-termination step[98]. This termination, coupled with second order initiation, also would preserve the overall $\frac{3}{2}$ order. However, as pointed out by Laidler, acetone also could have arisen via addition of methyl radicals to acetaldehyde (equation 42)[99].

$$CH_3CHO + CH_3\cdot \rightleftharpoons (CH_3)_2CHO\cdot \rightleftharpoons CH_3COCH_3 + H\cdot \qquad (42)$$

The induction period in the formation of hydrogen is attributed by Trenwith to a measurable time lapse before hydrogen atoms reach steady-state concentration, i.e. to a lag in the reaction $\cdot CHO$ (at wall) $\rightarrow CO + H\cdot$[97]. Laidler attributes it to the time required before equilibrium is reached in the reaction $CH_3CHO + H\cdot \rightleftharpoons CH_3\dot{C}HOH$[99].

The addition of fairly large quantities of inert gas, i.e. ethane[98,99] and methane, nitrogen, or carbon monoxide[99] (there is disagreement about the effect of CO_2[98,99]), decreases the rate and increases the reaction order (to about 1·6). This was attributed to a greater foreign body effect in the proposed third-order termination step (equation 40, X = foreign gas or acetaldehyde) than in the proposed second-order initiation step[98,99]. In the Laidler mechanism for initiation (equation 39), initiation should be unaffected since a specific role is assigned to the second acetaldehyde molecule. Certain details of the events that occur in the presence of inert gases have been considered to favor one or the other mechanism[98,99].

Work by Rabinovitch makes it appear unlikely that methyl radical coupling is largely third-order under the conditions used[101]. Nor does it seem likely that a second body, acting nonspecifically, would be required in the initiation step.

2. Propionaldehyde

The decomposition of propionaldehyde at around 500° has been reported to be first-order[102], 1·5 order[103,104], and most recently between 1·25 and 1·30 order[95,105]. The major products are carbon monoxide and ethane, and considerable amounts of ethylene and hydrogen are produced together with smaller amounts of methane[102,103,105]. The ethylene (and hydrogen) to ethane ratio increases with temperature[105]. It seems generally agreed that the ethyl radical is the most abundant one and that ethyl radical combination is a predominant chain-terminating step[95,103-106]. This conclusion is supported by the finding of n-butane to the extent of 0·05% of the total products[105]. Apparently ethyl radical decomposition ($CH_3\dot{C}H_2 \rightarrow CH_2{=}CH_2 + H\cdot$) competes with hydrogen abstraction ($CH_3\dot{C}H_2 + CH_3CH_2CHO \rightarrow CH_3CH_3 + CH_3CH_2\dot{C}O$), accounting for the formation of appreciable amounts of ethylene and hydrogen[95,105]. Since the latter reaction depends upon propionaldehyde and the former does not, it would be expected that the ratio of ethane to ethylene (and hydrogen) production should increase with propionaldehyde pressure. This has been observed; at 540° and 6% decomposition, the ratio of ethane to ethylene increases from about 3 at 20 mm pressure of propionaldehyde to about 12 at 200 mm pressure[105]. The production of ethylene and hydrogen by ethyl radical decomposition has the effect of lowering the observed overall order of propionaldehyde decomposition. The overall rate expression has been divided into two parts, $v = k_1'[\mathrm{EtCHO}]^{\frac{3}{2}} +$

$k_2'[EtCHO]^{\frac{1}{2}}$, where the first term represents ethane production and the second term ethylene production[105]. It was estimated that a nonradical-chain molecular reaction ($CH_3CH_2CHO \rightarrow CH_3CH_3 + CO$) could contribute as much as 10% (subject to 'serious error')[105]. The yield of hydrogen runs 30 to 80% higher than that of ethylene, and some reactions were suggested to account for this[105].

Inert gas (CO_2 or ethane) had no effect on the rate at 520°[105]. On this basis Laidler concluded that the initiation step is first-order (equation 31) and the termination step, ethyl radical combination, second-order (equation 36). Evidence that ethyl radical combination is second-order in other systems was cited. In other words the simple Rice–Herzfeld mechanism (equations 31–36) was assigned, with the addition of the ethyl radical decomposition step. However, it was put forth 'as representing the main features of the reaction' and as 'undoubtedly an oversimplification'[105].

There appears to be an inconsistency in the assignment on the one hand of a second-order initiation step (whether or not the second aldehyde molecule plays a specific role) and a third-order termination step for acetaldehyde, and, on the other hand, a first-order initiation and a second-order termination for propionaldehyde. One would not expect the two systems to be all that different.

3. Butyraldehyde and isobutyraldehyde

At 522·5°, butyraldehyde decomposition exhibits a change from approximately first-order at low pressure to higher orders at a pressure of about 200 mm[95]. Carbon monoxide, methane, and ethylene account for some 80% of the products. Lesser products were propane, propylene, and hydrogen, the latter two formed in equal amounts. Ethane and acrolein also were found. In terms of the Rice–Herzfeld scheme it appears that hydrogen abstraction by the intermediate propyl radical (equation 34) is not very competitive with its fragmentation into ethylene and methyl radical, which largely carries the chain. Thus, the yield of propane is small and that of ethylene and methane large. The splitting of the propyl radical to propylene and hydrogen atom is much less extensive. As expected, the relative yield of propane increased with aldehyde pressure, from 19% at 50 mm to 40% at 200 mm.

The decomposition of isobutyraldehyde at 500° showed an order of about 1·1 over a wide pressure range[95]. Relative to carbon monoxide, the following yields were obtained at an aldehyde pressure of 30 mm: propylene, 57%; hydrogen, 56%; propane, 23%;

methane, 12%; ethane, 5%. At 200 mm, the relative yields of the same compounds were 30%, 29%, 71%, 8%, and 3%, respectively. The material balance is only fair[95]. The fact that appreciable propane is formed indicates that hydrogen abstraction (equation 34) is more competitive with radical decomposition when the radical is the more stable isopropyl rather than the propyl radical. The product proportions indicate that the preferential decomposition course of isopropyl radical is $CH_3\dot{C}HCH_3 \rightarrow CH_3CH{=}CH_2 + H\cdot$. This reaction must be the principal source of hydrogen since the yields of propylene and hydrogen are practically the same. At higher aldehyde pressures one would expect increased hydrogen abstraction by the isopropyl radical, relative to splitting. This is borne out by the finding of an increased amount of propane and a decreased amount of propylene and hydrogen at higher aldehyde pressure[95].

4. Inhibition by propylene

The addition of propylene, or isobutylene, reduces the decarbonylation rates of the butyraldehydes, as well as of propionaldehyde and acetaldehyde, to well-defined limits[95,96]. Large amounts of inhibitor are required; e.g. maximum inhibition of the decomposition of isobutyraldehyde at 50 mm pressure required about 200 mm of propylene[95]. The extent of inhibition is not dramatic. At 522·5° and an aldehyde pressure of 100 mm, the ratio of maximally inhibited to uninhibited rate is 0·37, 0·71, 0·24, and 0·69 for acetaldehyde, propionaldehyde, n-butyraldehyde, and isobutyraldehyde, respectively[95]. The maximally inhibited reactions approach $\frac{3}{2}$ order. A product analysis made on isobutyraldehyde showed the product distribution to be dramatically changed in the inhibited reaction. Propane was now the major product, and hydrogen (and presumably also propylene) a minor product. Inhibition probably involves capture of chain-propagating alkyl radicals by propylene; e.g. $R\cdot + CH_3CH{=}CH_2 \rightarrow RH + \cdot CH_2CH{=}CH_2$. In the case of isobutyraldehyde the intermediate propyl radical evidently is largely captured before it has a chance to split[95]. The product distribution in propionaldehyde and n-butyraldehyde decomposition presumably should also be altered similarly by added propylene, but no values were reported.

It is not certain whether the maximally inhibited reaction is a molecular or radical-chain process. However, if the much less reactive allyl radical is able to carry the chain, a Rice–Herzfeld mechanism can be envisaged for the inhibited reaction, with allyl

radicals involved in the hydrogen abstraction step (34) and termination by allyl radical combination[95].

5. The effect of nitric oxide

Extensive investigations of the effect of nitric oxide on aldehyde decarbonylation have been made[57,95,96,107–109]. The situation is even more complicated than in the absence of nitric oxide. Small amounts of NO reduce the rate somewhat (the 'inhibited reaction') and the introduction of increasingly larger amounts of NO increases the rate beyond its original value (the 'catalyzed reaction'). Inhibition is not dramatic: at 525° and an aldehyde pressure of 100 mm, the ratio of maximally inhibited to uninhibited rate is 0·47, 0·34, and 0·56 for propionaldehyde, butyraldehyde, and isobutyraldehyde, respectively[95]. The amount of NO required to reach minimum rate varies from less than 1 mm for acetaldehyde to approximately 2 mm for isobutyraldehyde[95]. The extent of inhibition decreases with temperature and aldehyde pressure[95,96,108,109], and for acetaldehyde the minimum disappeared entirely at sufficiently high temperature (525°) and pressure (100 mm)[96,108]. The reaction rate tends to be $\frac{3}{2}$ order in aldehyde at the minimum[95,107–109], but shows more complicated kinetics on either side of the minimum[108,109]. The accelerating effect of added large amounts of NO is not very large either; for example, with acetaldehyde at 525° and 110 mm pressure, the rate with 50 mm added NO was only three times the rate without any added NO[95].

There is disagreement as to whether the maximally inhibited reaction is largely molecular[95,96] or radical-chain with the rate minimum a balance of two opposing effects[95,107–109]. Of course, if there is an appreciable contribution by molecular reactions, this would play havoc with many of the conclusions reached about the uninhibited reaction. Inhibition by NO may be the result of its combination with chain-propagating radicals, $R\cdot + NO \rightleftharpoons RNO$[95,108,109], but the question remains whether complete chain suppression results. The possibility that the alkyl nitroso compounds rearrange to oximes which then undergo further decomposition has been considered[110]. However, there appears to be no great consumption of NO during decarbonylation[95,107–109]. Chain initiation by NO (equation 43) could account for its catalytic effect at higher NO pressures. Laidler added this step to his schemes for acetaldehyde and propionaldehyde decomposition and also included the termination steps of equations (44) and (45)[108,109]. In agreement with this he observed that the

rate of decarbonylation is proportional to the half-power of the NO concentration as well as the $\frac{3}{2}$ power of the aldehyde pressure in the catalytic region (high pressure of NO). Other details, such as the changing kinetics as NO is added, are considered to be in agreement with this[108,109].

$$NO + RCHO \longrightarrow HNO + R\dot{C}O \quad (43)$$

$$R\cdot + RNO \longrightarrow RR + NO \quad (44)$$

$$RNO + RNO \longrightarrow RR + 2\,NO \quad (45)$$

6. Formaldehyde

The thermal decomposition of formaldehyde gives largely carbon monoxide and hydrogen[111,112]. A complicating side-reaction is the production of methanol[112–115]. The yield of methanol is about 20% at 547°, but decreases with increasing temperature[114]. Trace amounts of methane and carbon dioxide have also been found[111]. The kinetics of the decarbonylation have received relatively little study, and disagreement exists as to whether the reaction is molecular[112] or radical-chain[114]. Fletcher found second-order kinetics and concluded that the reaction was a bimolecular homogeneous process between 500° and 600°[112]. Klein, Scheer, and Schoen also found that at 547° and a formaldehyde pressure of 140 mm the formation of carbon monoxide and hydrogen is second-order in aldehyde and relatively insensitive to a change in the surface to volume ratio of the reaction vessel[114]. They concluded that a radical-chain process

$$CH_2O + CH_2O \xrightarrow{(wall)} H\dot{C}O + H\cdot + CH_2O$$

$$H\dot{C}O \longrightarrow H\cdot + CO$$

$$H\cdot + CH_2O \longrightarrow H_2 + H\dot{C}O$$

$$H\dot{C}O \xrightarrow{(wall)} \text{'Products'}$$

SCHEME 4.

predominates (Scheme 4). Evidence cited in support of a radical-chain mechanism was: (*a*) some sensitivity of the rate to the previous history and treatment of the reaction vessel, and (*b*) when mixtures of CH_2O and CD_2O were pyrolyzed, the ratio $P^2_{HD}/P_{H_2}P_{D_2}$ had a value of about four (i.e. 3·6) over a twenty-five fold variation in the initial P_{CH_2O}/P_{CD_2O} ratio[114]. This, it was claimed, excluded a molecular mechanism since 'the latter leads to a value of $P^2_{HD}/P_{H_2}P_{D_2}$ of

one or less. . .'. On the contrary, a bimolecular nonradical mechanism in which only HD is formed on reaction between CH_2O and CD_2O (such as a reaction proceeding through a cyclic six-membered transition state) also would be expected to give a value of about four for this ratio. This is because the collision probability for reaction between CD_2O and CH_2O is twice that for reaction between two CH_2O (or two CD_2O) molecules. Perhaps the most compelling reason for a radical-chain process is the analogy to the assigned mechanisms for homologous aldehydes (see above) and the mechanism assigned to the radical-sensitized decomposition of formaldehyde[115].

7. Other saturated aldehydes

The pyrolysis of isovaleraldehyde, reported in 1901[116], gave carbon monoxide, methane, propylene, ethylene, and butylenes. Hydrogen, ethane, and crotonaldehyde were identified as minor products.

Chloral has been decomposed at 445° to yield principally carbon monoxide (75% yield) and chloroform (20%)[117]. The low yield of chloroform was due to its subsequent decomposition to carbon, hydrogen chloride and hexachloroethane[117]. The decomposition was homogeneous and first-order in aldehyde, and could be initiated by isopropyl iodide[117] or nitric oxide[118], but not by nitrous oxide or oxygen[118].

The pyrolysis of cyclobutanecarboxaldehyde in the gas phase at 360–400° yielded only equal amounts of ethylene and acrolein in the early stages[119]. The decomposition was homogeneous, first-order, and not inhibited by nitric oxide or propylene. A simple unimolecular breakup of the aldehyde was postulated.

8. Aromatic aldehydes

Only benzaldehyde and furaldehyde have been studied, both to a very limited extent. Higher temperatures than for the aliphatic aldehydes are required. The gas-phase decomposition of benzaldehyde between 680 and 690° gave predominantly carbon monoxide and benzene[120]. Hydrogen, biphenyl, and a small amount of *p*-terphenyl have been noted[120,121]. The reaction is approximately first-order above 100 mm pressure and is partially inhibited by nitric oxide. The superposition of a radical-chain and a molecular reaction has been assumed[120,121].

A complex mixture of products was obtained in the pyrolysis of furaldehyde at 670 to 740°[122]. These include carbon monoxide and

lesser amounts of hydrogen, propylene, ethylene, and alkynes, alkenes, and alkanes of undetermined structure. No furan was found.

9. Unsaturated aldehydes

The gas-phase pyrolysis of unsaturated aldehydes leads to polymerization as well as decarbonylation. Acrolein at 530° and 150 mm gave mainly carbon monoxide, and presumably ethylene and butylene[123]. Hydrogen, methane, and ethane constituted about 25% of the gaseous products. In addition a dark solid (presumably polymer) was slowly deposited on the walls of the reaction vessel. The kinetics were very complicated, and no specific mechanistic assignments were made[123].

The decomposition of crotonaldehyde, which occurs at relatively low temperatures (140–400°), is apparently heterogeneous[124,125]. Carbon monoxide and propylene were obtained in high yield[124]. As the temperature was increased the propylene yield was reduced and hydrogen and methane yields increased.

Cinnamaldehyde, when passed through a hot tube, gave a 27% yield of styrene, benzene, and an unidentified styrene dimer[126]. Volatile components, obtained in 11·4% yield, consisted of 73% carbon monoxide, 9% hydrogen, 8·7% acetylene, 4% ethane, 3·1% benzene, and 2·1% methane.

B. Ketones

This section reviews a variety of thermal decomposition reactions of ketones, most of them leading to carbon monoxide production. The main discussion deals with the mechanistic work done on aliphatic ketones.

The thermal decomposition of aliphatic ketones proceeds at least in part with the intermediate formation of ketenes. Mechanistic

$$R^1CH_2COCH_2R^2 \longrightarrow R^1CH_3 + R^2CH_3 + R^1CH{=}C{=}O + R^2CH{=}C{=}O$$

$$R^2CH{=}C{=}O \text{ and } R^1CH{=}C{=}O \longrightarrow CO + \text{complex mixture}$$

discussion will be confined to the primary processes undergone by the ketones themselves. For discussion of ketene decomposition reactions the reader is referred to recent work by Young, and Guenther and Walters[127,128].

The fact that ketenes are intermediates and their decomposition closely follows upon their formation makes the study of ketone decomposition extremely complex. Although the evidence is not clear-cut,

it is generally accepted that ketenes are formed by radical-chain processes of the type proposed by Rice and Herzfeld for acetone[57,94].

$$CH_3COCH_3 \longrightarrow CH_3\dot{C}O + \cdot CH_3 \quad (46)$$

$$CH_3\dot{C}O \longrightarrow \cdot CH_3 + CO \quad (47)$$

$$\cdot CH_3 + CH_3COCH_3 \longrightarrow CH_4 + \cdot CH_2COCH_3 \quad (48)$$

$$\cdot CH_2COCH_3 \longrightarrow CH_2{=}C{=}O + \cdot CH_3 \quad (49)$$

$$\cdot CH_3 + \cdot CH_2COCH_3 \longrightarrow CH_3CH_2COCH_3 \quad (50)$$

$$\cdot CH_2COCH_3 + \cdot CH_2COCH_3 \longrightarrow CH_3COCH_2CH_2COCH_3 \quad (51)$$

$$\cdot CH_3 + \cdot CH_3 \longrightarrow CH_3CH_3 \quad (52)$$

With unsymmetrical ketones the problem of preferential hydrogen abstraction at one or the other α-position arises. Unfortunately, the specific composition of the mixtures of ketenes obtained as intermediates has not been determined in such instances. Instead, only the total concentration of 'acid-forming' materials has been followed. With larger ketones, products arising from abstractions of β-, γ-, etc., hydrogens are also conceivable, and the opportunity for the participation of molecular processes is enhanced. Secondary reactions, such as the splitting of larger alkyl radicals and condensation reactions, also add to the problems of mechanistic interpretation.

I. Acetone

The thermolysis of acetone proceeds in stages with the intermediate formation of ketene[57]:

$$CH_3COCH_3 \longrightarrow CH_4 + CH_2{=}C{=}O$$

$$CH_2{=}C{=}O \longrightarrow CO + \text{complex mixture}$$

Carbon monoxide thus originates largely in the second stage. Strictly speaking, the first stage is not a proper subject for this chapter, since it is not a decarbonylation reaction. Nevertheless, because of certain analogies to the thermal decarbonylation of simple aliphatic aldehydes, this reaction will be discussed. Only very early in the decomposition of acetone can the first stage be somewhat isolated from the second. However, after a time, ketene is decomposed as rapidly as it is formed[129]. The early onslaught of the second stage complicates the kinetics and conclusions based on product analysis. For example, at 500° the ratio of methane to carbon monoxide formed is 5–10 in the very early stages, and decreases to two after a few tenths of a percent reaction[130].

Rice and Herzfeld suggested the chain mechanism of equations

(46) to (50) for the first stage[94], which has an overall activation energy of about 68 kcal/mole[129]. Equation (50) was written as the only termination step in the early scheme. To this should be added the termination steps (51) and (52).

Summing up the evidence to 1954 on the first stage, Steacie concludes: '(*a*) Radicals are formed in the decomposition at least to some extent. (*b*) A plausible chain mechanism can be devised. (*c*) Chains are not propagated at low temperatures by the introduction of radicals. (*d*) Chains can be propagated under some circumstances at higher temperatures. (*e*) Results on inhibition indicate that chains occur but that the mean chain length is quite short'[57].

More recent work has focused on the nature of the chain termination and on the products obtained when mixtures of acetone and acetone-d_6 are pyrolyzed[130–132]. The nature of the chain-terminating step will, of course, influence the overall reaction order. If equation (50) represents the main terminating step and the Rice–Herzfeld scheme prevails, the overall reaction to ketene and methane should be first-order. In agreement with this Hinshelwood concluded that at 602° and between 120 and 300 mm pressure of ketone the reaction was around first-order[129]. On the other hand, McNesby, Davis, and Gordon, treating the data of Hinshelwood in a different way, concluded that it was 'more in harmony' with $\frac{3}{2}$ than first-order[130]. They failed to detect methyl ethyl ketone among the initial products at 500° and obtained small amounts of acetonylacetone and ethane. On this basis, they concluded that termination by equations (51) and (52) was more likely. Termination by methyl radical combination would give an overall $\frac{3}{2}$ order; termination by acetonyl radical combination, $\frac{1}{2}$ to first-order, depending upon the relative values of the rate coefficients for the previous steps. A small amount of acetylacetone also was found, and this was attributed to addition of acetonyl radical to ketene followed by hydrogen abstraction:

$$CH_3C\dot{O}CH_2 + CH_2{=}C{=}O \rightleftharpoons CH_3COCH_2C\dot{O}CH_2 \longrightarrow CH_3COCH_2COCH_3$$

In general agreement with a Rice–Hertzfeld scheme McNesby and Gordon obtained mainly CH_4, CH_3D, CD_3H, and CD_4, and very little CH_2D_2 early in the reaction when one to one mixtures of acetone and acetone-d_6 were pyrolyzed[132]. A buildup of CH_2D_2 occurred as the reaction progressed, due evidently to the fact that acetone and acetone-d_6 underwent slow deuterium exchange*. The

* The reported finding of CH_2D_2 very early in the reaction[130,131] was erroneous, due to an error in the interpretation of the mass spectrum[132,133].

CH_4/CH_3D and CD_3H/CD_4 ratios were nearly equal, as expected. The isotope effect for methyl radical abstraction from acetone *vs.* acetone-d_6 was about 3–4. Propylene, added in large amounts, suppressed the rate of decomposition and increased the CD_3H/CH_4 ratio[130]. This indicates that inhibition is due to the reaction of methyl (or $\cdot CD_3$) radicals with propylene to give the allyl radical ($\cdot CH_3 + CH_3CH{=}CH_2 \rightleftharpoons CH_4 + \cdot CH_2CH{=}CH_2$). The more stable allyl radical cannot carry the chain as well as the methyl radical. The same scheme has been used to explain the inhibition of acetaldehyde decomposition by propylene (see section V.A.4).

2. Methyl ethyl ketone

The decomposition of methyl ethyl ketone is said to resemble that of acetone in every way[57]. Approximate first-order kinetics was deduced from the change in initial rate with aldehyde pressure[134,135]. Ketenes are intermediates as evidenced by a buildup and then decline in acid-producing materials during the reaction[134]. The proportion of ketene and methylketene was not determined (Hurd reported obtaining both ketene and methyl ketene by a flow technique[136]). In the early stages of reaction at 580° and 200 mm pressure of ketone the products are: carbon monoxide (31·3%), methane (32·6%), ethylene (26·1%), hydrogen (4·5%), higher alkenes (4%), carbon dioxide (1·8%), 'ketenes', and condensation products[136]. The proportion of products changes as decomposition proceeds. Carbon monoxide, methane, and ethylene increase, hydrogen levels off, and ketenes decrease. Propylene in large amounts (> 100 mm) reduced the rate to a limiting value, 30 to 50% of the uninhibited rate[135]. The extent of inhibition decreased with increasing ketone pressure, indicating a competition between ketone and propylene for chain-carrying radicals[135]. Whether the maximally inhibited reactions are molecular or radical-chain (with the allyl radical also participating as a chain carrier) is uncertain. Adding nitric oxide in increasing amounts first depresses the rate slightly, then accelerates the decomposition[135]. The following processes were suggested. The methyl radical rather than the ethyl radical must be the main chain carrier since the methane yield is large and no ethane was reported[134,135].

$$CH_3COCH_2CH_3 \longrightarrow \cdot CH_3 + CO + CH_2{=}CH_2 + H\cdot \text{ (several steps)} \quad (53)$$

$$\cdot CH_3 + CH_3COCH_2CH_3 \longrightarrow CH_4 + \cdot CH_2COCH_2CH_3 \longrightarrow CH_3\dot{C}H_2 + CH_2{=}C{=}O \quad (54)$$

$$\cdot CH_3 + CH_3COCH_2CH_3 \longrightarrow CH_4 + CH_3\dot{C}OCHCH_3 \longrightarrow CH_3CH{=}C{=}O + \cdot CH_3$$

$$\downarrow$$

$$CH_2{=}CH_2 + CO \quad (55)$$

$$\cdot CH_3 + CH_3COCH_2CH_3 \longrightarrow CH_4 + CH_3COCH_2\dot{C}H_2 \longrightarrow$$

$$\cdot CH_3 + CO + CH_2{=}CH_2 \quad (56)$$

The β-hydrogen abstraction reaction (equation 56) was estimated to contribute to the extent of 18%. This conclusion is uncertain, however, in view of the complexities introduced by the ketene decompositions and other processes (e.g. condensation, and $CH_2{=}CH_2 \rightarrow CH_4 + C$).

The fact that no ethane was found appears to imply that few ethyl radicals are formed, i.e. reaction (54) is minor and hence methylketene is the predominant intermediate. Of course it is possible that ethyl radicals are formed appreciably, but α-hydrogen abstraction by the ethyl radical is not competitive with its cleavage to ethylene and hydrogen atom. (In propionaldehyde decomposition, discussed in section V.A.2, abstraction by the ethyl radical of *aldehydic* hydrogen was competitive with its split.) This appears unlikely, however, in view of the fact that ethane is a major product in the decomposition of diethyl ketone (see below).

3. Diethyl ketone

The decomposition of diethyl ketone between 500° and 570° appears to be first-order[137]. The major product is carbon monoxide. Ethane and ethylene are produced in nearly equal amounts along with small amounts of methane and carbon dioxide. The finding of ethane here contrasts with its absence in the pyrolysis of methyl ethyl ketone (above). Compounds which form carboxylic acids on treatment with water, presumably ketenes, build up and then decline in yield during pyrolysis[137]. The results indicate that ethyl radicals are the main chain carriers. Presumably then, methyl ketene is formed in a first stage, i.e.

$$Et\cdot + CH_3CH_2COCH_2CH_3 \longrightarrow EtH + CH_3\dot{C}HCOCH_2CH_3 \longrightarrow$$

$$CH_3CH{=}C{=}O + Et\cdot$$

Both nitric oxide (> 5 mm) and propylene (> 75 mm) reduce the rate somewhat to similar but not identical limiting values. The effect of nitric oxide is unusual in that no acceleration was detected up to an NO pressure of 20 mm. Increasing pressure of ketone lowers the extent of inhibition indicating a competition between ketone and inhibitor for chain propagating radicals[137].

4. Methyl propyl ketone

Waring and Garik decomposed methyl propyl ketone at 550° getting first-order kinetics from the initial pressure changes[138]. The proportion of gaseous products obtained varied with time. At one minute the relative yields of products were: CO (22·3), CH_4 (47), $CH_2{=}CH_2$ (15·6), $CH_3CH{=}CH_2$ (11·5), H_2 (1·9), CO_2 (1·6). Ketenes (structures undetermined) were intermediates. Methyl radical apparently was the main chain carrier. Propyl radicals, if appreciably formed, apparently underwent splitting preferentially to hydrogen abstraction, i.e. $CH_3CH_2\dot{C}H_2 \rightarrow CH_2{=}CH_2 + {\cdot}CH_3$ and $CH_3CH{=}CH_2 + H{\cdot}$. Propylene (as well as CO) also could arise from the breakdown of ethylketene. Added propylene had the usual inhibiting effect and nitric oxide accelerated the reaction. A mechanism involving only α-hydrogen abstraction, leading to ketenes, was proposed[138]. However, McNesby and Gordon also found an appreciable amount of acetone among the early products, and suggested that γ-hydrogen abstraction occurred (equation 57)[139]. In addition they proposed β-hydrogen abstraction (equation 58). Acetone also could have arisen by a Norrish type II molecular process (see next section). Methyl vinyl ketone also has been isolated as one of the

$$\cdot CH_3 + CH_3CH_2CH_2COCH_3 \longrightarrow CH_4 + \cdot CH_2CH_2CH_2COCH_3 \longrightarrow CH_2{=}CH_2 + \cdot CH_2COCH_3 \quad (57)$$

$$\cdot CH_3 + CH_3CH_2CH_2COCH_3 \longrightarrow CH_4 + CH_3\dot{C}HCH_2COCH_3 \longrightarrow CH_3\cdot + CO + CH_3CH{=}CH_2 \quad (58)$$

$$CH_3CH_2\dot{C}HCOCH_3 \longrightarrow \cdot CH_3 + CH_2{=}CH{-}COCH_3 \quad (59)$$

predominant products in the decomposition of methyl propyl ketone in a flow apparatus[140]. This suggests the reaction depicted by equation (59).

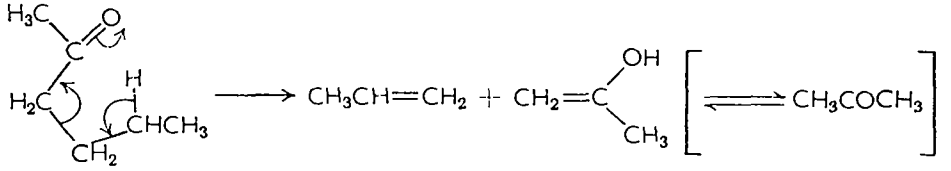
5. Methyl butyl ketone

At 450° and 160 mm pressure, methyl n-butyl ketone at 10% decomposition gave the yield order: propylene > acetone > ethane > methyl vinyl ketone > methane > carbon monoxide > butene > ethylene > ketenes (small)[141]. The proportion of products changes with reaction time. In particular the relative amount of carbon monoxide and methane increases and that of acetone and methyl vinyl ketone decreases. Condensation products also are formed. Acid-forming compounds, i.e. ketenes, are present in small amounts in the early stages. However, in addition to the usual α-hydrogen

abstractions leading to ketenes, other processes must be included, especially to account for methyl vinyl ketone and acetone production. Added propylene, which had the usual inhibitory effect on the overall rate, markedly reduced methyl vinyl ketone production. This suggests that methyl vinyl ketone is formed by some sort of radical chain process[141], possibly as in equation (60).

$$\cdot CH_3 + CH_3CH_2CH_2CH_2COCH_3 \longrightarrow CH_4 + CH_3CH_2CH_2\dot{C}HCOCH_3 \longrightarrow CH_3\dot{C}H_2 + CH_2{=}CHCOCH_3 \quad (60)$$

$$\cdot CH_3 + CH_3CH_2CH_2CH_2COCH_3 \longrightarrow CH_4 + CH_3\dot{C}HCH_2CH_2COCH_3 \longrightarrow CH_3CH{=}CH_2 + \cdot CH_2COCH_3 \quad (61)$$



(62)

Acetone could arise either via γ-hydrogen abstraction[141] (equation 61) or by a molecular process (equation 62). The latter reaction, labeled a Norrish type II process[142,143], has been postulated to occur in the photosensitized decomposition of large ketones[144]. There appears to be some inhibition of acetone formation by propylene, a point in favor of equation (61), but the experimental uncertainty is large[141].

6. Larger aliphatic ketones

Products obtained in the pyrolysis of higher saturated ketones have been partly characterized, but no kinetic work has been carried out. Methyl isobutyl ketone[140,145], methyl neopentyl ketone[140], isopropyl isobutyl ketone[145], di-n-hexyl ketone[145], stearone[146], and oleone[146] have been pyrolyzed. In general carbon monoxide, alkenes, hydrogen, methane, and other alkanes (uncharacterized) were obtained. Acetone in about 30% yield was detected as a product of the pyrolysis of methyl isobutyl and methyl neopentyl ketone. Acetone may have been formed in other instances, but its presence apparently was not sought. It evidently was formed either via γ-hydrogen atom abstraction or a Norrish type II process, as in the case of methyl propyl and methyl butyl ketone (equations 61 and 62 above).

Dibenzyl ketone, when passed through a hot copper tube at 550–600°, yielded carbon monoxide, toluene, fluorene, anthracene,

some hydrogen, and carbon dioxide and small amounts of alkenes and alkanes[147,148]. Similar results were obtained in the condensed phase at 200–360° (sealed-tube reaction)[149]. The only product mentioned in the thermolysis of 1,1,3,3-tetraphenylacetone was *sym*-tetraphenylethane, yield unspecified[149].

7. Cycloalkyl ketones

Methyl cyclobutyl ketone in the gas phase at 370–410° and 10–65 mm pressure yielded almost exclusively ethylene and methyl vinyl ketone[150]. The reaction was homogeneous and first-order over at least the first half-life, with $k = 3{\cdot}4 \times 10^{14} \exp(-54{,}500/RT)\ \text{sec}^{-1}$. Nitric oxide, propylene, or toluene exerted virtually no effect on the product distribution or rates. It was concluded that decomposition does not take place by a radical-chain process. Ethyl cyclobutyl ketone showed a strictly analogous behavior, the products being ethylene and ethyl vinyl ketone[151].

8. Cyclic ketones

The decomposition of cyclobutanone at 330–370° at pressures of 5 to 90 mm yielded mainly ethylene and ketene in high yield over the first half-life[152]. Decomposition products of ketene build up in the latter stages. The pressure change in single runs was first-order over a goodly portion of the decomposition, and the rate was unaffected by nitric oxide, propylene, or toluene. It was concluded that the formation of ethylene and ketene is not a radical-chain process.

The decomposition of cyclopentanone requires higher temperature (488–543°) and is much more complex than that of cyclobutanone. The percentage composition of the gaseous products obtained early in the decomposition was: carbon monoxide, 41; hydrogen, 22; ethylene, 13; propylene and butadiene, 15; methane, 5; ethane, 2; and propane, 2[153]. The pressure change during single runs showed an induction period and did not obey simple first- or second-order kinetics. No specific mechanistic assignments were made.

Cyclohexanone, when passed through a Pyrex combustion tube heated to 700°, gave carbon monoxide, propylene, ethylene, hydrogen, some cyclohexadiene, and small amounts of alkanes[154].

9. 1,2-Diketones

Only biacetyl has been studied to any extent. At 418–436° and 200 mm pressure, the major initial products are ketene, acetone,

carbon monoxide, and methane[155–158]. Decomposition products of acetone and ketene appeared in increasing amounts as reaction proceeded[157]. The kinetics are complicated, the apparent initial order being about unity[156–158]. The reaction is approximately 35% slower in the presence of 150 mm of propylene. A Rice–Herzfeld-type mechanism was assigned[157,158].

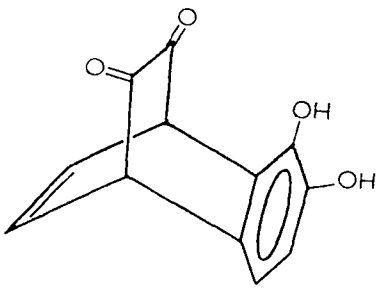
Benzil, investigated by the toluene-carrier technique at 660°, yielded carbon monoxide, benzene and dibenzyl[159]. The sequence proposed is:

$$PhCOCOPh \longrightarrow 2\ Ph\dot{C}O \longrightarrow 2\ CO + 2\ Ph\cdot$$

$$Ph\cdot + PhCH_3 \longrightarrow PhH + Ph\dot{C}H_2$$

$$Ph\dot{C}H_2 + Ph\dot{C}H_2 \longrightarrow PhCH_2CH_2Ph$$

In very early work it was found that ketones of the type $RCOCH_2COCOCH_2COR$ (where R = CH_3, Ph, and C_2H_5O), when heated to 220–250°, gave CO and $RCOCH_3$, amounts unspecified[160]. 1,4-Dicyano-1,4-diphenyl-2,3-butanedione was reported to yield carbon monoxide on being heated[160]. A bridged diketone (**24**) has recently been prepared and is reported to melt at 195–6° without decomposition[161].



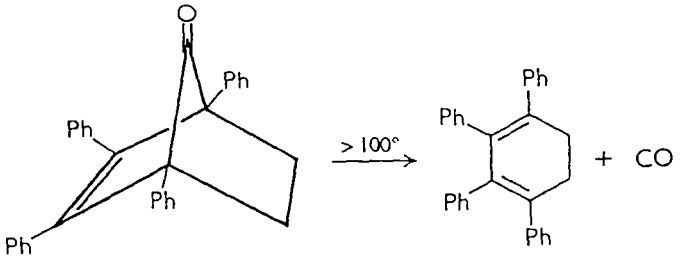
(**24**)

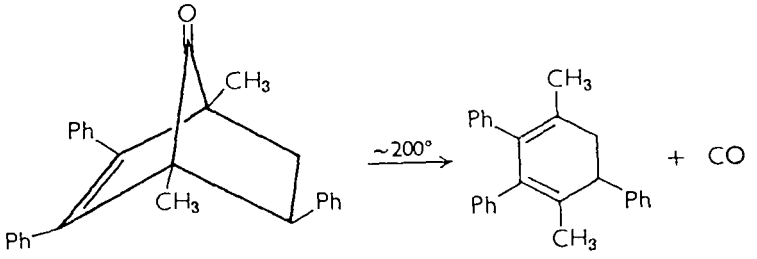
10. Carbonyl bridge compounds

The preparation, characterization, properties, and reactions of carbonyl bridge compounds have been reviewed by Allen[162,163]. Some aspects are also covered in the first volume of this series[164]. Readers who are interested in more detail are referred to these sources. Only the general features of the decarbonylation of the carbonyl bridge compounds will be considered here.

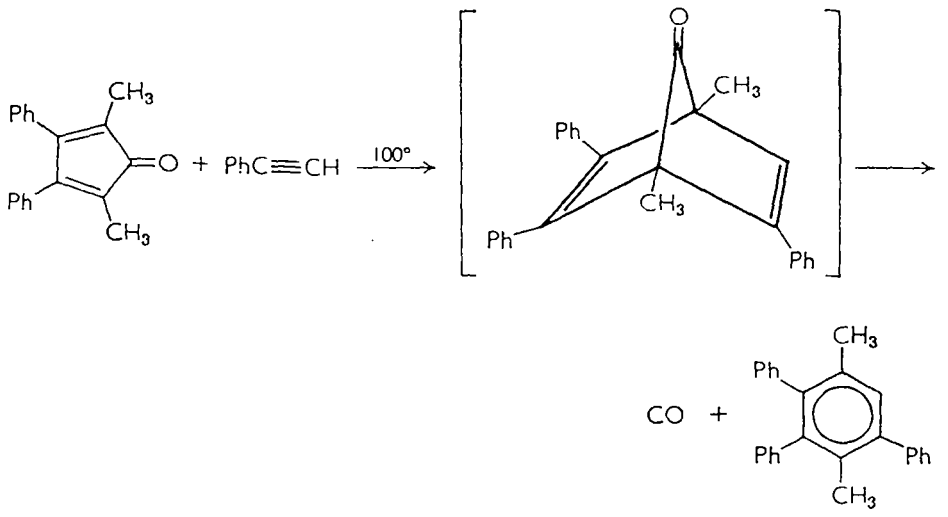
Substituted bicyclo[2.2.1]hept-2-en-7-ones readily lose carbon

monoxide on heating to give high yields of the corresponding hexadienes[162–164]. Typical examples are shown below:

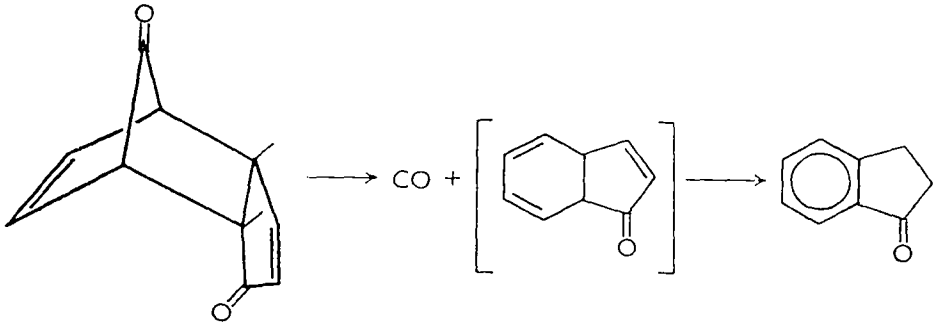




Saturated bridged carbonyl compounds and those with larger ring systems have been found to be thermally stable[162,163]. On the other hand, substituted bicycloheptadienones decarbonylate with particular ease[162–164]. Attempts to prepare them by Diels–Alder reactions often lead to substituted benzenes[162–165]. The bridged carbonyl compound presumably is an intermediate. An example is given below.

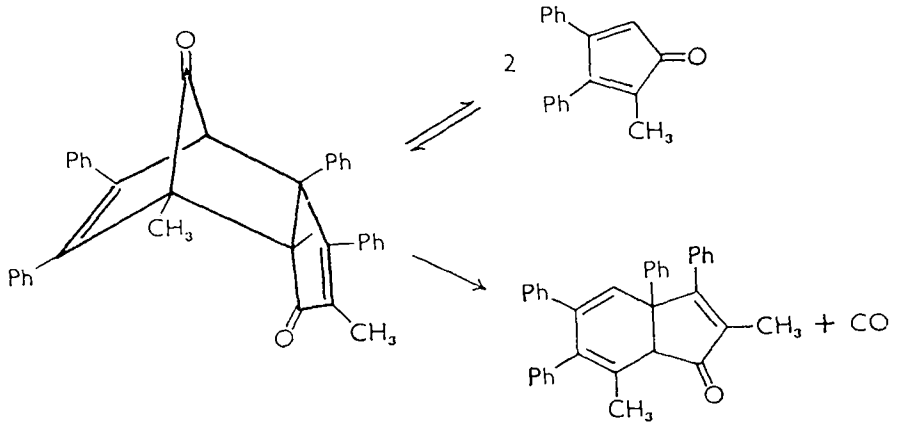


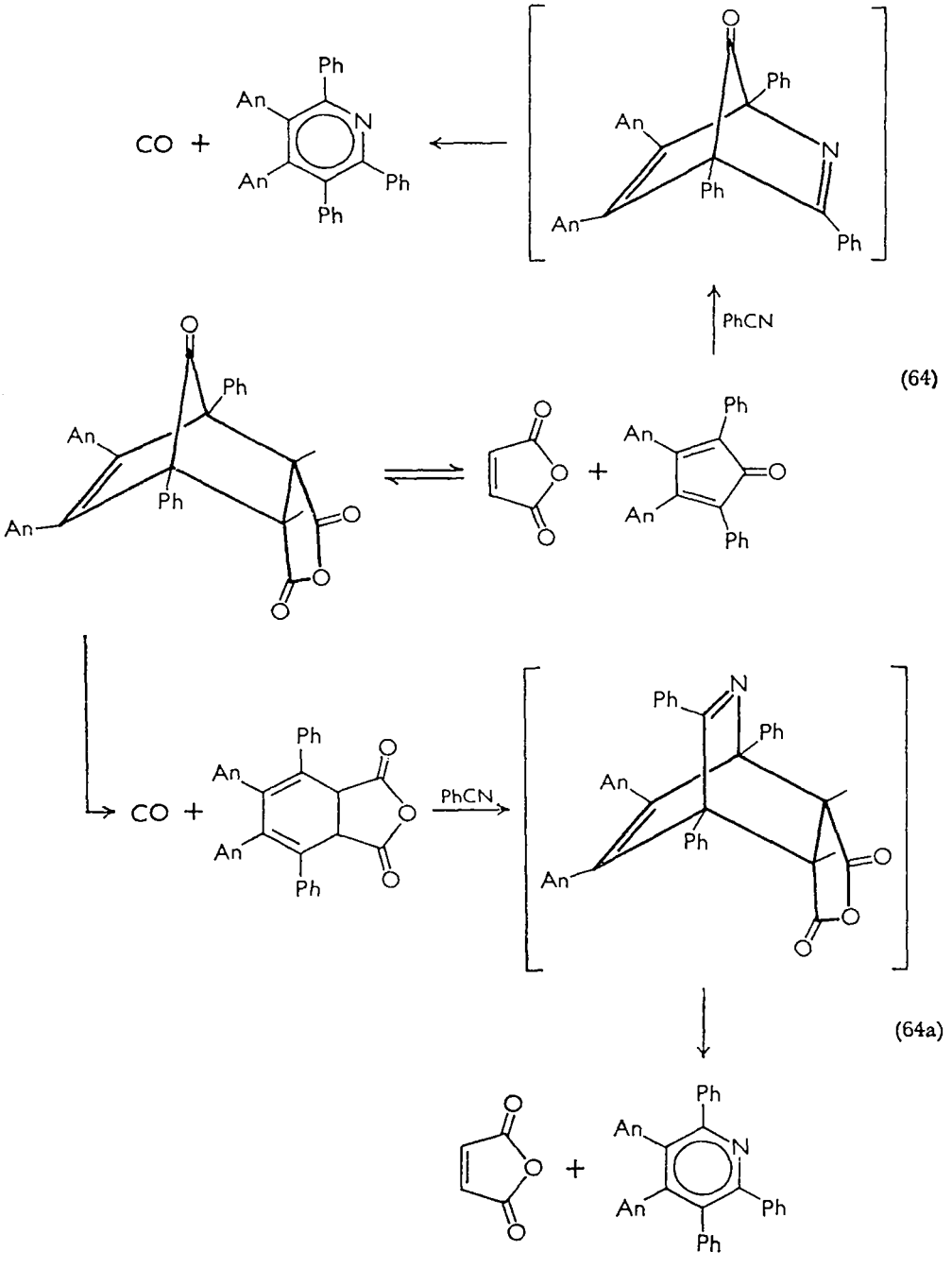
The degree to which decarbonylation is favored by substituents is not really known. Moderately substituted bicycloheptenones and bicycloheptadienones are not readily available. Attempts to prepare them by generating *in situ* the unknown compound cyclopentadienone in the presence of acetylenes or olefins usually give only cyclopentadienone dimer and recovered dienophile. However, a small yield of 2-phenylbicycloheptadien-7-one was obtained in this way from phenylacetylene[166]. On being heated, the ketone gave a low yield of carbon monoxide and biphenyl. Cyclopentadienone dimer itself decarbonylated above 240° to yield indanone (equation 63)[166]. The intermediate dihydroindenone could be trapped as the maleic anhydride adduct.



The preparation of unsubstituted bicyclohept-2-en-7-one by an indirect method has been reported recently[167]. It apparently was stable to vacuum distillation at 70°, but no mention was made of its behavior at higher temperatures.

Substituted bicycloheptenones are subject to a reverse Diels–Alder




CO +
Ph
An
N
An
Ph
Ph
O
Ph
An
N
An
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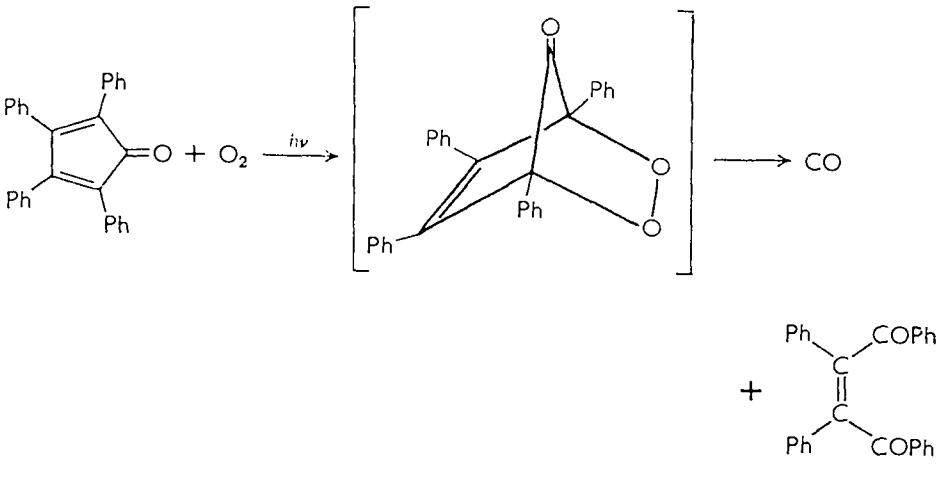


(65)

reaction[162–164] and in some instances they may dissociate during decarbonylation[162,163]. Decarbonylation could still occur in high yield, however, because the dissociation is reversible whereas the decarbonylation is not[162].

Allen has postulated a bridged carbonyl compound as an intermediate in the reaction that had been reported between 3,6-*endo*-carbonyl-3,6-diphenyl-4,5-bis-(*p*-anisyl)-1,2,3,6-tetrahydrophthalic anhydride and warm benzonitrile which yielded carbon monoxide and 2,3,6-triphenyl-4,5-bis-(*p*-anisyl)pyridine (equation 64)[163, 168]. Presumably, the alternative path (64a) is ruled out by experimental conditions. The original workers did not report treating 2,5-diphenyl-3,4-bis-(*p*-anisyl)cyclopentadienone with benzonitrile. Bikaless and Becker have suggested that the photooxidation of tetraphenylcyclopentadienone also proceeds via an intermediate bridged carbonyl compound (equation 65)[169].

VI. MISCELLANEOUS DECARBONYLATIONS

A. Decarbonylation over Catalysts

Carbonyl compounds can be decarbonylated in the presence of hydrogenation catalysts at temperatures (180–300°) considerably lower than required for strictly thermal decarbonylation. Most of the work has been restricted to aromatic and conjugated aldehydes, and no mechanistic studies have been made. The common procedure is to heat the neat aldehyde with a small amount of finely divided

catalyst (1% of the weight of aldehyde or less). The hydrocarbon product, boiling at a lower temperature than the aldehyde, often is distilled from the reaction mixture as formed. The most commonly used catalysts have been finely divided reduced nickel and dispersed palladium.

I. Saturated aldehydes

Propionaldehyde, when passed over reduced nickel at 235°, platinum at 275°, or copper at 400°, yielded ethane and carbon monoxide in unspecified yields[170]. Some butane and hydrogen also resulted when the latter two catalysts were used. Heptanal yielded carbon monoxide, a five-compound mixture (in which only 1-hexene was identified), and some water, hydrogen, and a high-boiling substance when refluxed for nine hours with 5% palladium on carbon[171]. Citronellal, heated to reflux under a carbon dioxide atmosphere with 5% palladium on barium sulfate, gave citronellene in 50% yield[172]. Newman and Mangham obtained a 97% yield of naphthalene upon heating 2-formyl-1,2,3,4-tetrahydronaphthalene with palladium on carbon[173,174]. Decarbonylation presumably preceded dehydrogenation since 2-naphthaldehyde is apparently resistant to decarbonylation (see below)[171].

2. α,β-Unsaturated aldehydes

Cinnamaldehyde, upon being heated at 360° with Raney nickel, gave carbon monoxide, styrene (45% of the liquid products), and smaller amounts of ethylbenzene (22%), toluene (22%), and benzene (11%). Some hydrogen and carbon dioxide also were formed[175].

A study has been made of the behavior of *trans*-cinnamaldehydes substituted in the α-position with alkyl or phenyl[176]. When the cinnamaldehyde was simply refluxed over palladium, a mixture of the *cis*- and *trans*-styrene was obtained, with the *trans* isomer predominating. However, when the styrene was distilled out as formed, the *cis* isomer predominated. Recovered cinnamaldehyde had not isomerized, but *cis*-styrene isomerized to *trans* when treated under the decarbonylation conditions. Clearly, the initial product is largely if not completely the *cis*-styrene. When the styrene was distilled as formed, the yields obtained from substituted cinnamaldehydes were: α-methyl, 92%; α-ethyl, 81%; α-propyl, 38%; α-isopropyl, 41%; α-phenyl, not reported. When the styrene was not removed during the reaction, the yields dropped markedly and a higher proportion of alkylbenzenes was obtained.

Citral when heated to reflux with palladium on barium sulfate, under carbon dioxide, is reported to yield the decarbonylation product geraniolene in 60% yield[172]. Under similar conditions, myrtenal gave carbon monoxide and apopinene in 85 and 75% yield, respectively[177].

3. Aromatic aldehydes

Aromatic aldehydes decarbonylate generally in good yield when refluxed over hydrogenation catalysts (see Table 4)[171]. The reaction fails, however, when an *o*-carboxyl group is present, due evidently to hydroxylactone formation[171]. A somewhat surprising observation is that 2-naphthaldehyde did not decarbonylate.

TABLE 4. Catalytic decarbonylation of aromatic aldehydes.

Aldehyde[a]	Decarbonylation product[b]	Ref.
Furaldehyde	Furan (30)	172
Benzaldehyde	Benzene (78)	171
4-Methylbenzaldehyde	Toluene (88)	171
2-Methoxybenzaldehyde	Anisole (94)	171
3-Nitrobenzaldehyde	Nitrobenzene (86)	171
4-Nitrobenzaldehyde	Nitrobenzene (79)	171
2-Formylpyridine	Pyridine (68)	171
Vanillin (Ni, 370–390°)[c]	Guaiacol, catechol	175
Piperonal (Ni, 370–380°)	Phenol, catechol	175
6-Formyltetralin (Pd, 275°, 6 h)[c]	Tetralin (74), naphthalene (21)	174
1-Naphthaldehyde	Naphthalene (80)	171
9-Formylanthracene	Anthracene (84)	171
4-Carbomethoxy-2′-formylbiphenyl	4-Carbomethoxybiphenyl (20)	171
2,2′-Diformylbiphenyl	Biphenyl (97)	171
1-Formylfluorenone	Fluorenone (82)	171

[a] Unless otherwise noted the catalyst was 5% Pd on carbon and the reaction conditions were refluxing neat aldehyde (179–250°/0·25–2·0 h) under an atmosphere of CO_2.
[b] Percent yields, where reported, are given in parentheses.
[c] H_2 as well as CO obtained.

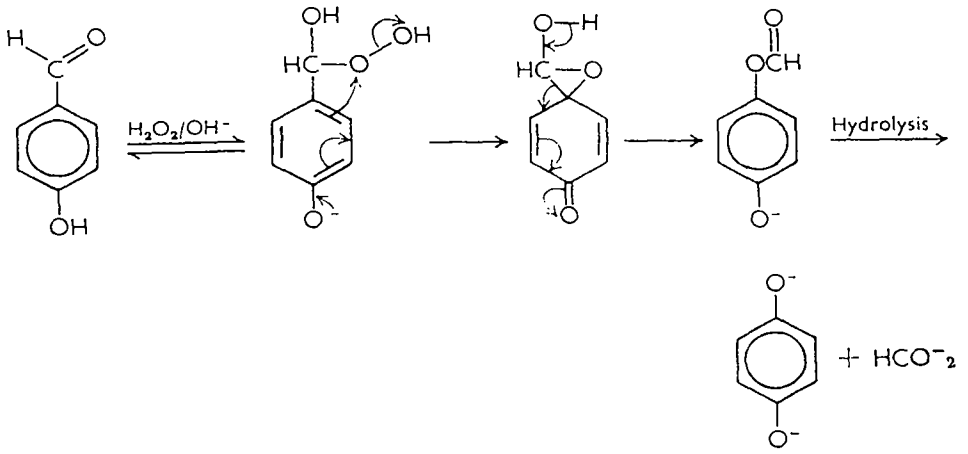
B. *Dakin-type Reactions*

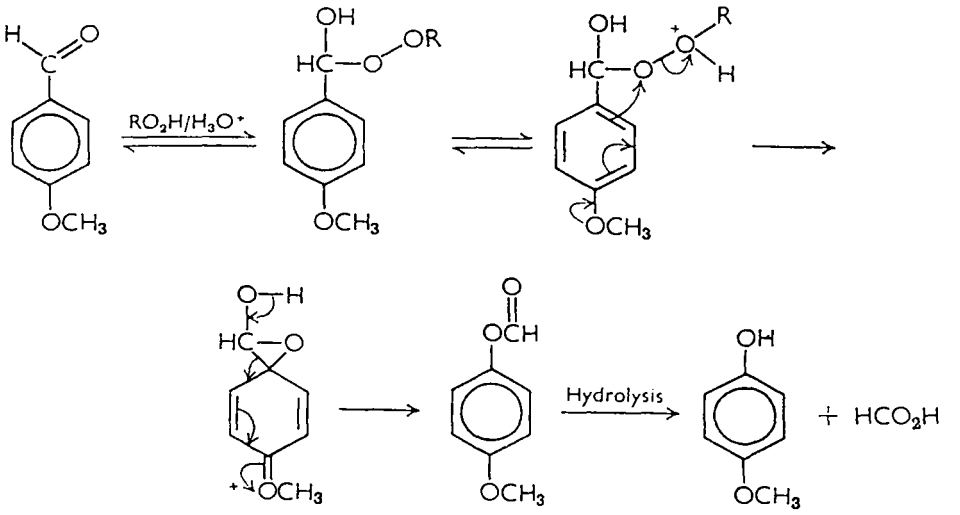
Dakin found that *o*- and *p*-hydroxybenzaldehydes, on treatment with aqueous base and hydrogen peroxide, gave good yields of the corresponding dihydroxybenzene and formate ion[178]. The yields were less when *o*- and *p*-hydroxyacetophenones were used, and *p*-hydroxypropiophenone gave very little hydroquinone. When the hydroxy substituent was *meta* to the formyl group only oxidation to the carboxylic acid occurred.

Aspects of the Dakin reaction were reviewed by Leffler in 1949[179]. Dakin-type reactions can be carried out under acidic or basic conditions. Alkaline hydrogen peroxide works successfully on a wide variety of *o*- and *p*-hydroxybenzaldehydes, but not on corresponding anisoles[180–182]. Under acidic conditions (e.g. hydrogen peroxide in sulfuric acid[183] and hydrogen peroxide[184] or peracetic acid[185] in acetic acid solvent) both the phenols[180,184,185] and anisoles[183,184] undergo the reaction. As oxidants, only hydrogen peroxide, peroxy acids, and hydroxyperoxy compounds (or sources thereof) are effective[178,183,184]. Ineffective are neutral solutions of hydrogen peroxide in water or acetone[180], and low yields were obtained with hydrogen peroxide in ether[186] or ozone passed into a chloroform solution[187].

Plausible mechanisms are given below (cf. Leffler[179]). Under basic conditions, apparently only the $-O^-$ substituent is sufficiently activating to promote the ring-closure step, an example of aromatic electrophilic substitution. Otherwise, acid catalysis appears to be required.

These mechanisms are consistent with the evidence, not conclusive, that the formate ester is an intermediate in the reactions of 4- and 5-methylsalicylaldehydes with hydrogen peroxide in anhydrous acetic acid[185]. They also account for the failure of acetylvanillin to undergo the reaction (acid conditions) although methylvanillin reacts readily[184]. The fact that a nitro substituent *ortho* to the hydroxyl prevents the reaction[178], but one *meta* to the latter does not[178,188] (alkaline conditions), is readily rationalized in terms of the above mechanism. The inability of *o*-hydroxy-α-hydrindone to



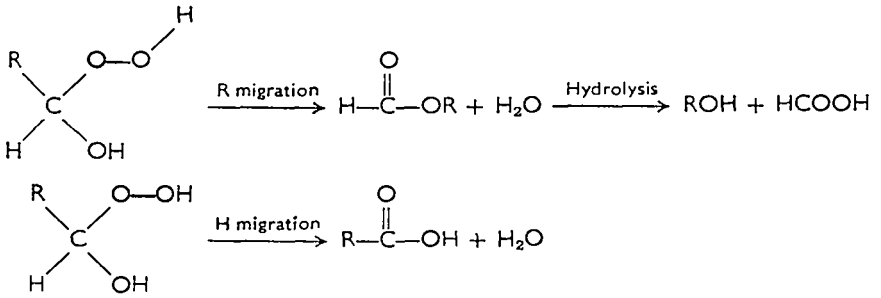


undergo the Dakin reaction[180] may be the result of excessive ring strain in the transition state of the ring closure step.

Isolated instances in which the activating substituent is amino or thio are reported. Bamberger, in work predating that of Dakin, found that treatment of *o*-aminobenzaldehyde with Caro's acid in the presence of magnesia produced a small yield of *o*-aminophenol, *o*-formylaminophenol, and also some *o*-nitrophenol[189]. The ozonide of thionaphthene gave on hydrolysis a 50% yield of 2,2'-dihydroxydiphenyldisulfide[190]. This presumably resulted from a Dakin reaction on the intermediate aldehyde. A similar reaction was shown by the ozonide of coumarone, which gave a 7% yield of 1,2-dihydroxybenzene[190].

The Dakin reaction has been used on a number of natural products. Some recent examples include formyl- and acetylcoumarins, flavones, and depsides[191–196].

Aliphatic aldehydes apparently also can show a Dakin-like

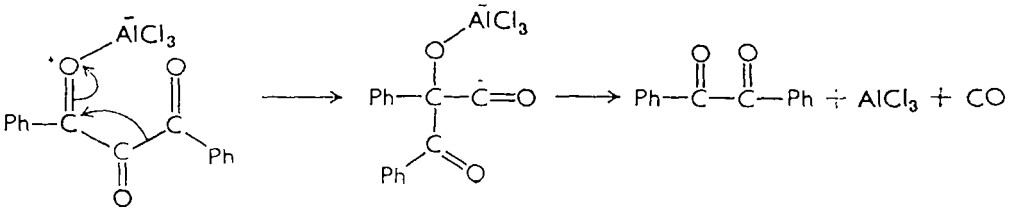


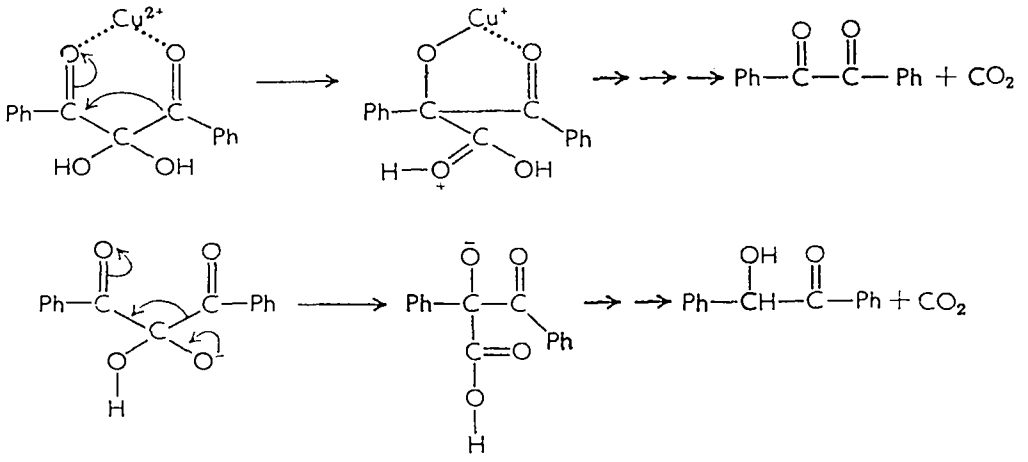
reaction. Thus when the hydroperoxide adducts of several long-chain aldehydes were heated to 80–120° and the reaction product then subjected to treatment with alkali in aqueous alcohol, 3–9% yields of alcohols containing one less carbon atom than the aldehyde were obtained[197]. Hydrogen migration apparently took precedence over alkyl migration since the carboxylic acid was the main product (>50%).

C. Diphenyl Triketone

Diphenyl triketone is reported to decarbonylate on treatment with various reagents[198–202]. Treatment with anhydrous aluminum chloride gave carbon monoxide and a 50% yield of benzil[189,200]. Treatment of the triketone hydrate with aluminium chloride yielded benzoin and carbon dioxide as the main products, benzil and carbon monoxide also being formed. In 50 or 60% H_2SO_4 or phosphoric acid (sp. gr. 1·71) the triketone yielded comparable amounts of benzil and benzoin in a combined yield of about 50%[199–201]. Carbon dioxide in unspecified amount was identified in one experiment. No mention was made of the yield of carbon monoxide[201]. Treatment with an aqueous alcohol solution of sodium hydroxide was reported to convert the triketone into carbon dioxide and a mixture of benzoin, benzoic acid, and mandelic acid in unspecified yield[202]. The yield of benzoin obtained in this way by Roberts was 5%[198]. The most-successful decarbonylation was carried out in a solution of cupric acetate hydrate in acetic acid. A high yield of carbon dioxide, but no carbon monoxide was obtained from either diphenyl triketone or *p*-methoxyphenyl phenyl triketone. Both compounds gave the corresponding benzil in high yield[198].

By labeling the α-carbonyl group with ^{14}C, Roberts was able to show that the central carbonyl group was lost in the decarbonylations catalyzed by cupric acetate, aluminum chloride and sodium hydroxide. The mechanisms suggested[198] for loss of the carbonyl group are given below.



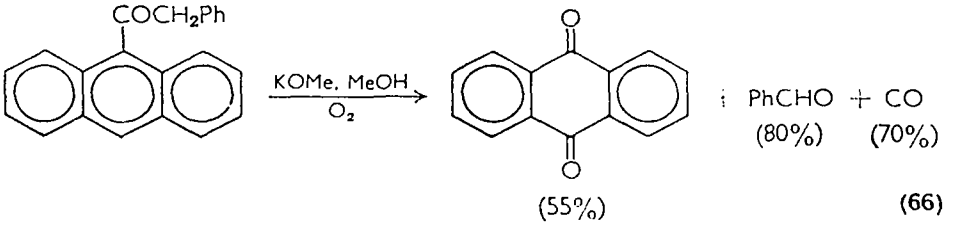


D. Phenanthraquinones

Heating 1,8-diaza-9,10-phenanthraquinone with dilute sodium hydroxide gave a nearly quantitative yield of 4,5-diazafluorenone[203]. Treatment of 9,10-phenanthraquinone with boiling dilute sodium hydroxide gave predominantly the benzilic acid in a short time, and mainly fluorenone (25% yield) after four days[204]. In neither instance was the fate of the lost carbonyl group determined. The implication that formate ion is formed[205] is refuted by the failure of specific attempts to detect it[204]. It has been suggested that air oxidation is necessary and hence that carbonate ion is produced. This finds support in the ready oxidation of the benzilic acid to fluorenone by permanganate[204] or chromate[206].

E. 9-Acylanthracenes

Certain 9-anthracenyl benzyl ketones were observed to lose the ketonic function when heated in a solution of 2% $KOCH_3$ in CH_3OH through which oxygen was passed[207]. The reactions are summarized in equations (66) to (69).



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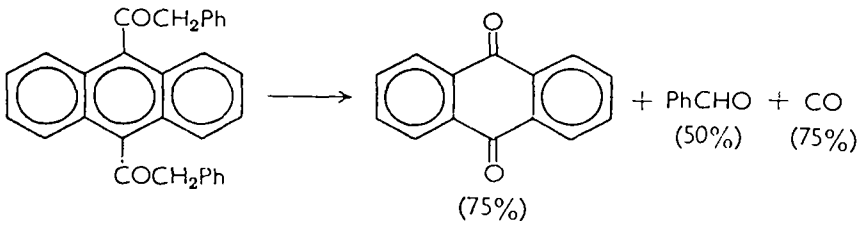

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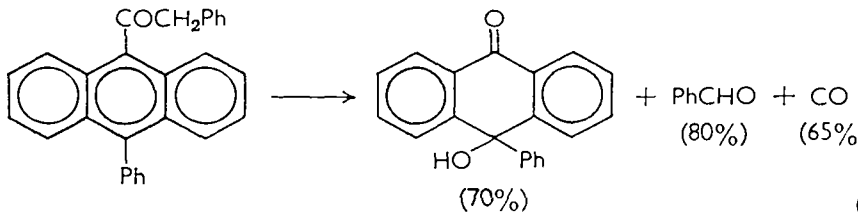

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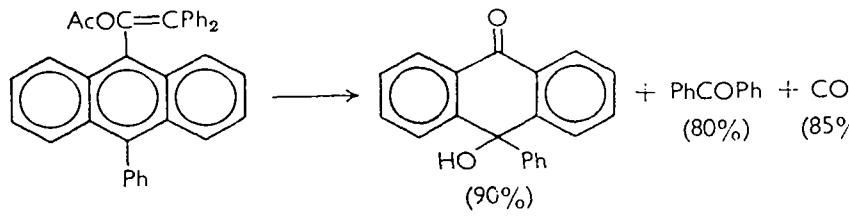

(69)

This reaction was not shown by 9-acetyl-10-phenylanthracene and methyl 4-(10-phenylanthracenyl)-4-oxobutanoate.

F. Anomalous Bucherer

Treatment of 2-hydroxynaphthaldehyde with aqueous ammonium sulfite and ammonia is reported to give 2-naphthylamine in 80% yield[208]. The fate of the lost carbonyl group was not determined. It is possible that the reaction proceeds via a preliminary base-catalyzed cleavage of the β-keto aldehyde tautomer of 2-hydroxy-naphthaldehyde, or an imine thereof.

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The Chemistry of the Carbonyl Group
Edited by Saul Patai

CHAPTER 15

Rearrangements involving the carbonyl group

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I. INTRODUCTION

The term 'molecular rearrangement' has been so widely used that it cannot be exactly defined. In order that a 'rearrangement' be included in this chapter we decided that there should be no change in the total number of carbons as the molecule in question changes into product, but one or more carbons in that molecule should

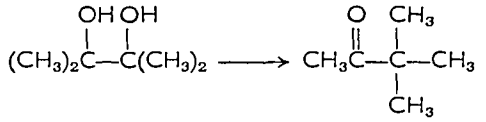
change position during reaction. We considered a carbonyl function to be involved in a rearrangement if it had been destroyed and/or formed during reaction. We have not hesitated, however, to discuss material excluded by these criteria when we thought it advisable or necessary. The Willgerodt reaction has been included, for example, because it has often been called a rearrangement.

Only rearrangements associated with aldehydes and ketones are discussed; reactions of carbonyl derivatives, of carboxylic acids and of esters and amides, in general, are excluded. These limitations seemed necessary to keep the chapter to a reasonable size and do at least a minimum of justice to the rearrangements discussed.

II. ACID- AND BASE-CATALYZED REARRANGEMENTS

A. *The Pinacol Rearrangements*

Fittig recorded the first example of the rearrangement of an α-glycol to a ketone[1]. Pinacol (**1**), obtained by the dimerization of

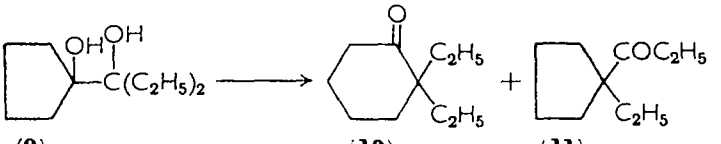


(**1**) (**2**)

acetone, yielded pinacolone (**2**) upon treatment with cold concentrated sulfuric acid. The reaction is general for α-glycols, and several reviews have appeared which adequately summarize the early[2-4] and recent[5] literature. Each of the two adjacent carbons bearing the hydroxyl groups can be primary, secondary, or tertiary, and each can be part of the same or different ring systems. Thus ethylene glycol (**3**) itself, as well as each of the compounds **4** to **8** obtained

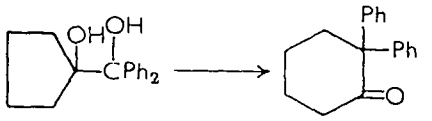
CH_2OHCH_2OH	$PhCHOHCH_2OH$	$PhCHOHCHOHPh$
(**3**)	(**4**)	(**5**)
Ph_2COHCH_2OH	$Ph_2COHCHOHPh$	$Ph_2COHCOHPh_2$
(**6**)	(**7**)	(**8**)

by successive phenyl substitution of the hydrogens of ethylene glycol, will undergo the pinacol rearrangement when treated with a

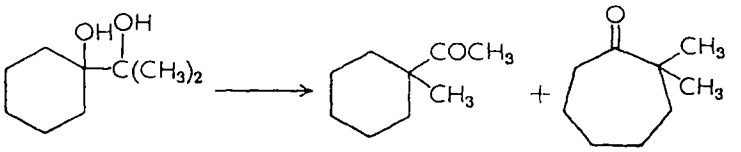


(**9**) (**10**) (**11**)

variety of acids. Compounds obtained through successive alkyl substitution also rearrange, as do the cyclic structures **9**, **12** and **14**[6]. Consequently, unusual ketones can often be synthesized through

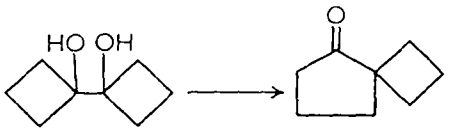


(**12**) (**13**)



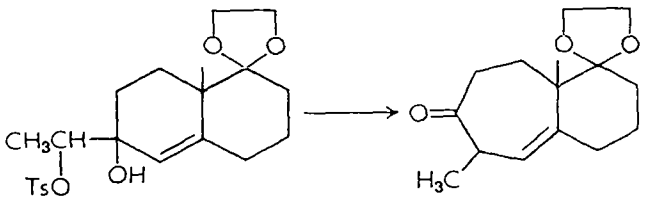
(**14**) (**15**) (**16**)

pinacol rearrangement of the appropriate α-glycol. For example, Vogel[7] prepared the spiroketone **18** through rearrangement of the α-glycol **17**, and Corey and coworkers[8] used a modified pinacol



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

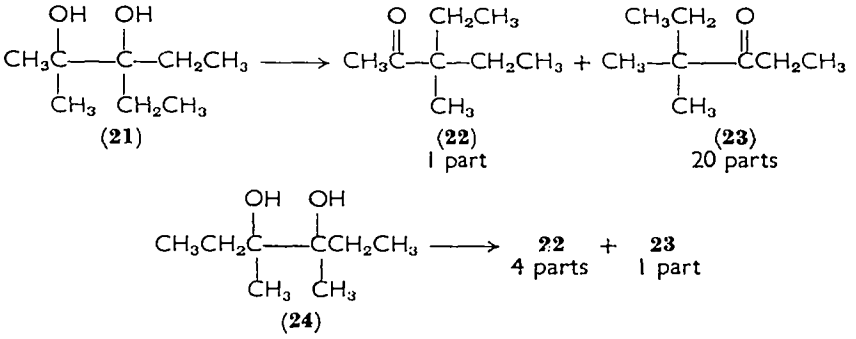
rearrangement of **19** (semipinacolic rearrangement, according to Bennett and Chapman[2]) to prepare the ketone **20**, a key intermediate in the total synthesis of longifoline[8].



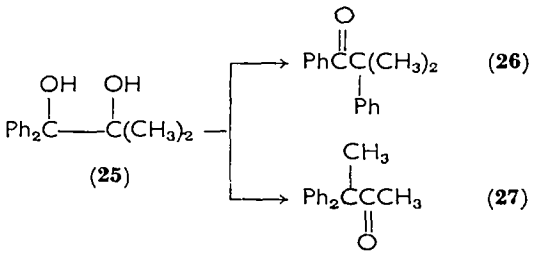
(**19**) (**20**)

Although the pinacol rearrangement is ordinarily a high-yield reaction, glycols whose four substituents are not all the same can yield more than one product. Further, the relative yields of the products can be varied by changing the concentration of acid, or even

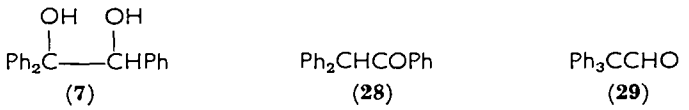
by changing the acid used to effect the rearrangement. Thus, the related α-glycols **21** and **24**, in cold concentrated sulfuric acid, both yield mixtures in different proportions of the same two ketones (**22** and **23**)[9]. The effect of different acidic media in bringing about



the rearrangement of the same α-glycol is illustrated in the rearrangement of **25**, whereby the action of cold concentrated sulfuric acid affords the ketone **27**, although a trace of sulfuric acid in acetic acid produces the ketone **26**[5].

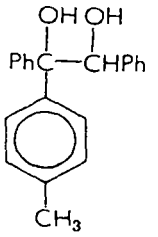


α-Glycols which are less than tetra-substituted can produce aldehydes as well as ketones. The relative yield of aldehyde and ketone is dependent upon temperature, and upon the strength and dilution of the acid used to effect the rearrangement. Ordinarily, lower temperatures and weaker acids favor aldehyde formation, for the aldehydes themselves are irreversibly converted into ketones under more drastic conditions. For example, in cold concentrated sulfuric acid, triphenylethylene glycol (**7**) is converted quantitatively

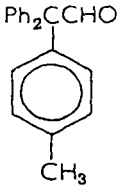


into benzhydryl phenyl ketone (**28**), whereas the action of 40% aqueous sulfuric acid affords mostly triphenylacetaldehyde (**29**)[10,11].

Similarly, either *threo-* or *erythro*-1,2-diphenyl-1-*p*-tolylethylene glycol (**30**) yields a mixture of two isomeric ketones in concentrated



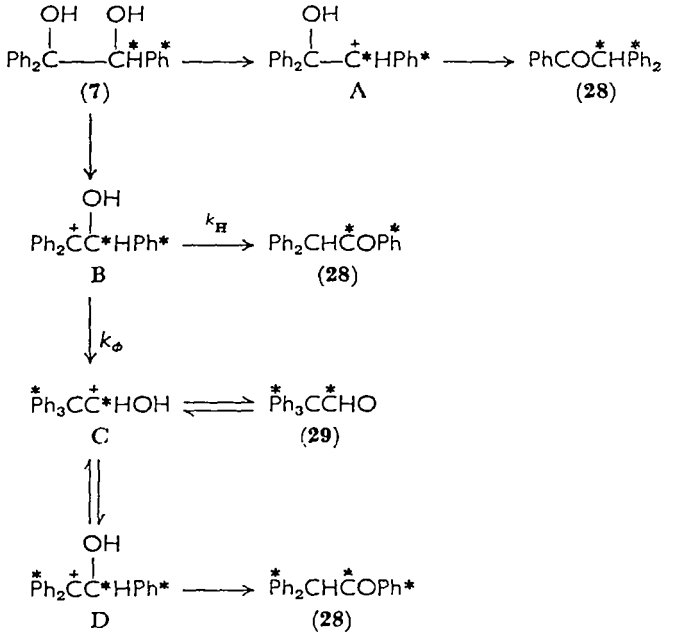
(**30**)



(**31**)

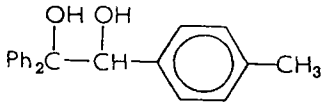
sulfuric acid at 0°c[12]. When the same glycol (**30**) is allowed to dissolve slowly in 98% formic acid at room temperature, diphenyl-*p*-tolylacetaldehyde (**31**) is the major product[12]. Phenyldi-*p*-tolylacetaldehyde[13] and diphenyl-*o*-tolylacetaldehyde[14] have been prepared by analogous rearrangements, in formic acid, of the appropriate glycols.

Considerable mechanistic information concerning the pinacol rearrangement is summarized in two papers[11,12]. In the first paper[11] ^{14}C-double-labeling experiments established the several pathways for rearrangement of triphenylethylene glycol (**7**) (Scheme 1) in a

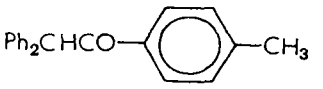


SCHEME 1.

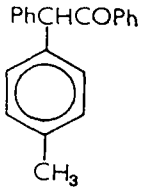
variety of acidic media. It was possible to calculate how much each path contributed to product formation and, in addition, to determine the migratory rate ratio k_{ϕ}/k_{H} for each medium. Removal of the secondary hydroxyl group was of insignificant importance under any



(32)



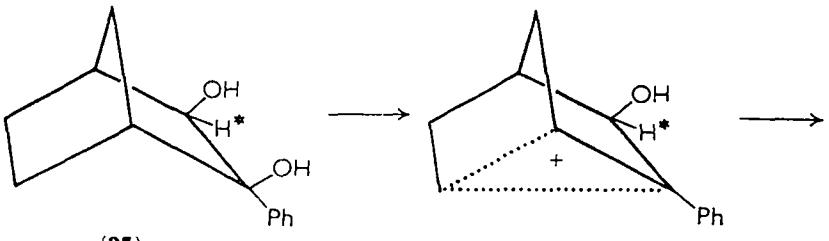
(33)



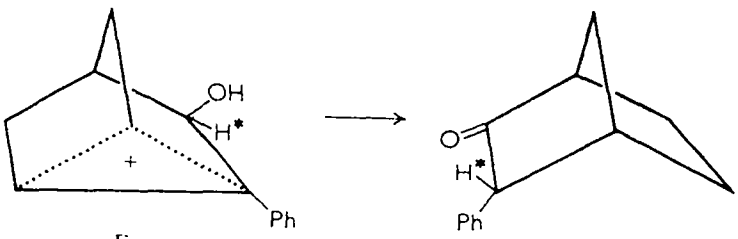
(34)

of the conditions studied. In the second paper[12] 1,1-diphenyl-2-*p*-tolylethylene glycol (**32**) was shown to suffer loss of its *secondary* hydroxyl group in cold concentrated sulfuric acid to the extent of 23% to yield the ketone **34**. Loss of the tertiary hydroxyl group of **32** (77%) led to a mixture of ketones **33** and **34**. The mechanism of the conversion of diphenyl-*p*-tolylacetaldehyde (**31**) into the two ketones **33** and **34** was also established[5,12].

In a very recent study Collins and coworkers[15] subjected 2-phenyl-2,3-*cis-exo*-norbornanediol (**35**) to rearrangement in cold concentrated sulfuric acid. The product, 3-*endo*-phenylnorbornanone (**36**), was shown to have been formed with intramolecular migration of the hydrogen at $C_{(3)}$ (shown with asterisk), and with inversion of



(35) E



F (36)

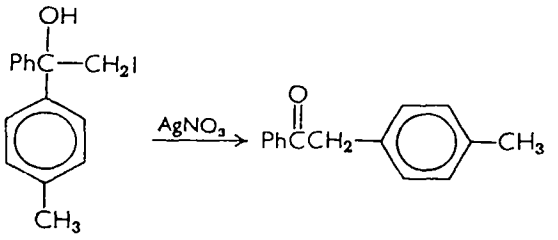
configuration. Experiments with a ^{14}C-label in the 2-position of **35** showed that the phenyl group in **36** was still attached to the original carbon. Although it is difficult to understand why the tertiary benzyl-type carbonium ion should prefer a bridged rather than an open structure, the results are best explained through the formation of the nonclassical ion E which rearranges to F by an intramolecular (6–1) migration of hydrogen.

Migratory aptitudes in the pinacol rearrangement have received exhaustive study[3–5], and it is clear that those groups which are the better electron donors are also better able to migrate to an adjacent carbonium center. Thus the usual order *p*-methoxyphenyl > *p*-tolyl > phenyl > *p*-nitrophenyl, etc., is maintained in the pinacol and also in the aldehyde–ketone rearrangement[12–14], in spite of the belief once held[3,4] that migratory aptitudes during the latter reaction were 'reversed'.

The early studies of Bachmann, Bailar, and others upon the migratory aptitudes of substituted phenyl groups in symmetrically substituted glycols are of considerable mechanistic importance, but have been reviewed so completely and so frequently[3–5] that they will not be discussed further in this chapter.

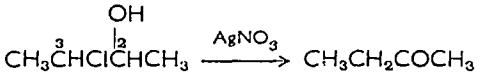
B. The Semipinacolic Rearrangements

The terms 'semipinacol' and 'semipinacolic change' were first applied by Tiffeneau[16] and later used by Bennett and Chapman[2] to signify rearrangement through secondary hydroxyl removal from an α-glycol containing both secondary and tertiary hydroxyl groups. Thus that fraction (23%) of the rearrangement[12] of 1,1-diphenyl-2-*p*-tolylethylene glycol (**32**) which yields ketone **34** through secondary hydroxyl loss followed by phenyl migration is a semipinacolic rearrangement. Unless the single alkyl or aryl substituent adjacent to the *s*-hydroxyl is strongly electron-donating, the semipinacolic rearrangement cannot usually compete with tertiary hydroxyl loss. Further, the semipinacolic rearrangement of an α-glycol often cannot be recognized without the use of an isotopic tracer. In the event that secondary hydroxyl is replaced with a better leaving group, such as halogen, amino, or *p*-toluenesulfonyl (compare with the conversion[8] **19** → **20**), then the semipinacolic reaction can be forced to take place at the expense of, and to the exclusion of, tertiary hydroxyl removal. Tiffeneau[17], for example, reported that the sole product resulting from treatment of 2-iodo-1-phenyl-1-*p*-tolylethanol (**37**) with silver nitrate was α-*p*-tolylacetophenone (**38**). Similarly, Alexander and Dittmer[18]



(37) (38)

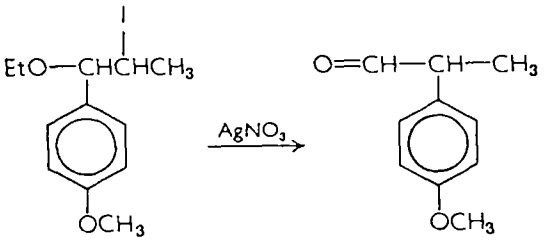
prepared methyl ethyl ketone (**40**) by the action of aqueous silver



(39) (40)

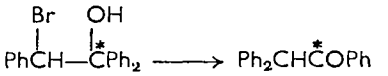
nitrate upon either of the diastereomers of structure **39**. The reaction can be formulated as proceeding with loss of chloride ion followed by a 1,2-shift of hydrogen from the 2-position to the carbonium center ($C_{(3)}$) so obtained.

Tiffeneau[19] prepared the aldehyde **42** by the action of silver nitrate on the iodohydrin **41**, a reaction which requires migration of the *p*-methoxyphenyl group to the carbon originally inhabited by the iodine atom.



(41) (42)

The action of mercuric ion upon an aqueous dioxane solution of 2-bromo-1,1,2-triphenylethanol (**43**) to yield benzhydryl phenyl ketone (**28**) was studied by Lane and Walters[20]. The same reaction

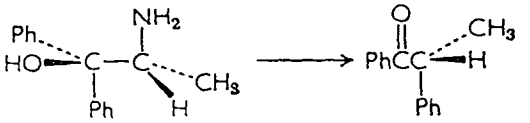


(43) (28a)

was investigated by Collins and Bonner[21] using ^{14}C to trace the course of the rearrangements. The tracer result is shown with the asterisks in the two formulae **43** and **28a**, and confirms that a

rearrangement of the carbon–carbon bonds has taken place; that is, a phenyl adjacent to the 1-position has shifted by means of a carbonium ion process to the carbon originally attached to bromine.

Another 'leaving group' often employed in semipinacolic rearrangements is the amino group. In an early study Luce[22] prepared 1-(α-naphthyl)acetophenone by the action of sodium nitrite in acid medium upon 2-amino-1-(α-naphthyl)-1-phenylethanol. One such reaction which has become a classic because of its mechanistic

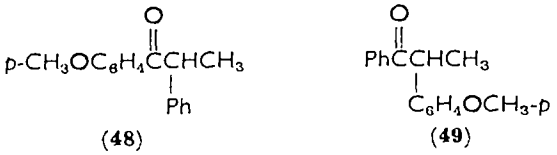


(+)-(**44**) (−)-(**45**)

importance is the deamination, originally studied by McKenzie, Roger and Wills[23], of (+)-2-amino-1,1-diphenypropanol (**44**) to yield (−)-α-phenylpropiophenone (**45**). The stereochemical study of McKenzie and coworkers[23], when combined with the configurational relationship later proved by Bernstein and Whitmore[24], was used for many years[3,4] as evidence that a Walden inversion takes place at the migration terminus during Wagner–Meerwein-type rearrangements which are accompanied by aryl or alkyl migration.

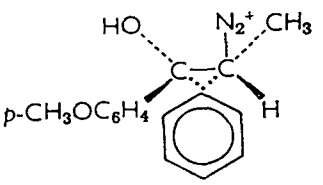
(**46**) (**47**)

Curtin and coworkers[25–29] carried out an extensive mechanistic investigation of the ketone-forming deamination of several amino alcohols. Of particular interest are their results for compounds **46** and **47**, which are closely related to the classic example[23,24] of 2-amino-1,1-diphenyl-1-propanol (**44**). Curtin showed that upon deamination of such amino alcohols as **46** the phenyl undergoes predominant migration (90%) to yield the ketone **48**, whereas the amino alcohol **47** undergoes deamination to produce predominantly (again about

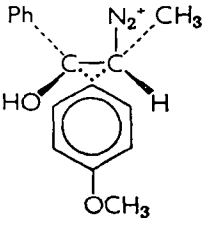


(**48**) (**49**)

90%) the ketone **49**. These and similar experiments were used by Curtin to state the '*cis* effect' in which **46**, for example, yields ketone **48** in greater amount because the transition state G, for



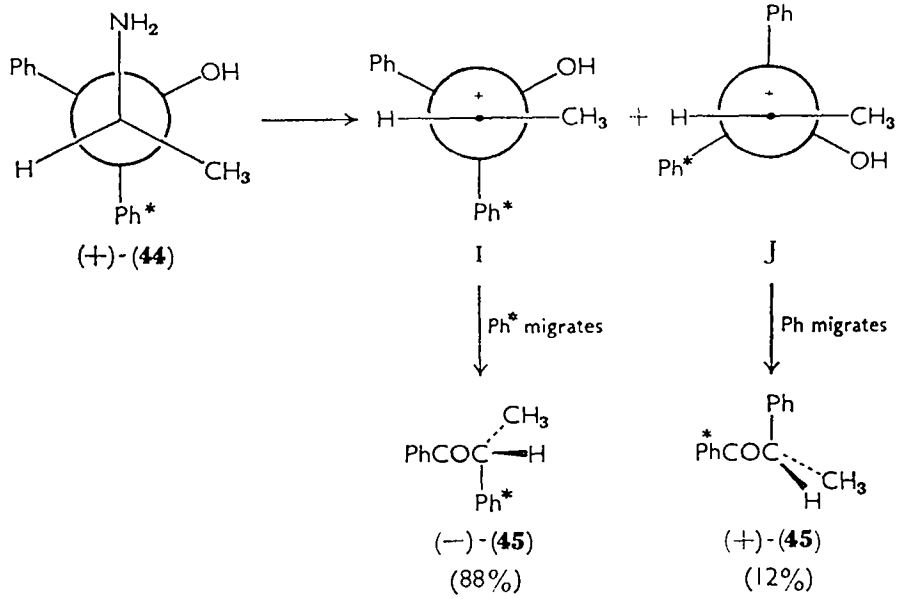
G



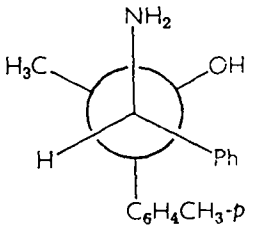
H

formation of ketone **48** places the two large bulky groups (methyl and anisyl) *trans* to each other. When, conversely, the anisyl group of **46** migrates, the methyl and phenyl must eclipse each other in the *cis* configuration to yield the transition state H. Since H is less favorable than G, the amino alcohol **46** reacts preferentially through G to form ketone **48**.

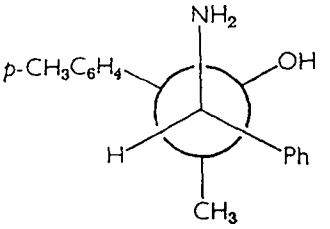
Collins and coworkers[30-33] studied several ketone-forming deaminations, combining stereochemical experiments with radioactive tracer techniques. Optically active 2-amino-1,1-diphenyl-1-propanol (e.g. (+)-**44**)[30] was subjected to deamination conditions, and the product was resolved. Oxidative degradation followed by radio-



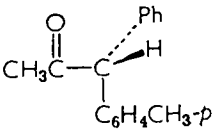
activity assay of the degradation products was used to demonstrate that *both* labeled and unlabeled phenyl groups undergo 1,2-shift through the *trans* transition state arising from ions I and J, respectively. The *cis* transition state similar to H, therefore, cannot be involved in the deamination of (+)-**44** (nor, by implication, during deaminations of **46**, **47** and other 2-amino-1,1-diarylpropanols studied by Curtin and coworkers[25-29]), for the unlabeled phenyl group of (+)-**44** shifts to the same side of the migration terminus originally bonded to the nitrogen. A further consequence of the important observation of Benjamin, Schaeffer and Collins[30] is that at least to the extent (12%) that ion J is involved in the deamination, the intermediate must be an *open carbonium ion*, for the carbon–nitrogen bond must cleave before migration of the unlabeled phenyl. In other studies Collins and coworkers[31-33] established that the optically active amino alcohol **50** undergoes deamination to produce predominately (−)-**52** with inversion (74%) at the migration terminus. The diastereomer (+)-**51**, however, when similarly treated



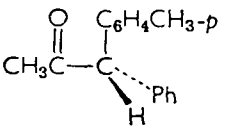
(−)-(**50**)



(+)-(**51**)



(−)-(**52**)



(+)-(**52**)

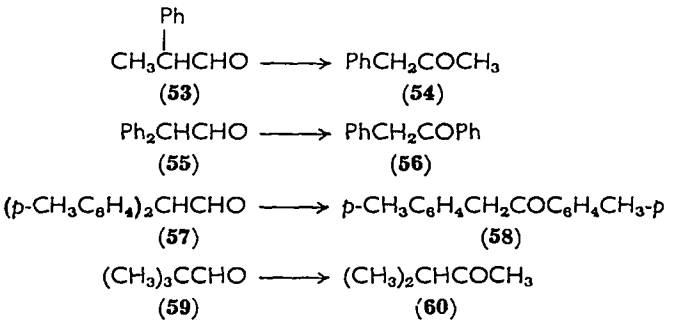
afforded more (+)-**52** than the levorotatory isomer in the approximate ratio 60:40. In the last example preponderant *retention* of configuration has occurred.

C. The Rearrangements of Aldehydes, Ketones, α-Ketols and Related Compounds (Acid-catalyzed)

Aldehydes, ketones, α-hydroxy aldehydes, α-hydroxy ketones, α-epoxy ketones and α-halo ketones all undergo rearrangement

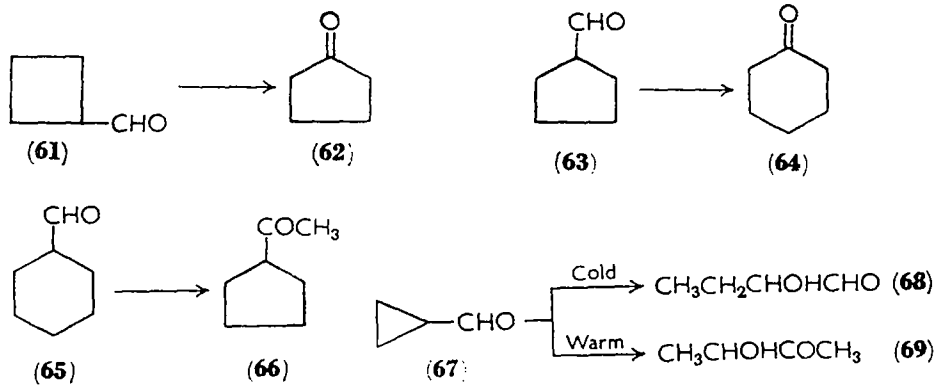
under both acidic and basic conditions. Some of these rearrangements are discussed in this section, whereas others, such as the Favorsky[34-36], and the rearrangement of α-diketones are taken up later.

The scope and synthetic value of the aldehyde–ketone rearrangement were demonstrated many years ago in a series of papers by Danilov and Venus-Danilova[37-43]. The rearrangements of, for example, triphenylacetaldehyde[10,37] to benzhydryl phenyl ketone (**29** → **28**), as well as the following transformations[43] were reported:



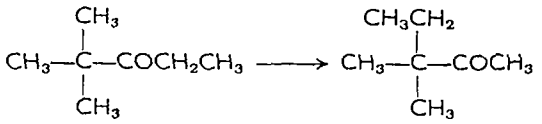
The mechanism of the aldehyde–ketone rearrangement has been clarified by Collins and coworkers[5,11,12], who correlated it with the pinacol rearrangement, and demonstrated that the apparently anomalous reversal of the migratory aptitudes exhibited during certain of these reactions could be explained through an equilibration of several carbonium ion intermediates. It was possible to calculate the migratory aptitudes[12-14] and to show that the normal order[3-5] was not reversed (see section II.A).

Venus-Danilova[44,45] reported the acid-catalyzed rearrangements of the cyclic aldehydes **61**, **63**, **65** and **67** with the results shown,



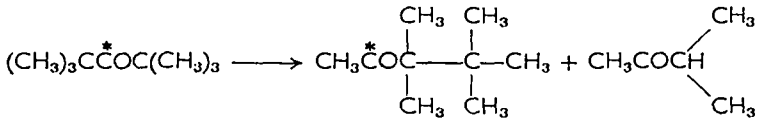
most of which are easily explainable by assuming that normal carbonium processes are taking place. The formation of cyclopentyl methyl ketone (**66**) from cyclohexanecarbaldehyde (**65**) is particularly intriguing.

Zook and coworkers[46,47] found that *t*-butyl ethyl ketone (**70**)



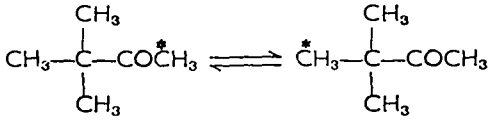
(**70**) (**71**)

was slowly converted, in concentrated sulfuric acid, into *t*-amyl methyl ketone (**71**). The rearrangement[47] of hexamethylacetone (**72**) (in 97% sulfuric acid) is most striking, since both methyl pentamethylethyl ketone (**73**) and methyl isopropyl ketone (**74**) are prod-



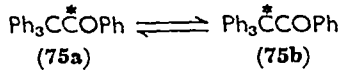
(**72**) (**73**) (**74**)

uced in approximately equal amounts. These same investigators[47] report the rearrangement of eight other ketones under similar conditions. Barton and Porter[48] also studied the rearrangement of **72** to **73** and showed, with ^{14}C-labeling, that the carbonyl carbon of **73** still possesses all of the ^{14}C activity originally present in the carbonyl group of **72**. Rothrock and Fry[49], in their study of the acid-catalyzed rearrangement of *t*-butyl ^{14}C-methyl ketone (**2a**) demonstrated that although no other ketone is formed, the labeled methyl group still undergoes deep-seated rearrangements, for the isotope position isomer (**2b**) was produced. Fry and coworkers[50-52] later demon-



(**2a**) (**2b**)

strated the remarkable isotope positional isomerization, catalyzed by strong acids, shown in the equilibrium **75a** ⇌ **75b**. These same

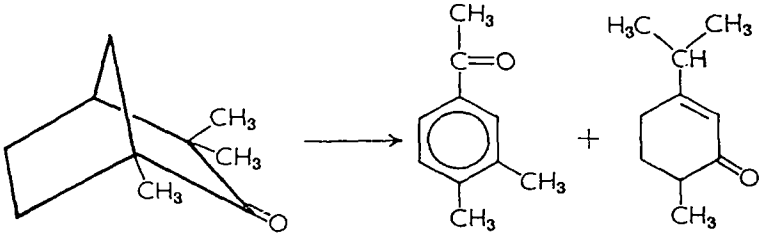


(**75a**) (**75b**)

investigators[50-52] also demonstrated that the action of perchloric

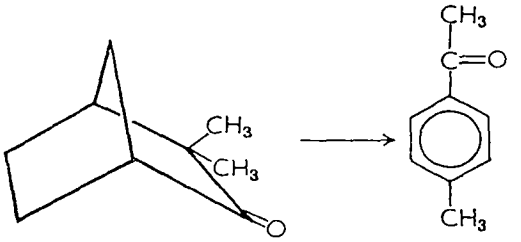
acid upon 2-butanone affords acetone, 2-pentanone, 3-pentanone, 3-hexanone and several unidentified products, illustrating disproportionation as well as rearrangement during the reaction. Similar results[50-52] were obtained by the action of perchloric acid upon 3-pentanone.

Fenchone (**76**), upon treatment with concentrated sulfuric acid,



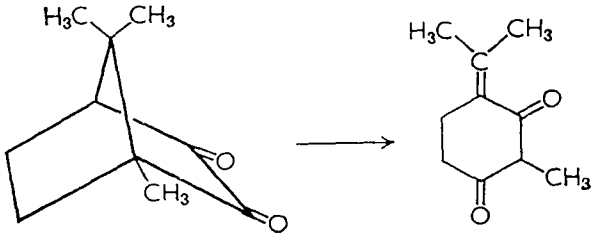
(**76**) (**77**) (**78**)

is converted into 3,4-dimethylacetophenone (**77**) and carvenone (**78**)[53,54]. Lutz and Roberts[55], using ^{14}C, have studied the mechanism of these transformations. In like fashion camphenilone (**79**)



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

affords *p*-methylacetophenone (**80**) in low yield[56], and camphorquinone (**81**) is converted into isocamphorquinone (**82**)[59].

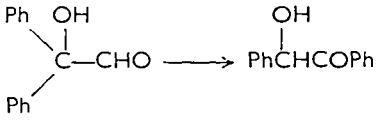


(**81**) (**82**)

All of the reactions so far discussed in section II on acid-catalyzed rearrangements can easily be rationalized through carbonium ion

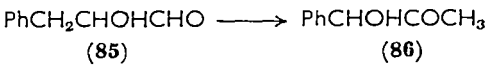
intermediates. The intimate details for many of these rearrangements, however, have not been so well established as for the pinacol and aldehyde–ketone transformations. In some cases (e.g. **65** → **66** and **72** → **73** + **74**) so many discrete steps must be written to explain the observed facts that it would appear worthwhile to reinvestigate these remarkable reactions, for it might be possible to uncover some novel and dramatic carbonium ion processes.

α-Hydroxy aldehydes also undergo rearrangement in acid medium, as shown by the conversion of diphenylglycolaldehyde (**83**) into benzoin (**84**)[58]. Benzylglycolaldehyde (**85**) upon similar treatment (alcoholic solution with a few drops of sulfuric acid) yields acetyl



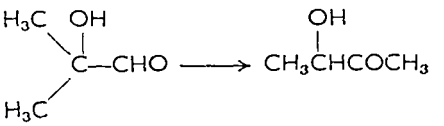
(**83**) (**84**)

phenyl carbinol (**86**)[59], whereas α-hydroxyisobutyraldehyde (**87**)



(**85**) (**86**)

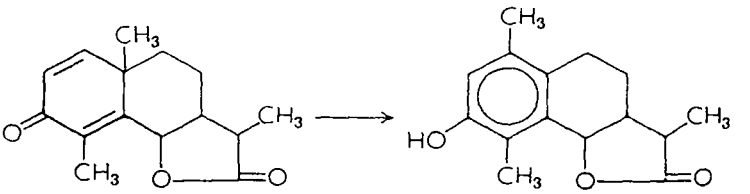
is reported to yield the α-hydroxy ketone **88**[60,61].



(**87**) (**88**)

D. The Dienone–Phenol, Quinamine and Some Related Rearrangements

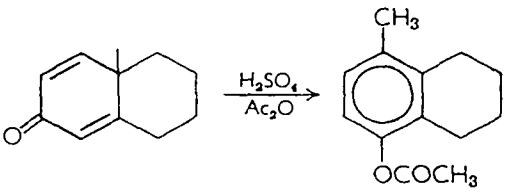
Santonin (**89**), upon being treated with mineral acid, is converted into the desmotroposantonin **90**[62–65], a transformation which appears



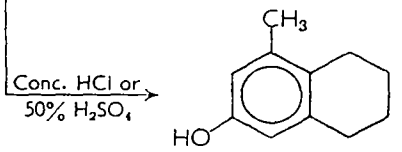
(**89**) (**90**)

to be the first known example of the dienone–phenol rearrangement. Since the dienone–phenol rearrangement has been reviewed

recently[66] and the mechanism has been very adequately treated, only one other example will be mentioned here, namely the rearrangement, in acetic anhydride and sulfuric acid, of compound **91**. Under the anhydrous conditions employed by Woodward and Singh[67] only the 4-methyl-1-tetralol acetate (**92**) was formed. Treatment of **91** with concentrated hydrochloric acid, or with 50% sulfuric acid, however, afforded the 4-methyl-2-tetralol **93**[68]. The formation of **92** can be rationalized through the intervention of a



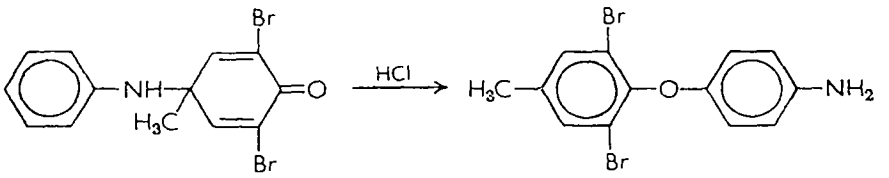
(**91**) (**92**)



(**93**)

spirane intermediate, whereas **93** must be formed as a result of methyl migration[66].

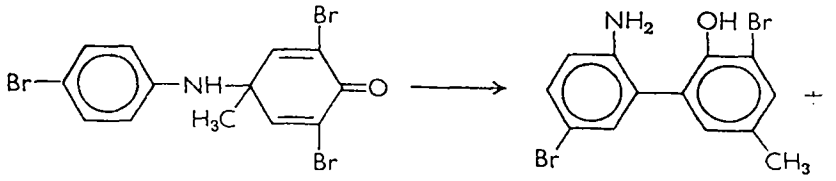
The acid-catalyzed rearrangements of quinamines (anilinocyclohexadienones)[69,70] resemble the dienone–phenol rearrangement, although the mechanisms of these two reactions are not necessarily similar. Miller[71,72] has recently studied the two major types of rearrangement exhibited by several such quinamines. When the aniline residue contains no *para* substituent, as in structure **94**,



(**94**) (**95**)

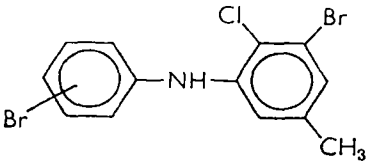
treatment of the quinamine with hydrochloric acid yields a substituted aminodiphenyl ether as shown in structure **95**. When the

para position is substituted (**96**), there are two major products, a substituted biphenyl (**97**) and the amine (**98**). Miller prefers a mecha-



(**96**)

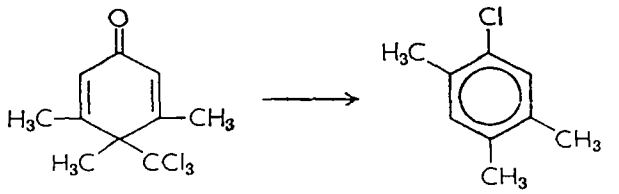
(**97**)



(**98**)

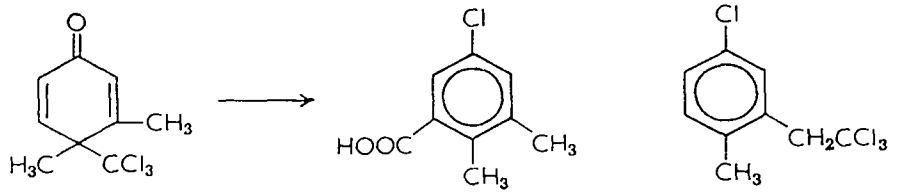
nism for these transformations in which π-complex intermediates are formed.

Newman and coworkers[73] studied the rearrangement, in poly-



(**99**) **100**

phosphoric acid, of the dienone **99** to 1-chloro-2,4,5-trimethylbenzene (**100**). With polyphosphoric acid, dienone **101** yields the acid **102**, whereas when **101** is treated with phosphorous penta-

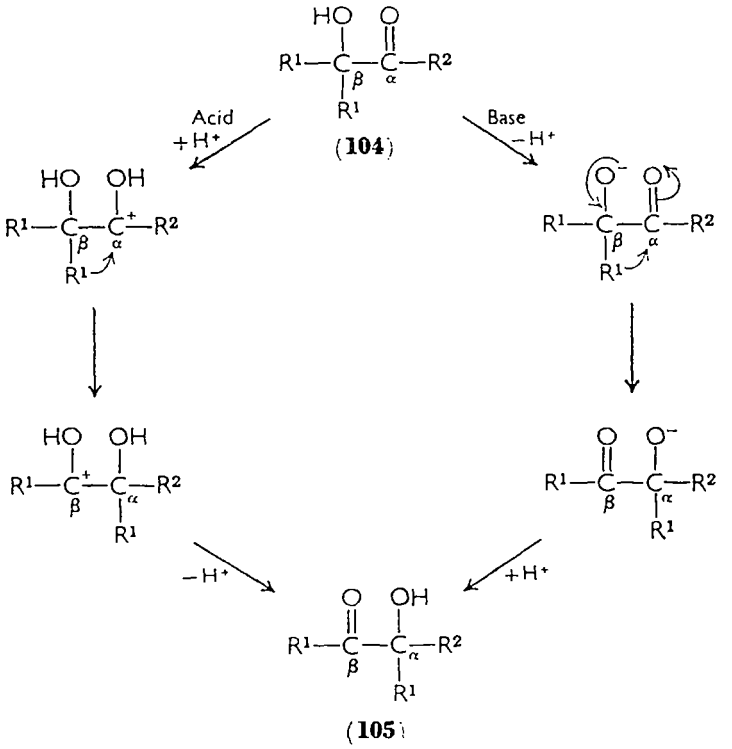


(**101**) (**102**) (**103**)

chloride[73]) 1-chloro-3-(β-trichloroethyl)-4-methylbenzene (**103**) is produced.

E. The α-Ketol and Related Rearrangements (Base-catalyzed)

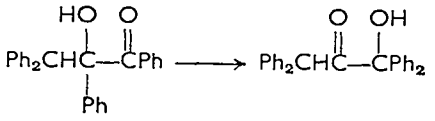
Most ionic molecular rearrangements involve migration of some group with its bonding electrons to an adjacent electron-deficient center. Such rearrangements are called 1,2-shifts. In a carbon-to-carbon rearrangement electron release to the migration origin (C_β) assists the rearrangement, whereas electron deficiency at the migration terminus (C_α) is required. If the assistance at C_β is sufficient, then the electron deficiency at C_α need not be large. In the reactions just discussed acid was used to promote a deficiency of electrons at C_α, whereas in the reactions to be considered now, base brings about electron release at C_β. The migration terminus will be electron-deficient because of an attached electronegative atom; in the benzilic acid rearrangement, for example, C_α is the carbon of a carbonyl group, and in certain Favorsky rearrangements it is a carbon attached to halogen. The similarity of the acid- and base-catalyzed rearrangements is illustrated in the following two-reaction sequences through which the α-ketol **104** can be converted either by acid or by base into the isomer **105.**



(**104**)

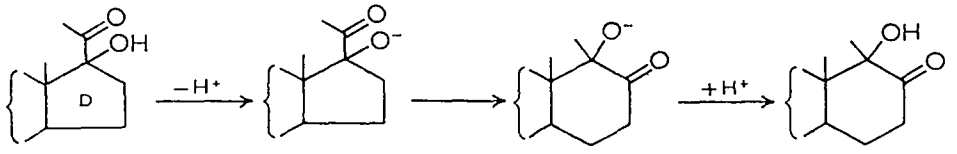
(**105**)

Two examples of the base-promoted rearrangement of α-ketols are (*a*) the formation of 2-oxo-1,1,3,3-tetraphenyl-1-propanol (**107**) from α-benzhydrylbenzoin (**106**)[74], and (*b*) the conversion of α-hydroxybutyraldehyde into acetoin[75]. The synthetic value of the



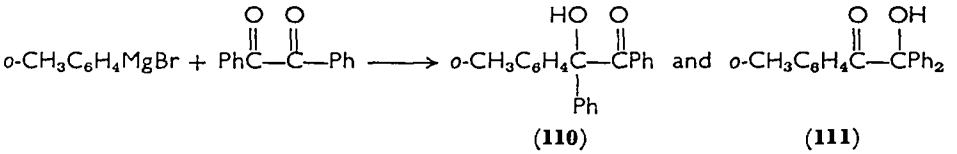
(**106**) (**107**)

α-ketol rearrangement, particularly in ring expansions to produce D-homosteroids, has been discussed by the Fiesers[76]. Ruzicka and Meldahl first observed this ring expansion in the treatment of 17-hydroxy-20-oxo steroids (**108**, ring D only shown) with alkali[77].



(**108**) (**109**)

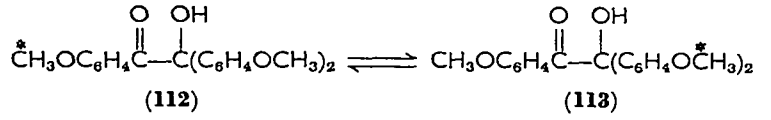
The possibility of rearrangement is always present during reactions which produce α-ketols, such as the benzoin condensation or the addition of one equivalent of an organometallic reagent to a diketone. A good example is the addition[78] of *o*-tolylmagnesium bromide to benzil to yield a compound which was mistakenly called '*α-o*-tolylbenzoin (**110**)'. The incorrect structure was the cause of some



(**110**) (**111**)

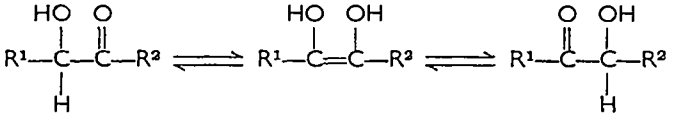
confusion[79] until subsequent workers isolated both the expected product (**110**) and the rearranged product (**111**) and proved their structures[80]. The '*α-o*-tolybenzoin' was shown, in fact, to be α-phenyl-2-methylbenzoin (**111**). Analogous rearrangements have been observed in the additions of mesitylmagnesium bromide to anisil[81], of mesitylmagnesium iodide to benzil[82], and of *o*-tolyllithium to benzil[83]. An interesting example of the rearrangement of an α-ketol under basic conditions was observed with α-*p*-methoxyphenylanisoin (**112**) labeled with ^{14}C in one of the methoxy groups[80]. Equilibration of the position of labeling in this case (**112** ⇌ **113**) is

analogous to the racemization of an optically active compound in that there is no free energy difference between reactant and product.



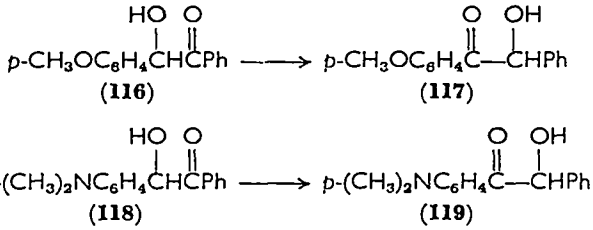
(112) (113)

The base-promoted α-ketol rearrangement resulting in a change of the carbon skeleton probably occurs only when the carbinol group is tertiary. If one R^1 in **104** is hydrogen, enolization presents a route for an isomerization (**114** ⇌ **115**) which is easily brought about by base. When R^1 and R^2 (in **114**) are aryl groups, the



(114) (115)

compound is a benzoin and its stability relative to **115** is easily predicted on the basis of ordinary electronic effects. Two such isomerizations (**116** → **117**[84] and **118** → **119**[85]) are shown. Because



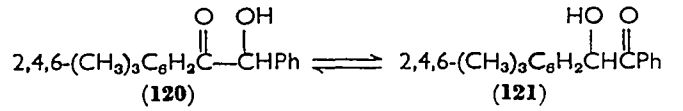
(116) (117)

(118) (119)

the catalyst (cyanide ion) for benzoin condensation is basic, the equilibrium **114** ⇌ **115** is established in the reaction of two aldehydes during the mixed benzoin condensation. If one isomer is markedly more stable, as from condensation[86] of benzaldehyde with *p*-dimethyl-

$$PhCHO + p\text{-}(CH_3)_2NC_6H_4CHO \xrightarrow{CN^-} \mathbf{119}$$

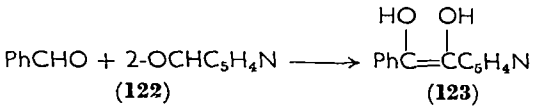
aminobenzaldehyde, then only one benzoin (**119**) is isolable. In other cases, e.g. with 2,4,6-trimethylbenzoin, both isomers (**120** and **121**) are isolable[87]. Synthetic techniques have been developed for



(120) (121)

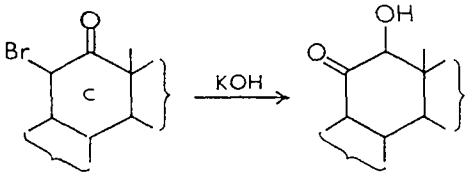
obtaining even the unstable isomer of a mixed benzoin[88]. In some

cases, particularly those involving certain heterocyclic aryl groups for R^1 or R^2 in the benzoin, the intermediate 'enediol' can be isolated from a condensation of mixed aldehydes, as for example, the production of **123** from benzaldehyde and 2-formylpyridine (**122**)[89]. In a recent review of enediols the stabilizing influence of chelation on structures like **123** has been discussed[90].



(122) (123)

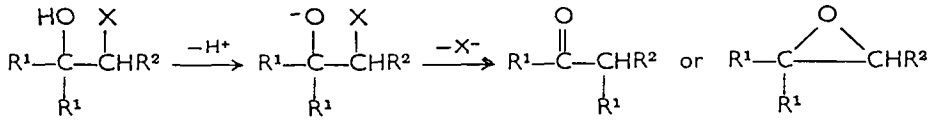
Acyloins **114**, where R^1 and R^2 are aliphatic or alicyclic residues, may also undergo easy equilibration with base to form **115**. Such a possibility should be considered when base-promoted reactions are used in the syntheses of α-hydroxy ketones, for example, by the hydrolysis of α-halo ketones. In the following illustration (**124** to **125**), which is taken from synthetic work in the steroid field, the substituted cyclohexane ring in **124** represents the c ring of 11β-brome-



(124) (125)

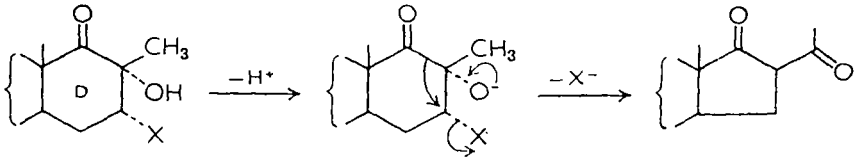
12-oxocholanate[91]. With certain structural features, the intermediate enediol may be more stable than either α-hydroxy ketone; ascorbic acid is an example. Isomerization of an aldose to a ketose, e.g. mannose to fructose, an important biosynthetic process effected by isomerase enzymes[92], most likely proceeds through an enediol, i.e. **114** to **115** with R^2 = H. The same carbohydrate rearrangement is brought about *in vitro* by alkali alone[93].

We have already pointed out that the base-induced α-ketol rearrangement with a tertiary carbinol (**104** → **105**) is analogous to the acid-induced pinacol rearrangement. One might also anticipate that tertiary carbinols α-substituted with good leaving groups might undergo a base-induced rearrangement, **126** → **127**, analogous to the



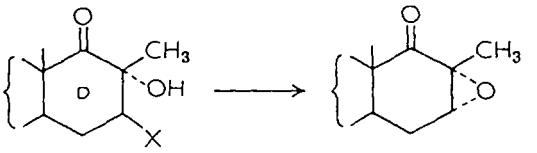
(126) (127) (128)

semipinacolic change, but a competing reaction which generally predominates is epoxide (**128**) formation. When stereochemical factors favor the rearrangement, however, ketone formation (**126** → **127**) does occur. The substituted D-homo ring of a pregnone derivative is shown in **129**; the leaving group is *cis* to the tertiary hydroxyl and therefore unsuitably located for epoxide formation; hence base causes the indicated rearrangement to **130**[94]. When the leaving



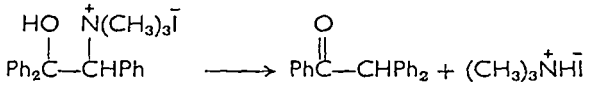
(**129**, X = OSO_2CH_3) (**130**)

group in the same system is *trans* to the tertiary hydroxyl, as in **131**, treatment with base results in simple epoxide (**132**) formation[95].



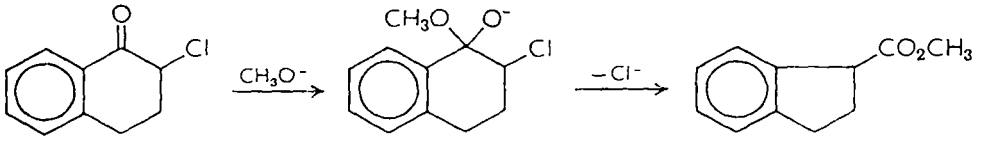
(**131**, X = Br) (**132**)

Another example of the rearrangement **126** to **128** is the formation[96]



(**133**) (**28**)

of benzhydryl phenyl ketone from **133**, and still other examples have been recognized[97]. Further, the ionic intermediate necessary for this rearrangement may be attained by attack of a nucleophile on an α-halo ketone. Thus the rearrangement[98] of 2-chloro-1-tetralone (**134**) by methoxide ion as the nucleophile probably proceeds as shown. An analogous reaction is formation of 1-phenyl-

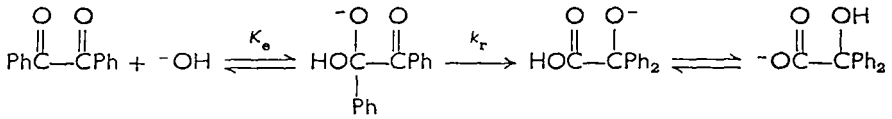


(**134**) (**135**)

cyclohexanecarboxylic acid from 1-chlorocyclohexyl phenyl ketone and hydroxide ion[99]. (Cases of the Favorsky reaction involving 'cyclopropanone' intermediates are discussed later.)

F. The Benzilic Acid and Related Rearrangements

The benzilic acid rearrangement is by far the best known 1,2-shift effected by base-promoted electron release to the migration origin (C_β). In fact the formation of benzilic acid (**137**) from benzil (**136**) would appear to be the first recognized molecular rearrangement reaction, having been discovered by Liebig in 1838[100]. There is little doubt that the mechanism of this reaction involves reversible addition (K_e) of hydroxide ion to one carbonyl group to give an intermediate anion which is completely analogous to the anionic intermediate in the α-ketol rearrangement (**104** → **105**). Following this, the 1,2-shift occurs in a rate-determining step (k_r) and prototropic equilibration yields the product. While alternatives to this



(**136**) (**137**)

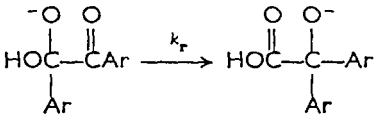
mechanism have been debated both before and since, in 1928 Ingold proposed these three steps as shown[101], and today there exists an extensive body of confirming data arising from application of virtually all of the physical organic chemist's tools, such as isotopic tracer techniques, kinetic analysis, migratory aptitude determinations, etc.

Reversibility of the first step (K_e) was established by the Roberts and Urey demonstration[102] that benzil exchanges oxygen in ^{18}O-enriched water in the presence of base more rapidly than it rearranges. Kinetically the overall reaction is second-order, first in benzil and in hydroxide ion, and certain bases such as phenoxide ion do not effect the reaction[103]. Thus, if the second step (k_r) is rate-determining, the overall second-order rate coefficient will contain the equilibrium constant of the first step (equation 1).

$$\text{Rate} = k_r K_e[\text{benzil}][\text{hydroxide}] \qquad (1)$$

From a study of the steric effect on the benzilic acid rearrangement, Eastham, Nations and Collins concluded that the transition state for the process closely resembles the intermediary anion produced in the first step[104]. In other words the key 1,2-shift has proceeded but

very little before the energy maximum for reaction is passed, and hence this energy requirement is predictable from the structure of the intermediary anion (**138**)[105]. Electron-attracting substituents on

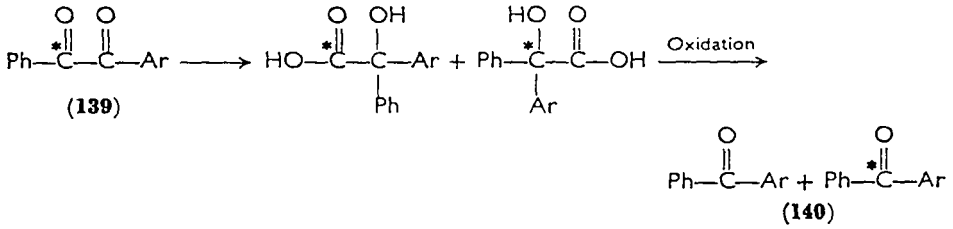


(**138**)

the aromatic ring (Ar in **138**) should stabilize this ion and enhance the overall reaction rate of a symmetrical benzil, whereas electron-releasing substituents then should slow the reaction. Indeed it is found that methoxy-, methyl- or amino-substituted benzils rearrange slower[106], while chloro-substituted benzils rearrange faster[107] than does benzil itself.

Numerous authors have proposed other transition states[108,109], particularly those in which the key 1,2-shift in **138** is *accompanied* by proton migration, i.e. a concerted process which obviates the prototropy Ingold depicted as a third and distinct step. Eastham and colleagues rejected the concerted process on the grounds that the required transition state would not resemble **138**[104]. Hine rejected it on the grounds that the rearrangement in a deuterated system is not retarded, as would be expected were proton transfer involved in the rate-determining step[110].

With an unsymmetrical benzil (**139**), whichever aromatic residue rearranges, the product structure is the same. Hence percentage migrations of Ar groups in **139** must be determined by isotopic labeling, e.g. as outlined below for **139** labelled with ^{14}C in the carbonyl adjacent to phenyl. It is seen that the ratio of radioactivity



(**139**) (**140**)

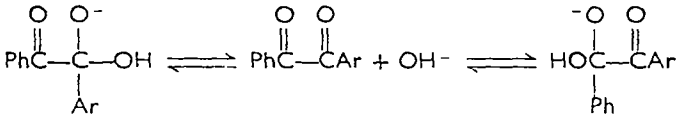
of the aryl phenyl ketone to that of the starting benzil will be the fraction of reaction proceeding by migration of the aryl group; values for a few selected aryl groups are shown in Table 1.

Inspection of Table 1 reveals that migratory aptitudes in the benzilic acid rearrangement do not correlate with those in the pinacol

TABLE 1. Percentage migrations of Ar in PhCOCOAr.

Ar	Migration (%)	Ref.
o-Tolyl	2·7	104
p-Methoxyphenyl	31·8	111
p-Tolyl	38·8	108
m-Chlorophenyl	81·2	108
Benzyl	100	112

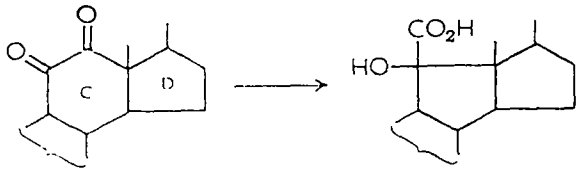
rearrangement, in which electron-releasing groups on an aryl group favor its migration. Here, however, electron release by an aryl group decreases the equilibrium concentration of the intermediate anion (**141**) in which Ar can migrate. Thus, since the relative amount of



(**141**) (**139**) (**142**)

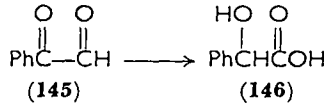
aryl *vs.* phenyl migration must be a function of the relative concentrations of this ion (**141**) and the ion (**142**) in which phenyl can migrate, electron release by the aryl group retards its migration. Conversely, ion **141** and aryl migration would be favored by an electron-attracting aryl group. In other words K_e is the factor which dominates the overall rate of migration expressed in equation (1). On this basis the effects revealed by data in Table 1 and by results with a number of other labeled unsymmetrical benzils can be explained. These results, as well as an historical summary of other mechanistic studies on the benzilic acid rearrangement, are available[113].

Examples of α-diketone systems which have been observed to undergo the benzilic acid rearrangement are multitudinous. Just a few examples are shown here to stress the generality of this reaction. The reaction will proceed in purely aliphatic systems and has been used to contract the steroid ring c (**143** → **144**). Hydrogen migrates

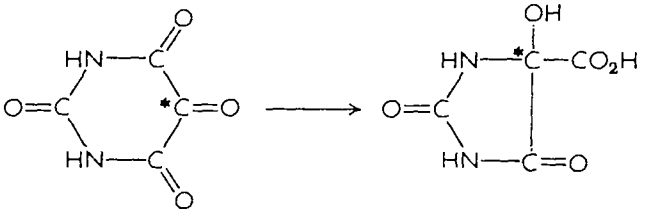


143 (**144**)

preferentially to phenyl[114] in the reaction **145** → **146**. Certain heterocyclic systems also rearrange, and in one such case, that of



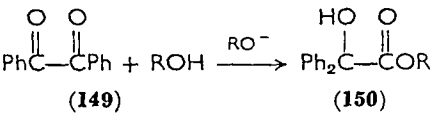
(**145**) (**146**)



(**147**) (**148**)

alloxan (**147** → **148**), nitrogen has been shown to migrate preferentially to carbon[115].

An interesting facet of the benzilic acid rearrangement is that it can be effected by certain bases other than hydroxide ion, in some cases even by bases and in solvents neither of which contain oxygen. Selman and Eastham have cited some examples and rationalized this unpredictable result, that is, unpredictable on the basis of the general mechanism **136** → **137**. A predictable result, but one not observed until rather recently, is that alkoxide ion will effect rearrangement of benzil to an alkyl benzilate. There were repeated studies of the reaction of benzil with alkoxide dating back to the last century, but it was not until 1956 that Doering and Urban[81] elucidated the conditions for the *benzilic ester rearrangement* (**149** → **150**). These workers formed both methyl and *t*-butyl esters

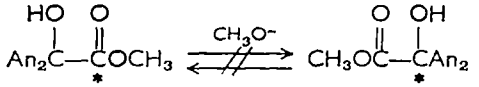


(**149**) (**150**)

by this rearrangement, rationalized the failures of previous workers to obtain esters, and gave a kinetic analysis of the rearrangement. All of their findings are consistent with the Ingold mechanism, cf. **136** → **137**, with the hydroxyl shown replaced with alkoxyl and without the third step (prototropy).

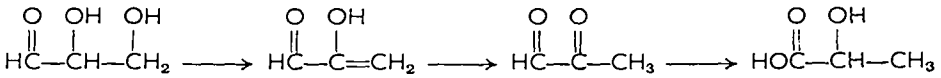
The view is held by some that the benzilic acid type rearrangement is reversible[116]. This view now seems unlikely since Eastham and Selman subjected ^{14}C-carbonyl labeled anisilic acid and its methyl

ester (**151**) to both mild and vigorous basic conditions and found no rearrangement of the ^{14}C-label[117].



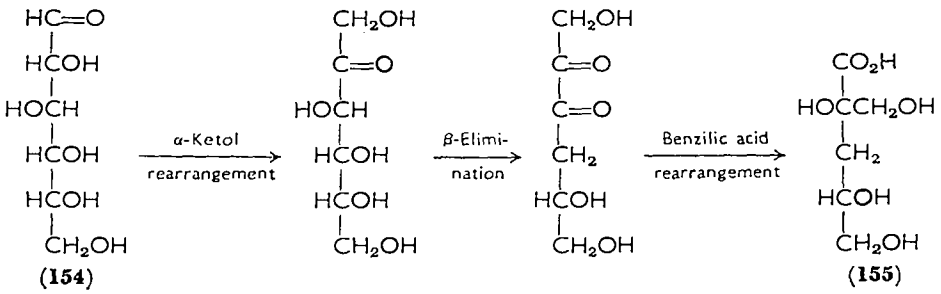
(**151**, An = *p*-$CH_3OC_6H_4$)

Because α-diketones undergo the benzilic acid rearrangement, any compound which is converted into an α-diketone by base may be expected to yield a rearrangement product. Thus, since base with an α,β-dihydroxy carbonyl compound can cause dehydration (β-elimination) to an α-diketone (or its enol)[118], the base may lead ultimately to an α-hydroxy acid. The transformation of glyceraldehyde to lactic acid (**152** → **153**) is an example of the two-step sequence[119]. To this sequence one must add a third step, the α-ketol



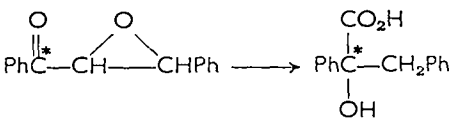
(**152**) (**153**)

rearrangement, in considering many of the alkali-induced transformations of carbohydrates. Thus the formation of some isosaccharinic acid (**155**) from glucose (**154**) may proceed as shown. Base-catalyzed carbohydrate rearrangements have been reviewed[120].



(**154**) (**155**)

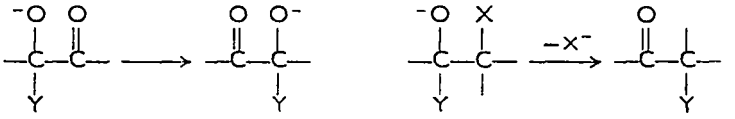
α,β-Epoxy ketones can also rearrange with base to α-diketones and hence produce α-hydroxy acids, as illustrated here with the rearrangement of labeled benzilideneacetophenone oxide (**156**)[112].



(**156**) (**157**)

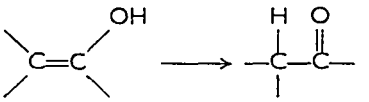
G. Generalizations Concerning Certain Ketogenic Rearrangements

To generalize the class of reactions which includes the α-ketol, benzilic acid and related rearrangements, we see that a property common to all is the formation of a carbonyl group from an oxide ion at C_β (migration origin) as the migrating group takes its bonding electrons to C_α (migration terminus). It is possible to look upon the energy gained in forming the carbonyl group as the 'driving force' for the reaction; perhaps all such cases should be classed as *ketogenic rearrangements*. Acceptance of electrons by C_α from the migrating group results either in addition to a carbonyl group at C_α or in nucleophilic substitution there. Selman and Eastham[113] have tabulated sixteen different functional arrangements for C_β—C_α which have been observed to rearrange; those cases involving nucleophilic substitution at C_α were not included. Perhaps the most interesting feature of these rearrangements is the variety of migrating groups which have been observed[113]. In general, then, one should anticipate the possibility of a ketogenic rearrangement with any ions of structures K or L, or in any reactions which may give rise to these ions.



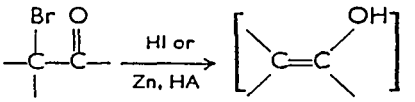
K L

The classical ketogenic reaction is reversal of enolization, commonly called ketonization. Although this process itself (equation 2) is



(2)

not generally classified as a molecular rearrangement, the enol may be an intermediate in rearrangement reactions (cf. **152** → **153**) leading to ketones. Hence one important aspect of ketonization, the stereochemistry of the process, is worthy of consideration here. A



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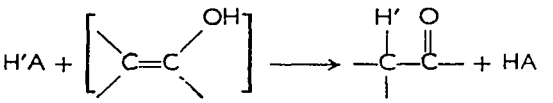
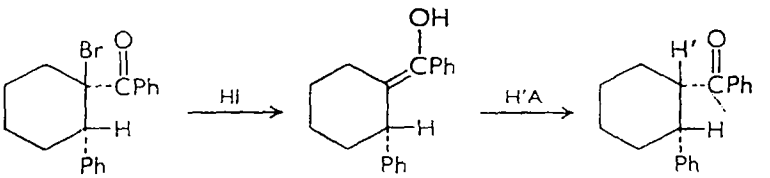


(4)

reaction which has proved useful in generating enols that ketonize, and which has been amenable to stereochemical studies, is the reduction of an α-bromo ketone to remove halogen. This reduction (equations 3 and 4) is accomplished in acid (HA) by either zinc or hydrogen iodide.

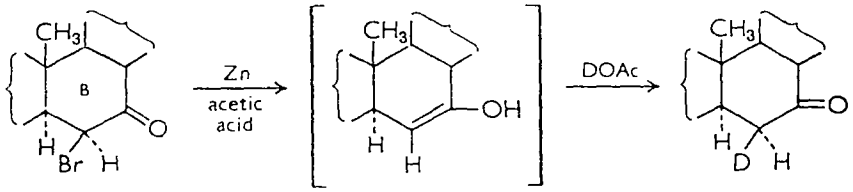
The stereochemistry of the ketone produced (equation 4) is apparently controlled by the direction of approach by acid to the enol. Thus Zimmerman has pointed out several cases in which approach to one side of an enol is obviously favored, and ketonization in these places the entering hydrogen on the less hindered side[121]. For example, debromination of 1-benzoyl-1-bromo-2-phenylcyclohexane (**158**) with hydrogen iodide produces *cis*-1-benzoyl-2-phenylcyclohexane (**160**), despite the fact this *cis* compound is less stable than the *trans* isomer[122]. The 2-phenyl group on one side of



(**158**) (**159**) (**160**)

enol **159** sterically hinders the approach of a proton donor to that side.

If the ketonization produces a cyclohexanone, there is a strong tendency for the hydrogen atom introduced (H′ in equation 4) to be axial. Corey and Sneen[123] have given a rational analysis of the electronic effect which favors the axial approach of the proton donor to a six-membered enol. An illustration of the effect[123], debromination of a 6-bromo-7-oxo steroid (**161**) with zinc and deuteroacetic acid (DOAc) produced a 6β-deutero steroid (**163**); deuterium was introduced into the axial position despite considerable hindrance to this approach by the axial methyl group of the steroid 10-position.

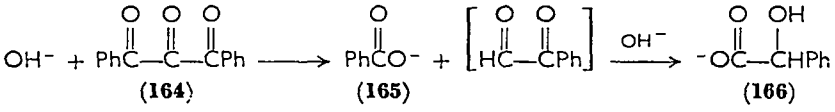


(**161**) (**162**) (**163**)

More recently Zimmerman employed both electronic and steric factors in rationalizing the stereochemistry of ketonization[124].

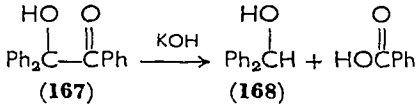
H. The Favorsky and Related Rearrangements

A competing reaction for benzilic acid type rearrangements, nucleophilic substitution on the carbonyl group, is fostered by strongly basic reaction conditions and is another consequence of the electron deficiency of carbon in the carbonyl group. Attachment of a second electron-withdrawing group to this group so enhances its electron deficiency, i.e. increases the electrophilicity of the carbonyl carbon, that S_N2 reactions readily occur there. For example, hydroxide ion causes cleavage of diphenyl triketone (**164**) to benzoic acid (**165**) and phenylglyoxal, which itself then rearranges to mandelic acid (**166**)[111].

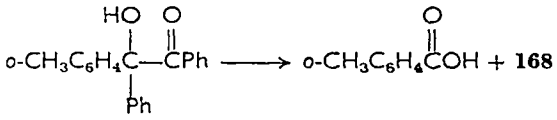


(**164**) (**165**) (**166**)

Under vigorous alkaline conditions, α-ketols undergo a similar cleavage (e.g., phenylbenzoin (**167**) to benzyhydrol (**168**) and benzoic acid), and this cleavage may be preceded by rearrangement of the ketol, e.g., *o*-tolybenzoin (**169**) to *o*-toluic acid (**170**) and benzhydrol.

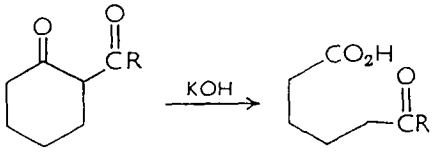


(**167**) (**168**)



(**169**) (**170**)

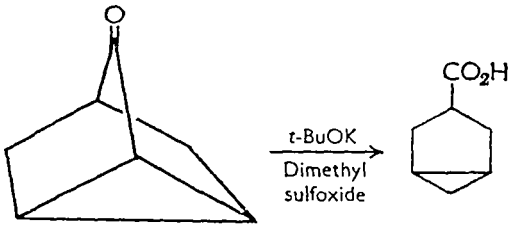
There are many other strictly analogous cases of carbon–carbon bond cleavage by nucleophilic substitution on the carbonyl group, including three such varied reactions as the 'acid hydrolysis' of β-dicarbonyl compounds[125], the haloform reaction[126], and aroyl cyanide alcoholysis[117], illustrated below. Even monofunctional



$$(CH_3)_3CCCH_3 \xrightarrow[NaOH]{Br_2} (CH_3)_3CCO_2H + HCBr_3$$

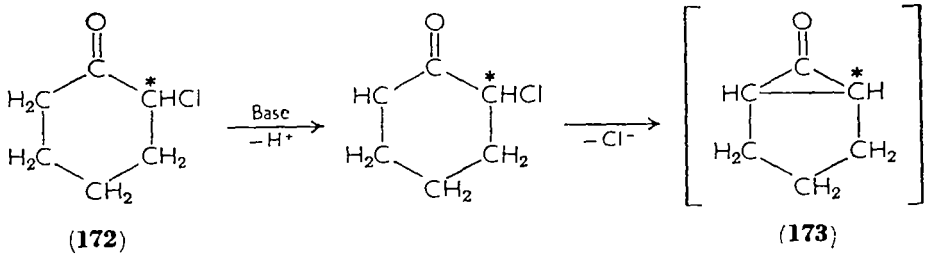
$$p\text{-}CH_3OC_6H_4CCN \xrightarrow{CH_3OH} p\text{-}CH_3OC_6H_4COCH_3 + HCN$$

ketones, if they cannot enolize, can be directly cleaved when treated with a sufficiently powerful base. A recent example is the cleavage of the tricyclic ketone (**171**) with potassium *t*-butoxide in dimethyl sulfoxide[127].

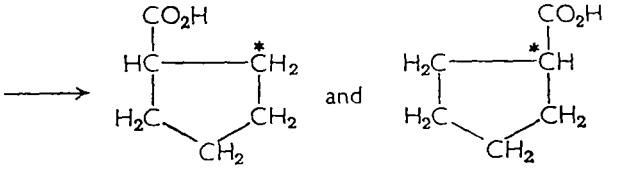


(**171**)

Bond cleavage from the carbonyl group in a cyclopropanone system should be particularly facile. Such electrophilicity of a cyclopropanone system (a consequence of the considerable *s* character of all three ring bonds) makes isolation of the structure itself elusive, but provides a rationale for its intermediacy in the Favorsky rearrangement[128]. Perhaps the best evidence for a cyclopropanone intermediate in the reaction of an α-halo ketone comes from the work of Loftfield with ^{14}C-labeled 2-chlorocyclohexanone (**172**)[129]. Starting

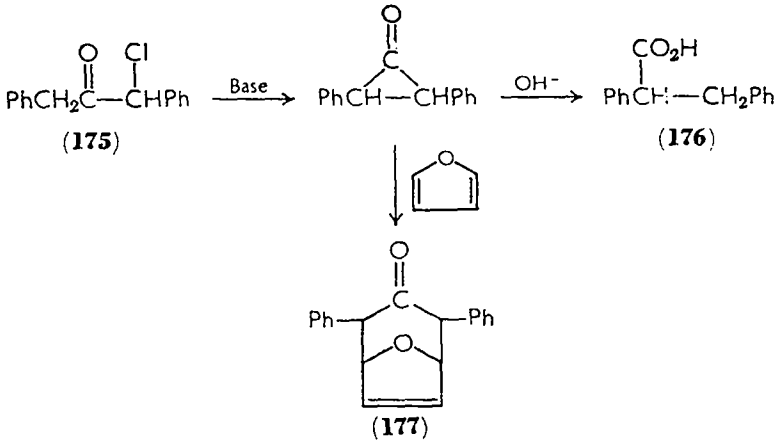


(**172**) (**173**)



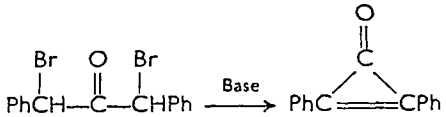
(**174**)

with the ketone specifically labeled at the 2-position, cyclopentanecarboxylic acid (**174**) was obtained in which the label was distributed between the 1- and 2-positions. This finding is consistent with the interpretation that the reaction proceeds by an intramolecular alkylation to give the symmetrical cyclopropanone **173**, which is then cleaved to give the acids. Additional evidence for this type of symmetrical intermediate comes from work with α-chlorodibenzyl ketone (**175**), which under the ordinary Favorsky conditions yields diphenylpropionic acid (**176**). However, Fort recently found that this ketone in the presence of the base and furan yields the Diels–Alder type adduct **177**, i.e. the cyclopropanone intermediate was 'trapped'[130].



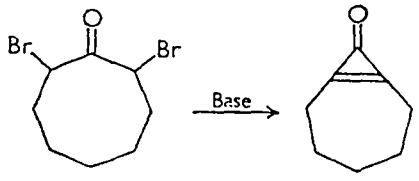
(**175**) (**176**) (**177**)

The α,α-dihalo derivative (**178**) of dibenzyl ketone undergoes dehydrohalogenation to the quite stable cyclopropenone system.



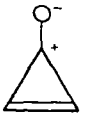
(**178**) (**179**)

Breslow treated **178** with triethylamine in methylene chloride and



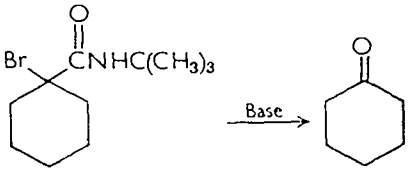
(**180**) (**181**)

obtained diphenylcyclopropenone (**179**) in 50–60% yield. Analogously, 2,8-dibromocyclooctanone (**180**) yielded cyclopheptenocyclopropenone (**181**). The special stability of a cyclopropenone may be rationalized by noting that when this system is written in valence-bond structure **182**, it abides by the aromaticity rule $(4n+2)$ of Hückel in which $n = 0$[131].



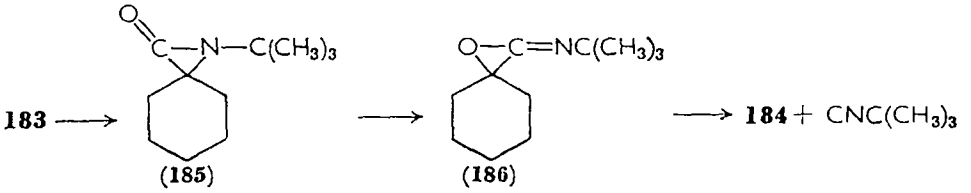
(**182**)

Other workers have adduced additional evidence for the formation of cyclopropanones as intermediates when α-halo ketones are treated with base[132] although there is no general agreement as to the proper set of valence bond structures to use to represent this intermediate[133]. An analogous heterocyclic system, an α-lactam, has been proposed by Baumgarten as a likely intermediate in certain reactions of α-haloamides[133]. In this connection the base-induced conversion of 1-bromo-1-*N*-*t*-butylcarboamidocyclohexane (**183**) into cyclohexanone (**184**) is of interest. Sheehan and Lengyel[134]



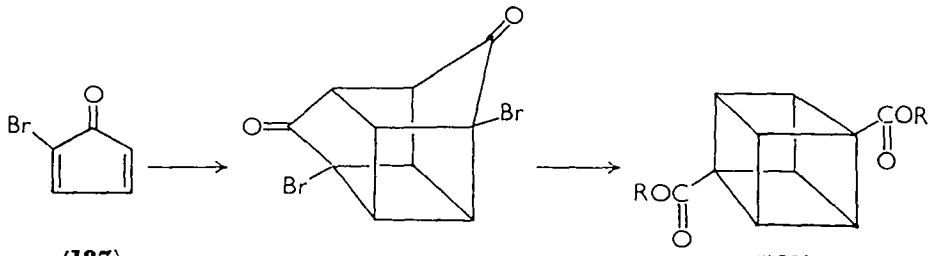
(**183**) (**184**)

propose that this reaction may proceed through the α-lactam **185**, which isomerizes to the epoxide **186**; the epoxide then loses *t*-butyl isocyanide, which was isolated.



(**185**) (**186**)

Synthetic applications of the Favorsky reaction were reviewed in 1960[135]. A recent interesting utilization involves two such rearrangements in the same compound as the final step in a preparation of cubanedicarboxylic acid (**188**). The α,α′-dibromodiketone needed for this preparation, which was effected by Eaton and



(187) (188)

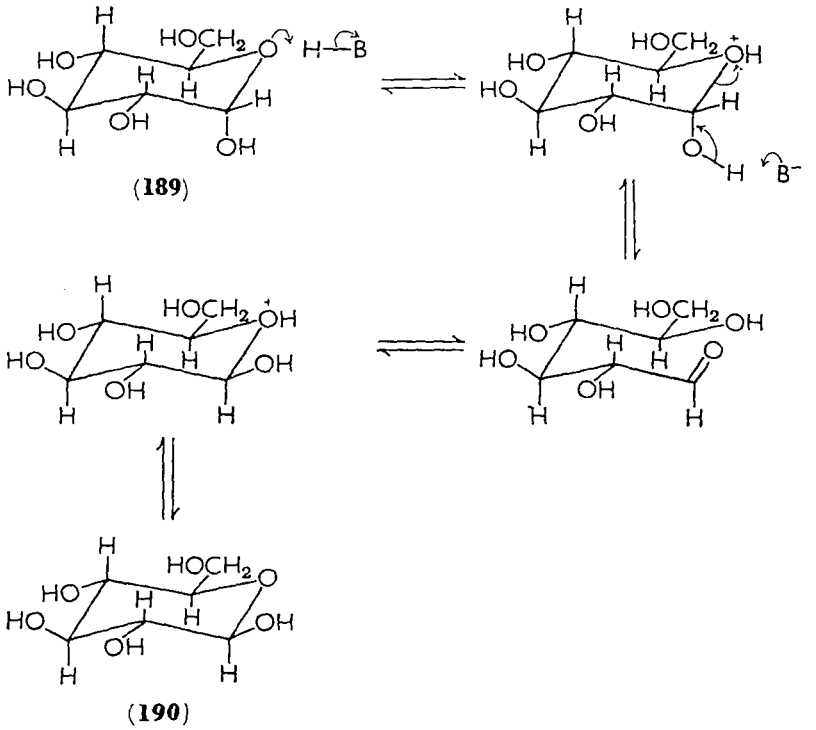
Cole[136], was obtained by dimerization of 2-bromocyclopentadienone (**187**).

I. Ring–Chain Tautomerism

Mechanistic similarities between acid- and base-induced rearrangements involving the carbonyl group have been stressed in this chapter. We have pointed out that the intramolecular 1,2-shift may be either preceded by association with an acid and followed by dissociation involving a base or *vice versa*. While both acid and base are thus involved, their involvement is commonly with hydrogen ion transfers (prototropy). For example, if base initiates a rearrangement by proton abstraction (e.g. the α-ketol rearrangement, **104** → **105**) the conjugate acid of the base is then available to serve in the subsequent step. In protic solvents several acids and bases and their conjugates may be recognized and may give rise to general acid and base catalysis of rearrangements[137]. The necessity of both acid and base for a rearrangement was first demonstrated in what was also the first reaction to be interpreted in the modern school of mechanistic organic chemistry: mutarotation. Indeed, Lowry's interpretation of the influence of both acid and base on the kinetics of mutarotation apparently coincided with Lowry's and Brönsted's postulation of their classical theory of the nature of acids and bases[138].

Mutarotation of sugars is a special type of a relatively large class of rearrangements known as ring–chain tautomerism. Many, but not all, rearrangements in this class involve the carbonyl group and are equilibrium processes. In mutarotation the carbonyl group is involved only as an intermediate; two (or more) ring forms of a sugar are equilibrated by each being reversibly converted to the chain (carbonyl) form. The process is illustrated below for glucose (**189** → **190**), where HB and B represent all available acids and bases, respectively, in the reaction medium. The development of this mechanism was reviewed by Lowry in 1925 in three papers,

which make provocative reading[139]. By that time all of the excellent early kinetic analyses of the reaction by Hudson[140] and others could be correlated with this mechanism, as could the finding by Lowry that the rearrangement would not occur if *both* HB and B were not present. Lowry had found[139] that while mutarotation was negligibly



(**189**)

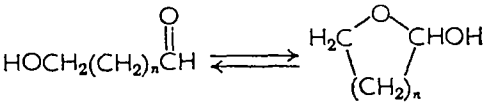
(**190**)

slow in dry cresol (HB) or in dry pyridine (B), it was rapid in a mixture of the solvents; it was also rapid in either solvent containing water, which is amphoteric.

Similarly, using other phenols and amines, Swain and Brown more recently have shown that the kinetics of mutarotation of a glucose derivative in dilute benzene solution are first-order in each species, acid, base and carbohydrate[141]. These workers found that an amphoteric organic structure, 2-hydroxypyridine, was particularly powerful as a catalyst for mutarotation[142]. Using these and other data, Swain[143] postulated a termolecular process involving the sugar, base and acid in one concerted step rather than in the two types of equilibria shown here (**189** → **190**). Swain's 'termolecular process' has not been generally accepted[144].

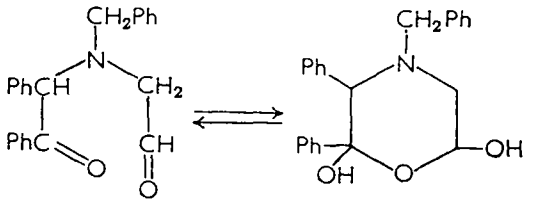
In accord with its historical role, mutarotation was the first organic reaction mechanism to be investigated via the kinetic isotope effect. In 1933 Pacsu[145] showed that mutarotation of glucose in H_2O is faster than in D_2O, where all of the hydroxylic hydrogens exchange essentially instantaneously. This is the normal effect expected for the mechanism shown (**189** → **190**) according to modern interpretations of kinetic isotope effects[146]. Another isotopic study consistent with this mechanism showed that the ^{18}O-exchange rate between water and the 1-position of glucose is much slower than mutarotation[147].

Mechanistic aspects of ring–chain tautomerism involving the carbonyl group other than in sugars have not been nearly so extensively investigated, although a large number of these reactions are recognized. Of course, the simple ω-hydroxy aldehydes (**191**), analogous to sugars, equilibrate with the cyclic form (**192**); the amount of cyclic form at equilibrium decreases with larger rings[148].



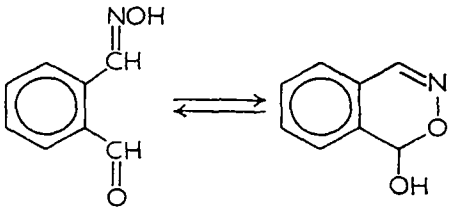
(**191**) (**192**)

Hydroxy ketones also tautomerize (e.g. mutarotation of fructose), and suitable keto aldehydes in the presence of water do the same.



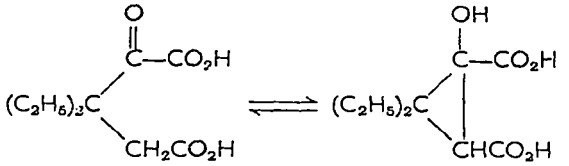
(**193**) (**194**)

Thus the morpholine derivative **194** is formed from compound **193** by hydration[149]. Functions other than simple hydroxyl groups will



(**195**) (**196**)

add reversibly to carbonyl, as in the tautomerism between **195** and **196**, discovered by Griffiths and Ingold[150]. In a suitable system even the carbon–hydrogen bond will tautomerize by carbonyl addition, as illustrated by **197** and **198**[151].

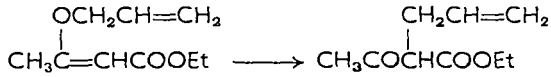


(197) **(198)**

Structural[152] and mechanistic[153] aspects specifically of mutarotation have been reviewed, and so has the generality of ring–chain tautomerism[154].

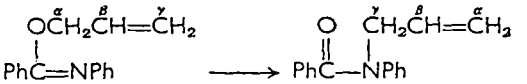
III. THERMAL REARRANGEMENTS

Aldehydes, ketones and amides are produced during many thermal reorganization reactions, and dienones have been identified as intermediates in certain Claisen rearrangements. Two recent reviews[155,156] consider the scope and mechanism of the Claisen and similar thermal rearrangements, the first example of which appears to be transformation of *o*-allylacetoacetic ester (**199**) into 4-carboethoxy-1-hexen-5-one (**200**)[157]. In the same paper[157]



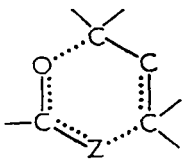
(199) **(200)**

Claisen reported the analogous rearrangement, under similar conditions, of *o*-allylacetylacetone.



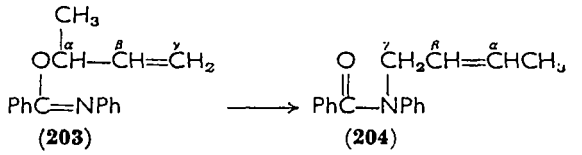
(201) **(202)**

A closely related reaction is the allylic rearrangement[158] of *N*-phenylbenzimidoyl allyl ether (**201**) to *N*-allylbenzanilide (**202**).



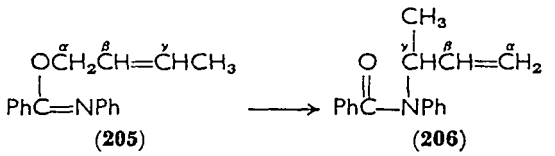
M

Such reactions (**199** → **200** and **201** → **202**) are of a general class which can be thought of as proceeding through bonding electron changes within a cyclic transition state (M). Consistent with the foregoing interpretation are the observations that *N*-phenylbenzimidoyl α-methylallyl ether (**203**) afforded *N*-γ-methylallylbenz-



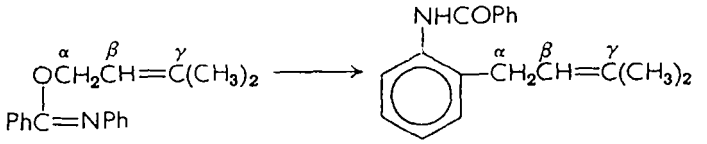
(**203**) (**204**)

anilide (**204**), and the γ-methylallyl analog (**205**) yielded *N*-α-methylallylbenzanilide (**206**)[158].



(**205**) (**206**)

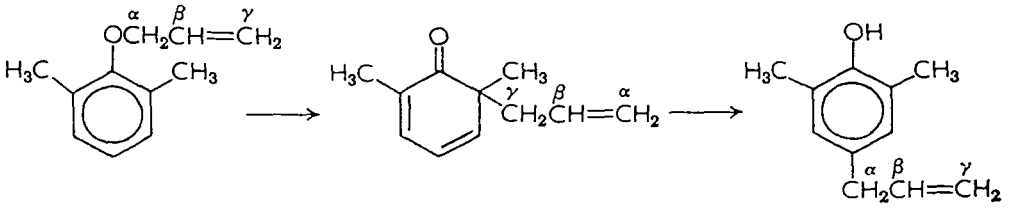
Lauer and Lockwood[159] prepared *N*-phenylbenzimidoyl γ,γ-dimethylallyl ether (**207**) and showed that rearrangement was to the



(**207**) (**208**)

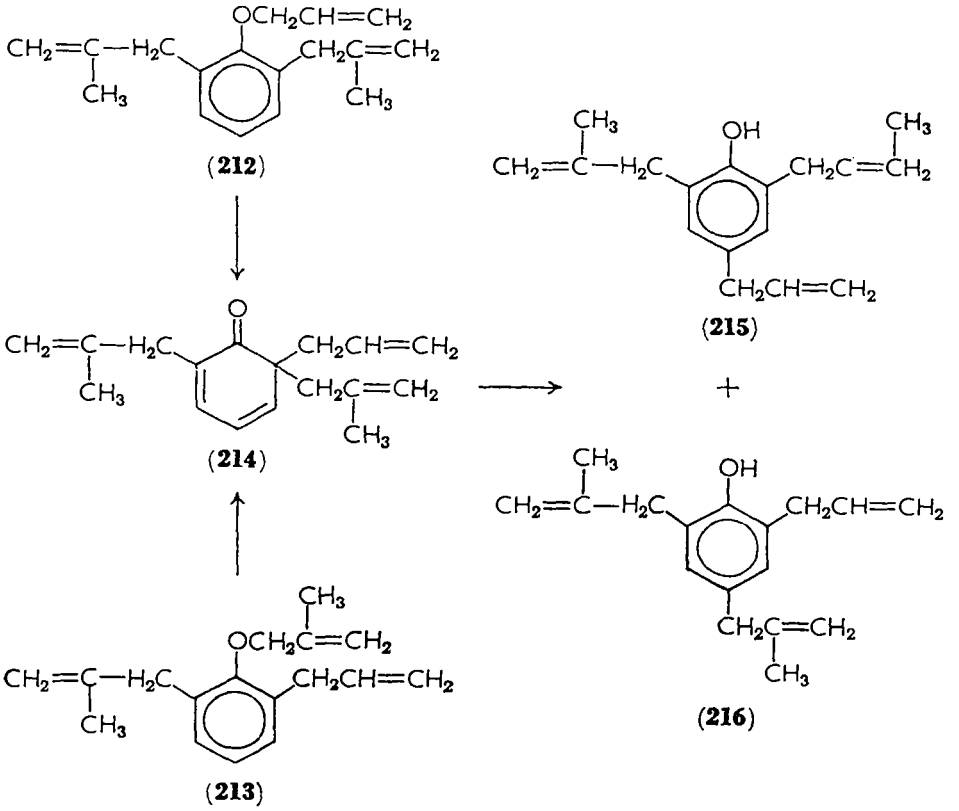
ortho position of the benzanilide ring *without* inversion of the allyl residue, for *o*-benzamide-γ,γ-dimethylallylbenzene (**208**) was produced. This reaction involves two allylic transformations and resembles the *para*-Claisen rearrangement (*vide infra*).

The intermediate formed in the *ortho*-Claisen rearrangement may be thought of as an enolizable dienone, although the question of whether it is a real intermediate or a transition state has not been settled[155,156]. In the *para*-Claisen rearrangement (e.g. **209** → **211**) however, there is no *o*-hydrogen available for enolization of the dienone intermediate (**210**), which should, therefore, be identifiable in the reaction mixture. Conroy and Firestone[160] demonstrated the presence of **210** in the rearrangement of **209** by trapping the intermediate with maleic anhydride to produce a Diels–Alder adduct. Curtin and Johnson[161] demonstrated the presence of the dienone **214** during rearrangement of **212** and **213** by showing that both



(209) (210) (211)

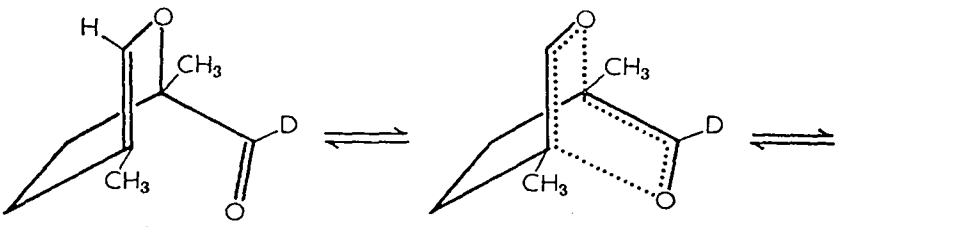
reactants afforded mixtures of the two possible rearrangement products **215** and **216.**



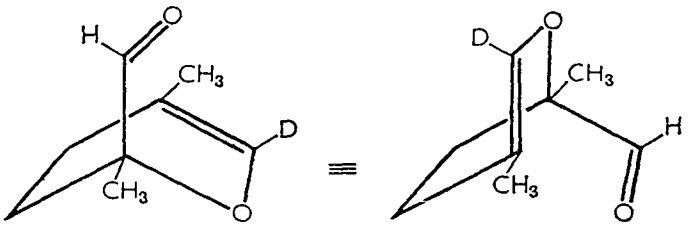
(212) (214) (213) (215) (216)

Lutz and Roberts have observed an isotope position isomerization during the thermal rearrangement of methacrolein dimer[162]. The deuterated isomer of this dimer yielded **218** with maintenance of stereospecificity. The change was explained by postulation of the the transition state N.

Thermal rearrangement of the vinyl ether of 4-cholesten-3β-ol

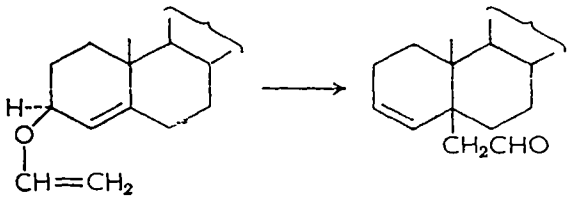


(217) N



(218) (218)

(**219**) leads to Δ^3-5β-cholesterylacetaldehye (**220**)[163,164], whereas



(**219**) (**220**)

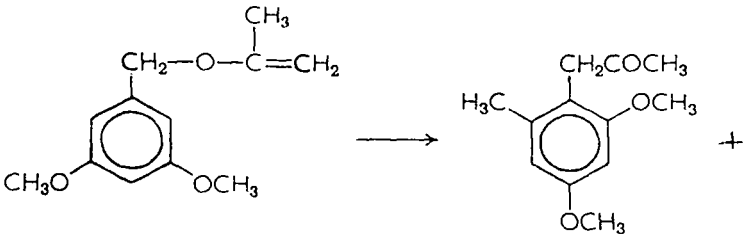
benzyl vinyl ether (**221**) yields β-phenylpropionaldehyde (**222**)[165].

$$\underset{\textbf{(221)}}{PhCH_2OCH{=}CH_2} \longrightarrow \underset{\textbf{(222)}}{PhCH_2CH_2CHO}$$

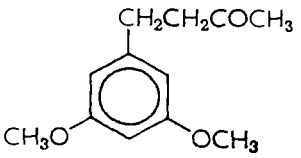
A similar reaction is the thermal conversion[166] of benzyl α-styryl ether (**223**) to β-phenylpropiophenone (**224**). Several examples of

$$\underset{\textbf{(223)}}{PhCH_2{-}O{-}\overset{\displaystyle Ph}{\overset{|}{C}}{=}CH_2} \longrightarrow \underset{\textbf{(224)}}{PhCH_2CH_2COPh}$$

thermal rearrangements of benzyl vinyl ethers are provided by Le Noble and Crean[167], who report that 3,5-dimethoxybenzyl isopropenyl ether (**225**) is converted, upon being heated at 240°c, into a mixture of 80% of 2,4-dimethoxy-6-methylphenylacetone (**226**) and about 10% of 3,5-dimethoxybenzylacetone (**227**). The



(225) (226)



(227)

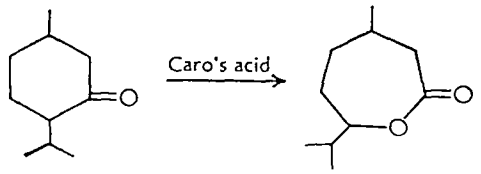
m-methoxybenzyl isopropenyl ether, when similarly treated yielded the two analogous ketones in approximately equal yields.

Thermal reorganization reactions involving ketones are but a small fraction of the overall class which includes the Cope rearrangement[156]. Such rearrangements most probably occur through cyclic transition states (M), and these are much more difficult to identify and study than are ionic or radical intermediates. As a result, the Cope and related rearrangements have not until recently begun to receive the intensive mechanistic study which has been expended on other reactions. The mechanistic aspects of these thermal reorganization reactions have been discussed at some length by Doering and Roth[168] and by Rhoads[156].

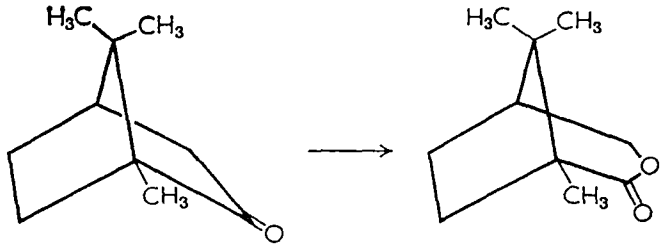
IV. OXIDATIVE REARRANGEMENTS

Many carbon-to-oxygen and carbon-to-carbon rearrangements take place during decomposition of the primary products of reaction of organic compounds with oxygen, with sulfur, with hydrogen peroxide, or with peroxy acids.

One of the best-known and most widely studied of the carbon-to-oxygen rearrangements is the Baeyer–Villiger reaction[169] of ketones with Caro's acid[170]. Menthone (**228**), for example, is converted into the ε-lactone **229**, and camphor (**230**) yields campholide (**231**)[169]. Ruzicka and Stoll[171] extended the series to include 13- to 17-membered monocyclic ketones which yielded 14- to 18-membered lactones upon treatment with Caro's acid. Friess[172], Friess and

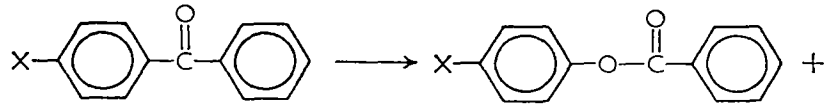


(228) (229)

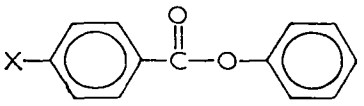


(230) (231)

Farnham[173], and Doering and Speers[174] studied the mechanism of the reaction and noted the migratory aptitudes for rearrangement of several unsymmetrical ketones with peracetic or perbenzoic acids. For example, in a study[174] of the oxidative rearrangements of the unsymmetrical ketones (**232**) (to yield esters **233** and **234**), it was



(232) (233)



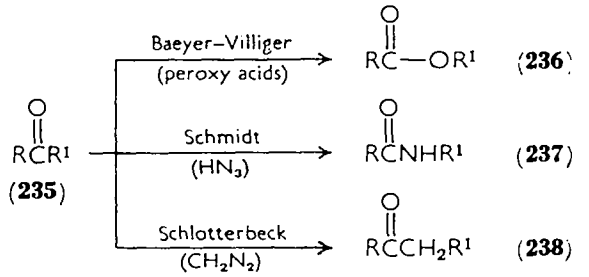
(234)

found that if X = methyl or methoxyl, the *p*-substituted phenyl migrates more readily than the phenyl (that is, more **233** was produced than **234**). The phenyl, however, migrates in preference to *p*-chloro-, *p*-bromo-, *p*-nitro- and the *p*-phenylammonium groups. Cyclohexyl methyl ketone yields cyclohexyl acetate, and acetophenone yields phenyl acetate[172] when similarly treated.

Three mechanisms have been proposed for the Baeyer–Villiger reaction; these are adequately discussed in the paper[174] by Doering and Speers. In a later paper[175] it was shown that when ^{18}O-labeled

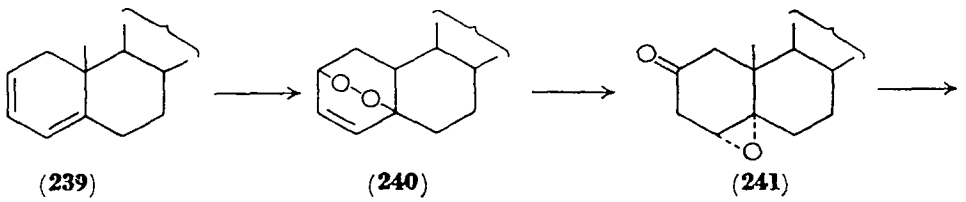
benzophenone is treated with perbenzoic acid, none of the label appears in the ether oxygen of the product (phenyl benzoate), but that all of it is still in the carbonyl oxygen. This result, which demonstrates that the rearrangement is concerted and intramolecular, is consistent with a mechanism proposed originally by Criegee[176].

The Baeyer–Villiger reaction bears a formal similarity to the Schmidt reaction of ketones with hydrazoic acid[177], and to the carbene-insertion reaction which occurs when a ketone is treated with diazomethane[178]. These three reactions are illustrated in the formulae **235** → **236**, **237** or **238**. The Schlotterbeck reaction[178] is use-

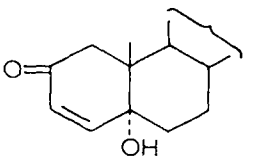


ful in the ring expansion of cyclic ketones, and has been employed in the conversion of camphorquinone into the methyl ether of homocamphorquinone[179].

Dienes often undergo autoxidation or photo-oxidation to yield cyclic peroxides which subsequently rearrange to hydroxy ketones. $\Delta^{2,4}$-Cholestadiene (**239**)[180] on photo-oxidation yields the peroxide (**240**) which upon exposure to sunlight rearranges to the keto oxide (**241**).

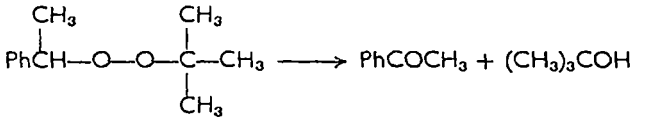


(**239**) (**240**) (**241**)



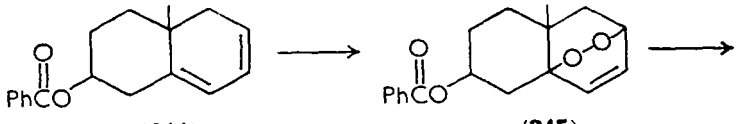
(**242**)

The keto alcohol (**242**) is obtained by heating **241**. The rearrangement of the peroxide (**240** → **242**) is the intramolecular equivalent of the decomposition[181] of α-phenylethyl-*t*-butyl peroxide (**243**) to

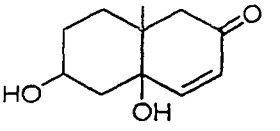


(**243**)

acetophenone and *t*-butyl alcohol. Examples of similar transformations are the rearrangements of the autoxidation products of methanofuran[182], and dehydroergosterol acetate[183], and of the photo-oxide **245** (in methanolic potassium hydroxide) to the keto glycol **246**[184].

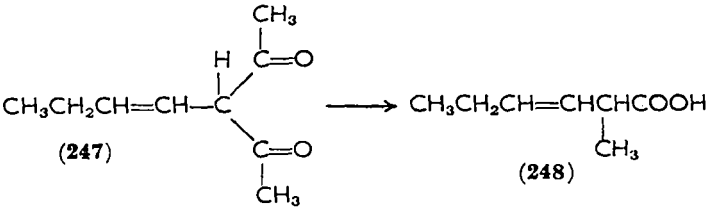


(**244**) (**245**)

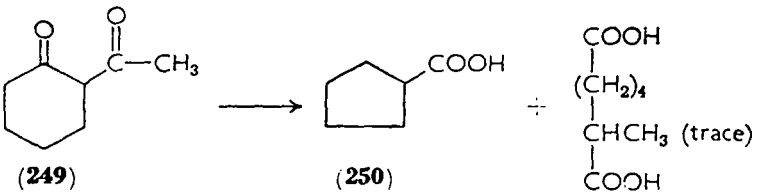


(**246**)

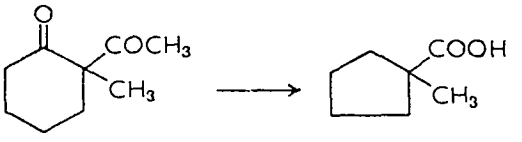
Payne[185] studied the results of the action of slightly acidic hydrogen peroxide on the series of β-diketones **247**, **249**, **251** and **253**.



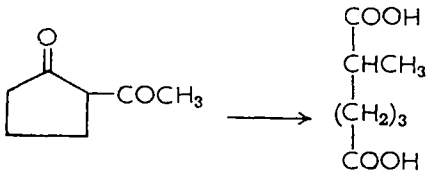
(**247**) (**248**)



(**249**) (**250**)

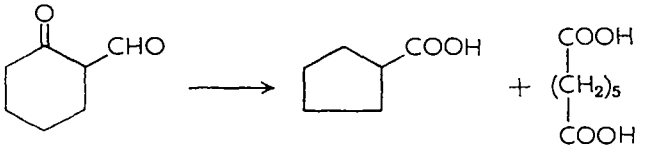


(251) (252)



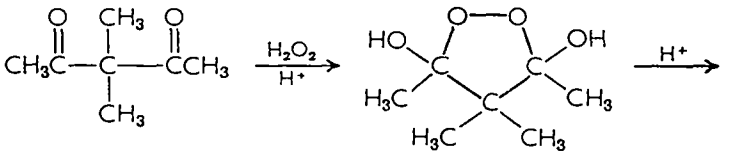
(253) (254)

The yields of the major products were 80–87%. 2-Oxocyclohexanecarbaldehyde (**255**) yielded cyclopentanecarboxylic acid (**250**) plus

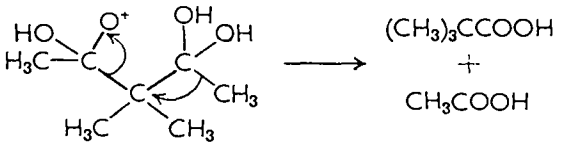


(255) (250) (256)

pimelic acid (**256**) in yields of 26% and 41%, respectively. The β-diketone **257** yields trimethylacetic and acetic acids. Payne[185]



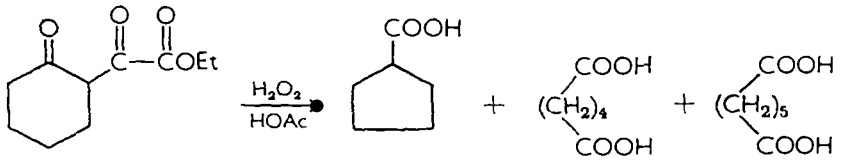
(257) (258)



O

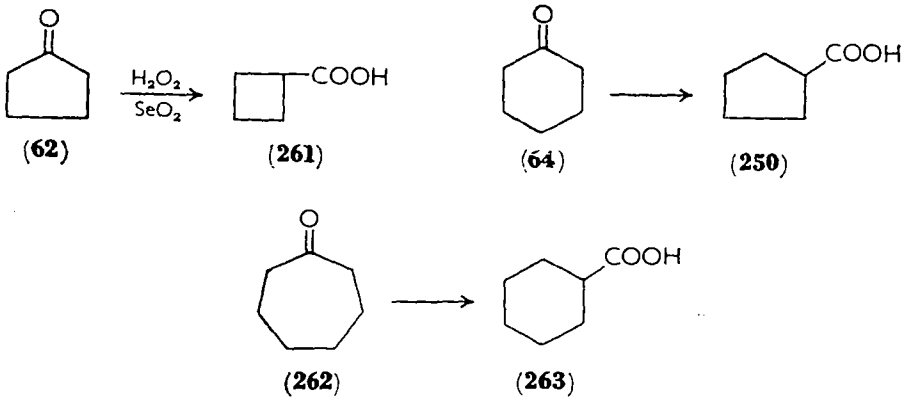
believes the mechanism of this, and similar rearrangements, involves formation of a peroxide bond (e.g., in **258**), bond scission to yield a cation (e.g. O) which then suffers cleavage and alkyl migration. A

similar intermediate has been proposed[186] in the acid-catalyzed oxidation of **259** to cyclopentanecarboxylic acid (**250**) plus adipic (**260**) and pimelic (**256**) acids.



(**259**) (**250**) (**260**) (**256**)

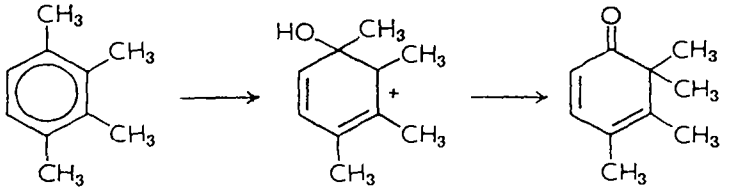
Payne[187] also found that hydrogen peroxide in the presence of selenium dioxide will cause ring contraction of monocyclic ketones to carboxylic acids, e.g. with **62**, **64** and **262**. The yields are 23–34%.



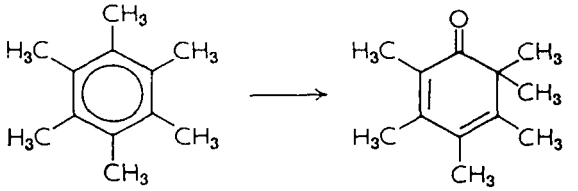
(**62**) (**261**) (**64**) (**250**)

(**262**) (**263**)

When treated with trifluoroperacetic acid and boron trifluoride[188,189] prehnitene (**264**) and hexamethylbenzene (**266**) are oxidized, with accompanying methyl migration, to the dienones **265** and **267**. The mechanism of the reaction is suggested[189] (e.g. for prehnitene) to proceed through attack on the hydrocarbon by OH^+



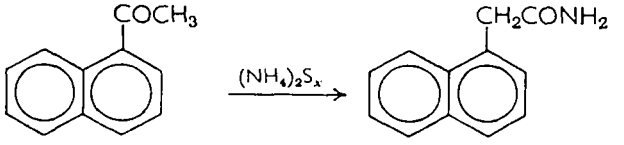
(**264**) I' (**265**)



(**266**) (**267**)

to yield an intermediate P which then suffers methyl migration and loss of a proton to produce the dienone.

In 1887 Willgerodt[190] reported that 1-acetylnapthalene (**268**), upon being heated with ammonium polysulfide in a sealed tube at 210–230° for several days, was converted into 1-naphthylacetamide (**269**)[191]. The reaction was shown to be a general one by extension



(**268**) (**269**)

to such ketones as acetophenone, propiophenone and butyrophenone to produce, respectively, phenylacetamide, β-phenylpropionamide and γ-phenylbutyramide. In some cases the ammonium salt of the corresponding acid was also obtained. It was shown rather early[192] that the carbon skeletons of the alkyl aryl ketones probably did not rearrange since branched alkyl skeletons remained intact during conversion of these ketones to amides. This observation has been adequately substantiated by King and McMellan[193], by Carmack and DeTar[194], and by Shantz and Rittenberg[195]. Subsequently M. Calvin and his coworkers[196], in one of the early tracer experiments with ^{14}C, concluded that in the conversion of aceto-1-^{14}C-phenone into phenylacet-2-^{14}C-amide there was no rearrangement of the carbon atoms of the side chain. They stated, however, that the ammonium salt of phenylacetic acid appeared to be produced through an alternate mechanism in which some rearrangement of the carbon skeleton did occur. This latter conclusion was later shown by Brown, Cerwonka and Anderson[197] to be erroneous. Any mechanistic interpretation must take into account the foregoing observations plus the fact that the Willgerodt reaction involves not only oxidation of the terminal carbon of an alkyl sidechain but also the reduction, probably by hydrogen sulfide, of an

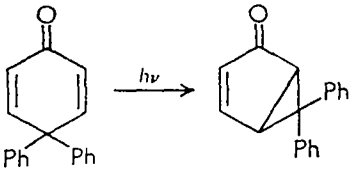
oxo group to a methylene. Two reviews[198,199] consider the scope and mechanism of the Willgerodt and related reactions.

Several important modifications of the Willgerodt reaction have been worked out, the first of which is that of Kindler[200], who carried out the reactions of alkyl aryl ketones with sulfur and amines at high temperatures. Others[201] have employed dioxane and morpholine, respectively, as solvents; use of the latter solvent does away with the necessity of a sealed tube reactor.

V. PHOTOCHEMICAL REARRANGEMENTS

Aldehydes and ketones are particularly susceptible to photo-chemical rearrangement, for the absorption of ultraviolet light (about 2700–3000 Å) by these groups leads to activated states which can undergo several kinds of transformation. In recent reviews[202–204] there are thorough discussions of the present state of knowledge of the triplet- and singlet-state intermediates, energy-transfer agents, and the types of spectral transition believed to be associated with particular transformations. The presentation here is limited, therefore, to an enumeration of several types of photochemical rearrangement which have been observed for compounds containing the aldehyde or ketone groups, with only occasional reference to the mechanistic importance of these rearrangements.

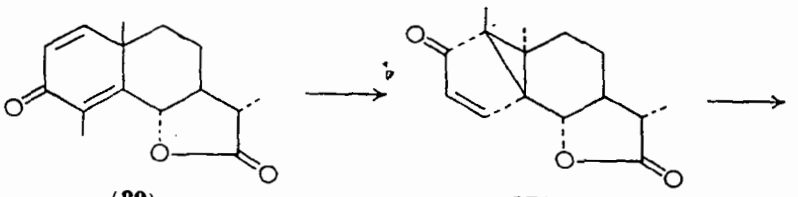
Many ketones are converted photochemically into other ketones whose carbon skeletons have been altered. Although the structures of reactant and product might imply noninvolvement of the carbonyl group, the carbonyl is, in fact, intimately associated with the reaction. A good example is the photochemical rearrangement of 4,4-diphenylcyclohexadienone (**270**) to 6,6-diphenylbicyclo[3.1.0]-



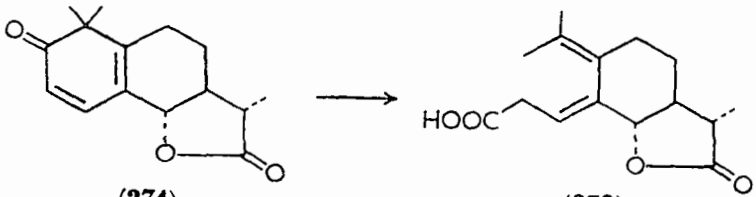
(**270**) (**271**)

hex-3-en-2-one (**271**), which Zimmerman and Swenton[205] have shown to proceed through a triplet state. The mechanism of the

conversion **270** → **271** is important to the photochemical transformation of santonin (**89**) through luminosantonin (**272**) and the intermediate (**274**) to photosantonic acid (**273**)[206-208], as are the

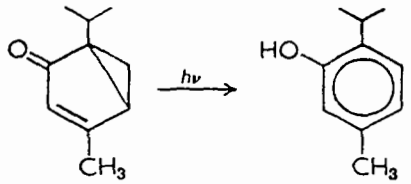


(**89**) (**272**)

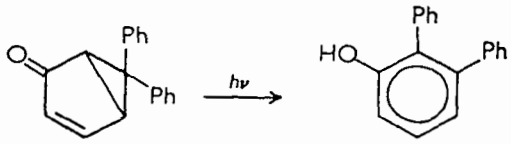


(**274**) (**273**)

related rearrangements **275** → **276** and **277** → **278**. γ-Tropolone methyl ether, colchicine, and other derivatives of cycloheptatrienone, upon irradiation, are converted into bicyclic compounds[202]. α-Tropolone as well as α-tropolone methyl ether (**279**) undergo similar

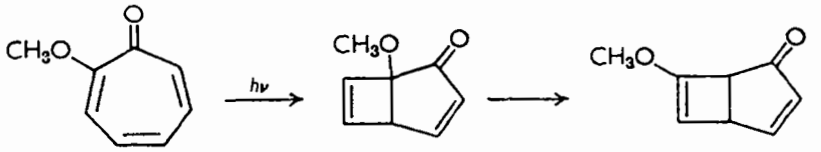


(**275**) (**276**)



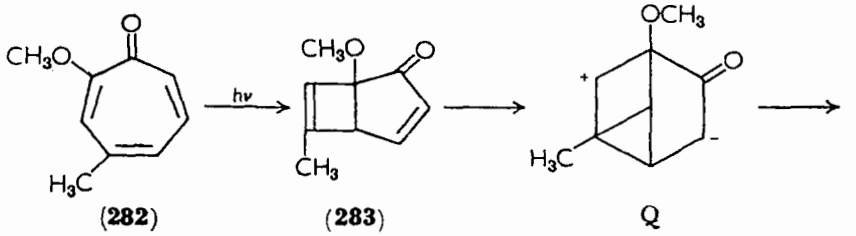
(**277**) (**278**)

cyclization reactions[209], and Dauben and coworkers[210] have shown that the initial product (**280**) undergoes a further photochemical rearrangement to yield the isomeric ether **281**. The latter reaction (**280** → **281**) could be explained either by a shift of the methoxyl

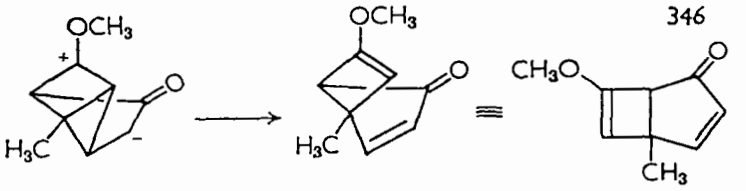


(279) (280) (281)

group, or by rearrangement of the carbon skeleton of **280**. The question was answered in favor of the skeletal rearrangement[210] by a study of the photochemical reaction of the 4-methyltropolone methyl ether (**282**) which yielded **283** and thence, on further



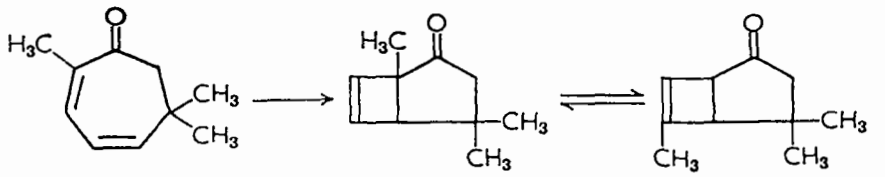
(282) (283) Q



R (284) (285)

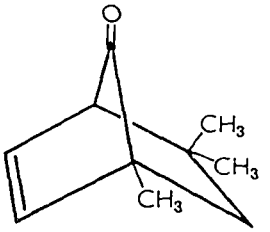
irradiation, the isomeric structure **285** through the postulated intermediates Q and R.

Another example of a ketone-to-ketone conversion is the formation[211] of the equilibrium mixture **287** ⇌ **288** upon irradiation



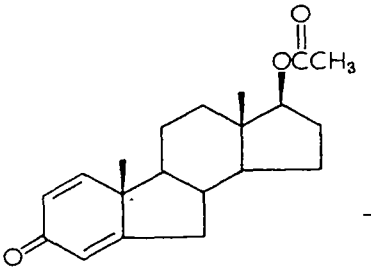
(286) (287) (288)

of eucarvone (**286**) in acetic acid-ethanol. When irradiation is carried out in aqueous acetic acid, 1,5,5-trimethylbicyclo[2.2.1]-7-hepten-7-one (**289**) is also produced[212].

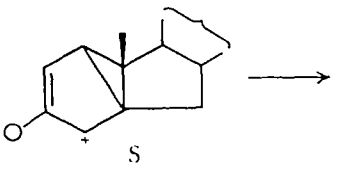


(289)

Recently the irradiation[213] of B-nor-1-dehydrotestosterone acetate (**290**) in dioxane (2537Å) was shown to cause rearrangement of the



(290)



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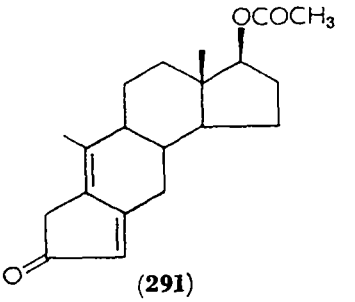
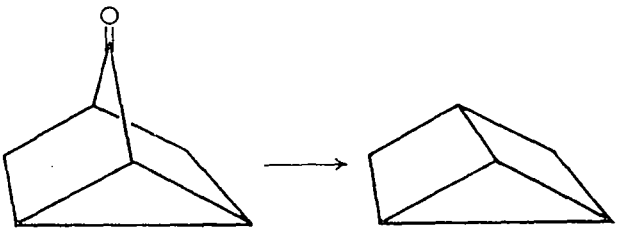


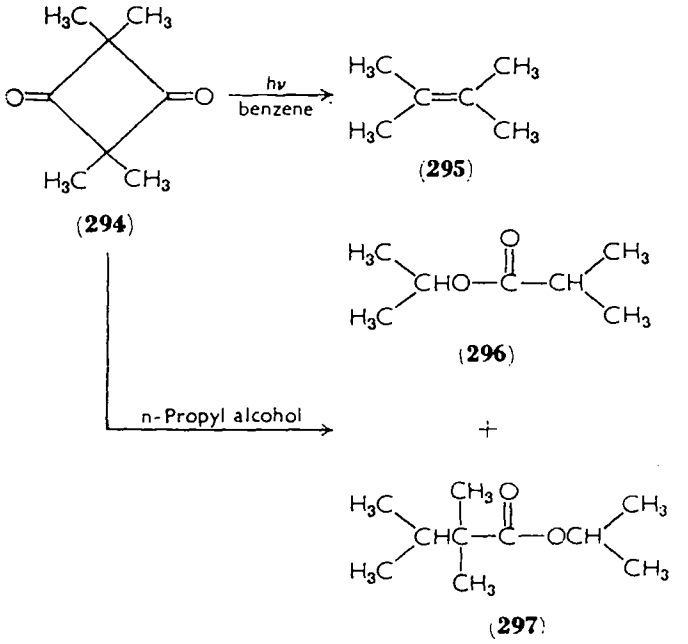
(291)

A and B rings to yield a product which most probably possesses structure **291**. The rearrangement is similar to those previously studied by Zimmerman[205] and others[207-210].



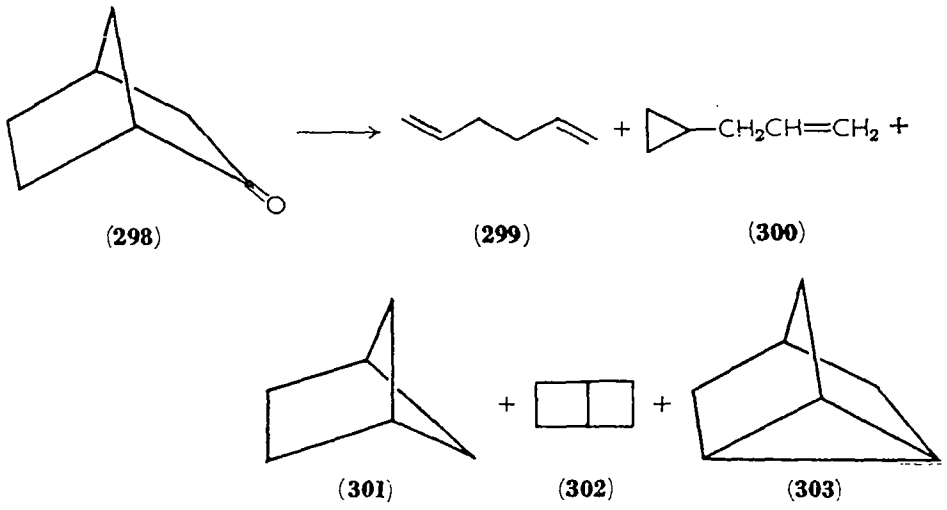
(292) (293)

Decarbonylation with the formation of new carbon–carbon bonds is often a consequence of the photochemical irradiation of ketones. An example is the mercury-sensitized photolysis[214] of nortricyclanone

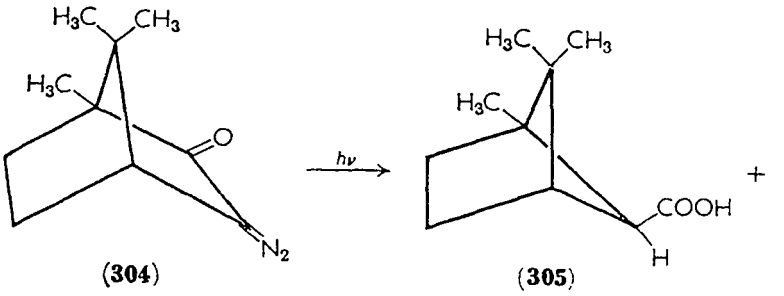


(294) (295) (296) (297)

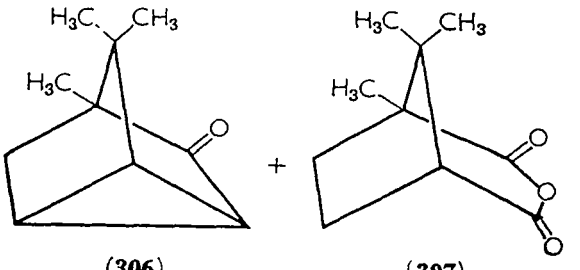
(292) to yield tricyclo[2.2.0.0^{2,6}]hexane (293). Irradiation of symmetrical tetramethylcyclobutanedione (294) yields tetramethylethylene (295)[215] when benzene is the solvent, whereas in n-propyl



(298) (299) (300) (301) (302) (303)



(304) (305)

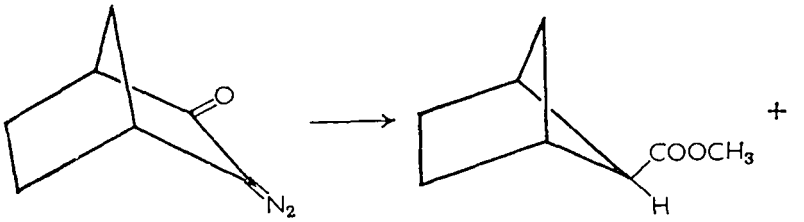


(306) (307)

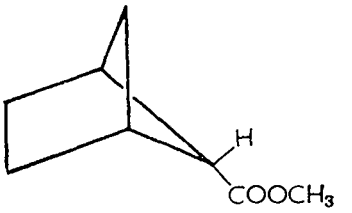
alcohol solution the same compound is converted into the two esters **296** and **297.**

Srinivasan[216] reports that the mercury-photosensitized decomposition of norbornanone (**298**) yields all of the products **299–303.**

The photolysis[217] of diazocamphor (**304**), obtained by the action of base on the tosylate of camphorquinonehydrazone, yields *exo*-1,5,5-trimethylbicyclo[2.1.1]hexane-6-carboxylic acid (**305**). The



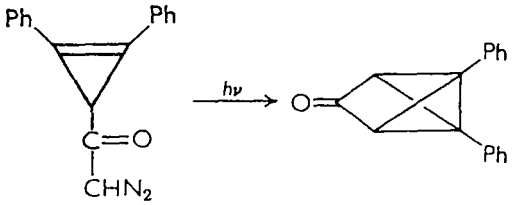
(308) (309)



(310)

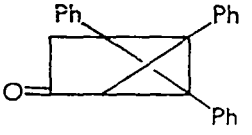
stereochemistry of **305** was proven by Meinwald and coworkers[218], who also identified additional products of the reaction to be the ketone **306** and the anhydride **307.** Photolysis of the analogous diazo ketone **308** in methanol yielded a mixture of the *exo-* (**309**) and *endo*-methylbicyclo[2.1.1]hexane-5-carboxylates (**310**)[219].

Photochemical rearrangement of diazoketones has led to some very interesting, new fused-ring systems. Masamune[220], for example, photolyzed 3-(2-diazoacetyl)- 1,2-diphenyl-1-cyclopropene (**311**) and

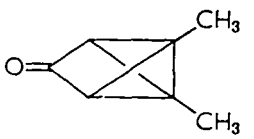


(**311**) (**312**)

obtained the highly strained ketone **312.** The similar compounds **313** and **314** have also been prepared by the action, on analogous diazo-



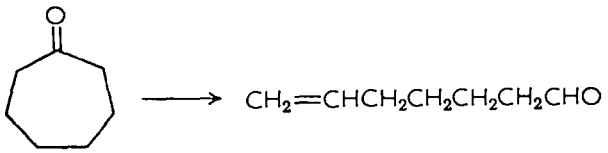
(**313**)



(**314**)

ketones[221,222] of copper-powder catalyst, a reaction which often yields products of similar nature to those obtained photochemically.

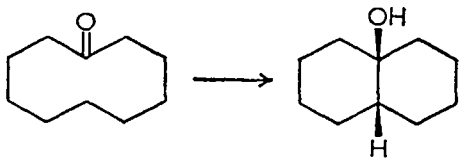
Cyclic aliphatic ketones cleave when photolyzed. The cleavage reaction has been studied by Srinivasan[223,224], who subjected cyclopentanone, cyclohexanone and 2-methylcyclohexanone to vaporphase photolysis. In each case an unsaturated aldehyde was produced, as illustrated by the formation of 6-heptenal (**315**) from



(**262**) (**315**)

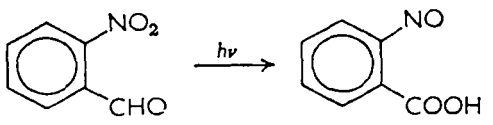
cycloheptanone (**262**). By-products in the reaction were carbon monoxide, propylene and traces of cyclohexane, 1-hexene and

ethylene. Other workers had found that cyclodecanone (**316**), however, undergoes self-condensation to yield *cis*-9-decalol (**317**)[225] in 35% yield.



(**316**) (**317**)

o-Nitrobenzaldehyde (**318**) yields *o*-nitrosobenzoic acid (**319**)



(**318**) (**319**)

when exposed to light[226]. The reaction takes place both in alcoholic solution and in the solid state. This, and other photochemical rearrangements involving transfer of oxygen, have been adequately discussed by de Mayo and Reid[202].

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The Chemistry of the Carbonyl Group
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CHAPTER 16

Photochemistry of ketones and aldehydes

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I. INTRODUCTION

With the development of modern experimental techniques, particularly in analysis of complex mixtures by liquid–gas chromatographic methods, photochemistry has assumed an increasing importance in studies of free-radical reactions, energy-transfer processes, and the synthesis of new and unique organic compounds. Perhaps the most widely studied class of compounds, historically and today, is that containing the carbonyl chromophore. This constant, and indeed ever growing, interest is inspired by both experimental and theoretical considerations. Thus, for example, the absorption spectra of most carbonyl compounds fall in the experimentally readily accessible region of the ultraviolet where quartz has high transmission and mercury arcs produce strong line emission spectra.

It is generally recognized that in order to obtain a thorough understanding of the photochemistry of a given system, one must elucidate the entire 'life history' of the photoprocess; this includes the primary process(es) and all secondary reactions in the system. Noyes and his colleagues have pointed out that:

> The *primary photochemical process* comprises the series of events beginning with the absorption of a photon by a molecule and ending either with the disappearance of that molecule or with its conversion to a state such that its reactivity is statistically no greater than that of similar molecules in thermal equilibrium with their surroundings[1].

In the primary photochemical process there is usually a variety of paths for degradation of the electronic energy of excitation. Chemical paths include intramolecular rearrangements or the formation of free radicals and excited molecules which may react in *secondary*

processes to form new products of chemical interest. However, also usually included in the overall photochemical reaction are radiative and nonradiative photophysical processes which do not lead to a net chemical change, yet are alternative paths for loss of the absorbed energy. Such processes involving electronically excited states are of great interest to the spectroscopist and photochemist alike[2]. Thus, 'The complete elucidation of a primary photochemical process must include an understanding of all that transpires, whether or not a chemical reaction occurs'[1].

The ground state and the manifold of lower excited states of a typical organic molecule, and the radiative (solid lines) and radiationless (wavy lines) transitions between these states are illustrated in Figure 1[3]. These will be discussed in the next section.

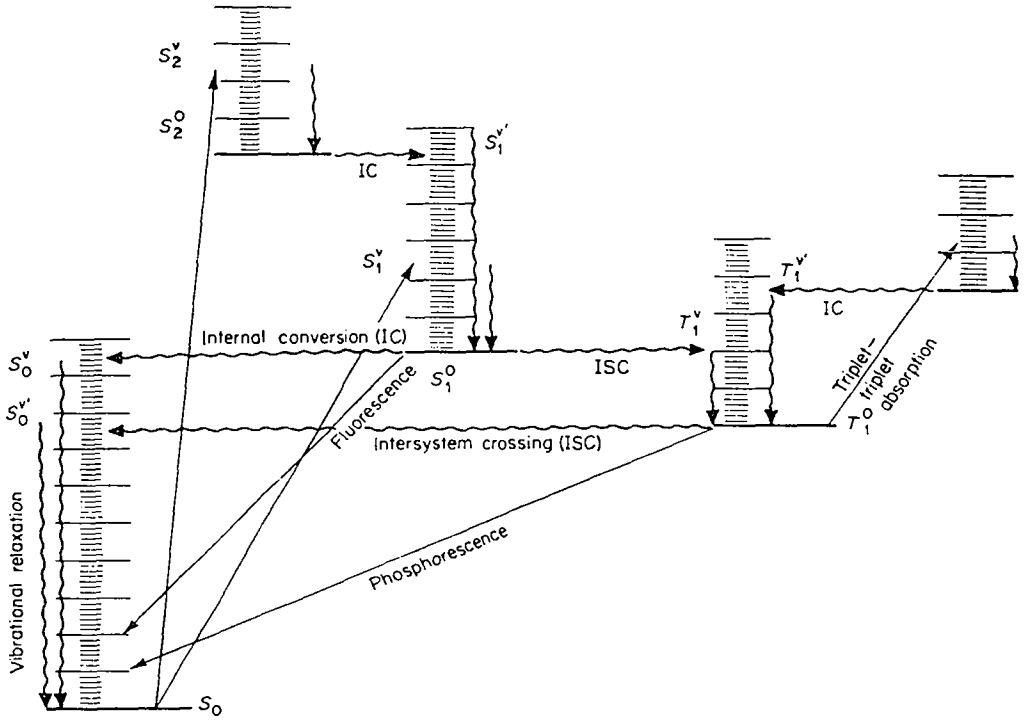


FIGURE 1. Manifold of excited states and intramolecular transitions between these states in a 'typical' organic molecule. Radiative and nonradiative transitions are solid and wavy lines respectively. IC = internal conversion between states of like multiplicity; ISC = intersystem crossing between states of unlike multiplicity; other wavy lines indicate vibrational relaxation processes. Vibrational and rotational levels are shown approximately equally spaced only for ease in presentation; in reality the levels become closer as their quantum numbers increase.

[Reproduced from ref. 3.]

Traditionally the spectroscopist has focused his attention on the photophysical events represented by absorption and the subsequent radiational and radiationless transitions, including intermolecular electronic-energy transfer. Such valuable information obtained by the study of molecular electronic spectra can often be utilized in deducing the actual photochemical processes. The photochemist, however, has tended to be more concerned with the overall chemical changes produced on irradiation and to deduce from these the nature of the primary energy-transfer processes involved. Today the fields have merged.

Clearly, completely understanding the photochemistry of a given system is a monumental task encompassing many scientific 'domains' even for simple organic compounds, and more so for complex molecules. However, despite this formidable challenge, in recent years photochemists, spectroscopists and photobiologists have combined their talents to make great progress. This is reflected in the wide range of articles in the recently initiated series *Advances in Photochemistry*[4].

It is clearly not feasible to present here a detailed review of all aspects of the thousands of photochemical studies of carbonyl compounds, nor will any effort be made to give a complete list of references to the enormous amount of work which has been done in this field. Rather, we shall focus our attention primarily on photochemical processes of ketones and aldehydes, referring the reader to reviews[1,1b,1c,5,30,89,232,276-280], the *Advances in Photochemistry* series[4], and the recent monograph *Photochemistry*[3] for other carbonyl compounds and detailed discussions of current theory and applications of photochemistry in general. We shall emphasize those compounds whose photophysical and photochemical processes are beginning to be understood, and consider the roles of molecular and electronic structure and overall molecular environment in determining the nature and degree of their primary and secondary processes. Interesting relationships between intramolecular processes of certain ketones and aldehydes initiated by photolysis, radiolysis, and electron impact also will be considered. We shall not consider experimental aspects of the photochemistry of carbonyl compounds, since recent techniques have been discussed in detail[3].

II. SPECTROSCOPY OF THE CARBONYL GROUP

A. Absorption Spectra

The first law of photochemistry states that for light to be effective

TABLE 1. Absorption spectra of some ketones and aldehydes*.

Compound	Absorption bands					
	λ_{max}(Å)	log ε_{max}	λ_{max}(Å)	log ε_{max}	λ_{max}(Å)	log ε_{max}
Saturated						
Formaldehyde (gas)	3040[f]	1·25[f]	1745[e]	3·89[e]	1560[e]	4·37[e]
Acetaldehyde (gas)	2934[d]	1·07[d]	1815[e]	4·01[e]	1693[e]	2·96[e]
Propionaldehyde (water)	2775[b]	1·12[b]				
Isobutyraldehyde (water)	2860[e]	1·4[e]				
Acetone (hexane)	2790[d]	1·17[d]	1900[e]	3·04[e]	1540[a]	Strong
Methyl ethyl ketone (alcohol)	2735[e]	1·24[e]				
Methyl *t*-butyl ketone (chloroform)	2850[d]	1·32[d]				
Di-*t*-butyl ketone (alcohol)	2950[b]	1·30[b]				
Cyclobutanone	2954[c]	1·17[c]				
Cyclopentanone	2900[c]	1·27[c]				
Bicyclo[3.1.0]-2-hexanone (isooctane)	2884[e]	1·26[e]	1880[e]	3·76[e]		
Unsaturated						
Acrolein (water)	3150[b]	1·41[b]	2100[b]	4·06[b]		
α-Methacrolein (hexane)	2130[e]	4·05[e]				
Crotonaldehyde (isooctane)	3410[b]	1·38[b]	2140[b]	4·20[b]		
Propargyl aldehyde (isooctane)	3820[e]	0·7[e]	2180[e]	3·6[e]		
Ketene	3300[c]	1·07[c]				
Methyl vinyl ketone (alcohol)	3200[b]	1·43[b]	2125[b]	3·85[b]		
Methyl isopropenyl ketone (alcohol)	3150[b]	1·4[b]	2180[b]	3·90[b]		
2-Cyclohexenone (alcohol)	2250[e]	3·68[e]				
1-Acetylcyclohexene	2320[d]	4·09[d]				
2,4-Hexadienal (alcohol)	2710[e]	4·49[e]				
trans-3-Hexen-5-yn-2-one (alcohol)	3300[c]	1·75[e]	2575[e]	4·22[a]		
Phorone	3747[a]	1·91[a]	2630[a]	4·30[a]		
1-Acetylazulene	5460[d]	2·64[d]				
Aromatic						
Benzaldehyde (alcohol)	3280[b]	1·30[b]	2800[b]	3·17[b]	2440[b]	4·17[b]
Acetophenone (alcohol)	3190[b]	1·69[b]	2780[b]	3·04[b]	2400[b]	4·11[b]
Benzophenone (alcohol)	3250[b]	2·25[b]	2520[b]	4·30[b]		
Benzoylpiperidine (methylene chloride)	3520[d]	2·40[d]	2420[d]	4·01[d]		

See next page for notes.

in promoting a photochemical reaction it must be absorbed. Thus, the first step in a proposed study of a photochemical process is to obtain the absorption spectrum of the compound.

The carbonyl chromophore in simple aldehydes and ketones has a relatively weak first absorption band in the ultraviolet starting at about 3300–3400 Å and reaching a maximum in the region of 2775–2875 Å depending upon the particular compound. In the far ultraviolet region simple aldehydes and ketones also exhibit two intense absorption bands with maxima at about 1900 Å and 1600 Å, respectively. The λ_{max} and molar extinction coefficient ε_{max} of some ketones and aldehydes are given in Table 1.

Theoretical analysis of these electronic transitions, particularly the first band, have been made by many spectroscopists, notably Kasha[5], Mulliken[6], and Sidman[7]. However, while a reasonably satisfactory treatment of the nature and energy of the lowest excited states of formaldehyde is available, the status of more complex compounds is derived more from analogy with formaldehyde and from semiemprical correlations (e.g. blue shift in polar solvents for $n \rightarrow \pi^*$ transitions) than from definitive theoretical calculations.

Two molecular orbitals (MO) make up the carbon–oxygen double bond: a σ-MO and a π-MO. Two pairs of unshared electrons on the oxygen atom occupy n orbitals (nonbonding): one of the two pairs is believed to be in an sp-hybrid orbital in which the electrons are firmly held, the other pair is in a $2p$ orbital from which an electron may be easily excited. For simple ketones and aldehydes, only the σ and π orbitals of the carbonyl group and the $2p$–n orbital on the oxygen atom seem to be important in electronic transitions in the ultraviolet.

The weak long-wavelength absorption band of simple aliphatic ketones and aldehydes (ε_{max} about 20) was first suggested by Mulliken[6] to have its origin in a singlet–singlet transition, forbidden on symmetry grounds. It involves the excitation of a *nonbonding* $2p$

For original references, see:

[a] G. W. Wheland, *Resonance in Organic Chemistry*, John Wiley and Sons, New York, 1955, Chap. 6.

[b] R. M. Silverstein and G. C. Bassler, *Spectrometric Identification of Organic Compounds*, John Wiley and Sons, New York, 1963, pp. 98–100.

[c] J. G. Calvert and J. N. Pitts, Jr., *Photochemistry*, John Wiley and Sons, New York, 1965.

[d] H. H. Jaffé and M. Orchin, *Theory and Applications of Ultraviolet Spectroscopy*, John Wiley and Sons, New York, 1962.

[e] J. P. Phillips and F. C. Nachod, *Organic Electronic Spectral Data*, Vol. IV, Interscience Publishers, New York, 1963.

[f] Unpublished data of G. R. McMillan and J. G. Calvert.

* λ_{max} is the wavelength of the absorption maximum in Ångstrom units. The molar extinction coefficient ε is defined by $I_D/I = \varepsilon bc$ where c = concentration of solute in mole/l and b = path length in cm.

electron on the oxygen atom to the *antibonding* π^*-MO; Kasha[5] describes it as a $n \rightarrow \pi^*$ transition. The second absorption band is probably related to an allowed $n \rightarrow \sigma^*$ singlet–singlet transition, while the third strong absorption band may be due to an allowed $\pi \rightarrow \pi^*$ singlet–singlet transition in which an electron of the π-MO is promoted to a higher energy π^*-MO of the same carbonyl chromophore. Detailed references to this subject are found in ref. 5.

An important, though perhaps not conclusively established, qualitative feature of an $n \rightarrow \pi^*$ transition is that excitation of the n electron into the antibonding orbital generates a partial formal positive charge, $\delta+$, on the oxygen atom and a partial formal negative charge, $\delta-$, on the carbon atom[8]. This is opposite in direction to the dipole moment in the ground state and has been used to explain certain hydrogen-atom abstracting properties of various carbonyl compounds (section III.G). An electron-redistribution mechanism based on this premise has been employed by Zimmerman to account for a large number of photochemical reactions of ketones[9]. Chapman has also developed a mechanistic interpretation of the photochemical reactions of unsaturated ketones[10].

It is worth noting here the original suggestion of Bäckström[11] in 1934 that the excited state of benzophenone can be written as the biradical $(C_6H_5)_2\dot{C}—\dot{O}$ in the classic hydrogen-atom abstraction process

$$(C_6H_5)_2CO + h\nu \longrightarrow (C_6H_5)_2\dot{C}—\dot{O} \xrightarrow{RH} (C_6H_5)_2\dot{C}—OH + R\cdot$$

It is a useful working concept, even though we now recognize that the biradical $(C_6H_5)_2\dot{C}—\dot{O}$ is actually the triplet state of benzophenone formed in the sequence[12–14]

$$(C_6H_5)_2CO\ (S_0) + h\nu \longrightarrow (C_6H_5)_2CO\ (S_1) \rightsquigarrow (C_6H_5)_2CO\ (T_1)$$

B. *Effects of Molecular Structure on the Absorption Spectra*

Varying the molecular structure of an aldehyde or ketone may be reflected in pronounced changes in both the absorption spectra and photochemical reactivity; this is the case with *p*-substituted butyrophenones and benzophenones (sections VII.B and VIII.B). On the other hand, there may be relatively small changes in the absorption spectra but pronounced differences in overall photochemical reactivities as, for example, in the series of methyl cyclopropyl ketones (Section V.B). These two general types of effects have recently been discussed by Pitts and colleagues[15]. Here we shall note briefly the effects of structure on absorption spectra.

1. Saturated ketones and aldehydes

All saturated ketones and aldehydes show a weak absorption band ($\varepsilon_{max} \cong 20$) in the near ultraviolet with the aldehyde band usually occurring at somewhat longer wavelengths. This band arises from an $n \rightarrow \pi^*$ transition. The bathochromic effect of substitution on the alkyl chain of some ketones is apparent in Table 1. The effect of ring size and structure on the absorption characteristics of alicyclic ketones has been reported[16,17].

2. Unsaturated ketones and aldehydes

Ketones and aldehydes containing a carbonyl group in conjugation with an ethylenic linkage (i.e. α,β-unsaturated) show a weak n,π^* band which is displaced toward longer wavelengths, around 3000–3500 Å. The second band, presumably resulting from an intense $\pi \rightarrow \pi^*$ transition, now appears in the 2150–2500 Å region, making it far more experimentally accessible than the second band of the aliphatic analogs which maximizes around 1900 Å. The position of the π,π^* band is subsequently affected by substitution on the α- and β-carbon atoms; a useful empirical generalization for this substitution effect has been proposed by Woodward[18].

3. Aromatic ketones and aldehydes

Replacement of an alkyl group in a ketone or aldehyde by an aromatic ring shifts the $n \rightarrow \pi^*$ transition toward longer wavelengths and increases ε_{max}. This is clearly demonstrated by comparing the spectral data for acetone, acetophenone and benzophenone in Table 1.

The effect of substituent groups on the absorption spectra of aromatic ketones and aldehydes is illustrated by the substituted butyrophenones[15] (approximately 10^{-3} M in benzene) shown in Figure 2. Butyrophenone and the *p*-methyl derivative display a low intensity band ($\varepsilon \approx 100$) in the 3000–3500 Å region. This displays the characteristic blue shift in polar solvents and is thus assigned to an $n \rightarrow \pi^*$ transition. In the case of *p*-methoxybutyrophenone a blue shift of the n,π^* band and a red shift (with increasing intensity) of the π,π^* band cause the two bands to merge and the n,π^* band is seen as a shoulder on the intense π,π^* band. The stronger electron-donating effects exhibited by *p*-NH_2 and *p*-OH substituents shift the absorption spectra to such an extent that the n,π^* band is completely masked by the strong π,π^* band. A similar shift of the intense π,π^* band is well known for such *p*-substituted benzophenone[19-22].

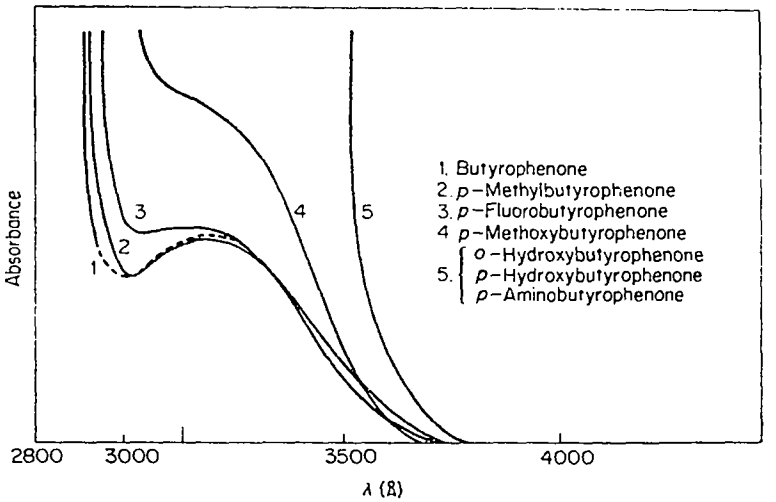


FIGURE 2. Absorption spectra of approximately 10^{-3} M solutions of several substituted butyrophenones in benzene. [Reproduced, by permission, from ref. 15.]

In *o*-hydroxybutyrophenone the intense π,π^* band centered at 3250 Å (Figure 2) does not alter position on changing from hydrocarbon to alcohol solvent. Coupled with other photochemical and n.m.r. spectroscopic evidence, it is assumed that the hydroxy proton is intramolecularly hydrogen bonded to the carbonyl chromophore in the ground state of *o*-hydroxybutyrophenone.

Recently it has been demonstrated that the nature of the *para* substituents of aromatic and aryl alkyl ketones also has a dramatic effect on their photochemical reactivity, phosphorescence spectra, and e.p.r. signals (at $g = 4$) [15,19,20-23]. Presumably substitution alters not only the singlet–singlet absorption but also the energy and nature of the lowest excited states, i.e. the state involved in emission and probably in photochemical reactions in solution. This is discussed in sections VII and VIII.

C. Effect of Solvents on the Absorption Spectra

The effect of solvents upon the $n\rightarrow\pi^*$ transitions in carbonyl compounds has been well recognized and discussed [5,24]. In changing from hydrocarbon solvents to polar hydroxylic solvents a relatively large blue shift is observed for an $n\rightarrow\pi^*$ transition and a smaller red shift is found for a $\pi\rightarrow\pi^*$ transition [24]. The n,π^* and the π,π^* bands are thus most widely separated in nonpolar solvents. In polar solvents under favorable conditions the blue shift of the n,π^* band and the

red shift of the π,π^* band can result in the merging of these two bands. In acidic media the n,π^* band may be shifted so far to the blue that it virtually 'disappears', whereas the π,π^* band may be shifted considerably to the red into the experimentally convenient photochemical region. Such solvent shifts may have important photochemical consequences.

D. Emission from Excited States

The electronic energy acquired by photoexcited molecules may be dissipated in various ways including both photophysical and photochemical processes. The former, shown schematically in Figure 1, includes all radiative and nonradiative transitions of the excited states that do not produce permanent chemical changes. Let us consider with the aid of this figure such processes of a 'normal' carbonyl compound.

The ground states of most organic molecules are singlet in character, S_0. Absorption of light produces an excited electronic state which, in accordance with spin-conservation rules, is also a singlet, S_1. The molecule also may be vibrationally excited; this is symbolized S_1^v. Such vibrational excitation is a particularly important effect in vapor-phase studies since dissociation (and perhaps intersystem crossing, see below) may occur from these states (S_1^v, $S_1^{v'}$, etc.). This is evidenced, for example, in the effect of wavelength on the photochemical quantum yields of simple aliphatic aldehydes and ketones. Although photodecomposition may occur from such levels, the vibrational cascades $S_1^v \rightsquigarrow S_1^{v'}$ are very fast compared to rates of emission so that except for very simple molecules at low pressures (e.g. iodine at 1 mm pressure) fluorescence always originates from the lowest vibrational level of the lowest excited singlet state, $S_1^0 \rightarrow S_0 + h\nu$.

Internal conversion between excited electronic states of carbonyl compounds (i.e. $S_2^0 \rightsquigarrow S_1^{v'}$) also is fast relative to emission so that although excitation may be to the second electronic absorption band, ($S_0 + h\nu \rightarrow S_2^v$), emission of fluorescence originates from the S_1^0 level. The sequence is

$$S_0 + h\nu \longrightarrow S_2^v \rightsquigarrow S_2^0 \rightsquigarrow S_1^{v'} \rightsquigarrow S_1^0 \longrightarrow S_0 + h\nu$$

Dissociation, however, may occur from the second excited state.

For each excited singlet state there is a corresponding triplet level, always at a lower energy. Thus a photoexcited 'normal' ketone or aldehyde in a fluid phase which has reached the S_1^0 level may have

the following intramolecular paths to degrade its energy (Figure 1): fluorescence ($S_1^0 \rightarrow S_0 + h\nu$), *internal* conversion to a highly vibrationally excited ground state ($S_1^0 \rightsquigarrow S_0^v$), *intersystem crossing* to a vibrationally excited level of the lowest triplet state ($S_1^0 \rightsquigarrow T_1^v$), or a photochemical reaction. There also may be, in certain cases, the possibility of intermolecular processes including sensitized decomposition and electronic energy transfer, $S_0^a + S_1^d \rightarrow S_1^a + S_0^d$, where a and d refer to acceptor and donor molecules respectively. For the sake of this discussion we shall not consider these intermolecular processes involving singlet states.

The intersystem crossing $S_1^0 \rightsquigarrow T_1^{v'}$ is a very important process; in the case of benzophenone, for example, the quantum yield of intersystem crossing, Φ_{isc}, is virtually unity (see Table 2). Having reached the lowest triplet level ($T_1^{v'} \rightsquigarrow T_1^0$ is also fast) the *intramolecular* processes available to the excited molecule are phosphorescence ($T_1^0 \rightarrow S_0^{v''} + h\nu$), intersystem crossing, or a chemical reaction. Intermolecular processes include chemical reactions and electronic energy transfer ($S_0^a + T_1^d \rightarrow T_1^a + S_0^d$); both are highly important processes in the carbonyl photochemistry as we shall see subsequently. Triplet energy levels and quantum yields for intersystem crossing for several aldehydes and ketones are shown in Table 2.

TABLE 2. Triplet state energies of some ketones and aldehydes and quantum yields for intersystem crossing in benzene solution at 29°C.

Compound	Triplet energy (kcal/mole)[a,d]		
	MCIP solution[b]	EPA solution[c]	Φ_{isc}
Benzophenone	68·5	69·2	0·99
Acetophenone	73·6	73·6	0·99
Benzaldehyde	71·9	71·3	—
2-Acetonaphthone	59·3	59·5	0·84
Fluorenone	53·3		0·93
p-Methylbenzophenone			1·03
p-Bromobenzophenone			1·01
1-Naphthaldehyde	56·3	56·3	
2-Naphthaldehyde	59·5		

[a] These values refer to the maximum of the 0–0 line of the phosphorescence measured spectrophotometrically at 77°K.
[b] MCIP: methyl cyclohexane–isopentane, 5:1 by volume.
[c] EPA: ether–isopentane–ethanol, 5:5:2 by volume.
[d] For original references, see ref. 25.
[e] Taken from ref. 26; we are indebted to Professor Hammond and Dr. Lamola for supplying these important data.

The fate of the highly vibrationally excited ground state S_0^v from internal conversion (also $S_0^{v\prime}$ from intersystem crossing) is usually considered to be simple vibrational cascade to the ground vibrational state. However, evidence is accumulating that in certain systems chemical reactions may occur from these higher vibrationally excited ground states[237].

Whether or not the internal conversion process ever occurs in ketone and aldehyde photochemistry is not definitely established, much less the type of reactions the highly vibrationally excited molecule S_0^v might undergo. However, it may in some systems be an important process (see, e.g., equation 154a[273]).

In the case of normal ketones and aldehydes, such as benzophenone, both the lowest singlet and triplet states are n,π^* in nature. In abnormal ketones and aldehydes, e.g. *p*-phenylbenzophenone, the π,π^* triplet appears to lie below the n,π^* triplet; hence the lowest energy states are the n,π^* singlet and the π,π^* triplet. This is of great interest since it is generally recognized that in solution the lowest excited states are those involved in photochemical reactions. Thus, in certain cases where the n,π^* and π,π^* triplets lie very close to each other, a change of solvent may result in an inversion in energy levels of the triplets and consequently alter the nature of the photochemical reaction.

For more details on the theoretical and experimental aspects of the important subject of primary photophysical processes, which because of space limitation we regretfully have had to treat in a cursory manner here, the reader is referred to the original references cited here and in ref. 3.

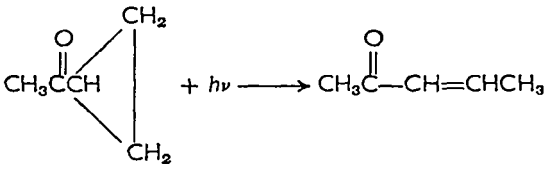
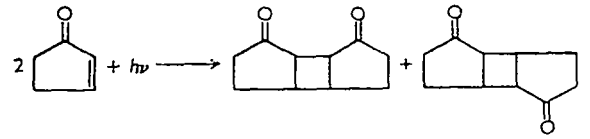
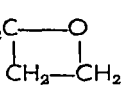
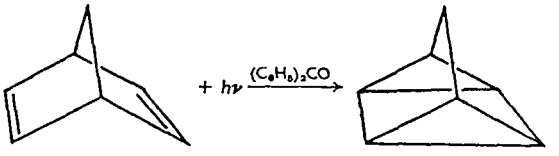
III. PRIMARY PHOTOCHEMICAL PROCESSES OF KETONES AND ALDEHYDES

A. Types of Primary Photochemical Reactions

An electronically excited molecule may undergo more than one primary photochemical reaction. Examples of several of the more common processes involving ketones and aldehydes are summarized in Table 3.

The relative efficiency of various overall reaction modes is governed by factors such as molecular structure, nature of the solvent, reaction phase, pressure, temperature, wavelength, and intensity of the light absorbed. Detailed correlations between such parameters and the overall modes of photochemical reaction require

TABLE 3. 'Primary' photochemical processes of ketones and aldehydes.

Sample reaction	Classification
$CH_3COCH_2CH_2CH_3 + h\nu \rightarrow CH_3\dot{C}O + \dot{C}_3H_7$ $\rightarrow \dot{C}H_3 + C_3H_7\dot{C}O$ $\rightarrow \dot{C}H_3 + \dot{C}_3H_7 + CO$	Dissociation into free radicals
$\rightarrow CH_3COCH_3 + C_2H_4$	Photocycloelimination into molecules; intramolecular hydrogen-atom abstraction
$\rightarrow CH_3C(OH)(CH_2)CH_2CH_2$	Photorearrangement into cyclic carbinol
trans-$CH_3COCH{=}CHCH_3 + h\nu \rightarrow$ *cis*-$CH_3COCH{=}CHCH_3$	Photisomerization
	Intramolecular skeletal rearrangement
$(C_6H_5)_2CO + h\nu \xrightarrow{RH} (C_6H_5)_2COH + \dot{R}$	Intermolecular hydrogen-atom abstraction
	Photocyclodimerization
$(C_6H_5)_2CO + h\nu \xrightarrow{C_2H_4}$ 	Carbonyl photocycloaddition to olefin
	Photsensitized isomerization

painstaking accumulation of quantitative experimental data; to date these are available only for a very few systems, notably the simple aliphatic ketones and aldehydes and benzophenone.

A wavelength effect within an absorption band on the quantum yield of a given photochemical process indicates that the reaction occurs before the excess vibrational energy can be equilibrated with the surroundings. The rate of equilibration of vibrational energy depends markedly on the collision frequency and the nature of the colliding partner. Thus, in gas-phase photolyses wavelength effects are often observed. However, in the liquid phase collisions are much more frequent and the rapid loss of vibrational energy in most cases 'masks' a possible wavelength effect. In addition to vibrational quenching, in some systems collisional quenching of the electronic energy is an important process (e.g. ketene and methyl propenyl ketone, both of which dissociate via an 'excited-molecule' mechanism).

Liquid-phase photochemical reactions differ from vapor-phase systems in two major respects. First, in liquids collisional deactivation of excited ketone or aldehyde molecules becomes much more important. This can be visualized as vapor-phase photolysis at very high pressures. Second, interactions between the excited ketone or aldehyde and a solvent molecule may lead to various new photochemical reactions or energy-transfer processes depending upon the nature of the solvent. Such bimolecular photochemical reactions between an excited ketone or aldehyde and an added gas are much less efficient in the vapor phase.

In addition 'cage' and 'diffusion' effects may become controlling factors in secondary thermal reactions in the liquid phase. This sometimes reflects directly upon the apparent yield of the primary photodecomposition. For example, a photoexcited ketone which dissociates into free radicals in the gas phase with a high quantum efficiency may appear to be relatively stable to photodissociation because of the rapid recombination of the primary radicals within the solvent 'cage'.

Temperature may play a variety of roles in photochemical reactions. For example, its effect on primary photochemical processes is small compared to its secondary effect on secondary free-radical thermal reactions with appreciable activation energies. Then again, for some 'diffusion-controlled' bimolecular reactions between an excited molecule and a ground-state molecule in the liquid phase, the effect of temperature on the viscosity of the medium becomes apparent in the overall reaction.

The effect of the intensity of light absorbed on photochemical reactions is most often manifested in the increased rates of secondary free-radical recombination reaction at high intensities. This effect is particularly obvious in flash photolysis experiments such as those on acetone and aliphatic aldehydes conducted in Claesson's laboratories[27]. Incidentally, we might caution the reader that in some conventional 'steady' photolyses reported in the literature, the so-called 'wavelength' effects are actually due to difference in the intensity of light absorbed.

In the following sections we shall discuss each of the various primary photochemical processes of ketones and aldehydes listed in Table 3 with reference to the factors mentioned above.

B. *Free-radical Decarbonylation*

Photodecomposition of ketones and aldehydes into free radicals is sometimes referred to as the 'Type I' split[30]. Apparently it may involve either the excited singlet state or the triplet state. As a rule, in solution at room temperature the free-radical decarbonylation occurs with a very low efficiency probably because of an efficient 'cage' recombination of the primary radicals. At elevated temperatures in solution the quantum yield of CO from acetone is still very small[28] but that of diethyl ketone is relatively large[29]. The difference is presumably due to the much greater stability of the acetyl *versus* the propionyl radical, since the difference in quantum yields of CO shows up also in vapor-phase photolyses of these two ketones at 25°.

$$R^1COR^2 + h\nu \longrightarrow \begin{cases} \dot{R}^2 + \dot{C}OR^1 & (1a) \\ R^1\dot{C}O + \dot{R}^1 & (1b) \\ \dot{R}^2 + \dot{R}^1 + CO & (1c) \end{cases}$$

If R^1 and R^2 are different alkyl groups, both of the alternative processes of bond cleavage (1a) and (1b) occur. However, a distinct preference is shown for the process involving the rupture of the weakest bond and formation of the most stable radicals when the absorbed light is at the longer wavelengths. As the energy of the absorbed quantum increases, this selectivity between the two processes decreases markedly.

Depending on the energy of the absorbed quantum, various fractions of the $R^1\dot{C}O$ and $R^2\dot{C}O$ radicals are vibrationally 'hot' and may decompose rapidly into an alkyl radical and CO in an early vibration following the primary act. The stability of equilibrated

$R^1\dot{C}O$ and $R^2\dot{C}O$ radicals depends markedly upon temperature with virtually complete dissociation of acetyl radicals at temperatures above 120°. Other simple acyl radicals are less stable than acetyl and the quantum yield of CO approaches unity at correspondingly lower temperatures.

For ketones in which R^1 and R^2 are alkyl groups without a γ-hydrogen atom, the free-radical decomposition is the major primary process in the near-ultraviolet photolysis. This process becomes relatively less efficient when one of the alkyl groups contains a hydrogen atom on the γ-carbon and a Type II process can occur (*vide infra*).

The situation is somewhat different for aldehydes with R^2 being a reactive hydrogen atom. Thus Blacet and coworkers[30] have established that the major mode of free-radical decomposition at all wavelengths in the first absorption band is reaction (2).

$$RCHO + h\nu \longrightarrow \dot{R} + \dot{C}HO \qquad (2)$$

Photodissociation of acetaldehyde into $H\cdot + CH_3\dot{C}O$ radicals has been observed to date only in flash photolysis[31], although it may be an important process at short wavelengths. We might note here that the aldehyde hydrogen is easily abstracted by radicals and hydrogen atoms producing $R\dot{C}O$ radicals in a secondary thermal reaction. This in turn leads to a chain production of CO which is not found in the photolysis of simple ketones until relatively high temperatures are reached.

An additional vapor-phase free-radical mode of primary photodecomposition has also been observed with the aliphatic aldehydes[32], reaction (3). It is of low efficiency at 3130 Å, but increases at shorter wavelengths and with increasing numbers of CH_3 groups at the β-carbon atom until at 1849 Å it is a major process. It is interesting to note that reaction (3) is a good example where energy initially

$$CH_3CH_2CH_2CHO + h\nu \longrightarrow \dot{C}H_3 + \dot{C}H_2CH_2CHO \qquad (3)$$

absorbed in a carbonyl group can be transferred down a side-chain and ultimately result in the rupture of a terminal carbon–carbon bond. No analogous decomposition has been reported for the aliphatic ketones.

C. Decarbonylation by Intramolecular Elimination

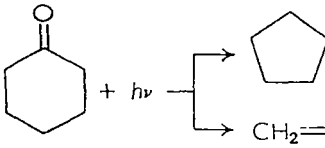
The intramolecular photodecomposition forming a hydrocarbon and CO has been observed only in aldehydes and cyclic ketones.

There appears to be no analog of reaction (4) with the aliphatic ketones.

$$RCHO + h\nu \longrightarrow RH + CO \qquad (4)$$

With aliphatic aldehydes including formaldehyde, reaction (4) is one of the general modes of photodecomposition. Although the nature of the excited state participating in reaction (4) is not well established, it is known that the intramolecular elimination of CO is negligible at 3130 Å but becomes a major process at 2537 Å. This suggests that the decomposition may involve dissociation from the upper vibrational levels of a short-lived excited singlet.

With cyclic ketones, decarbonylation appears to proceed mainly via an intramolecular elimination mechanism, and reaction (4) can now be replaced by two different processes as illustrated in (5) and (6). The relative efficiency of the decarbonylation processes is sensitive to the ring size, the ring structure and the physical state of the



(5)

$$CH_2{=}CHCH_2CH_2CH_3 + CO \qquad (6)$$

cyclic ketones being irradiated. Thus, while it is the major primary photochemical reaction in the gas phase at low pressures, it is much less important in the liquid phase. Presumably, decarbonylation arises from the first excited singlet state[33].

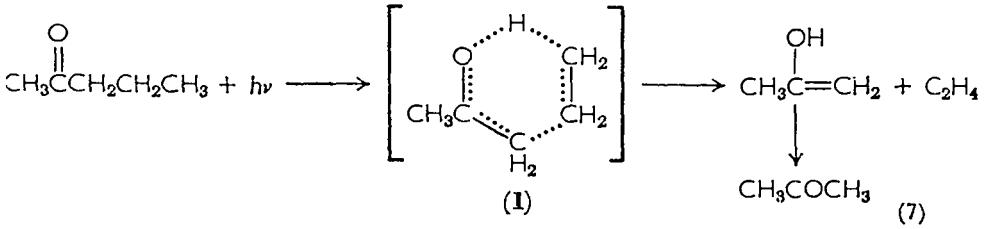
It has been suggested by Srinivasan[34] in his review article on the photochemistry of cyclic ketones that the photodissociative processes (5) and (6) involve a vibrationally excited diradical intermediate, $\dot{C}H_2(CH_2)_4\dot{C}O$, formed by cleavage of the carbon–carbon bond adjacent to the carbonyl chromophore. After losing CO in an early vibration, the remaining fragment of the diradical presumably undergoes a very rapid intramolecular combination (reaction 5) or self-disproportionation (reaction 6). Because of the very fast rate of these processes it is difficult to test this proposed mechanism with conventional radical-scavenger techniques so that one cannot rule out the alternate possibility of reactions (5) and (6) being concerted intramolecular processes that do not involve diradical intermediates. The diradical mechanism is the most attractive but we should note that the effects of temperature, light intensity, and wavelength on the decarbonylation processes of cyclic ketones have not been systematically and quantitatively investigated.

D. Photocycloelimination of Olefins

In this section we shall consider various intramolecular photodecompositions which do not involve decarbonylation. Most of these intramolecular decompositions of ketones and aldehydes can be rationalized in terms of a mechanism involving a cyclic intermediate.

1. The 'Type II' split with a six-membered cyclic intermediate

Reaction (7), often referred to as the Norrish 'Type II' split[40], or simply 'Type II' is a mode of intramolecular decomposition common to all aliphatic ketones and aldehydes having a γ-hydrogen atom on the alkyl chain. It occurs in the gas or liquid phase. There is no known case of a *saturated* ketone or aldehyde with γ-hydrogen atoms not undergoing this Type II split.

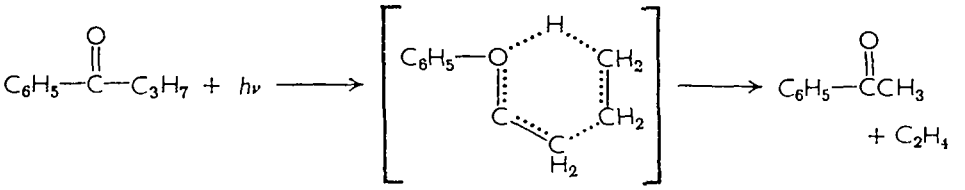


(1) (7)

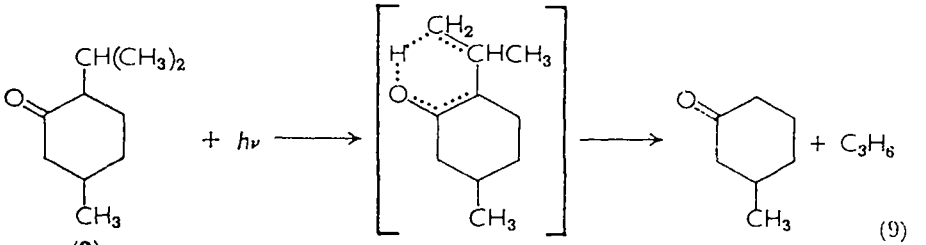
Davis and Noyes[35] first suggested a six-membered cyclic configuration (**1**) as an intermediate in reaction (7) and recently direct observation of the transient enol form by long-path infrared spectroscopy has been reported[36]. Based on this direct and other more indirect but compelling evidence involving deuterium substitution[37–39], it is now generally accepted that the intramolecular process (7) proceeds via photocycloelimination.

Intramolecular decompositions analogous to the Type II split have not been reported in halogen-substituted or unsaturated aliphatic ketones and aldehydes. Similarly 1,2-diketones having γ-hydrogen atoms do not undergo the Type II split. In the latter two cases intramolecular photocyclization occurs instead, at least in the liquid phase (see section III.F). Little is known about the gas-phase reactions.

Replacement of one of the alkyl groups by an aromatic ring or by a cyclic structure does not prevent the occurrence of the Type II decomposition. For example, both butyrophenone[23] (reaction 8) and menthone[40] (**2**, reaction 9) photodecompose predominantly by a Type II split mechanism. Methoxyacetone also photodecomposes by a Type II split (reaction 10)[41].

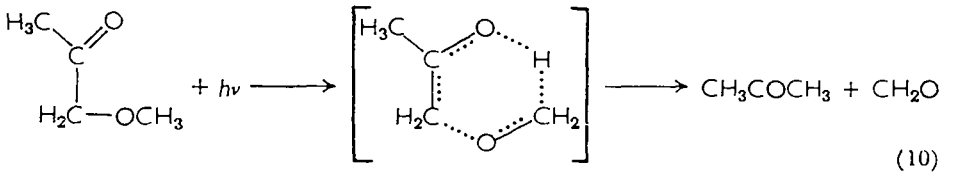


(8)



(2)

(9)



(10)

Temperature has little effect on the efficiency of the Type II intramolecular decomposition. Furthermore, the reaction is important in the liquid as well as in the vapor phase.

The nature of the excited state involved in the Type II process is still at the controversial stage. Brunet and Noyes[42], working with oxygen-quenching experiments, concluded that an excited triplet was not involved in the Type II process. In addition, Michael and Noyes[43] observed that addition of biacetyl quenches the Type II split in the photolysis of methyl n-propyl ketone and suggested that both the energy-transfer process and the Type II process occur via a singlet excited state of the ketone.

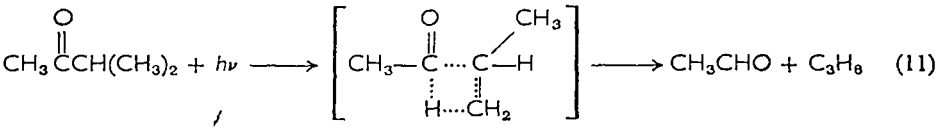
On the other hand, Ausloos and Rebbert[44] report that at 3130 Å Type II processes are quenched by the addition of biacetyl and that the light emitted by various ketone–biacetyl mixtures containing 1 mm of oxygen is identical with that emitted by pure ketone alone. Thus, they conclude that the energy-transfer process gives only triplet excited biacetyl and that consequently the Type II

process occurs via an excited triplet state. Their conclusion is further supported by the study of the photolysis of ketone–aldehyde mixtures at 3130 Å in which they show that the Type II process of n-butyraldehyde is photosensitized by triplet acetone[45].

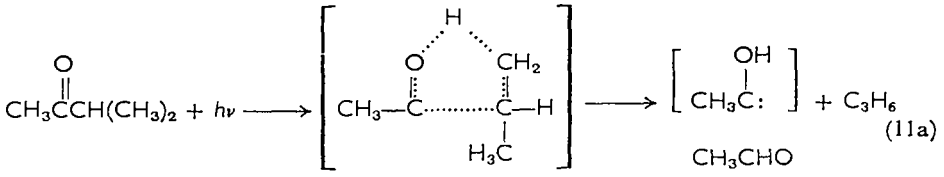
The significance of γ-hydrogen transfer mechanism in the photochemistry of 20-oxo steroids has been discussed in a recent review by Chapman[10]. This photochemical synthetic route has increasingly claimed more interest on the part of organic chemists in the field of natural products.

2. Other intramolecular photocycloeliminations

While the 'Type II' split via a six-membered cyclic intermediate is exclusive for saturated ketones and aldehydes with γ-hydrogen atoms, recent studies have shown that in some cases photocycloelimination can occur, presumably via a four-membered cyclic intermediate which involves participation of a β-hydrogen atom. For example, at 2537 Å a major process of methyl isopropyl ketone is the intramolecular decomposition into acetaldehyde and propylene[46].

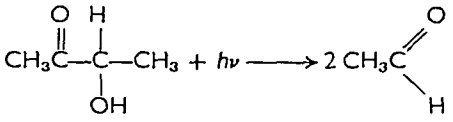


Reaction (11) in which a β-hydrogen atom is transferred has been suggested as a 'Type III' split[46]. It is found to be highly sensitive to wavelength in contrast to the virtually wavelength-independent nature of the Type II decomposition. Thus at 3130 Å reaction (11) is suppressed by the usually free-radical mode of decomposition and becomes important only toward shorter wavelengths. Its dependence upon temperature and pressure has, however, not been quantitatively studied. We should note that a five-membered cyclic intermediate (11a) is also a possibility. This was noted in the liquid-phase radiation chemistry of methyl propyl ketone where a Type III process apparently competes with a Type II split[47].



Another example of such a Type III process is the 3130 Å photolysis

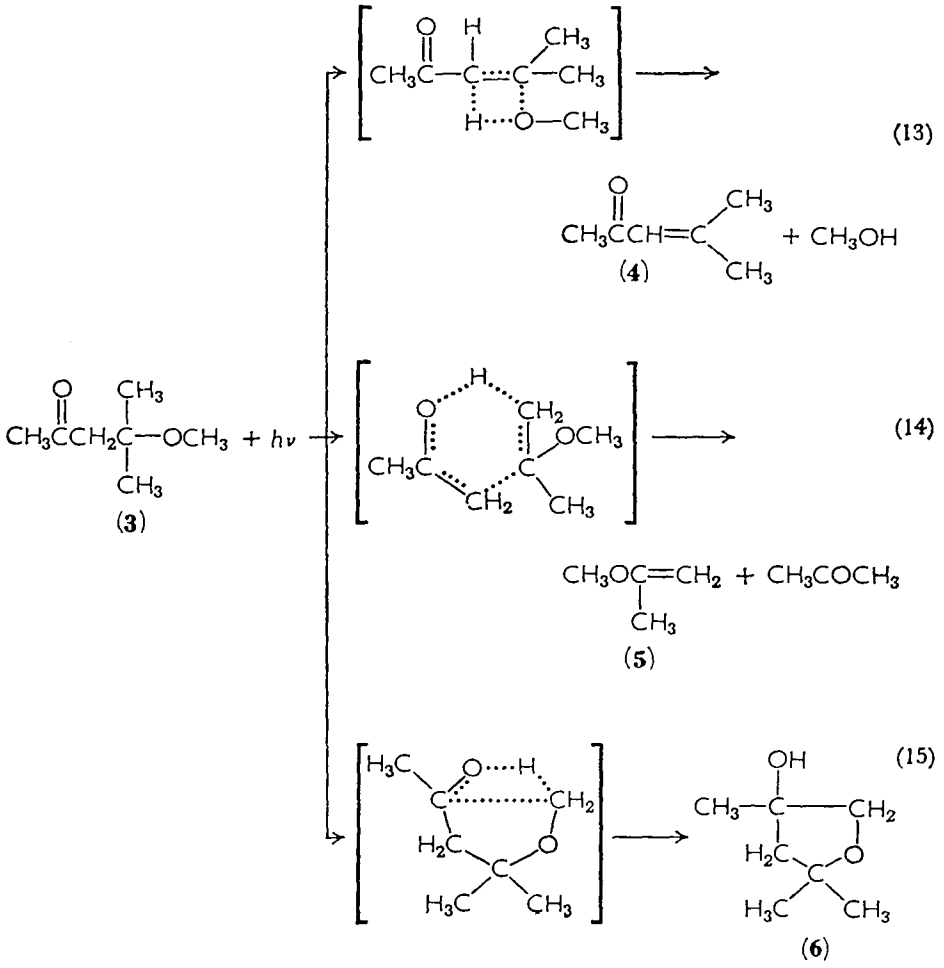
of 3-hydroxy-2-butanone in the vapor phase in which acetaldehyde is found to be a major product independent of temperature in the range of 40–150°c[48]. The formation of acetaldehyde is attributed to the intramolecular photocycloelimination process (12). The effects



(12)

of wavelength and pressure on this reaction have not yet been studied in detail.

A further example by Heicklen and coworkers[49] illustrates that in some ketones with favorable structure photocycloelimination can



(13)

(14)

(15)

occur via two or three different cyclic intermediates simultaneously. Thus, photolysis of 4-methoxy-4-methyl-2-pentanone (**3**) in various solvents leads to three different intramolecular decompositions involving four-, six-, and seven-membered cyclic intermediates[49] (reactions 13, 14, 15). The photolysis of **3** in heptane, ethanol, and allyl alcohol yields mesityl oxide (**4**), methanol, and a hydroxy-tetrahydrofuran derivative (**6**) as major products. The expected Type II process which produces acetone and methyl isopropenyl ether (**5**) was only observed as a minor reaction, while the intramolecular rearrangement to a cyclic alcochol was not found. The nature and ratios of products are not sensitive to a change of solvents. A free-radical mechanism in the photolysis was excluded, since allyl alcohol failed to show any radical-scavenging effects. The quantum-yield estimate indicates the following breakdown:

$$\Phi_{(13)} \approx 0{\cdot}25,\ \Phi_{(14)} \approx 0{\cdot}04,\ \Phi_{(15)} \approx 0{\cdot}17, \text{ and } \Phi_{\text{deactivation}} \approx 0{\cdot}54$$

The four-fold higher quantum efficiency of reaction (15) over that of the Type II process (14) suggests that in spite of the 2:1 ratio of γ-hydrogen atoms to methoxy hydrogens, the seven-membered ring is preferentially formed to the six-membered ring. It is not certain whether the preference is due to the more labile methoxy hydrogens or to the different nature of excited states involved in the two reactions. It is also not known whether these intramolecular decompositions are sensitive to wavelength and to a change of reaction phase.

The present status of photocycloelimination involving four-membered or seven-membered cyclic intermediates (or possibly five-membered) is still in a speculative stage, as no direct unequivocal evidence has been obtained. In most cases postulation of a cycloelimination mechanism is made by analogy to the more established 'Type II' process in order to explain the experimental results. However the proposed mechanisms do seem reasonable.

3. Intramolecular elimination from cyclic ketones

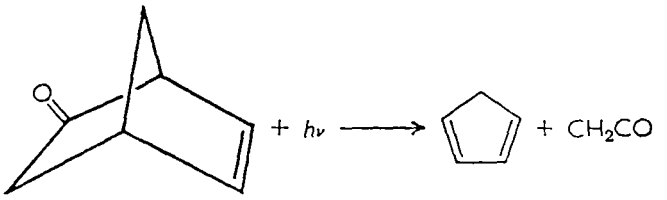
A few cyclic ketones photodecompose into an olefin and ketene. For example, cyclobutanone at 3130 Å decomposes largely to ethylene and ketene[50–52] (reaction 16). This reaction has not been

$$+ h\nu \longrightarrow C_2H_4 + CH_2CO \qquad (16)$$

quantitatively studied with respect to temperature, pressure, and wavelength and no data are available for the liquid phase.

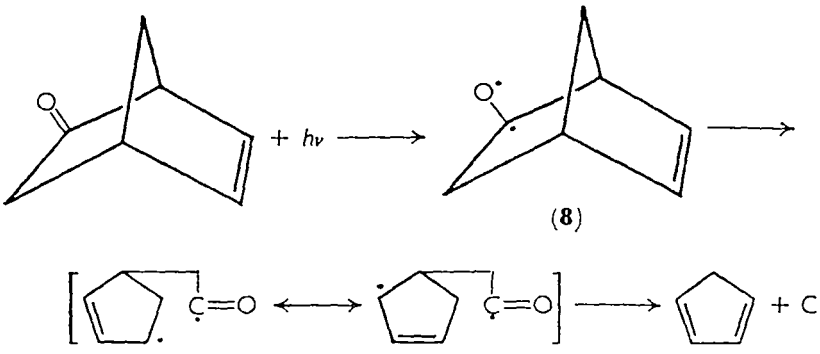
It is interesting that in the series of simple cyclic ketones (from cyclobutanone to cycloheptanone) only cyclobutanone undergoes dissociation into ketene and a corresponding olefin as a major process.

Similar elimination reactions have also been observed in the photolyses of bicyclic ketones. For example, liquid-phase irradiation of dehydronorcamphor (**7**) gives a very good yield of cyclopentadiene and ketene[53-54]. The attractive alkyl–acyl radical-pair mechanism



(7) (17)

(reaction 18) proposed by Quinkert[55] has been employed to account for the decomposition.



(18)

E. Intramolecular Skeletal Rearrangement

Skeletal photorearrangements are particularly important in the photochemistry of α,β-unsaturated ketones and cyclic ketones. They can be grouped into the following four general patterns.

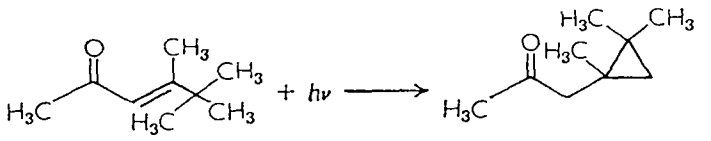
1. Rearrangement of the aliphatic chain

Saturated aliphatic ketones and aldehydes do not undergo intramolecular skeletal isomerization. However, unsaturated aliphatic

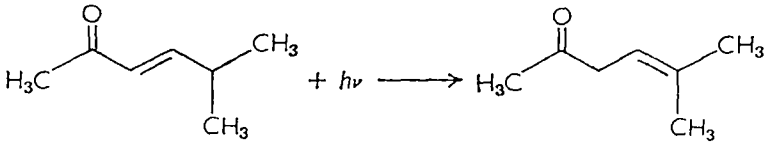
ketones undergo *cis–trans* isomerization, 'facile' isomerization, and cyclization of the carbon chain.

For example, irradiation of *trans*-methyl propenyl ketone at 3130 Å in the vapor phase and temperatures up to 275° leads to the conversion of the *trans* into the *cis* isomer as the only significant photoreaction[56]. The effect of pressure and wavelength on the yield of isomerization is under investigation[48]. Irradiation in the second absorption band at 2380 Å and elevated temperatures leads to photodecomposition apparently through an 'excited molecule' which then decomposes into free radicals. The nature of the excited states involved in either case is not known.

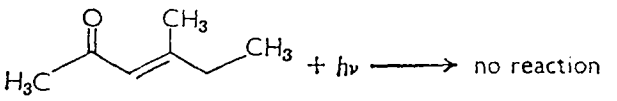
A 'facile' isomerization (shift of the double bond) and cyclization of the carbon chain is illustrated in the liquid-phase photolysis of certain α,β-unsaturated aliphatic ketones. Thus Yang and coworkers have shown that when the ketone has a quaternary carbon atom at the γ-position, irradiation in ether solution leads to cyclization of the chain[57] as shown in reaction (19). On the other hand, irradiation of α,β-unsaturated aliphatic ketones having no γ-quaternary carbon gives either 'facile' isomerization to the β,γ-unsaturated isomers (reaction 20) or no reaction at all (reaction 21)[58]. Reactions (19)



(9) (10) (19)



(11) (12) (20)



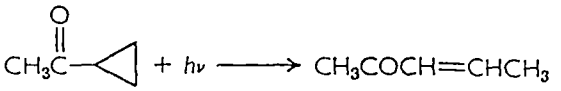
(13) (21)

and (20) have not been studied as a function of wavelength and temperature. Although the exact nature of the excited states involved in these reactions is not established, Yang has suggested that the difference in photochemical behavior among ketones **9**, **11**, and **13**

may be attributed to the possible difference in the nature of their low-lying triplet states[58].

2. Rearrangement of cyclic to chain structure

Irradiation of methyl cyclopropyl ketone with 2654–2537 Å in the vapor phase leads to both free-radical dissociation and to intramolecular rearrangement involving opening of the cyclopropyl ring (reaction 22)[59]. Rearrangement is the major process with a

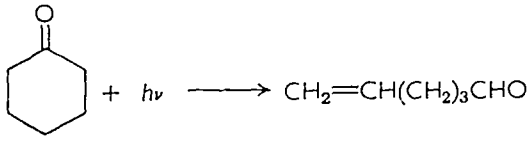


(22)

quantum yield of about 0·3 which is virtually independent of temperature in the range 25–170°.

The ratio of the quantum yields of rearrangement to free-radical split is strongly dependent on the molecular structure. Thus insertion of a methylene group(s) between the carbonyl chromophore and the cyclopropyl ring drastically reduces the rearrangement and increases the quantum yield of CO[15] (*vide infra*). A similar intramolecular rearrangement has been observed with dicyclopropyl ketone[60,124].

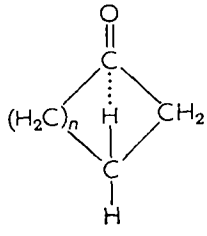
Another mode of rearrangement involving conversion of a cyclic into a chain structure is the general photoisomerization of cyclic ketones to unsaturated aliphatic aldehydes (e.g. equation 23).



(23)

This intramolecular isomerization is rather insensitive to a change of phase from vapor to liquid but self-quenching apparently occurs in the liquid phase[61].

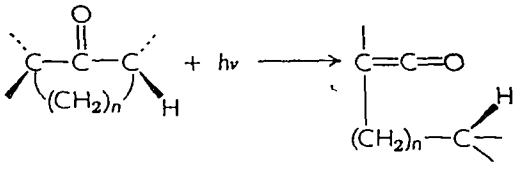
The quantum efficiency of the isomerization varies markedly with ring size. Thus it has been postulated that the isomerization is a



(14)

concerted process involving the transfer of a β-hydrogen atom to the carbonyl group via the four-center configuration represented in **14**. With increasing size of the ring, freedom to rotate about the C—C bond increases and the distance between the carbonyl chromophore and the β-hydrogen atom of the intermediate **14** can be considerably shortened resulting in a higher efficiency of the isomerization process[34].

Still another rearrangement of a cyclic ketone to a chain structure has been shown by Quinkert and coworkers[55] (reaction 24). The mechanism explaining the process involves an alkyl–acyl radical pair (reaction 25).



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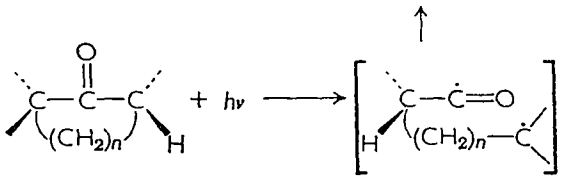
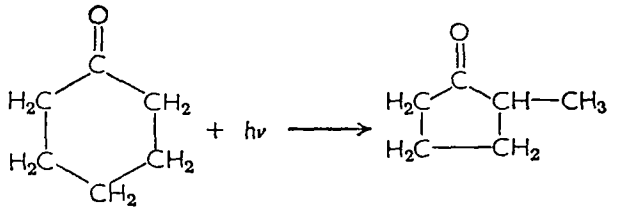


(25)

3. Ring contraction

The novel ring contraction shown in reaction (26) has recently been reported[61] in the liquid-phase photolysis of cyclic ketones containing five-, six-, seven-, and eight-membered rings. An isotopic experiment[62] indicates that the α-carbon with the deuterium atoms



(26)

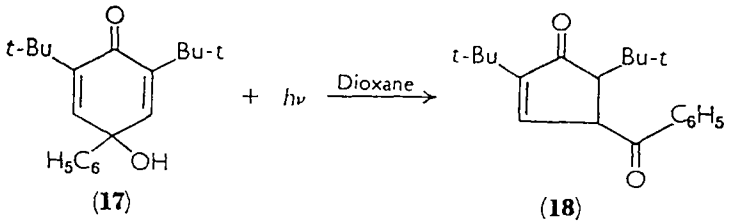
(15) (16)

becomes the methyl side-chain. For example, irradiation at 3130 Å of liquid cyclohexanone gives 2-methylcyclopentanone with a quantum yield of about 0·03. With larger rings, other products of ring contraction also occur. For example, irradiation of liquid cyclooctanone

yields both 2-methylcycloheptanone and 2-propylcyclopentanone[61]. The isomerization is proposed as an intramolecular process not involving free-radical intermediates, since addition of cyclohexene has no effect on the rate of this ring-contraction reaction.

Although the nature of the excited states involved in this isomerization is not established, it has been postulated[61] that it involves a different electronic state than that in reaction (23). This assumption is based on the experimental observation that in irradiation of pure liquid cyclohexanone at 3130 Å, the formation of 2-methylcyclopentanone by reaction (26) is not affected by the build-up of 5-hexenal. Further evidence, however, is necessary before definitive conclusions can be drawn.

Another recent example of ring contraction has also been reported in the photolysis of 2,6-di-*t*-butyl-4-hydroxy-4-phenyl-2,5-cyclohexadien-1-one (**17**). The rearranged product **18** is obtained in 20% yield[63]. The detailed mechanism and various factors on the efficiency of reaction (27) have not been elucidated.

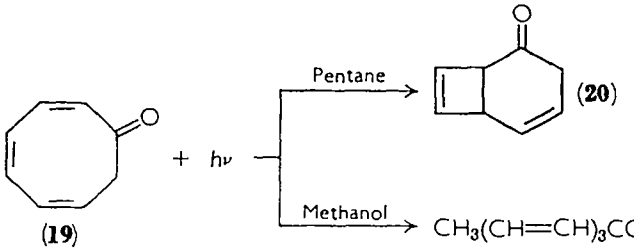


(17) (18) (27)

4. Rearrangement of mono- to bicyclic structures and *vice versa*

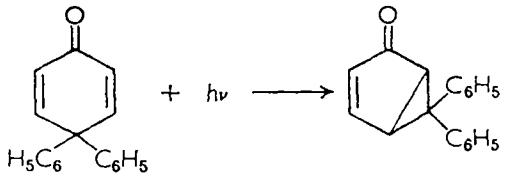
Photoisomerizations of cyclic ketones involving conversion of monocyclic into bicyclic structures and *vice versa* have been observed in the liquid phase. For example, irradiation of 2,4,6-cyclooctatrienone (**19**) in pentane solution leads to a skeletal rearrangement to a bicyclic ketone (**20**) in about a 30% yield[64].

However, in methanol solution **19** gives methyl 2,4,6-octatrienoate (**21**) as the photoproduct[64].



(19) (28) (29)

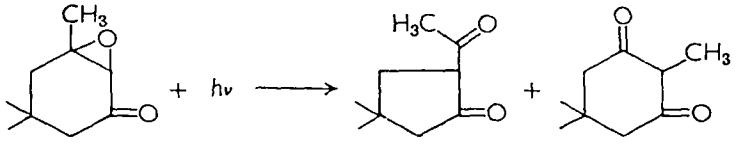
Liquid-phase photolysis of 4,4-diphenyl-2,5-cyclohexadienone (**22**) gives a bicyclic ketone product (**23**). The reaction has been studied



(**22**) (**23**) (30)

under a variety of experimental conditions[65]. The conversion yield is about 80% and independent of wavelengths in the regions 4200–3100 Å. By studying the photoreaction of **22** alone and of the mixtures of **22** + acetophenone and **22** + naphthalene, it was concluded that the isomerization reaction (30) proceeds via a triplet state[65].

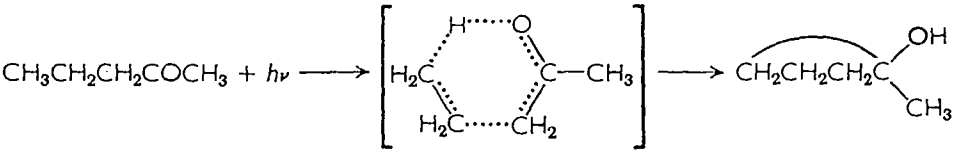
The photolysis of isophorone oxide (**24**) serves to illustrate the rearrangement of a bicyclic structure to a monocyclic product. In various solvents irradiation of **24** gave a 9:1 mixture of **25** and **26** in 10% yield[66].



(**24**) (**25**) (**26**) (31)

F. Intramolecular Reduction of the Carbonyl Group

Intramolecular rearrangement involving reduction of the carbonyl group seems to be invariably accompanied by cyclization. This primary mode of photorearrangement, common to all simple aliphatic ketones with a γ-hydrogen atom, leads to a cyclic carbinol as shown in reaction (32). However the analogous reaction has not



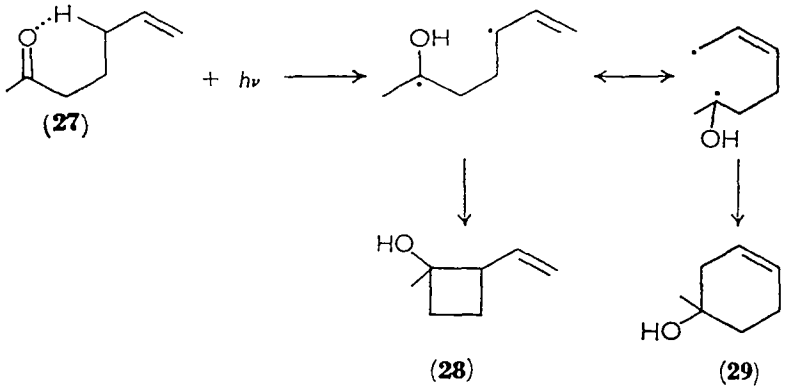
(**1**) (32)

been reported in the photolysis of aliphatic aldehydes with γ-hydrogen atoms.

The efficiency of reaction (32) is not sensitive to temperature and to a change of phase and it is assumed to proceed via a six-membered cyclic intermediate (**1**) as in the Type II split process. However, it is not clearly established whether the two processes arise from the same excited state or different states. It has been suggested that the cyclization conceivably proceeds via the lowest triplet state. In any case reaction (32) provides a simple readily accessible synthetic route to a group of cyclobutanol derivatives otherwise difficult to prepare.

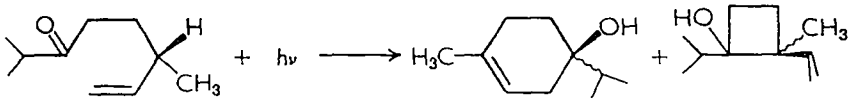
The effect of wavelength on the efficiency of reaction (32) has not been quantitatively and systematically studied. In general the yield of the cyclic carbinol is lower than those products resulting from the Type II split. It is also not certain if the structure of the alkyl chain plays an important role in the intramolecular reduction process.

Neither halogenated ketones nor unsaturated aliphatic ketones undergo the Type II split. Halogenated ketones also do not rearrange, but aliphatic ketones with a δ,ε-double bond and γ-hydrogen atoms isomerize to cyclic carbinols. The reaction may proceed either by way of an allyl diradical or via a concerted mechanism, but presumably not by the six-membered cyclic intermediate **1**. For example, liquid photolysis of ketone **27** leads to two isomeric cyclic carbinols (**28** and **29**), presumably via an allyl radical intermediate[67]. On the



(27) (28) (29) (33)

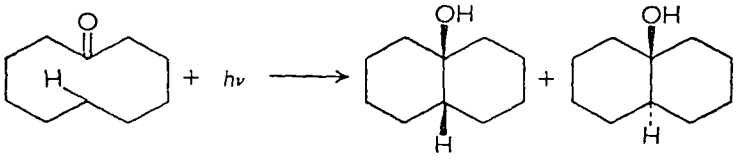
other hand, photolysis of 2,6-dimethyl-7-octen-3-one (**30**) in a 10% cyclohexane solution gives the reaction[68] shown in (34).



(30) (31) (32) (34)

The observed formation of **31** with retention of configuration is not possible via an allyl radical intermediate. Thus it is suggested that a concerted intramolecular six-center one-step process is responsible for the formation of **31**, and a similar four-center one-step process leads to **32** with stereospecific removal of the allyl γ-hydrogen atom[68].

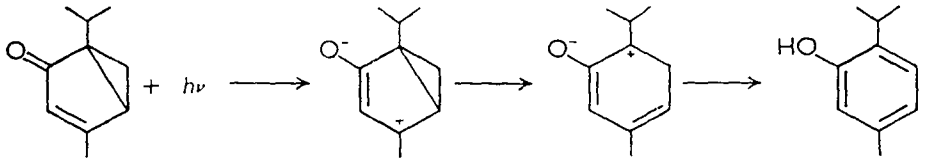
The intramolecular photoreduction of the carbonyl group also has been observed with cyclic ketones of larger ring size. For example, photolysis of cyclodecanone (**33**) at 2537 Å leads to the formation of the isomeric bicyclic alcohols **34** and **35** in 42% and 10% yields, respectively[69]. The reaction has not been systematically studied as a function of wavelength and ring structure.



(35)

(33) (34) (35)

Certain α,β-unsaturated cyclic ketones also undergo skeletal rearrangement with reduction of the carbonyl chromophore. For example, when neat liquid umbellulone (**36**) was irradiated with a full mercury arc, thymol (**39**) was recovered in quantitative yield[70]. However, when **36** was irradiated with the 2537 Å alone, only 10% conversion into **39** was observed[70].



(36) (37) (38) (39)

(36)

This intramolecular reduction of the carbonyl group can be rationalized using Chapman's approach[10] in which a positive charge is developed on the β-carbon and a negative charge on the carbonyl oxygen, as shown in reaction (36). However, unambiguous evidence supporting the existence of the polar excited state (**37**) and the subsequent transient (**38**) has not been established.

G. Intermolecular Hydrogen-atom Abstraction

The ability of a photoexcited ketone or aldehyde to abstract a hydrogen atom from good hydrogen donors in the solution phase has

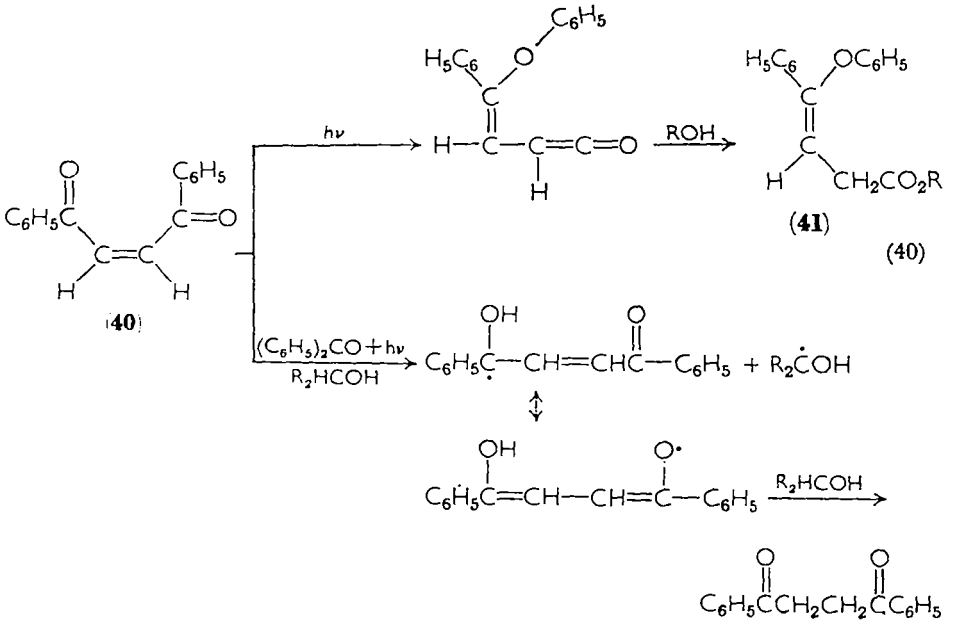
been well known for many years[71]. However, virtually no analogous photochemical reduction of ketones and aldehydes has been reported in the vapor phase. At least in one case, the aromatic ketones and aldehydes, the excited state involved in the photochemical reduction has been identified as the lowest n,π^* triplet of the carbonyl chromophore[12-14,20,72-73]. Thus, the first steps in the photochemical reduction sequence are believed to be (38) and (39).

$$R_2C{=}O + h\nu \longrightarrow R_2C{=}O\ (S_1) \rightsquigarrow R_2C{=}O\ (T_1) \tag{38}$$

$$R_2C{=}O\ (T_1) + RH \longrightarrow R_2\dot{C}OH + \dot{R} \tag{39}$$

The efficiency of the hydrogen-atom abstraction in reaction (39) depends upon the reactivity of the hydrogen donor, the structure of the abstracting ketone, and the nature of the solvent. In some cases, for example 1-naphthaldehyde[74], *p*-aminobenzophenone, and *o*-hydroxybenzophenone[20-22], abstraction of a hydrogen atom from the usual hydrogen donors is very inefficient. This nonreactivity of the first two compounds has been attributed in part to the fact that their lowest triplet states are $^3(\pi,\pi^*)$ rather than $^3(n,\pi^*)$ in character[20-22,74]. With the *o*-OH derivatives, the nonreactivity is due to photoenolization (section VIII.B).

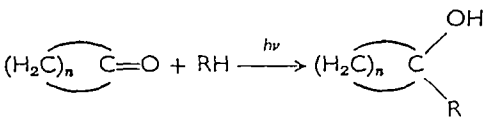
Dependence of chemical behavior upon the nature of the excited



states is illustrated by the photochemical reactions of *cis*-dibenzoylethylene (**40**) in alcoholic solvents. Thus Griffin and O'Connell[76] showed that direct photolysis of **40** involves an excited singlet state which mainly undergoes rearrangement involving a 1,5-phenyl migration followed by addition of alcohol to give the ester **41**. On the other hand, sensitization by triplet benzophenone produces **40** in its triplet state. This is subsequently photoreduced via intermolecular hydrogen-atom transfer from the solvent.

In contrast to the large amount of work on the Type II split involving intramolecular hydrogen abstraction, the photochemical reduction of aliphatic aldehydes and ketones has not been extensively studied. A few reports[76,77] indicate that photoexcited acetone molecules are to a small extent reduced either by self-quenching or by abstraction from the solvent. With aliphatic ketones containing γ-hydrogen atoms, little, if any, intermolecular photoreductions occur. Similarly, when butyrophenone is irradiated in hydroxylic solvents the Type II split is far more probable than intermolecular hydrogen-atom abstraction[23]. It is not yet established whether or not the intra- and intermolecular hydrogen abstraction involves the same excited state.

Finally, intermolecular photoreduction of cyclic ketones has not been systematically investigated but it is believed that in hydrocarbon or aqueous solutions the reaction between the photoexcited cyclic ketone and the solvent becomes important (reaction 42).



(42)

(42) (43)

For example, photolysis of cyclohexanone in cyclohexanol solution leads to the formation of cyclohexyl pinacol[78], and irradiation of 2-fluorocyclohexanone in methanol gave a very low yield of methyl 6-fluorohexanoate[79].

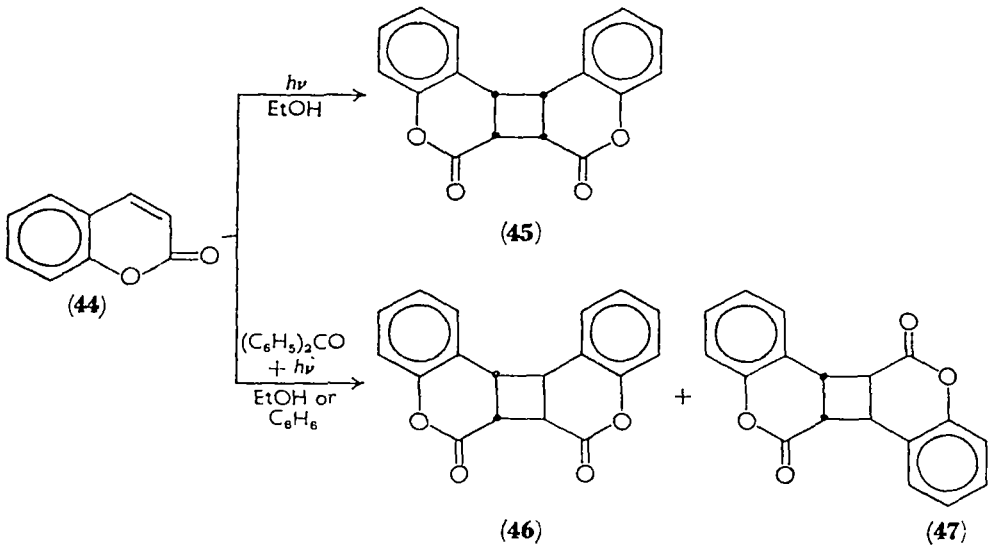
H. Photocyclodimerization

Photocyclodimerization to give cyclobutane derivatives has long been known for α,β-unsaturated carbonyl compounds[280]. Although the reaction has been studied extensively in the condensed phase the analogous reaction is not known in the vapor phase.

Presumably both excited singlet and triplet states may participate

in the dimerization and apparently either n,π^* or π,π^* states cyclodimerize. For example, irradiation of 9-anthraldehyde gives a head-to-tail dimer[80-81].

Solvent effects on the course of dimerization are illustrated by the photochemical reactions of coumarin (**44**)[82-84]. Thus, Anet[82], Schenck and coworkers[83], and Hammond and coworkers[84] showed that irradiation of **44** in ethanol solution gives a *cis* head-to-head dimer (**45**), but no reaction was observed with benzene as the solvent.



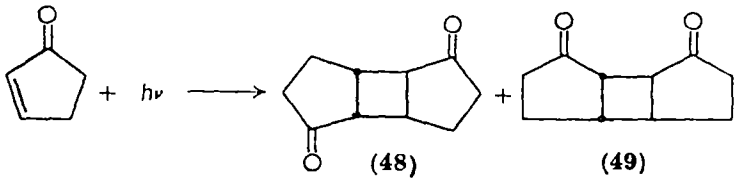
(43)

However, dimerization of **44** can be photosensitized by benzophenone in either ethanol or benzene solutions. The benzophenone photosensitized reaction gives the *trans* dimer (**46**) and a trace of the *trans* head-to-tail dimer (**47**).

Recently it has been shown in detailed mechanistic studies that direct photolysis of **44** produces an excited singlet state which leads only to self-quenching in nonpolar solvents such as benzene, and to the formation of **45** in very low yields in polar solvents such as ethanol[84]. In the sensitized reactions triplet coumarin (**44**) produced by energy transfer from the triplet benzophenone leads to the formation of **46** and **47** with relatively high quantum yields. At high dilution and in the absence of benzophenone, direct photolysis of coumarin also produces triplet coumarin via intersystem crossing, and **46** is formed. When benzophenone is present in small amounts

and most of the light is absorbed by **44**, they suggested that singlet excitation is transferred from **44** to benzophenone where intersystem crossing takes place efficiently. The triplet excitation is then transferred back to **44** to give the dimers **46** and **47**. They also suggest that the absence of dimer **45** in the sensitized reaction indicates that transfer of singlet excitation from benzophenone to coumarin (**44**) is not as efficient as the reverse process[84].

Another interesting example is the photodimerization of cyclopentenone in pure liquid or in various solvents to give *trans* head-to-tail and *trans* head-to-head dimers in equal yield[85]. This nonstereospecific behavior suggests that the cyclodimerization may involve highly reactive excited singlet states. In the presence of a



(44)

large excess of cyclopentene, cross-addition occurs in preference to dimerization, yielding exclusively the *trans* dimer[86].

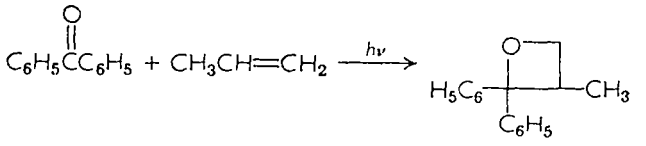
Most of the ketones that have been reported to undergo such photocyclodimerization are conjugated cyclic unsaturated ketones, some with heteroatoms on the ring; it is interesting that similar photochemical reactions have not been reported with α,β-unsaturated acyclic ketones or aldehydes. Still, this photochemical cycloaddition as either self-dimerization or cross-dimerization can be highly useful as a general synthetic method.

I. Carbonyl Photocycloaddition to Olefins

The cycloaddition of olefins to photoexcited carbonyl groups to form oxetanes, first studied in detail by Büchi and coworkers, appears to be a general reaction with aliphatic and aromatic ketones and aldehydes. Cyclic ketones and unsaturated ketones apparently do not undergo a similar carbonyl addition.

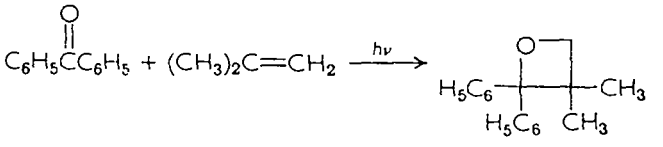
The yield of oxetanes from the photocycloaddition of benzophenone and derivatives to olefins depends markedly on the structure of the olefin as well as the structure of the benzophenone[87]. Thus, benzophenone derivatives which do not photoreduce do not undergo this addition and it has been suggested that the addition reaction requires the lowest excited state to be $^3(n,\pi^*)$ in character.

The effect of olefin structure is illustrated by the addition of benzophenone to propylene and isobutylene. This give the corresponding oxetanes **50** and **51** in 5% and 93% yield, respectively[87].



(45)

(**50**)

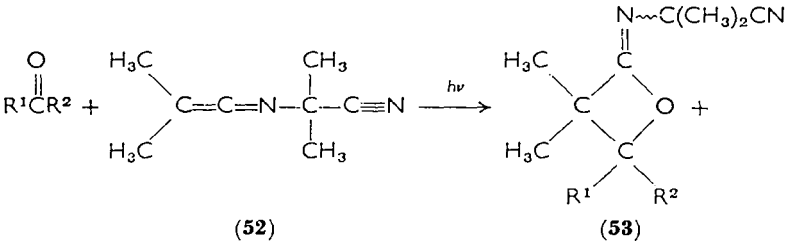


(46)

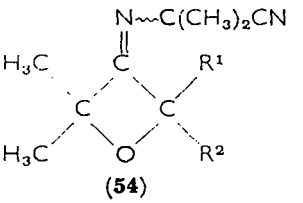
(**51**)

The results can be explained by assuming that the triplet energy level of the unreactive olefin is below that of the carbonyl triplet, and triplet–triplet energy transfer from the carbonyl group to the olefin takes place to the virtual exclusion of oxetane formation[87].

In a similar reaction Singer and Bartlett[88] showed that irradiation of several aromatic ketones and aldehydes led to addition across the carbon–carbon bond of dimethyl-*N*-(2-cyano-2-proyl)ketenimine (**52**) to give the α- and β-iminooxetanes **53** and **54**. With cyclo-



(**52**) (**53**)

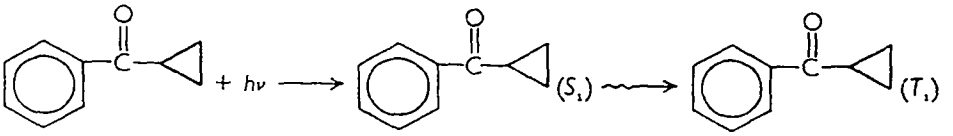


(47)

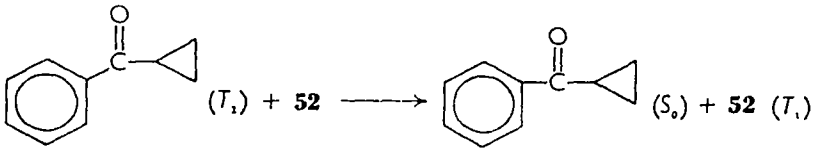
(**54**)

propyl phenyl ketone, transfer of triplet energy to ketenimine was found to take place so efficiently that the formation of oxetane was suppressed completely, and tetramethyl succinonitrile (**55**) was

formed exclusively. The ratio of oxetane formation to that of **55** was found to vary from one carbonyl compound to the other and those carbonyl compounds with higher triplet energy tend to give more **55**



(48)



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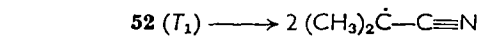

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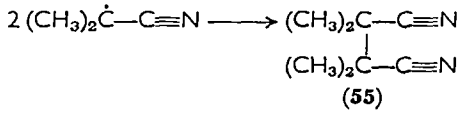
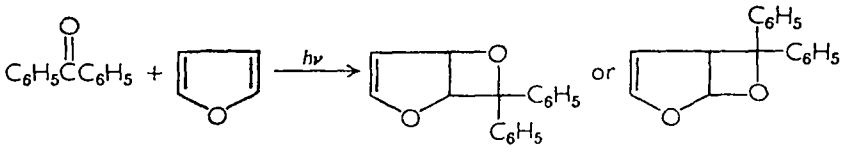


(51)

formation. 2-Acetonaphthone and 1-naphthaldehyde do not undergo photoreduction and the yields of oxetane and of **55** are zero[88].

Two additions to cyclic olefinic systems also have been reported[89]. These are given in reactions (52) and (53).



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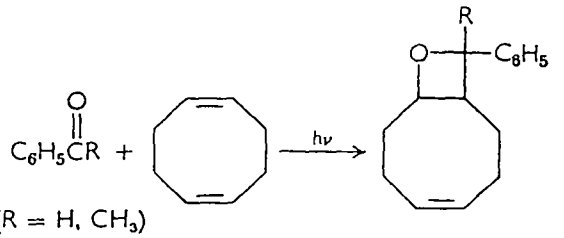
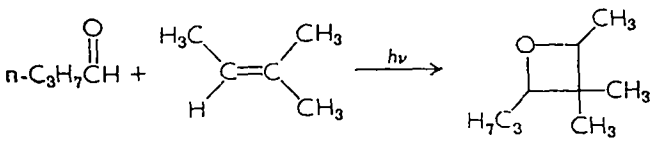


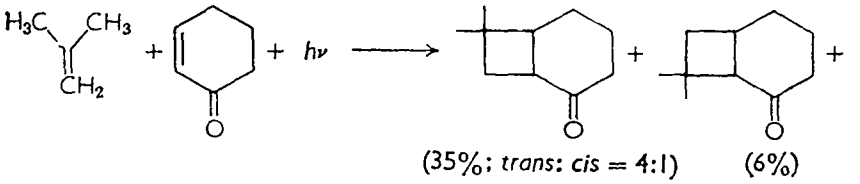
(53)

One example of the photoaddition involving aliphatic carbonyl compounds is the addition of n-butyraldehyde to trimethylethylene to give a corresponding oxetane (**56**)[89]. Fluoro aldehydes, fluoro

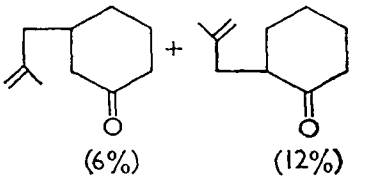


(56) (54)

ketones and fluoroacyl fluoride have also been reported to add photochemically across the olefinic bonds of vinylidene fluorides to give fluorooxetanes in good yield[90]. Acetaldehyde was found to undergo photocycloaddition in the vapor phase with fluoro- and other halo-substituted ethylenes to give oxetane in about 1·3 to 2·6% synthetic yield[91].



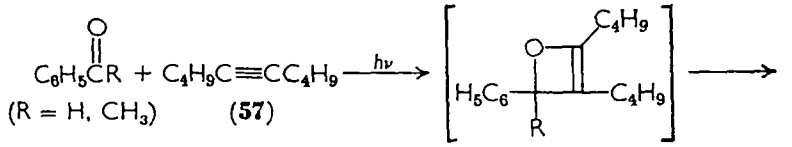
(35%; *trans*: *cis* = 4:1) (6%)



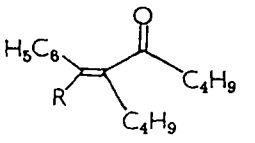
(6%) (12%)

(54a)

Addition of olefins across certain α,β-unsaturated ketones leads to derivatives of cyclobutane rather than of oxetane. Thus Yang and coworkers have studied the photoaddition of isobutylene to cyclo-



(R = H, CH_3) (57)

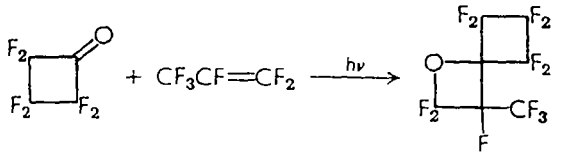


(55)

hexane and isolated the following products in the synthetic yields indicated[281] in reaction (54a).

Only two examples of carbonyl photocycloaddition to acetylenic bonds are known[92]. They are the addition of benzaldehyde and acetophenone to 5-decyne (**57**) to give α,β-unsaturated ketones. Apparently an oxetane is an intermediate reaction (55).

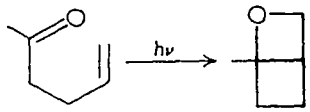
In one case, photoaddition of a cyclic fluoro ketone to a fluoro olefin gives an oxetane as the final product. Irradiation of hexafluorocyclobutanone in the presence of hexafluoropropylene results in the formation of a bicyclic oxetane (**58**) in 33% yield[90].



(56)

(**58**)

While intermolecular carbonyl photoaddition to ethylenic systems is amply illustrated above, apparently only one example[93] of intramolecular formation of an oxetane has been reported (reaction 57).



(57)

(**59**) (**60**)

IV. ALIPHATIC KETONES AND ALDEHYDES

We shall now consider in more detail the photochemistry of individual aldehydes and ketones. We shall emphasize both the primary photochemical processes and the nature and yields of the overall products. When the overall mechanism is well established this will be noted and detailed references cited, but space limitations (as well as lack of reliable data in most cases) preclude detailed treatments of the secondary free-radical reactions in these systems.

Pioneers and major contributors to our understanding of the qualitative and quantitative aspects of the photochemistry of the simple aldehydes and ketones include Blacet, Bowen, Leighton, Norrish, Noyes, and Steacie and their students. Much of modern photochemistry has been inspired by the research from their laboratories which was carried out when instrumental analytical techniques were in their infancy.

The current status of the photochemistry of simple aliphatic aldehydes and ketones can be summarized in the following terms. The absorption characteristics of the simple aliphatic ketones and aldehydes are similar and we have seen that the photochemical behavior of those with γ-hydrogen atoms varies markedly from those without. In general in the first absorption band aliphatic ketones without γ-hydrogen atoms undergo mainly free-radical photodecomposition (section III.B), whereas those with γ-hydrogen atoms also undergo the Type II split (section III.D) and intramolecular reduction to a cyclic carbinol (section III.F).

On the other hand, aliphatic aldehydes without a γ-hydrogen atom undergo predominantly free-radical photodecomposition and intramolecular elimination to CO and a corresponding hydrocarbon (section III.C). Those with γ-hydrogen atoms are found to participate also in the Type II process. For certain long-chain aliphatic aldehydes, an additional primary mode of photodecomposition in which the energy initially absorbed in the carbonyl chromophore is transferred down the side-chain and ultimately results in the rupture of a terminal C—C bond also has been observed.

Thus, the major differences in photochemical reactivity between aliphatic ketones and aldehydes are:

(*a*) Aldehydes possess an active aldehydic hydrogen atom which is abstracted more readily than a hydrogen atom on the alkyl group. This leads to chain production of CO which is not found in ketone photolyses.

(*b*) Aldehydes undergo intramolecular elimination of CO and yield the corresponding hydrocarbon. Ketones do not.

(*c*) Some long-chain aldehydes undergo a terminal C—C bond rupture. Ketones apparently do not.

(*d*) Ketones with γ-hydrogen atoms undergo rearrangement to cyclic carbinols. It is not certain whether or not aldehydes do the same.

A. Acetone

The current status of the photolysis of gaseous acetone recently has been reviewed critically by Hoare and Pearson[94]. The sole primary process in the near-ultraviolet photolysis of acetone is the formation of a methyl and an acetyl radical (reaction 58).

$$CH_3COCH_3 + h\nu \longrightarrow \dot{C}H_3 + CH_3\dot{C}O \qquad (58)$$

Depending upon the energy of the absorbed quantum, various fractions of the acetyl radicals are energy rich and thus decompose rapidly into a methyl radical and CO (reaction 59). The remaining

$$CH_3\dot{C}O \longrightarrow \dot{C}H_3 + CO \tag{59}$$

acetyl radicals undergo typical secondary reactions, e.g. recombine to give biacetyl (reaction 60). However, at temperatures above

$$2\,CH_3\dot{C}O \longrightarrow (CH_3CO)_2 \tag{60}$$

100°c practically all acetyl radicals dissociate according to reaction (59) and Φ_{CO} becomes 1·00 at 3130 Å and 120°c. Thus at elevated temperatures photolysis of acetone vapor provides a useful source of methyl radicals, and since Φ_{CO} is unity and not overly dependent on reaction conditions, acetone at 120° is widely used as an internal actinometer.

Secondary thermal reactions of the methyl radicals produced in (58) and (59) include abstraction and recombination (61, 62).

$$\dot{C}H_3 + CH_3COCH_3 \longrightarrow CH_4 + \dot{C}H_2COCH_3 \tag{61}$$

$$2\,\dot{C}H_3 \longrightarrow C_2H_6 \tag{62}$$

The fate of acetonyl radicals produced in reaction (61) has not been established quantitatively. They combine[95], as in (63) and (64) and,

$$CH_3CO\dot{C}H_2 + \dot{C}H_3 \longrightarrow CH_3COC_2H_5 \tag{63}$$

$$2\,CH_3CO\dot{C}H_2 \longrightarrow CH_3COCH_2CH_2COCH_3 \tag{64}$$

within a temperature range 217° to 327°c, the disproportionation of methyl and acetonyl radicals shown in (65) has been postulated.

$$\dot{C}H_3 + CH_3CO\dot{C}H_2 \longrightarrow CH_4 + CHCOCH_3\ (?) \tag{65}$$

At relatively high temperatures, 200–475°c, acetonyl radicals dissociate into ketene and methyl radicals with an activation energy of about 41 kcal[96] (reaction 66).

$$CH_3CO\dot{C}H_2 \longrightarrow CH_2CO + \dot{C}H_3 \tag{66}$$

It has been suggested that both excited singlet and excited triplet acetone may play a role in the photocomposition[97]. Presumably at 3130 Å dissociation from the first excited singlet predominates. The quantum yield of the primary decomposition at both wavelengths is unity at temperatures above 100°[3]. It is significant that the primary quantum yield of acetone photolysis at 40° with 3130 Å is a function of the irradiation time. Apparently triplet acetone undergoes

deactivation via energy transfer to the biacetyl[98] formed in the secondary reaction (60).

In the far-ultraviolet (1470–1165 Å) the photochemical behavior of acetone is significantly different. In some respects it resembles its radiation chemistry. Thus hydrogen is an important product and isotopic and scavenging experiments show that a fraction of the hydrogen and methane produced is from the molecular elimination processes (68) and (70), respectively[99]. It has been proposed that there are two excited states of acetone in the far-ultraviolet irradiation: the higher state gives either a hydrogen atom or hydrogen molecule, while the lower state decomposes either into $\dot{C}H_3 + CH_2\dot{C}O$ or $CH_4 + CH_2CO$[99].

$$[CH_3COCH_3]' \longrightarrow H + \dot{C}H_2COCH_3 \quad (67)$$

$$[CH_3COCH_3]' \longrightarrow H_2 + CHCOCH_3(?) \quad (68)$$

$$[CH_3COCH_3]'' \longrightarrow \dot{C}H_3 + CH_3\dot{C}O \quad (69)$$

$$[CH_3COCH_3]'' \longrightarrow CH_4 + CH_2CO \quad (70)$$

The major gaseous products from irradiation of acetone neat or in solution are CO, methane and ethane[28,76–77,100–103]. They appear to be formed by a free-radical mechanism similar to that of the vapor-phase photolysis but their quantum yields are considerably lower, presumably because of cage recombination and deactivation processes. Comparative data are given in Table 4.

TABLE 4. Quantum yields from the photolysis of acetone at 2537 Å and 25° c.

System	Φ_{CO}	Φ_{CH_4}	$\Phi_{C_2H_6}$	Ref.
Acetone vapor	0·25	2×10^{-3}	0·35	104
Acetone liquid	1×10^{-4}	2×10^{-3}	1×10^{-4}	76
Acetone liquid (at 2800–3300 Å)	1×10^{-4}	2×10^{-3}	1×10^{-4}	76
0·023 M acetone in perfluorodimethylcyclobutane	1×10^{-3}	1×10^{-3}	2×10^{-3}	102
0·1 M acetone in perfluorodimethylcyclobutane	$2{\cdot}6 \times 10^{-4}$	$3{\cdot}5 \times 10^{-4}$	$2{\cdot}5 \times 10^{-4}$	103
0·01 M acetone in the fluorinated cyclic ether, $C_8F_{16}O$[a]	2×10^{-2}	8×10^{-2}	1×10^{-4}	102
0·1 M acetone in water	2×10^{-3}	4×10^{-2}	3×10^{-2}	28
0·1 M acetone in water at 73°c	$4{\cdot}2 \times 10^{-2}$	15×10^{-2}	$9{\cdot}8 \times 10^{-2}$	28

[a] Fluorochemical 0–75 from the Minnesota Mining and Manufacturing Co.

In pure liquid acetone and in hydrocarbon solutions of high acetone concentrations minor amounts of diacetone alcohol and other alcohols are produced, apparently by self-quenching of photo-excited acetone[76,77]. Thus irradiation of a 1:8 mixture of acetone and cyclohexane yielded 2-propanol, pinacol, acetonylacetone, and cyclohexyl dimethyl carbinol[76,77]. The mechanism of interaction of photoexcited acetone with the hydrocarbon solvents is not established in detail.

Irradiation of acetone in carbon tetrachloride solvent gives a substantial amount of hydrogen chloride. It has been suggested that acetone photosensitizes the decomposition of CCl_4 into a Cl atom and a CCl_3 radical.

To avoid as much as possible chemical reactions involving the solvent, acetone has been irradiated in perfluorinated solvents which are inert toward both photoexcited acetone and the free radicals produced in the photolysis. Apparently quenching of electronically excited acetone by these solvents plays an important part in the photodecomposition[28,102].

At lower temperatures the disproportionation reaction of methyl and acetyl radicals becomes an increasingly important liquid-phase process. Thus Pieck and Steacie[76] photolyzed mixtures of acetone and deuterated acetone and estimated that 4% of the methane formed at 55° and 33% of the methane at −24° arises from reaction (71).

$$\dot{C}H_3 + CH_3\dot{C}O \longrightarrow CH_4 + CH_2CO \qquad (71)$$

Peterson and Mains[102] used perfluorinated solvents and reported that reaction (71) accounts for about 6 to 10% of the methane produced at 25°. The same disproportionation reaction was postulated by Volman and Swanson[28] for the photolysis of aqueous acetone solutions with added allyl alcohol as radical scavenger.

B. Formaldehyde and Acetaldehyde

Formaldehyde photodecomposes at 3130 Å to give hydrogen, CO, and minor products. Reactions (72) and (73) have been suggested

$$H_2CO + h\nu \begin{cases} \longrightarrow H + H\dot{C}O & (72) \\ \longrightarrow H_2 + CO & (73) \end{cases}$$

as primary processes[105–110]. Recent experiments with D_2CO by McQuigg and Calvert[112] confirm these processes. The total primary quantum yield $\Phi_{(72)} + \Phi_{7(3)}$ is about 0·9 with $\Phi_{(73)}$ greater than $\Phi_{(72)}$.

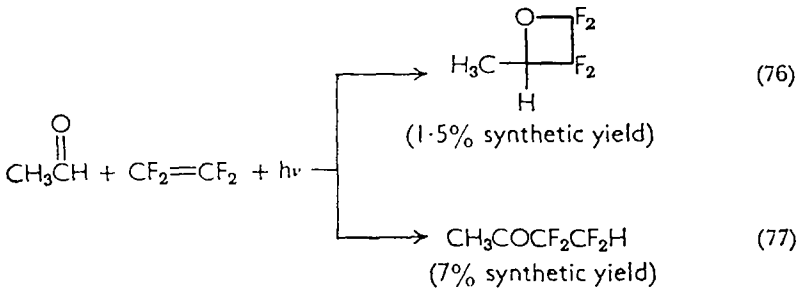
Two major primary processes (74) and (75) have been demon-

$$CH_3CHO + h\nu \rightarrow \dot{C}H_3 + H\dot{C}O \quad (74)$$

$$CH_3CHO + h\nu \rightarrow CH_4 + CO \quad (75)$$

strated in the photolysis of acetaldehyde[113-118]. At 3130 Å the primary reaction is almost exclusively (74) but at 2537 Å reaction (75) becomes equally important. In a beautiful set of flash spectroscopic experiments of HĊO and DĊO, Herzberg and Ramsey confirmed the existence of the formyl radical and established its structure as bent in the ground state (about 120°) and linear in the excited state[164].

Irradiation of acetaldehyde vapor in the presence of tetrafluoroethylene gives both fluorooxetane (76) and a fluorinated ketone[91] (77). The fluoro ketone presumably results from addition of an



(76)

(77)

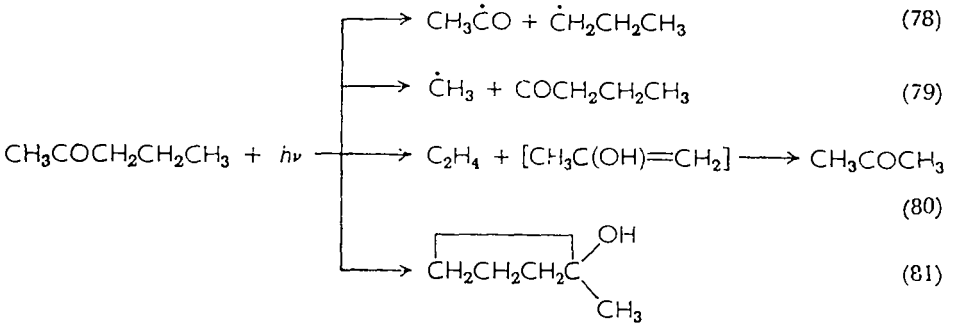
acetyl radical to the carbon–carbon double bond[119-120], whereas the oxetane arises from intermolecular cycloaddition (section III.I).

Irradiation of solutions containing terminal olefins and acetaldehyde gives the ketone $CH_3COCH_2CH_2R$. Presumably photodecomposition of acetaldehyde gives acetyl radicals which attack the terminal carbon of the C=C bond[121]. This reaction also is initiated by peroxides.

C. *Aliphatic Ketones and Aldehydes with γ-Hydrogen Atoms*

1. Methyl propyl ketone

This furnishes a good illustration of the typical behavior of ketones with γ-hydrogen atoms[3]. The primary photochemical processes are shown in reactions (78) to(81) and their quantum yields for the Type II split, Φ_{II}, and production of CO are given in Table 5. The quantum yield of the photocyclization process (81) varies with the experimental conditions. Values of Φ at 3130 Å are 0·11 and 0·028 at 28°



and 32 mm and 1·3 mm pressure, respectively, and 0·044 at 15 mm and 150°[3].

The photochemical behavior of other aliphatic methyl ketones with a γ-hydrogen atom are similar to methyl propyl ketone. Thus, in addition to the Type I split, methyl butyl ketone gives propylene

TABLE 5. Quantum yield of the Type II process, Φ_{II}, and of CO production at 3130 Å (100–120°C).

Ketone	Φ_{II}	Φ_{CO}	Ref.
CH_3COCH_3	0·0	1·00	104
$CH_3COCH_2CH_3$	0·0	0·84	123
$CH_3CO(CH_2)_2CH_3$	0·24, 0·27, 0·31	0·28	3,124
$CH_3CO(CH_2)_3CH_3$	0·48	0 11	35
$CH_3COCH_2CH(CH_3)_2$	0·35	0·15	122
$CH_3COCH_2C(CH_3)_3$	0·23	0·04	122
$(CH_3CH_2CH_2)_2CO$	0·21	0·31	125
$[(CH_3)_2CHCH_2]_2CO$	0·37[a]	0·19[a]	126
$[CH_3CH_2C(CH_3)_2]_2CO$	0·27[a]	0·37[a]	126
$[(CH_3)_3C]_2CO$	0	1·0[a]	126

[a] Irradiated with full Hg arc.

and acetone[42,43] and methyl neopentyl ketone yields isobutylene and acetone[122]. Presumably these products all arise from Type II splits. The quantum yields for some ketones are listed in Table 5.

Irradiation of methyl butyl ketone in cyclohexene gave mainly acetone and ethylene from a Type II split[77] but 1-methylcyclobutanol was also formed with a 12% synthetic yield[77]. Irradiation of methyl heptanone in cyclohexane solution gave acetone and 1-methyl-2-propylcyclobutanol with a 17% yield[77]. It was also found that no other isomeric pentene was present. This is reasonable if all the 1-pentene is formed by a Type II split.

2. n-Butyraldehyde

The primary photochemical processes and their yields[32,127-128] at several wavelengths are given in Table 6.

TABLE 6. Primary processes and quantum yields in the vapor-phase photolysis of butyraldehyde at various wavelengths[3].

Primary process		Quantum yields			
		3130 Å	2804 Å	2654 Å	2537 Å
$CH_3CH_2CH_2CHO + h\nu \longrightarrow$					
$\dot{C}_3H_7 + H\dot{C}O$	(82)	0·35	0·28	0·28	0·31
$C_3H_8 + CO$	(83)	0·017	0·11	0·25	0·33
$C_2H_4 + CH_3CHO$	(84)	0·164	0·27	0·38	0·30
$\dot{C}H_3 + \dot{C}H_2CH_2CHO$	(85)	0·005	0·006	0·010	0·015
$C_3H_6 + H_2CO$	(86)		trace		

D. Halogen-substituted Aliphatic Ketones and Aldehydes

In general all halogen-substituted aliphatic ketones photodecompose predominantly via free-radical processes. It is interesting that the Type II process has not been reported in the photolysis of these ketones.

The quantum yield of HCl formation from the photolysis of monochloroacetone is near unity[129]. Presumably the energy absorbed in the carbonyl chromophore breaks the carbon–chlorine bond giving Cl atoms and acetonyl radicals (reaction 87)[129]. A small

$$CH_3COCH_2Cl + h\nu \longrightarrow CH_3CO\dot{C}H_2 + \dot{C}l \qquad (87)$$

fraction of the HCl formed ($\Phi < 0{\cdot}15$) is considered due to a minor primary process (88).

$$CH_3COCH_2Cl + h\nu \longrightarrow HCl + C_3H_4CO(?) \qquad (88)$$

A different situation exists with hexachloroacetone. At 183° the quantum yield of CO production is 0·5 and is independent of pressure. The major vapor-phase primary process at 3130 Å appears to be the breaking of a C—C bond[130] as with acetone itself (reaction (89).

$$Cl_3CCOCCl_3 + h\nu \longrightarrow \dot{C}Cl_3 + \dot{C}OCl_3 \qquad (89)$$

It is interesting to compare the photochemistry of 4-chloro-2-butanone and 3-chloro-2-butanone. It seems that the C—Cl split

occurs efficiently with a Cl atom on the α-carbon atom (reaction 92), but not when it is on the β-carbon atom (reactions 90, 91)[131].

$$ClCH_2CH_2COCH_3 + h\nu \longrightarrow \begin{cases} \longrightarrow ClCH_2\dot{C}H_2 + CH_3\dot{C}O & (90) \\ \longrightarrow ClCH_2CH_2\dot{C}O + \dot{C}H_3 & (91) \end{cases}$$

$$CH_3CHClCOCH_3 + h\nu \longrightarrow Cl + CH_3\dot{C}HCOCH_3 \quad (92)$$

The vapor-phase photolysis of hexafluoroacetone at 3130 Å gives as the main products CO and C_2F_6. Detailed analysis of the quenching of fluorescence plus kinetic studies at different temperatures and pressures strongly support a mechanism which involves a long-lived excited molecule in the primary process. This excited molecule subsequently emits fluorescence, is quenched, or dissociates as in reaction (93)[132-136]. The absence of attack by the $\dot{C}F_3$ radicals on

$$CF_3COCF_3^* \longrightarrow \dot{C}F_3 + \dot{C}OCF_3 \quad (93)$$

$$CF_3\dot{C}O \longrightarrow \dot{C}F_3 + CO \quad (94)$$

$$2\,\dot{C}F_3 \longrightarrow C_2F_6 \quad (95)$$

the hexafluoroacetone makes this system a clean source for $\dot{C}F_3$ radicals.

It is interesting that in the photolysis of 1,1,1,-trifluoroacetone at 3130 Å, reaction (96) predominates over reaction (97)[137]. Both

$$CF_3COCH_3 + h\nu \longrightarrow \begin{cases} \longrightarrow CF_3\dot{C}O + \dot{C}H_3 & (96) \\ \longrightarrow \dot{C}F_3 + CH_3\dot{C}O & (97) \end{cases}$$

$\dot{C}H_3$ and $\dot{C}F_3$ radicals undergo hydrogen-atom abstraction, self-recombination, and cross-recombination to give CH_4 and CF_3H, C_2H_6 and CH_3CF_3, respectively.

The presence of one or more halogen atoms on the carbon chain of the aliphatic aldehydes does not lead to any new photochemical reactions. Thus, at 3130 Å, trifluoroacetaldehyde decomposes similarly to acetaldehyde[138-139]. The quantum yields of reactions (98) and (99) are 0·14 and 0·02, respectively.

$$CF_3CHO + h\nu \longrightarrow \begin{cases} \longrightarrow \dot{C}F_3 + H\dot{C}O & (98) \\ \longrightarrow CF_3H + CO & (99) \end{cases}$$

In the photolysis of heptafluorobutyraldehyde[140], no analog to the Type II process occurs.

Finally, as noted earlier (section III.I), irradiation of a refluxing

mixture of fluoro ketones or fluoro aldehydes and fluorinated olefins gives fluorooxetanes in good yield.

E. Unsaturated Aliphatic Ketones and Aldehydes

1. Unsaturated aliphatic ketones

The introduction of unsaturation into the aliphatic chain causes a remarkable increase in stability of the photoexcited ketones. Thus, photodissociative primary processes in both conjugated and non-conjugated unsaturated ketones proceed with low efficiency even at elevated temperatures. Furthermore, the presence of hydrogen atoms on a γ-carbon adjacent to a double bond in unsaturated ketones does not lead to an intramolecular Type II process.

At 3130 Å and temperatures up to 275°c, irradiation of gaseous *trans*-methyl propenyl ketone, $CH_3COCH{=}CHCH_3$, leads almost exclusively to the conversion of the *trans* into the *cis* isomer. This is an example of *direct* photoisomerization (Table 3). Photodissociation is negligible. However, at 2380 Å and elevated temperatures, primary free-radical photodissociative processes arising from a long-lived excited molecule become important (reactions 100–102). At 275°c

$$CH_3COCH{=}CHCH_3 + h\nu \longrightarrow CH_3COCH{=}CHCH_3^* \qquad (100)$$

$$CH_3COCH{=}CHCH_3^* \longrightarrow \dot{C}H_3 + \dot{C}OCH{=}CHCH_3 \qquad (101)$$

$$CH_3COCH{=}CHCH_3^* \longrightarrow CH_3\dot{C}O + \dot{C}H{=}CHCH_3 \qquad (102)$$

and pressures below 10 mm, the quantum yield of CO exceeds unity. This is attributed to the free-radical 'displacement' reaction (103) giving 2-butene and $CH_3\dot{C}O$. The latter then decomposes to $CO + \dot{C}H_3$ and a short chain is set up (reaction 103)[56]. Other α,β-unsaturated ketones will be discussed in section VI.

$$\dot{C}H_3 + CH_3COCH{=}CHCH_3 \longrightarrow CH_3CH{=}CHCH_3 + CH_3\dot{C}O \qquad (103)$$

Similarly, but somewhat surprisingly, 5-hexen-2-one was found to be stable to 3130 Å irradiation[93]. Several olefinic ketones having γ-hydrogen atoms in the allyl position have been investigated. Photolysis of these ketones in solution leads to cyclocarbinols (see section III.F, reaction 33).

The photolysis of ketene has been used by many workers to generate and to study the reactions of methylene. Thus, direct photolysis of ketene in the vapor phase at moderate pressures produces free methylene presumably in the singlet state[144–148]. Methylene in the triplet state is believed to be formed by triplet energy

transfer, from $Hg(^3P_1)$ atoms in the gas phase and triplet benzophenone in solution (see recent reviews by Bell[141], Frey[142], and Cvetanovic[143]).

$$CH_2CO + h\nu \longrightarrow CH_2\uparrow\downarrow + CO \quad (104)$$

The quantum yield of CO production is unity at 3130 Å and pressures below 50 mm. At 2700 Å, Φ_{CO} is independent of temperature, pressure, and light intensity. Most of the methylene generated reacts with ketene according to reactions (105)–(107).

$$CH_2 + CH_2CO \longrightarrow C_2H_4 + CO \quad (105)$$

$$CH_2 + CH_2CO \longrightarrow \dot{C}H_3 + \dot{C}HCO \quad (106)$$

$$2\,\dot{C}HCO \longrightarrow C_2H_2 + CO \quad (107)$$

In the presence of added hydrocarbon singlet methylene adds stereospecifically across olefinic double bonds and inserts into carbon–hydrogen bonds. Triplet methylene adds to olefinic bonds in a non-stereospecific manner and apparently does not insert into C—H bonds[141–143].

Photolysis of methylketene[149,150] and dimethylketene[151] at wavelengths shorter than 3130 Å gives $CH_3CH + CO$ and $(CH_3)_2C + CO$, respectively.

2. Unsaturated aliphatic aldehydes

The vapor-phase photochemistry of unsaturated aldehydes is complex, in part because of a competing photopolymerization reaction. Both acrolein and crotonaldehyde are similar to methyl propenyl ketone in that they are remarkably stable to photodissociation at 3130 Å even at elevated temperatures[152–154]. At shorter wavelengths (e.g. 2600–2300 Å) and higher temperatures, a chain photodecomposition of crotonaldehyde occurs producing propylene and CO (with quantum yield greater than unity) plus a variety of minor products. On the basis of detailed kinetic studies an excited molecule mechanism has been proposed[155]. The gas-phase photoisomerization of crotonaldehyde to 3-buten-1-al has been reported[154], but in the liquid phase this product was not found[156], nor was it found in more recent vapor-phase studies[155].

F. Aliphatic Diketones and Dialdehydes

1. Biacetyl

The first absorption band of biacetyl falls in the region 4600–3500

Å[157]; its photochemistry has been investigated at a variety of wavelengths by a number of authors[158–161]. At 4358 Å and room temperature, decomposition in the vapor phase occurs presumably via the interaction of two excited triplet state molecules (108). However

$$2\,CH_3COCOCH_3^* \longrightarrow 2\,CH_3\dot{C}O + CH_3COCOCH_3 \qquad (108)$$

at 100° and above, the decomposition becomes first-order with respect to the excited triplet molecule. In the absence of perturbing gases, emission from both first excited singlet and triplet states is observed and the intersystem crossing from singlet to triplet occurs with a high efficiency. The quantum yield of decomposition at this wavelength is generally relatively low.

At 3130 Å, dissociation from both the first and second excited singlet states appears possible. The quantum yield of reactions (109)

$$CH_3COCOCH_3 + h\nu \begin{cases} \longrightarrow 2\,CH_3\dot{C}O\ (\text{hot}) & (109) \\ \longrightarrow 2\,\dot{C}H_3 + 2\,CO & (110) \\ \longrightarrow CH_3COCH_3 + CO & (111) \end{cases}$$

and (110) at 150° is about 0·1. At 2537 Å and 150°, when dissociation apparently is from the second excited singlet, the quantum yield for reactions (109) and (110) is 0·44. In both cases reaction (111) is inefficient.

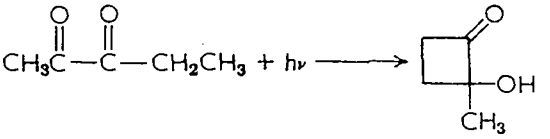
2. Glyoxal

Glyoxal has a first absorption band at 4600–3400 Å and second band at 3200–2300 Å. The primary photochemical decompositions of glyoxal in the vapor phase at 4358 Å and at 3130 Å can be represented by reactions (112) and (113) with (112) predominating at both wavelengths[111,162–164]. Reaction (114) also occurs only when radiation shorter than 2537 Å is used. Irradiation of glyoxal in the second band gives excited molecules which all dissociate, 86% going by (112) and 15% by (113). In the first band emission also occurs to an appreciable extent (about 13% fluoresce). The rest cross over to the triplet state and dissociate mainly by reaction (112) or are deactivated.

$$HCOCOH + h\nu \begin{cases} \longrightarrow H_2CO + CO & (112) \\ \longrightarrow H_2 + 2\,CO & (113) \\ \longrightarrow 2\,H\dot{C}O & (114) \end{cases}$$

3. Other 1,2-diketones with γ-hydrogen atoms

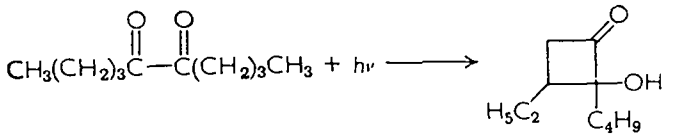
Intramolecular photocyclization has been observed in 1,2-diketones having γ-hydrogen atoms[161,165]. For example, irradiation of 2,3-pentanediones gives 2-hydroxy-2-methylcyclobutanone (**61**) in



(115)

(**61**)

49% yield, whereas photolysis of 5,6-decanedione gives 89% 2-butyl-3-ethyl-2-hydroxycyclobutanone (**62**). There is some indication that photocyclization of 1,2-diketones involves the triplet



(116)

(**62**)

state of the ketones and the mechanism may well be the general cyclic γ-hydrogen atom transfer[161,165].

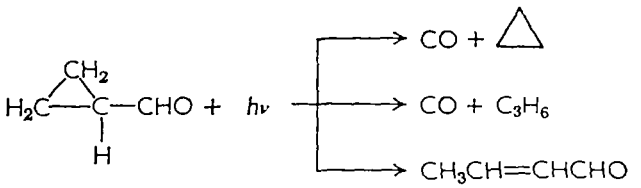
V. CYCLIC KETONES AND ALDEHYDES

A. Cyclic Aldehydes

Only cyclopropyl aldehyde and glycidaldehyde, the simplest three-membered ring epoxy aldehyde, have been investigated in detail. In contrast to methyl cyclopropyl ketone significant decarbonylation occurs in the vapor-phase photolysis of cyclopropan aldehyde at 3130 Å[166,167]. Thus, at 3130 Å and 107°c, CO and propene are major products and cyclopropane, hydrogen, and propane are the minor products. Φ_{CO} is a function of pressure, ranging from 0·12 to 0·58 as the pressure decreases from 90 to 4 mm[166].

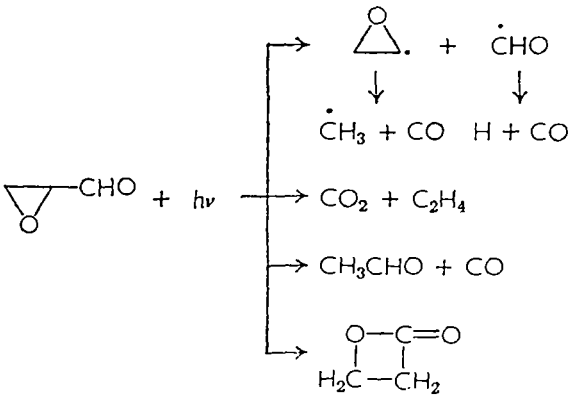
Recently, crotonaldehyde has been identified as a major product of the reaction[167]. It is not certain whether other isomers are present in trace amounts. The quantum yield of the photoisomerization is found to be about 0·4 and virtually independent of temperature and light intensity. At high temperatures, the sum of the quantum yields of CO and crotonaldehyde exceeds unity (about 1·5). The quantum

yield of cyclopropane decreases strongly with increased light intensity, while propylene yield is constant. These results suggest that a free-radical mechanism is operative at elevated temperature in addition to other intramolecular reactions, and that cyclopropyl radical, if formed, is fairly stable. Although it is too soon to draw definitive conclusions about the detailed mechanism, important primary processes appear to be (117) to (119)[167].



(117)
(118)
(119)

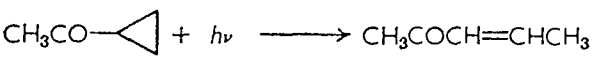
Irradiation of glycidaldehyde in the vapor phase gives CO, CO_2, CH_4, and C_2H_4 with quantum yields of 1·10, 0·71, 0·23, and 0·66, respectively[168]. Hydrogen is also a major product. The quantum yields of C_2H_4 and CO_2 are independent of temperature, suggesting that they are formed in a concerted intramolecular elimination process. On the other hand, the quantum yields of CO and CH_4 depend both upon temperature and wavelength. The proposed mechanism includes the primary processes (120) and (121)[168]. Based on a material balance, reaction (121a) accounts for 75% of the photochemical reaction and reaction (120) about 10%[168].



(120)
(121a)
(121b)
(121c)

B. Methyl Cyclopropyl Ketone

The major primary photochemical reaction of gaseous methyl cyclopropyl ketone is an intramolecular rearrangement to methyl



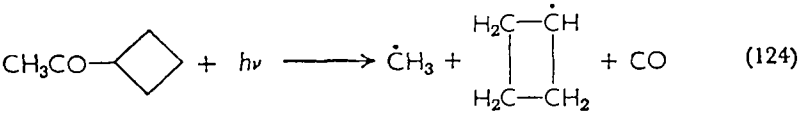
(122)

propenyl ketone (122)[169]. A minor free-radical primary process (123) also occurs[169]. The quantum yield of CO production is very low,

(123)

about 0·03 to 0·11 in the temperature range 25–170° 2537–2654 Å. On the other hand, the quantum yield of methyl propenyl ketone is about 0·3 and virtually independent of temperature.

In striking contrast methyl cyclobutyl ketone photodissociates to give CO, cyclobutane, CH_4, and C_2H_4 as major products at 120° and 2537–2654 Å[170]. A free-radical mechanism analogous to the simple aliphatic ketones has been suggested with reaction (124) as the 'effective' process at 120°.



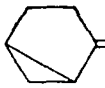
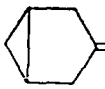
(124)

The drastic difference in photochemical behavior between these two ketones may be due either to the unsaturation characteristics of the cyclopropyl ring and/or the difference in C—C bond strength of the two rings.

The results for methyl cyclopropyl ketone suggest that the energy absorbed by the carbonyl chromophore may be transferred intramolecularly to the cyclopropyl ring, and in a recent investigation the cyclopropyl group was used as a 'structural probe' to examine intramolecular energy transfer processes. Thus at 3130 Å and 120°c the quantum yields of CO formation, which might be viewed as an inverse measure of the efficiency of energy transfer from the carbonyl chromophore to the cyclopropyl ring, vary drastically with the molecular structure[15,171]. This is seen in Table 7.

Apparently insertion of a methylene group(s) between the carbonyl chromophore and the cyclopropyl ring impedes the flow of excitation energy from the carbonyl group to the ring and enhances the free radical split. The fact that Φ_{CO} for the ketone **65** with two methylene groups is lower than Φ_{CO} for **64** with one CH_2 group, is attributed to the Type II process becoming important. In the case of the bicyclic

TABLE 7. Quantum yields of CO production for cyclopropyl ketones at 3130 Å and 120°C[15,171].

Ketone	Φ_{CO}
CH_3CO—  (63)	0·04
CH_3COCH_2—  (64)	0·88
$CH_3COCH_2CH_2$—  (65)	0·65
 (66)	0·009
 (67)	0·76

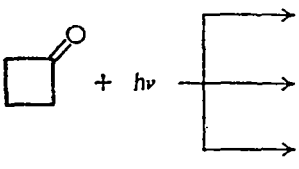
ketone **66**, which is analogous to methyl cyclopropyl ketone, intramolecular rearrangement leading to 3-methyl-2-cyclopentenone is an important photochemical process.

At 3130 Å the major product from the irradiation of dicyclopropyl ketone vapor is the isomer cyclopropyl propenyl ketone. Free radical processes are very inefficient[60].

C. Cyclic Ketones and Diketones

1. Cyclobutanone

Irradiation of cyclobutanone vapor in its first absorption band yields ethylene, ketene, CO, propylene, cyclopropane, and an isomer, presumably 3-butenal[50-52]. The C_3H_6 formed in reaction (126) is

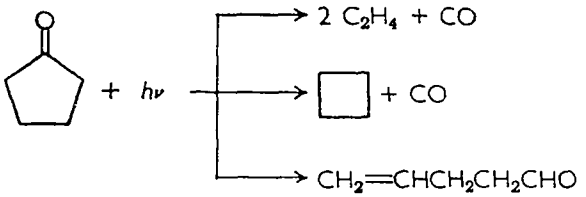


(125)
(126)
(127)

presumably a 'hot' cyclopropane which then is thermalized by collisional deactivation or rearranges to propylene. At 3130 Å, $\Phi_{(126)} = 0{\cdot}35$, $\Phi_{(125)} = 0{\cdot}51$, $\Phi_{(127)} = 0{\cdot}004$.

2. Cyclopentanone

Irradiation of cyclopentanone vapor in its first absorption band gives CO, ethylene, cyclobutane, and 4-pentenal[33,50,51,172–174]. The primary processes (128) to (130) are proposed. Isotopic experi-



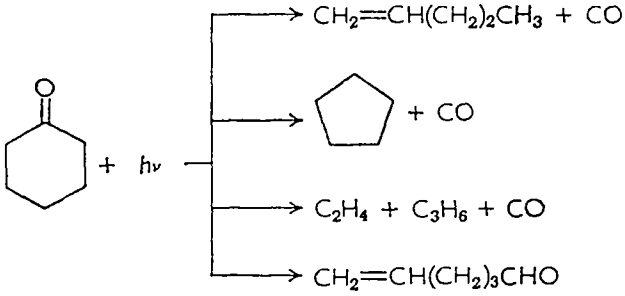
(128)
(129)
(130)

ments indicate that processes (128) and (129) are independent reactions[173]. At 3130 Å and 124°C, the total quantum yield of the three processes (128), (129), and (130) is 0·72, and is independent of pressure. However, the relative quantum efficiency $\Phi_{(130)}/(\Phi_{(128)} + \Phi_{(129)})$ is highly sensitive to pressure, being 1·08 at 106 mm, 0·75 at 53 mm, and 0·16 at 12 mm.

A preliminary investigation of 2-methyl- and 3-methylcyclopentanone showed that the photodissociative processes are analogous to reactions (128) and (129)[174].

3. Cyclohexanone

Major products at 3130 Å are CO, ethylene, propylene, cyclopentane, 1-pentene, and 5-hexenal; the primary reactions (131) to (134) are proposed[50,51,175,176]. At 3130 Å and 300°C, Φ_{CO} is 0·91.



(131)
(132)
(133)
(134)

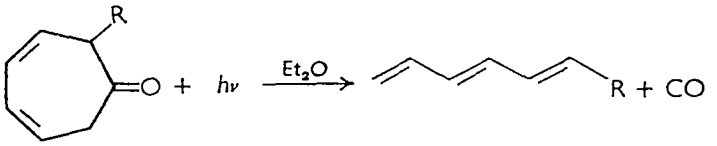
In the presence of shorter wavelength radiation other complicated side-reactions occur.

Irradiation of cyclohexanone neat and in various solvents at 3130 Å gives CO with a quantum yield of the order of 0·02; the yield of isomeric aldehyde produced by reaction (134) is of the same order of magnitude in the vapor, liquid, or solution phase[62,176–178]. A

ring-contraction process also has been observed in the irradiation of pure liquid cyclohexanone at 3130 Å; 2-methylcyclopentanone is produced with a quantum yield of about 0·03[62] (see section III.E.3). In an aqueous solution irradiation of cyclohexanone also leads to the formation of caproic acid, while in cyclohexanol solvent cyclohexyl pinacol is formed in good yield.

4. 3,5-Cycloheptadienone and cyclopropenones

The nonconjugated unsaturated cyclic ketones are usually much less stable towards photodissociation than their unsaturated aliphatic analogs. Thus, irradiation of 3,5-cycloheptadienone (**68**) and its 2-methyl derivative in ether solutions gives CO and a 1,3,5-triene (**69**) in 95% yield[179,180]. This photochemical reaction has two interesting aspects: no cyclic hydrocarbon is observed and the elimination of CO proceeds with a high efficiency comparable to that of a saturated ketone in the vapor phase.

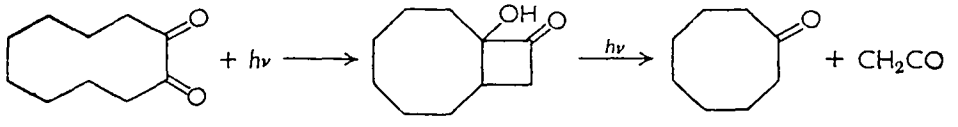


(68) (69) (135)

Irradiation of diphenylcyclopropenone also leads to decarbonylation giving diphenylacetylene and CO as the main products[181].

5. Cyclic diketones

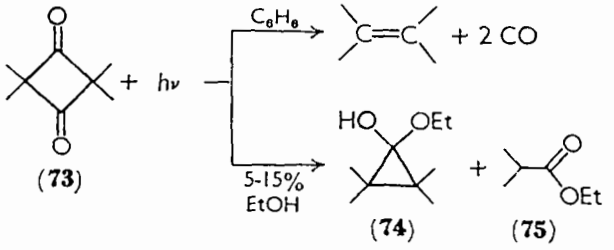
Most of the photochemical studies of cyclic diketones have been carried out in liquid systems. Their photochemical behavior seems to be affected by both the structure of the ketones and the nature of the solvent. Thus, photolysis of 1,2-cyclodecanedione (**70**) gives (**71**) in 75% yield and (**72**) in 9% yield[165].



(70) (71) (72) (136)

1,3-Diketones behave quite differently. For example, tetramethyl-1,3-cyclobutanedione (**73**) undergoes efficient photodecarbonylation in benzene solution to give tetramethylethylene[182].

However, when the same ketone **73** is irradiated in a 5–15% ethanol solution, tetramethylcyclopropanone ethyl hemiketal (**74**) and ethyl isobutyrate (**75**) are obtained in good yields[183].

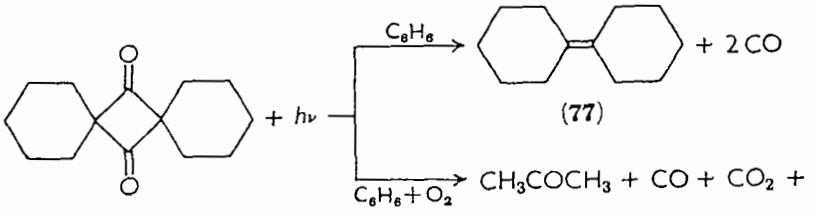


(73) (74) (75)

(137)

(138)

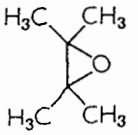
Similarly, photolysis of dispiro[5.1.5.1]-7,14-tetradecanedione (**76**) in degassed benzene gives CO and a 61% yield of cyclohexylidenecyclohexane (**77**). In the presence of added oxygen the photochemical reaction is altered to give acetone, CO, CO_2, and tetramethylethylene oxide (**78**) as the major products[184].



(76) (77)

(139)

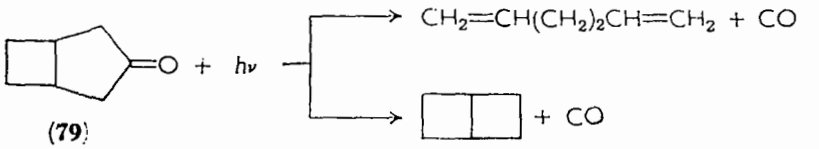
(140)



(78)

D. Bicyclic and Tricyclic Ketones

Only a few bicyclic ketones have been photolyzed in the gas phase[171,185–186]. Irradiation of bicyclo[3.2.0]-3-heptanone (**79**) at wavelengths longer than 3100 Å leads to the two reactions[185] shown.



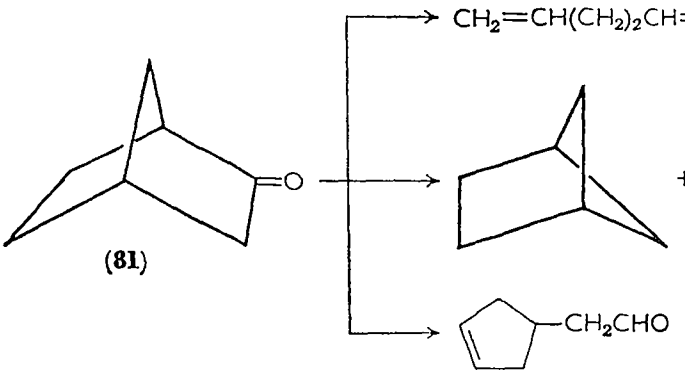
(79) (80)

(141)

(142)

Reaction (141) is far more efficient than reaction (142) producing the strained bicyclo[2.2.0]hexane (**80**).

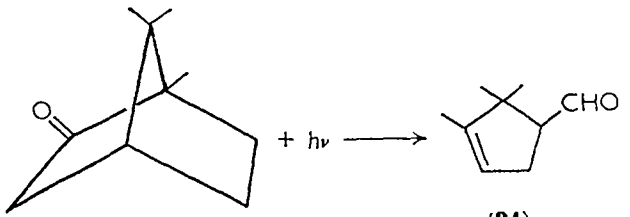
At 3130 Å and 80°c, norcamphor (**81**) photodecomposes according



(**81**) (**82**)

to reactions (143) to (145)[186]. In an analogous fashion reaction (143) is much more probable than reaction (144). The structure of the aldehyde (**82**) shown in reaction (145) has not been established conclusively. It is interesting to note that a similar reaction leading to an aldehyde production is absent when (**79**) is irradiated.

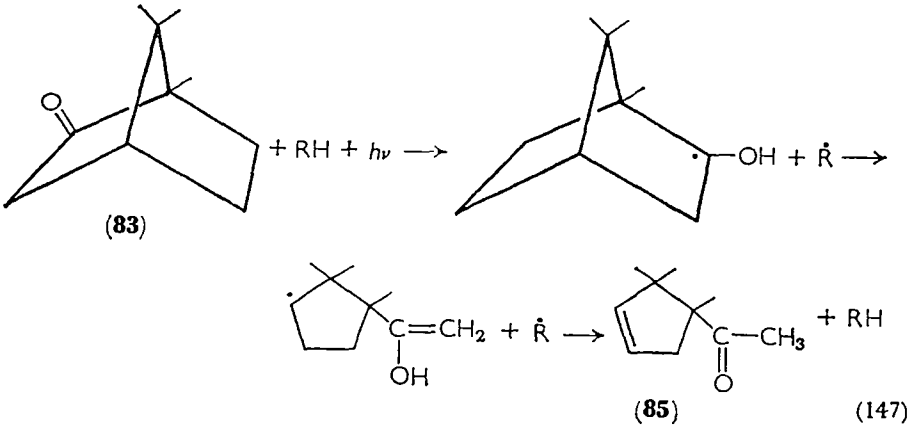
Decarbonylation is not important when camphor (**83**) is irradiated in various solvents. At 3130 Å, the major products are campholenic aldehyde (**84**) and 1,2,2-trimethyl-3-cyclopentenyl methyl ketone (**85**)[187-188]. The sum of the quantum yields of **84** and **85** is found to



(**83**) (**84**)

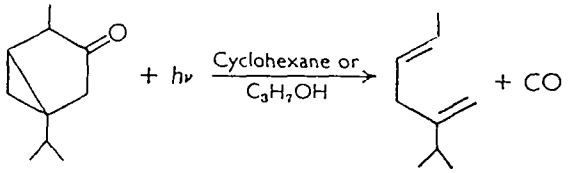
be independent of the nature of solvent, while their ratio markedly depends upon the solvent. On this basis, it was postulated that **84** is formed in an intramolecular rearrangement reaction (146) and that the formation of **85** involves interaction with the solvent molecule as in reaction (147)[188].

Bicyclic ketones **66** and **67** containing a cyclopropyl group were mentioned in section V.B. A similar bicyclic ketone, thujone (**86**),



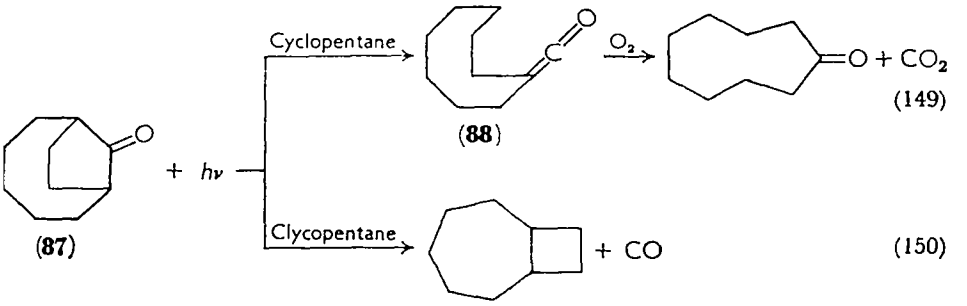
(83) (85) (147)

has been photolyzed in cyclohexane and in propyl alcohol solutions. The reaction leads to production of CO with a yield comparable to vapor phase photolysis (reaction 148)[189].



(86) (148)

Irradiation of the bicyclic ketone **87** in cyclopentane solution leads to isomerization to the ketone derivative **88** and to decarbonylation in 65% and 15% yields, respectively[190]. The formation of **88** may



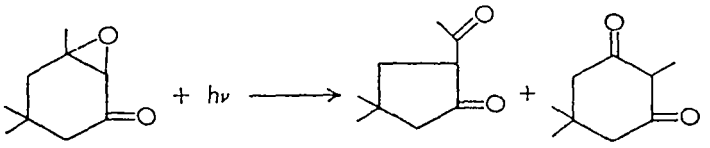
(88) (149)

(87) (150)

involve an intramolecular disproportionation of an alkyl–acyl radical pair.

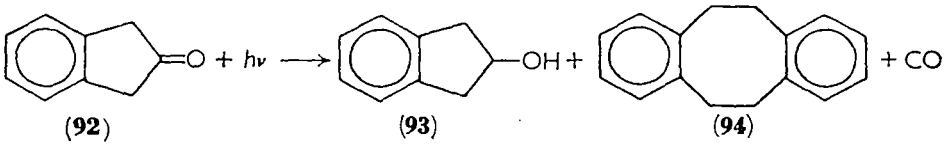
The photochemical reactions of α,β-epoxy ketones have not been widely studied although interesting skeletal rearrangements in the photochemistry of some steroidal epoxy ketones have been discussed

by Lehmann, and coworkers[191]. Several simpler epoxy ketones which undergo skeletal transformation have also been reported[66]. Thus irradiation of isophorone oxide in various solvents gave a 9:1 mixture of **90** and **91** in 10% yield[66].



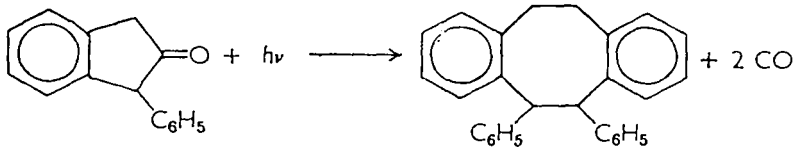
(89) (90) (91) (151)

The irradiation of indenones provides an interesting study of the substituent effect on photodecarbonylation. Unsubstituted 2-indenone (**92**) gives an alcohol (**93**) as the major product and about 5% of



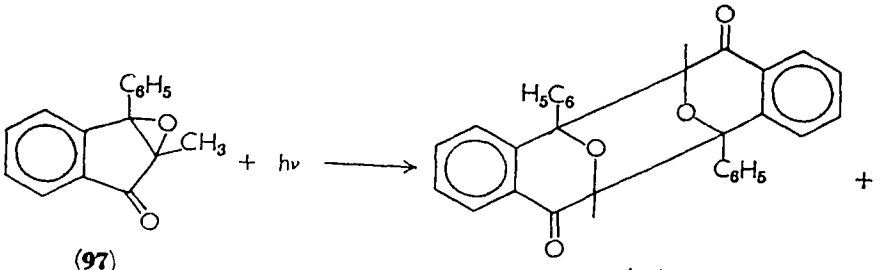
(92) (93) (94) (152)

94, while 1-phenyl-2-indenone (**95**) gives an 80% yield of product (**96**)[193]. Irradiation of 2,3-epoxy-2-methyl-3-phenylindenone (**97**) in benzene, however, gives a 27% yield of the rearranged product (**99**) and possibly a small amount of the dimer **98**[194].

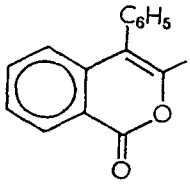


(95) (96) (153)

Ullman and Henderson[273] have studied quantitatively and in detail the mechanism of the reversible photochemical valence tautomerization of 2,3-diphenylindenone oxide (**100**) with the pyrylium oxide (**101**). Their results are most readily interpreted by assuming intermediate vibrationally excited ground states formed by nonradiative processes (see Figure 1) from the lowest excited singlet and triplet states of **100** in the forward and **101** in the reverse reactions. As part of their argument they note that 3,4-diphenylisocoumarin (**102**) is formed exclusively from **101** on irradiation with



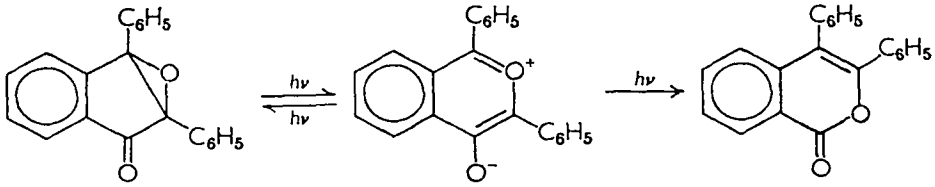
(97) (98) (154)



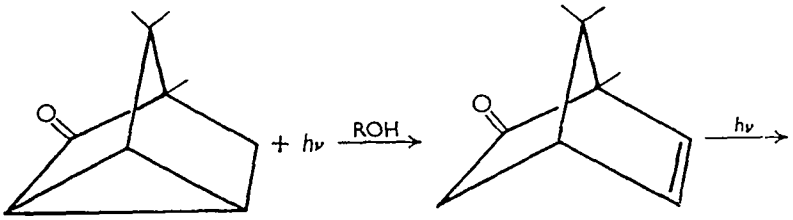
(99)

visible light ($\lambda > 450$ mμ). **102** was not formed by irradiation of **100** alone at 365 mμ.

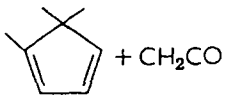
Irradiation of the tricyclic ketone cyclocamphanone (**103**) in a



(100) (101) (102) (154a)

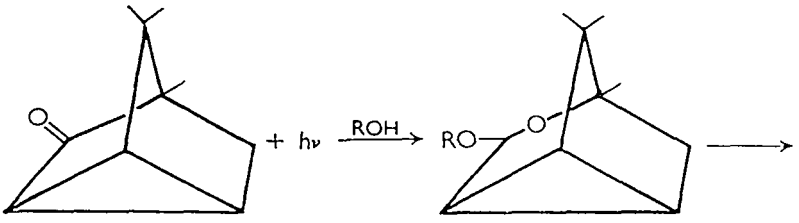


(103) (104a) (155)

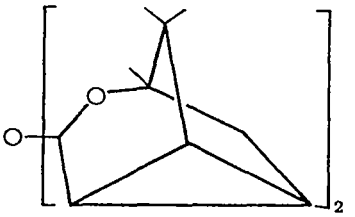


(104b)

1% alcohol solution leads to the two novel modes of rearrangements shown[195]. The first step of reaction (155) is assumed to be a skeletal rearrangement to **104a** which then decomposes into **104b** and ketene. The other reaction (156) is evidently an interaction with the alcohol



(**103**) (**105a**) (156)



(**105b**)

solvent. The isomerization of **103** first to **105a** is substantiated by various authors who have shown that photolysis of dehydronorcamphor (**7**) gives a very high yield of cyclopentadiene and ketene as shown in reaction (17).

VI. α,β-UNSATURATED KETONES

A. *Aliphatic α,β-Unsaturated Ketones*

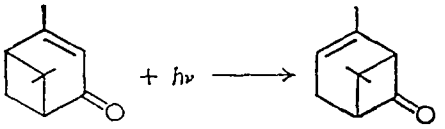
Only a few photochemical reactions of simple aliphatic α,β-unsaturated ketones have been reported in the literature. To date, only gaseous methyl propenyl ketone[56] and 4,5,5-trimethyl-3-hexen-2-one (**9**) and other structurally similar ketones in ether solution have been investigated[57, 58]. These were discussed in section III.E.1.

B. *Cyclic α,β-Unsaturated Ketones*

The photochemical reactions of some cyclic α,β-unsaturated ketones have been discussed in section III.E, III.F, and III.H. Others will now be grouped according to their types of photochemical behavior.

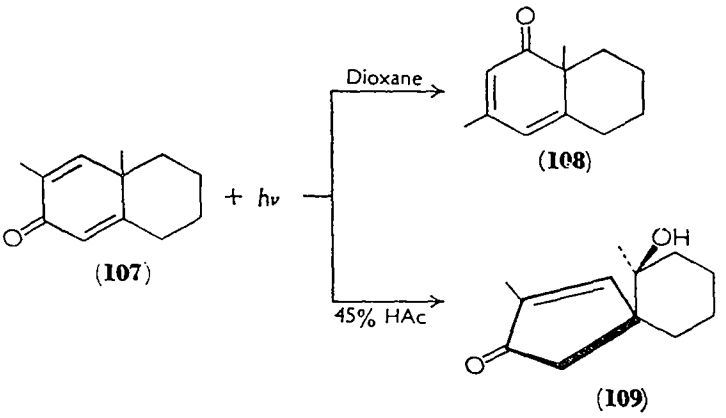
1. Skeletal rearrangement without reduction of the carbonyl group

Irradiation of verbenone (**106**) in cyclohexane solution gives chrysanthenone[196]. The reaction was shown to be irreversible. Other products (esters, acids, and amides) were also obtained when the solvents were ethanol, wet ether, and etheral ammonia, respectively.



(**106**) (157)

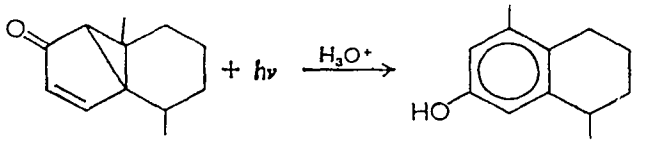
The effects of substituent and solvent in the photochemical rearrangement of cross-conjugated cyclohexadienones have been pointed out by Kropp[197] in a recent study of some 2-methyl-1,4-dien-3-ones in various solvents. For example, he found that in a neutral solvent, dioxane, the major photoproduct of **107** is the conjugated isomer **108**. In a 45% acetic acid solution irradiation of **107** gives mainly the spiro ketone (**109**). Thus the photochemical reactions involve intermediate steps which are markedly sensitive to the nature of solvent medium as well as to the alkyl substituents.



(**107**) (158) (**108**) (159) (**109**)

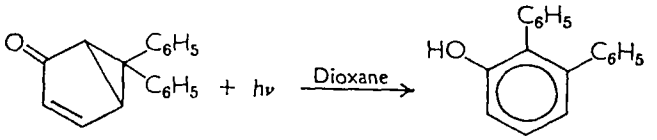
2. Skeletal rearrangement accompanied by reduction of the carbonyl group

Irradiation of the tricyclic ketone (**110**) in acidic solution with a mercury arc (Pyrex filter) at 20°c gives a phenol (**111**)[198]. The



(110) (111) (160)

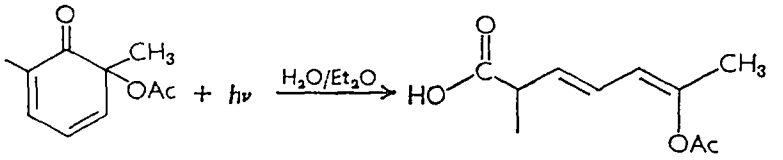
photorearrangement of **112** to **113** has been reported in aqueous dioxane solution irradiated with $\lambda > 3100$ Å[192].



(112) (113) (161)

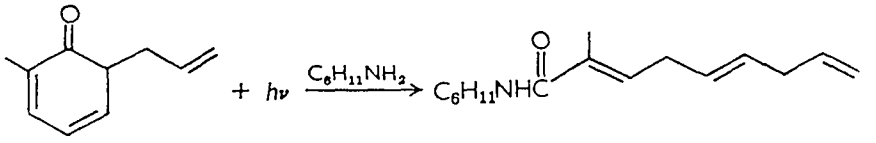
3. Rearrangement with ring fission

Upon irradiation with a mercury arc (Pyrex filter) in the presence of a suitable refluxing nucleophilic solvent, all α-substituted cyclohexadienones such as **114** and **116** undergo smooth fission to acids



(114) (115) (162)

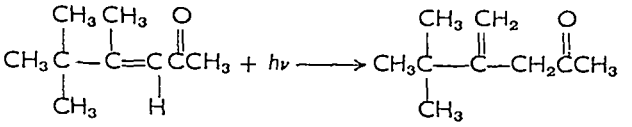
115 and their derivatives **117**, respectively. In an oxygen-free solution of 0·1 to 1%, the conversion yield was found to be quite high[199].



(116) (117) (163)

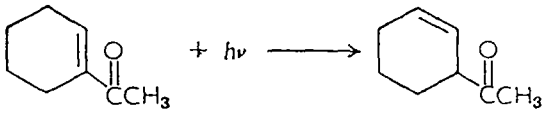
4. Rearrangement via enolization

Upon irradiation with ultraviolet light in a quartz cell, it was observed that the vinyl ketone **118** isomerized quantitatively to β,γ-allyl ketone (**119**), presumably by a photoenolization mechanism.



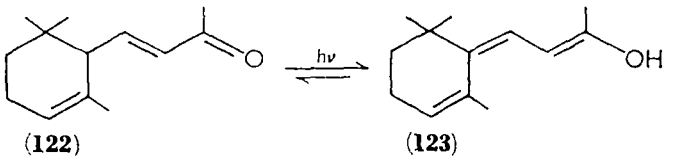
(118) (119) (164)

It has been reported that irradiation of 1-acetylcyclohexene (**120**) gives 3-acetylcyclohexene (**121**) with a conversion yield of about 50%[200]. However, in recent experiments using highly purified solvents, reaction (165) did not seem to occur[201].

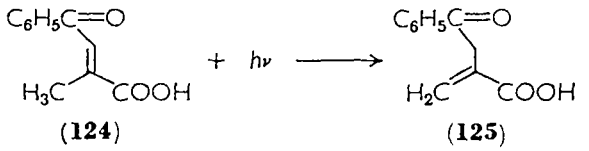


(120) (121) (165)

Other examples of photoenolization are the rearrangements of α-ionone (**122**) to (**123**)[202] and the photoisomerization of **124** to **125** in sunlight[203].



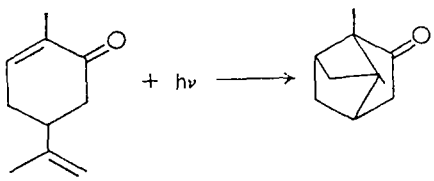
(122) (123) (166)



(124) (125) (167)

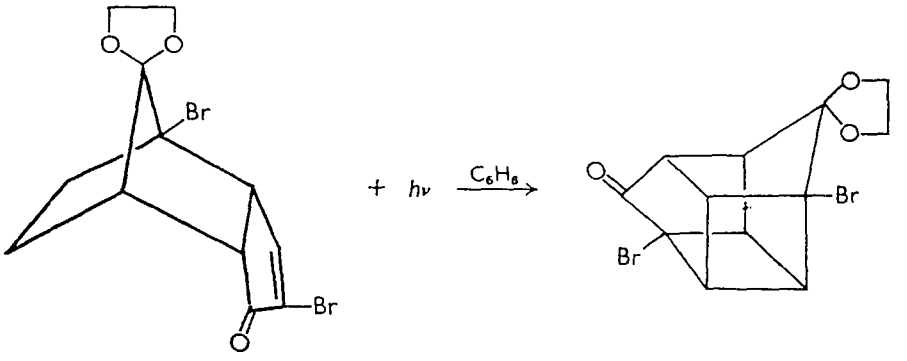
5. Addition to ethylenic bonds

Irradiation of carvone (**126**) in 95% ethanol by sunlight (Pyrex reaction cell) gives carvone camphor (**127**)[204]. The photocyclization is a type of intramolecular addition.



(126) (127) (168)

Irradiation of the 1-oxo-8-ethyleneketal (**128**), in benzene solution provides another example of intramolecular addition. The product is a 'cage' ketone (**129**) in 95% yield[205].

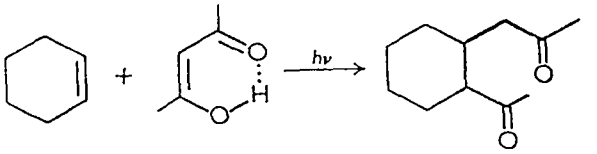


(**128**) (**129**)

(169)

Intermolecular additions to ethylenic systems have been observed between the same ketone molecules or between the ketone and other molecules. In this respect the self-addition of cyclopentenone has been illustrated in reaction (44).

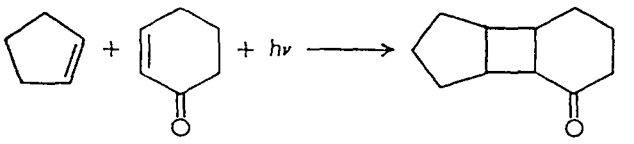
Another type of photoaddition in which cyclization is not involved in the final product has been reported. Irradiation of acetylacetone in cyclohexene gives **130** in 78% yield[206]. Similar reactions have also been observed in good yields with 1-octene and other olefins[206].



(**130**)

(170)

An example is the photoaddition of cyclopentene to cyclohexenone.



(*trans*/*cis* = 1)

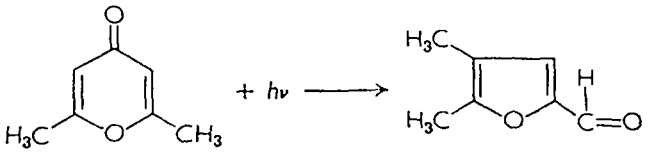
(170a)

C. Heterocyclic α,β-Unsaturated Ketones

The photochemical reactivity of heterocyclic α,β-unsaturated ketones is closely related to their cyclic hydrocarbon analogs.

1. Skeletal rearrangement

Photoarrangement of 2,6-dimethyl-4-pyrone (**131**) to a furan derivative (**132**) has been reported[207]. Upon irradiation of a dilute aqueous solution of **131** in a quartz cell with unfiltered light from a high pressure mercury arc, the isomerized product (**132**) was ob-

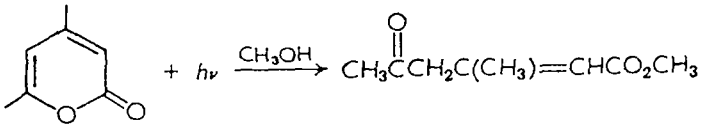


(131) (132) (171)

served in about 1% yield. The major reaction was photodimerization of **131** as in equation (173) below.

2. Rearrangement with ring fission

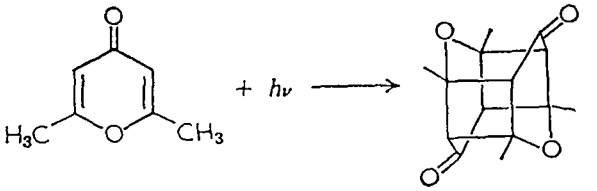
Photoisomerization accompanied by ring fission of 4,6-dimethyl-2-pyrone (**133**) in methanol has been observed[208].



(133) (172)

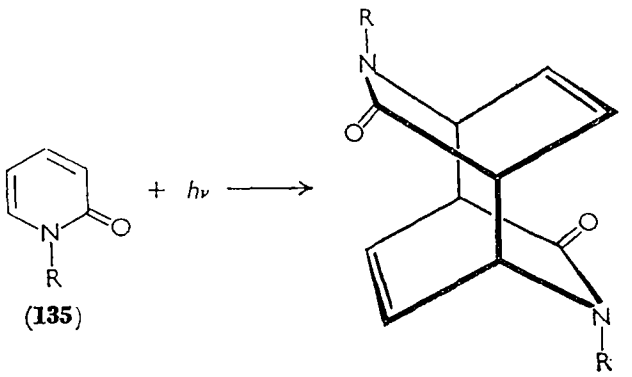
3. Dimerization

Irradiation of **131** in either the solid state or in aqueous solution leads to dimerization in good yields[207,209].



(131) (134) (173)

Irradiation of α-pyridones (**135**) in aqueous solution with an unfiltered high pressure mercury arc resulted in dimerization[210-212].



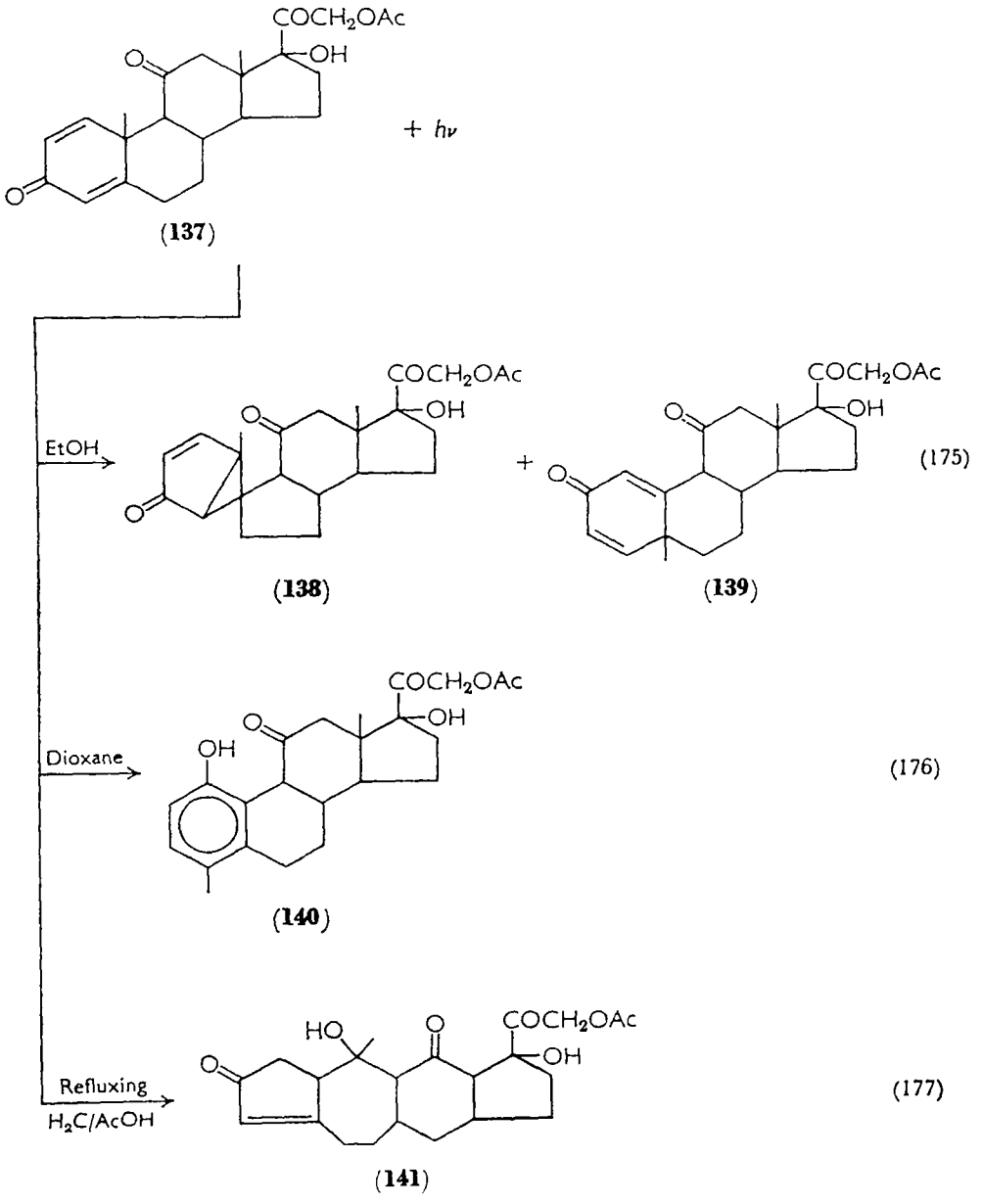
(135) (136) (174)

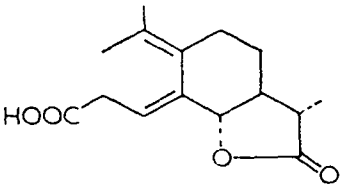
D. Steroid Dienones

The course of photochemical rearrangements of steroid dienones often shows a striking dependence upon solvent. In addition the nature of the products is sometimes affected by the presence or absence of a 4-alkyl substituent in the dienones. Thus, irradiations of prednisone acetate (**137**) with no 4-alkyl substituent in several solvents leads to the products shown in reactions (175), (176), and (177)[213]. Santonin (**142**) irradiated in similar solvents gives a different set of products (reactions 178 and 179)[214,215].

Probable mechanisms of the photochemical reactions of **137** and **142** have been reviewed in detail by Chapman[10]. He rationalizes that the three different rearrangements of **137** in equations (175) to (177) involve a series of alkyl shifts in polar intermediates followed by formation of new rings. The difference in the nature of rearrangements of **137** and **142** is attributed to the presence or absence of a 4-methyl substituent. This latter structural effect has also been demonstrated by the different photochemical rearrangements of 1-dehydro-4-methyltestosterone (**146**) and of 1-dehydrotestosterone (**148**). The former (**146**) gives a clean photorearrangement to **147** in 60–70% yield[216-217], while irradiation of the latter leads to a complex mixture of ketones and phenols of which only the structures of **149** and **150** have been established[218].

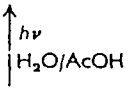
Another type of photochemical rearrangement has been reported at 2537 Å for 10β,17β-diacetoxyl-1,4-estradien-3-one (**151**)[219]. It loses an OAc group and rearranges to **152**.

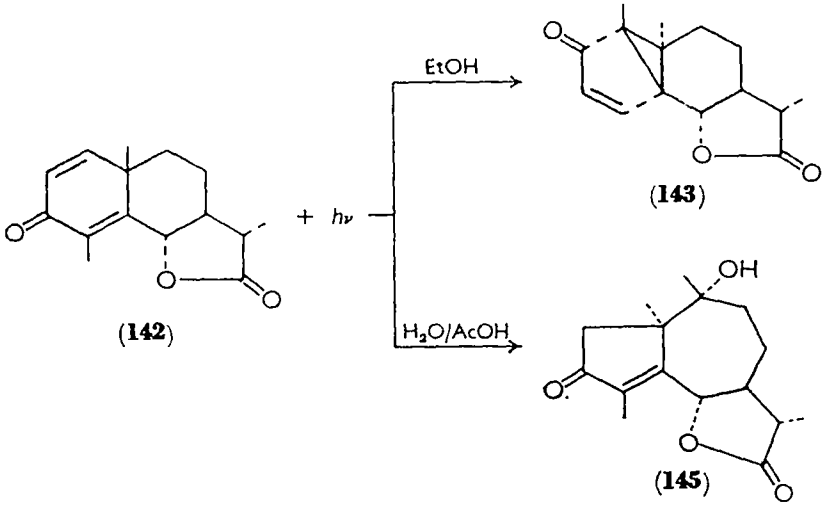

COCH2OAc
OH
O
O
+ hν
(137)
EtOH
COCH2OAc
OH
O
O
(138)
+
COCH2OAc
OH
O
O
(139)
(175)
Dioxane
COCH2OAc
OH
OH
O
(140)
(176)
Refluxing
H2C/AcOH
HO
O
O
COCH2OAc
OH
(141)
(177)



(178)

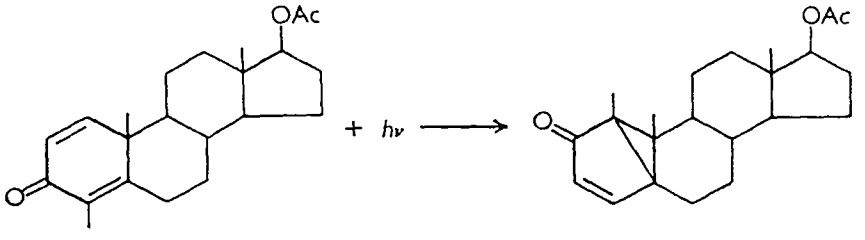
(**144**)





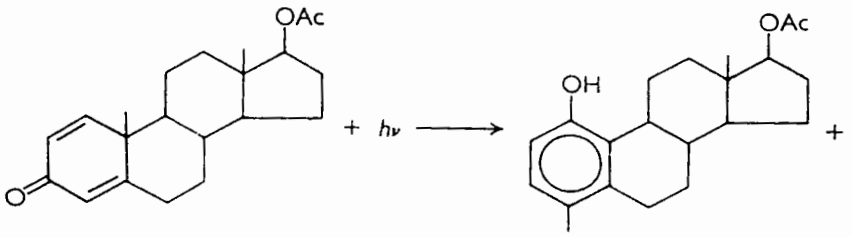
(**142**) (**143**) (**145**)

(179)

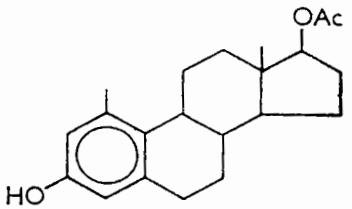


(**146**) (**147**)

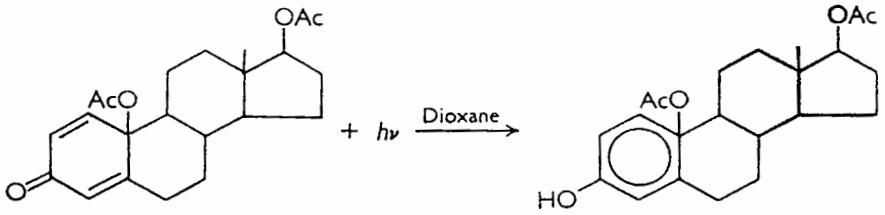
(180)



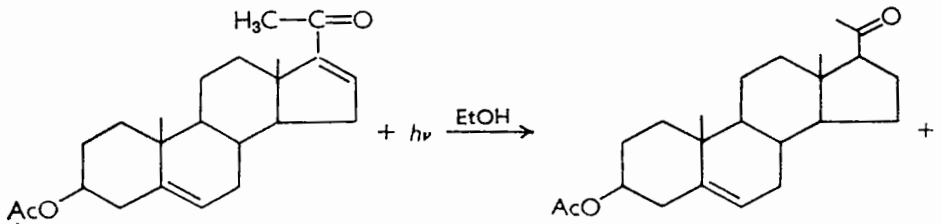
(148) (149) (181)



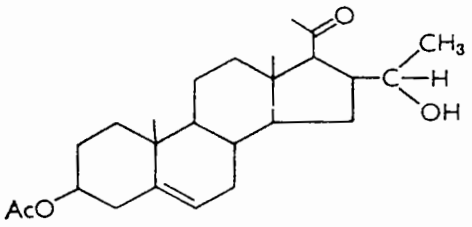
(150)



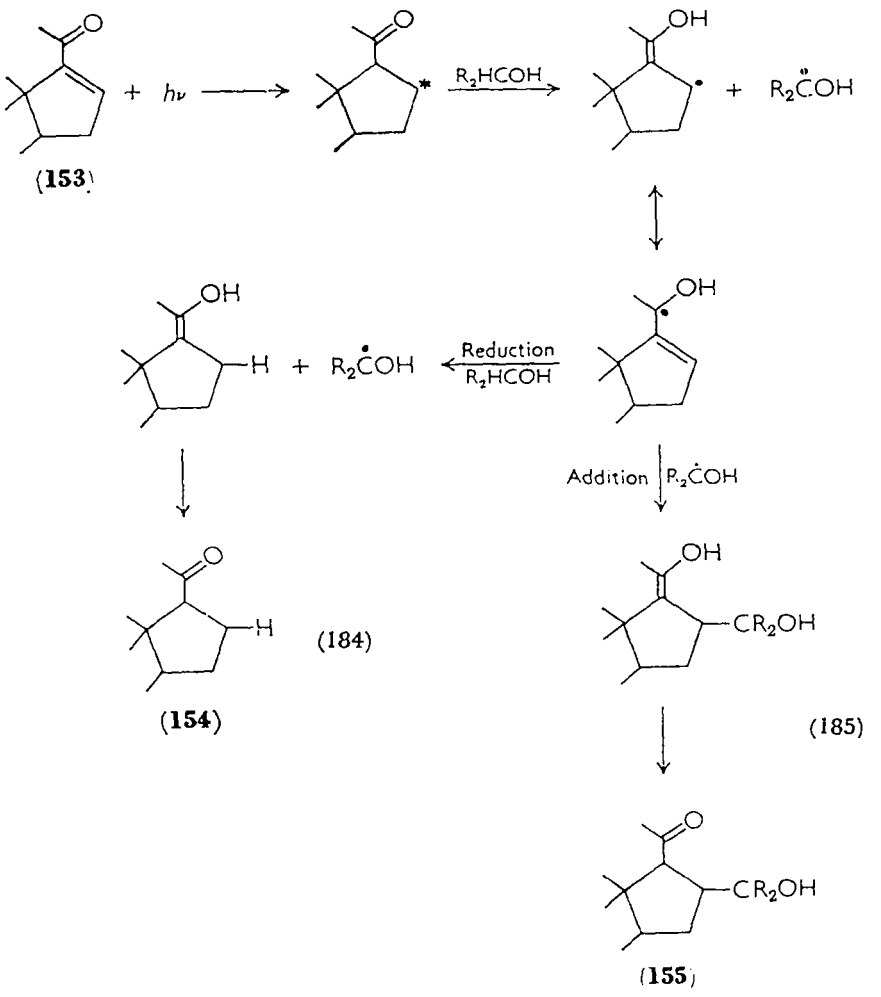
(151) (152) (182)



(153) (154)



(155) (183)



Recently a novel photochemical reaction of 3β-acetoxy-5,16-pregnadien-20-one (**153**) has been reported[220] in which **153** gives **154** in 40–50% yield and in addition ethanol is added to **153** giving **155** in 30–40% yield. The reaction was found to be general with both primary and secondary alcohols, thus giving a new method for the introduction of an oxygen-bearing 16α-alkyl substituent into the steroid nucleus. A general mechanism for the reaction was postulated.

VII. PHOTOLYSIS OF ALKYL ARYL KETONES

Alkyl aryl ketones may behave photochemically as both aromatic and aliphatic ketones. Thus in the gas phase, they can undergo free-

radical photodissociation and in the liquid phase they participate mainly in hydrogen-atom abstraction processes from hydrogen-atom donating solvents and carbonyl cycloaddition to olefins. In certain alkyl aryl ketones with γ-hydrogen atoms on the alkyl chain, the Type II split process is also important.

A. Acetophenone

This simplest alkyl aryl ketone photodecomposes at elevated temperature in the vapor phase according to reaction (186)[221, 222].

$$C_6H_5COCH_3 + h\nu \longrightarrow \dot{C}_6H_5 + \dot{C}H_3 + CO \qquad (186)$$

The photopinacolization of acetophenone in 2-propanol and in a benzene solution of α-methylbenzyl alcohol has been studied in detail by Cohen and coworkers[223]. In the first solvent the photoreduction leads to the *meso* and *dl* forms of 2,3-diphenyl-2,3-butylene glycol and one mole of acetone is formed from the solvent for every two moles of acetophenone reduced. This result is similar to the photoreduction of benzophenone in 2-propanol[72]. In the second solvent case, irradiation also produces the *meso* and *dl* forms of 2,3-diphenyl-2,3-butylene glycol.

It was further demonstrated uniquely that the photopinacolization of acetophenone in both systems can be quenched physically as well as chemically[223]. Physical quenching is brought about by energy transfer from the triplet acetophenone to naphthalene. Chemical quenching involves inhibition by either mercaptans (ASH) or disulfides (ASSA); the latter oxidize ketyl radicals to ketones while mercaptans reduce them to the corresponding carbinol.

$$C_6H_5COCH_3 + h\nu \longrightarrow C_6H_5COCH_3(S_1) \longrightarrow C_6H_5COCH_3(T_1) \qquad (187)$$

$$C_6H_5COCH_3(T_1) + C_6H_5CH(OH)CH_3 \longrightarrow 2\,C_6H_5\dot{C}(OH)CH_3 \qquad (188)$$

$$2\,C_6H_5\dot{C}(OH)CH_3 \longrightarrow [C_6H_5C(OH)CH_3]_2 \qquad (189)$$

$$C_6H_5\dot{C}(OH)CH_3 + ASSA \longrightarrow C_6H_5COCH_3 + ASH + \dot{A}S \qquad (190)$$

$$C_6H_5\dot{C}(OH)CH_3 + ASH \longrightarrow C_6H_5CH(OH)CH_3 + \dot{A}S \qquad (191)$$

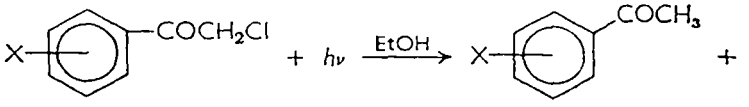
It was observed that mercaptans and disulfides were equally effective, each being converted into a common mixture of the two during irradiation[223]. Thus when optically active α-methylbenzyl alcohol is used, the residual alcohol is not racemized if the acetophenone is reduced in the absence of sulfur compounds. In the presence of sulfur compounds the optically active alcohol is racemized

and the reduction is retarded. The uninhibited reduction is zero-order with respect to acetophenone; the quantum yield of pinacol formation is a function of alcohol concentration and approaches unity at high alcohol concentrations. A simplified mechanism which accounts for the observed results is represented by reactions (187) to (191).

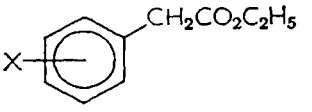
Another well-known general photochemical reaction of aromatic ketones is photoaddition to olefinic systems (section III.I).

In contrast to acetophenone, 2-acetonaphthone does not photopinacolize or add across olefinic bonds[74,88]. Cyclopropyl phenyl ketone also does not readily undergo reduction and addition reactions[88].

The photoinduced rearrangement of various substituted phenacyl chlorides (**156**) in ethanolic solution has been investigated[224]. The

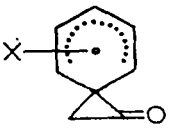


(**156**) (**157**) (192)



(**158**)

major rearrangement is represented in reaction (192). The production of acetophenone (**157**) probably involves the decomposition of **156** into a chlorine atom and a ketonyl radical which then abstracts a hydrogen atom from the solvent. However, the ester **158** is formed only when the substituent X is an electron-donating group in an *ortho* or *para* position. It was postulated that formation of the ester (**158**) could proceed via a cyclic intermediate of the ketonyl radical (**159**) since such an intermediate is stabilized by *ortho* or *para* electron-donating substituents[224].



(**159**)

B. Butyrophenone

The quantum efficiency of the photoelimination of ethylene (reaction 8) from butyrophenone is highly sensitive to the electron-donating character of *para* substituents, dropping from 0·04 in both butyrophenone and *p*-methylbutyrophenone to 0·29, 0·10, and 0·00 in the *p*-fluoro, *p*-methoxy, and *p*-amino derivatives, respectively[23]. A zero quantum yield of ethylene production is also observed in both *o*- and *p*-hydroxybutyrophenone. These effects are similar to those observed for the efficiency of intermolecular hydrogen-atom abstraction by benzophenone derivatives and, in the case of the *para* substituents, may be qualitatively correlated with the absorption and phosphorescence spectra (i.e. singlet or triplet levels) of these butyrophenones. It appears that the lowest triplet states of the non-reactive *p*-NH_2 and *p*-OH substituted butyrophenones are $^3(\pi,\pi^*)$ rather than $^3(n,\pi^*)$, and the electron-donating *para* substituents result in increased negative charge on the excited carbonyl oxygen, thus diminishing its hydrogen-atom abstracting power.

In the case of *o*-hydroxybutyrophenone, the nonreactivity may be due to an intramolecular photoenolization process analogous to that established by Yang[225] for *o*-hydroxybenzophenone (*vide infra*)[23].

VIII. AROMATIC KETONES AND ALDEHYDES

Photochemical reactions of aromatic ketones and aldehydes in solution have been the subject of many investigations since the original discovery of Ciamician and Silber[71] that the action of sunlight on a solution of benzophenone in ethanol gave a good yield of benzopinacol. Up to 1950 most of the work was directed toward synthetic applications of photoreductions, since the yields in many cases are good and the products more readily prepared than by the usual nonphotochemical routes. This was well illustrated in an important early review article by Schonberg and Mustafa[226] who did much of the pioneer synthetic photochemistry of the carbonyl compounds. In the last decade the mechanistic aspects of these systems, first examined critically by Bäckström[11], and by Weizmann, Bergmann and Hirshberg in the 1930s[78], have received a great deal of attention. Another important photochemical reaction of aromatic ketones and aldehydes is the photocycloaddition of olefins to the carbonyl group; it was also exploited synthetically and studied mechanistically during this period. Very few quantitative vapor-phase studies have been reported and these will not be treated in detail here.

A. Aromatic Aldehydes

Benzaldehyde photodecomposes in the vapor phase presumably according to the free-radical mechanism (193) and (194). At 25°c

$$C_6H_5CHO + h\nu \begin{cases} \longrightarrow \dot{C}_6H_5 + \dot{C}HO & (193) \\ \longrightarrow C_6H_5\dot{C}O + H & (194) \end{cases}$$

only a very low quantum yield of decomposition was observed but at elevated temperatures, chain decomposition to give CO seems probable[227].

In hydroxylic solvents benzaldehyde undergoes photoreduction by intermolecular hydrogen-atom abstraction. It also adds photochemically to olefinic systems (reactions 53, 47) as well as to acetylenic bonds (reaction 55).

The effect of substituents on the photoreactivity of benzaldehyde has not been systematically studied. However, the photoreactions of *p*-methoxybenzaldehyde and *p*-chlorobenzaldehyde with the ketenimine **52** have been investigated[88]. The results are shown in Table 8[88].

TABLE 8. Photochemical behavior of substituted benzaldehyde.

Compound	Photoreduction	Reaction with ketenimine	
		% Iminooxetane (**54**) yield[a]	% Sensitized product (**55**)[b]
Benzaldehyde	yes	50 (β-isomer formed only)	10
p-Methoxybenzaldehyde	not known	34 (β-isomer formed only)	66
p-Chlorobenzaldehyde	not known	60 (β-isomer formed only)	21
1-Napthaldehyde	no	0	0

[a] See reaction (47). [b] See analogous reactions (48) to (51).

Anisaldehyde is found to behave photochemically similar to benzaldehyde. With 1-naphthaldehyde, however, no photoreduction is observed in usual hydrogen donor solvents unless tributylstannol, a very good hydrogen donor, is used as solvent[74].

B. Aromatic Ketones

1. Benzophenone

Irradiation of benzophenone in thoroughly deoxygenated hydrogen-donor solvents such as isopropyl alcohol gives a quantitative

yield of benzopinacol and acetone[72]. Quantum yields of benzophenone disappearance in various solvents are shown in Table 9. If air is bubbled through the solution continuously during irradiation,

TABLE 9. Photoreduction of benzophenone in various solvents.

Solvent	Molar concentration of benzophenone	$\Phi_{\text{disappearance}}$
Water	10^{-4}	0·02
Benzene	10^{-2}	0·05
Toluene	10^{-2}	0·45
Hexane	10^{-2} to 10^{-4}	1·0
Ethanol	10^{-4} to 10^{-1}	1·0
Isopropanol	10^{-5} to 10^{-1}	0·80 to 2[a]

[a] This variation is due to a light intensity effect.

the acetone quantum yield remains unchanged but that of benzopinacol drops to zero. Some hydrogen peroxide is formed but benzophenone itself is unchanged. The overall reaction is thus the benzophenone photosensitized oxidation of the alcohol solvent[72].

Photosensitized oxidations have important theoretical and synthetic aspects, as illustrated by the important long-term research of Schenck and coworkers[228-231]. We should also cite the studies on reactions of *singlet* oxygen by Foote and Wexler[274] and by Bayes[275]. However, it is beyond the scope of this article to treat this subject here.

A detailed review of the solution-phase photochemistry of benzophenone would justify a separate article. We shall simply point out here several interesting aspects of the primary processes and not consider the secondary free-radical reactions. For references to the latter, see the papers of Frenzen, Hammond, Moore, Pitts, Porter, Schenck, and others.

It has now been well established by a variety of techniques, such as physical quenching[13], flash spectroscopic detection of intermediates[73], emission spectra[12,20], etc., that the hydrogen-atom abstracting state of benzophenone is the lowest n,π^* triplet formed by intersystem crossing from the original excited singlet state (reactions 38 and 39).

Intermolecular transfer of triplet energy to an organic molecule was first demonstrated[232] in the gas-phase mercury-photosensitized reactions of hydrocarbons. The first demonstration of triplet–triplet transfer in organic systems was by Terenin and Ermolaev who observed the benzophenone-sensitized phosphorescence of naphthalene

in glassy solvents at 77°K[233]. Subsequently Bäckström and Sandros reported the benzophenone-sensitized phosphorescence of biacetyl in fluid solutions[12]. Concurrently Porter and Wilkinson[14] demonstrated energy-transfer processes between triplet benzophenone and naphthalene in various solvents by flash spectroscopic and chemical techniques.

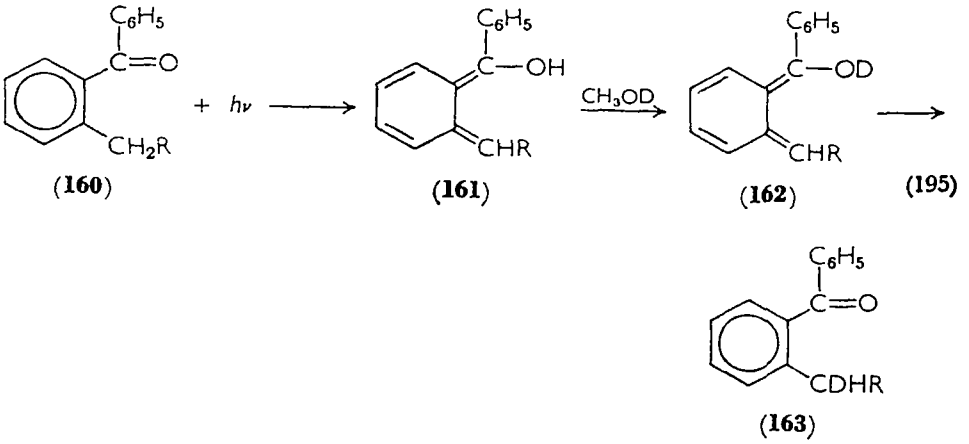
The phenomenon of triplet energy transfer is of great theoretical and practical significance. Thus, Hammond and coworkers[13,234-237] have demonstrated beautifully that triplet transfer in solution may lead merely to degradation of energy by physical processes of the acceptor (e.g. with naphthalene), or the acceptor molecule may undergo chemical reactions, often to produce unique compounds in good synthetic yields (e.g. with olefins). Although space limitations preclude a discussion of this fascinating field, we should note the definitive paper on the mechanism of sensitized and direct photochemical *cis–trans* isomerization in solution by Hammond and coworkers[237]. Detailed studies of four pairs of *cis–trans* isomers, the stilbenes, the 1,2-diphenylpropenes, the piperylenes (1,3-pentadienes), and ethyl maleate–ethyl fumarate led to the important conclusion that all their results could be understood if transfer of triplet excitation may involve excitation of acceptors to *nonspectroscopic* (i.e. '*phantom triplets*') as well as spectroscopic states[237]. Such 'phantom triplet' states may also be important in other systems.

While the photopinacolization of benzophenone can be quenched by energy transfer to naphthalene[13], it can also be suppressed by chemical scavenging of the ketyl radicals with mercaptans or disulfides[223]. The mechanism is similar to that of acetophenone represented in reactions (187) to (191).

As pointed out earlier, substituted benzophenones show dramatic differences in their reactivity. *Ortho* substitution of a group having a hydrogen atom which can participate in a six-membered ring with the carbonyl oxygen (e.g. OH or CH_3) completely quenches the intermolecular hydrogen-atom abstraction process[281] and ketones of this type are widely used commercially as 'sun screening' agents.

The process by which this quenching occurs has been termed 'photoenolization' by Yang[225] and coworkers who demonstrated the effect by irradiating **160** in CH_3OD and showing that deuterium was introduced into the alkyl side-chain.

The intramolecular quenching effect of substituents such as OH, NH_2 or C_6H_5 in the *para* position on the intermolecular hydrogen-atom abstraction process has been discussed earlier. We should add



(160) (161) (162) (195) (163)

that Porter and Suppan[19] recently reported the interesting observation that certain 'nonreactive' *p*-substituted benzophenones become reactive in other solvents; e.g. they abstract hydrogen atoms from alkanes but not alcohols.

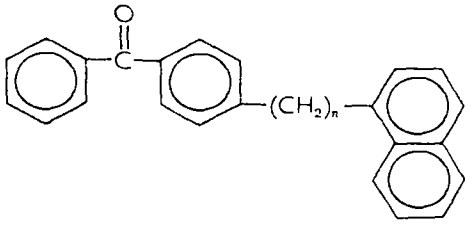
Only one report has appeared concerning the possible formation of cross pinacols in the photolysis of mixtures of substituted benzophenones[238]. The study involved three systems in which conditions were adjusted so that both ketones were absorbing the same amount of incident radiation. It is interesting that only one system, mixtures of benzophenone and 4,4'-dichlorobenzophenone, gave about 15–20% of cross pinacols. The failure of cross pinacol formation in the other systems may be due to a triplet–triplet energy transfer, or it could result from an intermolecular hydrogen atom transfer from one ketyl radical to the other ketone molecule. Work is in progress to clarify this point.

The photochemistry of thiobenzophenone differs significantly from that of benzophenone. Thus, irradiation of thiobenzophenone in alcoholic solvents gives benzhydryl mercaptan, dibenzhydryl disulfide and tetrasulfide as the reduction products[239]. Irradiation of thiobenzophenone in the presence of olefins gives reaction (196)[240].

$$(C_6H_5)_2C{=}S + R^1CH{=}CHR^2 + h\nu \longrightarrow R^1CH{=}C(C_6H_5)_2 + R^2CH{=}C(C_6H_5)_2 + R^1CH{=}S + R^2CH{=}S \qquad (196)$$

2. Naphthylalkylbenzophenones

An interesting case of intramolecular electronic energy transfer occurs in 4-(1-naphthylalkyl)benzophenone (**164**)[241]. The absorption spectrum of **164** shows that the molecule contains two

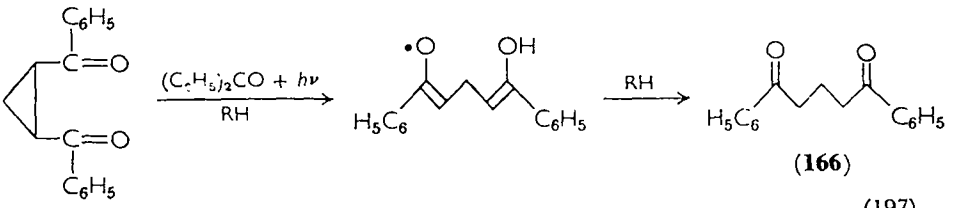


(164)

independent absorbing systems, the benzophenone moiety and the naphthalene moiety. Using light absorbed only by the benzophenone moiety, Leermaker and colleagues demonstrated by emission spectra that efficient transfer of triplet excitation from the benzophenone moiety to the naphthalene moiety occurs. Because of the higher singlet energy level of naphthalene than that of benzophenone, singlet energy transfer from the latter to the first is unlikely. On the other hand, when **164** is excited with light absorbed by the naphthalene moiety, efficient transfer of singlet excitation to the benzophenone moiety occurs. Apparently, the rate of triplet energy transfer is not influenced by the length of the methylene chain, whereas a decrease in the efficiency of singlet transfer is observed as the chain increases from $n = 1$ to $n = 3$.

3. Diketones

The photochemical behavior of aromatic diketones depends markedly on the multiplicity of the excited states. Irradiation of *cis*-dibenzoylethylene (**42**) has been discussed in section III.G (reactions 40, 41). Another recent example is the photochemical reactivity of



(165) (166) (197)

trans-dibenzoylcyclopropane (**165**) [242]. Direct photolysis of **165** leads only to *cis–trans* conversion. In hydrogen donor solvents with a good triplet photosensitizer, such as benzophenone, the reaction follows a different course giving 1,3-dibenzoylpropane (**166**).

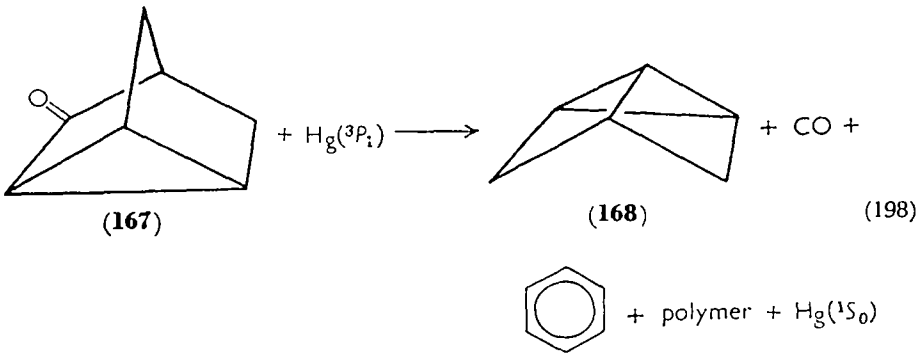
IX. OTHER ASPECTS OF CARBONYL PHOTOCHEMISTRY

Several important and interesting research areas involving the photochemistry of aldehydes and ketones cannot be discussed in detail here. We shall refer to them briefly and cite key references.

A. Mercury-photosensitized Reactions of Ketones and Aldehydes

The salient features of mercury-photosensitized reactions have been thoroughly discussed by Gunning and Strausz[243], Cvetanovic[143], and Calvert and Pitts[3]. We shall not consider them in detail here, particularly since only relatively few ketones and aldehydes have been investigated.

We might note, however, that Srinivasan[34] has shown that mercury photosensitization represents a convenient synthetic method for certain bicyclic hydrocarbons. In another example Lemal and Shim successfully prepared for the first time a highly strained tricyclo[2.2.0.0^{2,6}]hexane (**168**) in significant yield (about 36%) by the mercury-photosensitized decomposition of nortricyclanone (**167**)[244].



(**167**) (**168**) (198)

B. Photochemistry of Ketones and Aldehydes in the Solid State

Photochemical studies of the organic solid state can be classified generally into two groups. The first involves irradiation of organic molecules isolated in inert solid matrices (usually a noble gas or glassy solvent) at low temperatures. Such low-temperature studies usually deal with spectroscopic characteristics of the compound or with the identification of trapped reactive intermediates which may play an important role in the reaction mechanism. The other group includes photochemical studies of organic solids at ordinary temperatures either as crystals or in solid matrices.

It is evident from the review of Gilmour[245] that relatively very little work has been done on the photochemistry, as apart from the spectroscopy, of ketones and aldehydes in the solid state. Recently, however, some important definitive work has been published, for example that of Cohen, Schmidt, and coworkers[246-247] on 'topophotochemistry'. Current interest in the basic and applied aspects of such areas as organic photoconductors and photochromism[248] makes the field of organic solid state photochemistry particularly significant and challenging.

1. Low-temperature studies

a. Formaldehyde. In an e.p.r. study Cochran and coworkers irradiated a solid argon matrix containing 1% formaldehyde with a hydrogen discharge lamp[249-250]. A two-step mechanism (reactions 199, 200) was proposed to account for their observations. These authors demonstrated that hydrogen atoms formed in reaction (200) are less energetic than those produced in reaction (199).

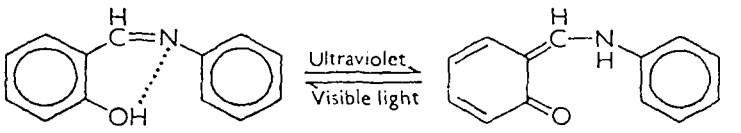
$$HCHO + h\nu \longrightarrow H + \dot{C}HO \qquad (199)$$

$$\dot{C}HO + h\nu \longrightarrow H + CO \qquad (200)$$

b. Acetone and acetaldehyde. Solid solutions of acetone and acetaldehyde in methylcyclohexane have been irradiated with a full mercury arc at 77°K. No overall decomposition of acetone was detected but acetaldehyde gave small amounts of CO and methane[251]. Using e.p.r. spectroscopy, Piette showed that methyl radicals are formed and stabilized by ultraviolet irradiation of acetone at 77°K[252].

2. Photochromism of anils

A large number of anils have been studied in the solid state, particularly because of their photochromic behavior, illustrated by the anil of salicylaldehyde (**169**)[253].

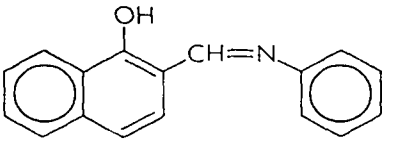


(201)

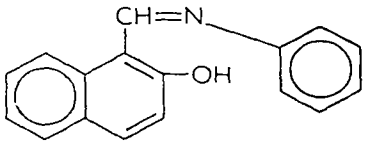
(**169**) (**170**)

Early workers believed that the photochromic process involved aggregation and crystal lattice interactions[248]. Contrary to this, Cohen, Hirshberg, and Schmidt found that isolated anil molecules in

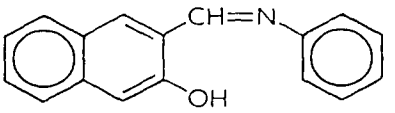
a rigid matrix at −80°c also exhibited photochromic behavior[246]. In a recent series of publications they concluded that the photochromic behavior of anils is topochemically controlled and is restricted to anils of aldehydes with an *o*-hydroxyl group[247]. Thus in the absence of an *o*-hydroxyl group or when the *o*-hydroxyl is methylated, photochromism is not observed. In addition they found that in rigid solutions the photoproperties of anils of 1-hydroxy-2-naphthaldehyde (**171**) and of 2-hydroxyl-1-naphthaldehyde (**172**) are sensitive to solvent, temperature, and wavelengths, while those of the anils of 2-hydroxy-3-naphthaldehyde (**173**) and 2-methoxy-1-naphthaldehyde (**174**) are not.



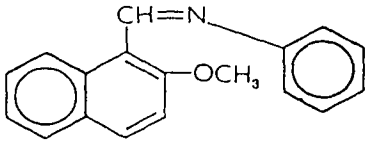
(**171**)



(**172**)

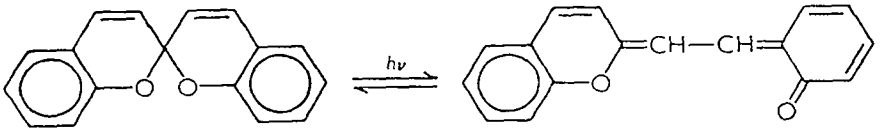


(**173**)



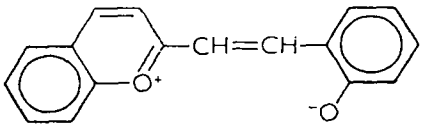
(**174**)

Bercovici and Fischer[254] have also investigated some novel benzophenone photosensitized colorations of spiropyranes (**175**) at low temperature. At temperatures below −100°c with light at



(**175**)

(202)

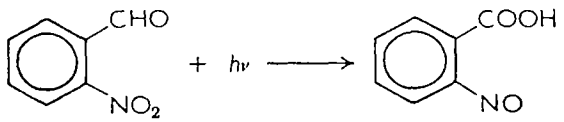


(**176**)

3650 Å, the photosensitized reaction (202) proceeds with a unit quantum yield as compared to a yield of about 0·10 in direct photolysis at 3130 Å.

3. Room-temperature studies

a. Intramolecular rearrangement. The photochemical rearrangement of *o*-nitrobenzaldehyde (**177**) to *o*-nitrosobenzoic acid (**178**) has been the subject of many investigations. It was discovered by Ciamician and Silber in 1900[71]. Pioneering quantitative as well as qualitative research in solution and in the crystalline state was carried out by Bowen[255] in the early 1920s. He found the quantum yield was 0·5 in solid crystals. About a decade later Leighton and Lucy in a detailed study showed that the photorearrangement of *o*-nitrobenzaldehyde occurs in both the solid and in solution phase with the same quantum efficiency of 0·5 and is independent of the exciting wavelength from 4000°–3100 Å[256].



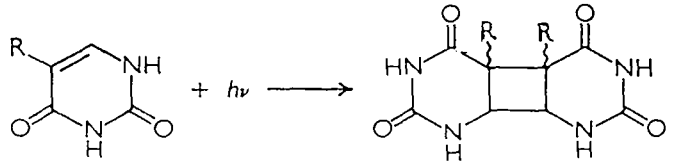
(177) (178) (203)

An e.p.r. free-radical spectrum during the irradiation of solid powdered *o*-nitrobenzaldehyde has been reported[257]. However, the photoradicals in the solid state were stabilized only at low temperatures and are probably not intermediates in the photoisomerization. Recently, Coppens and Schmidt investigated similar solid-state reactions of some substituted *o*-nitrobenzaldehydes by x-ray diffraction techniques[258]. Correlation of the geometry of the reaction centres (CH and NO), rather than their distances, with the reaction rates in the solid state was attempted.

Recently this photoisomerization was used as an actinometer to measure light intensities in quantitative photochemical studies in a KBr pellet of the type customarily used for obtaining infrared spectra of solids. Quantum yields and the kinetics of photopinacolization in the system benzophenone–benzhydrol dispersed in KBr pellets were obtained by this technique which involves irradiation by filtered light at an angle to the analyzing infrared beam from the infrared spectrophotometer. Current studies on several photochemical systems are aimed at determining the physical nature of the substrates in these alkali halide matrices[259].

b. Photodimerizations. Irradiation of solid chalcone, $C_6H_5CH{=}CHCOC_6H_5$, yields both head-to-tail and head-to-head dimers[260]. While *m*-nitrochalcone undergoes similar photodimerization in the solid state, solid *p*-nitrochalcone yields only a small quantity of photodimers[261].

A few α,β-unsaturated ketones have been found to dimerize when irradiated as solids. Thus, coumarin (**44**) yields a head-to-head photodimer[262]; uracil[263] (**179**) and thymine[264] (**180**) apparently photodimerize giving cyclobutane derivatives (**181**) formed from the carbon–carbon double bonds. The structure of **181**, however, has not been established.

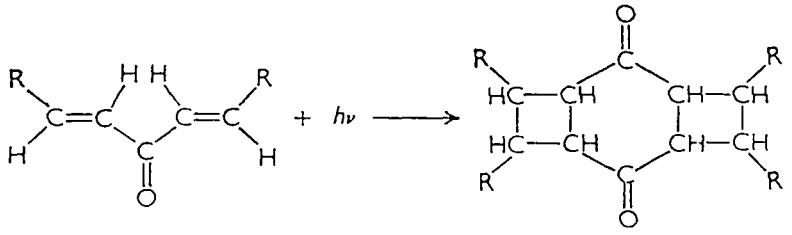


(204)

(**179**, R = H;
180, R = CH_3)

(**181**)

Some unsaturated ketones form photodimers involving cyclization of two pairs of double bonds; this is sometimes referred to as double dimerization. The solid 4-pyrone (**131**) is a good example (see equation 173). A cyclic structure is not required for a double dimerization. Thus, the solid cyclic ketone 2,5-disubstituted thymoquinone yields open dimers[265] when irradiated whereas solid dimethyl 4-pentadien-3-one-1,5-dicarboxylate (**182**) with an open-chain structure gives tricyclo[6.2.0.$0^{3,6}$]decane (**183**)[266,267].



(205)

(**182**, R = CO_2CH_3)

(**183**)

C. The Photolysis of Carbonyl Sulfide: A Novel Synthetic Method for Organic Sulfur Compounds

In a recent series of studies on reactions of sulfur atoms the photolysis of gaseous carbonyl sulfide was examined in detail by Gunning

and coworkers[268-271]. In the wavelength region of 2290–2550 Å pure COS yields CO and sulfur as the main products. The primary process is believed to be (206).

$$COS + h\nu \longrightarrow CO + S(^1D) \qquad (206)$$

Saturated and unsaturated hydrocarbons react with the sulfur atoms. Presumably both types of hydrocarbons can deactivate the primary $S(^1D)$ atoms to the $S(^3P)$ state. However, it was demonstrated that only singlet sulfur atoms can insert into saturated C—H bonds, whereas the triplet sulfur atoms readily add stereospecifically to carbon–carbon double bonds.

Photolysis of COS in both the vapor and solution phase is an excellent source of reactive sulfur atoms for synthetic purposes since their subsequent reactions with hydrocarbons give high yields of either mercaptans or cyclic sulfides with virtually no complicating side-reactions. This interesting field will be reviewed by Gunning and Strauz in a forthcoming article[272].

X. ACKNOWLEDGMENTS

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The Chemistry of the Carbonyl Group
Edited by Saul Patai

CHAPTER 17

Thioketones

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I. GENERAL COMMENTS

This chapter will be limited, as far as possible, to a discussion of the preparation and properties of compounds containing the thione (C=S) group as it appears in true thioketones. Thiono acid derivatives, as for example thiourea or thiophosgene, will not be discussed. With one possible exception, pure monomeric thioaldehydes have not yet been isolated and hence emphasis will be on thioketones.

The preparation of thioketones is complicated by many side-reactions. While this may be interpreted as evidence of the high degree of reactivity of the thione group in these compounds, it also means that in many preparations substances other than the desired thione are the principal products. Chief among such products are trimeric thiones, or 1,3,5-trithianes, but polymers, dimers, sulfides, *gem*-dithiols, and more complicated products are also obtained. The discussion of the structure and chemistry of these side-products will be limited in order to keep the chapter to a reasonable length. However, leading references will be given, since these complex thione derivatives frequently provide the most interesting chemistry.

Thiocarbonyl chemistry has been the subject of several reviews[1-4] and the reader is referred to these for more detailed accounts of reactions from the older literature. The present discussion will be limited to the preparation and properties of well-characterized thioketones and to the more interesting aspects of unusual behavior, particularly as described in the more recent literature.

The most outstanding characteristic of the true thione group is the color it imparts to the molecule. All of the monomeric thiones which have so far been described in the literature are intensely colored, ranging from red to green, with most of them in the blue or violet

range. The preparation and reactions of thiocarbonyl compounds is frequently accompanied by color changes in the solution; the appearance of such colors has been taken as evidence of thione intermediates in some reactions.

While thioacetone was claimed to have a powerful and unpleasant odor[5], most of the well-characterized thiones are of relatively high molecular weight and have a rather pleasant, but clinging, odor. The lower molecular weight compounds usually associate to form trithianes, which are both colorless and odorless.

II. PREPARATION OF THIONES

A. Conversion of Carbonyl or Incipient Carbonyl Groups into the Thiocarbonyl Group

1. Treatment of aldehydes or ketones with hydrogen sulfide

a. Acid-catalyzed additions. The reaction of hydrogen sulfide with a carbonyl group (equation 1) may lead to the formation of a thio-

$$R^1COR^2 + H_2S \rightleftharpoons R^1\text{—}\underset{\displaystyle SH}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}\text{—}R^2 \rightleftharpoons R^1CSR^2 + H_2O \qquad (1)$$

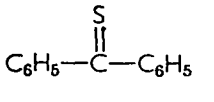
carbonyl compound. This reaction has been most extensively exploited in the preparation of thioketones. However, the intermediate hydroxythiol may trimerize, dimerize, or polymerize, or it may eliminate water to form an enethiol if an α-hydrogen is present, and the enethiol may react with reagents present to form other substances. The thione may dimerize, trimerize, or polymerize, or it may react with oxygen of the air. Hence this reaction may be quite complicated[6].

Best results have been obtained when the reaction is acid-catalyzed and in general the reaction is carried out by passing hydrogen sulfide and hydrogen chloride gas into a solution of the ketone. Solvents used have varied widely, with alcohol (ethanol or methanol) the most common, but acetic acid, ethyl acetate, dioxane, ether, and others have been used. Best results have been obtained with polar solvents. Elofson and coworkers[7] carried out this reaction in liquid hydrogen fluoride and by this means were able to convert Michler's ketone and 3,3′-dinitrobenzophenone into the corresponding thiones in high yield, whereas these compounds could not be converted into thiones in alcohol saturated with hydrogen chloride. On the other

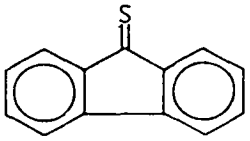
hand, certain compounds, such as benzophenone, could not be converted into thiones by treatment with hydrogen sulfide in liquid hydrogen fluoride but these thiones were readily formed in alcohol saturated with hydrogen chloride. The reaction is also quite susceptible to temperature effects and is generally carried out at or below 0°. This is particularly true of those ketones which have α-hydrogens, where the lower temperature may be effective in preventing side-reactions.

The following examples illustrate the preparation of simple thiones by the use of hydrogen sulfide and hydrogen chloride. Treatment of a solution of benzophenone in 95% ethanol, cooled in an ice–salt bath, with hydrogen sulfide and hydrogen chloride for 2–3 h, followed by continuous addition of hydrogen sulfide for 20 h, produced deep blue-violet needles of **1** in 66–77% yield, which melted at 53–54° after two recrystallizations from ligroin under carbon dioxide[8,9]. This and related preparations may require careful purification to eliminate unreacted ketone. Several good examples are given by Westheimer and coworkers[10].

A solution of fluorenone in 95% ethanol, cooled to −12°, was



(**1**)



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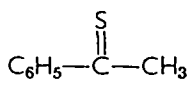
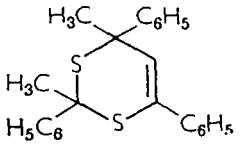


(**3**)

treated with hydrogen sulfide and hydrogen chloride at such a rate as to keep the temperature below 0°. After 3 h a deep green sludge of crystals had formed. After treatment with hydrogen sulfide for a further 2 h, the crystals were collected under carbon dioxide, dried over calcium chloride *in vacuo*, and recrystallized from petroleum ether under carbon dioxide. The green needles of **2**, obtained in 57% yield, melted at 75–76°[11].

Thioacetophenone (**3**) forms as a deep purple oil when acetophenone is treated as above[12], but efforts to isolate it always lead to mixtures containing some trimer. The pure trimer can be obtained readily, however, and then pyrolyzed to produce monomer. In this case it is necessary to control carefully the temperature and acid concentration[13] in order to obtain the trimer in good yield and avoid the formation of a different product, 'anhydrotriacetophenone disulfide' (**4**), which can be the major product in this reaction[14]. The structure of **4** has been established[15] as 2,4-

dimethyl-2,4,6-triphenyl-1,3-dithiene by nuclear magnetic resonance and chemical degradation. It is probably formed via the intermediate thiodypnone[14] (**5**), since its formation is promoted



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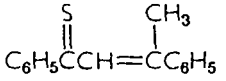
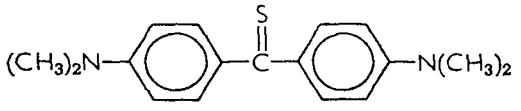


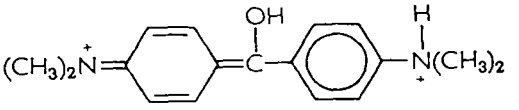
(**5**)

under conditions which favor chalcone formation. Some *para*-substituted acetophenones have yielded similar results[16].

A solution of Michler's ketone in anhydrous hydrogen fluoride, cooled to $-10°$ to $-20°$, treated with hydrogen sulfide for 2 h, and worked up from an aqueous solution, yielded red crystals of Michler's thioketone (**6**), m.p. 208–209° after recrystallization from chloroform, in nearly quantitative yield[7]. It is interesting that this com-

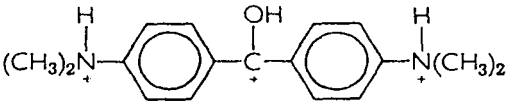


(**6**)



(**7**)

pound is not formed by hydrogen sulfide–hydrogen chloride treatment of the ketone in alcohol[17]. It seems likely that in alcoholic hydrochloric acid Michler's ketone is diprotonated to the relatively unreactive species **7** but in liquid hydrogen fluoride it picks up another proton to produce the reactive species **8**. The effect of acid

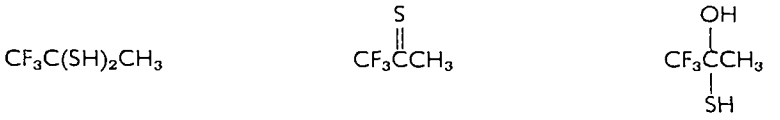


(**8**)

catalysis on the addition of hydrogen sulfide has been discussed by Elofson and coworkers[7].

Other products of addition of hydrogen sulfide, such as the olthiol or *gem*-dithiol, may be readily converted into the corresponding

thione in many cases. For example, treatment of 1,1,1-trifluoroacetone with hydrogen sulfide under pressure in the presence of phosphorus pentoxide produced a distillable oil, the *gem*-dithiol **9**[18]. Pyrolysis of **9** in a quartz tube at 550° *in vacuo* yielded the thioketone **10**, which was collected, along with hydrogen sulfide, in a



(9) (10) (11)

trap at −196°. This same reaction conducted in the presence of hydrogen chloride yielded 1,1,1-trifluoro-2-mercapto-2-propanol (**11**) which on distillation produced a mixture of **10**, trifluoroacetone, water, and hydrogen sulfide.

In certain cases only the enethiol or *gem*-dithiol has been obtained by treating ketones with hydrogen sulfide under acid catalysis. An interesting example is 1,1,3-triphenyl-2-propanone, which produced 1,1,3-triphenylpropene-2-thiol (**12**) in 90% yield under the usual conditions. **12** was a white crystalline solid, melting at 90–91°.

(12) (13)

That the compound exists only in the form **12** and does not contain any thione **13** is shown by the lack of color, quite uncommon in these systems, and by the n.m.r. spectrum, which shows no evidence of benzhydryl proton and gives a ratio of 1:2 for thiol to methylene protons[19]. Dibenzyl ketone, treated with hydrogen sulfide and hydrogen chloride in cold alcohol, yielded the *gem*-dithiol **14**[20,21] as a

(14) (15)

white crystalline product, which on heating or treatment with base loses hydrogen sulfide to form a red oil which has not been purified but is presumed to be principally **15** on the basis of its reactions. Some related compounds behave similarly[19]. The formation of enethiols in certain cyclic systems has been described by Campaigne and Moss[22].

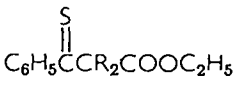
Mayer and Berthold[23] report a synthesis of thiones involving treatment of ketals with hydrogen sulfide in acetic acid containing

a trace of sulfuric acid (equation 2). The reaction has the advantage of being quite rapid; with aliphatic and alicyclic ketals good yields

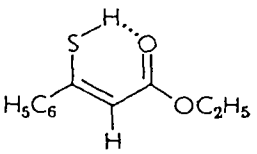
$$R^1_2C(OR^2)_2 + H_2S \longrightarrow R^1_2C{=}S + 2\,R^2OH \qquad (2)$$

of deep red oils, which were purified by distillation, were obtained in 15–20 min. These authors also found that treatment of the enol ether of acetophenone with hydrogen sulfide in aqueous hydrogen chloride containing zinc chloride (Lucas' reagent) gave **3** as a blue oil, b.p. 97–100°/12 mm.

β-Thioketo esters and monothio-β-diketones have been investigated because of their possible interest as chelating agents. This field has been the subject of an excellent review[24]. Efforts to form β-dithioketones by treatment of β-ketones with hydrogen sulfide in strong acid solution[25] led to the formation of dimers which were shown to have the tetrathiaadamantane structure[26]. β-Thioketo esters were formed in good yield when a cold alcoholic solution of the β-keto ester was treated with hydrogen sulfide and hydrogen chloride[27]. Ethyl thioacetoacetate, a red-orange oil, b.p. 75–80°/12 mm, was purified by precipitation as the lead salt and decomposition of this salt with hydrogen sulfide. More recently, Reyes and Silverstein[28,29] have prepared the ethyl thiobenzoylacetates (**16**) using a



(**16**)

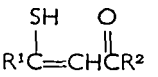


(**17**)

slight modification of Mitra's[27] procedure. They found that ethyl thiobenzoylacetate itself (**16**, R = H) was a blue distillable oil which existed largely as the enethiol chelate, **17**. Ethyl α,α-dimethylthiobenzoylacetate (**16**, R = CH_3) was a deep blue oil which did not form a precipitate with lead; it was purified by chromatography.

Chaston, Livingstone, and coworkers[24,30] reported the preparation of a series of monothio-β-diketones (**18**) and found conditions for their preparation rather critical. It was necessary to reduce the amount of hydrogen chloride drastically to produce the monothioketones **18b** to **18e**. Thus, following Mitra's method[27], an alcoholic solution of acetylacetone was saturated with hydrogen chloride for 30 min at −10°. Hydrogen sulfide was then passed through the solution for 6 to 10 h, resulting in a low yield of **18a** which was purified via

the lead salt. However, neither **18b** nor **18c** were obtained by this procedure; dimers or polymer resulted when benzoylacetone or



(**18a**, $R^1 = R^2 = CH_3$, golden yellow oil;
18b, $R^1 = CH_3$, $R^2 = C_6H_5$, orange crystals;
18c, $R^1 = R^2 = C_6H_5$, red crystals
18d, R^1 = 2-thienyl, $R^2 = CF_3$, red crystals;
18e, $R^1 = R^2 = C(CH_3)_3$, red-orange liquid)

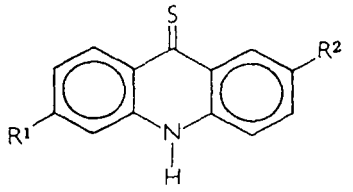
dibenzoylmethane was treated in this manner. An improved procedure involved first saturating a cold dilute alcoholic solution of the diketone with hydrogen sulfide and then passing a small amount of hydrogen chloride gas into the solution (5–10 min). In this way compounds **18b** to **18e** were obtained in 60–75% yields, via isolation as the lead salt, direct crystallization, or distillation. There appears to be a correlation between the concentration of hydrogen chloride in alcohol required to catalyze addition of hydrogen sulfide and the percent enol form of the diketone in alcohol. This would imply that the chelated enol tautomer does not react with hydrogen sulfide but that reaction occurs with the diketone. Higher concentrations of hydrogen chloride are required for those β-diketones which exist largely as enols in alcohol solution in order to shift the tautomeric equilibrium toward the diketo form. This observation is consistent with the conclusions regarding the formation of Michler's thioketone in strong acid, as described earlier.

b. Amine-catalyzed additions. Addition of hydrogen sulfide to imines and enamines occurs readily in certain cases. The base-catalyzed reactions of ketones with hydrogen sulfide has been discussed by Mayer and coworkers[31]. The products are usually *gem*-dithiols but in certain cases the thioketone may be obtained either directly or by decomposition of the *gem*-dithiol. Reddelien and Daniloff[32] prepared several diaryl thiones by treating the corresponding anil or anil hydrochloride with hydrogen sulfide (equation 3). The reaction was complicated by the hydrogen sulfide reduction

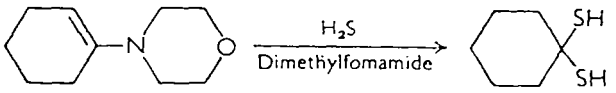
$$Ar_2C{=}NR + H_2S \longrightarrow Ar_2C{=}S + RNH_2 \qquad (3)$$

of the anil or thione to the corresponding diarylmethane. Tarbell[17] used the imine of Michler's ketone, auramine, adding hydrogen

sulfide to it in boiling ethanol, and obtained a 60% yield of **6**. 9-Aminoacridines, treated with hydrogen sulfide in alcoholic ammonium hydroxide solution, formed the corresponding 9-thioacridones (**19**)[34].



(**19**)

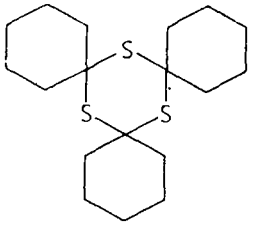


(**20**) (**21**)

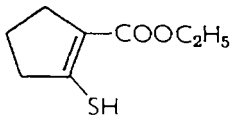
Mayer[31] reports that ammonia and primary, secondary, and tertiary amines are suitable catalysts for this reaction whereas alkali metal hydroxides and alkoxides are not. However, a tertiary amine was effective in only one example, and produced a very poor yield. Butylamine seemed to be the best catalyst, except for cyclohexanone and cyclopentanone, where morpholine was most effective. Polar solvents such as dimethyl sulfoxide, dimethylformamide, and methanol gave the best results. The yields are relatively poor, being less than 50% except for the cyclohexanone and cyclopentanone cases catalyzed by morpholine which gave *gem*-dithiols in 83 and 72% yields respectively. Benzophenone could not be converted into the thione by this method.

It seems quite probable that enamines are intermediates in this reaction. Djerassi and Tursch[35] found that treatment of the enamine **20** with hydrogen sulfide in dimethylformamide resulted in over 90% yield of cyclohexane-1,1-dithiol (**21**), a compound which had previously been obtained by treating cyclohexanone with hydrogen sulfide under pressure[36]. This reaction had been reported to yield cyclohexanethione[37] but the isolation of *gem*-dithiols under these reaction conditions has been confirmed by Mayer[31], who found, however, that certain ketones, namely acetophenone, cycloheptanone, and cyclohexyl methyl ketone, did produce the thione or

enethiol in low yield when treated with hydrogen sulfide in dimethylformamide, using butylamine as a catalyst. The reaction is quite susceptible to solvent effects as well as structural differences of the enamine. In a dimethylformamide–ether mixture **20** gave the trisspirotrithiane **22** rather than **21**[35]. Examination of a variety of



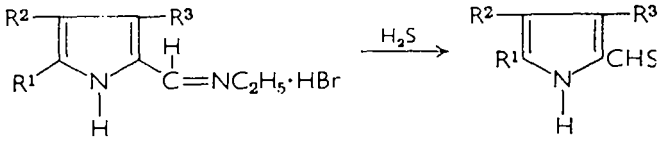
(**22**)



(**23**)

solvents indicates that dimethylformamide is the best choice for *gem*-dithiol formation[31]. Further studies on systems leading to more stable thiones are needed. The enamine method has recently been applied to a β-keto ester system[38], 2-morpholino-1-carbethoxycyclopentene being converted into the enethiol **23** by treatment with hydrogen sulfide in acetic acid. β-Diketones are also reported to yield monothio-β-diketones on treatment with hydrogen sulfide in the presence of morpholine[31] (see ref. 24, however) but α-diketones are reduced under these conditions.

The only well-characterized thioaldehyde which has yet been reported is a unique case reported by Woodward and coauthors[39], who treated the ethylimine hydrobromide of a complex pyrrole-2-aldehyde (**24**) with hydrogen sulfide in a benzene–methanol solution



(**24**) (**25**)

containing sodium methoxide and isolated the thial **25**, which proved useful in later condensations because of the high reactivity of the thiocarbonyl group.

2. Conversion of ketodichlorides into thiones

A convenient method for preparing some simple diaryl thiones involves treatment of the ketodichloride with bisulfide ion or a

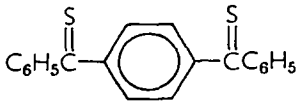
related sulfur nucleophile (equation 4). For example, treatment of a cold alcoholic solution of benzophenone dichloride under carbon

$$Ar_2CCl_2 + 2\,SH^- \longrightarrow Ar_2C{=}S + H_2S + 2\,Cl^- + KCl \qquad (4)$$

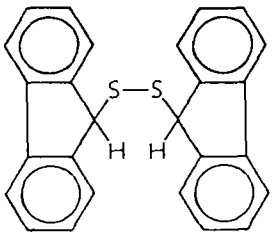
dioxide with sodium bisulfide in alcohol yields thiobenzophenone in 50–63% yield[40]. While better yields have been obtained by the hydrogen sulfide/hydrogen chloride method[9], it is likely that the yields in this reaction would be improved if the reaction were run under nitrogen, since a reaction between carbon dioxide and bisulfide ion can interfere. For example, Schönberg and Frese[41] obtained diaryl thiones in over 90% yield by refluxing ketodichlorides with potassium ethyl xanthate in petroleum ether (equation 5). Several

$$Ar_2CCl_2 + KSCSOC_2H_5 \longrightarrow Ar_2C{=}S + ClCSOC_2H_5 \qquad (5)$$

new thiones were prepared in this way, including 1,4-dithiobenzoylbenzene (**26**), a dark blue-green solid.



(**26**)



(**27**)

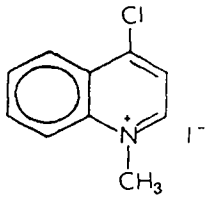
Care must be taken to maintain the ketodichloride in excess during the course of the reaction, as excess bisulfide causes reduction of the thione. Smedley[42] treated 9,9-dichlorofluorene with potassium bisulfide and obtained what he thought was the dimer of thiofluorenone (**2**), but the compound was later shown by Bergman and Hervey[43] to be the disulfide **27**. Benzhydryl disulfide was obtained in 70% yield when benzophenone dichloride was added to excess bisulfide solution[40].

A useful variation of this reaction is to reflux the ketodichloride in thioacetic acid (equation 6). This reaction has been applied to simple diaryl thiones[44] but has proved to be most useful in heterocyclic cases, particularly the thioxanthiones and xanthiones (cf. ref. 45 *et seq.*).

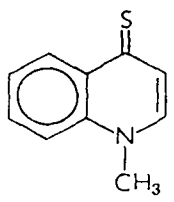
$$Ar_2CCl + CH_3COSH \longrightarrow Ar_2C{=}S + HCl + CH_3COCl \qquad (6)$$

The method of choice for the synthesis of thiopyridones and related compounds is to treat the corresponding chloropyridinium

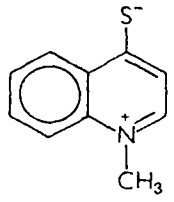
salt with a thiolating agent such as bisulfide, thiosulfate, or thiourea[46]. For example, refluxing 4-chloroquinoline methiodide (**28**) with a slight excess of sodium hydrosulfide resulted in the isolation of **29** in 97% yield. Spectral data confirm the prediction that **29b** represents



(**28**)

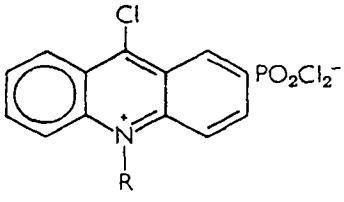


(**29a**)

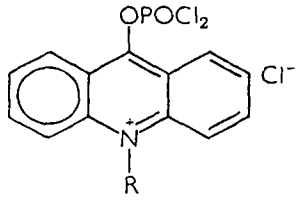


(**29b**)

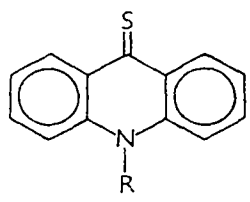
the major contributing structure of these molecules. Gleu and Schaarschmidt[47] found that the chloroacridinium dichlorophosphates (**30a** or **30b**) were highly reactive, forming the thioacridones (**31**) in nearly quantitative yield with sodium thiosulfate, a reagent which did not react with nonquaternarized chloroacridines.



(**30a**)



(**30b**)

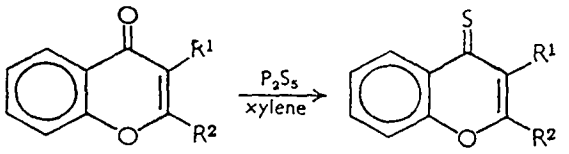


(**31**)

3. Treatment of ketones with phosphorus pentasulfide

Thioamides are readily formed from amides by heating with phosphorus pentasulfide, but conversion of a simple ketone into a thione by this method is limited by side-reactions. It has, however, proved quite useful in the preparation of heterocyclic thiones, which may be regarded as vinylogs of amides or esters. Some of the earlier investigators used phosphorus trisulfide to prepare thioborneol, thiocamphor, etc., (cf. refs. 1 and 2) but the thiones or enethiols were not well characterized. Legrand[48] has described the preparation of a series of thiochromones (**33**) in 60–75% yield by refluxing the chromones **32** in xylene with phosphorus pentasulfide. Removal of solvent followed by recrystallization results in crystalline red to violet thiones (**33**). Other examples have been reviewed[1,2,49].

Treatment of aryl aldehydes and aryl alkyl ketones under these

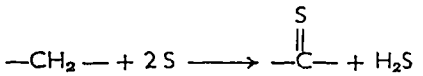


(32) (33)

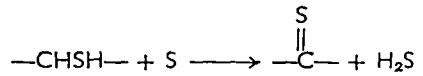
conditions led to the formation of more complex compounds[50], which may have been formed by way of thione intermediates. Some diaryl thiones are reported by Lozac'h and Guillouzo[51], who prepared them by refluxing the ketone with phosphorus pentasulfide in xylene and distilling the resulting thione. No yields are given for these preparations, however.

B. Oxidative Methods of Forming Thiones

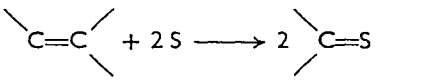
In theory it should be possible to form the thione group by sulfurizing a carbon atom with sulfur (equations 7, 8, and 9) in the same way as the ketone group can be formed in oxidation reactions. In fact examples of all these reactions are known, but only examples



(7)

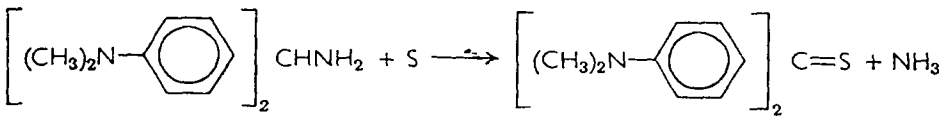


(8)



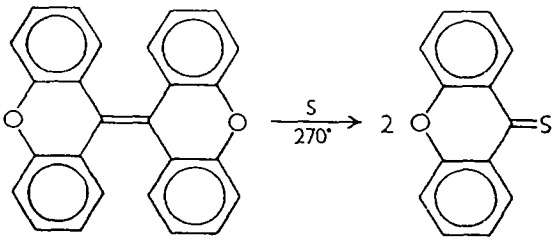
(9)

of equation (9) have been useful in the general preparation of thiones in suitable yield and reasonable purity. Several of the older examples of equation (7) may be found in Schönberg's review[1]. The yields are apt to be low, however[17]. Moreau[33] found that reaction (7) was base-catalyzed, and isolated dibenzhydryl polysulfide along with thiobenzophenone, when diphenylmethane was allowed to react with sulfur, indicating that benzhydrylthiol was an intermediate (equation 8). While no direct example of equation (8) is available, a related reaction is the conversion of leukauramine into Michler's thioketone (equation 10) by sulfur[52] in about 60% yield.



(10)

Schönberg and Askar[53] investigated the reactions of sulfur with ethylenes and found that a variety of heterocyclic ethylene derivatives underwent this reaction[45]. For example, heating dixanthylene (**34**) to 270° with sulfur gave the thione **35** in about 80% yield. On



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

the other hand, tetraarylethylenes, like tetraphenylethylene and tetra-*p*-dimethylaminophenylethylene, failed to yield thiones by this procedure. The reaction seems limited to the synthesis of thio- and dithiopyrones.

One would expect the phosphorus ylides to react with sulfur to produce thioketones and phosphorus sulfides. Although there has been much recent work on these phosphorus compounds, they have apparently not been examined extensively in this regard. However, Staudinger and Meyer[54] reported that sulfur heated with the phosphorus derivative **36** gave triphenylphosphine sulfide and thiobenzophenone.

$$\underset{(\mathbf{36})}{(C_6H_5)_3P{=}C(C_6H_5)_2} \xrightarrow{2\,S} (C_6H_5)_3PS + (C_6H_5)_2CS$$

C. *Thiones from Acid Derivatives*

The preparation of diaryl ketones from phosgene and aromatic compounds by the Friedel–Crafts reaction (equation 11) is common practice but the reaction illustrated by equation (12) has been much

$$2\,ArH + COCl_2 \xrightarrow{AlCl_3} Ar_2CO + 2\,HCl \qquad (11)$$

$$2\,ArH + CSCl_2 \xrightarrow{AlCl_3} Ar_2CS + 2\,HCl \qquad (12)$$

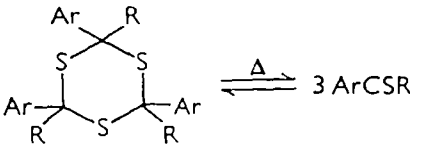
less exploited. Gatterman[55] prepared a variety of alkoxythiobenzophenones by this means but the yields were low and some of the products were of questionable purity. The instability of the product is detrimental to the use of such vigorous conditions. The reaction did not take place with benzene itself. Activation of the aromatic

ring by electron-releasing groups such as alkoxy seems necessary in this case. In contrast Vorländer and Mittag[56] obtained a reasonable yield of thiobenzophenone when aluminum chloride was added to a benzene solution of perchloromethyl mercaptan (Cl_3CSCl). Since this compound is now commercially available, it might be desirable to reinvestigate this reaction.

D. Pyrolysis of Sulfur Derivatives

1. Pyrolysis of trithianes

A number of trithianes, particularly those carrying aryl groups, can be decomposed by heat to the monomeric thiones (equation 13). This is a reversible reaction and is only useful as a preparative



(37) (38) (13)

method where both forms may be isolated. Most alkyl-substituted trithianes are so stable that no monomer is produced. For example, trithiane itself can be distilled *in vacuo* as a water-white liquid which resolidifies to the white solid trimer melting at 219–220° without decomposition. On the other hand, thiobenzophenone may be stored for years under carbon dioxide as brilliant blue monomeric crystals and no trimer has ever been reported. All the trimeric thioacetophenones (**37**, R = CH_3) mentioned in the literature[16] dissociate to deep purple oils above their melting points. The most convenient preparation of these monomers, which must be protected from oxidation by air during isolation, requires preparation of the trimer, which is easily purified by recrystallization under ordinary conditions, followed by a flash distillation of the monomer under nitrogen or carbon dioxide[12,57]. The deep purple oils so obtained rapidly become milky in appearance and set to white solid trimers again. Thioacetophenone exhibits characteristic thiocarbonyl reactions (*vide infra*) when the purple oil is distilled directly into typical reagent solutions, whereas the trimer is quite stable to these reagents[57].

The yellow dimer dithiofluorenone forms a brilliant green melt above 227°, this being the characteristic color of the monothione, but on cooling it resolidifies to a yellow solid[11,57].

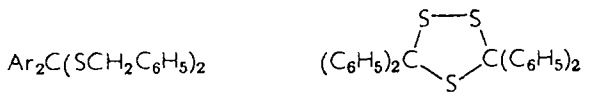
2. Pyrolysis of other sulfur compunds

The pyrolysis of *gem*-dithiols (equation 14) has been discussed in

$$R_2C(SH)_2 \xrightarrow{\Delta} R_2CS + H_2S \qquad (14)$$

sections II.A.1 and A.2. It is less satisfactory as a synthetic method since the hydrogen sulfide which is produced is a reducing agent and causes further complicating reactions (cf. refs. 18 and 31). This difficulty may be avoided by first condensing the dithiol with malononitrile to form a stable 4-amino-5-cyano-1,3-dithiolene, which may then be decomposed above 130° to the monomeric thiones in 70–90% yield[58].

The pyrolysis of a variety of sulfur derivatives may lead to the formation of thiones in the most unexpected ways. These have been adequately reviewed[1], but a few examples will be given to illustrate the point. It should be emphasized that alternative better ways of preparing the thiones are usually available. Schönberg[59] has shown that vacuum distillation of molten mercaptoles (**39**) produces the



(**39**) (**40**)

corresponding thiones, as does similar treatment of the tetraaryl-substituted 1,2,4-trithiolanes (**40**)[8]. A surprising case is illustrated by equation (15), in which a tetraarylethanethiol disproportionates to a

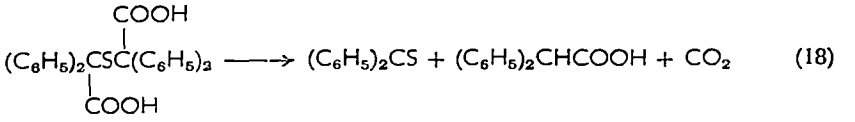
$$Ar_2CHCSHAr_2 \xrightarrow{\Delta} Ar_2CH_2 + Ar_2CS \qquad (15)$$

diarylmethane and a diarylthione. Several examples of this have been observed[60].

Similar disproportionations of sulfides (equation 16) and disulfides[61] (equation 17) have been observed. An interesting example has been examined by Barkenbus and Brower[62]. Tetraphenylthiodiacetic acid formed thiobenzophenone, diphenylacetic acid, and carbon dioxide on standing in pyridine or quinoline, or on warming

$$Ar_2CHSCHAr_2 \longrightarrow Ar_2CH_2 + Ar_2CS \qquad (16)$$

$$Ar_2CHSSCHAr_2 \longrightarrow Ar_2CH_2 + Ar_2CS + S \qquad (17)$$

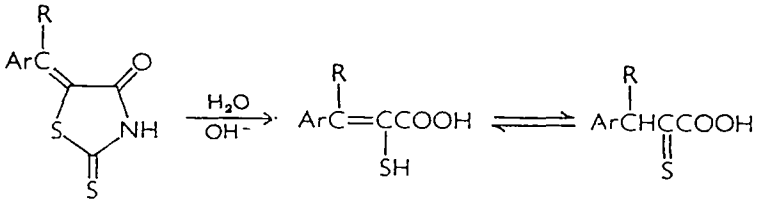


in benzene (equation 18). A free-radical mechanism was proposed to explain this reaction but a cyclic mechanism seems more likely.

E. Condensation Reactions

1. α-Thioketo acids by condensation of rhodanine

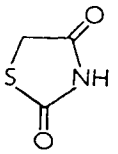
An aldehyde or ketone condenses with rhodanine in acetic acid–sodium acetate mixture to give the corresponding ylidenerhodanine (**41**), which on alkaline hydrolysis yields the thiopyruvic acid **42**, a substance which exists chiefly in the enethiol form[63]. The yields are



(**41**) (**42**)

excellent, but great care must be taken in the hydrolysis step to prevent the readily occurring further hydrolysis to the corresponding pyruvic acid. The thiopyruvic acids **42** are useful intermediates in a variety of syntheses. The general reaction has been reviewed[2] and some more complex examples have been described[64]. The evidence for the enethiol structure of **42** rests heavily on the ultraviolet absorption spectra, which are characteristic of cinnamic acids[63]. However, it seems quite likely, on the basis of relative intensities of the ultraviolet absorption peaks of the free acid and its corresponding disulfide (formed by oxidation of the thiol group in **42**), that some of the thione form is indeed present. The relative effect of mercapto and disulfide groups on the ultraviolet absorption spectra of conjugated chromophores of this and related types has been examined[63,65,66], but more quantitative work on the tautomeric system **42** is needed.

An alternate procedure, using thiazolidinedione (**43**) in the place of rhodanine, has been stated to have advantages by Libermann and



(**43**)

coworkers[67], chiefly in the ease of hydrolysis, but this method does not appear to have been widely used.

2. The Claisen condensation

β-keto esters are frequently synthesized via the Claisen condensation (cf. Chapter 5, section H.1.b). Since this is usually base-catalyzed, attempts to apply it to thiocarbonyl systems have failed, probably because of side-reactions or the further decomposition of products. However, Kostir and Kral[68] reported that treatment of ethyl thionacetate under Claisen conditions gave a 30% yield of ethyl dithionoacetoacetate (equation 19). However, further work along this line has not come to our attention.

$$CH_3CSOC_2H_5 \longrightarrow CH_3CSCH_2CSOC_2H_5 \qquad (19)$$

III. PHYSICAL PROPERTIES OF THE THIOCARBONYL GROUP

A. *Bond Distances, Bond Energies, etc.*

It should be emphasized that because of the instability of the thiocarbonyl group in 'pure' thiones, there are few data on the basic physical structure of these compounds. Leermakers and Weissberger[69] summarized the available data on C=S structures, based on the thiocarbonyl bond in carbon disulfide, thiourea, thiophosgene, etc. Since other properties of these thiocarbonyl compounds differ from those of thiobenzophenone, thioacetophenone, and related structures, it is likely that there will be differences in these basic physical properties also. The valence orbitals of sulfur have been discussed[70] and it was pointed out that $2p$–$3p$ π bonds are less stable than $2p$–$2p$ π bonds. Still, the $2p$–$3p$ π bond of the thiocarbonyl group makes an exceptionally large contribution to molar refraction and ultraviolet absorption.

The interatomic distance in C=S, based on average atomic radii of 0·67 Å for double-bonded carbon and 0·94 Å for sulfur, is 1·61 Å compared to 1·26 Å for C=O. Electron-diffraction measurements on carbon oxysulfide indicate 1·56 Å for C=S and 1·16 Å for C=O, and similar measurements on carbon disulfide give 1·54 Å for C=S. The C=S bond energy, based on an average value for all *like* bonds (?), is 103 kcal/mole as contrasted to 152 kcal/mole for C=O.

The dipole moment can give some indication of the polarity of the molecule. The dipole moment of thiobenzophenone in benzene at 20° is 3·40 D[71] as contrasted to 2·5–3·0 for benzophenone measured

in benzene at related temperatures. Lüttringhaus and Grohmann[72] compared the moments of several thiobenzophenones and benzophenones (Table 1). Since there is a lesser difference in electro-

TABLE 1. Dipole moment of some thioketones and ketones (in benzene)[72].

Ar	Dipole moment (D)	
	Ar_2CS	Ar_2CO
p-$(CH_3)_2NC_6H_4$	6·12	5·16
p-$CH_3OC_6H_4$	4·44	3·90
C_6H_5	3·37	2·95
p-$CH_3C_6H_4$	3·45	3·45
p-ClC_6H_4	1·58	1·79
p-BrC_6H_4	1·71	1·93

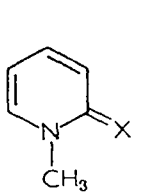
negativity of the atoms in the C=S bond as compared to C=O, one might expect a lower dipole moment for the former. However, the higher moment frequently observed is consistent with a more highly ionized bond in the thione case.

The dipole moment of thioacetoacetic ester has been measured in benzene, hexane, carbon tetrachloride and carbon disulfide[73]. The observed values ranged from 2·2–2·4 D, which these authors believe fit the calculated value for a mixture of predominantly *trans*-thioketo–*trans*-enethiol tautomers. Spectroscopic data (cf. Reyes and Silverstein[28]) do not substantiate this conclusion.

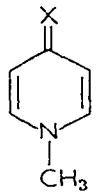
B. Infrared Spectral Data

Until recently little information was available on the position of thiocarbonyl bands in the infrared. Most of the available information was based on thioamides and related structures, which are stable and convenient to handle. Spinner[74], in a careful study of thioamides and their vinylogs, found that the frequency of the unperturbed thiocarbonyl stretching vibration occurs at 1140 ± 80 cm^{-1}, in agreement with semiempirical calculation. Conjugated C=S groups were found to give rise to absorption bands as intense as carbonyl stretching bands. For example, the infrared spectra of **44** and **45** (X = S) were compared to those of the corresponding carbonyl compounds (X = O). Strong absorptions in the range 1110–1145 cm^{-1} were observed in the spectra of the thiocarbonyl derivative, while the

carbonyl compounds showed only weak absorption in this region ($\varepsilon = 60$). No other band characteristic of C=S, and absent from the spectra of C=O derivatives, was found. The maximal intensity



(44)



(45)

observed for **45** (X = S) is among the highest recorded for infrared absorption bands.

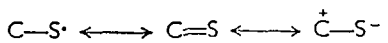
The characteristic band for diaryl thiones was found to be at the high end of the region assigned by Spinner to thiocarbonyl absorption in a study by Lozac'h and Guillouze[51]. These workers studied a series of diaryl thiones, both symmetrical and unsymmetrical, prepared by the phosphorus pentasulfide method and distilled. These compounds all showed a strong band in the 1207–1225 cm^{-1} range.

A series of monothio-β-diketones were studied in this regard[24], and a strong band at 1190–1269 cm^{-1} in the monothiodiketones and a more intense band at 1220–1261 cm^{-1} in the nickel chelates of these compounds was assigned to C=S stretching. Bellamy has summarized the recent data[75] and reports a wide range of intense bands in the region 1025–1400 cm^{-1} for a wide variety of thiocarbonyl structures.

C. Ultraviolet and Visible Spectral Data

1. The K and R bands

The characteristic intense color of thiones has attracted a number of studies on ultraviolet absorption[10,29,76–78]. The colored thiones vary from deep blue for thiobenzophenone to red-orange for the nitrogen-conjugated systems such as 4-thioquinolone. It is clear that this color is associated with the resonance system **46**, and that those



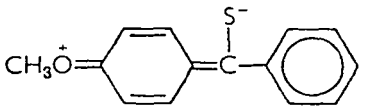
(46a) (46b) (46c)

compounds exhibiting the red colors are those in which **46c**, stabilized by conjugation, is a major contributor. The red color is characteristic of systems containing a vinyl thiol group in conjugation, for

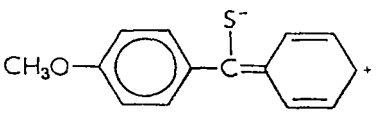
example structures **12**, **15**, and **18**. While **1** is deep blue, **3** is clearly violet, showing the shift toward the red color.

The electronic spectra of thiocarbonyls has been discussed in some detail by Burawoy and coworkers[76,77]. Thiobenzophenone in hexane shows three characteristic bands, at 233 mμ (ε = 8000), 315 mμ (ε = 17,800), and 609 mμ (ε = 184). The intense *K* (conjugation) band at 315 mμ is associated with the polarizing transition (**46b** ↔ **46c**), while the low-intensity long-wavelength absorption *R* (radical) band at 609 mμ is caused by the $\pi^* \leftarrow n$ transition (**46a** ↔ **46b**). Hydrogen-bonding solvents and others of high polarity cause the *K* band to shift to a longer wavelength. A similar effect is observed when electron-releasing groups such as alkoxy or dialkylamino are placed in a conjugative position in the molecule, causing an increase in polarization and/or polarizability.

Unsymmetrical substitution of such groups has been the subject of some interest[76,78], since the *K* band is now split into two bands associated with the two chromophores, as for example in **47a** and



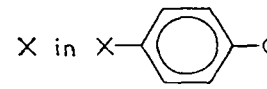
(**47a**)



(**47b**)

47b. The two bands will not necessarily be of the same intensity, since the steric and electronic requirements of the two substituents differ. A related series is listed in Table 2 to illustrate these effects.

TABLE 2. Ultraviolet absorption spectra of unsymmetrical thiones[a].

X in 	K_1mμ(ε)	K_2mμ(ε)
H	316·5 (ε = 15,600)	
CH_3O	359 (12,100)	322 (9000)
HO	368 (16,000)	317 (10,800)
^-O	450 (32,600)	306 (6600)

[a] Taken in ethanol, cf. ref. 76.

Hydrogen-bonding solvents and substituents which make electrons available to the system cause a characteristic 'blue' shift of the *R* band to a shorter wavelength, while electron-withdrawing groups have the opposite effect. Some solvents have an anomalous effect on

this band, suggesting the formation of a specific and perhaps novel association between the thione function and solvent[70], but the nature of this association is not clear.

2. Optical rotatory dispersion

The report that certain steroidal thiones are relatively stable[80] prompted Djerassi and Herbst[79] to examine the optical rotatory disperson curves of these compounds. The rotatory dispersion curve of 2-thionoprogesterone was found to be completely different from that of progesterone itself. The 20-keto group of progesterone exhibits a strongly positive Cotton effect with a peak near 320 mμ, while the 2-thiono analog exhibits this strong positive peak in the visible region, with little effect on the fine structure of the 350 mμ region due to the Δ^4-3-ketone. Because of the instability of thiones, it has not been possible to test the general applicability of the octant rule to this class of compounds, but it has been shown that the long wavelength *R* band of thiones can show optical activity.

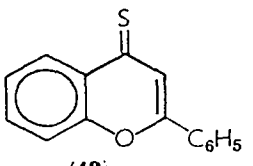
IV. REACTIONS OF THIONES

A. Addition Reactions

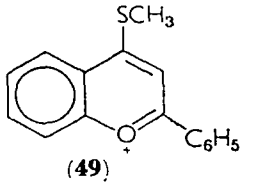
1. Nucleophilic addition

The strongly polar character of the C=S bond makes it quite susceptible to nucleophilic addition, and this property may be turned to advantage in syntheses (cf. ref. 39). The thiocarbonyl group is readily hydrolyzed in acidic or basic solution and reacts rapidly with amines to form Schiff bases and with the usual carbonyl reagents (hydroxylamine, semicarbazide, etc.) to form the known derivatives. Powers and Westheimer[81] showed that thiobenzophenone reacts with phenylhydrazine at pH 4 ten times faster than benzophenone, and at pH 6 about 2000 times faster, the difference becoming much larger in alkaline solution. Anils and imines of flavones have been readily prepared via the thioflavones[82].

The elimination of sulphur from the thione group is greatly enhanced by conversion into the alkymercapto salt by reaction with



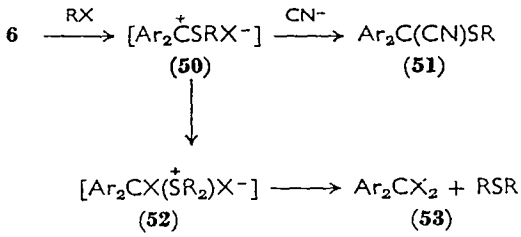
(48)



(49)

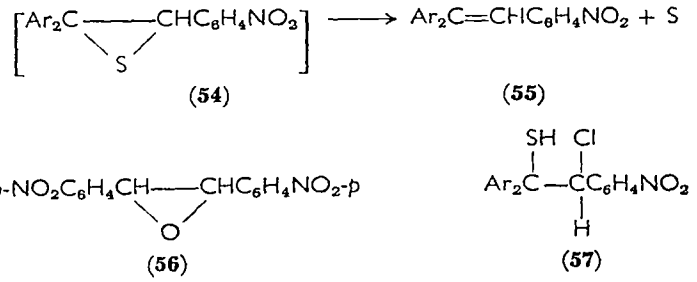
an alkylating reagent. For example, the thionoflavone **48** is not hydrolyzed by boiling water but its methiodide **49** rapidly eliminates methyl mercaptan under these conditions to form the flavone[49]. The salt **49** also reacted rapidly with a variety of amines in the cold to form the corresponding imines. Heterocyclic thiones usually form stable alkylmercapto salts, which may be isolated and are useful in further synthetic reactions[83,84] but simple thiones usually undergo further reactions with alkylating reagents.

Michler's thioketone (**6**) was found to react with ethyl iodide and cyanide ion to form the alkylmercapto nitrile **51** by attack of the cyanide on the intermediate salt **50**. A similar salt was also postulated for the conversion of **6** by benzyl chloride into the ketodichloride **53** and dibenzyl sulfide. In this case the salt **50** must react with a second molecule of benzyl chloride to produce a sulfonium salt (**52**) from which chloride ion displaces the sulfide[2]. The reactions are summarized in equation (20). Compound **6** produced a different product with *p*-nitrobenzyl chloride in the presence of base[43]. In this case the



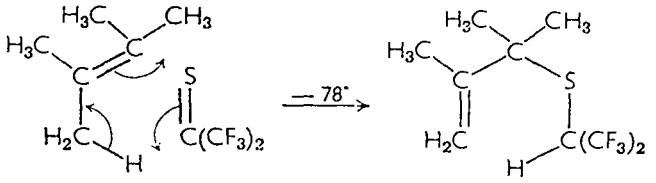
(20)

ready formation of a carbanion on the α-carbon of the *p*-nitrobenzyl group caused an intramolecular condensation of the intermediate ion **50** to form the unstable ethylene sulfide **54**, which loses sulfur to produce the unsymmetrical stilbene **55**. Since *p*-nitrobenzyl chloride condenses directly with *p*-nitrobenzaldehyde to form the epoxide **56**, an alternate mechanism, involving the chloroethylthiol **57**, has also been suggested[85].



The reactivity of the thiocarbonyl group is illustrated by its

susceptibility to addition by hydrocarbons having allylic or benzylic hydrogens. Schönberg[61] first showed that fluorene or xanthene could be condensed with a diaryl thione to form the ethylene with elimination of hydrogen sulfide. Hexafluorothioacetone is extremely reactive, combining with olefins having allylic hydrogen atoms even at low temperatures[86]. For example, tetramethylethylene formed



(58)

the allyl sulfide **58** rapidly at −78°. A cyclic mechanism was proposed to account for this facile reaction. Moreau[87] restudied the condensation of hydrocarbons such as xanthene, fluorene and diphenylmethane with thiones. When diphenylmethane and thiobenzophenone were heated together, tetraphenylethane, as well as tetraphenylethylene, was obtained (equation 21). Moreau proposed

$$(C_6H_5)_2CH_2 + (C_6H_5)_2CS \longrightarrow (C_6H_5)_2C{=}C(C_6H_5)_2 + (C_6H_5)_2CHCH(C_6H_5)_2 + H_2S \quad (21)$$

a free-radical mechanism to account for the formation of the reduced product but the possibility of direct reduction of the ethylene by hydrogen sulfide under the conditions of the reaction was not eliminated.

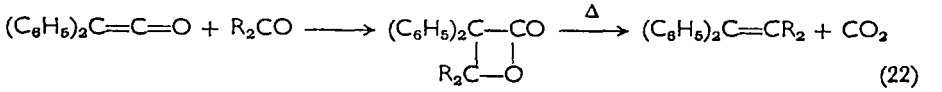
2. Formation of complexes with heavy metal salts

In contrast to ketones the thiones form quite stable complexes with salts of heavy metals. For example, the mercuric chloride complex is frequently used for purification and may serve as a useful derivative of unstable thiones[11,101]. These compounds are readily hydrolyzed in water, and may be represented as $[Ar_2CSHgCl]^+Cl^-$. However, under certain conditions, the ratio of metal salt to thione may be other than 1:1, varying with the nature of the solvent as well as with the salt and structure of the thione. For example, in fuming hydrochloric acid, 2,3-dimethyl-4-thiochromone gave $(Ar_2CS)_2 \cdot HgCl_2$ but in ether or absolute alcohol $Ar_2CS \cdot HgCl_2$ was isolated. In fuming hydrochloric acid the ratio of thione to metal salt was 2:1 for platinic chloride, 1:2 for bismuth iodide, and 3:1 for gold

chloride. There has been little recent work on these complexes; the earlier literature has been summarized[1,2].

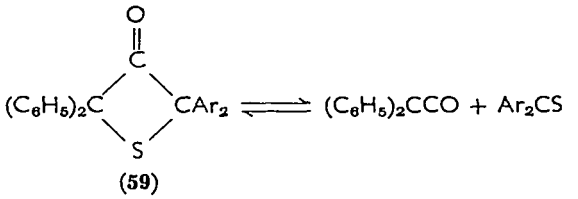
3. Dipolar additions

The thiocarbonyl group is especially susceptible to dipolar addition and several examples are known in which the corresponding addition to the carbonyl group does not occur or occurs in a different manner. Diphenylketene, for example, reacts with a ketone to produce a β-lactone which decomposes to carbon dioxide and a substituted ethylene on heating (equation 22). Although *p,p'*-tetra-



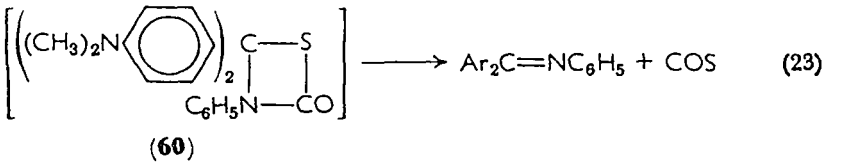
(22)

methyldiaminothiobenzophenone (**6**) reacts with diphenylketene in a similar manner, producing carbon oxysulfide and the ethylene derivative (the β-thiolactone could not be isolated), thiobenzophenone and *p,p'*-dimethoxythiobenzophenone behaved differently in this reaction, forming the tetrasubstituted thietanone **59**[8,88]. The heterocyclic ketone **59** dissociated on melting but recombined on



(**59**)

cooling; this was useful in purifying thiones. Michler's thioketone (**6**) also reacts with phenyl isocyanate to produce the anil and carbon oxysulfide, possibly through the unstable intermediate **60** (equation 23)[89], but further studies to determine whether other thioketones

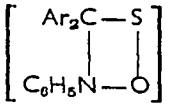


(**60**)

(23)

behave differently have apparently not been made. A similar condensation of nitrosobenzene with thiobenzophenone or *p,p'*-dimethoxythiobenzophenone led to the isolation of the corresponding anil, sulfur dioxide, and sulfur[90]. The interesting heterocycle **61**

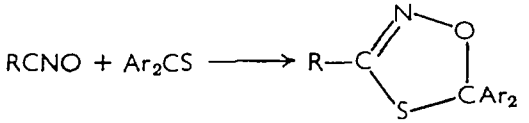
was suggested as an intermediate, which could eliminate sulfur monoxide, a substance which would disproportionate to sulfur and sulfur dioxide.



$$\longrightarrow Ar_2C{=}NC_6H_5 + SO_2 + S \qquad (24)$$

(61)

Huisgen[91] has described a variety of 1,3-dipolar additions, several involving the addition to thiones to produce sulfur-containing heterocycles. For example, nitrile oxides react readily with thiobenzophenone or di-*p*-anisyl thioketone to form the 4-oxa-1,3-thiazoles **62** (equation 25)[92]. The reaction of azides with thiones probably takes

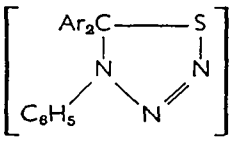


(25)

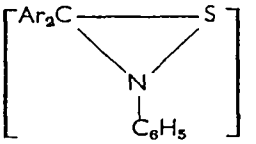
(62)

a similar course. Ketones do not react with azides, but thiones react readily to form Schiff bases, with the evolution of nitrogen and sulfur[93] (equation 26). The reaction occurs with thiobenzophenone,

$$C_6H_5N_3 + Ar_2CS \longrightarrow C_6H_5N{=}CAr_2 + N_2 + S \qquad (26)$$



(63)



(64)

di-*p*-anisylthioketone, and xanthione, and a variety of azides. While it presumably proceeds through formation of the dipolar adduct **63**, the possibility of nitrene addition to form an unstable intermediate **64** exists.

4. Addition of organometallic compounds

The reaction of diphenylmethylsodium with aromatic ketones and thioketones was shown to follow similar courses, but the mercaptans lost hydrogen sulfide more readily than the alcohols were dehydrated so that the ethylene was usually isolated from the thione reactions

(equations 27 and 28)[94]. Thiobenzophenone, *p,p'*-dimethoxythiobenzophenone and Michler's thioketone all react in this way.

$$(C_6H_5)_2CHNa + Ar_2CO \longrightarrow (C_6H_5)_2CHCHOHAr_2 \quad (27)$$

$$(C_6H_5)_2CHNa + Ar_2CS \longrightarrow (C_6H_5)_2C{=}CAr_2 + H_2S \quad (28)$$

The less-hindered thiones probably react with Grignard reagents in the normal way. Monothioacetophenone gave a low yield of 1,1-diphenylethylene with phenylmagnesium bromide, but the reaction was complicated by formation of benzene from the enethiol and Grignard reagent[57]. On the other hand, the diaryl thiones apparently are reduced by both aryl and alkyl Grignard reagents, forming tetraarylethylene sulfides (equation 29)[95].

$$2\,Ar_2CS + 2\,RMgX \longrightarrow Ar_2C\underset{S}{\diagdown\!\diagup}CAr_2 + RR + MgX_2 + MgS \quad (29)$$

B. Reduction of Thiones

1. Hydrogen additions

The thiocarbonyl group is readily reduced by metal–hydrogen donor systems, forming either the thiol, the methylene derivative, or coupled product. For example, reduction of thiopyruvic acids with sodium amalgam in water formed the α-mercaptopropionic acids in yields of 22–92% (equation 30)[96]. Reduction of thiopyruvic acids

$$ArCH_2CSCOOH \xrightarrow[H_2O]{Na/Ng} ArCH_2CHSHCOOH \quad (30)$$

$$ArCH_2CSCOOH \xrightarrow[HCl]{Zn} ArCH_2CH_2COOH \quad (31)$$

(equation 31) or diaryl thiones with zinc and hydrochloric acid converted the C=S group into CH_2. Schönberg[97], however, obtained a coupled product, 9,9'-bixanthyl, when xanthione was reduced by zinc in glacial acetic acid. In these reactions the thione group seems to behave like a normal ketone.

Basic reductions of thiones give different results from ketones under certain conditions. Reduction of thiobenzophenone with sodium borohydride in alcohol to the thiol proceeds ten times faster than the similar reduction of benzophenone[81]. Westheimer attributes this to the greater stability of the $(C_6H_5)_2CHS^-$ ion over the corresponding oxide ion. This may also account for the fact that reduction of thiones with ammonium bisulfide leads to disulfides

(equation 32), while similar reduction of ketones forms pinacols[98]. Similarly, hexafluorothioacetone reacts differently than acetone with aqueous tetramethylammonium bisulfite, forming the Bunte

$$2\,(C_6H_5)_2CS \xrightarrow{(NH_4)HS} (C_6H_5)_2CHSSCH(C_6H_5)_2 \qquad (32)$$

salt **65** rather than the usual bisulfite addition product[86]. The higher reactivity of thioketones over ketones has led Westheimer[10] to study

$$(CF_3)_2CHSSO_3^-N^+(CH_3)_4$$
(65)

their reduction to thiols by a coenzyme model, 1-benzyl-1,4-dihydronicotinamide. These studies lead to the conclusion that the hydrogen atom is transferred, with its electron pair in a bimolecular rate-controlling step, to the carbon atom of the thione. A similar reaction was not observed with structurally related ketones.

2. Coupling reactions

a. Reactions with metals. One of the most interesting reactions which distinguishes thiones from ketones is the coupling reaction which occurs when thiones are heated in inert solvents with certain metals (equation 33). This is one of the earliest reactions of thiones

$$Ar_2CS + 2\,M \longrightarrow \left[\begin{array}{c} Ar_2C \text{———} CAr_2 \\ | \qquad\quad | \\ S \qquad\quad S \\ \diagdown \quad / \\ M \end{array}\right] \longrightarrow Ar_2C{=}CAr_2 + MS \qquad (33)$$

(66)

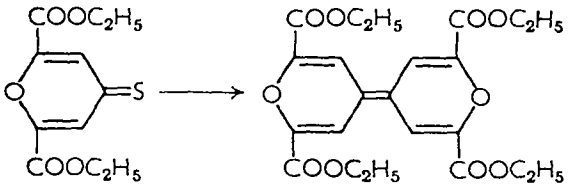
investigated; the literature has been summarized[1-3]. The most commonly used metals were copper powder, iron powder, and zinc dust, but more recent studies have shown that dehydrogenated Raney nickel[99], silver, antimony, and bismuth are effective for reaction in difficult cases. In the coupling of thioacetophenone (**3**) to form *trans*-α,α'-dimethylstilbene, copper was not effective but

$$3 \xrightarrow[\Delta]{\text{Metal}} C_6H_5\overset{\displaystyle CH_3}{\overset{|}{C}}{=}C\overset{\displaystyle CH_3}{\overset{|}{C}}C_6H_5 \qquad (34)$$

bismuth powder, freshly prepared by reduction of the oxide in a stream of hydrogen, resulted in a 35% yield[57]. The reaction may well proceed by way of a dithiol salt such as **66**, since it is best catalyzed by metals which form highly insoluble sulfides, like

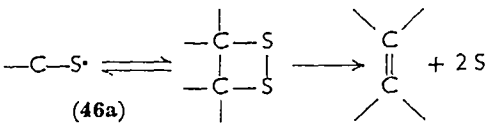
copper, zinc, nickel, and bismuth. The decomposition of **66** may then proceed via the formation of an ethylene sulfide, which is easily decomposed by heat and in the presence of a sulfur-accepting metal, to the ethylene. In fact such sulfides were isolated when diaryl thiones were reduced with magnesium (I) iodide[100], and some of these were unstable, losing sulfur spontaneously.

b. Coupling by heat. Similar coupling reactions occur with certain thiones merely on heating. Sulfur is eliminated and the ethylene is obtained. The reaction is especially facile for some heterocyclic thiones. For example, diethyl 4-thiochelidonate (**67**) was converted into the dipyrylene derivative **68** at its melting point (51°)[101]. The reaction is facilitated by carbethoxy or phenyl groups in the 2- and 6-positions of thiopyrones and dithiopyrones, and therefore seems to



(**67**) (**68**)

occur most readily with those thioketones in which the dipolar character is decreased. This suggests that the reaction occurs by association of the biradical **46a**, whose concentration is enhanced over that of the dipole **46b** (section III.C.1), in those compounds which

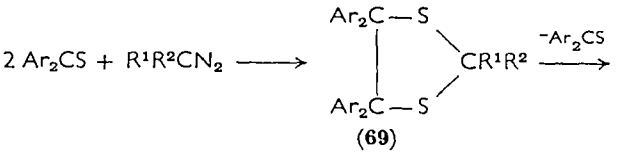


(**46a**)

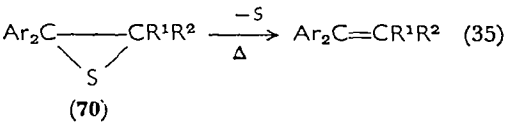
readily undergo the reaction. It is surprising that this reaction has not yet been observed upon irradiating simple thiones (but see section IV.D (photochemistry) below).

c. Reaction with diazoalkanes. Diazomethane and its derivatives, including ethyl diazoacetate and diphenyldiazomethane, react differently with thiones than with ketones. It was observed that a coupling reaction was involved, and treatment of a variety of thioketones with diazomethane, diazoethane, or ethyl diazoacetate led to the formation of 1,3-dithiolanes **69** (equation 35)[102]. Compound **69** (R^1 = H, R^2 = H, CH_3, or $COOC_2H_5$) decomposed on heating to

produce the ethylene sulfide **70** ($R^1 = H$, $R^2 = H$, CH_3, or $COOC_2H_5$). Since the reaction of diphenyldiazomethane with thioketones forms **70** ($R^1 = R^2 = C_6H_5$), which by treatment with

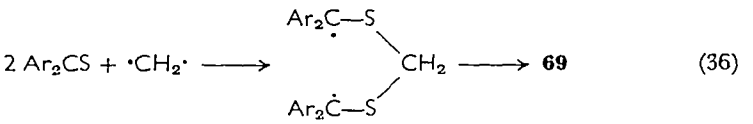


(69)



(70)

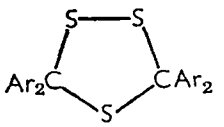
metals or heat easily loses sulfur to form the ethylenes, it has been assumed that this reaction also proceeds via the intermediate **69** ($R^1 = R^2 = C_6H_5$), which in this case is unstable, and decomposes spontaneously to **70**. The reaction has been used to prepare a variety of unsymmetical ethylenes and ethylene sulfides[103-105]. The mechanism of this reaction is not clear but must involve attack of the diazomethane carbon on the sulfur atom of the thioketone, in contrast to ketone reactions where the diazomethane carbon adds to the carbonyl carbon to produce a methylene insertion or epoxide. Latif and Fathy[106] indicate that the reaction of sulfur with diaryldiazomethanes is light-catalyzed and suggest that a biradical (or carbene) may be involved. The biradical suggestion would indicate the mechanism of equation (36) for the thioketone reaction.



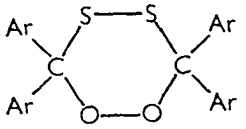
C. Oxidation of Thiones

Schönberg and Mustafa[107] found that passing oxygen through a benzene solution of thiobenzophenone produced benzophenone, sulfur and sulfur dioxide. The reaction was light-catalyzed, since *p,p'*-dimethoxythiobenzophenone and related thiones which were stable to oxygen in the dark were readily oxidized in bright sunlight. Other thiones, such as 2,6-diphenyldithiopyrone, were completely stable under these conditions, even in sunlight. In aqueous alkaline hydrogen peroxide the thiones are converted into ketones and sulfur dioxide.

When thiobenzophenone and some related thiones are exposed to dry air or dry oxygen for some time, a trithiolane (**71**) is formed[108].



(**71**)



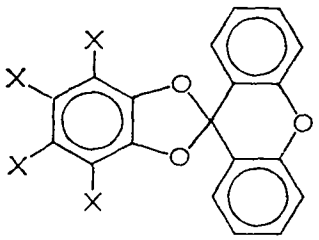
(**72**)

It is interesting that no sulfur dioxide is formed under these conditions. The stoichiometry of the reaction is as shown in equation (37), which led Staudinger and Freudenberger[109] to propose the formation of an

$$6\,Ar_2CS + O_2 \longrightarrow \underset{(71)}{2\,Ar_2CO} + 2\,Ar_4C_2S_3 \qquad (37)$$

intermediate peroxide (**72**), which decomposes to the ketone and molecular sulfur. The latter must then combine with two molecules of thioketone to form **71**. To date, no heterocyclic peroxide of structure **72** has been isolated, although analogous tetrathianes are known. It would be interesting to conduct this oxidation in the presence of a trapping agent for molecular sulfur.

A unique oxidation of thiones by *o*-quinones has been described by Latif and Fathy[110]. Xanthione, on refluxing in benzene with a negatively substituted *o*-quinone such as 3,4,5,6-tetrachloro-*o*-quinone, produced the spirodioxolane **73** in high yield. Sulfur was



(**73**)

eliminated in this reaction. The reaction occurs slowly at room temperature and is not catalyzed by light or peroxides[111]. The mechanism, which would seem at first glance to be biradical in character, is not clear.

A thioaldehyde *S*-oxide has been reported for the first time by Strating and coworkers[112a]. The compound was synthesized by elimination of hydrogen chloride from a sulfinyl chloride with

triethylamine (equation 38). This thioaldehyde *S*-oxide is remarkably stable, in contrast to the related *S*-dioxides (sulfenes), but on ultraviolet irradiation in dichloromethane liberated sulfur with the

$$ArCH_2SOCl + (C_2H_5)_3N \longrightarrow ArCH{=}S{=}O + (C_2H_5)_3\overset{+}{N}HCl^- \qquad (38)$$

formation of the aldehyde. Similar *S*-oxides, which may be intermediates in the oxidation of thiones, have also been obtained from secondary sulfinyl chlorides[112b].

D. Photochemistry of Thiones

Despite the high degree of reactivity of thioketones and their relatively intense ultraviolet absorption (section III.C), there has been little work on the photochemical reactions of these compounds. The photochemically induced oxidation of thiones has already been mentioned in the previous section[107]. This reaction has been restudied[113] and it was shown that irradiation of thioketones with visible light in the presence of oxygen transforms them quantitatively to their oxygen analogs. Near ultraviolet light, in the absence of oxygen and in the presence of a hydrogen-donor solvent such as alcohol, converts thiobenzophenone into benzhydrylthiol, benzhydryl disulfide, and tribenzhydryl tetrasulfide (**74**) (equation 39).

$$(C_6H_5)_2CS \xrightarrow[315\ m\mu]{h\nu} (C_6H_5)_2CHSH + (C_6H_5)_2CHSSCH(C_6H_5)_2 + (C_6H_5)_2CHSSC(C_6H_5)_2SSCH(C_6H_5)_2 \qquad (39)$$

(**74**)

This reaction, which is inhibited by oxygen, is in contrast to the behavior of benzophenone, which under identical conditions is converted into the pinacol. The intermediate radicals in the two cases must therefore differ (equations 40 and 41). Compound **74**,

$$Ar_2CO \xrightarrow[\text{H donor}]{h\nu} [Ar_2\dot{C}OH] \xrightarrow{\text{Coupling}} Ar_2CO(OH)C(OH)Ar_2 \qquad (40)$$

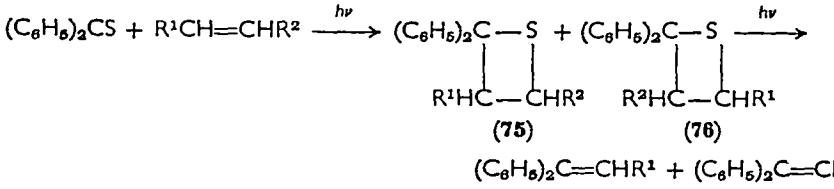
$$Ar_2CS \xrightarrow[\text{H donor}]{h\nu} [Ar_2CHS\cdot] \xrightarrow{\text{Coupling}} Ar_2CHSSCHAr_2 \qquad (41)$$

$$[Ar_2CHS\cdot] \xrightarrow{\text{H donor}} Ar_2CHSH$$

obtained in relatively small quantities, must be formed by further reactions of the disulfide and intermediate sulfur radical.

Although irradiation of carbonyl compounds in the presence of

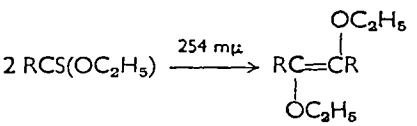
olefins give oxetanes, similar irradiation of thiobenzophenone produced a mixture of 1,1-diphenylethylenes (equation 42)[114]. Irradiation of the thioketones with olefins in cyclohexane under nitrogen, in the range of 210–280 mμ, produced the 1,1-diphenylethylenes in



(42)

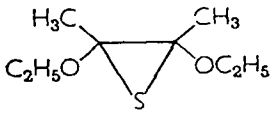
good yield and, in the case of terminal olefins, in roughly equivalent amounts. The photosensitive thietanes **75** and **76** were suggested as intermediates but no trithianes, which should be formed as products of the second cleavage, were isolated.

In a preliminary report on related work with thionoesters Schmidt and Kabitzke[115] have found that irradiation of ethyl thionoacetate or ethyl thionopropionate neat at 254 mμ produced the corresponding enediol ether in 60–65% yield (equation 43). The *cis/trans* ratio



(43)

for the thionoacetate was 2:3. A small amount of the episulfide **77** was isolated. This reaction may proceed via a carbene intermediate



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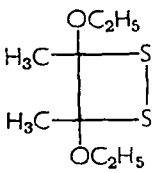


(78)

(79)

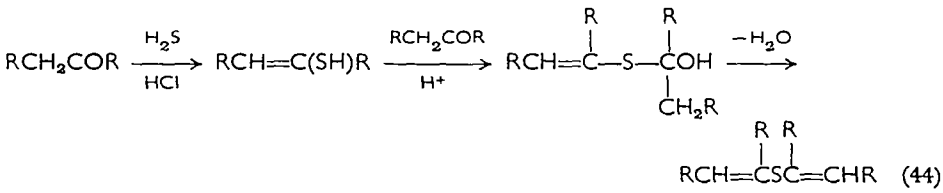
(**79**), but the addition of carbene-trapping agents have not shown the presence of **79**[116]. The formation of the dithiacyclobutane **78** as an unstable intermediate seems more reasonable.

E. Thione–Enethiol Tautomerism and Activated α-Methylene Groups

The thione–enethiol tautomerism has been the subject of a recent review[24] and will therefore only be summarized here. In general, where possibilities of thione–enethiol tautomerism exist, there will be

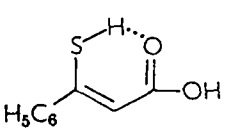
a higher percentage of enethiol at equilibrium than of enol in the analogous keto–enol system. Because of the instability of simple thiones, most of these studies have been on thiones stabilized by adjacent resonance groups, such as the monothio-β-diketones and thioketo acids. Ultraviolet spectra indicate that β-phenylthiopyruvic acid is chiefly in the enethiol form[63]. Sen[117] prepared monomeric thiocyclohexanone by distillation and then rapidly oxidized aliquots with iodine. He reported 38% enethiol in freshly distilled thione and 70% enethiol in a sample one hour old. The reaction is complicated by trimerization, however.

The existence of enethiols in thioketones having α-hydrogens is clearly shown by the fact that many ketones are converted into vinyl sulfides when treated with hydrogen sulfide and an acid (equation 44)[6,22]. (For a recent complex example of this reaction, see Stynler and Weiss[118].)

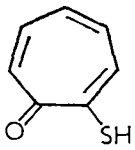


(44)

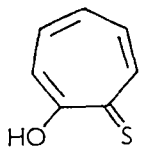
The most careful study of thione–enethiol tautomerism has been carried out on ethyl thiobenzoylacetate and its derivatives by Reyes and Silverstein[28,29]. From infrared and nuclear magnetic resonance spectra and from iodometric titration, the equilibrium was estimated to be approximately 87–95% enethiol in ethyl thiobenzoylacetate. This material was obtained as a blue oil, which was rapidly decolorized by small amounts of oxygen without the loss of the characteristic enethiol spectrum, indicating rapid oxidation of the thione but not of the enethiol. It is interesting to note that ethyl thiobenzoylacetate could be hydrolyzed to a crystalline colorless acid (**80**) with-



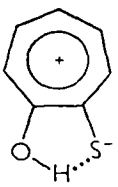
(**80**)



(**81a**)



(**81b**)

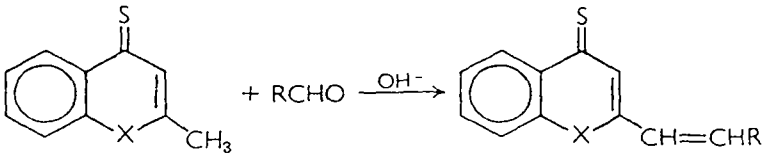


(**81c**)

out extensive decarboxylation. This acid melts at 110–111° to a blue liquid which on further heating was decarboxylated to thioacetophenone[28].

Nozoe and Matsui[119] examined the structure of 2-mercaptotropone (**81**) and reported that the ultraviolet, infrared, and n.m.r. spectra are more consistent with **81b**, while chemical reactions favor **81a** for the structure. This is contrary to studies on the monothio-β-diketones[24], where mass spectrometry and infrared studies show the compounds to exist chiefly, if not entirely, as the β-mercapto-α,β-unsaturated ketones (cf. section II.A.1.a). Since the mercaptide ion is more stable than the corresponding oxide ion, the thiotropolone system should probably be written as in **81c**, which would account for both the spectral and chemical properties of this compound. The appearance of a thiocarbonyl infrared band in the 1200 cm^{-1} region in this compound implies that the characteristic infrared bands of the thione group (section III.B) are chiefly caused by frequencies associated with the polar form.

There is a notable lack of studies involving activation of α-hydrogen by thioketone groups. The instability of thiones and the existence of such compounds almost exclusively as enethiols probably account for this. Schönberg and coworkers[120] have shown that in 2-methyl-4-thio- and 2-methyl-1,4-dithiochromones (**82**) the methyl group is activated and condenses readily with aldehydes under basic catalysis



(45)

(**82** X = O, S) (**83**)

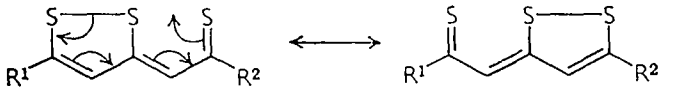
(equation 45). In most examples the nucleophilic competition between sulfur and carbon is won by the sulfur atom, yielding vinyl sulfides. Base-catalyzed alkylation of ethyl thioacetylacetate with alkyl halides, for example, leads to the formation of β-alkylthiocrotonates.

F. *Thiocarbonyl Contribution to No-bond Resonance*

1. The thiothiophthene system

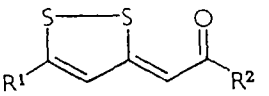
No discussion of thioketone chemistry would be complete without reference to certain unique heterocycles whose structures have recently been elucidated. Treatment of diacetylacetone with phosphorus pentasulfide produced a stable trisulfide shown to have structure **84**[121]. Thus x-ray analysis showed that the three sulfur atoms in this compound are colinear and equally spaced at 2·36 Å,

compared to the normal S—S bond of 2·04 Å. Nuclear magnetic resonance of the dimethyl derivative **84** ($R^1 = R^2 = CH_3$) showed only two peaks, in a ratio of 3:1, showing that the two methyl groups and the two aromatic hydrogens of the dithiolium rings are

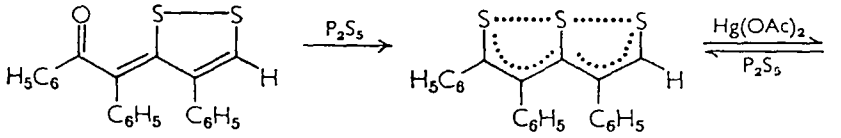


(**84a**) (**84b**)

identical. The thioketone group is stable and unreactive. On the other hand, when a ketone or aldehyde group is inserted into the resonance system, as in **85**, the resonance was destroyed and **85** (R^2 = H or CH_3) showed normal carbonyl reactions.

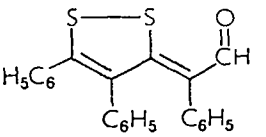


(**85**)



(**86**) (**87**)

(46)

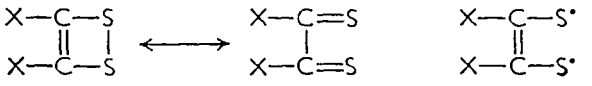


(**88**)

The resonance structure of this system has been reviewed by Klingsberg[122], who describes a convenient synthesis of unsymmetrical thiothiopthenes. He demonstrated chemically the existence of a true resonance system by converting the oxo-1,2-dithiolylidene **86** into the unsymmetrical thiothiophthene **87**. This substance was hydrolyzed by mercuric acetate to produce the aldehyde **88**, which had characteristic carbonyl properties but was converted back into **87** by phosphorus pentasulfide (equation 46).

2. 1,2-Dithietes

A second example which apparently involves no-bond resonance in thiocarbonyl systems has recently been described[123,124]. Krespan, McKusick, and Cairns[123], on passing hexafluorodimethylacetylene through boiling sulfur, isolated a yellow liquid, b.p. 95–96°, in 80%



(89a) (89b) (89c)

yield to which they assigned the structure of 3,4-bistrifluoromethyl-1,2-dithiete (**89a**, X = CF_3). Simmonds and coworkers[124] have attempted to isolate the dicyano derivative **89a** (X = CN) without success. They have, however, discussed some of the reactions of these dithietes and indicate that those which are stable probably are stabilized by resonance with the *s-cis* form of the α-dithione **89b**. The biradical **89c** may also account for some of the facile additions to olefins which these compounds undergo.

V. THIOCARBONYLS AS TRANSIENT INTERMEDIATES

Thiocarbonyl compounds have been proposed as reactive intermediates in a number of instances, some of which seem justified on the basis of evidence while others are more nebulous. For example, Kohman[125] suggested that thioaldehydes such as thiopropionaldehyde were the bacteriocidal and phytoncidal principles of onion vapor, responsible for wound-healing. The formation of thioketone groups as intermediates in the vulcanization of rubber has been claimed[126].

A. Alkaline Cleavage of Disulfides

The proposal that disulfides may be cleaved by alkali to form thiocarbonyl intermediates (equation 47) was first put forward by

$$R_2CHSSCHR_2 \xrightarrow{B^-} R_2\bar{C}—S—\bar{S}CHR_2 \longrightarrow R_2CS + \bar{S}CHR_2 \qquad (47)$$

Rosenthal and Oster[127]. Although this equation can account for all of the products of alkaline cleavage of disulfides derived from thioglycolic acid derivatives, it does not seem to be general, since cystine and other aliphatic disulfides do not cleave in this way[128].

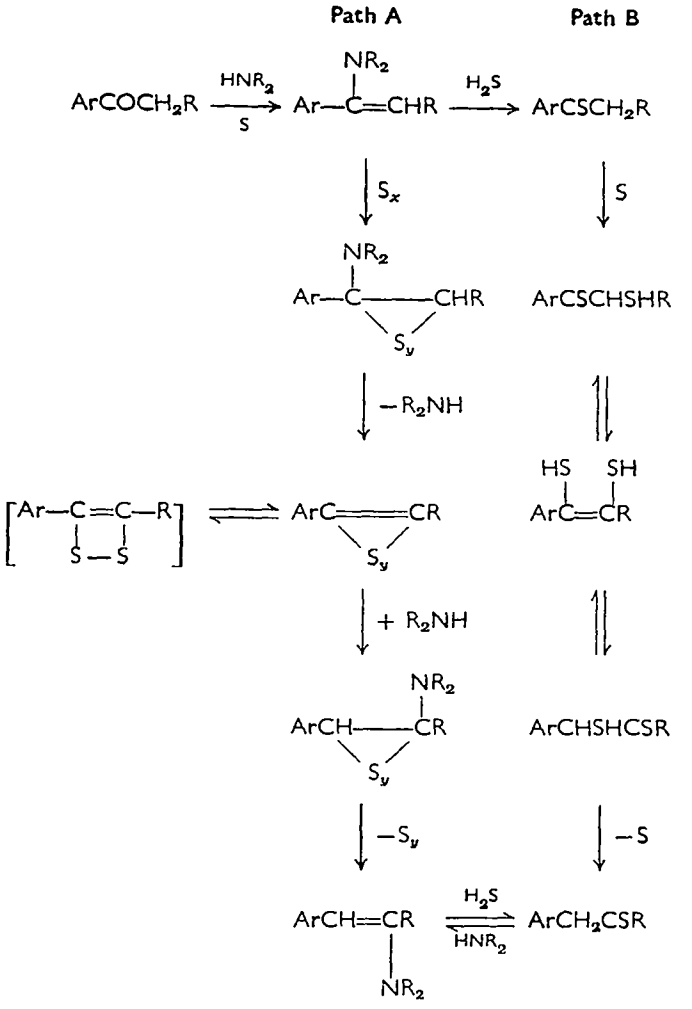
The reaction illustrated by (47) may occur in those disulfides having an activated α-hydrogen. Treatment of benzhydryl disulfide by aqueous alcoholic base causes the appearance of a transient blue color, which must be due to the presence of thiobenzophenone by cleavage according to equation (47).

B. Thiocarbonyl Intermediates in the Willgerodt–Kindler Reaction

One reaction which must surely involve thiocarbonyl or incipient thiocarbonyl groups is the Willgerodt–Kindler reaction. The reaction involves migration of a carbonyl group along an aliphatic chain and is usually terminated by an oxidation step at the terminal carbon atom, forming an acid derivative. The reaction is carried out in the presence of sulfur and an amine or ammonia, and was reviewed in 1946[129]. The facts that it always required sulfur, that hydrogen sulfide was produced, and that when an organic amine was used the final product was a thioamide, led King and McMillan[130] to suggest that thioketones were involved in the oxidation–reduction steps involved (equation 48). In fact thioacetophenone was shown to take part readily in this reaction[131]. The fact that amines or ammonia are also essential to the reaction has suggested that the highly reactive enamines are also involved in various addition and elimination steps[132,133].

$$\mathrm{ArCOCH_3} \underset{}{\overset{\mathrm{H_2S}}{\rightleftharpoons}} \mathrm{ArCSCH_3} \underset{-\mathrm{H_2S},\,+\mathrm{S}}{\overset{+\mathrm{H_2S},\,-\mathrm{S}}{\rightleftharpoons}} \mathrm{ArCHSHCH_3} \qquad (48)$$

The mechanism of the reaction has received careful study in recent years by Carmack[134] and by Asinger, who has published a recent review[135]. The important questions to be answered are: (*a*) how does each methylene group become oxidized to the carbonyl stage, and (*b*) how does each carbonyl get reduced to methylene? The present consensus of opinion is summarized in Scheme 1. As can be seen, two pathways (A and B) are suggested for the migration of the carbonyl group and at present there is insufficient evidence to prefer one over the other. Both mechanisms require the formation of enamine, which Asinger[133] has shown to be catalyzed by sulfur. Both mechanisms involve thiocarbonyl groups. The cyclic sulfur compounds shown in path A may actually be reactive dithietes, the existence of which have been demonstrated (section IV.F.2). The complete elucidation of the mechanism of this reaction should shed some light on the chemistry of thiocarbonyl groups.



SCHEME 1. Mechanisms of the Willgerodt–Kindler reaction.

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The Chemistry of the Carbonyl Group
Edited by Saul Patai

Subject index