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ISBN 0-315-60105-1

UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

Dedicated to my parents and Ping

Abstract

Liquid phase oxidation of organic substrates under an atmosphere of oxygen catalyzed by metal complexes is reviewed in Chapter 1. Aiso included in the review are homogeneous and heterogeneous catalysis and free radical autoxidation reactions.

The selective catalytic oxidation of aromatic hydrocarbons is described in Chapter 2. Anhydrous $CoCl_2$, $CoCl_2/CrCl_3$, or $CoCl_2/ZrCl_4$ were used as the catalysts to oxidize a variety of substrates in the presence of diglyme or a mixture of diglyme and MEK (1:3). These substrates included substituted toluenes and other benzylic hydrocarbons. The reactions afforded fair to excellent yields of the product aldehydes or ketones under mild conditions. It was discovered that the selectivity of these reactions is strongly influenced by the catalyst and the solvent.

Selective catalytic oxidation of ethers and cyclic acetals using cobalt chloride is described in Chapter 3. The oxidation of cyclic ethers gives the corresponding lactones in reasonable to excellent yields. However, 2,3-dihydrobenzofuran leads to no reaction. Oxidation of acyclic alkyl benzyl ethers to the corresponding esters afforded yields which were dependent on the stability of the alkyl radicals. The more stable the alkyl radical, the lower the yield of the ester obtained. In addition, oxidation of acyclic and heterocyclic ethers is described. An investigation of the reaction mechanism of this process was also studied.

Finally, the oxidation of 2-substituted 1,3-dioxolanes afforded high yields of formate esters and acids. It was found that the presence of catalytic amounts of $ZnCl_2$ promoted the rate of oxidation.

Acknowledgements

I would like to express my deepest gratitude to Dr. Howard Alper for his guidance, encouragement and patience throughout the course of this work, especially during the "lean" periods. I also greatly appreciated his assistance and kindness over the years.

I wish to thank my colleagues who have been members of our research group for their help in the laboratory. I also would like to thank Livain and Chantal Breau for their enlightening discussions in academic matters and particularly for their friendship outside the laboratory.

I acknowledge and thank the Department of Chemistry, University of Ottawa for the financial support for this research.

Thanks are owed to Raj Capoor and Dr. Heather Dettman for recording NMR spectra, and to Dr. Clem Kazakoff for the mass spectral data.

Finally, I want to thank Kelly Walsh for reading the first draft of this thesis.

List of Abbreviations

$Co(OAc)_2$	Cobalt acetate
$Co(OCOPh)_2$	Cobalt benzoate
$CoCl_2(PPh_3)_2$	Cobalt dichloride bis(triphenyl phosphine)
$Cu(OCOCF_3)_2$	Copper(II) trifluoroacetate
Diglyme	Bis(2-methoxyethyl)-ether
DME	1,2-Dimethoxyethane
DMP	2,2-Dimethoxy propane
HOAc	Glacial acetic acid
MEK	Methyl ethyl ketone (2-butanone)
$Pd(OCOCF_3)_2$	Palladium trifluoroacetate
PEG	Poly(ethylene glycol)
IR	Infrared
^1H NMR	Proton nuclear magnetic resonance
MS	Mass spectra
GC	Gas chromatography
TLC	Thin layer chromatography
s	Singlet
d	Doublet
q	Quartet
m	Multiplet
M	Molecular ion
mmol	Millimole

List of Table

Contents

Chapter 1 General Introduction

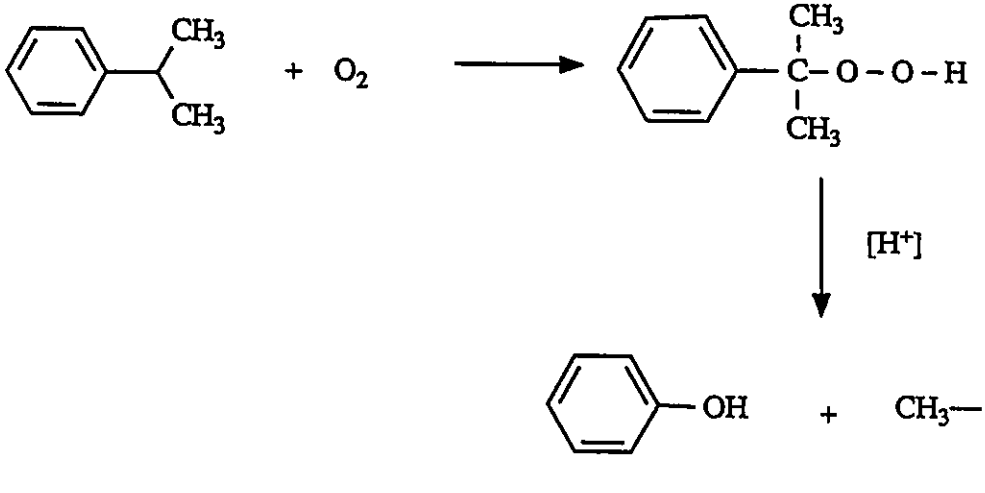
Oxidation reactions are important in chemistry generally, as well as in biochemistry, biology and life sciences. Oxygen is a plentyful, inexpensive and highly reactive reagent which, if properly controlled, can effect a variety of useful synthetic transformations. Oxidation of hydrocarbons with oxygen is among the least energy-intensive functionalization reactions. Thus, the liquid phase oxidation of organic substrates using metal complexes as catalysts has become a profitable means of obtaining industrially important chemicals.

1.1 Metal-Catalyzed Oxidations

The stoichiometric oxidation of organic compounds by traditional oxidants is well established in the laboratory synthesis of fine organic chemicals as well as in the manufacture of large-scale petrochemicals. However, these processes usually show poor selectivity and produce vast amounts of inorganic effluents which are difficult to dispose of. Futhermore, they often involve complicated work-up procedures. As a result, a greater emphasis has been placed on the development of new, improved catalytic oxidation processes during the past three decades.

1.1.1. HISTORICAL DEVELOPMENT

The oxidation of organic compounds by molecular oxygen has a long history.[1] Early studies were mainly concerned with the inhibition of oxidative degradation of many organic materials, such as rubber, natural oils and fats. It was recognized later that these oxidative processes involved the formation of organic peroxides. Subsequent mechanistic studies of the interaction of simple hydrocarbons with dioxygen carried out in the 1940's provided the basic concepts for the free radical chain process known as autoxidation.[2] Later, it was found that the control of autoxidation was desirable not only for inhibiting the oxidative deterioration of plastics, gasoline, lubricating oils and rubber, but also for promoting the selective oxidation of petroleum hydrocarbons in a variety of industrial organic chemicals. For example, the autoxidation of cumene to cumene hydroperoxide is the first step in the well-known commercial process for the coproduction of phenol and acetone[3] (eq.[1.1]).



[1.1]

Metal-catalyzed oxidations play an important role in the control of selective oxidation of alkanes, olefins and aromatic hydrocarbons to useful products. Indeed, one of

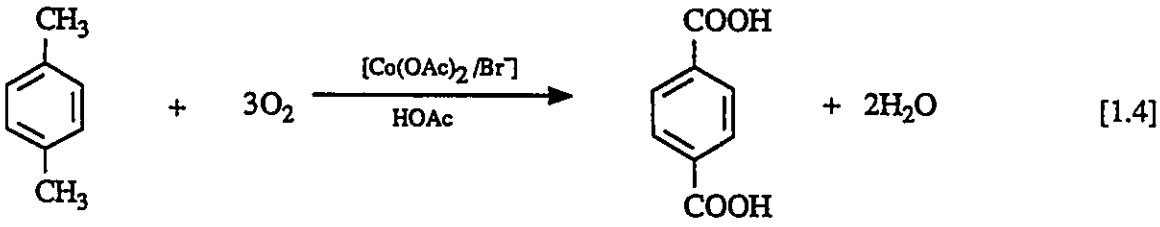
the most important types of petrochemical process is catalytic oxidation.[4-6] The first observation of a catalytic oxidation is probably attributed by Davy,[7] who showed in 1820 that ethanol is oxidized to acetic acid in the presence of platinum (eq.[1.2]).

$$CH_3CH_2OH + O_2 \xrightarrow{[Pt]} CH_3COOH + H_2O \qquad [1.2]$$

Although there were some other industrial processes, such as the silver-catalyzed oxidation of ethylene to ethylene oxide discovered in 1933, the field of metal-catalyzed oxidation assumed importance only in the 1940's while the theory of free radical autoxidation was developed. Initially, several important industrial processes for the selective oxidation of hydrocarbons involved vapor-phase oxidations over heterogeneous catalysts (e.g., ethylene to ethylene oxide). The serious study and application of homogeneous catalysis to liquid-phase oxidation originated in the 1950's. For example, the Celanese process[8] for the liquid-phase oxidation of n-butane to acetic acid (eq.[1.3]) is still in use today.

$$n\text{-}C_4H_{10} + 5/2\ O_2 \xrightarrow{Co(III)} 2CH_3COOH + H_2O \qquad [1.3]$$

The production of terephthalic acid from p-xylene[9] (eq.[1.4]) and the Wacker process for



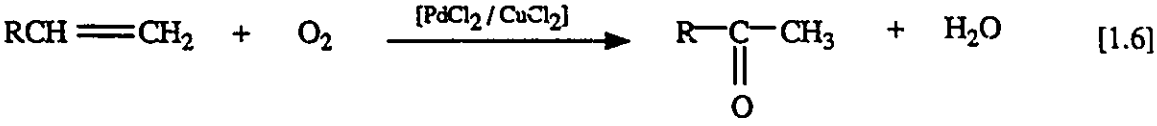
[1.4]

acetaldehyde from ethylene[10] (eq.[1.5]) were both reported in 1959. The application of

$$2CH_2{=}CH_2 + O_2 \xrightarrow[H_2O]{[PdCl_2\,/\,CuCl_2]} 2\,CH_3CHO \qquad [1.5]$$

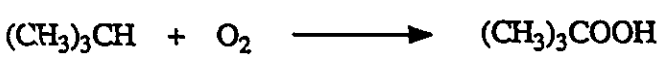
the Wacker oxidation of various higher terminal olefins affords methyl ketones

selectively[11] (eq.[1.6]).

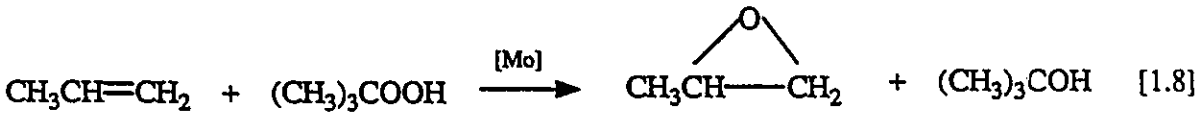


[1.6]

In the last decade, an efficient metal-catalyzed liquid phase epoxidation of olefins (such as propylene) with an alkyl hydroperoxide produced from hydrocarbon autoxidation has been developed. This process is now effected on a large scale to produce propylene oxide[12] (eq.[1.7] and [1.8]).



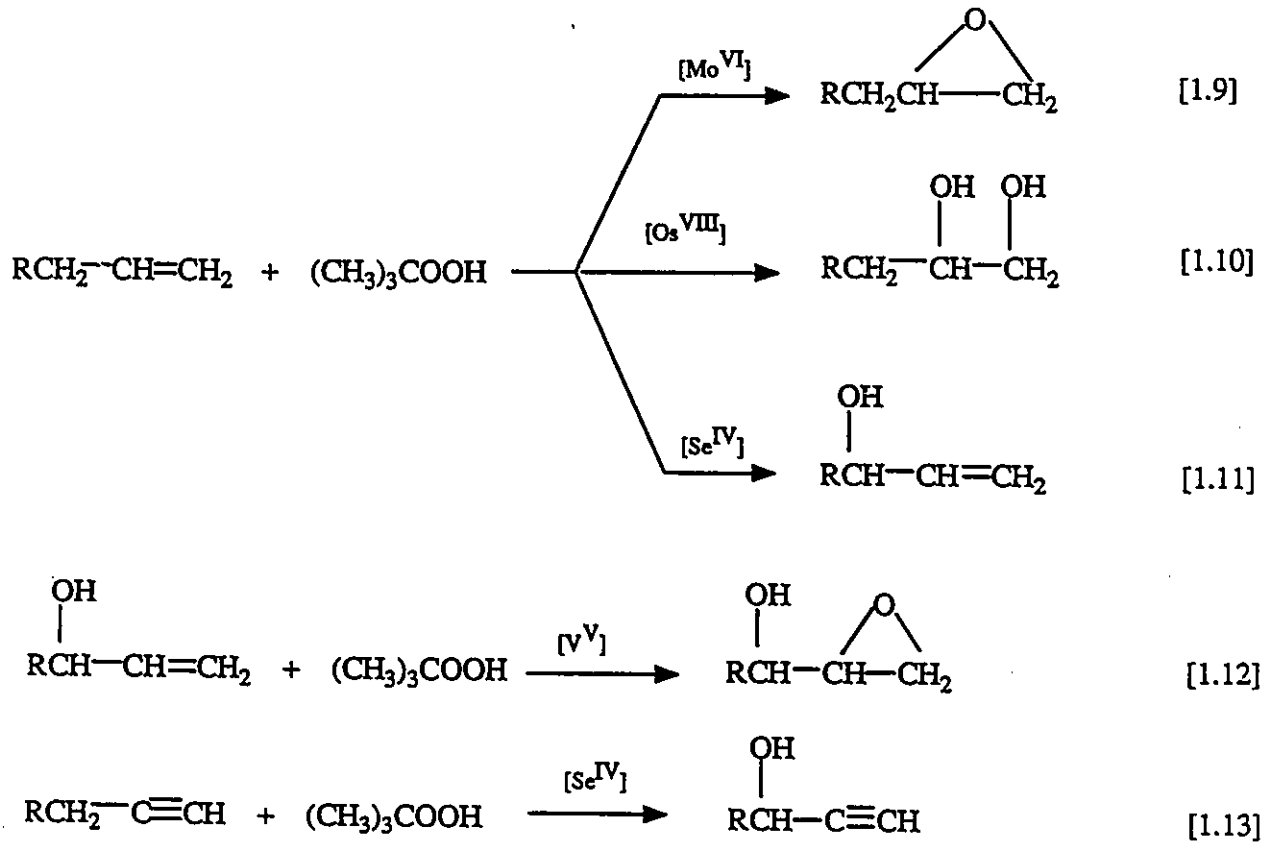
[1.7]



[1.8]

A variety of metal-catalyzed oxidations have also been developed for selective oxidations that can be carried out in laboratory-scale synthesis. The importance of metal catalysis is illustrated in the following transformations of olefins and acetylenes with tert-butyl hydroperoxide[13] (Scheme [1.1]). The catalytic oxidation can also be effectively employed in the systhesis of a variety of natural products.[14]

Scheme [1.1]



[1.9] [1.10] [1.11] [1.12] [1.13]

1.1.2. HOMOGENEOUS AND HETEROGENEOUS CATALYSIS

The use of transition metal complexes as catalysts for the synthesis of organic compounds is of academic and industrial importance. Catalysts are conventionally divided into homogeneous and heterogeneous systems on the basis of whether a reaction takes place throughout one phase or at a phase boundary. A homogeneous reaction is defined as one in which all the constituents of the reaction including the catalyst, are present in the same phase, generally implied to be a liquid phase. A heterogeneous reaction is defined as

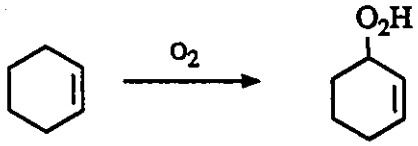
one in which one or more of the constituents are in a different phase, usually with the catalyst as a solid and the reactants as liquids or, more frequently, as gases. The reaction takes place at the interface, e.g., on the surface of the catalyst.

Homogeneous catalysts usually can be used under mild conditions, allowing for a better control of reaction and less energy consumption, while heterogeneous catalysts often require high temperature and consequent waste of energy to achieve high reaction rates. Moreover, homogeneous catalysts can be made much more reproducibly than their heterogeneous counterparts, and can be studied using the well-established techniques of physical organic chemistry and X-ray crystallography. An increased understanding of homogeneous catalyzed reactions can be obtained from mechanistic studies which can lead to improved control of the reactions and eventually to a rational design of catalytic systems. As a result, use of homogeneous catalysis for the synthesis of a variety of organic chemicals has been steadily increasing in the last 45 years.[15] However, separation of the homogeneous catalyst from the reaction mixture is often much more difficult than a heterogeneous catalyst. Since heterogeneous catalysis has the significant advantage of an easy separation from the reaction products and a generally higher thermal stability, they still are the most widely used processes in industry.

During the past 20 years, progress made in the knowledge and synthesis of homogeneous catalysts for oxidation reactions has surpassed that realized in the last 50 years for hetergeneous catalysts. This may be attributed to the greater ease of detecting and identifying intermediate products, the milder reaction conditions permitting simpler technology and greater selectivity and reproducibility.

1.2 Free Radical Autoxidation Reactions

Autoxidation is defined as oxidation of an organic compound with molecular oxygen, usually via a free radical chain process. Many liquid-phase oxidations which are known as autoxidations, proceed under relatively mild conditions of temperature and oxygen pressure.[16] The pioneering work of Backstrom[17] demonstrated that liquid-phase autoxidations are chain reactions. Criegee[18] made an important contribution in 1939 when he showed that the primary product of autoxidation of cyclohexene is the allylic hydroperoxide (eq.[1.14]). Subsequent studies of the interaction of a variety of simple



[1.14]

hydrocarbons with molecular oxygen provided the basis of the development of the free radical chain theory of autoxidation.[19-23] Although initial studies were concerned mainly with finding ways of preventing autoxidation, it was soon recognized that the controlled oxidation of hydrocarbons can be a useful method for preparing a wide range of oxygen-containing compounds. In 1944, Hock and Lang[3] discovered the most well-known commercial process involving the conversion of cumene to phenol and acetone (eq.[1.1]).

The liquid-phase autoxidation of hydrocarbons has been studied extensively.[24-29] The reaction mechanisms are described by the following general scheme [1.2].

Alkylperoxy radicals ($RO_2\cdot$) play vital roles in both the propagation and the termination steps. Hydroperoxides (RO_2H) are usually the primary products, then converted into stable products. In some cases, hydroperoxides may be isolated in high yields. Many studies of autoxidation reactions involving alkylperoxy radicals and alkyl hydroperoxide radicals ($RO\cdot$) have been carried out and well characterized.[30-33]

Scheme [1.2]

a) Initiation

By addition of radical initiator

$$In_2 \xrightarrow[\text{or } h\nu]{\text{heat}} 2In\cdot \qquad [1.15]$$

$$In\cdot + RH \longrightarrow InH + R\cdot \qquad [1.16]$$

Self-initiation

$$RH + O_2 \longrightarrow R\cdot + HO_2\cdot \qquad [1.17]$$

$$2RH + O_2 \longrightarrow 2R\cdot + H_2O_2 \qquad [1.18]$$

Thermal decomposition

$$ROOH \longrightarrow RO\cdot + \cdot OH \qquad [1.19]$$

Radical induced decomposition

$$RO\cdot + ROOH \longrightarrow ROH + RO_2\cdot \qquad [1.20]$$

$$HO\cdot + ROOH \longrightarrow RO_2\cdot + H_2O \qquad [1.21]$$

Carbanions with oxygen

$$R^- + O_2 \longrightarrow R\cdot + O_2^- \qquad [1.22]$$

b) Propagation

$$R\cdot + O_2 \rightleftharpoons RO_2\cdot \qquad [1.23]$$

$$RO_2\cdot + RH \longrightarrow RO_2H + R\cdot \qquad [1.24]$$

$$RO\cdot + RH \longrightarrow ROH + R\cdot \qquad [1.25]$$

c) Termination

$$R\cdot + R\cdot \longrightarrow R{-}R \qquad [1.26]$$

$$R\cdot + RO_2\cdot \longrightarrow RO_2R \qquad [1.27]$$

$$2RO_2\cdot \rightleftharpoons RO_4R \longrightarrow ROH + RCOR + O_2 \qquad [1.28]$$

1.2.1. CHAIN-INITIATION

A radical chain oxidation process can be initiated by one of the following mechanisms.

a) Addition of radical initiators such as aliphatic diazo compounds, dialkyl peroxides, diacyl peroxides and peroxy esters. Table [1.1] gives the bond energies of several common initiators for autoxidation.

Table [1.1] Some Common Initiators for Autoxidation

Name	Structure	Activation energy (kcal mol^{-1})	Temp (°C) for 1 hr half-life
Hydrogen peroxide	HO—OH	48	—
t-Buty. hydroperoxide	*t*-BuO—OH	42	—
t-Butyl peroxide	*t*-BuO—O—*t*-Bu	37	150
t-Butyl perbenzoate	*t*-BuO—OCPh (O above C)	34	125
Benzoyl peroxide	PhCO—OCPh (O above each C)	30	95
Acetyl peroxide	$CH_3CO—OCCH_3$ (O above each C)	30–32	85
Azoisobutyronitrile	$(CH_3)_2C(CN)—N=N—C(CN)(CH_3)_2$	30	85
t-Butyl hyponitrite	*t*-BuO—N=N—O—*t*-Bu	28	60
t-Butyl peroxalate	*t*-BuO—OCCO—O—*t*-Bu (O above each C)	25.5	40

[Ref.] R. A. Sheldon, and J. K. Kochi,"Metal-Catalyzed Oxidation of Organic Compounds", Academic Press, (1981) p.20

In practice, these initiators should have substantial rates of decomposition in the temperature range between 50°C and 150°C (eq.[1.15]).

b) Radical initiators can be generated by the decomposition of the intermediate hydroperoxides formed by the reaction of substrate with the oxygen in the initial period of oxidation.[34-37] The formation of radicals may occur by a bimolecular (eq.[1.17]) or trimolecular (eq.[1.18]) mechanism depending on the structure and bond energies in the substances undergoing oxidation.[38]

c) Unless hydrocarbons are rigorously purified prior to use, trace amounts of hydroperoxides present in the substrate can also thermally decompose to alkoxy and hydroxy radicals (eq.[1.19]).

d) Radical induced decomposition of alkyl hydroperoxide (eq.[1.20] and [1.21]).

e) Radical initiators can be generated by the reaction of carbanions with molecular oxygen (eq.[1.22]). This pathway is not very common, with the exception of highly acidic hydrocarbons.

1.2.2. CHAIN-PROPAGATION

In the propagation steps, the reaction of the alkyl radicals (R·) with oxygen [eq.1.23] is extremely rapid, in most cases diffusion-controlled (e.g., $K>10^9 M^{-1}Sec^{-1}$).

The rate determining step in autoxidations usually is hydrogen atom abstraction by a free radical (eq.[1.24]) and (eq.[1.25]). The relative reactivity of RO· and RO_2· in H-atom transfer are shown in Table [1.2].

Table [1.2] Relative Reactivity of RO· and RO_2· in H-Atom Transfer at 100^0C

CH bond	RO·	RO_2·
Primary	1.0	1.0
Secondary	10	50
Tertiary	50	1000
Allylic	30	3000

[Ref.] C. H. Bamford and C. F. H. Tipper, "Comprehensive Chemcal Kinetics" Vol.16, p.49 (1980)

The above results show that the reactivity of (RO_2·) toward hydrogen abstraction is much higher than that of (RO·).

The hydrogen abstraction reaction by (RO_2·) usually is fast if the bond that is formed (ROO-H) is at least as strong as that which is broken (R-H). The ROO-H bond strength is estimated[39]to be about 90 $Kcalmol^{-1}$, which means that this bond is stronger than a benzylic or allylic C-H bond (85 $Kcalmol^{-1}$) or an aldehydic C-H bond (86

Kcalmol^{-1}). It is comparable to a tertiary C-H bond in a saturated hydrocarbon(90-92 Kcalmol^{-1}). The relatively weak O-H, S-H, N-H and P-H bonds of phenols, thiols, aromatic amines and phosphines, respectively, also provide readily abstractable hydrogens (Table [1.3]).

Table [1.3] X-H Bond Energies[a]

Compound	Energy (kcal mol^{-1})	Compound	Energy (kcal mol^{-1})
CH_3—H	103	$PhCH_2$—H	85
n-C_3H_7—H	99	RCO—H	86
i-C_3H_7—H	94	CH_3S—H	88
t-C_4H_9—H	90	CH_3PH—H	85
CH_2=CH—H	105	PhO—H	88
C_6H_5—H	103	PhNH—H	80
CH_2=CH—CH_2—H	85	ROO—H	90

[a] Data from J. A. Kerr, *Chem. Rev.* 66, 465 (1966); S. W. Benson and R. Shaw, *in* "Organic Peroxides" (D. Swern, ed.), p. 105. Wiley (Interscience), New York, 1970.

up-date data for the Bond Energies, see J. L. Holmes and F. P. Lossing, Mass Spectrometry and Ion Processes, 58, 113 (1984); J. Am. Che. Soc. 108, 1086 (1986); 110, 7343 (1988).

Relatively stable and persistent alkylperoxy radicals are quite selective and preferentially abstract only the most weakly bound hydrogen. The selectivity of alkylperoxy radicals is similar to that of the bromine atoms [D(H-Br)=87Kcalmol^{-1}]. The relative rates of attack at the primary, secondary and tertiary C-H bonds increase in the order 1:30:300.[40]

The propagation rate constants are also dependent on the reactivity and stability of the attacking alkylperoxy radical (ROO·). The stability of the alkyl peroxy radical toward dissociation (eq.[1.29]) depends on the strength of the bond formed between the radical R·

$$ROO\cdot \longrightarrow R\cdot + O_2 \qquad [1.29]$$

and oxygen. The bond strength is 47 Kcal/mol for HOO· ; 26-29 Kcal/mol for alkyl-OO· ; and 13-15 Kcal for resonance-stablized radicals such as allyl and benzyl.[39] Benson[39] has estimated the equilibrium constant of reaction [1.23] over a range of temperatures for a number of peroxy radicals. The HOO· radicals are stable up to 1000^{0}C. The saturated alkyl peroxy radical are quite stable below 300-400^{0}C. However, the unsaturated

resonance-stabilized radicals are much less stable. At an O_2 pressure of 0.1 atm, the R· and ROO· concentrations for allyl radicals will be equal at 200^0C, and for benzyl radicals will be equal at 100^0C.

The reactivities of peroxy radicals are strongly dependent on their structure, and are influenced by both steric and polar effects.[41-45] In general, the primary and secondary peroxy radicals are about three to five times more reactive than tertiary peroxy radicals in hydrogen abstraction.[46,47] Furthermore, the reactivity increases with increasing electron-withdrawing capacity of the α-substituent. Acylperoxy radicals, which possess a strong electron-withdrawing carbonyl group, are considerably more reactive than alkylperoxy radicals. For example, the benzoylperoxy radical is 4×10^4 times more reactive than the tert-butylperoxy radical towards benzaldehyde. On the basis of bond dissociation energies (Table [1.3]) alone, one would expect aldehydes and alkylaromatic compounds to be autoxidized at roughly the same rates since they have similar bond dissociation energy. However, the experimental results show that aldehydes actually exhibit a much higher rate of autoxidation which may be due to higher reactivities of their peroxy radicals[41].

1.2.3. CHAIN-TERMINATION

In the termination step, the path of chain termination depends on the concentration of oxygen. At a low concentration of dissolved oxygen, when $[R\cdot] >> [RO_2\cdot]$, chain termination takes place only by reaction [1.26]. At a high concentration of dissolved oxygen, when $[RO_2\cdot] >> [R\cdot]$, chain termination takes place by reaction [1.28]. In general, it is necessary to take all three chain termination steps [1.26], [1.27] and [1.28] into account.

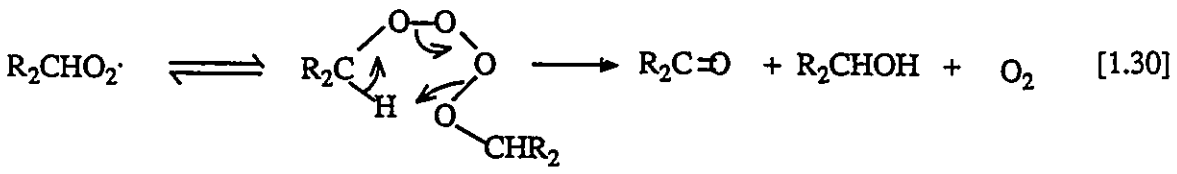
Steric effects of chain termination reactions are presented in Table [1.4]. It is shown that the chain termination rate constants increase following the series tertiary

peroxy < secondary peroxy < primary peroxy.

Table [1.4] Chain Termination Constants for Hydrocarbon Oxidation at 30^0C

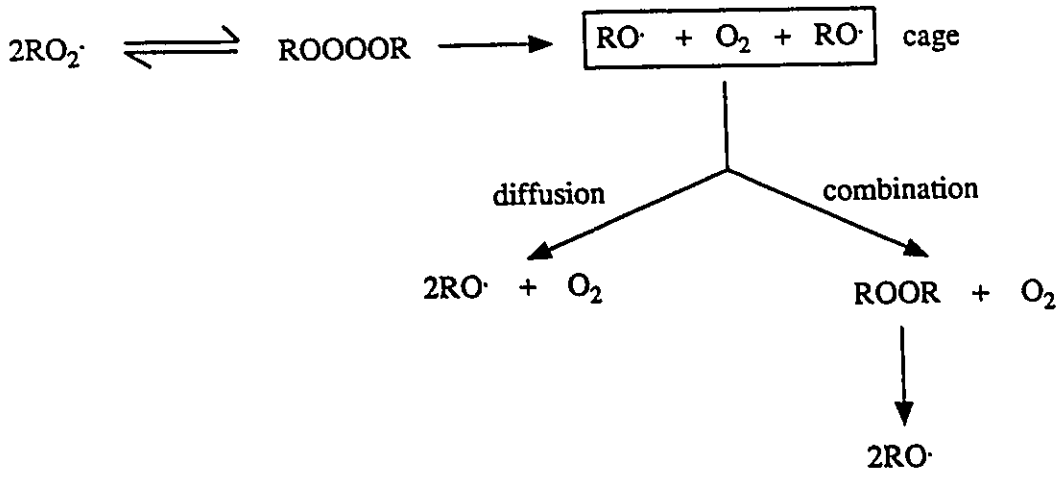
Peroxy radical	Rate Constants K, $M^{-1}Sec^{-1}$	Examples
Primary, $RCH_2OO\cdot$	$2\text{-}4 \times 10^8$	p-Xylene, 1-Octene
Secondary, RR'CHOO·	$20\text{-}40 \times 10^6$ (benzylic)	Ethylbenzene, styrene
	$1\text{-}10 \times 10^6$ (allylic)	3-Heptene, Methyl oleate
	$6\text{-}8 \times 10^6$ (cyclic)	Cyclohexene, tetralin
Tertiary, RR'R"COO·	$0.1\text{-}60 \times 10^4$	Cumene, α-methylstyrene
Hydroperoxy, HOO·	$2.0. \times 10^6$ 1.2×10^9	Hydrogen peroxide 1,4-Cyclohexadiene

The modes of decomposition of tetroxides (RO_4R) are dependent on the structure of the alkyl group.[43-45] For example, the tetroxides derived from primary and secondary alkylperoxy radicals undergo disproportionation to an alcohol and a carbonyl compound via a cyclic mechanism[48](eq.[1.30]).

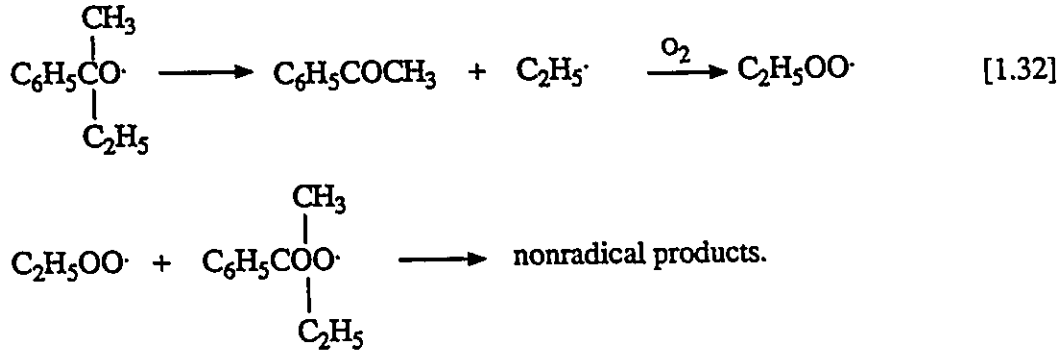


[1.30]

The tetroxides derived from tert-alkylperoxy radicals undergo decomposition to alkoxy radicals and molecular oxygen [1.31]. The tertiary alkoxy radicals (RO·) then



undergo rearrangement to nonradical products (eq.[1.32]). In general, the chain termination step proceeding via a disproportionation mechanism (eq.[1.30]) results in faster radical termination than by a decomposition mechanism (eq.[1.31]). These



pathways explain in part, the much higher rates of termination of primary and secondary alkylperoxy radicals compared to the tertiary alkylperoxy radical. The overall rate of autoxidation of a substrate is determined not only by the propagation rate constant, but also by the termination rate constant.

1.2.4. SOLVENT EFFECTS

Studies have been made of media effects of the oxidation of organic compounds in radical reactions.[38] In the chain initiation steps, the rates of self-initiation reactions (eq.[1.17] and [1.18]) are usually low compared to the rate of degenerate chain-branching

reactions (eq.[1.19]-[1.21]). Thus, if there are traces of hydroperoxides or other compounds present which can be oxidized more readily than the initial hydrocarbon, the rate of formation of radicals in the initial stage will increase. Therefore, the decomposition of hydroperoxide plays an important role in the chain initiation step.

The influence of solvents on the rate constant for the decomposition of hydroperoxides has been examined.[38] The nature of the solvents has a considerable influence, both on the rate and mechanism of the decomposition of hydroperoxides into free radicals. For example, in benzene, pyridine, xylene, anisole, carbon tetrachloride, chloroform, cyclohexane and chlorobenzene, tert-butyl hydroperoxide undergoes virtually no decomposition in 5hrs. at 74°C, whereas in benzyl alcohol over 90% decomposition occurs in the same period. This is due to the formation of a hydrogen bond between molecules of hydroperoxide and the solvent, resulting in the accelerated decomposition of hydroperoxides into radicals (eq.[1.33]) in the propagation and termination steps. When

$$\mathrm{ROOH} + n\mathrm{R'OH} \rightleftharpoons \left[\begin{array}{c}\text{hydrogen bonding}\\ \text{complex}\end{array}\right] \longrightarrow \begin{array}{l}\text{Free radical}\\ + m\mathrm{R'OH}\end{array} \qquad [1.33]$$

substances which have a dipole moment greater than zero are oxidized, the reactions can be considered as the interaction of two dipoles in both the propagation and termination steps. Moreover, when substances which have a dipole moment equal to zero are oxidized, the chain-termination reaction can still be considered as the interaction of two dipoles. Due to the presence of the O-O· functional group, the dipole moment of the alkyl peroxy radical is always different from zero. Hence the rate constants of propagation and termination must depend on the dielectric constant of the medium.[50,51] In general, the higher the dielectric constant, the higher the rate of autoxidation is in the oxidation of hydrocarbons.

Another important factor which should also be taken into account is the formation of hydrogen bonding between a peroxy radical (ROO·) and solvent molecules. This was first postulated and formulated by Denisov in 1960.[52] The chemical interaction between a

peroxy radical and solvents containing hydroxyl groups (HOX, where X can be H, R, R-C=O or OR) should result in the formation of "free radical" hydrogen bonds, ROO·---HOX. The reactivity of these radicals is lower than the unsolvated peroxyl radical, leading to the lower rate in the chain propagation step (eq. [1.24]).

1.3 Mechanistic Principles of Cobalt-Catalyzed Autoxidation Reactions

The application of catalysts in the liquid phase oxidation of hydrocarbons is an important tool for the acceleration of such processes as well as for the increase in the selectivity of product formation. Catalysts may affect the reaction both by changing the kinetic parameters of certain elementary processes and by offering new routes which do not take place (or take place to a negligible extent) in the absence of catalysts. As a result, the rate of formation for certain products also change and consequently the yields of the various products differ from those observed in the non-catalyzed process.

The liquid phase metal-catalyzed oxidation of organic compounds fall into three categories: 1) Metal-catalyzed autoxidation. 2) Activation of molecular oxygen by metal complexes. 3) Direct homolytic oxidation by metal complexes.

1.3.1. METAL-CATALYZED AUTOXIDATION

The metal-catalyzed homolytic decomposition of alkyl hydroperoxidic intermediates (ROOH) is the most common pathway for the catalysis of liquid-phase autoxidations. Information concerning the roles of metal complexes in oxidations has been gained from the separate studies of their interactions with alkyl hydroperoxides under nonautoxidizing conditions.[53-57] The rapid decomposition of alkyl hydroperoxides in

hydrocarbon solutions in the presence of trace amounts of iron, manganese, cobalt, or copper compounds is well known. The two principal reactions of alkyl hydroperoxides with metal complexes are shown below:

1) Reduction:

$$ROOH + M^{(n-1)+} \longrightarrow RO\cdot + M^{n+} + HO^- \qquad [1.34]$$

2) Oxidation:

$$ROOH + M^{n+} \longrightarrow ROO\cdot + M^{(n-1)+} + H^+ \qquad [1.35]$$

In general, metal complexes catalyze autoxidations by generating chain-initiating radicals via reaction [1.34] or [1.35]. The relative rates of both reactions are roughly correlated with the redox potential of the $M^{n+}/ M^{(n-1)+}$ couple. Table [1.5] lists the redox potentials of some metal ions that are known to react with hydroperoxides.

Table [1.5] Redox Potentials (Aqueous Solution)

$M^{n+} + e \rightarrow M^{(n-1)+}$	E_0(V)	$M^{n+} + 2e \rightarrow M^{(n-2)+}$	E_0(V)
Ag(II) + e → Ag(I)	1.98	Pb(IV) + 2 e → Pb(II)	1.69
Co(III) + e → Co(II)	1.82	Tl(III) + 2 e → Tl(I)	1.25
Ce(IV) + e → Ce(III)	1.61	2 Hg(II) + 2 e → $Hg(I)_2$	0.92
Mn(III) + e → Mn(II)	1.51		
Fe(III) + e → Fe(II)	0.77		
Cu(II) + e → Cu(I)	0.15		
Mo(VI) + e → Mo(V)	~0.2[a]	$HO_2\cdot + e + H^+ \rightarrow H_2O_2$	1.68[b]
W(VI) + e → W(V)	−0.03	$H_2O_2 + 2e + 2H^+ \rightarrow 2H_2O$	1.77[c]
V(III) + e → V(II)	−0.20	$O_2 + e + H^+ \rightarrow HO_2\cdot$	−0.32[b]
Ti(IV) + e → Ti(III)	−0.37	$O_2 + 2e + 2H^+ \rightarrow H_2O_2$	0.68[c]
Cr(III) + e → Cr(II)	−0.41	$O_2 + e \rightarrow O_2^-$	−0.45[b]

[a] R. J. P. Williams, *Adv. Chem. Coord. Compd.* p. 279 (1961).
[b] See P. George, "Oxidases," Vol. I. Wiley, New York, 1965.
[c] See M. M. Jones, "Ligand Reactivity and Catalysis." Academic Press, New York, 1968.

These values pertain to aqueous solutions, since redox potentials of metal complexes in organic solvents are not generally known. Redox potentials are influenced by the nature of the ligands and the solvent.

Since alkyl hydroperoxides are fairly strong oxidants but weak reducing agents,

reaction [1.34] is generally faster than reaction [1.35]. When the metal ion is a strong reducing agent, reaction [1.34] predominates. For example, chromous ion Cr^{2+} reduces alkyl hydroperoxides to the corresponding alcohols in a stoichiometric reaction.[58]

$$RO_2H + Cr^{2+} \longrightarrow RO\cdot + Cr^{3+}OH \qquad [1.36]$$

$$RO\cdot + Cr^{2+} \longrightarrow ROCr^{3+} \qquad [1.37]$$

The lack of a convenient route for regeneration of the Cr^{2+} precludes a catalytic process. Copper (I) complexes similarly reduce alkyl hydroperoxides to the corresponding alcohols, but a catalytic process is possible since there are several routes available for regenerating copper (I).[58,59] Iron (II) complexes also reduce alkyl hydroperoxides leading to a series of synthetically useful reactions.[60]

When the metal has two oxidation states with comparable stability, reactions [1.34] and [1.35] can occur concurrently. Thus, cobalt and manganese compounds are the most effective catalysts for autoxidations, since they are able to induce efficient catalytic decomposition of alkyl hydroperoxides (eq.[1.38] and [1.39]). The net transformation is a

$$ROOH + Co^{2+} \longrightarrow RO\cdot + Co^{3+} + OH^- \qquad [1.38]$$

$$ROOH + Co^{3+} \longrightarrow RO_2\cdot + Co^{2+} + H^+ \qquad [1.39]$$

catalytic decomposition of the hydroperoxide into alkoxy and alkylperoxy radicals (eq. [1.40]). In fact, cobalt complexes are generally effective catalysts and have received the

$$2ROOH \xrightarrow{[Co^{2+}/Co^{3+}]} RO_2\cdot + RO\cdot + H_2O \qquad [1.40]$$

most attention.[52,61,62]

The relative rates of reactions [1.38] and [1.39] are markedly dependent on the solvent.[61,62] In nonpolar solvents, reaction [1.39] constitutes the slower, rate-determining step, and the cobalt catalyst is present mainly in the trivalent oxidation state. Other workers[52] have reported that the commencement of the cobalt-catalyzed autoxidation of hydrocarbons is accompanied by the oxidation of Co^{2+} to Co^{3+}. The transformation is

easily observed by the change in color from pale violet or pink of Co^{2+}species to the dark green of Co^{3+} intermediates. The concentration of Co^{3+} reaches a maximum during the autoxidation and then decreases.

In the case of non-catalytic oxidations, the rate of chain-initiation is dependent on the thermal or radical induced decomposition of alkyl hydroperoxide (ROOH). The catalytic effect, however, usually becomes so strong that such decomposition may become less important. Summarizing briefly, it is clear that the presence of transition metal complexes in oxidation of hydrocarbons can affect the rate not only of hydroperoxide decomposition, but also of chain propagation as described in following:

Initiation:

$$2ROOH \xrightarrow{[M^{(n-1)}/M^{n+}]} RO_2\cdot + RO\cdot + H_2O \qquad [1.41]$$

Propagation:

$$RO\cdot + RH \longrightarrow ROH + R\cdot \qquad [1.42]$$

$$RO_2\cdot + RH \longrightarrow RO_2H + R\cdot \qquad [1.43]$$

$$R\cdot + O_2 \longrightarrow RO_2\cdot \qquad [1.44]$$

1.3.2. ACTIVATION OF MOLECULAR OXYGEN BY COBALT COMPLEXES

The direct participation of dioxygen in the oxidation of organic compounds, as effected by transition metal complexes, is referred to as oxygen activation. When oxygen is bubbled through an organic solution of a transition metal complex, it is often brought into the coordination sphere of the metal complex. The nature of coordinated dioxygen and its reactivity with the organic substrate is a function of the metal, its oxidation state, its ligand system and the reaction conditions. The best known example of a metal-mediated transfer of oxygen to an organic substrate is the commercially important gas-phase oxidation of ethylene to ethylene oxide over a supported silver catalyst in which

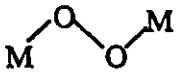
a silver-dioxygen complex of ethylene has been implicated[63](eq.[1.45]).

$$CH_2{=}CH_2 + O_2 \xrightarrow[250^0C]{[Ag\,/\,Al_2O_3]} H_2C\!-\!\underset{\diagdown O \diagup}{}\!CH_2 \qquad [1.45]$$

The interaction of metal complexes with dioxygen can lead to successive one-electron transfers from the metal species, giving the superoxo and peroxo complexes, MO_2· and MOOM, respectively. Vaska[64] has represented such complexes as shown in Figure [1.1].

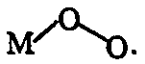
Peroxo Complexes:

side-bonded
O-O = 1.4-1.5 Å
diamagnetic



μ-peroxo
O-O = 1.4-1.5 Å
diamagnetic

Superoxo Complexes:

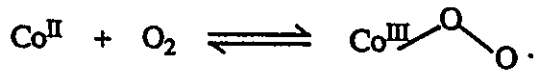


end-bonded
O-O = 1.25-1.3 Å
Paramagnetic

Fig. [1.1]

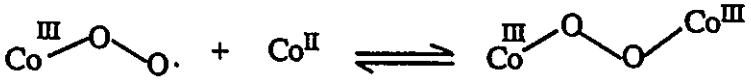
Examples of both peroxo and superoxo complexes have been identified in which oxygen is coordinated to either one metal center or to two metal centers.[64-69] Peroxo complexes are far more numerous than those of transition metal superoxo complexes. In all cases, coordination of dioxygen to the metal center results in lengthening of the O-O bond. This is a consequence of transfer of electron density into π^* orbitals of ligated dioxygen. In both side-bonded and μ-peroxo complexes the O-O bond length is generally between 1.4 and 1.5Å while in superoxo complexes bond lengths vary from 1.25 to 1.3Å compared with the O-O bond length of 1.21Å in the ground state dioxygen moelcule. Among the three different types of bonding shown in Figure [1.1], side-bonded peroxo complexes are the most common. Often they may be readily formed by merely bubbling oxygen through solutions of the complexes of the lower valent group VIII metals. Side-bonded peroxo complexes of the group V or VI metals are usually formed by

reactions with hydroperoxides. Superoxo complexes are the least common type and occur only in some Co(III) complexes. In fact, cobalt is the only metal for which all three bonding modes have been observed. For example, superoxocobalt(III) complexes are formed through an one-electron reduction of dioxygen by Co(II). In many cases, the superoxocobalt(III) species is only a transient intermediate and is rapidly reduced by a second Co(II) to a μ-peroxocobalt(III) complex.[70] Table [1.6] shows four examples of peroxo and superoxo cobalt complexes.



[1.46]

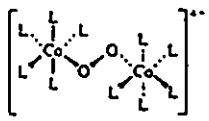
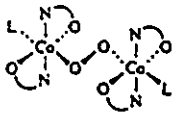
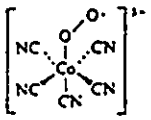
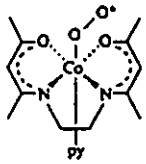
Superoxocobalt (III)



[1.47]

μ-Peroxocobalt (III)

Table [1.6] Examples of peroxo and superoxo cobalt complexes.

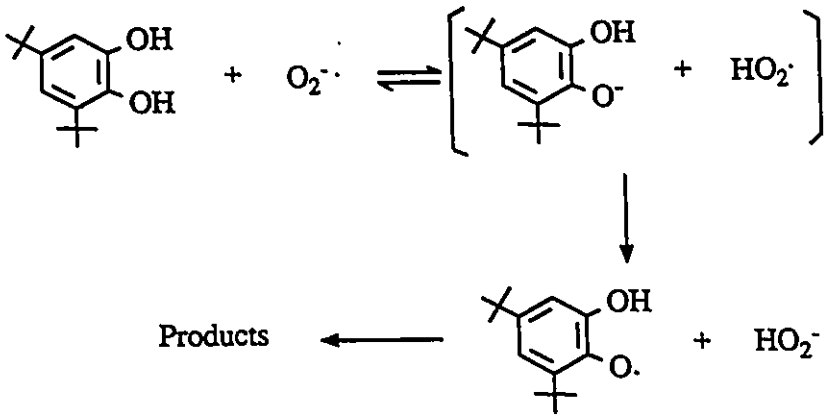
Structure		O—O (Å)	Reference*
μ-Peroxo complexes			
	L = NH_3	1.47	a.
		1.35	b
= $[Co(Salen).DMF]_2O_2$			
Superoxo complexes			
		1.24	c
		1.26	d

Abbreviations: py, pyridine; pyO, pyridine oxide; DMF, dimethylformamide; HMPA, hexamethylphosphorus triamide; Bipy, bipyridine; Salen, salicylaldehyde ethylenimine.

a) W. P. Schaeffer, Inorg. Chem. 7, 725 (1968). b) M. Calligans, G. Nardis, L. Randaccio, and A. Ripamonti, J. Chem. Soc. A, p.1069 (1970). c) L. O. Brown and K. N. Raymond, Inorg. Chem. 14, 2595 (1975). d) G. A. Rodley and W. T. Robinson, Nature (London) 235, 438 (1972)

In general, the reactivity of cobalt complexes toward molecular oxygen is increased by strong σ-donor ligands and by highly polarizable ligands.[66] In contrast, it is decreased by strong π-acceptor ligands, and metals in a high oxidation state.

Electrochemical studies[71] show that the superoxide ion ($MO_2^{-\cdot}$) is a moderate reducing agent and a weak oxidant. Furthermore, solutions of superoxide behave as bases although the pKa of $HO_2^{\cdot}$ in water is 4.88. Thus the first step in the reaction of superoxide with dipolar protic substrates is probably proton removal to produce the hydroperoxy radical, as in the oxidation of 3,5-tert-butylcatechol (eq.[1.48]).



[1.48]

Some authors[72-74] have also suggested with experimental evidence that metals or metal ions, in some cases, act as radical initiators for autoxidation by forming a complex with oxygen (Fig. [1.2]).

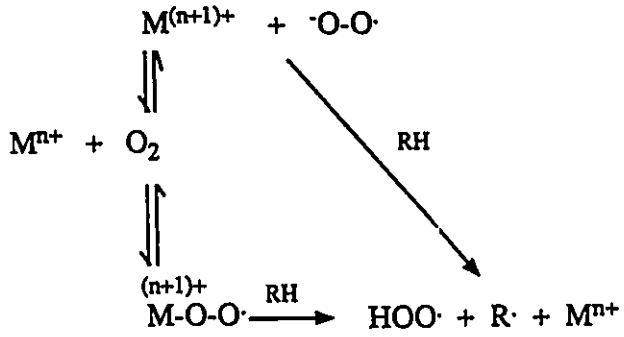


Fig. [1.2]

Therefore, activation of molecular oxygen by metal complexes would be a source for radical initiators in autoxidation. However, the metal complex itself can react directly with alkyl hydroperoxides to generate chain-initiating radicals. Since a trace amount of alkyl hydroperoxides may be present in most hydrocarbon mixtures, it is often difficult to distinguish between the metal-hydroperoxide interactions and those involving oxygen activation.

1.3.3. DIRECT HOMOLYTIC OXIDATION BY METAL COMPLEXES

Catalytic oxidations as described in sections 1.3.1. and 1.3.2. involve the interaction of the metal catalyst with either hydroperoxide or dioxygen. There is another class of catalytic oxidations that involves the direct attack on the substrate by the metal complex. The catalyst is regenerated with peroxidic intermediates or dioxygen. The industrially important oxidation of p-xylene to terephthalic acid with a cobalt catalyst is a relevant example (eq.[1.4]).[9]

The direct interaction of strong metal oxidants with organic substrates can lead to the production of radical intermediates in two ways. Both processes are depicted below for the reaction of a metal triacetate with a hydrocarbon RH. The net result in both cases is a

a) Electron transfer:

$$M(OAc)_3 + RH \rightleftharpoons RH^{+\cdot} + M(OAc)_3^- \qquad [1.49]$$

$$RH^{+\cdot} \longrightarrow R\cdot + H^+ \qquad [1.50]$$

b) Electrophilic substitution:

$$RH + M(OAc)_3 \longrightarrow RM(OAc)_2 + HOAc \qquad [1.51]$$

$$RM(OAc)_2 \longrightarrow R\cdot + M(OAc)_2 \qquad [1.52]$$

one-electron reduction of the metal oxidant with concomitant formation of the substrate radical (R·). The ease of electron transfer oxidation of hydrocarbons to produce the

cation-radical ($RH^{+\cdot}$) is related to the ionization potential.[75]

Electrophilic substitution is expected to parallel electron transfer, and there is little distinction between these two processes based on structure-reactivity relationships alone. Moreover, they are probably competing processes in a number of instances, and the dominant pathway with a particular oxidant may vary with a change in substrate.

The oxidation of alkylbenzene at relatively low temperature (90-100°C) and oxygen pressures (0.2-1 bar) can be achieved in acetic acid in the presence of relatively high concentrations (0.1M) of cobalt acetate.[76] The generally accepted mechanism of this reaction is by electron transfer (eq.[1.53] and [1.54]). The formation of benzyl acetate is derived from the subsequent reaction of the benzyl radical with cobalt acetate (eq.[1.55] and [1.56]). However, under autoxidizing conditions, the benzyl radical is trapped by

$$ArCH_3 + Co^{III} \rightleftharpoons [ArCH_3]^{+\cdot} + Co^{II} \qquad [1.53]$$

$$[ArCH_3]^{+\cdot} \longrightarrow ArCH_2^{\cdot} + H^+ \qquad [1.54]$$

$$ArCH_2^{\cdot} + Co^{III} \longrightarrow ArCH_2^+ + Co^{II} \qquad [1.55]$$

$$ArCH_2^+ + HOAc \longrightarrow ArCH_2OAc + H^+ \qquad [1.56]$$

dioxygen. The aromatic aldehydes are the primary products which are formed by reaction of benzylperoxy radicals with Co(II) (eq.[1.57] to [1.60]).

$$ArCH_2^{\cdot} + O_2 \longrightarrow ArCH_2O_2^{\cdot} \qquad [1.57]$$

$$ArCH_2O_2^{\cdot} + Co^{II} \longrightarrow ArCH_2O_2Co^{III} \qquad [1.58]$$

$$ArCH(H)-O-O-Co^{III} \longrightarrow ArCHO + HOCo^{III} \qquad [1.59]$$

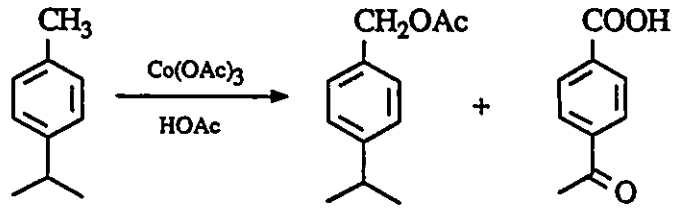
$$HOCo^{III} + HOAc \longrightarrow AcOCo^{III} + H_2O \qquad [1.60]$$

Some alkylbenzene radicals are also formed during the oxidation by the efficient trapping of the benzylperoxy radical with a relatively high concentration of the starting

material (eq.[1.61]).

$$ArCH_2O_2\cdot + ArCH_3 \longrightarrow ArCH_2OOH + ArCH_2\cdot \qquad [1.61]$$

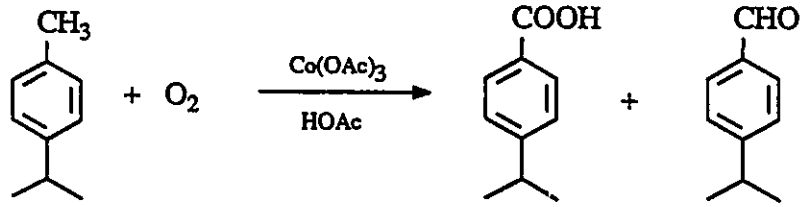
Onopchenko and co-workers[77-79] found the relative rates of oxidation of alkylbenzenes by Co(III) acetate in acetic acid to be the reverse of that expected from a classical free radical mechanism. For example, toluene is oxidized approximately 10 times faster than cumene. Similarly, the oxidation of p-cymene with stoichiometric amounts of Co(III) acetate occurs exclusively at the methyl group (eq.[1.62]). Under an oxygen



[1.62]

81% 15%

atmosphere, p-isopropylbenzoic acid is the major product (eq.[1.63]). Similarly,



[1.63]

90% 10%

p-ethyltoluene and sec-butyltoluene afforded products derived mainly from the oxidation of the methyl groups. This can be accounted for by proton loss from the intermediate cation-radical in (eq.[1.54]) as governed by stereoelectronic considerations and not by the thermodynamic stability of the formed radical.[78]

Furthermore, in contrast to free radical autoxidations with direct oxidation of alkylaromatics via electron transfer, no deuterium kinetic isotope effect was observed for the latter reaction. This was rationalized by a mechanism involving reversible one-electron

transfer to produce the cation-radical, followed by proton loss to the alkyl radical (eq.[1.64] and [1.65]). The rate determining step is the electron transfer (eq.[1.64]).

$$RH + Co^{III} \underset{}{\overset{k_1}{\rightleftharpoons}} RH^{+\cdot} + Co^{II} \qquad [1.64]$$

$$RH^{+\cdot} \xrightarrow{K_2} R^{\cdot} + H^{+} \qquad [1.65]$$

$$R^{\cdot} \xrightarrow{Co^{III}} R^{+} \xrightarrow{HOAc} ROAc \qquad [1.66]$$

$$R^{\cdot} \xrightarrow{O_2} RO_2^{\cdot} \longrightarrow Product \qquad [1.67]$$

The rates of oxidation of aromatic hydrocarbons via the electron transfer mechanism are greatly affected by additives such as halide ion. For example, the rate of oxidation of toluene by Co(III) acetate is enhanced in the presence of halide, especially bromides such as R-Br, HBr, NH_4Br or NaBr.[80-85] The active catalyst is considered to be acetato-halide cobalt, formed in the reactions shown below:

$$Co(OAc)_3 + NaX \longrightarrow Co^{III}(OAc)_2X + NaOAc \qquad [1.68]$$

X = Br, Cl

This active species then reacts with aromatic hydrocarbons via two competing processes, namely, the direct oxidation of the substrate to the cation-radical (eq.[1.69]) as mentioned above and hydrogen abstraction by a ligand-derived radical (X·) (eq.[1.70]).

$$XCo^{III} \xrightarrow{ArH} XCo^{II} + ArH^{+\cdot} \qquad [1.69]$$

$$XCo^{III} \longrightarrow Co^{II} + X^{\cdot} \qquad [1.70]$$

The halide radical in reaction [1.70] acts as a chain transfer agent. (eq.[1.71]-[1.74])

$$X^{\cdot} + ArCH_3 \longrightarrow HX + ArCH_2^{\cdot} \quad [1.71]$$

$$ArCH_2^{\cdot} + O_2 \longrightarrow ArCH_2O_2^{\cdot} \quad [1.72]$$

$$ArCH_2O_2^{\cdot} + Co^{II}(OAc)_2 \longrightarrow ArCHO + Co^{III}(OAc)_2(OH) \quad [1.73]$$

$$Co^{III}(OAc)_2(OH) + HX \longrightarrow Co(OAc)_2X + H_2O \quad [1.74]$$

The relative rates of the two processes [1.69] and [1.70] are dependent on several factors: (1) the ionization potential of ArH, (2) the oxidation potential of the ligand (X), in which the relative ease of oxidation is in the order $X = Br^- > Cl^- >> AcO^-$, and (3) the temperature. An electron transfer oxidation of ArH is generally observed with X = OAc (eq.[1.69]), where ligand oxidation predominates with X= Br (eq.[1.70]).

The rate of oxidation of aromatic hydrocarbons by metal acetate oxidants are also dramatically affected by strong acids. Thus, Mn(III) and Co(III) acetates in the presence of sulfuric or trifluoroacetic acid (TFA) rapidly and selectively oxidize aromatic side chains at 25°C[86] (eq.[1.75]-[1.77]). Enhancement of the oxidizing (electrophilic) properties by strong acids such as TFA is a general feature of oxidation with metal acetates.

$$ArCH_3 + Co(OAc)_3 \xrightarrow{\text{TFA-HOAc}} \begin{cases} \xrightarrow{N_2} ArCH_2OAc & [1.75] \\ \xrightarrow{O_2} ArCOOH & [1.76] \end{cases}$$

$$ArCH_3 + Mn(OAc)_3 \xrightarrow[O_2]{HOAc\text{-}H_2SO_4} ArCHO, \text{ etc.} \quad [1.77]$$

1.4 Aims of Research

Catalytic methods are not limited to the manufacture of bulk chemicals. They are increasingly being used in the industrial production of fine organic chemicals and even in laboratory scale syntheses. The emphasis in organic synthesis today is placed firmly on selectivity. In industry, increasing raw materials costs have made selectivity a key factor in process economics. Academic organic chemists, striving to synthesize organic molecules of ever-increasing complexity, are continuing to seek new methods for achieving chemo-, regio- and stereoselectivity.

The controlled oxidation of hydrocarbons and of other organic compounds has recently become of considerable importance as a means for the direct synthesis of valuable oxygen-containing compounds. Although many kinetic studies and efficient oxidation processes of this type have been well established, the development of the chemical industry requires further improvements in their ability to control the course of oxidative processes.

The aim of this research project was to discover and develop new processes, catalyzed by metal complexes, for the controlled oxidation of hydrocarbons under homogeneous conditions. A variety of substrates to be studied included substituted toluenes, benzylic hydrocarbons, cyclic and acyclic ethers as well as acetals. In each case, the product aldehydes, acids, ketones, esters and lactones were characterized and the reaction conditions were optimized in order to maximize the yield and the selectivity.

Chapter 2

Selective Catalytic Oxidation of Aromatic Hydrocarbons

2..1 Introduction

Aromatic hydrocarbons constitute one of the major groups of basic building blocks of the petrochemical industry.[87] The most important source is the catalytic reforming of naphtha, which affords a mixture of benzene, toluene, ethylbenzene, and xylenes, together with C_9 and C_{10} aromatic hydrocarbons. Oxidation is probably the most widely used unit process in the conversion of aromatic hydrocarbons to such industrial chemicals as phenol, terephthalic acid and acetone.[88]

2.1.1. AROMATIC ALDEHYDES VIA OXIDATION

Aromatic aldehydes are important intermediates in the industrial synthesis of a wide variety of speciality chemicals. Some of their applications are shown in Table [2.1].

Table [2.1] Application of substituted Benzaldehydes

BENZALDEHYDE	MAIN APPLICATIONS
p-Methoxy	Flavours and fragrances
p-tert-Butyl	Flavours and fragrances
o-Chloro	Agrochemicals, dyes, pharmaceuticals
2,6-Dichloro	Agrochemicals, dyes, pharmaceuticals
m-Phenoxy	Pyrethroid insecticides
o-Nitro	Pharmaceuticals
p-Nitro	Dyestuffs, pharmaceuticals
o-Hydroxy	Flavours and fragrances
m-Hydroxy	Dyestuffs
p-Hydroxy	Pharmaceuticals, agrochemicals, flavours
3,4,5-Trimethoxy	Pharmaceuticals
3-Methoxy-4-hydroxy (Vanillin)	Flavours, Pharmaceuticals

[Ref.] W. Ando, and Y. M. Oka, "The Role of Oxygen in Chemistry and Biochemistry" p.243 (1988).

Benzaldehyde, for example, is used in the manufacture of a range of flavour and fragrance chemicals, dyes, agrochemicals, and the artificial sweetener aspartame. In the pharmaceutical industry benzaldehyde is an important raw material in the manufacture of chloramphenicol, ephedrine and ampicillin.[89] Many of these compounds are not produced from benzaldehyde, but from the corresponding substituted toluene via oxidation. Despite the enormous amount of research which has been carried out in this area, there are still problems in a paucity of efficient, commercially valuable methods for the conversion of substituted toluenes to the corresponding benzaldehydes.

The most frequently applied methods for the synthesis of aromatic aldehydes are summarized in Table [2.2].

Table [2.2] ArCHO --- Synthetic Methods

General	1) Halogenation / Hydrolysis 2) Oxidation 3) $ArCO_2H$ hydrogenation
Specific	4) Carbonylation (Gattermann - Koch) 5) Formylation (Gattermann; Reimer -Tiemann; Vilsmeier - Haack)

Side-chain chlorination of toluene to the corresponding benzal chlorides, followed by hydrolysis,[90] is widely applied. However, the process possesses several disadvantages, such as the formation of substantial amounts of the corresponding benzoic acid and/or benzyl alcohol as by-products, contamination of chlorinated impurities, which are difficult to remove, as well as production of large amounts of chloride effluent.

As we know, oxidative methods are fraught with many problems, the main one being selectivity. Direct catalytic hydrogenation of the corresponding benzoic acid is potentially attractive but difficult to realize. In certain cases, the aldehyde group can be

introduced via carbonylation and formylation as shown below:

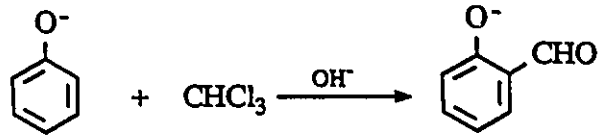
1) Carbonylation with carbon monoxide and HCl (The Gattermann-Koch reaction).[91]

$$ArH + CO + HCl \xrightarrow[CuCl]{AlCl_3} ArCHO \qquad [2.1]$$

2) Formylation with zinc cyanide and HCl (The Gattermann reaction).[92]

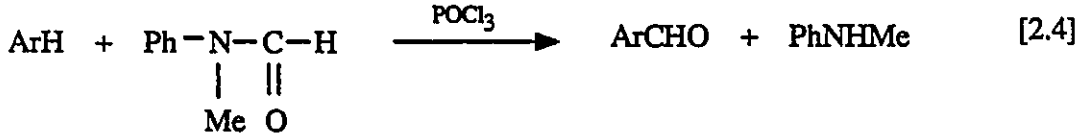
$$ArH + Zn(CN)_2 \xrightarrow{HCl} ArCH{=}NH_2^+Cl^- \xrightarrow{H_2O} ArCHO \qquad [2.2]$$

3) Formylation with chloroform (The Reimer-Tiemann reaction).[93]



[2.3]

4) Formylation with disubstituted formamides (The Vilsmeier-Haack reaction).[94]



[2.4]

These methods have selectivity problems in terms of the formation of isomers. Because of these disadvantages, the synthesis of aromatic aldehydes via oxidation is an attractive method.

Some major oxidative methods which can, in principle, be used for converting toluenes to the corresponding benzaldehydes can be summarized as follows:

1) Stoichiometric oxidation

2) Electrolytic / Electrocatalytic oxidation

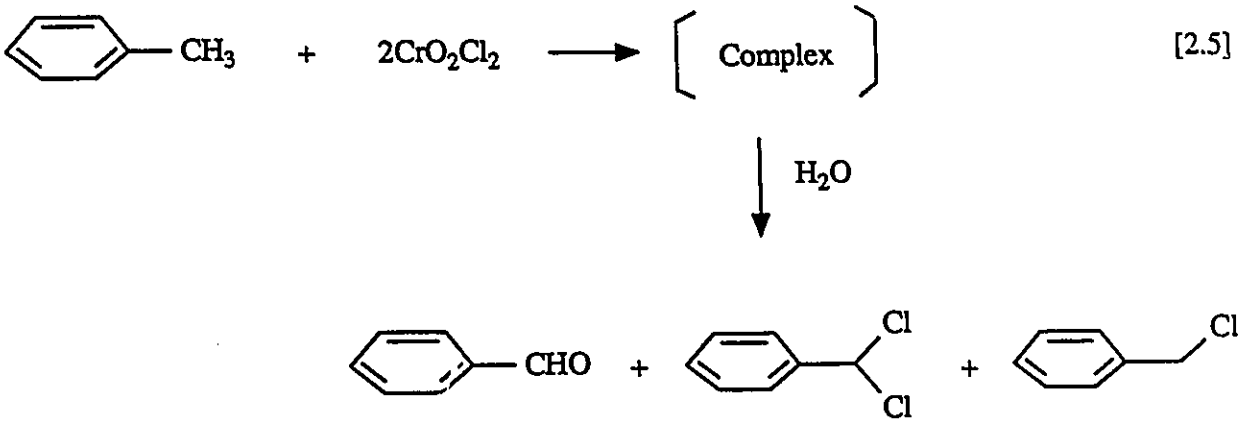
3) Catalytic oxygen transfer

4) Oxidative halogenation

5) Catalytic autoxidation

6) Biocatalytic oxidation

Stoichiometric oxidation with inorganic oxidants such as CrO_2Cl_2 (Étard reaction), CrO_3 / Ac_2O, CrO_3 / Py, MnO_2, Ce^{IV} or SeO_2 is the traditional method for aromatic aldehydes synthesis. For example, The Étard reaction[95] gives aromatic aldehydes in high yield.[eq. 2.5]

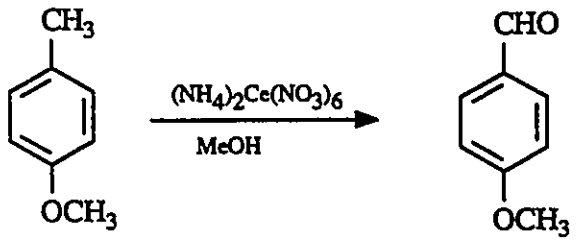


[2.5]

The serious effluent problems associated with these methods as mentioned in chapter 1 make them largely obsolete. However, this problem in stoichiometric oxidation can be largely solved via electrolytic regeneration of the oxidant.[96] BASF, for example, has reportedly commercialized the production of p-tert-butylbenzaldehyde and p-alkoxybenzaldehydes via direct anodic oxidation of the corresponding toluenes.

Alternatively, aldehydes may be produced by the indirect electrolytic oxidation of toluenes whereby the inorganic oxidant is regenerated in a seperate step (ex-cell method) or in-situ (in-cell, electrocatalytic method). For example, Torii and co-workers[97] have

reported the indirect electrolytic oxidation of p-methoxytoluene to p-anisaldehyde using ceric ammonium nitrate as the primary oxidant (eq.[2.6]).



[2.6]

In-cell method: 77% yield

Ex-cell method: 94% yield

Another way of solving the heavy metal effluent problem is to utilize a cheap single oxygen donor in combination with a metal oxidant in catalytic amounts, e.g., catalytic oxygen transfer.[98] Possible combinations of metal oxidants and oxygen donors are shown in (eq. [2.7]). For example, the selective oxidation of electron-rich

$$ArCH_3 + 2XO \xrightarrow{\text{catalyst}} ArCHO + 2X + H_2O \qquad [2.7]$$

Catalysts	Oxygen Donors
Cr^{VI}	H_2O_2
Ce^{IV}	t-BuO_2H
MnO_2	R_3NO
SeO_2	NaOCl
V^V	$Na_2S_2O_8$
	HNO_3

alkylaromatics to the corresponding aldehydes utilizing peroxydisulfate and a Fe^{II}/Cu^{II}

catalyst combination has been reported.[99] p-Methoxytoluene afforded p-anisaldehyde in 85% yield. A disadvantage of peroxydisulfate is its high molecular weight (1Kg aldehyde = 4 Kg $Na_2S_2O_8$), resulting in a low space-time yield.

The most attractive oxygen donor from the point of view of price, molecular weight and environmental aspect is H_2O_2. Unfortunately the use of H_2O_2 as the oxidant in these systems suffers from several problems, such as competing hydroxylation of the aromatic nucleus. Since the H_2O_2 is needed only for regeneration of the primary oxo-metal oxidant, a possible way of overcoming this problem is to separate the substrate and H_2O_2 in two phases and use a phase transfer catalyst for shuttling the metal catalyst back and forth.

Another way of utilizing H_2O_2 as the terminal oxidant is via oxidative bromination. In this trivial, but effective method, the aldehyde is produced via side-chain bromination / hydrolysis and the co-produced hydrogen bromide is re-oxidized with H_2O_2 in a separate reaction (Scheme [2.1]).

Scheme [2.1]

$$ArCH_3 + 2Br_2 \xrightarrow[\text{or } In^{\cdot}]{h\nu} ArCHBr_2 + 2HBr$$

$$\downarrow H_2O$$

$$ArCHO + 2HBr \qquad [2.8]$$

$$2HBr + H_2O_2 \longrightarrow Br_2 + H_2O \qquad [2.9]$$

$$\text{Overall: } ArCH_3 + 2H_2O_2 \longrightarrow ArCHO + 2H_2O \qquad [2.10]$$

However, this method is only applicable to substituted toluenes which are not readily susceptible to ring bromination.

Substituted benzyl bromides can also be converted to the corresponding benzaldehydes by oxidation with amine oxides.[100] In principle, this can be combined with regeneration of both the amine oxide and bromine by oxidation with H_2O_2, resulting in an overall oxidation of the toluene to the corresponding benzaldehyde with H_2O_2 as the stoichiometric oxidant (Scheme [2.2]). In practice, side-chain bromination yields mixtures of benzyl and benzal bromides which in principle can be converted to aldehydes by employing a combination of the two methods outlined in Scheme [2.1] and [2.2].

Scheme [2.2]

$$ArCH_3 + Br_2 \xrightarrow[\text{or } In\cdot]{h\nu} ArCH_2Br \qquad [2.11]$$

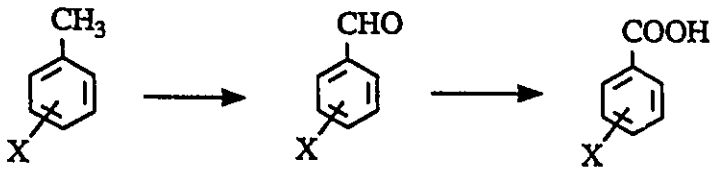
$$ArCH_2Br + R_3NO \longrightarrow ArCHO + R_3NHBr \qquad [2.12]$$

$$R_3NHBr + 2H_2O_2 \longrightarrow R_3NO + 2H_2O + Br_2 \qquad [2.13]$$

$$\text{Overall:} \quad ArCH_3 + 2H_2O_2 \longrightarrow ArCHO + 2H_2O \qquad [2.14]$$

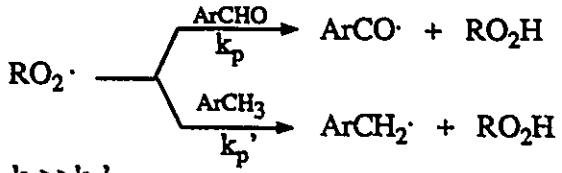
The most attractive oxidant from the point of view of cost is molecular oxygen. Because of this, metal-catalyzed autoxidation of substituted toluenes to the corresponding aldehydes has led to numerous patents and studies in attempts to increase the activity of homogeneous metal catalysts and the selectivity of aldehydes.

Unfortunately, these oxidations suffer from one basic problem: autoxidation of the aldehyde to the corresponding carboxylic acid is much more facile than its formation $k_p >> k_p'$ [eq.[2.16]). The kinetic data showed in Table [2.3] illustrate this point.



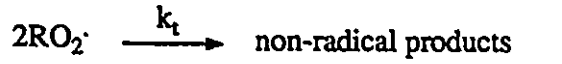
[2.15]

Chain propagation



[2.16]

Chain termination



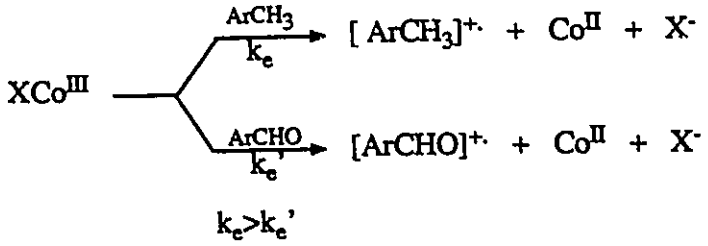
[2.17]

Table [2.3]

Substrate (RH)	k_p ($M^{-1}S^{-1}$)	$2k_t \times 10^{-6}$ ($M^{-1}S^{-1}$)	$k_p / (2k_t)^{1/2} \times 10^3$ ($M^{-1/2}S^{-1/2}$)
$PhCH_3$[a]	0.24	300	0.014
$PhCH_2OH$[a]	4.8	32	0.85
PhCHO[b]	1900	210	130

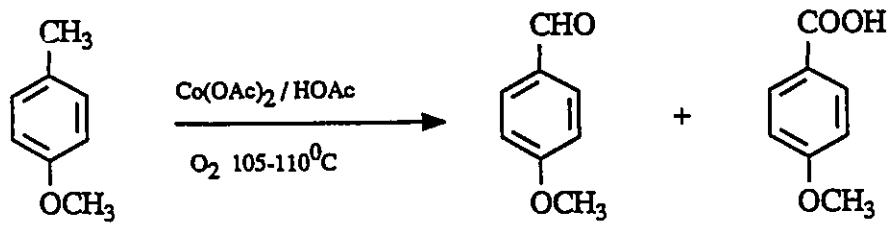
a) 30°C b) 5°C

However, in the presence of a high concentration of cobalt catalyst, the rate determining step is usually oxidation of the substrate by Co(III) via an electron transfer process. Since the electron- withdrawing effect of the carbonyl group increases the ionization potential of the benzaldehyde, the aldehyde is now oxidized at a slower rate (k_e') than the corresponding methylbenzene (k_e) (eq.[2.18]).



[2.18]

A consequence of the above dichotomy is that the selective oxidation of methylbenzenes to the corrsponding benzaldehydes is feasible in the presence of high concentrations of cobalt catalysts under mild conditions. Imamura and co-workers[101-103] have reported the selective oxidation of a variety of alkoxy- and aryloxy toluenes to the corresponding benzaldehydes using high concentrations (0.1-0.5 mol per mole substrate) of $Co(OAc)_2$ as the catalyst in acetic acid at moderate temperatures (90-120^{0}C). Selectivities ranged typically between 50 to 76% at 40-80% conversion. For example, the oxidation of p-methoxytoluene catalyzed by high concentrations of $Co(OAc)_2$ (0.24 mol per mole substrate) in acetic acid at 105-110^{0}C afforded p-anisaldehyde in 76% selectivity with 44% conversion.[103] (eq.[2.19]).

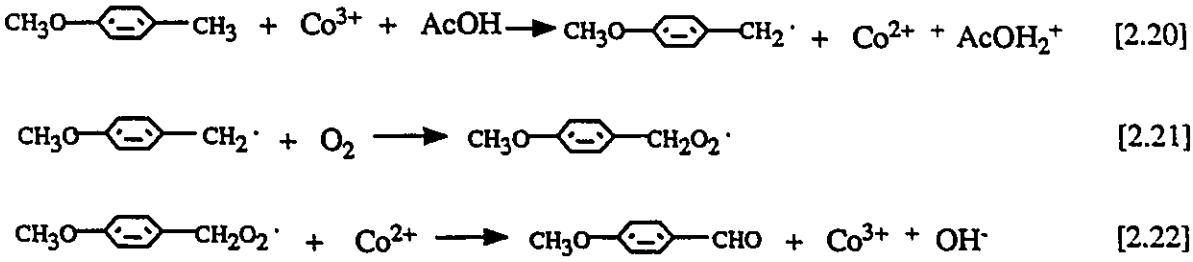


[2.19]

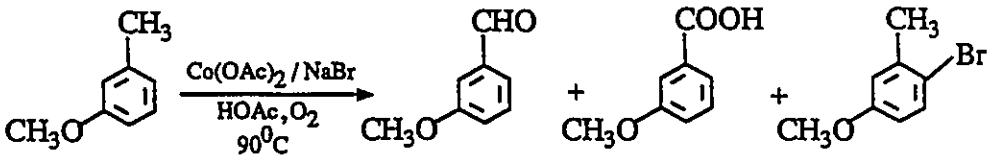
Conversion: 44%, Selectivity: 76%

This reaction occurs via an electron transfer mechanism as shown in Scheme [2.3].

Scheme [2.3]



However, the above conclusion does not strictly apply to the $Co(OAc)_2$ / NaBr catalyst, in which the selectivity may be determined by the relative rates of hydrogen abstraction by bromine atoms (eq. [1.71]). In other words, in the presence of bromine atoms, the selective oxidation of methylbenzenes to the corresponding benzaldehydes can be carried out at low concentrations of cobalt catalysts. Consequently, this is the most useful system for liquid phase autoxidation of substituted toluenes to the corresponding aldehydes. The selectivity of aldehydes is in the range of 60-75% with 40-60% conversion.[104] For example, autoxidation of m-methoxytoluene to the corresponding aldehyde and other products catalyzed by $Co(OAc)_2$ with NaBr in the presence of HOAc afforded m-methoxybenzaldehyde in 60% selectivity with 40% conversion[105](eq. [2.23]).

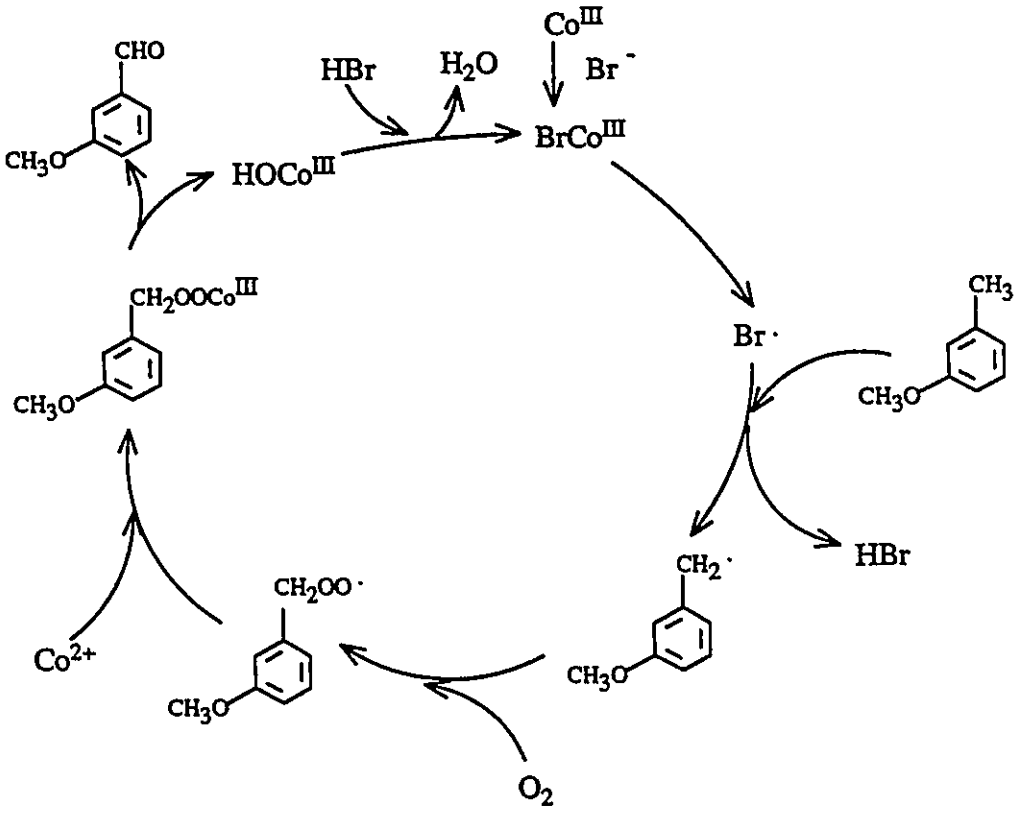


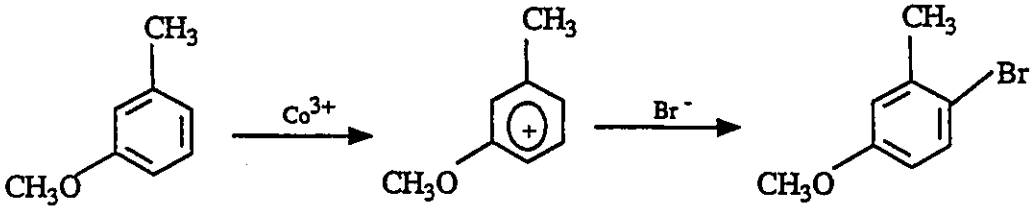
[2.23]

Ratio of m-Methoxytoluene : $Co(OAc)_2$: NaBr = 10:1:0.5 (mmol)
Conversion: 40% Selectivity towards aldehyde: 60%

The bromide ion mainly acts as a radical chain transfer agent to abstract the benzylic hydrogen atom (Scheme [2.4]). The brominated product may arise via the route shown in equation [2.24].

Scheme [2.4]





[2.24]

In recent years, extensive studies have been devoted to elucidating the influence of bromine atoms on the catalytic activity and mechanism.[103,106] The genuine synergistic effect of bromide ions was attributed to the enhancement of the cobalt acetate

monobromide [$Co^{3+}(OAc)_2Br$] which enables the reaction to proceed at a higher rate under mild reaction conditions and is a catalytic process (eq.[2.25-2.27]). Furthermore, a

$$ArCH_3 + Co^{III}Br \longrightarrow ArCH_2\cdot + Co^{II}Br \qquad [2.25]$$

$$ArCH_2\cdot + O_2 \longrightarrow ArCH_2OO\cdot \qquad [2.26]$$

$$ArCH_2OO\cdot + Co^{II}Br \longrightarrow Co^{III}Br + \text{Products} \qquad [2.27]$$

variety of bromine-containing compounds have also been examined for the oxidation of substituted toluenes. For example, the influence of various bromine-containing compounds on the oxidation of mesitylene (1,3,5-trimethylbenzene) in acetic acid at 50-52°C is shown in Table [2.4].[107]

Table [2.4] Effect of Addition of Various Bromine Containing Compounds on the Oxidation of Mesitylene in Acetic Acid at 50-52°C

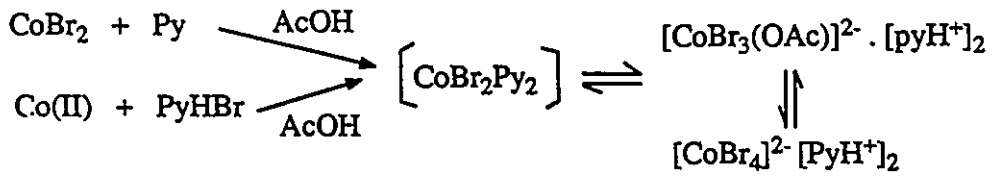
Bromine-Containing Compound	Reaction Time (min)	Extent of Conversion (%)	Aldehyde Selectivity (mol%)
HBr*1)	30	63	67
KBr	40	61	66
NaBr	30	47	70
NaBr*2)	30	27	42
NaBr*3)	30	34	46
$MgBr_2 \cdot 6H_2O$	40	74	62
$LiBr \cdot H_2O$	60	71	62
$CoBr_2 \cdot 6H_2O$	30	60	68
NH_4Br	40	54	65
$AlBr_3 \cdot 6H_2O$	50	70	61
$CaBr_2 \cdot 2H_2O$	50	63	60
CH_3COBr	50	68	67
Bromobenzene*4)	85	42	28
None*5)	150	58	23

Mesitylene : AcOH : $Co(OAc)_2$: Br = 1 : 12.5 : 0.3 : 0.03 (molar ratio). *1) Commercial 47% aq. solution was used. *2) Molar ratio 0.003. *3) Molar ratio 0.3. *4) Reaction temperature 97~100°C. *5) Reaction temperature 100~102°C.

The results indicate that the presence of HBr and $CoBr_2 \cdot 6H_2O$ in the oxidation system gives comparable results regarding conversion and selectivity. In the case of

oxidation of p-xylene to terephthalic acid in acetic acid by air, Hronec[108a] has reported that cobalt bromide is more reactive than cobalt acetate. In general, oxidation of aromatic hydrocarbons with molecular oxygen is strongly influenced by the type of metal catalyst and by the solvent. For example, cobalt acetate alone in catalytic concentrations is a poor catalyst for the one step oxidation of p-xylene to terephthalic acid in many solvents, but its activity is particularly high in the presence of p-toluic acid and water.[108b] Cobalt bromide catalysts are highly effective especially in acetic acid or benzoic acid, but are practically inactive in o-dichlorobenzene and aliphatic or aromatic acids containing larger amounts of water.

Oxidation using $Co(OAc)_2$ /HOAc /O_2 in the presence of additives such as amines (e.g., pyridine,[108a] triethanolamine,[109a] and N,N-diethylaniline[109b]) has been found to result in higher reaction rates and lower induction periods. This effect may be due to the formation of the highly active tetrahedral ionic complexes which participate in the catalytic cycle (eq.[2.28]). For instance, pyridine significantly affects the activity of cobalt bromine catalyst in many solvents and a high yield of terephthalic acid is attained.



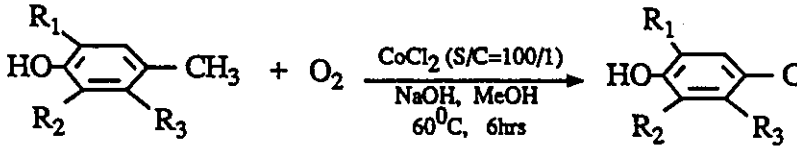
[2.28]

Synergistic effects have also been observed with mixed metal catalysts. For example, replacing 20% of the cobalt(II) by manganese(II) in the $Co(OAc)_2$ /NaBr system resulted in a five-fold increase in rate.[110a] More recently, it was found that the addition of zirconyl acetate [$ZrO(OAc)_2$] led to a significant reduction in the induction period and an increase in the rate of oxidation of p-xylene and other alkylaromatic hydrocarbons catalyzed by $Co(OAc)_2$ in acetic acid at 100°C.[110b] The liquid-phase oxidation of

substituted toluenes by the cobalt-copper-bromide system has also been reported.[110c]

In the presence of strong acids (such as H_2SO_4 and CF_3COOH), Co(III) or Mn(III) acetates oxidize alkylbenzenes at room temperature in acetic acid.[111a] (The reaction proceeds via electron transfer with both Co(III) and Mn(III), and the strong acid considerably enhances the electrophilicity of the oxidant, as described in Chapter 1). Toluene, for example, is oxidized by stoichiometric amounts of $Mn(OAc)_3/H_2SO_4$ in acetic acid in an oxygen atmosphere to give benzaldehyde in 71% yield, together with 24% benzyl acetate and 5% benzoic acid. There is a two-stage process for the production of benzaldehydes from methylbenzenes by oxidation with Mn(III) sulfate in sulfuric acid at 30°C and subsequent electrolytic regeneration of the Mn(III) oxidant.[111b] p-Methoxytoluene can be oxidized to p-anisaldehyde in very high selectivity using this process.

Under basic conditions, the p-cresols are readily oxidized with dioxygen to the corresponding p-hydroxybenzaldehydes with high conversion and selectivity in the presence of catalytic amounts of cobalt chloride.[111c] For example:



[2.29]

	Conversion	Selectivity
$R_1 = R_2 = R_3 = H$	92%	78%
$R_1 = Me, R_2 = R_3 = H$	100%	66%

Beside cobalt, other metals such as manganese and cerium have been used in liquid phase oxidation. The reported yields and selectivities for aldehydes are usually lower compared to cobalt.[112,113]

The gas phase oxidation of substituted toluenes to the corresponding aldehydes is

also an important industrial process. However, the results are not very satisfactory. For example, oxidation of toluene over a MoO_3 / UO_3 catalyst affords benzaldehyde in 30-50% selectivity and < 20% conversion.[89]

In summary, the most attractive way of oxidizing substituted toluenes to the corresponding aldehydes is metal-catalyzed autoxidation, especially by use of $Co(OAc)_2$ / NaBr / HOAc / O_2. However, this system still possesses several drawbacks as described below:

1) low conversion and / or poor selectivity.

2) recovery of aldehydes from the reaction mixture containing acetic acid, substituted toluenes and aromatic acids would be quite difficult.

3) formation of considerable amounts of the corresponding benzyl bromide and acetate derivative as by-products.

4) the oxidation system is only applicatable to substrates which are not sensitive to acid.

5) the presence of bromide ion in the reaction mixture is known to cause severe corrosion.

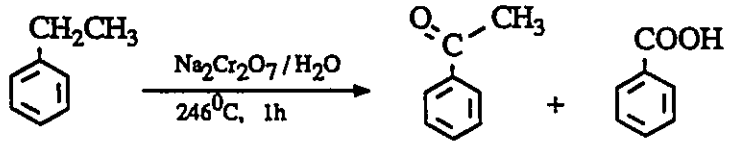
Therefore, our research was focused on the development of a new process using molecular oxygen as an oxidant to increase the selectivity and conversion of metal-catalyzed oxidation of substituted toluenes to the corresponding aldehydes.

2.1.2. BENZYLIC OXIDATION

Direct conversion of a methylene group into a carbonyl function (eq. [2.30]) is a very useful method in organic systhesis.

[2.30]

Usually, the conversion of an unactivated methylene group into a carbonyl is a challenging task in the laboratory. Such reactions tend to lack regiospecificity and generally are only of synthetic use if the molecule has high symmetry leading to equivalence among the possible positions for attack. A methylene group which is activated by a substituent such as an aryl, carbonyl or an alkenyl group, may be oxidized to the carbonyl stage by a great variety of oxidants. These include chromyl chloride, chromyl acetate, sodium dichromate, chromium trioxide in pyidine, ceric ammonium nitrate, selenium dioxide, and nitrous acid. For example, in an aqueous solution, sodium dichromate oxidizes ethylbenzene to acetophenone and benzoic acid in 48% and 11% yield respectively after 1h at 246°C[114] (eq. [2.31]). Recently, Chandrasekaran[115] has



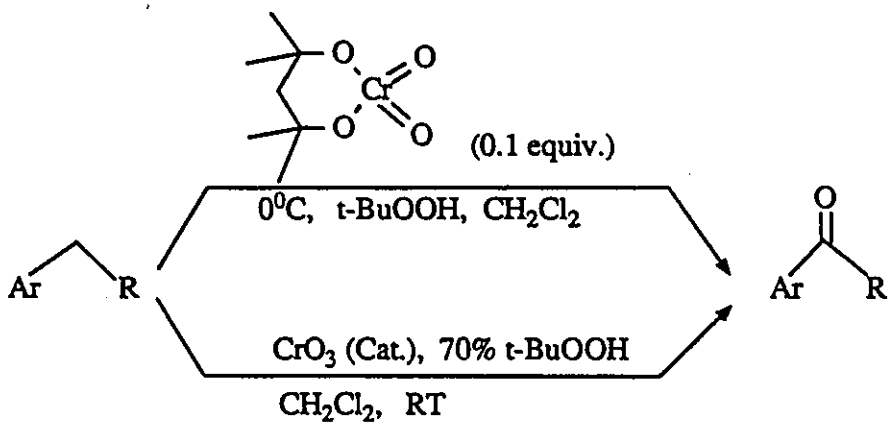
[2.31]

Yield: 48% 11%

reported a convenient method of benzylic oxidation with pyridinium chlorochromate, e.g., oxidation of ethyl benzene with five molar equivalents of pyridinium chlorochromate in benzene under reflux for 15 hours afforded a 71% yield of acetophenone. Furthermore, oxidation of ethylbenzene with chromyl trifluoroacetate gives moderate yields of

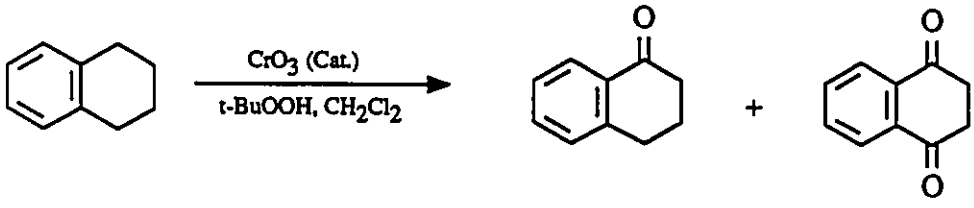
acetophenone at room temperature.[116]

In general, benzylic oxidations by Cr^{VI} complexes require a large excess of the chromium reagents.[117] As these reagents are relatively expensive and environmentally hazardous, it would be advantageous to develop oxidizing methods which require only catalytic amounts of Cr^{VI}. More recently, Muzart[118] has reported the catalytic oxygen transfer oxidation of alkyl aromatics to ketones with tert-butyl hydroperoxide in the presence of a Cr^{VI} catalyst. For example, oxidation of tetralin catalyzed by 0.05 molar



[2.32]

equivalents of CrO_3 and seven equivalents of t-BuOOH for 22 hours at room temperature afforded α-tetralone in 43% yield and 23% of 1.4-naphthoquinone. When this reaction was carried out at 0°C, 65% of α-tetralone and 5% of 1.4-naphthoquinone were formed(eq.[2.33]).



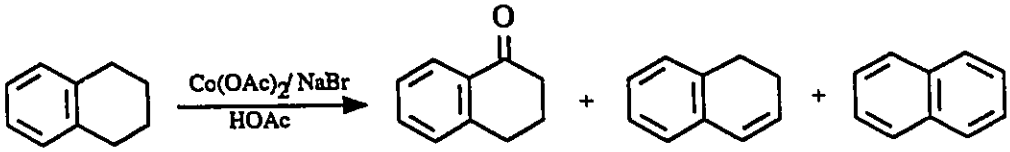
α-tetralone 1.4-naphthoquinone

[2.33]

Electrochemical oxidation of benzylic hydrocarbons has also been extensively studied.[119] As an example, a mixture of MeOH, NaOMe and EtPh was electrolyzed at

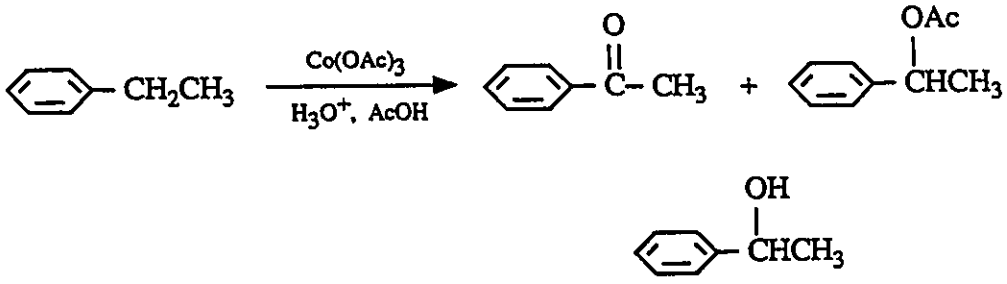
7.0-9.0 V to form the α,α-dimethyl ketal of ethylbenzene which further converted to acetophenone by HCl.[120]

As discussed before, the most attractive method for the oxidation of benzylic hydrocarbons is metal-catalyzed liquid phase oxidation. The best known system using $Co(OAc)_2$ with bromide ion in the presence of HOAc has been successfully used in oxidation of benzylic methylene groups to ketones. For example, the $Co(OAc)_2$ / NaBr catalyzed autoxidation of tetralin give α-tetralone, 1.2-dihydronaphthalene (10-15%), and naphthalene (0.5-3%)[121](eq. [2.34]). In the presence of strong acid, ethylbenzene is



[2.34]

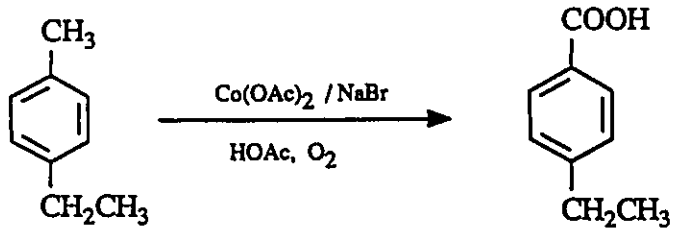
oxidized primarily to acetophenone by $Co(OAc)_3$ accompanied by methyl phenyl acetate and carbinol as by-products (eq. [2.35]).[122] The [ketone / alcohol] ratio is much higher



[2.35]

than in the non-catalyzed reaction. This is due presumably to the enhanced oxidation of alcohol under the influence of the catalyst.

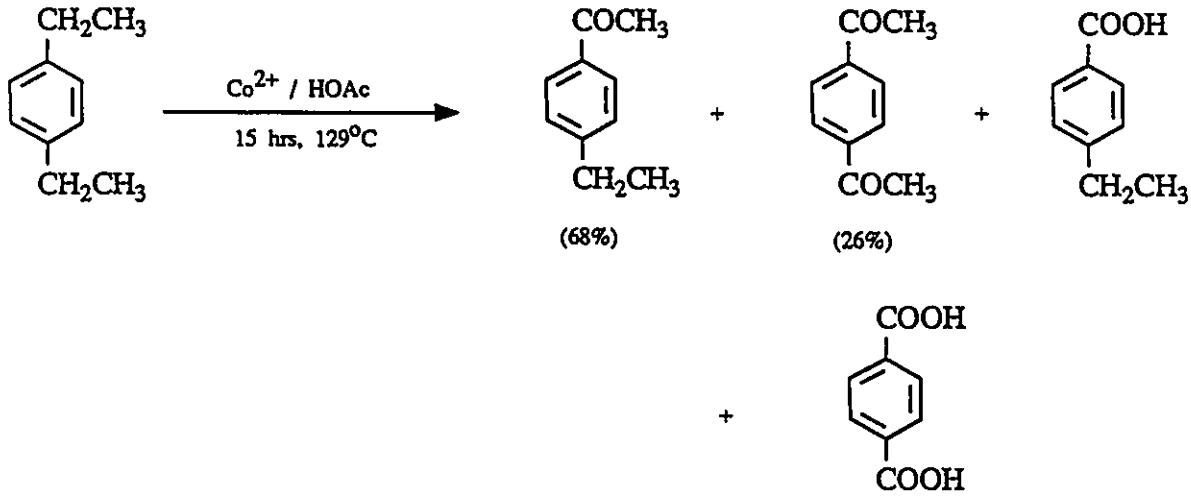
In the oxidation of dialkylbenzenes, the molecule may have more than one possible position for attack. Thus, the regiospecific oxidation becomes a very challenging task. For instance, p-ethyltoluene is oxidized in acetic acid to p-ethylbenzoic acid in 78% yield when a high concentration of $Co(OAc)_2$ is used in combination with bromide ion[123] (eq.[2.36]). The oxidation occurred selectively at the methyl group. As a result, an electron



[2.36]

transfer pathway is probably included which is governed by stereoelectronic considerations and not by the thermodynamic stability of the radical formed.

Overoxidation usually occurs in the case of symmetrical dialkylbenzenes. Kayumova[124] has reported that liquid-phase oxidation of p-diethylbenzene in the presence of a cobalt complex as catalyst (15 hours at 120°C) affords 68% of a monoketone and 26% of a diketone, together with small amounts of alcohol as well as mono- and di-acids (eq. [2.37]).

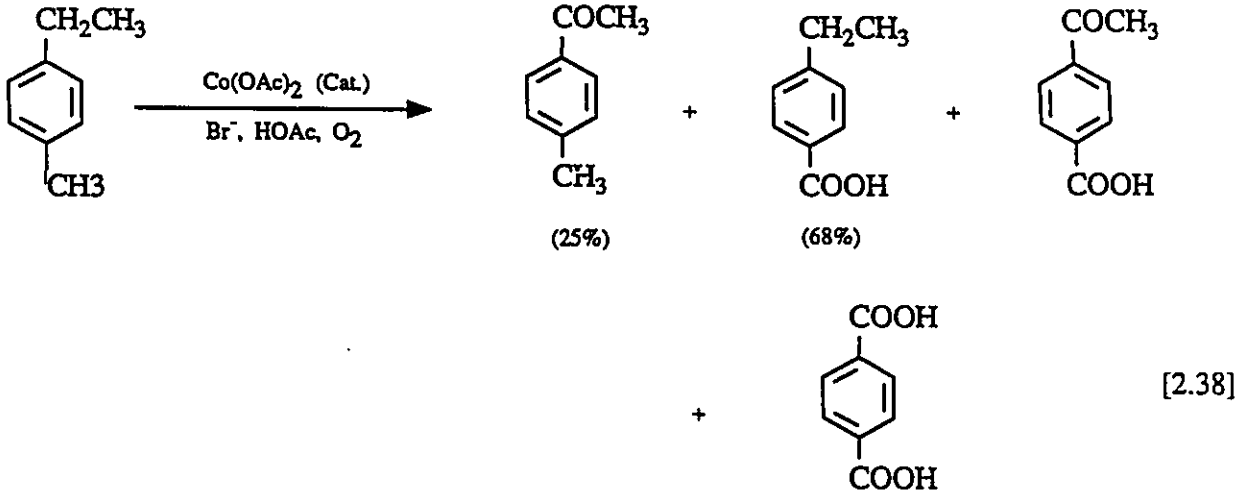


[2.37]

Studies of other metal catalysts have been carried out for the oxidation of benzylic methylene groups to ketones.[125-128] As an example,[129] it was found that, in the liquid phase oxidation of ethylbenzene at 70°C in the presence of lead naphthenate, initiation of the process was due not only to the free-radical decomposition of the hydroperoxide, but

also to the activation of oxygen by the catalyst. Furthermore, Nesterov[130] has observed the synergism phenomenom in the oxidation of ethylbenzene in the presence of a mixed Cu (II) and Mg catalysts. The formation of bimetallic complexes increase the oxidation rate and alter the ratio of radical to the decomposition of PhCHMeOOH.

Kinetics studies for the liquid-phase oxidation of benzylic hydrocarbons in the presence of cobalt acetate catalyst have been extensively established.[131] The reaction mechanism is similar to that for oxidation of substituted toluenes to the corresponding aldehydes involving two main competing processes: electron-transfer oxidation of benzylic hydrocarbons to the radical cation or the electron-transfer oxidation of the metal ligand to the corresponding radical. These two competing processes result in a mixture of various products. In fact, the oxidation of p-ethyltoluene using $Co(OAc)_2$ as the catalyst in the presence of bromide ion produced a mixture of p-ethylbenzoic acid (68%) and p-methylacetophenone (25%), together with other over-oxidized products like p-acetobenzoic acid and terephthalic acid (eq.[2.32]).[132] The drawbacks of the system



[2.38]

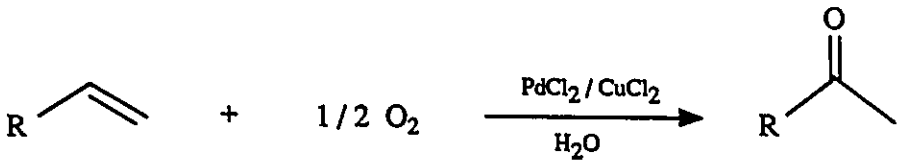
using HOAc as a solvent have limited its application in both industrial processes and laboratory syntheses. As a result, it would be very useful to develop a mild system capable

of selectively oxidizing benzylic hydrocarbons to useful carbonyl products.

2.2 Results and Discussion

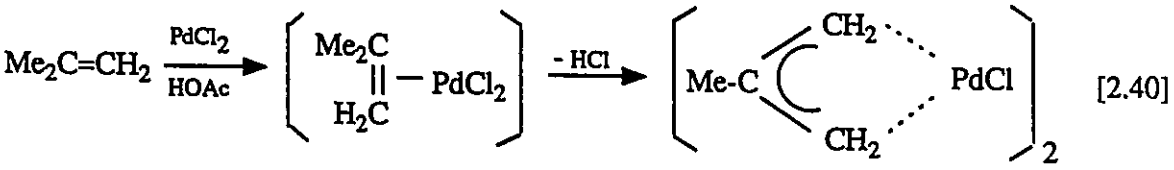
2.2.1. OXIDATION OF SUBSTITUTED TOLUENES TO THE CORRESPONDING ALDEHYDES

Palladium-catalyzed oxidations are potentially useful for many transformations of olefins. Of particular interest is the palladium-catalyzed oxidation of ethene to acetaldehyde (generally known as the Wacker Process)[133] and its application to long-chain, terminal olefins (eq.[2.39]),[134] which is a useful synthetic method for the preparation of methyl ketones.[135] In the case of allylic oxidation, π-allyl complexes of



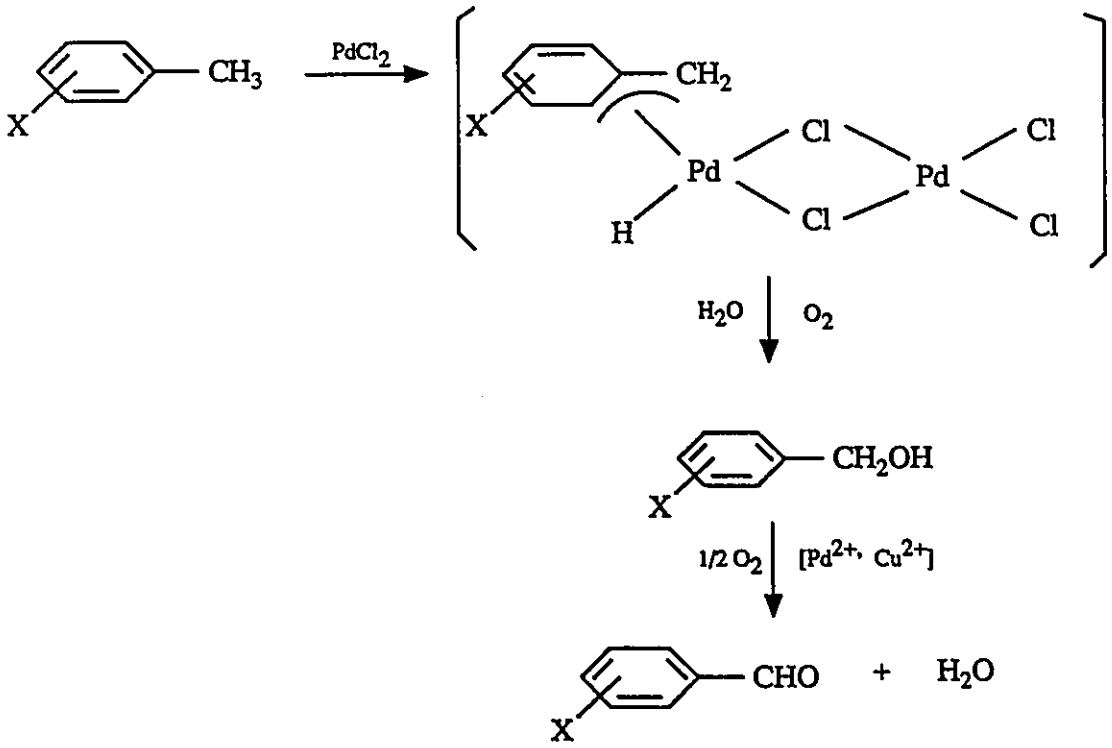
[2.39]

palladium are remarkably stable and form under a variety of conditions. Isobutylene, for example, is known to give a π-methallyl palladium complex, as well as a simple olefin complex[136] (eq. [2.40]). When considering these results, it was conceivable that



[2.40]

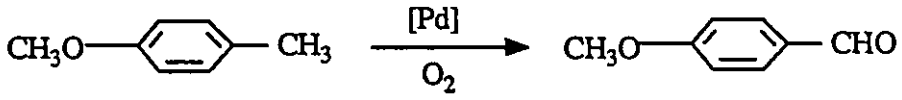
substituted toluenes may also form π-allylic complexes with palladium (eq. [2.41]). Water may then attack this complex to generate a benzylic alcohol which could be further oxidized to the corresponding aldehyde. The selective oxidation of alcohols to aldehydes with Pd^{2+} salts has been reported to proceed catalytically when copper (II) is used as a cocatalyst.[137]



[2.41]

Poly(ethylene glycol), referred to as PEG, is an inexpensive, nontoxic, thermally stable compound. Recently, a number of publications have noted its importance as a phase transfer catalyst, a solvent promoter for various reactions[138] and a co-solvent in metal-catalyzed reactions.[139] Therefore, our initial research focused on the oxidation of substituted toluenes using palladium complexes as catalysts in the presence of PEG-H_2O under an oxygen atmosphere. p-Methylanisole was employed as a model substrate. The results are listed in Table [2.5].

Table [2.5] Oxidation of p-methylanisole to the corresponding aldehyde catalyzed by palladium complexes.

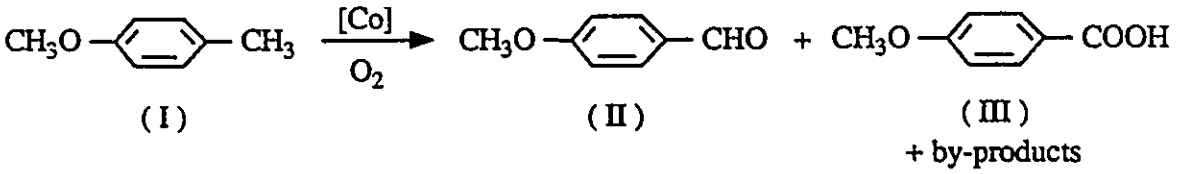


Catalysis	Substrate /Cat. (mmol /mmol)	PEG-400 (ml)	H_2O (ml)	Others	Time (h)	T (^{0}C)	Reaction
$PdCl_2$ / $CuCl_2$	25 / 1 / 10	20	1.5	——	45	55	No
$PdCl_2$ / $CuCl_2$	25 / 1 / 10	20	20	——	67	55-90	No
$PdCl_2$ / $CuCl_2$	25 / 1 / 10	20	—	CH_2Cl_2 (20ml)	46	65	No
$Pd(OCOCF_3)_2$ / $CuCl_2$	25 / 1 / 10	15	1.5	——	47	65-70	No
$Pd(OCOCF_3)_2$ / $Cu(OCOCF_3)_2$	20 / 1 / 2	0.2	—	THF (15ml)	48	50	No

The results in Table [2.5] demostrate that our initial assumption was not correct. The reaction failed even with a strongly electrophilic palladium complex such as $Pd(OCOCF_3)_2$. This indicates that the oxidation of a substituted toluene does not proceed via a Wacker type system.

However, when the palladium complexes were replaced with those of cobalt complexes in the reaction mixture, the formation of aldehydes and acids was observed. The results are shown in Table [2.6].

Table [2.6] Oxidation of p-methylanisole with cobalt complexes



(I) (II) (III) + by-products

No.	Hydrated Cobalt Complexes	(I) / Co^{2+} (mmol)	PEG-400 (ml)	H_2O (ml)	Time (h)	T (°C)	G. C. (%) [b]		
							(I)	(II)	(III) + by-products
1	$Co(OAc)_2$	2.5 / 1	20	15	47	80	2.8	52	45
2	$Co(OAc)_2$	2.5 / 1	20	—— [a]	47	50	48	3.2	48
3	$Co(OAc)_2$	2.5 / 1	1	15	50	80	No Reaction		
4	$Co(OAc)_2$	10 / 1	20	15	50	70	96	3	1
5	$CoCl_2$	10 / 1	20	——	46	55	16	23	61
6	$CoCl_2$	10 / 1	——	15	28	65	No Reaction		
7	$CoCl_2$	10 / 1	20	5	46	60	78	7	15
8	$Co(OAc)_2$	10 / 1	15 [c]	——	41	60	81	6	13
9	$CoCl_2$ [d]	10 / 1	15 [c]	——	48	60	30	23	47

a) The reaction was carried out in the presence of CH_2Cl_2

b) The reaction was monitored by gas chromatography and the percentage of products was calculated in terms of peak area regardless of their response factors. This method was also applied in subsequent studies.

c) In PEG-200

d) anhydrous $CoCl_2$

As Table [2.6] indicates, PEG plays a vital role in these oxidative reactions. In the presence of small amounts, or the absence of PEG (e.g., entries 3 and 6), a reaction did not take place. The results in entries 5 and 7 indicate that the presence of water may inhibit the reaction resulting in a lower rate of oxidation. Furthermore, if one compares the results in entries 8 and 9, $CoCl_2$ seems to be much more catalytically active than $Co(OAc)_2$ in the anhydrous solvent system.

Based on the above findings, a series of solvents containing an ethylene ether unit was studied in the absence of water for the oxidation of p-methylanisole to the corresponding aldehyde catalyzed by anhydrous $CoCl_2$. The results as shown in Table [2.7].

Table [2.7] Oxidation of p-methylanisole catalyzed by anhydrous $CoCl_2$ in the presence of various ether solvents

Cobalt Complex	(I) / Co^{2+} (mmol)	Solvents	Time (h)	T (°C)	G. C. (%) [b]			
					(I)	(II)	(III)	by-products
$CoCl_2$	10 / 1	PEG - 1000 [a]	43	60	8	5	52	35
$CoCl_2$	10 / 1	PEG - 400	36	60	28	19	40	13
$CoCl_2$	10 / 1	PEG - 200	48	60	30	23	47	Nil
$CoCl_2$	10 / 1	Diglyme	46	60	42	33	25	Nil
$CoCl_2$	10 / 1	DME	41	60	87	13	Nil	Nil
$CoCl_2$	10 / 1	$CH_3OCH_2CH_2OH$	23	90	No Reaction			

a) PEG-1000 was dissolved in 1,2-dimethoxy ethane (DME). b) GC percentage was calculated without internal standard.

The formula of bis(2-methoxyethyl)-ether (diglyme), is $CH_3OCH_2CH_2OCH_2CH_2OCH_3$. This species contains two ethylene ether groups which are identical to the basic molecular unit of PEG [$H(OCH_2CH_2)_nOH$] except that the

terminal carbons are linked with methoxy groups instead of hydroxy groups. The abbreviation DME refers to 1,2-dimethoxyethane. It has a similar structure to diglyme, but contains only one ethylene ether group.

High average molecular weight PEG compounds (e.g., PEG-1000) were found to favour the formation of p-methoxybenzoic acid. Decreasing the number of units of the monomer in the solvent structure increased the relative selectivity of the reaction towards p-methoxybenzaldehyde. For example, the reaction carried out in the presence of DME at 60°C for 41 hours afforded 13% aldehyde as measured by gas chromatography. Formation of acid and other by-products were not detected. Surprisingly, the use of 2-methoxyethanol ($CH_3OCH_2CH_2OH$) as a solvent led to no reaction at all. This may be due to the presence of a proton which is known to inhibit radical reactions. Therefore, diglyme and DME were the preferred solvents. It was found that in the presence of these solvents, the only major products of the reaction were the aldehyde and the corresponding acid. Other products such as benzyl alcohol were not obtained. However, the rate of reaction was slow for the oxidation of p-methylanisole in both solvents. Increasing the reaction temperature was found to increase the rate of oxidation (Table [2.8]). This was especially the case for the reaction using diglyme as the solvent. Furthermore, the reaction temperature seemed not only to enhance the rate of the oxidation but also had an appreciable effect on the selectivity. Indeed, when the reaction was carried out in diglyme at 60°C, only 33% aldehyde and 25% acid were formed after 46 hours, while at 90°C, 59% aldehyde and 19% acid were detected by GC after 5 hours.

Table [2.8] Effect of temperature on the oxidation of p-methylanisole [a]

Solvents	T (°C)	Time (h)	G. C. (%) [b]		
			(I)	(II)	(III)
diglyme	60	46	42	33	25
diglyme	90	2	79	21	—
		5	31	50	19
DME	60	41	87	13	—
DME	90	9	98	2	—

a) p-methylanisole : $CoCl_2$ = 10 : 1

b) GC percentage was calculated without internal standard.

It seems from the above results that the rate of oxidation and the selectivity of the reaction are greatly influenced by the nature of solvents. Thus a further study of solvent effects was necessary. The results are summarized in Table [2.9]. In principle, solvents chosen in this study must dissolve anhydrous $CoCl_2$ in order to obtain the best catalytic effect. Therefore, non-polar and moderately polar solvents like benzene, CH_2Cl_2 etc., could not be used. Oxidizable protic solvents such as alcohols, could not be used either because their oxidation may compete with the desired reaction. Moreover, as discussed earlier, liquid phase oxidation involves radical intermediates, and the presence of alcoholic solvents may inhibit the radical reaction depending on the nature of the alcohol. As an example (Table [2.7]), the oxidation reaction does not occur in the presence of 2-methoxyethanol. Finally, the use of cyclic ethers such as THF or 1,4-dioxane is possible. In fact, the experimental results showed that p-methoxybenzaldehyde was obtained. However, large amounts of other products were obtained from the oxidation of cyclic ethers. Also the low boiling point of THF and 1,4-dioxane further limits their application in these reactions. Although anhydrous $CoCl_2$ dissolves very well in DMF, DMSO as well

Table [2.9] Effect of solvents on the oxidation of p-methylanisole[a]

Solvent	T (°C)	Time (h)	GC (%) [b]		
			I	II	III
Diglyme	90	5	31	50	19
PEG (400) dissolved in DME	90	5	82	11	8
DME / Acetone (2 / 1)	60	65	89	11	—
Dimethyl formamide (DMF)	60	24	No Reaction		
Dimethyl sulfoxide (DMSO)	60	24	No Reaction		
Tetramethylene sulfone	60	45	No Reaction		

a) p-Methylanisole : $CoCl_2$ = 10:1 b) GC percentage was calculated without internal standard.

as in tetramethylene sulfone, no oxidation reactions were observed after 24 hours at 60°C. The $CoCl_2$ dissolved quite well in a mixture of DME and acetone (2:1), but the rate of oxidation was very slow, with only 11% aldehyde detected by G.C. after 65 hours at 60°C. In terms of early results, PEG has been shown to lead to higher rates of oxidation, but poorer selectivity towards aldehyde formation. In contrast, DME led to lower rates of oxidation, but higher selectivity towards the aldehyde. It was of interest to determine the effect of using a combination of these two solvents. Experimental results in Table [2.9] showed that the reaction rate was much lower in this mixed solvent system as compared to the use of diglyme as the solvent. Although small amounts of diglyme also participated in the reaction to produce two unidentified by-products, these two by-products were easily removed with water during the work-up. Therefore, diglyme became the preferred solvent in subsequent work.

The above results indicate that oxidations catalyzed by anhydrous $CoCl_2$ work well

in the presence of those solvents containing ethylene ether groups like PEG, diglyme, as well as DME. A possible role of such solvents is to complex with cobalt chloride (Fig.2.1). The oxygen atoms in these solvents may act as electron donors coordinating

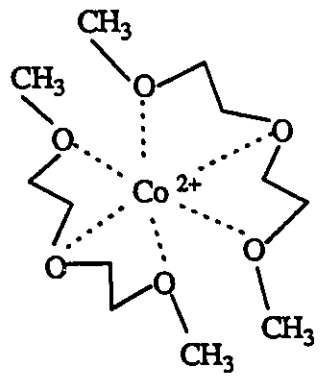


Fig [2.1]

with the metal compound. As discussed in Chapter 1, the reactivity of cobalt complexes towards molecular oxygen is increased by strong σ-donor ligands. Therefore, one would expect that the $CoCl_2$ in these solvents may result in an increase of reactivity towards molecular oxygen.

As noted earlier, additives are known to significantly affect both the rate of the reaction and the ratio of products when the oxidation of aromatic hydrocarbons is carried out with $Co(OAc)_2$ as a catalyst in the presence of HOAc. For example, the presence of bromide greatly promotes the cobalt-catalyzed autoxidation of alkylbenzenes.[9a,140] Methyl ethyl ketone can be used as an activator to reconvert Co(II) in the presence of dioxygen to Co(III), since long induction periods are otherwise observed.[141,142] Addition of amine compounds promotes the dissociation of dimeric Co(III) complexes into reactive monomeric species. In order to determine whether the additives can enhance the oxidation catalyzed by anhydrous $CoCl_2$ in diglyme, the addition of halogen ions, amines, and phase transfer agents as well as peroxide compounds were investigated. The results are presented in Table [2.10]. The addition of KI, HBr or

Table [2.10] Effect of additives on the oxidation of p-methylanisole [a]

Additives	Add. / (I) (mmol)	T (°C)	Time (h)	G. C. (%) [c]		
				(I)	(II)	(III)
KI	1 / 10	60	22	No Reaction		
HBr	1 / 10	60	22	No Reaction		
$C_6H_5N(CH_3)_2$	7.9 / 10	60	32	No Reaction		
PBu_3	1 / 10	90	28	No Reaction		
Dibenzo-18-crown-6 [b]	1 / 10	60	24	No Reaction		
β-cyclodextrin	1 / 10	80	5	40	27	33
Benzoyl peroxide	1 / 10	90	5	62	33	5

a) p-Methylanisole : $CoCl_2$ = 10 : 1

b) Dibenzo-18-crown-6 was dissolved in benzene.

c) GC percentage was calculated without internal standard.

N,N-dimethylaniline to this oxidation system led to no reaction. The effect is opposite to that observed in the $Co(OAc)_2$-HOAc system. Addition of tributyl phosphine has also led to no reaction. Dibenzo-18-crown-6 has a similar structure to PEG and diglyme with respect to the basic ethylene ether unit, and is known to be a phase transfer catalyst and complexing agent.[143] If the ethylene ether units in PEG or diglyme play an important role in the activation of the cobalt catalyst, one might expect that addition of catalytic amounts of dibenzo-18-crown-6 would have the same effect as the PEG and diglyme. However, when $CoCl_2$ (0.5 mmol) was dissolved in benzene containing a small amount of water and dibenzo-18-crown-6 (0.5 mmol), and the mixture stirred under oxygen at 60°C for 24 hours, there was no reaction. This result might be explained if one considers the reactants

to be in two phases with little interaction since $CoCl_2$ was dissolved in water (2ml), and the dibenzo-18-crown-6 in benzene (10ml). This would demostrate once again the importance of the interaction between $CoCl_2$ and the solvents. In the recent literature, β-cyclodextrin has been reported to promote olefin oxidation catalyzed by palladium chloride.[144] When β-cyclodextrin was used for the $CoCl_2$ catalyzed reaction, it was found that a lower percentage of aldehyde was obtained with a comparable conversion of starting material. In other words, the presence of β-cyclodextrin promotes the formation of the acid. As well, the addition of catalytic amounts of benzoyl peroxide has been studied. It was noted that the selectivity of the reaction for aldehyde was relatively high. However, the formation of benzoic acid produced from the decomposition of benzoylperoxide caused problems during work-up.

As mentioned earlier, synergistic effects of mixed catalysts have been observed to enhance the reactivity of the cobalt complexes and the selectivity of the reaction. It was of interest to determine whether there are synergistic effects of a mixed catalyst in the presence of diglyme under O_2 with an increase of the selectivity. In addition, other metal catalysts such as $MnCl_2.4H_2O$, $CrCl_3$ and $Co(OAc)_2$ have also been studied. The results are presented in Table [2.11].

Table [2.11] Effect of metal catalysts on the oxidation of p-methylanisole [a]

Metal Catalysts	(I) /Cat. (mmol)	T (°C)	Time (h)	G. C. (%) [b]			By-products
				(I)	(II)	(III)	
$CoCl_2$	10 / 1	90	3	75	24	1	
			5	31	50	19	
$Co(OAc)_2 \cdot 4H_2O$	10 / 1	75	5	61	22	18	
$MnCl_2 \cdot 4H_2O$	10 / 1	90	3	83	14	3	
			5	71	18	3	8
$CrCl_3$	10 / 1	90	5	90	8	2	
$CoCl_2$ / $MnCl_2 \cdot 4H_2O$	10 / 1/ 1	90	3	86	14	—	
			5	83	17	—	
$CoCl_2$ / $CrCl_3$	10 / 1/ 1	90	5	59	39.5	1.5	
$CoCl_2$ / CuCl	10 / 1/ 1	90	5	No Reaction			
$CoCl_2$ / $PdCl_2$	10 / 1/ 1	90	3	100	—	—	
			5	98	2	—	
$CoCl_2$ / $MnCl_2 \cdot 4H_2O$/ $CrCl_3$	10 /1/1/1	90	5	60	36	4	

a) Diglyme as the solvent under O_2 atmosphere.

b) GC percentage was calculated without internal standard.

The results shown in Table [2.11] indicate that when a reaction mixture containing cobalt chloride and chromium trichloride (10:1:1 ratio of p-methylanisole to $CoCl_2$ to $CrCl_3$) was bubbled with O_2 at 90°C, p-methylanisole was converted mainly to p-methoxybenzaldehyde, as well as small amounts of the corresponding acid. Even though the rate of reaction under these conditions is slower than with $CoCl_2$ alone, it gives better results with respect to the selectivity, alone with relatively high conversions in comparison to other metal catalysts and mixed catalysts. In an attempt to further improve the

selectivity towards the aldehyde, studies of the ratio of $CoCl_2$ and $CrCl_3$ to substrate have been performed (Table [2.12]).

Table [2.12] Effect of the ratio of $CoCl_2$ and $CrCl_3$ to substrate on the oxidation of p-methylanisole [a]

Mixed Catalysts	I / Cat. (mmol)	Time (h)	G. C. (%) [b]		
			(I)	(II)	(III)
$CoCl_2$ / $CrCl_3$	10 / 1 / 1	5	59	39.5	1.5
$CoCl_2$ / $CrCl_3$	20 / 1 / 1	3.5	45	39	16
		5	12	30	58
$CoCl_2$ / $CrCl_3$	40 / 1 / 1	3.5	76	22	2
		5	47	29	24
$CoCl_2$ / $CrCl_3$	60 / 1 / 1	4	60	26	14
		6	37	26	37
$CoCl_2$ / $CrCl_3$	20 / 2 / 1	5	45	55	—
$CoCl_2$ / $CrCl_3$	20 / 1 / 2	5	45	52	3

a) Diglyme as solvent at 90^0C.

b) GC percentage was calculated without internal standard.

It was found that decreasing the concentration of the catalyst decreased the selectivity. Furthermore, when a 2:1 ratio of $CoCl_2$ to $CrCl_3$ was used, p-methylanisole was converted to the corresponding aldehyde with optimal selectivity. Gas chromatography showed that the reaction mixture contained 45% starting material and 55% p-methoxybenzaldehyde after 5 hours at 90°C. The acid was not detected. The effect of $CrCl_3$ in this reaction is still not clear.

When this reaction was followed by gas chromatography, an induction period was observed during the first hour of the reaction (Fig.[2.2]). This plot indicates that the reaction is zero-order in p-methylanisole.

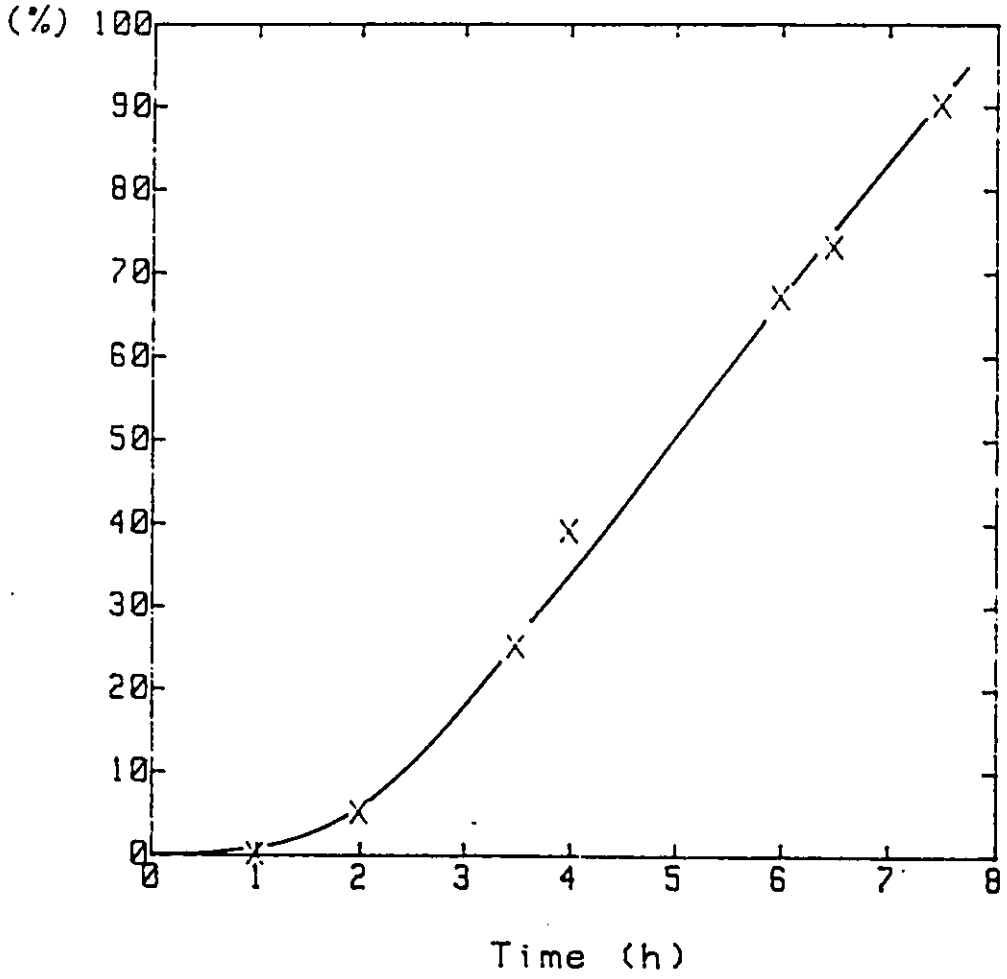


Fig. [2.2]

x Conversion of p-methylanisole.

Reaction conditions: anhydrous $CoCl_2$ (0.25 mmol), $CrCl_3$ (0.25 mmol), diglyme (8 ml), p-methylanisole (5mmol) at 90°C under O_2, dodecane as an internal standard.

Methyl ethyl ketone (MEK) is known to reduce the induction periods for the oxidation of aromatic hydrocarbons via a liquid phase reaction. Thus the addition of MEK to the diglyme in various ratios in this oxidative system was studied. The results are listed in Table [2.13].

Table [2.13] Effect of MEK on the oxidation of p-methylanisole [a]

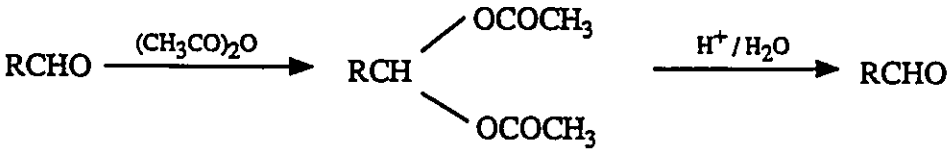
Mixed Solvents	diglyme / MEK (ml)	Time (h)	G. C. (%) [b]		
			(I)	(II)	(III)
diglyme	8 / 0	2	95	5	–
		5	45	55	–
diglyme / MEK	4 / 1	2	81	13	–
		4	75	23	2
diglyme / MEK	2 / 1	2	94	6	–
		6	63	23	14
diglyme / MEK	1 / 3	9	No Reaction		

a) $CoCl_2 : CrCl_3 = 2:1$, 90^oC, O_2

b) GC percentage was calculated without internal standard.

Indeed, a shortened induction period was observed in the presence of MEK (e.g. diglyme/MEK = 4/1). But the overall rate of reaction as well as the selectivity was also less. Thus a mixed solvent system of diglyme and MEK is less favourable than diglyme alone for the selectivity of the reaction.

Other attempts have been made to enhance the selectivity towards aldehyde, including the rapid conversion of the aldehyde to a stable derivative. It is known[145] that acetic anhydride would react rapidly with an aldehyde to form a acylal which is more resistant to oxidation than the aldehyde. The acylal is then hydrolyzed readily back to the aldehyde by aqueous acid (eq. [2.42]). When the oxidation of p-methylanisole (5 mmol)

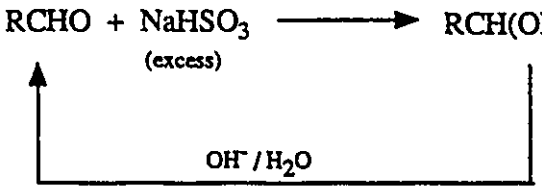


[2.42]

was catalyzed by anhydrous $CoCl_2$ (0.5 mmol) in the presence of acetic anhydride (20

mmol) under oxygen atmosphere at 80°C for 23 hours, the acylal derivative was not formed. Instead, p-methoxybenzoic acid was produced in 69% yield from the over-oxidation of p-methoxybenzaldehyde.

Another known approach to convert aldehydes to derivatives is by a reaction with saturated sodium bisulphite to yield crystalline bisulphite derivatives (eq.[2.43]). When



[2.43]

the oxidation of p-methylanisole was carried out in the presence of $NaHSO_3$ under standard reaction conditions, no reaction took place. Therefore, attempts to prepare the derivative of the aldehyde were not successful.

During the autoxidation of p-methylanisole catalyzed by anhydrous $CoCl_2$, there was an obvious change in the color of the solution. Initially, the solution was clear blue, and then changed to a deeper blue tinged with green. At the end of reaction, some pink precipitate was observed and the solution had become light blue, and sometimes even pink. The color change of the solution during the reaction indicates a change of oxidation state of the cobalt metal since Co^{2+} ions are blue or pink in solution while Co^{3+} ions are green. The pink precipitate formed in this reaction was tested by a simple inorganic reaction. When this pink solid was dissolved in a concentrated sodium hydroxide solution, a deep blue solution was observed. This observation indicated that the pink solid must have been a hydrated cobalt chloride $[Co(H_2O)_6]Cl_2$ (eq.[2.44]).[147] This hydrous cobalt

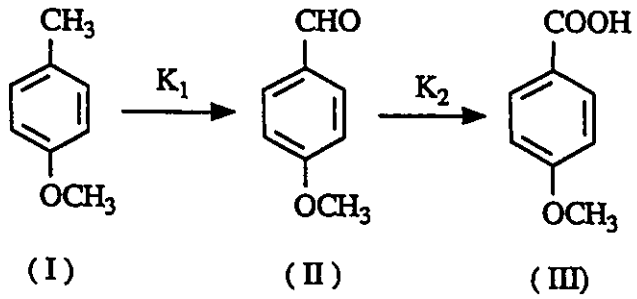
$$[\,Co(H_2O)_6\,]^{2+} + 4OH^- \longrightarrow Co(OH)_4{}^{2-} \qquad [2.44]$$

Pink — deep blue

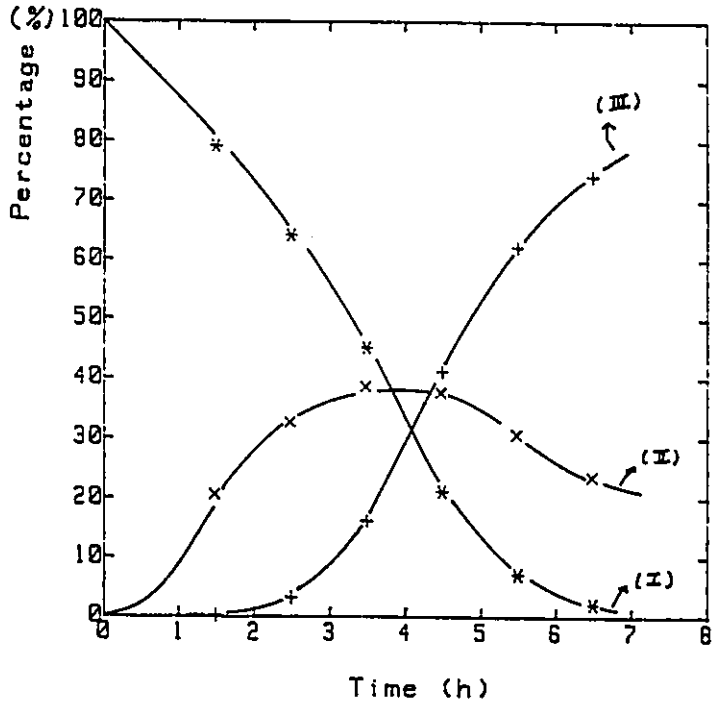
chloride was formed from the reaction of catalyst with H_2O which was generated during the reaction (eq.[2.45]).

$$CoCl_2 + 6H_2O \longrightarrow [Co(H_2O)_6]^{2+} Cl_2 \qquad [2.45]$$

When the oxidation process was followed carefully by gas chromatography, it was found that the reactions can be divided into three periods (Fig.[2.3]).



(I) (II) (III) [2.46]



Reaction conditions: p-methylanisole : $CoCl_2$ = 20 : 1 in diglyme at 90°C with one hour induction period.
(I) starting material; (II) p-methoxybenzaldehyde; (III) p-methoxybenzoic acid.

Fig. [2.3]

The initial period consisted of the first 3 hours. During this period, the average rate for disappearance of p-methylanisole (k_1) was much greater than that for the formation of benzoic acid (k_2), implying that the rate of formation of p-methoxybenzaldehyde is much faster than its disappearance ($k_1 >> k_2$). It was interesting to note that with the further increase in the reaction period from 3 to 5 hours (the second period), the percentage of the aldehyde in the reaction mixture measured by GC was almost unchanged, indicating that during this time interval, the rate of formation of p-methoxybenzaldehyde from p-methylanisole was almost equal to its rate of disappearence to p-methoxybenzoic acid ($k_1 \approx k_2$). Thus the yield of p-methoxybenzaldehyde decreased with an increase in the overall conversion of p-methylanisole. If the reaction was continued for more than 5 hours (the third period), the rate of formation of p-methoxybenzoic acid was greater than the formation of the aldehyde ($k_2 > k_1$), eventually converting all the p-methylanisole and its aldehyde to the corresponding acid.

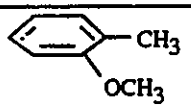
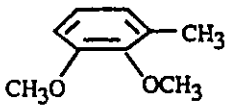
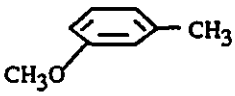
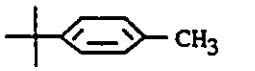
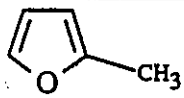
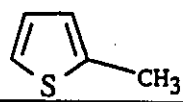
The oxidation of substituted toluenes to the corresponding aldehydes with high selectivity was a goal of this research. Therefore, in the subsequent studies of oxidation for various substituted toluenes, the reactions were stopped at the first period of reaction in which the selectivity towards aldehyde reached the maximum.

After determination of the optimal reaction conditions for oxidation of p-methylanisole to the corresponding aldehyde, extended studies of oxidation of various substituted toluenes were carried out under similar conditions. The results are summarized in Table [2.14]. Unless otherwise stated, the conversion and the selectivity of the reaction were determined by gas chromatography using n-dodecane as the internal standard, and based on the following calculations.

$$\text{Conversion} = \frac{\text{The amount of reactant consumed for the formation of products}}{\text{The initial amount of reactant}}$$

$$\text{Selectivity} = \frac{\text{The amount of reactant consumed for the formation of aldehyde}}{\text{The total amount of reactant consumed}}$$

Table [2.14] Oxidation of a variety of substituted toluenes catalyzed by cobalt in the presence of diglyme under an oxygen atmosphere

Substrates	Metal Catalysts	Substrate / Cat. (mmol)	T (°C)	Time (h)	Conversion (%)	Selectivity (%)	By Products
	$CoCl_2$ / $CrCl_3$	20/2/1	90	3.5	34	90	Acid
	Same	20/2/1	90	3	35	83	Acid
	$CoCl_2$	10/1	90	2.5	32	96	
	$CoCl_2$	10/1	60 \ 80	69	17 [a]	80 [a]	
	$CoCl_2$ / $CrCl_3$	20/2/1	90	43	0		
	$CoCl_2$	10 /1	80	21	12	100	
	$CoCl_2$	10/1	90	48	0		
	$CoCl_2/CrCl_3$	20/2/1	90	48	0		
	$CoCl_2$	10/1	90	48	0		
	$CoCl_2$	10/1	90	23	36 [a]	42 [a]	Acid + unknown
	$CoCl_2/CrCl_3$	20/2/1	90	23	19 [b]	53 [b]	
	$CoCl_2$	10/1	60	48	0		
	$CoCl_2$	10/1	65	72	0		
	$CoCl_2$	10/1	90	24	0		
	$CoCl_2$	10/1	40	96	0		
	$CoCl_2$	10/1	60	48	Polymerized		

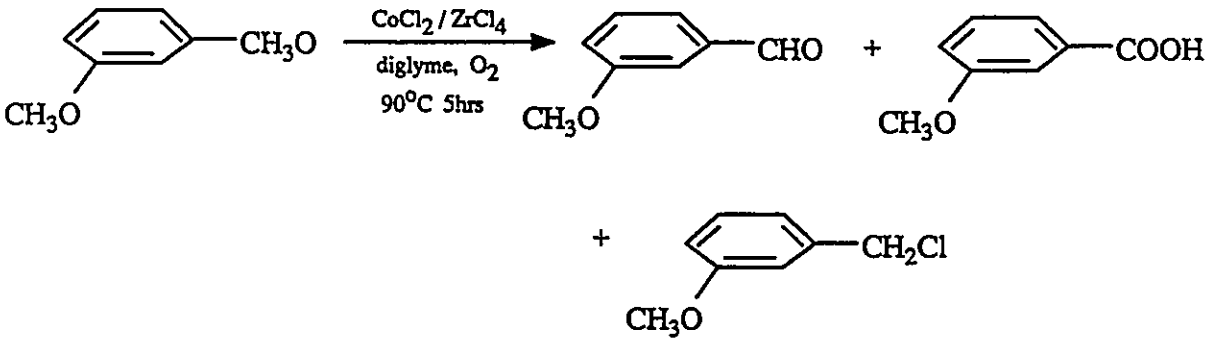
a) Based on isolated yield, b) based on ^1H NMR.

The results in Table [2.14] demonstrate that the rate of oxidation strongly depends on the structure and position of the substituents on the ring. An increase in the electron-donating ability of the substituent leads to a higher conversion. For example, electron-donating ability decreases as follows: p-ethoxy > p-methoxy > p-t-butyl > p-methyl. Under similar conditions, oxidation of p-ethoxytoluene and p-methylanisole afforded 35% and 34% conversion after 3 and 3.5 hours, respectively. For oxidation of p-t-butyltoluene, only 19% of the substrate was converted after 23 hours, while oxidation of p-xylene did not take place at all. These results imply that the oxidation reaction may proceed via a cobalt-catalyzed autoxidation reaction since they are in accord with tendencies in free radical autoxidation reactions as have mentioned in Chapter 1. In principle, the better the electron-donating groups on the benzene ring, the higher the reactivity of the benzylic C-H bond and the greater the stability of the benzylic radical intermediate.

As can be seen from the table, the selectivity of the oxidation of p-ethoxytoluene and p-t-butyltoluene towards the corresponding aldehydes did not improve when a mixed catalyst ($CoCl_2$:$CrCl_3$ /2:1) was used as compared to the use of $CoCl_2$ alone. During the oxidation of 2,3-dimethoxytoluene in the presence of $CoCl_2$ and $CrCl_3$, the color of the reaction mixture changed to green from blue after 10 minutes, then to dark-green. However, oxidation of the substrate was not observed. When the oxidation of o-methylanisole was carried out in the presence of anhydrous $CoCl_2$, the rate of reaction was very slow; only 17% of this compound was converted to the aldehyde after 69 hours at 60°C. This is probably due to steric effects during the radical termination step as was discussed in Chapter 1. Oxidation of other substituted toluenes such as p-xylene, toluene, p-chlorotoluene as well as 2-methylfuran did not take place in either catalytic system, while polymerization occurred in the case of 2-methylthiophene. Furthermore, meta-alkoxy and phenoxy substituted toluenes under similar conditions also gave no reaction. This is not very surprising since the electron-donating ability of an alkoxy group in the

meta- position of a benzene ring is weaker than that of an ortho- or para- methoxy substituent. The experimental results discussed above demonstrate that this oxidation system is limited to methyl benzenes which are relatively activated.

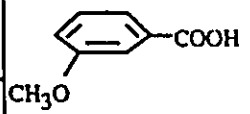
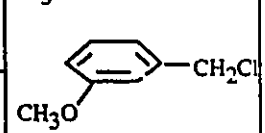
Further attempts were made to find a system for the oxidation of the m-alkoxy substituted toluenes to their corresponding aldehydes. Chester and co-workers have reported[148] that the rate of the $Co(OAc)_2$ catalyzed oxidation of p-xylene to terephthalic acid can be enhanced dramatically by the addition of small amounts of zirconium (IV) and hafnium (IV) acetates. The addition of $ZrO(OAc)_2$ led to a rate which was higher than that observed with a tenfold increase in the cobalt concentration. Therefore, it was of interest to determine whether the zirconium chloride could promote the oxidation of m-substituted toluenes under similar reaction conditions. Indeed, when the oxidation of m-methylanisole was catalyzed by a mixture of $CoCl_2$ (0.5 mmol) and $ZrCl_4$ (0.5 mmol) in the presence of diglyme under an oxygen atmosphere at 90°C for 5 hours, 28% of m-methylanisole was converted to m-methoxybenzaldehyde with 70% selectivity. Small amounts of m-methoxybenzoic acid and m-methoxybenzyl chloride were also observed (eq.[2.47]). When the ratio of $CoCl_2$ to $ZrCl_4$ changed from 1:1 to 2:1, the rate of reaction was



[2.47]

increased with the realization of a comparable selectivity. The conversion reached 27% with 72% selectivity and 37% with 61% selectivity after 3.5 and 5 hours, respectively (Table [2.15]).

Table [2.15] Effect of the ratio of catalysts ($CoCl_2/ZrCl_4$) on the oxidation of m-methylanisole to the corresponding aldehyde.

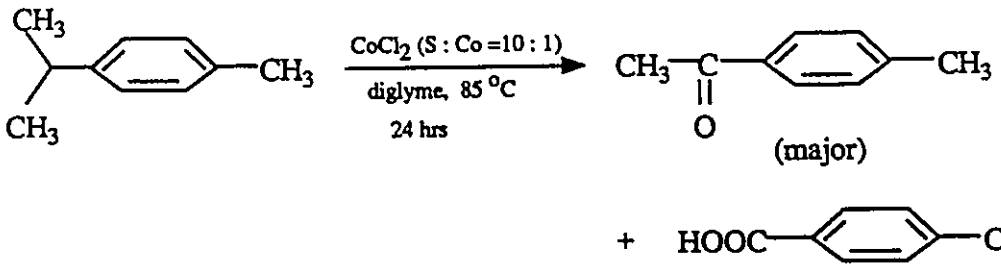
Metal Catalysts	Ratio of substrate to catalysts (mmol)	T (°C)	Time (h)	Conversion[a] (%)	Selectivity[a] (%)	Other by-products
$CoCl_2 / ZrCl_4$	10 / 1 / 1	90	5	28	70	
$CoCl_2 / ZrCl_4$	20 / 2 / 1	90	3.5	27	72	
			5	37	61	

a) The conversion and selectivity of aldehyde were calculated by gas chromatography using biphenyl as the internal standard.

Studies of other zirconium complexes such as $Zr(OC_3H_7)_4$ under similar oxidation conditions failed because the addition of this complex to the reaction mixture resulted in immediate precipitation. Thus the co-catalytic effects of $ZrCl_4$ may be due to the redistribution of the dimer-monomer equilibrium of the cobalt ion from the formation of a weak complex with the active monomeric Co(III) species.

Application of the $CoCl_2$-$ZrCl_4$ catalytic system to the oxidation of m-phenoxytoluene and p-xylene resulted in no reaction. When the oxidation of o-methylanisole, 2,3-methoxytoluene and p-t-butyltoluene were carried out in this system, the selectivity was much poorer than that using only $CoCl_2$ as catalyst.

Finally, when the oxidation of p-cymene catalyzed by anhydrous $CoCl_2$ was carried out in the presence of diglyme at 85°C for 24 hours, p-methylacetophenone was obtained as a major product in 43% isolated yield (eq.[2.48]). No p-isopropyl benzaldehyde was produced. This result is consistent with the oxidation of p-cymene proceeding through a free radical mechanism. Therefore, the mechanism of the oxidation by the cobalt chloride system has been proposed on the basis of the results discussed earlier. It could be considered to proceed via a pathway involving a benzylic radical,



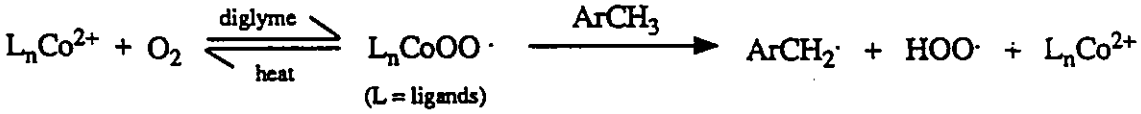
[2.48]

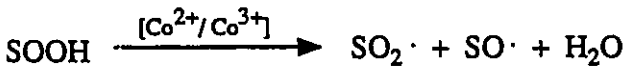
60% conversion 43% isolated yield

which could be produced from hydrogen abstraction by superoxocobalt(III). This species would arise from the rapid reaction of cobalt chloride and oxygen assisted by the presence of diglyme, and from the cobalt catalyzed decomposition of hydroperoxide compounds, which may have been a contaminant in the diglyme and substrate since these compounds had not been purified prior to use. The reaction mechanism is outlined in Scheme [2.3].

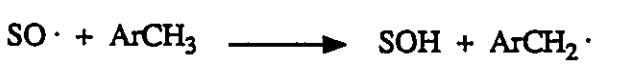
Scheme [2.3]

Initiation:





(Solvent contaminated with hydroperoxide)



(Substrate contaminated with hydroperoxide)

Propagation:

$$ArCH_2\cdot + O_2 \rightleftharpoons ArCH_2O_2\cdot$$

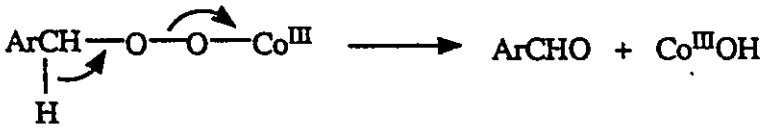
$$ArCH_2O_2\cdot + ArCH_3 \longrightarrow ArCH_2OOH + ArCH_2\cdot$$

$$ArCH_2O\cdot + ArCH_3 \longrightarrow ArCH_2OH + ArCH_2\cdot$$

$$ArCH_2OOH + Co^{III}OH \longrightarrow ArCH_2O_2\cdot + Co^{2+} + H_2O$$

Termination:

$$ArCH_2O_2\cdot + Co^{III} \longrightarrow ArCH_2O_2Co^{III}$$



$$2ArCH_2O_2\cdot \rightleftharpoons ArCH_2O_4CH_2Ar \longrightarrow ArCHO + ArCH_2OH + O_2$$

Since substituted toluenes are primary alkyl benzenes, the rate of termination of the radical reaction is so high that it is not possible to achieve a high yield of the hydroperoxide. Moreover, a cobalt catalyst can rapidly decompose the hydroperoxide intermediate. Thus aldehydes and alcohols are formed as primary products by the chain termination of benzylperoxy radicals. As shown in Table [1.2] in Chapter 1, the reactivity of the peroxy radical ($RO_2\cdot$) towards hydrogen abstraction is much higher than the hydroperoxy radical ($RO\cdot$). Hence the amount of benzyl alcohol formed in the propagation step is much less than benzyl hydroperoxide. In the termination step, the benzylperoxy radicals ($ArCH_2OO\cdot$) may interact with the metal more rapidly resulting in direct formation of the aldehyde rather than dimerization, and then decomposition to the aldehyde and alcohol. As a result, the concentration of alcohols formed during the reaction may be too low to be observed by gas chromatography.

In conclusion, our systems using $CoCl_2$, $CoCl_2$-$CrCl_3$ and $CoCl_2$-$ZrCl_4$ for the oxidation of alkoxy substituted toluenes to their corresponding aldehydes give comparable results to the well known system employing $Co(OAc)_2$-NaBr in acetic acid. Unfortunately, the reactions either fail or give poor selectivity with other substituted toluenes. With

regard to the above variable studies, it was found that the reactions likely proceed through free radical autoxidation in which the reactivity of the benzylic C-H bond plays a very important role. Since these systems are so sentitive to the reactivity of the benzylic C-H bond, it could be advantageous to selectively oxidize the most reactive benzylic hydrocarbon for those compounds containing two or more benzylic C-H bonds which have close reactivity. These special features have been successfully applied in the oxidation of dialkyl substituted benzenes. The results will be discussed in next section.

From a comparision of the present oxidation systems with the use of $Co(OAc)_2$-NaBr-HOAc, it is clear that our oxidation system possesses several advantages:

1) No radical initiator is needed to start the free radical autoxidation reaction.

2) Recovery of the aldehydes from the reaction mixture is very easy, removal of the low-boiling components under reduced pressure, addition of ice water to the residue, followed by filtration of the precipitated acid, and then extraction with diethyl ether.

3) The selectivity is generally higher in comparison to the use of $Co(OAc)_2$-NaBr-HOAc in which benzyl bromide and acetate derivatives are usually formed as by-products.

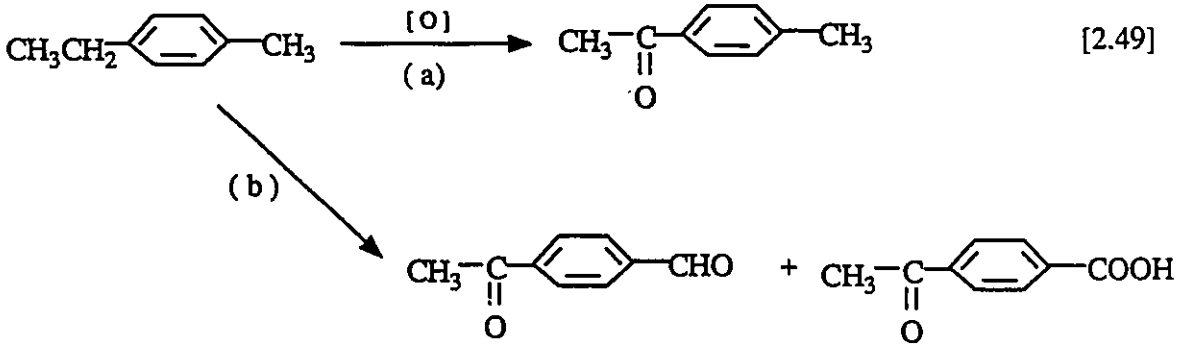
4) No corrosion problems.

5) This system is applicable to those substrates which are unstable in the presence of acid since diglyme is a neutral solvent.

Finally, the oxidation of alkylbenzenes carried out with relatively high catalyst concentration proceeds via a free radical autoxidation mechanism which is governed by the thermodynamic stability of the formed radical. However, the mechanism of the $Co(OAc)_2$-HOAc system involving a similar concentration of cobalt ion is generally an electron transfer one.

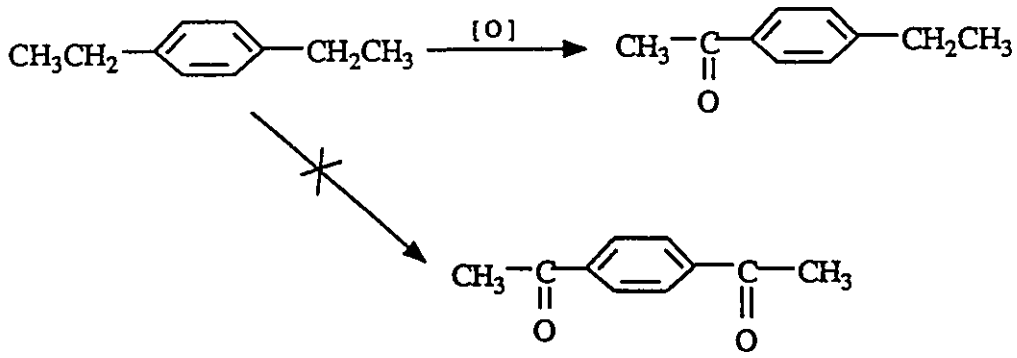
2.2.2. OXIDATION OF OTHER BENZYLIC HYDROCARBONS

As discussed in section 2.2.1., the oxidation of substituted toluenes to the corresponding aldehydes using anhydrous $CoCl_2$ as the catalyst, in the presence of diglyme, was unique in that the oxidation reaction apparently proceeds via free radical autoxidation. A continuation of the study utilizing this oxidation system was carried out in attempts to selectively oxidize dialkylbenzenes such as p-ethyltoluene. The reactivity and chemical behaviour of the C-H bond of benzylic methyl and methylene groups are not significantly different. In general, the reactivity of a secondary benzylic C-H bond is greater than a primary one in radical reactions. Thus it would be of interest to determine whether the reaction could result in selective oxidation of a secondary benzylic C-H bond to form a ketone (eq.[2.49], path a), and not both benzylic alkyl groups (path b) since oxidation of benzylic methylene groups to the corresponding ketones results in decreasing reactivity of the C-H bonds of the other alkyl substituent on the ring. Similarly,



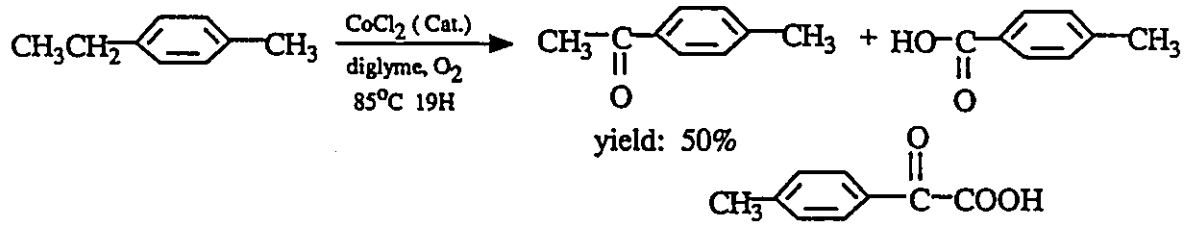
[2.49]

determination of the selectivity of the oxidation of p-diethylbenzene is also of value (eq. [2.50]).



[2.50]

The study of the oxidation of p-ethyltoluene catalyzed by anhydrous $CoCl_2$ (substrate : $CoCl_2$ = 10:1) was initially carried out in the presence of diglyme under an oxygen atmosphere. p-Methylacetophenone was obtained in 50% isolated yield after a reaction time of 19 hours at 85°C (eq.[2.51]), together with other by-products. The mass spectral fragmentation patterns of two major by-products (GC/MS), suggested that they are p-methylbenzoic acid (p-$CH_3C_6H_4COOH$) (m/e: 136$[M]^+$, 119$[M\text{-}OH]^+$, 91$[C_6H_5CH_2]^+$) and p-methylbenzoyl formic acid (p-$CH_3C_6H_4COCOOH$) (m/e: 164 $[M]^+$, 119 $[p\text{-}CH_3C_6H_4CO]^+$, 91 $[C_6H_5CH_2]^+$, 77 $[C_6H_5]^+$). The structure of p-methylbenzoic



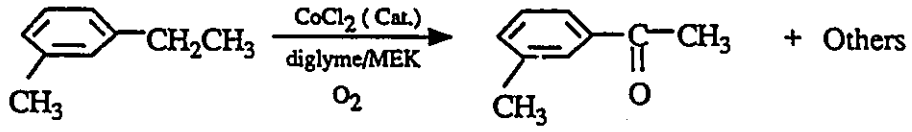
[2.51]

acid was confirmed by IR and ^1H NMR after purification using preparative TLC. p-Methylbenzoyl formic acid, however, was never isolated successfully. The formation of these two acids was believed to occur via oxidation of the formed p-methylacetophenone. In order to confirm this hypothesis, oxidation using p-methylacetophenone as starting material was carried out with this system. Indeed, p-methylbenzoic acid was obtained in 82% yield after reaction for three days. In addition, a small amount of p-methylbenzoyl

formic acid was detected by GC/MS.

Although the oxidation of p-ethyltoluene under these conditions afforded mainly the desired product, the selectivity was not satisfactory because of the further oxidation of the monoketone. Thus attempts were made to prevent such over-oxidation. It was observed that when the oxidation of p-ethyltoluene was carried out in the presence of a 1:1 ratio of diglyme to methyl ethyl ketone (MEK) under similar reaction conditions, the selectivity towards p-methylacetophenone was increased from 53% to 69%. Hence a variety of ratios of diglyme and MEK have been examined in order to achieve higher yields of the monoketone. The results are shown in Table [2.16].

Table [2.16] Effect of ratio of diglyme and MEK on the oxidation of m-ethyltoluene to the corresponding ketone



Substrate / $CoCl_2$ (mmol)	Ratio		T (^{O}C)	Time (h)	Conversion (%)	Selectivity (%)
	diglyme	MEK				
10 / 1	1	0	70	20	100	45
5 / 1	1	2	60	37	59	76
5 / 1	1	3	60	46	62	93
5 / 1	1	4	65	40	40	95

As can be seen in the table, increasing the ratio of MEK to diglyme tends to increase the selectivity of the monoketone, preventing further oxidation of this species. At the same time, the rate of oxidation decreases. Considering both the selectivity and the

rate of reaction, a diglyme to MEK ratio of 1:3 seemed to give the best results.

How can one account for the beneficial effect of methyl ethyl ketone in this reaction ? First of all, let us consider the stability of the following (Fig. [2.4]).

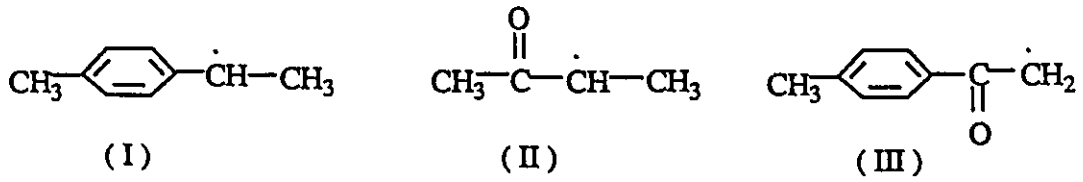
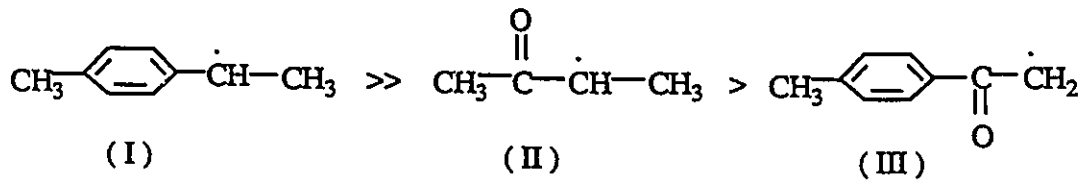


Fig. [2.4]

Radical (I) is stabilized considerably by resonance with the benzene ring, while radical (II) is slightly stabilized by conjugation with the π-electrons of the carbonyl group. For compound (III), there is a modest stabilization of the radical by the carbonyl π bond which is weakened by conjugation with the benzene ring. Both (I) and (II) are secondary radicals and have higher stability in comparision to primary radicals. Thus the stability of these three radical intermediates decreases in the order:



Also, the reactivity of the benzylic C-H bond for p-ethyltoluene, methyl ethyl ketone and p-methylacetophenone groups decreases in the same order. Therefore, one can predict that MEK (II) is more readily oxidized than p-methylacetophenone (III), especially when the concentration of MEK is much higher than p-methylacetophenone in the reaction mixture. These competing reactions resulted in an increase in the selectivity of the reaction since further oxidation of p-methylacetophenone is inhibited by the presence of MEK. Products produced from the oxidation of MEK are usually compounds with low boiling points, and can be easily removed under reduced pressure at the end of reaction.

During the oxidation reaction, considerable amounts of water were generated. The anhydrous $CoCl_2$ which was dissolved in diglyme solution, changed color from blue to pink. This was due to the formation of the hydrated cobalt chloride complex $[Co(H_2O)_6]^{2+}$. This species usually has poorer catalytic activity as compared to anhydrous $CoCl_2$. For example, the oxidation of m-ethyltoluene catalyzed by small amounts of anhydrous $CoCl_2$ (substrate : $CoCl_2$ = 10:1) in the presence of diglyme led to 40% conversion after 45 hours at 65°C. The color of the solution changed completely to pink indicating the formation of the hydrated $CoCl_2$ after one day.

Attempts were made to absorb or remove the water generated during the reaction, including the addition of molecular sieves (4Å) to the reaction mixture or removal of the water as an azeotrope. However, the addition of molecular sieves resulted in poorer yields and a more difficult work-up since the sieves became powdery at the end of the reaction. When the oxidation was carried out in the presence of diglyme (5ml) and benzene (20ml) under reflux using a Dean-Stark trap, the water generated during the reaction might be removed as an azeotrope between benzene and water. Unfortunately, the experimental result indicated that the oxidation did not occur in this solvent system. However, the hydrated cobalt complex $[Co(H_2O)_6]^{2+}$ which precipated during the reaction could easily be recovered by filtration of the mixture at the end of reaction. As a result, the hydrated $CoCl_2$ could be re-used. Consequently, a considerable quantity of anhydrous $CoCl_2$ (e.g., substrate : $CoCl_2$ = 5:1) was used in subsequent studies of the oxidation of various benzylic hydrocarbons.

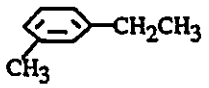
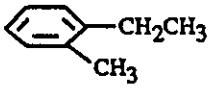
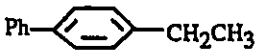
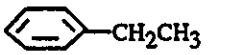
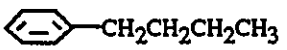
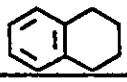
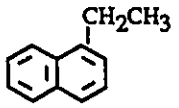
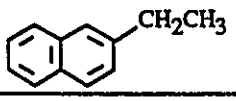
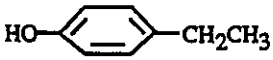
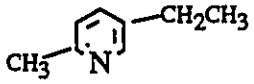
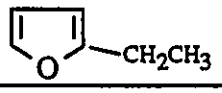
A mixed catalytic system of $CoCl_2$ and $CrCl_3$ (2:1) was utilized to increase the selectivity in the oxidation of p-methylanisole to the corresponding aldehyde. However it was found that the use of this catalytic system for the oxidation of a benzylic methylene group was not advantageous in comparison to anhydrous $CoCl_2$ alone. For example, oxidation of m-ethyltoluene in the presence of $CoCl_2$ and $CrCl_3$ gave m-methylacetophenone in 43% yield and 88% selectivity, while the use of only $CoCl_2$

afforded the ketone in 58% yield and 93% selectivity. Moreover, the oxidation of benzylic hydrocarbons catalyzed by $Co(OAc)_2$ in the presence of HOAc is known to give the corresponding carbonyl compounds in moderate yields (as discussed earlier). However, the experimental results showed that the rate of oxidation using this system was much slower, and that the selectivity was also poorer in comparison to the use of $CoCl_2$ in the mixed solvent, diglyme and MEK. The lower selectivity was caused by the formation of the acetate derivative as a by-product. As an example, the oxidation of p-diethylbenzene catalyzed by $CoCl_2$ in our system gave p-ethylacetophenone in 72% yield with 82% selectivity while this reaction catalyzed by $Co(OAc)_2$ in the presence of HOAc only afforded the product in 35% yield and 68% selectivity. The above studies led to the conclusion that anhydrous $CoCl_2$ was the most suitable metal salt to catalyze the oxidation of benzylic hydrocarbons under an oxygen atmosphere.

The low boiling point of methyl ethyl ketone (80°C) limited the reaction temperatures to below 70°C. Otherwise, evaporation of MEK under a flow of oxygen occurred, which changed the ratio of MEK and diglyme, and resulted in a poorer selectivity of the reaction. Therefore, the overall reaction time was prolonged in order to obtain a reasonable conversion. An induction period in this type of oxidation was not necessary because of the long reaction time. However, it was useful to heat a mixture of catalyst in diglyme and MEK for 30 minutes in order to completely dissolve the complex.

Having found a process to selectively convert methyl and ethyl substituted ethyl benzenes to their corresponding monoketones, an investigation was undertaken to study the scope of this system for the oxidation of a variety of ethylbenzenes to their ketones. The results are illustrated in Table [2.17].

Table [2.17] Oxidation of various benzylic hydrocarbons to their corresponding ketones catalyzed by anhydrous $CoCl_2$

Substrate [a]	Diglyme / MEK (ml)	T (°C)	Time (h)	Yield (%)	Selectivity (%)
	1 / 3	63	43	60	85
	1 / 3	60	46	58	93
	1 / 3	60	56	30	48
	1 / 3	60	45	72	82
	1 / 3	60-70	42	87	97
	1 / 3	60-70	46	48	98
	1 / 3	60	109	45	95
	1 / 3	60	109	41	77
	1 / 3	70	45	75	94
	1 / 3	60	45	23	66
	1 / 3	60	45	20	65
	1 / 4	60-70	48	No Reaction	
	1 / 0	70	41	No Reaction	
	1 / 0	70	41	No Reaction	

a) Substrate / $CoCl_2$ = 5 /1

The results in Table [2.17] illustrate the applicability of the oxidation system to the selective oxidation of the following types of benzylic hydrocarbons.

a) Alkyl substituted ethylbenzenes. (e.g., p-; m-; o-ethyltoluenes as well as p-diethylbenzene)

b) Alkoxy and phenyl substituted ethylbenzenes. (e.g., p-ethylanisole and 4-ethylbiphenyl)

c) Alkyl benzenes. (e.g., ethylbenzene and n-butylbenzene)

d) Cyclic alkyl substituted benzene (e.g., tetralin)

e) Ethylnaphthalenes (e.g., 1- or 2-ethylnaphthalene)

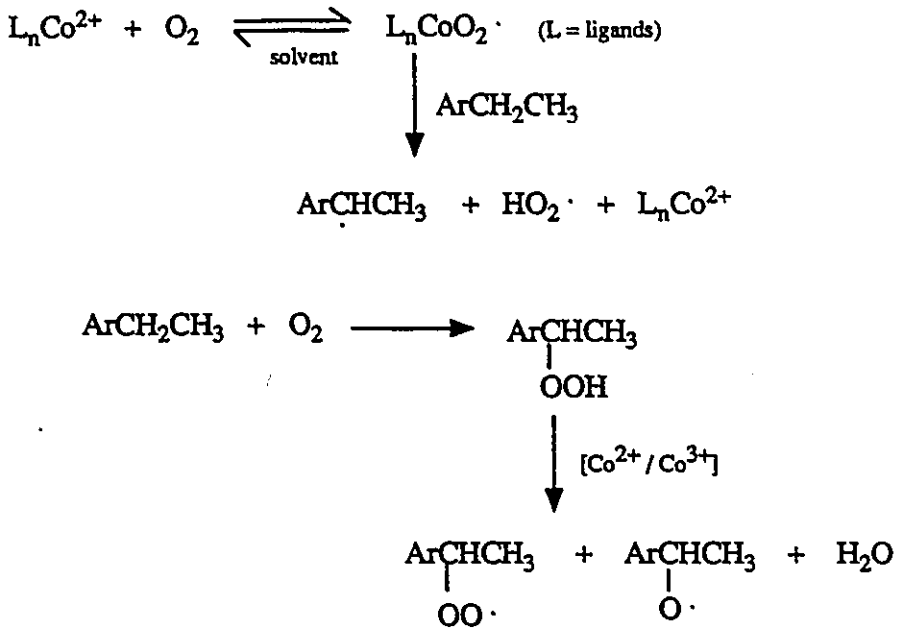
However, this system is not capable of oxidizing other types of aromatic compounds such as 5-ethyl-2-methylpyridine and 2-ethylfuran. Furthermore, oxidation of p-ethylphenol did not occur. This is not surprising since the reaction presumably proceeds via a radical process, and substituted phenols are known to be good radical inhibitors.[149]

In general, the rate of reaction is dependent on the reactivity of the benzylic methylene C-H bond which is strongly influenced by resonance, as well as by the electron donating ability of substituents on the ring. This is illustrated by the yield of the reactions listed in the table for the oxidation of p-ethylanisole, p-diethylbenzene, p-ethyltoluene as well as m-ethyltoluene. The yields of the reactions decreased with a decrease in the reactivity of their C-H bonds. Moreover, steric factors should also be taken into account. For example, when the oxidation of o-ethyltoluene was carried out under standard conditions, the obtained yield and selectivity was much lower as compared to the oxidation of p-ethyltoluene. This result may be due, at least in part, to the steric hindance of the o-methyl group.

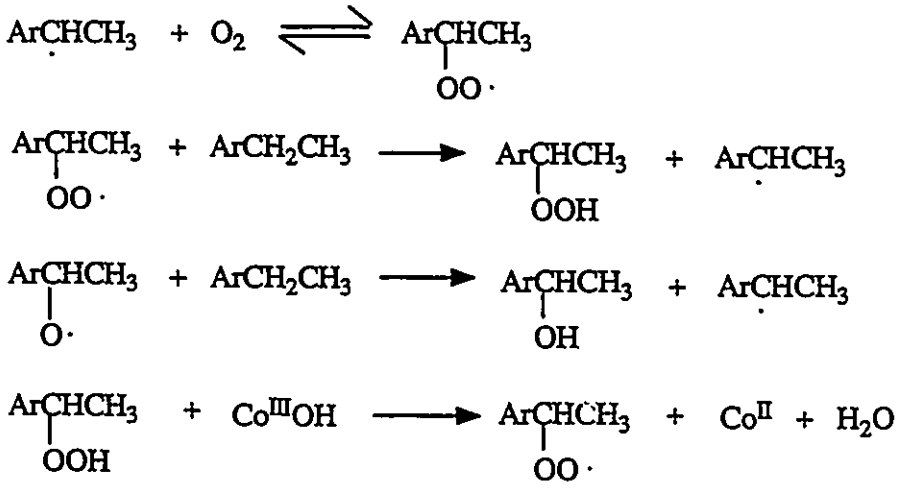
On the basis of experimental evidence, the following reaction mechanism is proposed for the oxidation of a variety of benzylic methylene groups to their corresponding monoketones catalyzed by anhydrous $CoCl_2$ in the mixture of diglyme and MEK (1:3) (Scheme [2.4]).

Scheme [2.4]

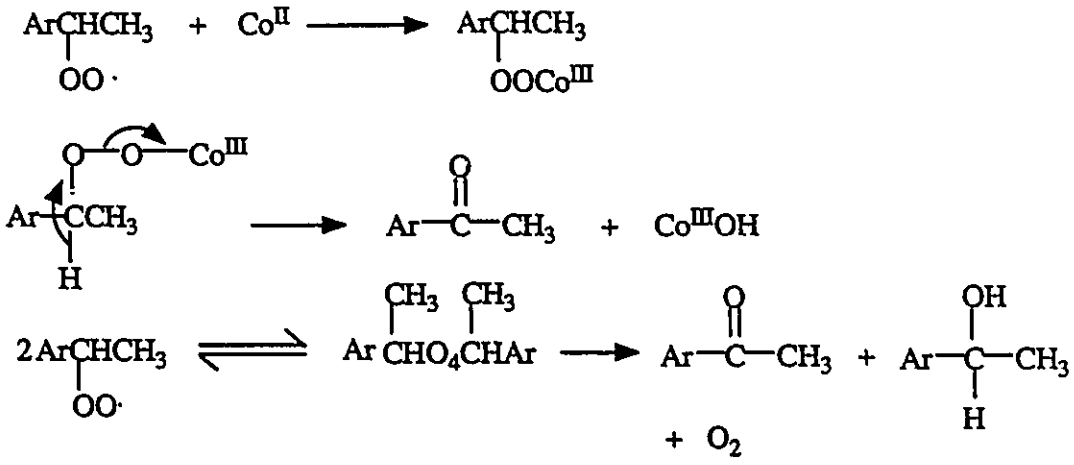
a) Initiation:



b) Propagation:

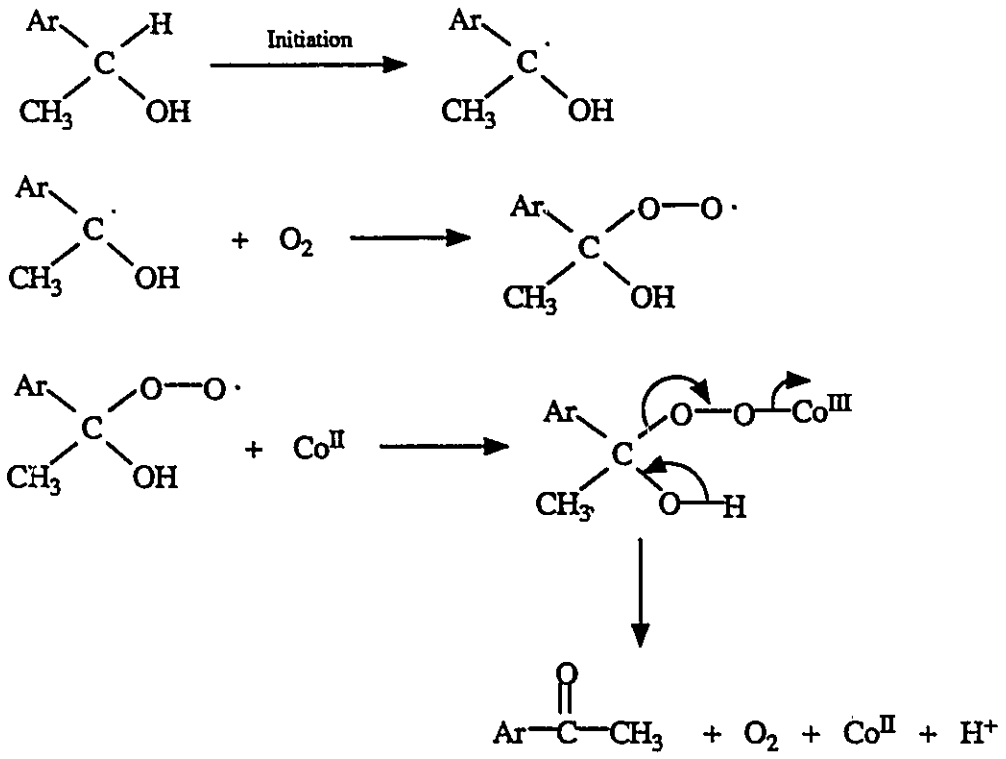


c) Termination:

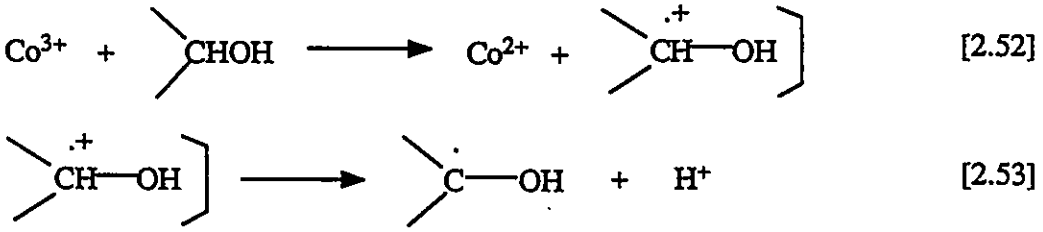


The proposed reaction mechanism is similar to that suggested for the oxidation of substituted toluenes. The formation of a variety of alcohol intermediates was detected by GC/MS. For example, the oxidation of m-ethyltoluene at 60°C for 24 hours gave an alcohol intermediate noted in the GC/MS. Its framentation pattern was m/e 136$[M]^+$, 121$[M\text{-}CH_3]^+$, 91$[C_6H_5CH_2]^+$, 77$[C_6H_5]^+$. Unfortunately, the alcoholic intermediates were produced in amounts too low to be isolated. At the end of the reaction, most of the alcohol compound had been converted to the corresponding ketone. A possible reaction mechanism for this conversion is outlined in Scheme [2.5].

Scheme [2.5]



The oxidation of secondary alcohols to ketones by cobalt(III) acetate in the presence of dioxygen has been reported[150] to involve a direct, one-electron oxidation of the alcohol by Co(III) (eq. [2.52-2.53]. However, we believe that the oxidation of the



[2.52]

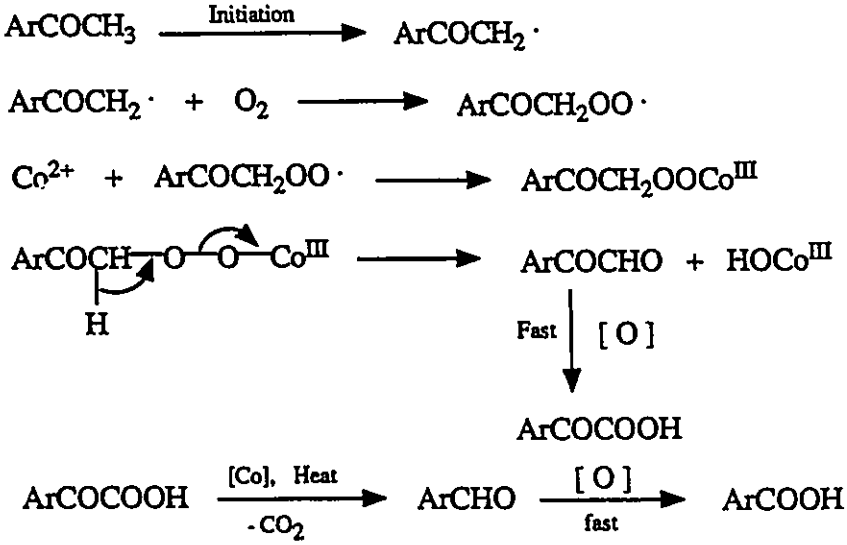
[2.53]

secondary alcohol intermediates in our system proceeds via hydrogen abstraction from the α-C-H bond of the alcohol (Scheme [2.5]), and not by a one-electron oxidation. This may be due to the oxidation of hydrocarbons selectively at the most reactive C-H bond regardless of its size. For example, the oxidation of p-ethyltoluene took place exclusively

at the benzylic methylene group, not at the benzylic methyl group. This result is consistent with a metal-catalyzed autoxidation in which hydrogen abstraction is characteristic as mentioned in Chapter 1.2. The introduction of an oxygen-containing funtionality into a hydrocarbon backbone (e.g., an aldehyde or alcohol) results in a significant increase in the oxidizability of the adjacent C-H bond[28, 151]. Indeed, the oxidation of alcoholic intermediates in our system was quite fast. Thus only very low yield of the alcohols could be obtained.

As discussed earlier, ketones can also undergo metal-catalyzed autoxidation to give an α-keto carboxylic acid (ArCOCOOH) as the primary product, with a carboxylic acid resulting from subsequent C-C bond cleavage. Although the α-keto carboxylic acids have never been isolated, their GC/MS indicated the presence of a compound with a formula consistent with an α-keto acid. One can thus consider the mechanism in Scheme [2.6] for the reaction:

Scheme [2.6]



In conclusion, use of anhydrous cobalt chloride as an oxidation catalyst in the

presence of a mixed solvent of diglyme and methyl ethyl ketone (1:3) constitutes a versatile method for the selective oxidation of a variety of benzylic methylene groups to the corresponding ketones. These reactions may occur via a metal-catalyzed autoxidation mechanism which is controlled by the thermodynamic stability of the radical formed and the reactivity of the C-H bond towards hydrogen abstraction by the radicals. In addition, this system proceeds under relatively mild oxidation conditions. It can only oxidize those benzylic hydrocarbons in which the benzylic carbon possesses a relatively high reactivity. For instance, the oxidation of p-diethylbenzene afforded p-ethylacetophenone in 72% yield. No diketone was produced (eq. [2.54]). This might be due to the deactivation of the benzylic methylene C-H bond by the formation of a carbonyl group which is a strong electron withdrawing group. As a result, the low reactivity of the benzylic methylene C-H bond of p-ethylacetophenone prevents further oxidation.

2.3 Experimental Data

2.3.1. GENERAL COMMENTS

Infrared spectra were recorded using a Perkin-Elmer 783 spectrometer and were calibrated with a polystyrene standard. Sodium chloride cells (for solutions), disks or KBr pellets were used for running the spectra. Proton magnetic resonance spectra were obtained with a Varian T60, EM360A, or XL300 spectrometer whereas carbon magnetic resonance spectra were recorded on a Varian XL300 spectrometer. Mass spectra were recorded with a VG Micromass 7070E spectrometer equipped with a Digital Equipment Corporation PDP8A data system. Gas chromatograph-mass spectrometric determinations were made with a Varian 3300 chromatograph, fitted with a Megabore DB5 capillary column in tandem with the VG Micromass 7070E spectrometer.

Analyses by gas chromatography were carried out with programmable Varian Vista 6000 or Varian 3400 gas chromatographs equipped with flame ionization detectors and a Varian 4270 intergrator. Glass columns (3m) packed with 3% OV101 or 3% OV-17 on Chromosorb W 80-100 mesh were utilized for gas chromatographic determinations.

The organometallic complexes and organic chemicals used were purchased from Fisher Scientific Company, Alfa Products Company and Aldrich Chemical Company. They were used as received in almost all cases. Methyl ethyl ketone, however, was stored over 4Å molecular sieves prior to use. Oxygen was obtained from Air Products Company. Solvents employed for extraction were distilled following standard procedures.

Thin layer chromatographic plates [TLC plates-silica gel or neutral (type E) alumina

oxide $60F_{254}$] were purchased from Terochem Co. as were the silica gel and aluminum oxide used for column chromatography.

2.3.2. COBALT-CATALYZED OXIDATION OF SUBSTITUTED TOLUENES TO CORRESPONDING ALDEHYDES

General procedure for the oxidation of substituted toluenes

Oxygen was slowly bubbled into a solution of the metal complex (0.5-0.75 mmol) in diglyme (8-10 ml) for about 60 minutes at 60-95°C (oil bath). A substituted toluene was then added dropwise to this mixture and stirring was continued for 2.5 to 69 hours (see Table [2.14] and [2.15] for reaction times). The reaction was monitored by gas chromatography, and work-up was effected in most cases as follows: The reaction mixture was cooled to room temperature and concentrated by rotary evaporation. Ice water (15-20ml) was added to the residue and the precipitate was filtered if formed. The filtrate was extracted with diethyl ether (3x30 ml). The ether layer was washed with water (2x50 ml), and dried over $MgSO_4$. The dried organic phase was concentrated and the crude mixture was analyzed by comparing GC retention times with those of authentic materials, where available, and confirmed by GC/MS. Pure products were isolated by thin layer or column chromatography on silica gel using a variety of hexane / ethyl acetate ratios as the eluant. Isolated products were identified by ^1H NMR, IR, and mass spectrometry. The results and reaction conditions are listed in Table [2.14] and [2.15].

Oxidation of p-methylanisole

p-Methylanisole (0.61g, 5.0mmol) was oxidized in the presence of anhydrous $CoCl_2$ (0.066g, 0.5mmol) and $CrCl_3$(0.04g,0.25mmol) at 90°C for 3.5 hours. Two products were

detected in the crude sample by GC. The major one was identified as p-methoxybenzaldehyde affording 90% selectivity, and another one was p-methoxybenzoic acid.

p-methoxybenzaldehyde

IR(neat): ν_{H-CO} 2850cm^{-1}, $\nu_{C=O}$ 1685^{-1}, ν_{C-O} 1263cm^{-1}.

^{1}H NMR($CDCl_3$): δ 3.78 (s, 3H, OCH_3), 6.82 (d, 2H, J=8Hz, protons meta to carbonyl), 7.63(d, 2H, protons ortho to carbonyl), 9.60 (s, 1H, CHO).

MS: m/e 136$[M]^+$, 135$[M-H]^+$, 107$[M-CHO]^+$, 77$[C_6H_5]^+$.

p-methoxybenzoic acid

IR($CDCl_3$ + DMSO-d_6): ν_{COO-H} 3500-2500cm^{-1}, $\nu_{C=O}$ 1705cm^{-1}, ν_{C-O} 1260cm^{-1}.

^{1}H NMR($CDCl_3$ + DMSO-d_6): δ 3.70 (s, 3H, OCH_3), 6.70 (d, 2H, J=8Hz, protons meta to carbonyl), 7.68 (d, 2H, protons ortho to carbonyl), 10.01 (s, 1H, COOH).

MS: m/e 152$[M]^+$, 135$[M-OH]^+$, 107$[M-COOH]^+$, 77$[C_6H_5]^+$.

Oxidation of p-ethoxytoluene

p-Ethoxytoluene (0.68g, 5.0mmol) was added to a solution of anhydrous $CoCl_2$ (0.066g, 0.5mmol) and $CrCl_3$ (0.04g, 0.25mmol) in diglyme (8ml) at 90°C for 3 hours. 35% of substrate was converted to p-ethoxybenzaldehyde in 83% selectivity. p-Ethoxybenzoic acid was obtained as the by-product. When this reaction was carried out with 0.066g (0.5 mmol) of anhydroous $CoCl_2$ alone, 32% p-ethoxytoluene was oxidized to p-ethoxybenzaldehyde in 96% selectivity.

p-ethoxybenzaldehyde

IR(neat): $\nu_{C=O}$ 1688cm^{-1}, ν_{C-O} 1263cm^{-1}.

^{1}H NMR($CDCl_3$): δ 1.40(t, 3H, CH_3), 3.98 (q, 2H, CH_2), 6.78 (d, 2H, J=8Hz, protons meta to carbonyl), 7.60 (d, 2H, protons ortho to carbonyl), 9.62(s, 1H, CHO).

MS: m/e 150[M], 121[M-CHO]$^+$, 93[C_6H_5O]$^+$, 77[C_6H_5]$^+$.

p-ethoxybenzoic acid

IR($CDCl_3$ + DMSO-d_6): ν_{COO-H} 3500-2600cm^{-1}, $\nu_{C=O}$ 1702cm^{-1}, ν_{C-O} 1256cm^{-1}.

^{1}H NMR($CDCl_3$+ DMSO-d_6): δ 1.40(t, 3H, CH_3), 3.90 (q, 2H, CH_2), 6.68 (d, 2H, J=8Hz, protons meta to carbonyl), 7.77 (d, 2H, protons ortho to carbonyl), 9.53 (s, 1H, COOH).

MS: m/e 166[M]$^+$, 121[M-COOH]$^+$.

Oxidation of o-methylanisole

o-Methylanisole (0.61g, 5.0mmol) was oxidized in the presence of anhydrous $CoCl_2$ (0.066g, 0.5mmol) at 60°C for 69 hours. The major product detected by GC was o-methoxybenzaldehyde which was identified by the comparison of GC retention time with that for authentic material. It was isolated in 0.11g (0.85mmol) by TLC (80% selectivity), and 0.51g (4.2mmol) of substrate was recovered. Thus the conversion was only 17%.

o-methoxybenzaldehyde

IR(neat): ν_{H-CO} 2855cm^{-1}, $\nu_{C=O}$ 1690cm^{-1}, ν_{C-O} 1250cm^{-1}.

^{1}H NMR($CDCl_3$): δ 3.82(s, 3H, OCH_3), 6.83 (m, 2H, protons meta to carbonyl), 7.42 (m, 2H, protons ortho and para to carbonyl), 10.37(s, 1H, CHO).

MS: m/e 136$[M]^+$, 135$[M-H]^+$, 107$[M-CHO]^+$, 77$[C_6H_5]^+$.

Oxidation of 2,3-dimethoxytoluene

a) A mixture of 2,3-dimethoxytoluene (0.76g, 5mmol), anhydrous $CoCl_2$ (0.066g, 0.5mmol) and $CrCl_3$ (0.4g, 0.25mmol) in diglyme (8ml) was stirred at 90°C for 10 minutes. The color of the solution became green. The reaction was monitored by gas chromatography. No reaction was observed even after 43 hours.

b) Addition of this substrate to a solution of anhydrous $CoCl_2$ (0.066g, 0.5mmol) in diglyme (10ml) resulted immediately in a change in the color of solution from blue to green. However, this green solution had become blue after stirring for 15 minutes. The reaction was stopped after 21 hours at 80°C. 2,3-Dimethoxybenzaldehyde was the only product detected by GC (12% yield).

IR(neat): $\nu_{H\text{-}CO}$ 2880, 2842cm^{-1}, $\nu_{C=O}$ 1690cm^{-1}, $\nu_{C\text{-}O}$ 1248, 1266cm^{-1}.

^1H NMR($CDCl_3$): δ 3.80(s, 3H, OCH_3), 3.87(s, 3H, OCH_3), 7.08(m, 4H, aromatic), 10.19(s, 1H, CHO).

MS: m/e 166$[M]^+$, 151$[M\text{-}CH_3]^+$, 135$[M\text{-}OCH_3]^+$, 105$[C_6H_5CO]^+$, 77$[C_6H_5]^+$.

Oxidation of m-methylanisole

Stirring a mixture of m-methylanisole (0.61g, 5mmol) and anhydrous $CoCl_2$ (0.066g, 0.5mmol) or together with $CrCl_3$ (0.4g, 0.25mmol) at 90°C for 48 hours gave recovered starting material.

When the substrate was added to a solution of anhydrous $CoCl_2$ (0.066g, 0.5mmol) and $ZrCl_4$ (0.058g, 0.25mmol) and stirred for 5 hours at 90°C, 37% of the substrate was converted to products. m-Methoxybenzaldehyde was obtained as a major product (61% selectivity). m-Methoxybenzoic acid (13% selectivity) was also identified after the purification. Small amounts of m-methoxybenzyl chloride was detected by GC/Mass Spec..

m-methoxybenzaldehyde

IR($CDCl_3$): ν_{H-CO} 2847, 2735cm^{-1}, $\nu_{C=O}$ 1705cm^{-1}, ν_{C-O} 1266cm^{-1}.

^1H NMR($CDCl_3$): δ 3.74(s, 3H, OCH_3), 7.10(m, 4H, aromatic), 9.73(s, 1H, CHO).

MS: m/e 136$[M]^+$, 135$[M]^+$, 107$[M-CHO]^+$, 77$[C_6H_5]^+$.

m-methoxybenzoic acid

IR($CDCl_3$): ν_{COO-H} 3400-2500cm^{-1}, $\nu_{C=O}$ 1686cm^{-1}, ν_{C-O} 1283, 1244cm^{-1}.

MS: m/e 152$[M]^+$, 135$[M-OH]^+$, 107$[M-COOH]^+$, 77$[C_6H_5]^+$.

MS of trimethylsilylated derivative: m/e 224, 209, 165, 135.

m-methoxybenzyl chloride

MS: m/e 156$[M]^+$, 141$[M-CH_3]^+$, 121$[M-Cl]^+$, 91$[C_6H_5CH_2]^+$, 77$[C_6H_5]^+$.

Oxidation of p-tert-butyltoluene

A mixture of p-tert-butyltoluene (0.74g, 5mmol) and anhydrous $CoCl_2$ (0.066g, 0.5mmol) was stirred at 90°C for 23 hours. Three products were detected in the crude sample by GC. Thin-layer chromatography using 5% ethyl acetate in hexane gave 0.12g (0.74mmol, 42% selectivity) of t-butylbenzaldehyde, while starting material was recovered in 0.47g (3.18 mmol, 36% conversion). In addition, another two products were also isolated. One was identified as p-tert-butylbenzoic acid (12% selectivity), and another was unidentified.

Oxidation of this substrate in the presence of anhydrous $CoCl_2$ (0.066g, 0.5mmol) and $ZrCl_4$ (0.116g, 0.5mmol) afforded very low conversion even after 48 hours at 90°C.

p-tert-butylbenzaldehyde

IR(neat): $\nu_{C=O}$ 1708cm^{-1}

^{1}H NMR($CDCl_3$): δ 1.30 [s, 9H, -C(CH_3)$_3$], 7.47 (d, 2H, J=8Hz, protons meta to carbonyl), 8.02 (d, 2H, protons ortho to carbonyl), 9.94(s, 1H, CHO).

MS: m/e 162[M]$^+$, 147[M-CH_3]$^+$, 91[$C_6H_5CH_2$]$^+$.

p-tert-butylbenzoic acid

IR($CDCl_3$+ DMSO-d_6): ν_{COO-H} 3450-2500cm^{-1}, $\nu_{C=O}$ 1703cm^{-1}, ν_{C-O} 1272cm^{-1}.

^{1}H NMR($CDCl_3$+ DMSO-d_6): δ 1.37[s, 9H, C(CH_3)$_3$], 7.27 (d, 2H, J=8Hz, protons meta to carbonyl), 7.77 (d, 2H, protons ortho to carbonyl), 10.58(s, 1H, COOH).

MS of trimethylsilylated derivative: m/e 250, 235, 191, 161, 118.

Unknown product

IR(neat): $\nu_{C=O}$ 1722 cm^{-1}, ν_{C-O} 1218cm^{-1}.

^{1}H NMR($CDCl_3$): δ 1.26(s, 9H), 2.10(s, 1H), 5.12(s, 2H), 7.3(m, 3H), 8.06(s, 1H).

MS: m/e 192[M]$^+$, 177[M-15]$^+$, 131[M-61]$^+$, 91[$C_6H_5CH_2$]$^+$, 77[C_6H_5]$^+$.

Oxidation of p-i-propyltoluene (p-cymene)

A mixture of p-cymene (0.67g, 5mmol) and anhydrous $CoCl_2$ (0.066g, 0.5mmol) was stirred at 85-90°C for 24 hours, affording 0.29g (2.2mmol, 43% yield) of p-methylacetophenone.

p-methylacetophenone

IR(neat):	$\nu_{C=O}$ 1690cm^{-1}
^{1}H NMR($CDCl_3$):	δ 2.35(s, 3H, Ar-CH_3), 2.52(s, 3H, Ar$COCH_3$), 7.10 (d, 2H, J=8Hz, protons meta to carbonyl), 7.70 (d, 2H, protons ortho to carbonyl).
MS:	m/e 134$[M]^+$, 119$[M-15]^+$, 91$[C_6H_5CH_2]^+$.

Attempted oxidation of other methylbenzenes

m-Phenoxyltoluene, p-xylene, toluene, p-chlorotoluene and 2-methylfuran were not oxidized by either catalytic system ($CoCl_2$, $CoCl_2/CrCl_3$ and $CoCl_2/ZrCl_4$). When oxidation of 2-methylthiophene (0.49g, 5mmol) was carried out in the presence of anhydrous $CoCl_2$ (0.066g, 0.5mmol) for 48 hours at 60°C, the color of the solution changed to dark green from blue. Gas chromatography indicated that the starting material had completely disappeared. Two products were observed in the GC and were isolated by TLC using 3:2 hexane to ethyl acetate as the eluant. ^{13}C NMR and IR showed that both products do not have a carbonyl group. Their mass spectra (m/e 194$[M]^+$, 179$[M-15]^+$; m/e 208$[M]^+$, 193$[M-15]^+$) suggested that these two products were dimers or polymers of 2-methylthiophene.

2.3.3. COBALT-CATALYZED OXIDATION OF BENZYLIC METHYLENE GROUPS TO THE CORRESPONDING KETONES

General procedure for the oxidation of benzylic methylene groups.

Oxygen was slowly bubbled into a solution of anhydrous $CoCl_2$ (0,13g, 1.0mmol) in diglyme (4ml) and dried MEK (12ml) for about 45-60 minutes at 60-70°C (oil bath). Then a benzylic hydrocarbon (5mmol) was added to this mixture, which was stirred under oxygen for 41-109 hours (see Table [2.17]). At the end of reaction, the color of solution usually became light blue or green, and some pink precipiate was deposited. The following work-up was used in all cases.

The reaction mixture was cooled to room temperature, and then filtered to remove the pink precipitate. The filtrate was concentrated by rotary evaporation, and the residue was added to 30ml of distilled water and then extracted with ether (3x30ml). The organic layer was washed with distilled water (2x20ml), and dried over $MgSO_4$. The solution was filtered and concentrated to afford the crude product. Any further purification was effected by thin-layer and column chromatography on silica gel, using a mixture of hexane and ethyl acetate (3:2) as eluant. Unless otherwise stated, isolated products were identified by IR, ^1H NMR, and mass spectrometry. The results and reaction conditions are listed in Table [2.17].

Oxidation of p-ethyltoluene (p-$CH_3C_6H_4C_2H_5$)

Oxidation of p-ethyltoluene afforded p-methylacetophenone (p-$CH_3C_6H_4COCH_3$) in 60% yield. (See previous section for spectral data).

Two major by-products were observed. One was identified as p-methylbenzoic acid (4% yield), the other was not characterized. The mass spectrum of the latter is consistent with p-methylbenzoyl formic acid (p-$CH_3C_6H_4COCOOH$), but isolation of pure product was not possible.

p-methylbenzoic acid

IR($CDCl_3$+DMSO-d_6): ν_{COO-H} 3440-2500cm^{-1}, $\nu_{C=O}$ 1708cm^{-1}, ν_{C-O} 1270cm^{-1}.

^1H NMR($CDCl_3$+DMSO-d_6): δ 2.31 (s, 3H, CH_3), 7.02 (d, 2H, J=8Hz, protons meta to carbonyl), 7.65 (d, 2H, protons ortho to carbonyl), 10.67 (s, 1H, COOH).

MS: m/e 136$[M]^+$, 117$[M-OH]^+$, 91$[C_6H_5-CH_2]^+$.

MS of trimethylsilylated derivative: m/e 208, 193, 149, 119, 91, 65.

p-methylbenzoyl formic acid

MS: m/e 164$[M]^+$, 119$[M-COOH]^+$, 91$[C_6H_5CH_2]^+$, 77$[C_6H_5]^+$.

Oxidation of m-ethyltoluene (m-$CH_3C_6H_4CH_2CH_3$)

Oxidation of m-ethyltoluene afforded m-methylacetophenone (m-$CH_3C_6H_4COCH_3$) in 58% yield. Although the conversion in this reaction reached only 63% after 46 hours at 60°C, the reaction was very clean. m-Methylacetophenone was obtained as the main product. Traces of m-ethylbenzaldehyde (m-$CH_3CH_2C_6H_4CHO$) and m-methylbenzoyl formic acid (m-$CH_3C_6H_4COCOOH$) were detected by mass spectrometry.

m-methylacetophenone

IR(neat): $\nu_{C=O}$ 1685cm^{-1}

^1H NMR($CDCl_3$): δ 2.33(s, 3H, $ArCH_3$), 2.52(s, 3H, $ArCOCH_3$), 7.22 (m, 2H, protons meta and para to carbonyl), 7.58 (m, 2H, protons ortho to carbonyl).

MS: m/e 134$[M]^+$, 119$[M-CH_3]^+$, 91$[M-COCH_3]^+$.

m-ethylbenzaldehyde

MS: m/e 134[M]$^+$, 133[M-H]$^+$, 105[M-CHO]$^+$, 91[$C_6H_5CH_2$]$^+$, 77[C_6H_5]$^+$.

m-methylbenzoylformic acid

MS: m/e 164[M]$^+$, 119[M-COOH]$^+$, 91[$C_6H_5CH_2$]$^+$, 77[C_6H_5]$^+$.

Oxidation of o-ethyltoluene (o-$CH_3C_6H_4CH_2CH_3$)

Oxidation of o-ethyltoluene afforded o-methylacetophenone (o-$CH_3C_6H_4COCH_3$) in 30% yield. The low yield was due to the low conversion and poor selectivity. Several by-products were observed in GC, two of which were identified by GC/MS as m-ethylbenzaldehyde (o-$CH_3CH_2C_6H_4CHO$) (15% yield) and its alcoholic intermediate (o-$CH_3C_6H_4CH(OH)CH_3$) (8% yield).

o-methylacetophenone

IR(neat): $\nu_{C=O}$ 1688cm^{-1}

^{1}H NMR($CDCl_3$): δ 2.44(s, 3H, $ArCH_3$), 2.50(s, 3H, $ArCOCH_3$), 7.09 (m, 3H, protons meta and para to carbonyl), 7.47 (m, 1H, proton ortho to carbonyl).

MS: m/e 134[M]$^+$, 119[M-CH_3]$^+$, 91[$C_6H_5CH_2$]$^+$.

o-ethylbenzaldehyde

MS: m/e 134[M]$^+$, 133[M-H]$^+$, 105[M-CHO]$^+$, 77[C_6H_5]$^+$.

o-$CH_3C_6H_4CH(OH)CH_3$

MS: m/e 136[M]$^+$, 121[M-CH_3]$^+$, 91[$C_6H_4CH_2$]$^+$, 77[C_6H_5]$^+$.

Oxidation of p-diethylbenzene ($p\text{-}CH_3CH_2C_6H_4CH_2CH_3$)

Oxidation of p-diethylbenzene afforded p-ethylacetophenone ($p\text{-}CH_3CH_2C_6H_4COCH_3$) in 72% yield. p-Ethylbenzoylformic acid was also detected by mass spectrometry.

p-ethylacetophenone

IR(neat): $\nu_{C=O}$ 1685cm^{-1}

^1H NMR($CDCl_3$): δ 1.22(t, 3H, $\underline{CH_3}CH_2Ar$), 2.50(s, 3H, $ArCO\underline{CH_3}$), 2.64(q, 2H, $CH_3\underline{CH_2}Ar$), 7.05 (d, 2H, J=8Hz, protons meta to carbonyl), 7.68 (d, 2H, protons ortho to carbonyl).

MS: m/e 148$[M]^+$, 133$[M\text{-}CH_3]^+$, 105$[M\text{-}COCH_3]^+$, 77$[C_6H_5]^+$.

p-ethylbenzoylformic acid

MS: m/e 178$[M]^+$, 133$[M\text{-}COOH]^+$, 105$[C_6H_5CH_2CH_2]^+$, 91$[C_6H_5CH_2]^+$, 77$[C_6H_5]^+$.

Oxidation of p-ethylanisole ($p\text{-}CH_3OC_6H_4CH_2CH_3$)

Oxidation of p-ethylanisole afforded p-methoxyacetophenone ($p\text{-}CH_3OC_6H_4COCH_3$) in 87% yield.

IR(neat): $\nu_{C=O}$ 1678cm^{-1}, $\nu_{C\text{-}O}$ 1260cm^{-1}.

^1H NMR($CDCl_3$): δ 2.47(s, 3H, $ArCOCH_3$), 3.77(s, 3H $ArOCH_3$), 6.77 (d, 2H, J=8Hz, protons meta to carbonyl), 7.80 (d, 2H, protons ortho to carbonyl).

MS: m/e 150$[M]^+$, 135$[M\text{-}CH_3]^+$, 107$[M\text{-}COCH_3]^+$, 77$[C_6H_5]^+$.

Oxidation of 4-ethylbiphenyl ($C_6H_5\text{-}C_6H_4CH_2CH_3$)

Oxidation of 4-ethylbiphenyl afforded p-phenylacetophenone ($p\text{-}C_6H_5C_6H_4COCH_3$) in 48% yield. Even though the rate of oxidation was slow (only 49% conversion after 46 hours), p-phenylacetophenone was the only product obtained in this reaction.

IR($CDCl_3$): $\nu_{C=O}$ 1684cm^{-1}

^1H NMR($CDCl_3$): δ 2.50 (s, 3H, $CO\underline{CH_3}$), 7.28 (m, 7H, phenyl and protons meta to carbonyl), 7.80 (d, 2H, J=8Hz, protons ortho to carbonyl).

MS: m/e 196$[M]^+$, 181$[M-CH_3]^+$, 153$[M-COCH_3]^+$.

Oxidation of ethylbenzene ($C_6H_5CH_2CH_3$)

Oxidation of ethylbenzene under the usual conditions was a slow reaction affording acetophenone in only 45% yield after 109 hours at 60°C. However, oxidation selectively occurred at the benzylic methylene group.

IR(neat): $\nu_{C=O}$ 1688cm^{-1}

^1H NMR($CDCl_3$): δ 2.50(s, 3H, $ArCOCH_3$), 7.30 (m, 3H, protons meta and para to carbonyl), 7.70 (m, 2H, protons ortho to carbonyl).

MS: m/e 120$[M]^+$, 105$[M-CH_3]^+$, 77$[C_6H_5]^+$.

Oxidation of n-butylbenzene ($C_6H_5CH_2CH_2CH_2CH_3$)

Oxidation of n-butylbenzene afforded n-butyrophenone ($C_6H_5COCH_2CH_2CH_3$) in 41% yield. The rate of reaction was slow with the conversion being 53% after 109 hours at 60°C.

IR(neat): $\nu_{C=O}$ 1688cm^{-1}

^1H NMR($CDCl_3$): δ 1.00 (t, 3H, CH_3), 1.72(m, 2H $COCH_2\underline{CH_2}CH_3$), 2.83(t, 2H, $CO\underline{CH_2}CH_2CH_3$), 7.28 (m, 3H, protons meta and para to carbonyl), 7.72 (m, 2H, protons ortho to carbonyl).

MS: m/e 148$[M]^+$, 105$[C_6H_5CO]^+$, 77$[C_6H_5]^+$.

Oxidation of tetralin

Tetralin was oxidized to α-tetralone in 75% yield.

IR(neat): $\nu_{C=O}$ 1685cm^{-1}

^{1}H NMR($CDCl_3$): δ 2.10(m, 2H, $CH_2\underline{CH_2}CH_2$), 2.56 (t, 2H, $CO\underline{CH_2}$), 2.87(t, 2H, $Ar\underline{CH_2}CH_2CH_2$), 7.20 (m, 3H, protons meta and para to carbonyl), 7.90 (m, 1H, J=8Hz, proton ortho to carbonyl).

MS: m/e 146$[M]^+$, 118$[M\text{-}CH_2CH_2]^+$, 90$[C_6H_5CH]^+$.

Oxidation of 1-ethylnaphthalene (1-$C_{10}H_7CH_2CH_3$)

Oxidation of 1-ethylnaphthalene afforded 1-acetonaphthone (1-$C_{10}H_7COCH_3$) in 23% yield. The rate of reaction was slow with only 35% of starting material converted after 45 hours at 60°C.

IR(neat): $\nu_{C=O}$ 1680cm^{-1}

^{1}H NMR($CDCl_3$): δ 2.63 (s, 3H, $COCH_3$), 7.42 (m, 6H, aromatic), 8.47 (m, 1H, J=8Hz, proton on C-8).

MS: m/e 170$[M]^+$, 155$[M\text{-}CH_3]^+$, 127$[M\text{-}COCH_3]^+$.

Oxidation of 2-ethylnaphthalene (2-$C_{10}H_7CH_2CH_3$)

Oxidation of 2-ethylnaphthalene afforded 2-acetonaphthone (2-$C_{10}H_7COCH_3$) in 20% yield. The rate of reaction was similar to the oxidation of 1-ethylnaphthalene. The conversion reached 31% after 45 hours at 60°C.

IR($CDCl_3$): $\nu_{C=O}$ 1680cm^{-1}

^{1}H NMR($CDCl_3$): δ 2.61(s, 3H, $COCH_3$), 7.52 (m, 6H, aromatic), 8.14 (s, 1H, proton on C-1).

MS: m/e 170$[M]^+$, 155$[M\text{-}CH_3]^+$, 127$[M\text{-}COCH_3]^+$.

Attempted oxidation of other methylene groups to corresponding ketones

Oxidation of p-ethylphenol, 2-ethylfuran and 5-ethyl-2-methylpyridine did not take place under the noted conditions.

Variation in reaction conditions

a) Oxidation of m-ethyltoluene catalyzed by anhydrous $CoCl_2$ and $CrCl_3$.

Oxidation of m-ethyltoluene was carried out according to the general procedure except that anhydrous $CoCl_2$ was replaced by a mixture of anhydrous $CoCl_2$ (0.066g, 0.5mmol) and $CrCl_3$ (0.04g, 0.25mmol). m-Methylacetophenone was obtained in 43% yield after 46 hours at 60°C.

b) Oxidation of p-diethylbenzene catalyzed by $Co(OAc)_2 \cdot 4H_2O$ in the presence of HOAc.

Oxygen was slowly bubbled into a solution of $Co(OAc)_2 \cdot 4H_2O$ (0.25g, 1.0mmol) in HOAc (10ml) for about 30 minutes at 60°C. The color of the solution was red brown. p-Diethylbenzene (0.67g, 5.0mmol) was then added and the mixture was stirred for 48 hours. Purification by TLC using 3:1 hexane/ethyl acetate afforded p-ethylacetophenone in 35% yield, and 0.32g (2.4mmol) starting material was recovered (52% conversion).

c) Oxidation of p-methylacetophenone catalyzed by anhydrous $CoCl_2$ in the presence of diglyme

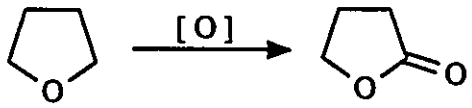
Addition of p-methylacetophenone (0.67g, 5.0mmol) to a mixture of anhydrous $CoCl_2$ (0.66g, 5.0mmol) and diglyme (10ml) followed by stirring for 3 days at 80-90°C gave p-toluic acid in 82% yield.

Chapter 3
Selective Catalytic Oxidation of Ethers and Cyclic Acetals with Cobalt Chloride

3.1 Introduction

3.1.1. OXIDATION OF ETHERS

The oxidation of ethers to the corresponding esters (or lactones in the case of cyclic ethers) is a very important reaction. From an industrial point of view, such a process would be quite profitable. For example, the selective oxidation under mild reaction conditions of cheap, easily available tetrahydrofuran (THF) to γ-butyrolactone, a more expensive chemical, would be a useful industrial process (eq. [3.1]). The conversion of

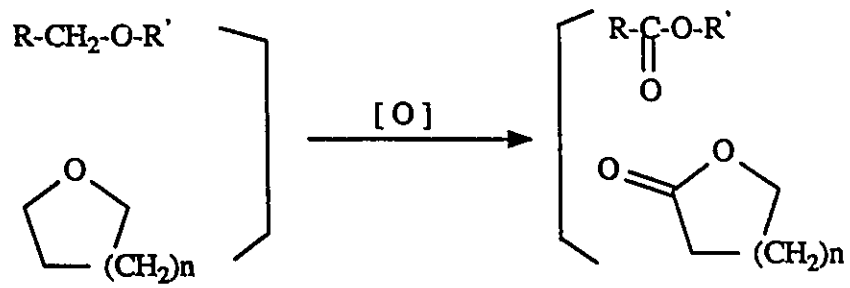


[3.1]

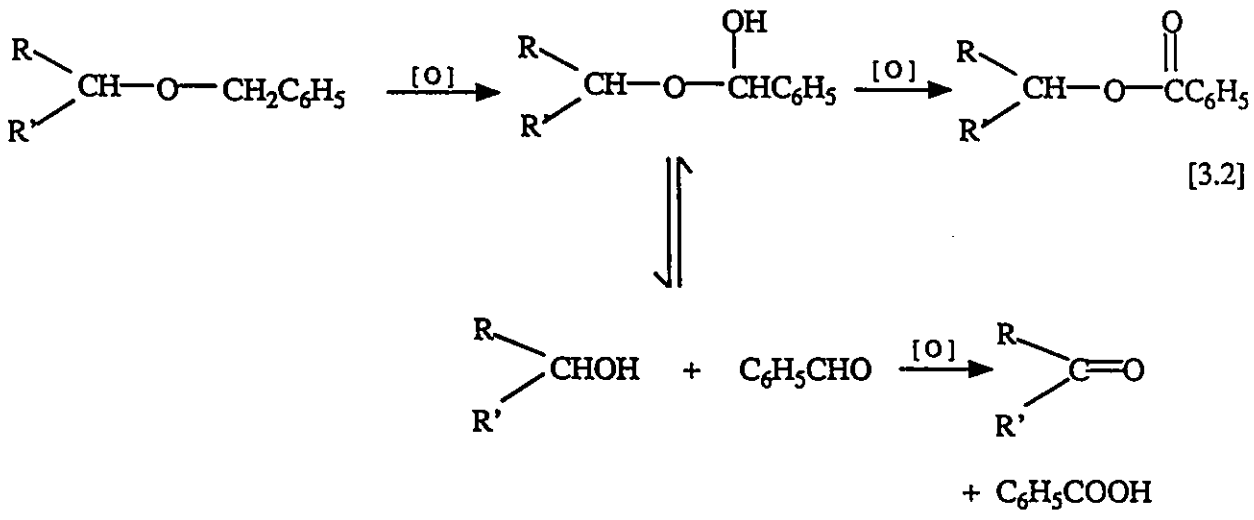
	THF	γ-butyrolactone
Aldrich sells:	1 Kg $12.65	500g $8.60

ethers to the corresponding esters (or lactones) is also of synthetic interest [Scheme 3.1], especially in natural product systhesis.

Scheme [3.1]



The oxidation of ethers can usually be accomplished with the use of chromium trioxide, lead tetraacetate, or ruthenium tetraoxide as oxidants.[152] For example, the oxidation of benzyl ethers with Jones reagent is a generally applicable reaction.[153] The oxidation products apparently arise via initial formation of a hemiacetal which is further oxidized to the ester, ketone, and benzoic acid (eq. [3.2-3.3]).

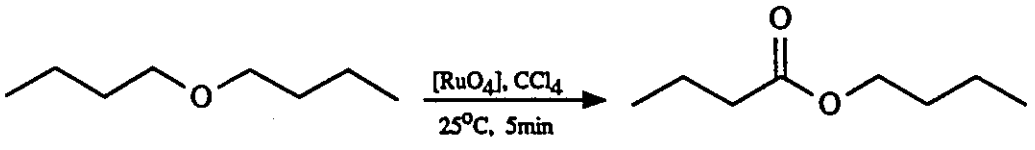


[3.2]

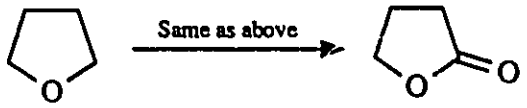
[3.3]

The most effective of these reagents, ruthenium tetraoxide, has been used in the oxidation of a variety of acyclic, cyclic, and bicyclic ethers.[154-157] The reaction which

can be carried out in either aqueous solutions or non-oxidizable, non-polar solvents (e.g., carbon tetrachloride or chloroform) is free of side reactions and usually gives quantitative yields of pure products. Two examples are shown in equation [3.4] and [3.5]. The use of



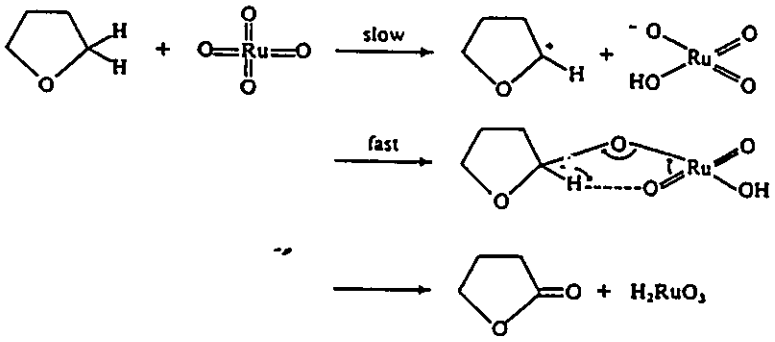
100% [3.4]



100% [3.5]

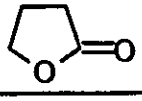
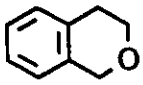
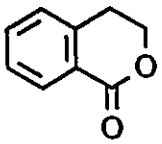
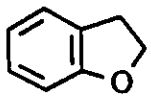
catalytic amounts of RuO_4 and aqueous NaOCl or periodate as the oxidants in the presence of a phase transfer catalyst may provide an improved procedure for achieving this reaction.[158] The mechanism of the oxidation by ruthenium tetraoxide has been studied (Scheme [3.2]).[159]

Scheme [3.2]



Recently, several new systems have been reported to effectively oxidize ethers to the corresponding esters or lactones.[160-163] In addition, the catalytic oxidations of benzylalkyl, dialkyl, cyclic and acyclic ethers with $RuCl_3$/NaOCl or $Ca(OCl)_2$ systems have also been reported.[164a] The reactions were performed with CH_2Cl_2/H_2O as solvents at room temperature under phase transfer catalysis conditions. Some results are listed in Table [3.1].

Table [3.1] Oxidation of ethers by NaOCl in the presence of $RuCl_3 \cdot nH_2O$ [a]

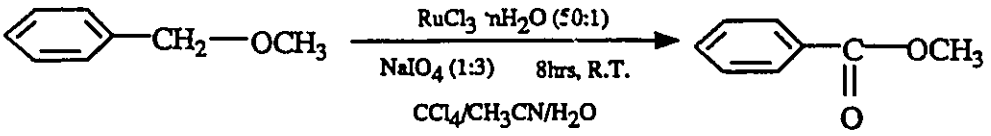
Ethers	Time (h)	Conversion (%)	Products [b]
$(n\text{-}Bu)_2O$	20	100	n-Bu-O-C(=O)-Pr (65%) n-PrCOOH (15%)
	18	100	 (43%) + Succinic acid (12%)
	8	100	 (18%)
	8	100	Completely degradated to CO_2
$PhCH_2OCH_3$	8	91	$PhCO_2CH_3$ (62%) + PhCHO (5%) + CO_2 (24%)
$PhCH_2OPh$	18	55	PhCOOH (6%)

a) Solvent: CH_2Cl_2/H_2O, 20°C, $RuCl_3 \cdot nH_2O$/ether=0.022, NaOCl/ether=9

b) Isolated yield.

Sharpless and his co-workers also have reported[164b] the catalytic oxidation of ethers by $RuCl_3 \cdot nH_2O/NaIO_4$ in a mixed solvent system of carbon tetrachloride, acetonitrile and water. One example was the oxidation of methyl benzyl ether which

afforded methyl benzoate in 89% yield after 8 hours at room temperature (eq.[3.6]).

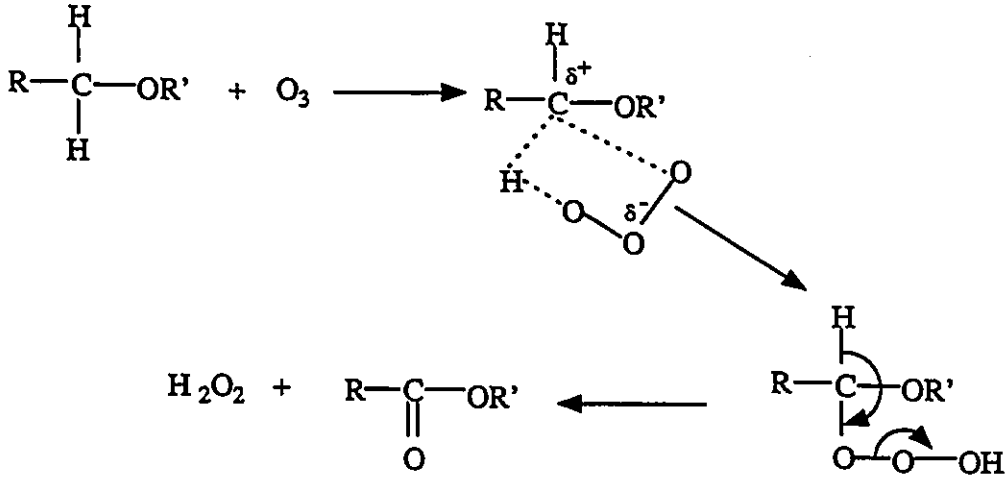


[3.6]

89%

The oxidation of ethers by ozone also has been studied sporadically. The work of Price and Tumolo[165-166] is the only thorough study carried out since the advent of modern instrumental methods of product analysis. Briefly, they suggested that the mechanism involves as a first step an ozone "insertion" type of reaction into the C-H bond (Scheme [3.3]). Studies of the reaction mechanism have been performed subsequently.[167]

Scheme [3.3]

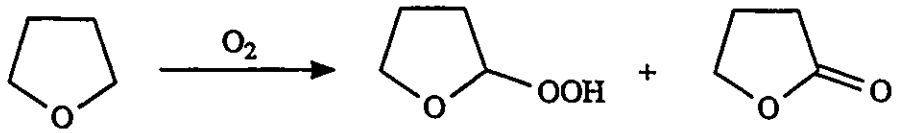


All the oxidation systems discussed above are stoichiometric. Unfortunately, these systems suffer from at least one of the following disadvantages: 1) cost of preparation, 2) hygroscopicity, 3) photosensitivity and/or instability, 4) long reaction times, 5) high acidity of the media, 6) use of a powerful oxidant lacking selectivity, and 7) dangerous

procedures for their preparation. Therefore, the search for new oxidative systems is still a necessity, especially a metal-catalyzed process using oxygen as the oxidant.

Surprisingly, the study of metal-catalyzed liquid-phase autoxidation of ethers has attracted little attention. There has only been one paper which reported[168] that dibenzyl ether can be oxidized to its corresponding ester and benzaldehyde as well as benzoic acid in low yields by a variety of transition metal complexes in air. However, the purpose of this paper was only to report the fact that various metal complexes might catalyze the oxidation of ethers. The authors did not do any further studies.

It has been known for several decades that ethers react with molecular oxygen at ambient temperatures to form peroxides and hydroperoxides.[169-172] For instance, the free radical-initiated oxidation of tetrahydrofuran (EH is used to represent this molecule only in this case) has been shown to yield α-hydroperoxytetrahydrofuran, together with small amounts of γ-butyrolactone and other products with oxygen under pressure (eq.[3.7]). The

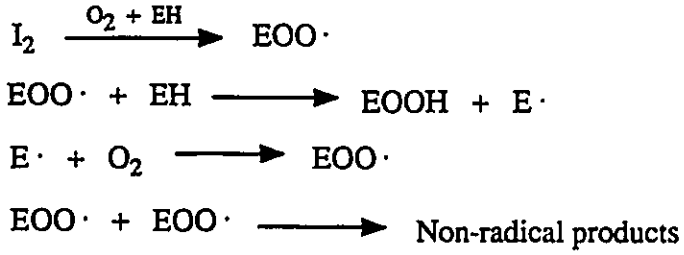


[3.7]

+ Other products

reaction mechanism is similar to that used to describe the autoxidation of many organic substrates (Scheme [3.4]). E· is the tetrahydrofuranyl radical, EOO· the tetrahydrofuranylperoxy radical, and I_2 is the free radical chain initiator.

Scheme [3.4]

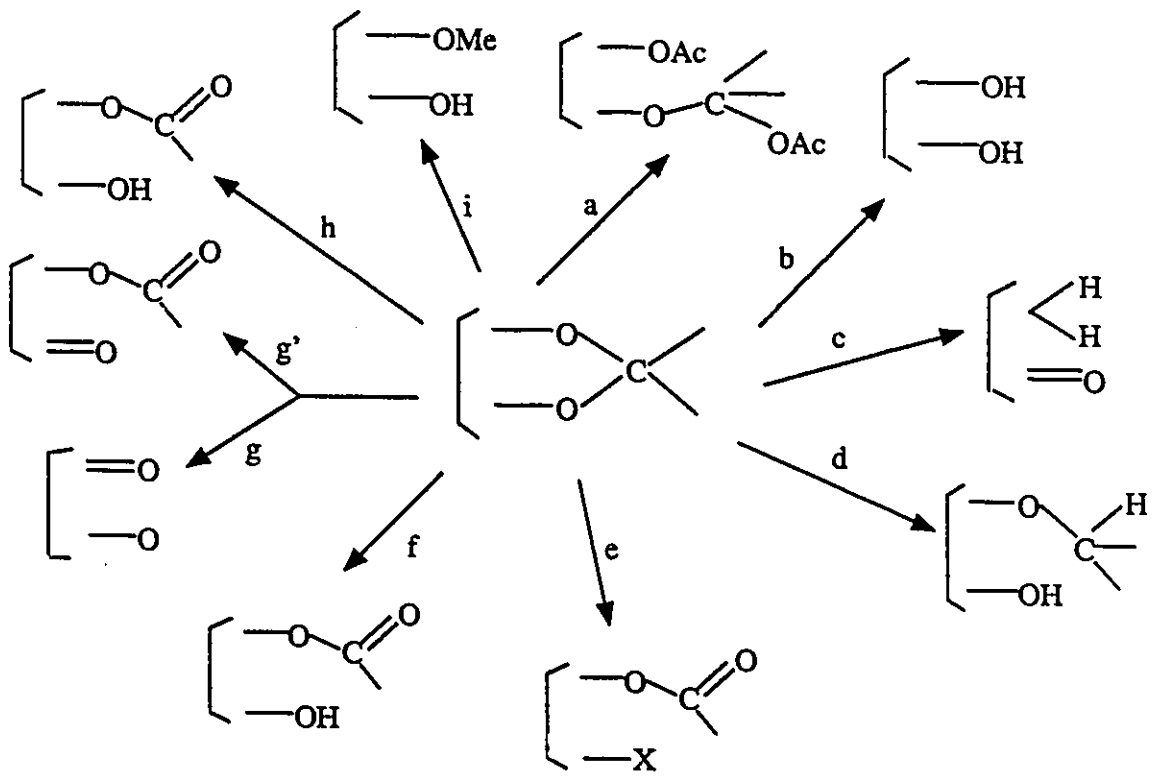


As discussed in Chapter 1, cobalt complexes are the most effective catalysts to induce decomposition of alkyl hydroperoxides (ROOH). Therefore, to extend our previous work with anhydrous $CoCl_2$ in the presence of diglyme or mixed diglyme and MEK, it would be of interest to study and develop a metal-catalyzed system for the oxidation of ethers to the corresponding esters or lactones under an oxygen atomsphere, and an investigation of the mechanism as well as the scope and limitations of this new process would be very useful.

3.1.2. OXIDATION OF CYCLIC ACETALS

Since 1895, when Emil Fischer[173] described the reaction of aldehydes and ketones with glycoses, an impressive part of the chemistry of carbohydrates has dealt with acetals, and especially cyclic acetals (mainly 1,3-dioxolanes and 1,3-dioxanes). There is no doubt that the objective of many reported studies was the synthesis of cyclic acetals as temporary protecting groups for aldehydes and ketones. However, during the past few years, the role of acetals, especially in carbohydrate chemistry, has been changing. Routes for opening cyclic acetals to afford synthetically useful derivatives have been introduced, and some of them already have proved to be major tools for structural modifications.[174] Therefore, it is obvious that cyclic acetals may now be considered not only classical protecting groups, but also functional groups. Scheme [3.5] summarizes most of the reactions that have been utilized in carbohydrate chemistry.[174-175]

Scheme [3.5]



a) Acetolysis

b) Selective hydrolysis

c) Action of strong base

d) Hydrogenolysis

e) Halogenation

f) Photolysis

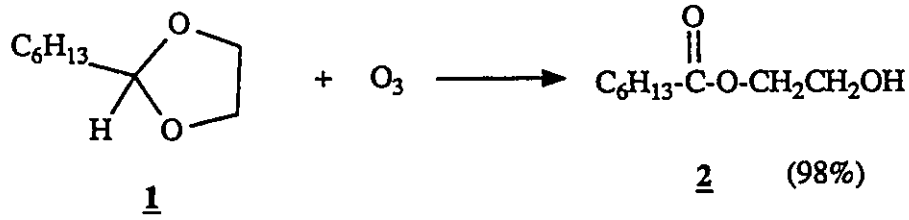
g) Oxidation with CrO_3-AcOH

g') Oxidation with $KMnO_4$

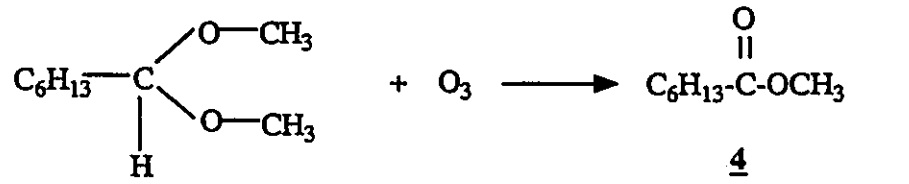
h) Ozonolysis

i) Methanolysis

In 1971, Deslongchamps and Moreau[176] first discovered that ozone could react readily with acetals to give the corresponding esters in high yield. For example, acetal 1 in dichloromethane or ethyl acetate reacts quantitatively within 10 minutes at -78°C with ozone to give the β-hydroxy ester 2 (eq. [3.8]). Similarly, acetal 3 gives the methyl ester 4 in 90% yield, but the rate of this reaction is considerably slower (15 hours at -78°C or



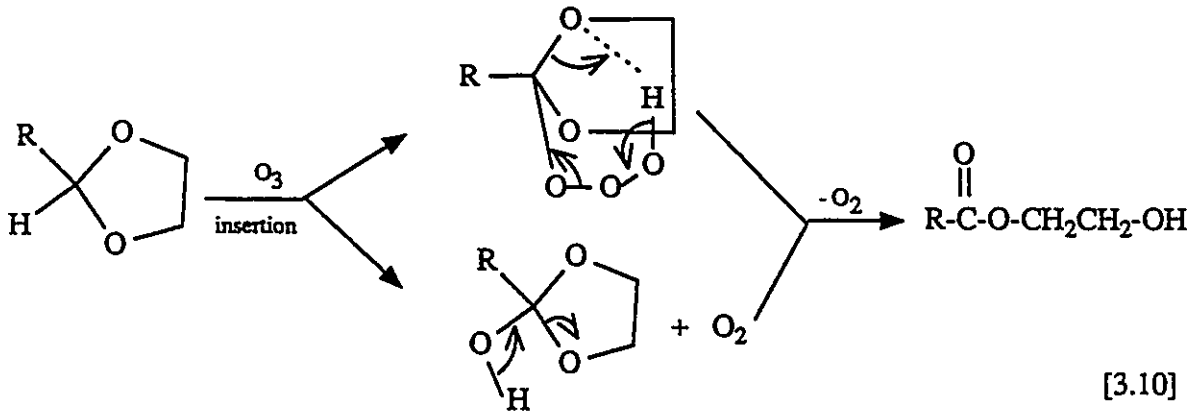
1 2 (98%) [3.8]



3 4 (90%) [3.9]

more conveniently 1.5 hours at room temperature (eq. [3.9])). This type of reaction constituted a novel method for converting an aldehyde into an ester.

Moreover, the mechanism for the oxidation of acetals by ozone has been extensively studied.[177-180] It was proposed that the oxidation proceeds via insertion of ozone in the C-H bond of the acetal to give a hydrotrioxide intermediate which in turn gives the corresponding ester and alcohol functions (eq. [3.10]).

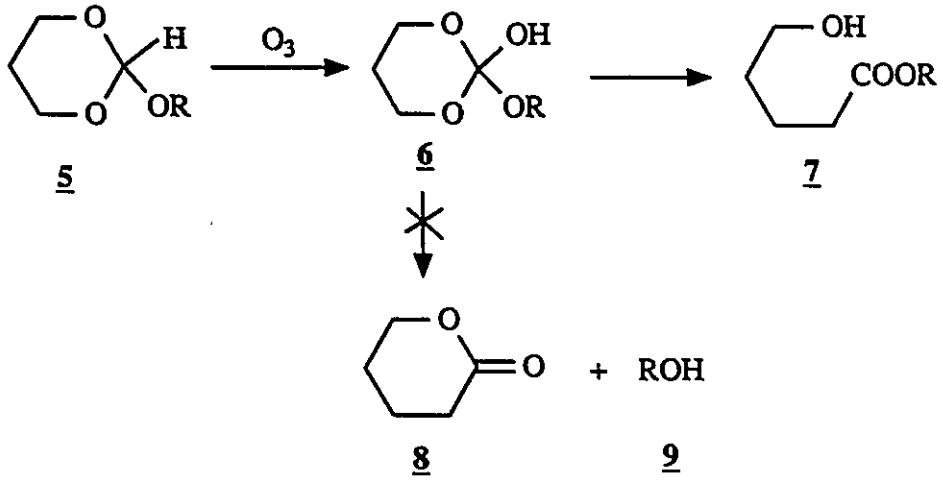


[3.10]

Oxidation of unsymmetrical acetals by ozone was carried out under similar reaction conditions, and it was found[181] that the reaction proceeds selectively cleaving

the ring. For instance, if a tetrahedral intermediate is formed during the oxidation of an acetal function, a substrate such as 5 should lead to an intermediate like 6 which can in principle decompose in two different ways to give the hydroxy ester 7, or the lactone 8 plus the alcohol 9 (Scheme [3.6]). However, it was observed that ozonation of

Scheme [3.6]



tetrahydropyranyl ether (R=CH_3) yields the hydroxy ester 7 exclusively, and no trace of lactone 8 could be detected.

More recently, Kuramshin and his co-workers have reported[182] that the oxidation of dioxolanes by nitrogen tetroxide (N_2O_4) afforded glycol esters in 85-92% yield. The reactions proceeded via a free radical chain mechanism.

There is very little information in the literature about the metal-catalyzed oxidation of acetals. Only one paper by Kuramshin from the USSR has been published.[183] It involved the homogeneous catalytic oxidation of 1,3-dioxacyclanes under an oxygen atmosphere. Here, it was noted that, in the absence of a catalyst, the oxidation of 1,3-dioxacyclanes was not observed at 20-40°C. The addition of a catalyst to the substrate containing small quantities of radical initiator led to a sharp increase in the rate of oxidation. In the absence of a radical initiator, an induction period of 15-20 hours was

necessary. In this paper, Kuramshin obtained the following results:

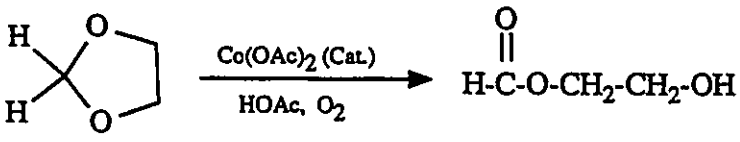
1) The catalytic effect of metal complexes increases in the order as followed: $Fe^{3+} < Cr^{3} < Co^{2+}$. Copper gave a negative catalytic effect.

2) The catalytic activity of various cobalt complexes in the oxidation of 1,3-dioxolane increases in the order: $CoCl_2(CyhexSO)_2 < CoCl_2 < Co(acac)_2 < Co(C_{17}H_{35}COO)_2 < Co(C_{15}H_{31}COO)_2 < Co(OAc)_2$. In other words, the cobalt complex with the highest catalytic activity in this oxidative system is cobalt acetate. This species is almost 15 times more catalytically active than cobalt chloride.

3) The rate of the oxidation of dioxolane increases linearly with an increase in cobalt acetate concentration over the range $(0.3\text{-}2)\times10^{-3}$M.

4) The ease of oxidation of 1,3-dioxacyclanes under the influence of cobalt salts increases in the order: 1,3-dioxanes< 1,3-dioxepanes< 1,3-dioxolanes.

5) In the oxidation of dioxolanes with cobalt acetate in a polar medium such as a mixture of chlorobenzene and acetic acid in the ratio of 5:1, ester glycols ($RCOOCH_2CH_2OH$) are formed as the main products. For example, when the oxidation of 1,3-dioxolane with oxygen is catalyzed by cobalt acetate in a mixed acetic acid/chlorobenzene solution, 20% conversion of the initial dioxolane is obtained, and the yield of monoformate is 90% (based on conversion) after 4 hours at 40°C (eq. [3.11]).



[3.11]

Although the oxidation of acetals by ozone or other oxidants has been well established and used in organic syntheses, these methods suffer from one serious drawback: lack of selectivity. For example, if acetal derivatives contain other oxidizable groups, the reactions with ozone usually results in a mixture of products. Furthermore, the above discussed catalytic oxidation of acetals by cobalt was carried out in an acidic

medium. This limits its application to those acetals which are not sensitive to acids.

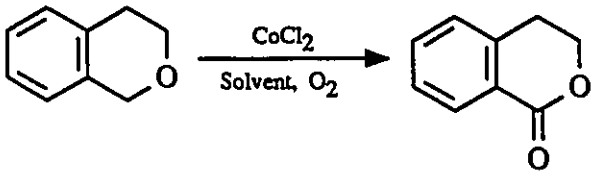
Therefore, the goal of this research project was to develop a catalytic process which would oxidize cyclic acetals to the corresponding ester derivatives in a neutral medium under oxygen. As mentioned earlier, 1,3-dioxolanes are the most readily oxidizable compounds in comparison to 1,3-dioxepanes and 1,3-dioxanes. Hence our study was focused on the oxidation of a variety of 1,3-dioxolanes. The scope and limitation of this new reaction was also investigated.

3.2 Results and Discussion

3.2.1. OXIDATION OF CYCLIC AND ACYCLIC ETHERS TO THE CORRESPONDING ESTERS AND LACTONES

3.2.1.1. Determination of the Reaction Conditions

Our previous studies have demostrated that solvents play a very important role in cobalt catalyzed oxidation reactions. Thus the solvent effect for the oxidation of ethers in the presence of anhydrous $CoCl_2$ was studied (eq.[3.12]). Isochroman was used as a model substrate, and the results are listed in Table [3.2].



[3.12]

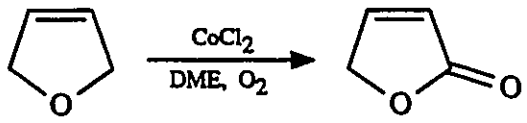
Table [3.2] The effect of solvents on catalytic oxidation of ethers[a]

Substrate/ $CoCl_2$ (mmol)	Solvent	Time (h)	T (°C)	Conversion (%)
200/1	Diglyme	2.5	80	100
200/1	DME	3	80	96
200/1	$ClCH_2CH_2Cl$	3	90	17
100/1	$(CH_3)_3COH$	3	70-80	62
100/1	MeOH	No Reaction		

a) Reaction conditions: anhydrous $CoCl_2$ (0.0125 mmol), isochroman (2.5 mmol), O_2 bubbling through the solution.

The experimental results in Table [3.2] show that the oxidation of isochroman in the presence of diglyme and DME neared completion in 3 hours. When this reaction was carried out in the presence of dichloroethane, only 17% of the starting material was converted after 3 hours at 90°C. The oxidation did not take place at all with methanol as the solvent. Although the use of diglyme and DME as solvents afforded comparable results, DME was the preferred solvent for further study. This was due to the fact that any low-boiling compounds produced from the oxidation of DME during the reaction could be easily removed under reduced pressure. As a result, the work-up for the reaction with DME as solvent is simpler than that for the reaction with diglyme.

In order to study the influence of catalyst concentration, the oxidation of 2,5-dihydrofuran was followed in the presence of DME using different concentrations of anhydrous $CoCl_2$ (eq.[3.13], see Table [3.3] for results).



[3.13]

Table [3.3] Effect of concentration of anhydrous $CoCl_2$ on the oxidation of 2,5-dihydrofuran[a]

substrate/$CoCl_2$ (mmol)	2(5H)-furanone (%)[b]
10 / 1	60
50 / 1	64
100 / 1	66
200 / 1	63

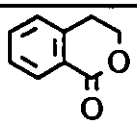
a) DME as solvent, 50°C, 24 hours

b) Isolated yield

The results illustrate that the catalyst concentration has no significant effect on this oxidation reaction. Furthermore, in order to determine whether the catalyst plays an important role in such a reaction, the oxidation of isochroman in the absence of anhydrous $CoCl_2$ was run and it was observed that the reaction, in fact, took place (e.g., 16% conversion after 3 hours), and achieved a 95% conversion after 18 hours at 80°C. However, this rate is much slower as compared to the reaction carried out in the presence of a catalytic amount of $CoCl_2$ (96% conversion after 3 hours at 80°C). Thus the presence of a catalyst dramatically increases the rate of oxidation. As a result, the substrate to catalyst ratio of 200:1 was used for further investigations.

The oxidation of isochroman to the isochromanone catalyzed by other cobalt complexes has been studied (Table [3.4]).

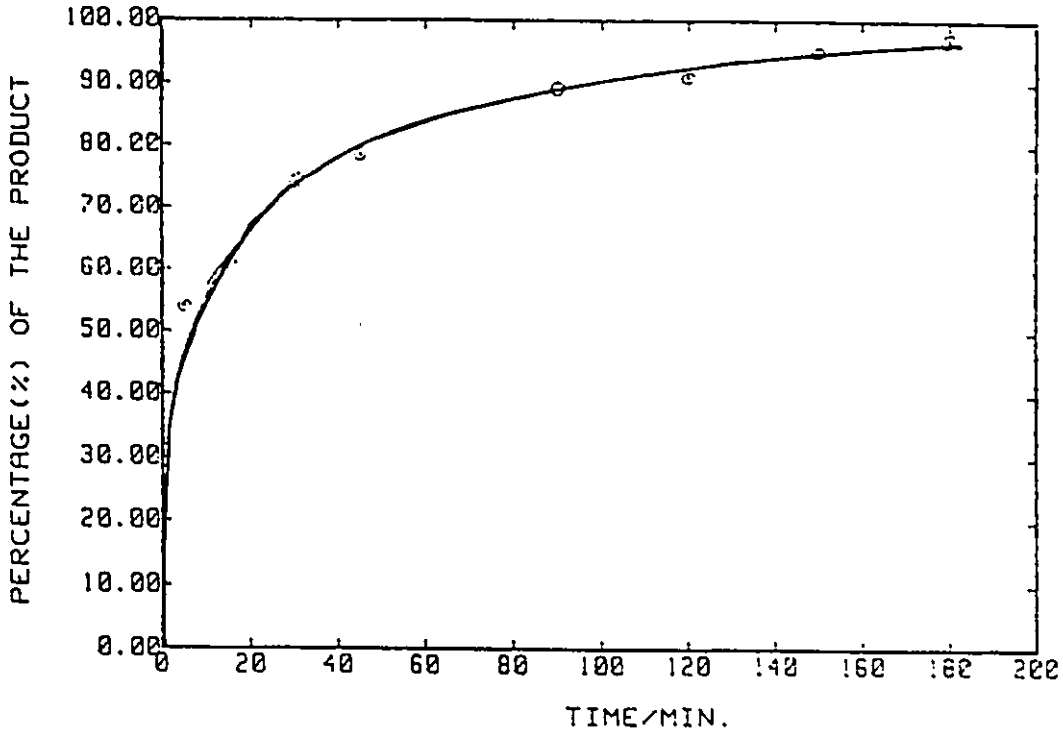
Table [3.4] Study of other cobalt complexes on the oxidation of isochroman to the corresponding lactone in the presence of DME

Catalysts	Substrate / Cat. (mmol)	T (°C)	Time (h)	 yield [a] (%)
$CoCl_2$	200 / 1	80	3	90
$CoCl_2 \cdot 6H_2O$	100 / 1	80-85	3	79
$Co(OAc)_2 \cdot 4H_2O$	200 / 1	80	5	65
$CoCl_2(PPh_3)_2$	200 / 1	80	5	65

a) Isolated yield

The results in Table [3.4] demostrate that anhydrous $CoCl_2$ has a higher catalytic acitivity than $CoCl_2 \cdot 6H_2O$, $Co(OAc)_2 \cdot 4H_2O$ and $CoCl_2(PPh_3)_2$. Thus anhydrous cobalt chloride was used in subsequent studies.

When the $CoCl_2$-catalyzed oxidation of isochroman was carefully followed by GC during the reaction, no induction period was observed (Fig.[3.1]).

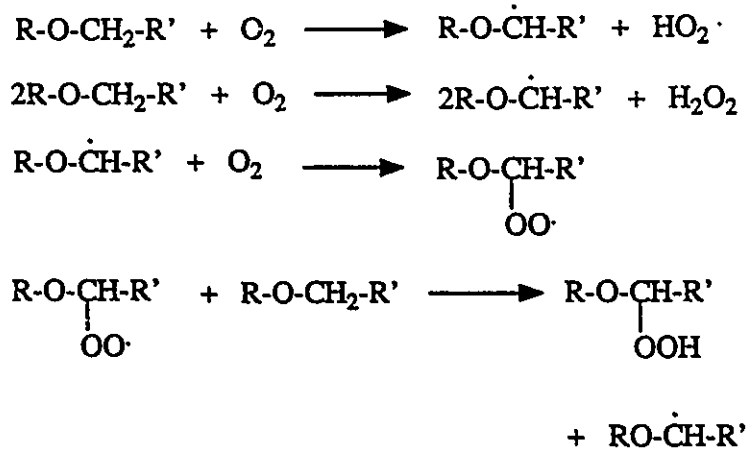


Reaction conditions: $CoCl_2$ (0.025 mmol), isochroman (2.5 mmol), DME (5 ml), 80°C, percentage product was measured by GC.

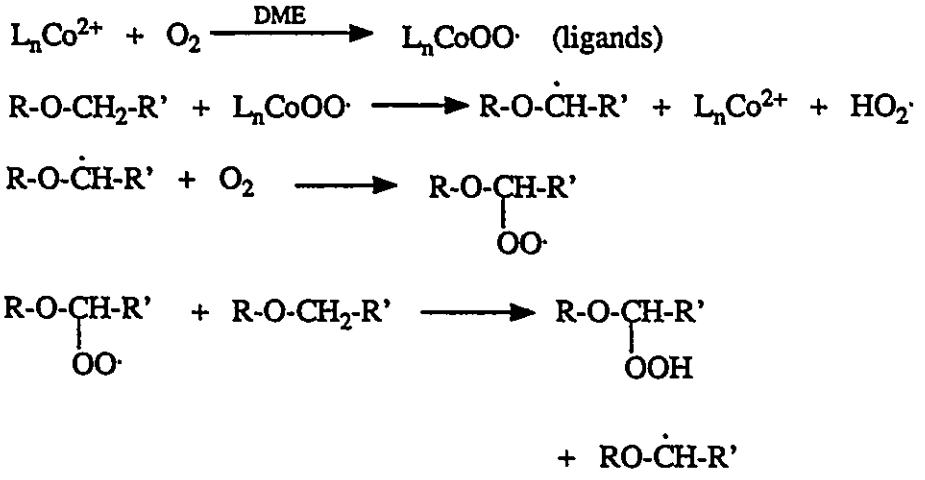
Fig. [3.1]

The lack of an induction period in the reaction of isochroman is especially interesting when compared with the induction periods observed during previous studies of the oxidation of hydrocarbons catalyzed by anhydrous cobalt chloride or other mixed catalysts. There may be three sources of the peroxide intermediates in the ether oxidation. The first is directly from the chain reaction between the ethers and oxygen (Scheme [3.7]). The second is from the chain reaction between the ethers and the cobalt activated molecular oxygen which was mentioned in the last chapter (Scheme [3.8]), and the third is from small amounts of peroxide contaminated in the substrate and DME during storage (Scheme [3.9]).

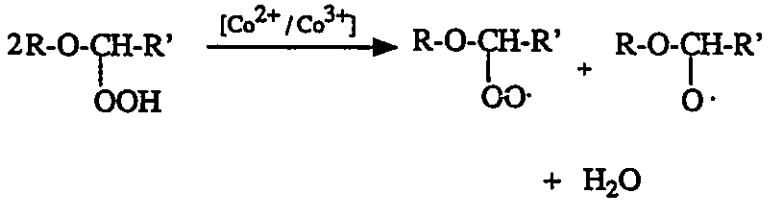
Scheme [3.7]



Scheme [3.8]



Scheme [3.9]

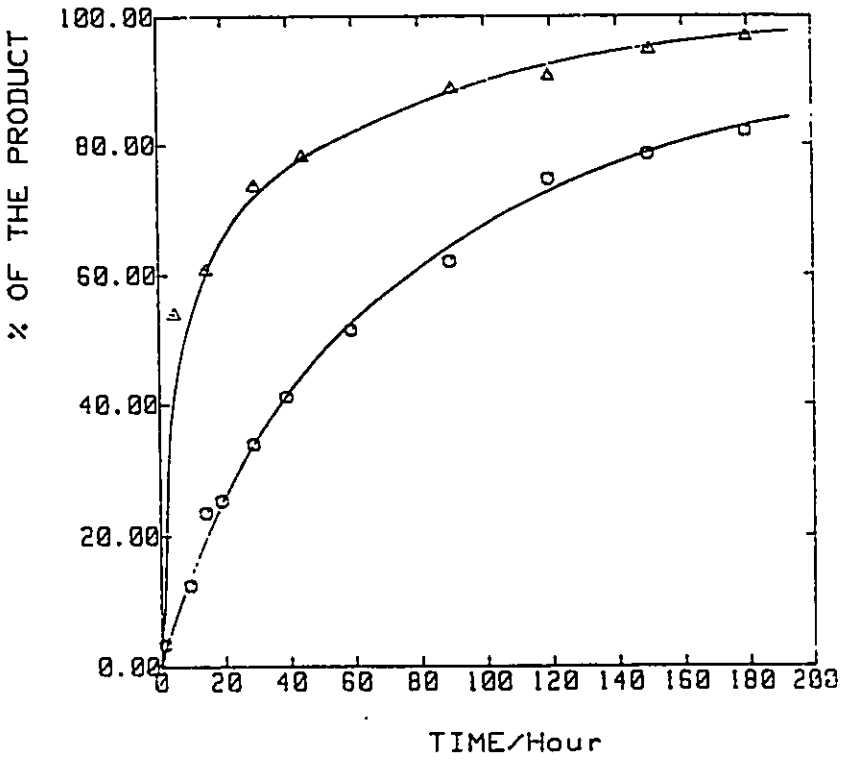


In order to understand which is the main source for the formation of the peroxide intermediates, two experiments were performed:

1) The oxidation of isochroman was catalyzed by anhydrous cobalt chloride using dichloroethane ($ClCH_2CH_2Cl$) as the solvent. Since dichloroethane does not contain an

oxygen atom or an activated C-H bond, it is not capable of coordination with the cobalt complex nor participates in the formation of the peroxide. Thus the possibility of the second and third source can be neglected. It was found that only 17% of the isochroman was converted after 3 hours at 90°C. When this result is compared to that with DME as solvent (about 96% conversion after 3 hours at 80°C), it is obvious that the first source was not the major one.

2) The substrate and DME were carefully purified prior to use in order to remove all the peroxide compounds formed during the storage. The purification procedure was that described in the literature.[184] Thus the third source of peroxide intermediates can be neglected. The experimental results showed that no induction period was observed (Fig. [3.2]) although the rate of oxidation was slower than that of the oxidation effected without purification of the substrate and DME. This indicated that the presence of small amounts of peroxide compounds promoted the initial rate of reaction, but it was not a major factor.



Reaction conditions: $CoCl_2$(0.025 mmol), isochroman (2.5 mmol), DME (5 ml)."Δ" Substrate and DME were used as purchased."O" Substrate and DME were purified prior to use.

Fig. [3.2]

Therefore, we could conclude that the major source of peroxide intermediates was from the chain reaction between the ether and the cobalt activated molecular oxygen (Scheme [3.8]). Moreover, the lack of an induction period during the oxidation of isochroman may be attributed to the fact that the reactivity of the benzylic ether C-H bond towards a radical is higher than that of the benzylic C-H bond since the adjacent oxygen atom can also stablize the radical via a perturbation effect. As a result, the initial rate of reaction was too fast to observe an induction period.

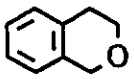
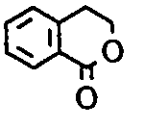
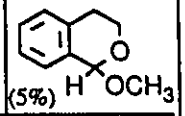
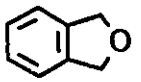
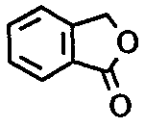
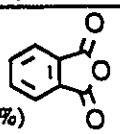
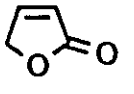
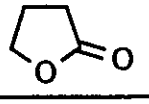
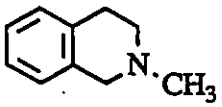
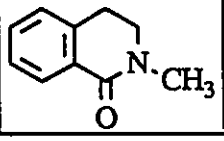
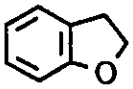
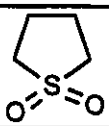
Also noteworthy in the oxidation of isochroman catalyzed by anhydrous $CoCl_2$ (Fig. [3.1]) is that after a period of time the rate of reaction decreased with time rather than increased. The interpretation of this result will be discussed later. Thus reactions were usually stopped when a reasonable conversion was obtained.

In principle, the reaction temperature should be maintained below the boiling point of the substrate, and not exceed 90°C (oil bath) because under a flow of oxygen the solvent may be lost at higher temperature.

3.2.1.2. Scope and limitations

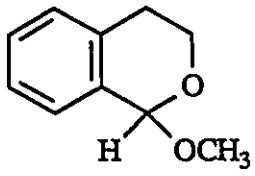
Having determined the reaction conditions [use of anhydrous $CoCl_2$ as the catalyst (substrate : Co^{2+} = 200:1), DME as solvent, no induction period under an oxygen atomsphere], an investigation was undertaken to study the scope of this reaction for the oxidation of a variety of ethers to their esters (or lactones in the case of cyclic ethers). The results are illustrated in Table [3.5].

Table [3.5] Oxidation of various ethers to the corresponding esters or lactones catalyzed by $CoCl_2$ in the presence of DME

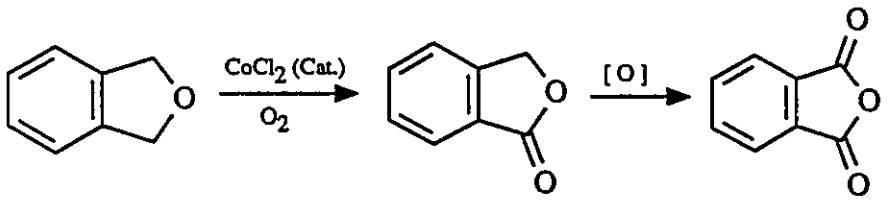
Substrate	T (°C)	Time (h)	Conversion (%)	Yield (%) [a] Desired Product		Other Product
	80	3	96	90		 (5%)
	80	3	100	82		 (5%)
	50	24	89	63		Unknown
	40	48	87	34 [c]		Formate ether (43%)
C_6H_5-CH_2-OCH_3	80	24	96	84	C_6H_5CO-OCH_3	C_6H_5COOH (10%)
C_6H_5-CH_2-OC_2H_5	80	24	100	47	C_6H_5CO-OC_2H_5	C_6H_5COOH (50%)
$(C_6H_5$-CH_2-$)_2$-O	80	18	100	13	$C_6H_5COOCH_2C_6H_5$	C_6H_5COOH (85%)
$C_6H_5CH_2OC_6H_5$	90	42	17	7 [b]	$C_6H_5COOC_6H_5$	$\phi CH(OH)O\phi$ (6%)
$(CH_3(CH_2)_3$-$)_2$-O	80	24	30	21 [b]	C_3H_7-COO-C_4H_9	Unknown
	80	36	42	13 [b]		Unknown
	80	24	No Reaction			
	60	24	No Reaction			
	85	43	No Reaction			

a) Isolated yield, b) Crude yield, c) In the absence of DME.

As can be seen from Table [3.5], the oxidation of isochroman afforded isochromanone in excellent yield, together with small amount of acetal as a by-product. This acetal is



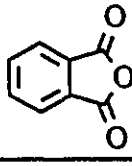
presumably produced from a reaction with the solvent. The formation of this species will be discussed in more detail in the next section. When phthalan was oxidized under similar reaction conditions, phthalide was also obtained in good yield (82%). However, the selectivity of this reaction was poor in comparison to the oxidation of isochroman. Phthalic anhydride generated from the over-oxidation of phthalide was identified as a major by-product (eq.[3.14]). This experimental result indicated that phthalan probably could be



[3.14]

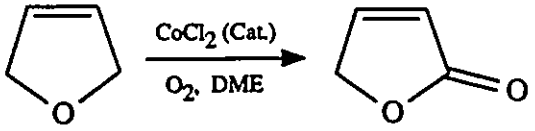
oxidized to the corresponding phthalic anhydride in a one-step reaction using our system. If this reaction could be achieved in high yield, it would be a very useful process. As a result, the oxidation of phthalan was carried out using several different conditions, e.g. changing the concentration of the cobalt catalyst, reaction time and an oxygen pressure (Table [3.6]).

Table [3.6] Oxidation of phthalan to the corresponding phthalic anhydride under modified reaction conditions

Substrate / $CoCl_2$ (mmol)	T (°C)	Time (h)	Oxygen pressure (psi)	 Yield (%)
200 / 1	80	18	0	8
50 / 1	60-70	120	0	8.5
100 / 1	80	42	20-80	18

It was found that the yield of phthalic anhydride was enhanced by increasing the oxygen pressure, but was not affected by catalyst concentration nor the reaction time. However, the use of DME as the solvent for oxidation reactions carried out under high pressures is a very dangerous procedure because the rate of reaction between DME and oxygen increases dramatically and produces large amounts of peroxides. The accumulation of the peroxide compounds could easily cause a serious explosion when heated. Therefore, further attempts were not undertaken.

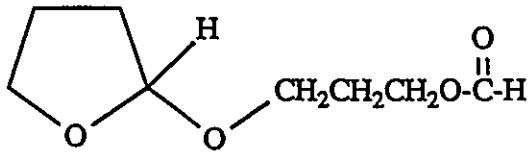
2(5H)-Furanone is a very important chemical. It is often used in the preparation of human lignans,[185] as a fish growth promoter[186] as well as in organic synthesis.[187-188] Moreover, it is a relatively expensive chemical. Thus direct oxidation of 2,5-dihydrofuran to 2(5H)-furanone catalyzed by a cobalt complex using oxygen as the oxidant is a very important and probably profitable process (eq.[3.15]). In fact, the oxidation of 2,5-dihydrofuran catalyzed by anhydrous $CoCl_2$ (substrate : Co^{2+} = 200:1) in the presence of DME afforded the corresponding lactone in 63% yield after 24 hours at 50°C.



[3.15]

Aldrich sells: 25g $8.50 1g $16.75

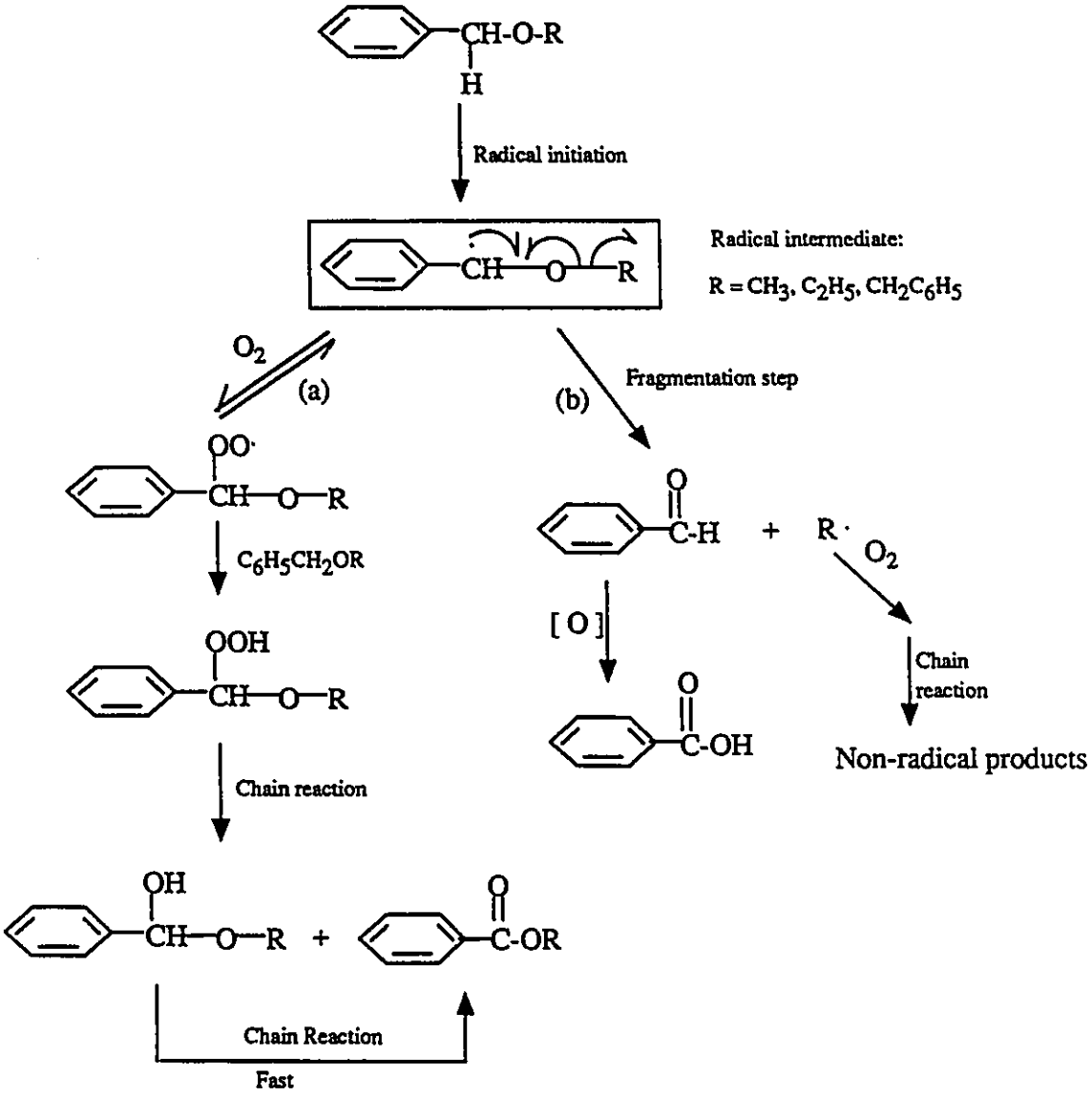
When the oxidation of tetrahydrofuran (THF) was carried out under the standard conditions, the selectivity towards the desired product (γ-butyrolactone) was only 40%, while in the absence of a solvent (DME), 51% selectivity was obtained. Hence this is an exceptional case in that the oxidation of an ether in the absence of a solvent gave superior results. During the reaction, another major product was observed. This compound was carefully isolated in 43% yield, and was identified as formate acetal.



As the results for the oxidation of acyclic benzylic ethers demostrate (Table [3.5]), the rate of the reaction and the selectivity for esters are strongly influenced by the nature of the R group ($C_6H_5CH_2OR$). For example, the oxidation of methyl benzyl ether ($R=CH_3$) afforded methyl benzoate in 84% yield, while the oxidation of ethyl benzyl ether ($R=C_2H_5$) gave ethyl benzoate in only 47% yield, together with 50% benzoic acid under similar reaction conditions. Moreover, the oxidation of dibenzyl ether ($R=CH_2C_6H_5$) afforded the desired product in only 13% yield. The major product was benzoic acid (85% yield), along with small amounts of benzaldehyde. In the case of the oxidation of phenyl benzyl ether, the rate was very slow, only 17% of the starting material having been converted after 42 hours at 90°C.

How could one interpret these results? On the basis of our previous experience, these reactions may possibly proceed via radical intermediates. Therefore, the rates of oxidation and the distribution of the products must be strongly influenced by the stability of the radical intermediates. Scheme [3.10] outlines the reaction pathways for the formation of various products.

Scheme [3.10]



It is conceivable that the oxidation of benzylic ethers to the corresponding esters proceeds via path (a). However, the radical intermediate can undergo an internal rearrangement depending on the stability of the newly formed radical (R·). The more stable the (R·) radical is, the more favourable is the fragmentation path (b), which leads to higher yield of benzoic acid. This interpretation receives support from our experimental results. For example, the stability of the radicals increases in the order: $\cdot CH_3 < CH_3CH_2\cdot < C_6H_5CH_2\cdot$. The oxidation of dibenzyl ether under standard reaction conditions afforded benzoic acid in 85% yield, together with small amounts of benzaldehyde after 18 hours, while the oxidation of ethyl benzyl ether gave benzoic acid in 50% yield after 24 hours, and the oxidation of methyl benzyl ether led to benzoic acid in only 10% yield.

Furthermore, the rate of oxidation of phenyl benzyl ether was much slower than that of dibenzyl ether. These results are also due to the stability of the radical intermediate. Comparing the radical stability of these two compounds (Fig. [3.3]), dibenzyl ether radical

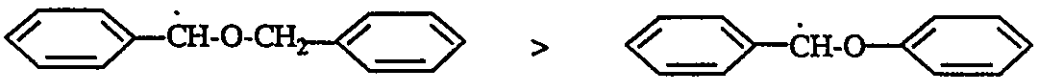


Fig. [3.3]

can be predicted to be more stable than phenyl benzyl ether radical because the dibenzyl ether radical can be stablized by both the π orbitals of the benzene ring and the lone pair electrons of the oxygen atom (Fig. [3.4] and [3.5]). In the case of the radical of phenyl benzyl ether, there is also stabilization by the benzene ring. However, the lone pair electrons of the oxygen atom in this molecule also tend to delocalize towards the other benzene ring by conjugation. Therefore, in this case, the benzene ring may be viewed as an electron withdrawing group. As a result, the capability of the oxygen atom to stablize the adjacent radical is greatly weakened. Consequently the reactivity of the benzylic C-H bond

of phenyl benzyl ether is much lower than that of dibenzyl ether resulting in a much slower rate of oxidation.

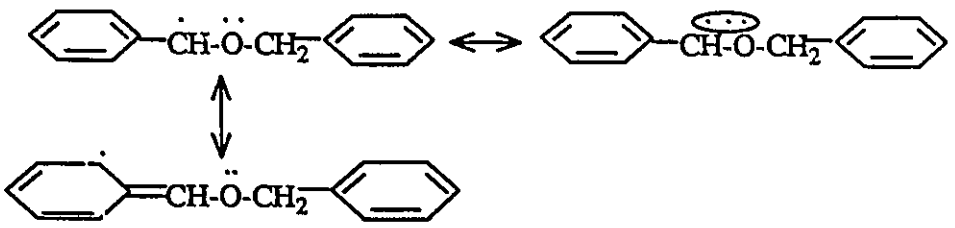


Fig. [3.4]

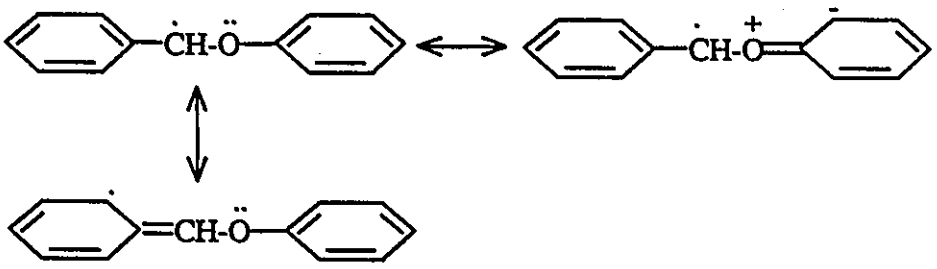


Fig. [3.5]

In addition, this catalytic system is applicable to the oxidation of simple acyclic alkyl ethers like dibutyl ether as well as cyclic amines to the corresponding esters and lactam. Unfortunately, the yields of these reactions are poor.

As one may expect, if the oxidation of THF works in this system, the oxidation of 2,3-dihydrobenzofuran should also take place since these species have the same basic structure: a furan ring. Surprisingly, no oxidation of 2,3-dihydrobenzofuran occurred under standard conditions after 24 hours at 80°C. How can one rationalize this result? Considering the radical species of 2,3-dihydrobenzofuran and THF (Fig. [3.6]), 2,3-dihydrobenzofuran radical should be less stable than THF radical, due to the fact that the delocalization of the radical electron by the oxygen lone pair is weakened by the influence of the benzene ring. This effect is similar to that of the phenyl benzyl ether radical. Further attempts were made

Fig. [3.6]

to oxidize 2,3-dihydrobenzofuran, for example, by increasing the catalytic concentrations, or the use of other solvent systems such as diglyme and a mixed diglyme and MEK. Unfortunately, there was still no oxidation.

Likewise, no oxidation of tetrahydrothiophene was observed. The color of solution of cobalt chloride and DME changed from blue to deep red as soon as the starting material was added. Such a color change indicates that the sulfur atom in tetrahydrothiophene might complex with the cobalt chloride resulting in a change in the characteristics of the catalyst. In addition, when tetramethylene sulfone was oxidized under similar reaction conditions, no reaction was observed after 43 hours at 85°C. The color of solution remained blue. Here coordination of the sulfur atom to cobalt can not occur.

Finally, the oxidation of 2-methyltetrahydrofuran and tetrahydropyran in this system has also been studied. The results of both reactions were poor with respect to their yields

2-methyltetradrofuran Tetrahydropyran

and selectivity. For example, the oxidation of 2-methyltetrahydrofuran afforded 85% conversion after 48 hours at 60°C. However, at least eight compounds were observed in the GC, and the desired compound was not a major product. In the case of the oxidation of tetrahydropyran, only 10% conversion was obtained after 24 hours at 60°C. At least six

products were detected by GC.

Summarizing briefly, the scope and limitations of our oxidation system using anhydrous $CoCl_2$ as catalyst (substrate : $CoCl_2$ = 200:1), DME as solvent under an oxygen atomsphere are as follows:

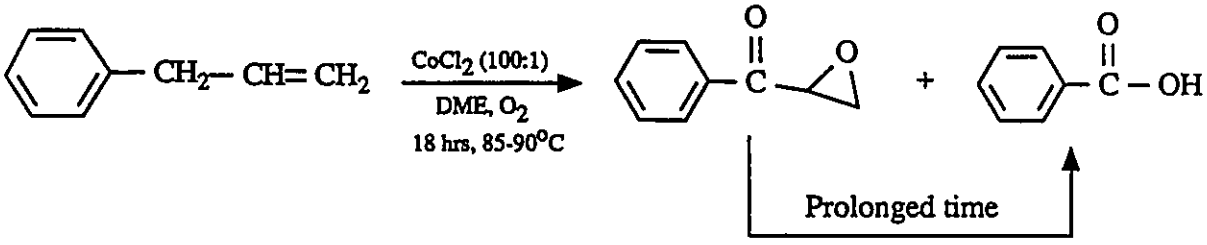
a) The oxidation of cyclic ethers to the corresponding lactones gave reasonable to excellent yields (e.g., isochroman or 2,5-dihydrofuran). However, attempted oxidation of a 2,3-dihydrobenzofuran type of substrate led to no reaction.

b) Oxidation of acyclic alkyl benzyl ethers to the corresponding esters afforded yields which varied from one substrate to another depending on the reactivity of the benzylic C-H bond and the stability of the alkyl radical.

c) The oxidation of acyclic alkyl ethers gave the corresponding esters in low yields.

d) The oxidation of other heterocyclic ethers such as N-methyl-1,2,3,4-tetrahydroisoquinoline or tetrahydrothiophene result in either low yield and selectivity or no reaction.

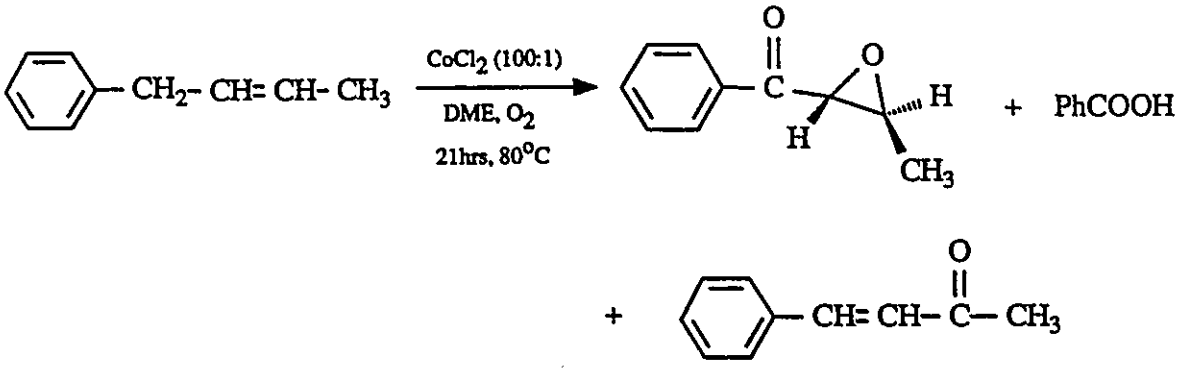
In addition to the above studies, attempts were initially made to oxidize allylic hydrocarbons to the corresponding ketones or alcohols by using this oxidation system. When the oxidation of allyl benzene was catalyzed by $CoCl_2$ (substrate : $CoCl_2$ = 100:1) in DME at 85-90°C for 18 hours, surprisingly, an epoxy ketone was isolated in 14% yield, together with 47% yield of benzoic acid (eq.[3.16]. Prolonging the reaction time resulted in decomposition of the epoxy ketone to benzoic acid. Similarly, the oxidation of



[3.16]

1-phenyl-2-butene also afforded a trans-epoxide ketone in 20% yield, along with 4-phenyl-3-butene-2-one and benzoic acid in 27% and 44% yield, respectively (eq.[3.17]).

These results demonstrate that allylic hydrocarbons can be oxidized under this system. The



[3.17]

direct formation of epoxy ketones from allylic hydrocarbons has never been reported in the literature. As a result, study of oxidation of allylic hydrocarbons affording high yield of epoxy ketones would be very important and necessary.

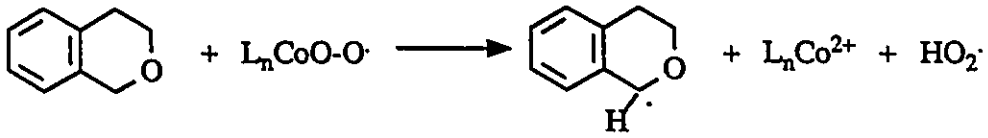
3.2.1.3. Study of the Reaction Mechanism

As can be seen from the experimental results discussed earlier, cobalt chloride catalyzed oxidation reactions under an atmosphere of oxygen utilizing solvents such as diglyme or DME are a versatile method for the oxidation of benzylic hydrocarbons and ethers. However, the reaction mechanism is not well known. In attempts to obtain some insight into the reaction mechanism, isochroman was used as a model substrate to carry out this study.

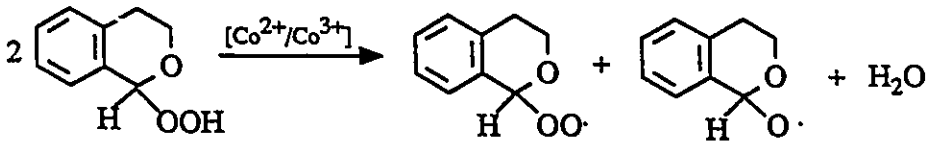
A possible reaction mechanism for the oxidation of isochroman to the 1-isochromanone is shown below:

1) Initiation:

$$L_nCo^{2+} + O_2 \xrightarrow{DME} L_nCoO\text{-}O\cdot \quad (L_n = \text{ligands}) \qquad [3.18]$$



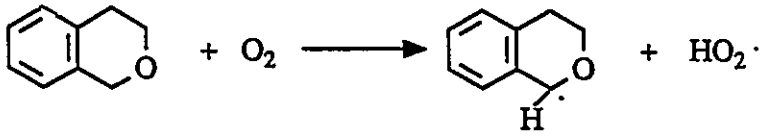
[3.19]



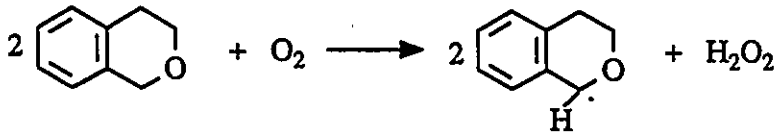
[3.20]

$$2\,ROOH \xrightarrow{[Co^{2+}/Co^{3+}]} RO_2\cdot + RO\cdot + H_2O \qquad [3.21]$$

(ROOH is an hydroperoxide contaminant in DME)

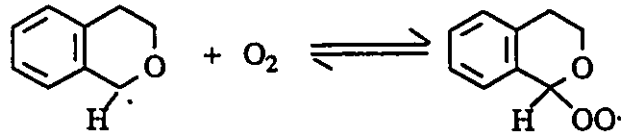


[3.22]

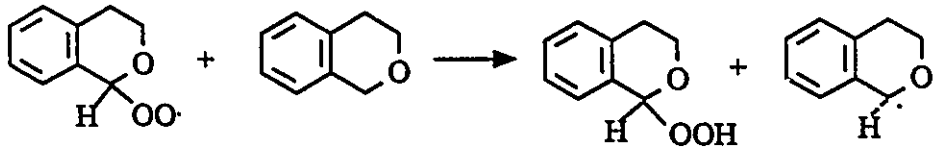


[3.23]

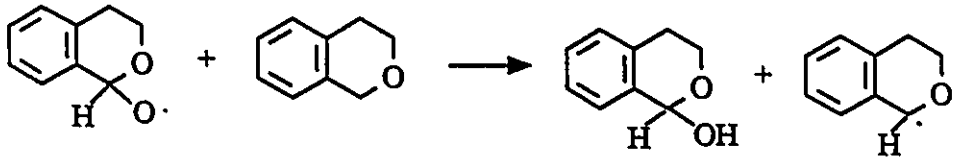
2) Propagation:



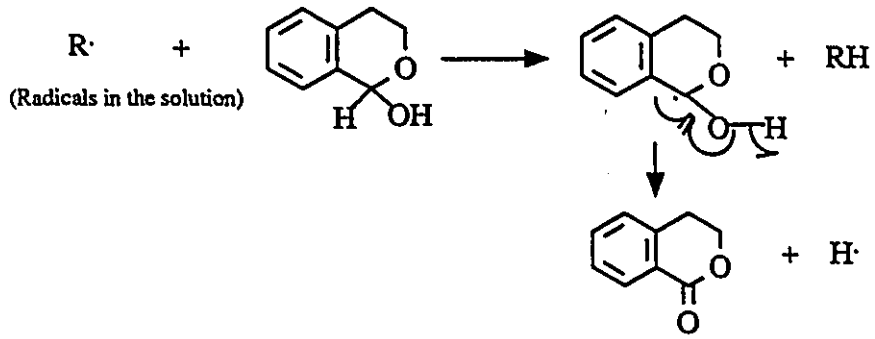
[3.24]



[3.25]

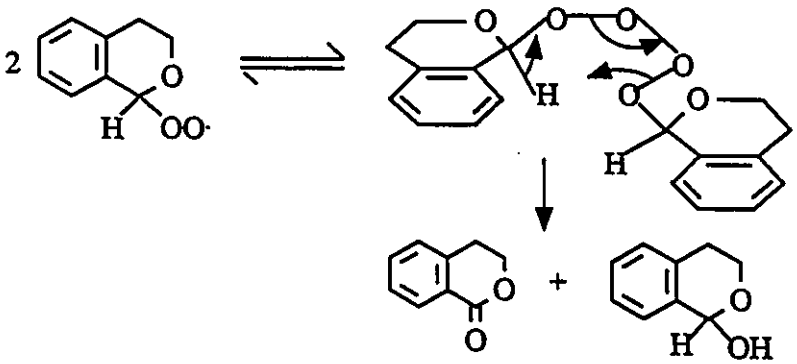


[3.26]

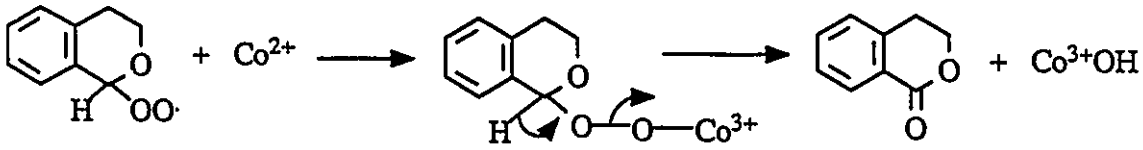


[3.27]

3) Termination



[3.28]



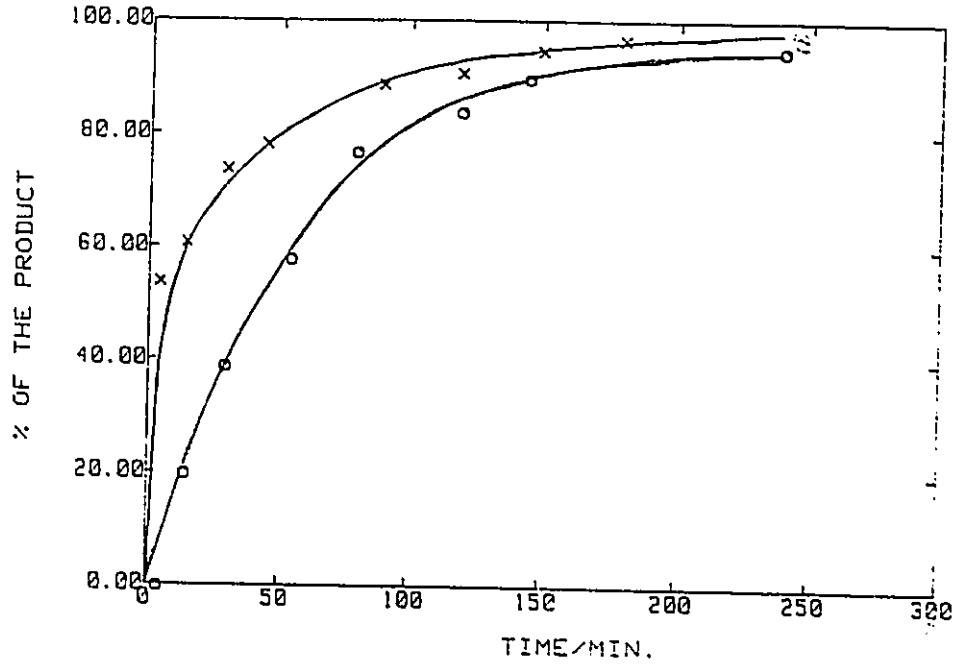
[3.29]

Concerning the induction period discussed in chapter 3.2.1.1., the initiation steps involve mainly the reaction between isochroman and the cobalt activated molecular oxygen (eq. [3.18] and [3.19]). Other reactions in the initiation steps (eq. [3.20] to [3.23]) could promote the rate of the initial reaction. Hence experimental details about the study of the initiation reactions will not be discussed again here.

As can be seen from the proposed reaction mechanism for the oxidation of isochroman to the 1-isochromanone, it is believed that the reaction proceeds via radical processes. In order to prove this hypothesis, several methods were used to study whether or not radical intermediates are involved.

1) If the oxidation of isochroman proceeds via a radical chain reaction, the addition of a radical inhibitor should result in a significant decrease of the rate or no reaction. In fact, in the presence of p-methoxyphenol (2.5mmol), which is a good radical inhibitor, isochroman (2.5mmol) gave no reaction under standard conditions. The color of the solution changed from blue to dark yellow. Because of the obvious color change during the reaction , there is the possibility that the failure of reaction was caused by the destruction of the cobalt chloride catalyst as a result of the formation of a complex with p-methoxyphenol rather than radical quenching effect. In order to clarify this point, oxidation of isochroman (2.5mmol) catalyzed by anhydrous $CoCl_2$ (0.025mmol) in the presence of a small amount of p-methoxyphenol was carried out and followed by GC (Fig. [3.7]).

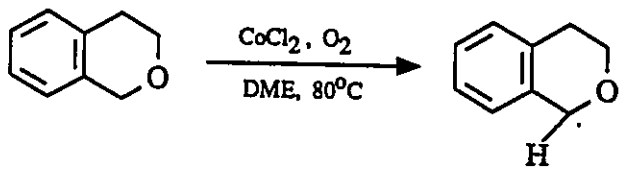
As the Fig.[3.7] shows, the oxidation of isochroman proceeds in the presence of a small amount of p-methoxyphenol ($CH_3C_6H_4OH$: $CoCl_2$ = 1.2:1) even though the initial rate of reaction was slower compared to the oxidation in the absence of p-methoxyphenol.



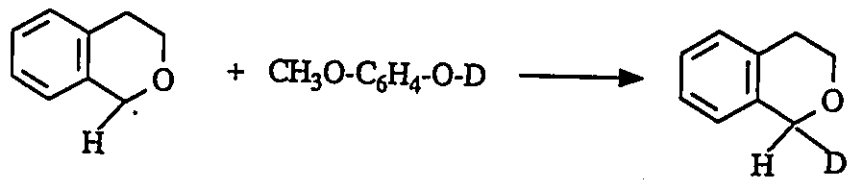
x Isochroman (2.5mmol), $CoCl_2$ (0.025mmol).
o Isochroman (2.5 mmol), $CoCl_2$ (0.025 mmol), p-methoxyphenol (0.3 mmol).

Fig. [3.7]

Moreover, when the oxidation of isochroman was carried out in the presence of p-methoxyphenol (isochroman:p-methoxyphenol=1:1) which contained 58% of monodeuterated p-methoxyphenol ($CH_3OC_6H_4OD$), none of the desired product was obtained. However, the mass spectrum of isochroman showed that the intensity of [M+1] peak was increased by 44.1% indicating that monodeuterated isochroman was formed via a isochroman radical intermediate (eq.[3.30] and [3.31]).

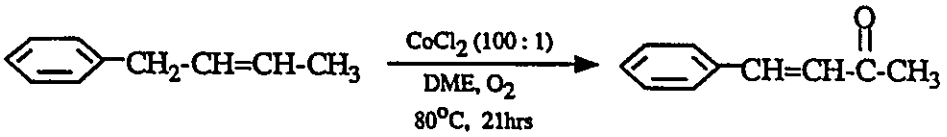


[3.30]



[3.31]

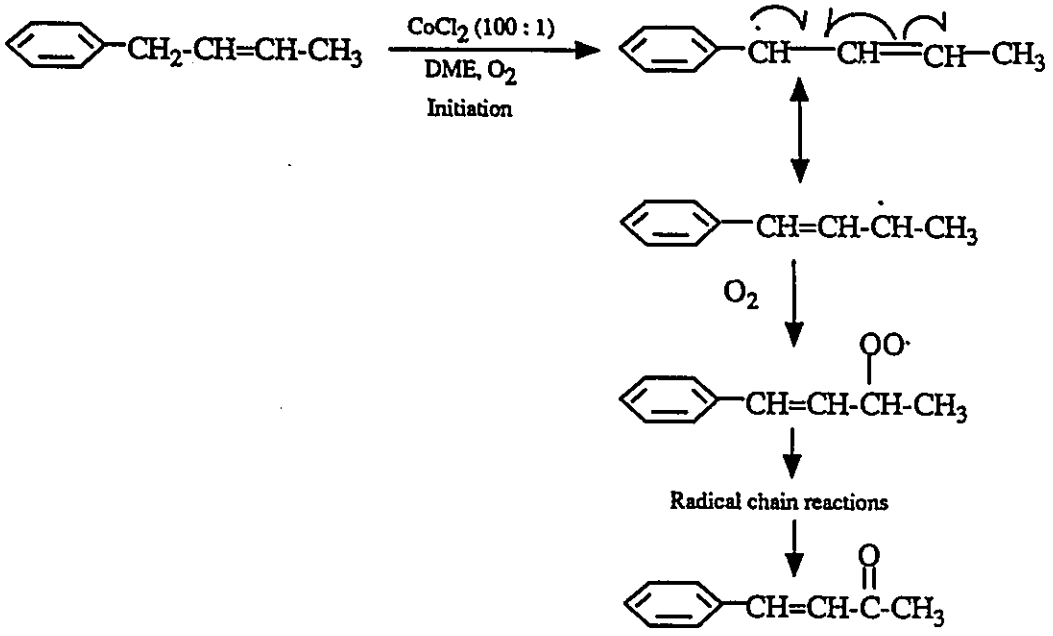
In addition, when the oxidation of 1-phenyl-2-butene was carried out using this oxidation system, one of the products was identified as 4-phenyl-3-buten-2-one (eq.[3.32]), and was isolated in 27% yield. The formation of this product can be accounted for by a



[3.32]

reaction involving a radical rearrangment (Scheme [3.11]). With reference to the above evidence, we can conclude that the reaction mechanism may involve radical intermediates.

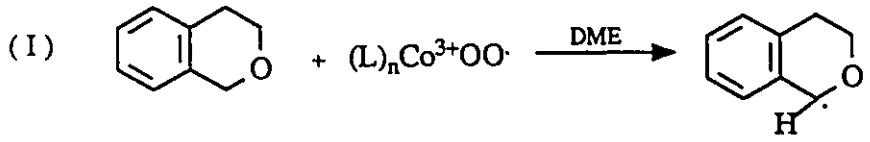
Scheme [3.11]



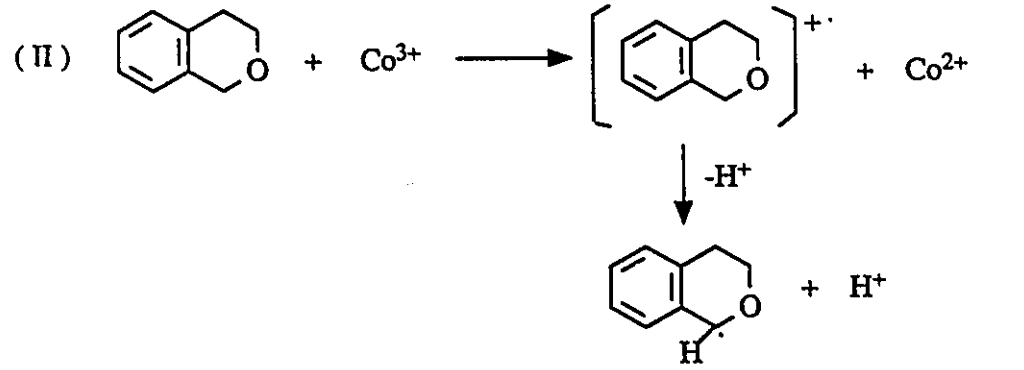
c) Isotope effects

As has been specified in Chapter 1, during a cobalt catalyzed oxidation reaction the radical intermediate can be generated by two processes: (I) the abstraction of an α-C-H hydrogen by a superoxocobalt (eq.[3.33]); (II) a direct attack on the substrate by a cobalt

complex via an one-electron transfer oxidation (eq.[3.34]). One good method to distinguish



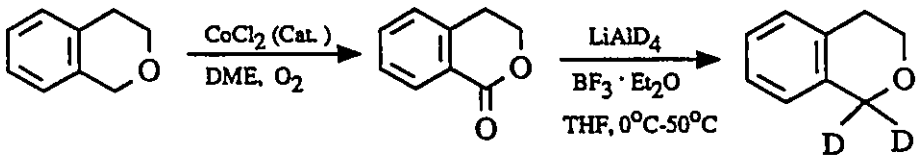
[3.33]



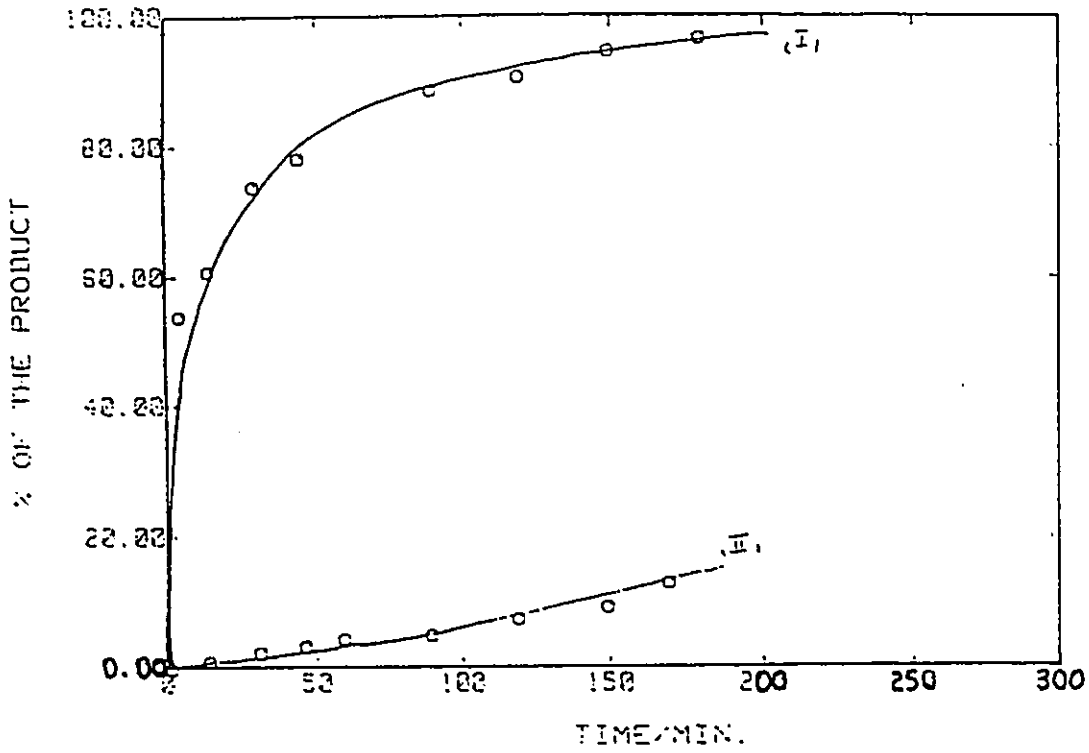
[3.34]

between these two processes is their isotope effects since process (I) is determined by the abstraction of an α-hydrogen while (II) is related to the ionization potential of the substrate and thus should not exhibit an isotope effect. Dideuterated isochroman was prepared according the reaction scheme [3.12].

Scheme [3.12]



When the oxidation of 1,1-dideuterated isochroman was monitored by GC, it was observed that the rate of reaction was much slower than the reaction with isochroman as substrate (Fig.[3.8]). This result clearly illustrates the strong isotope effect in this reaction. That is, the oxidation reaction may proceed via process (I), and not (II). In addition, the isotope effect showed in Fig.[3.8] indicates that the reaction involves not only the primary isotope effect, but also a complicate mechanism which also contributes to the isotope effect since the shape of the curve for dideuterated isochroman is different from the one with isochroman.



Reaction conditions: Curve (I): isochroman (2.5 mmol), $CoCl_2$ (0.025 mmol), DME, 80°C. Curve (II): 1,1-dideuterated isochroman : $CoCl_2$ = 30:1, DME, 80°C.

Fig. [3.8]

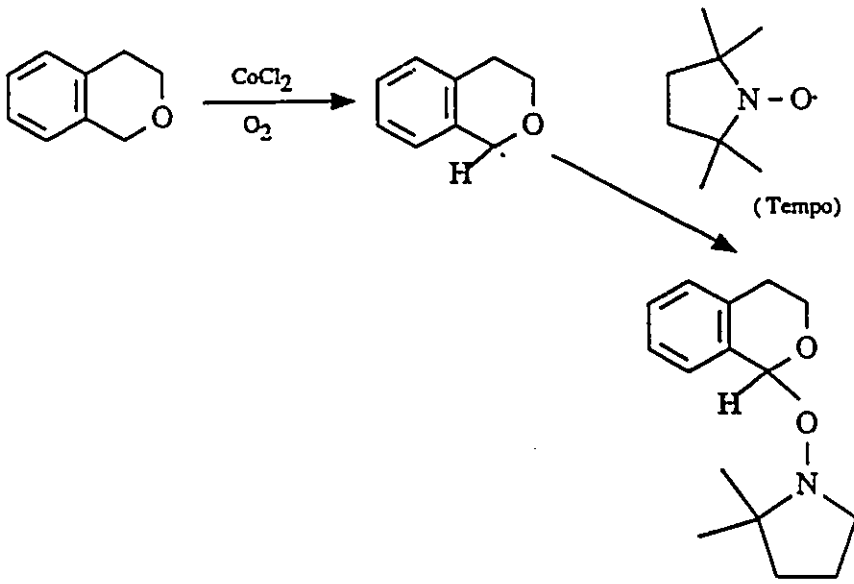
d) Trapping experiments:

Attempts were made to intercept the radical intermediates by addition of a trapping agent. For example, nitroxides usually react rapidly with radicals to give stable molecular products (eq.[3.35]).[189] Therefore, the use of 5,5-dimethyl-1-pyrroline-N-oxide (Tempo), a

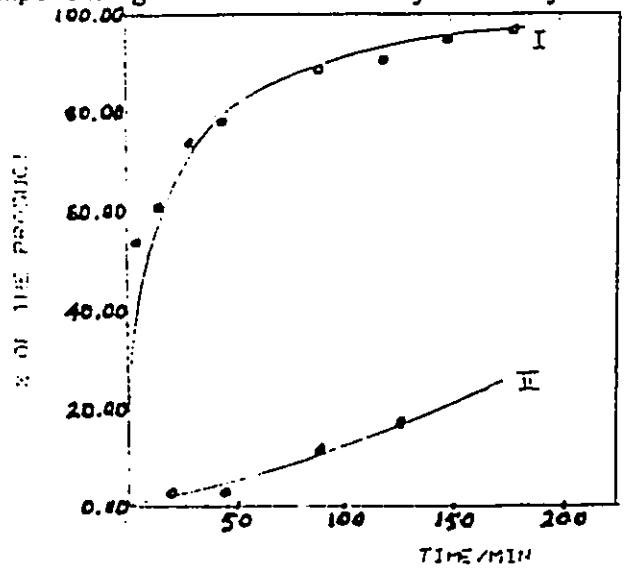
$$R_2'NO\cdot + R\cdot \longrightarrow R_2'NO\text{-}R \qquad [3.35]$$

trapping agent, is expected to result in capture of the isochroman radical intermediate if it is present in the reaction mixture (Scheme [3.13]). Unfortunately, when an equal amount of tempo to substrate was employed in the oxidation process, no reaction was observed. The color of the solution changed from blue to red as soon as tempo was added. Such a change

Scheme [3.13]



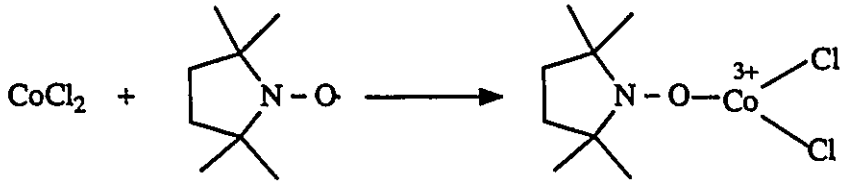
of color indicated that the tempo may react with the cobalt chloride forming a new complex. As a result, the addition of a small amount of tempo (substrate : tempo : $CoCl_2$ = 100:1.2:1) was studied. It was found that the reaction proceeded, but at a much slower rate than that observed in the absence of tempo (Fig. [3.9]). This result indicates that the anhydrous $CoCl_2$ was poisoned by tempo leading to a decrease of catalytic activity.



Reaction conditions: Curve (I): Isochroman(2.5mmol), $CoCl_2$(0.025mmol), DME, 80°C. Curve (II): Same as above except with tempo (0.03mmol).

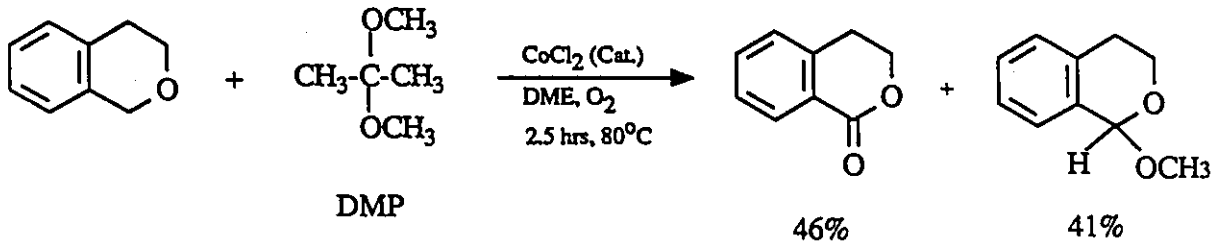
Fig. [3.9]

It is clear that the presence of tempo deactivated the cobalt catalyst. This effect might have resulted from the formation of a complex between $CoCl_2$ and tempo (eq.[3.36]). Excessive tempo might also inhibit the radical reaction.



[3.36]

Radical intermediates formed during the oxidation of isochroman were further studied using 2,2-dimethoxypropane (DMP) as a trapping agent. It was found that when the oxidation of isochroman (2.5 mmol) was carried out in the presence of DMP (3mmol), two products were formed. One was isochromanone, the other was identified as an acetal (eq.[3.37]). Moreover, when the reaction was carried out at 70°C for 17 hours using



DMP

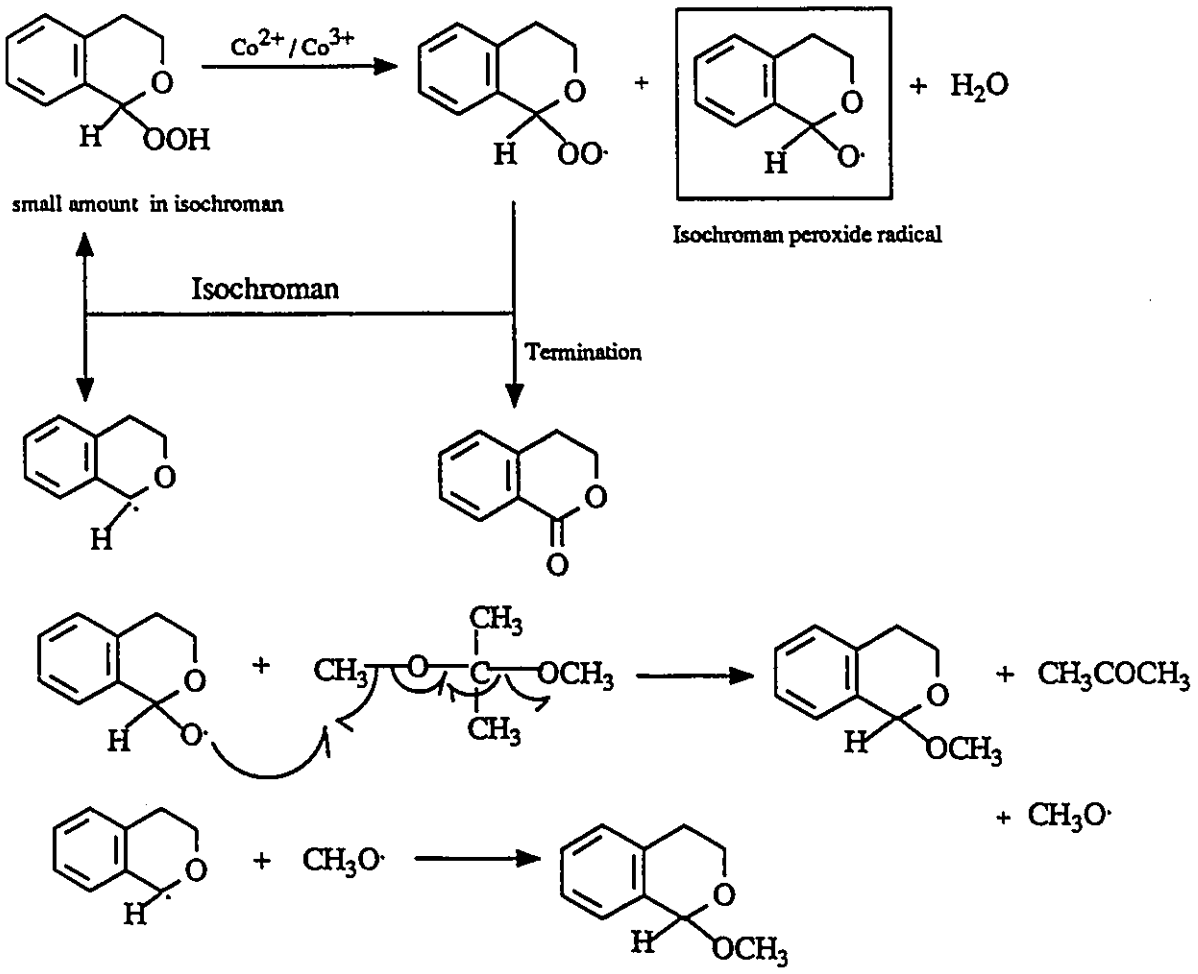
46%

41%

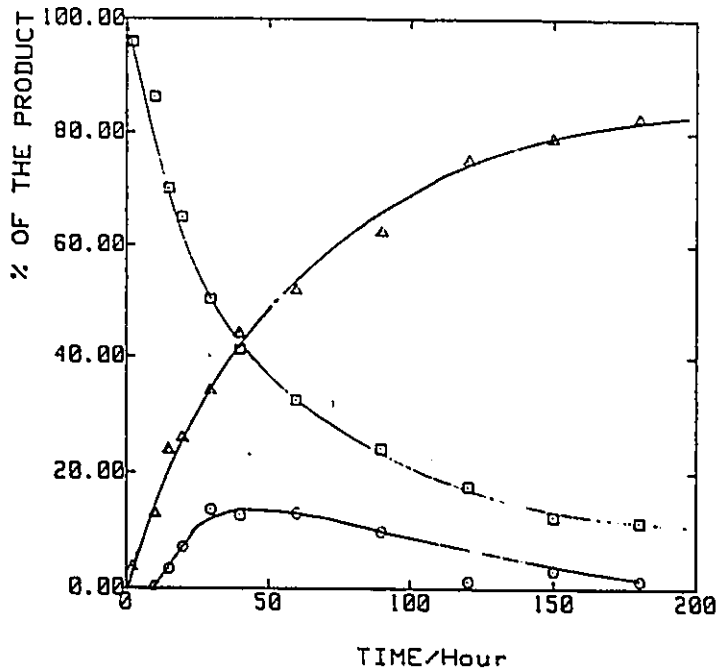
[3.37]

nitrogen instead of oxygen, GC analysis indicated that 89% of the starting material remained, 8% and 3% of the acetal and lactone were formed, respectively. That is, the acetal was a major product in the absence of oxygen. As a result, one may conclude that an isochroman peroxide radical intermediate may have been generated in the reaction (Scheme [3.14]).

Scheme [3.14]



In addition, it was observed that the acetal could be oxidized to the lactone under these conditions. As mentioned earlier, small amounts of this acetal were detected during the oxidation of isochroman catalyzed by $CoCl_2$ in the presence of DME. This result may be due to a hydrogen abstraction reaction of the isochroman peroxide radical intermediate with DME. In fact, when this reaction was followed by GC, it was observed that the quantity of the acetal increased at the beginning of the reaction, but almost completely disappeared after 3 hours (Fig.[3.10]). That is, the selectivity of the reaction was not significantly affected by the reaction between the radical intermediate and DME.

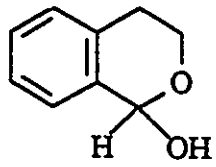


Reaction conditions: $CoCl_2$(0.025 mmol), isochroman(2.5 mmol), DME, O_2, 80°C (Both DME and isochroman were purified prior to use). □ Isochroman, Δ Isochromanone, O acetal.

Fig. [3.10]

e) Analysis of reaction intermediates and other by-products.

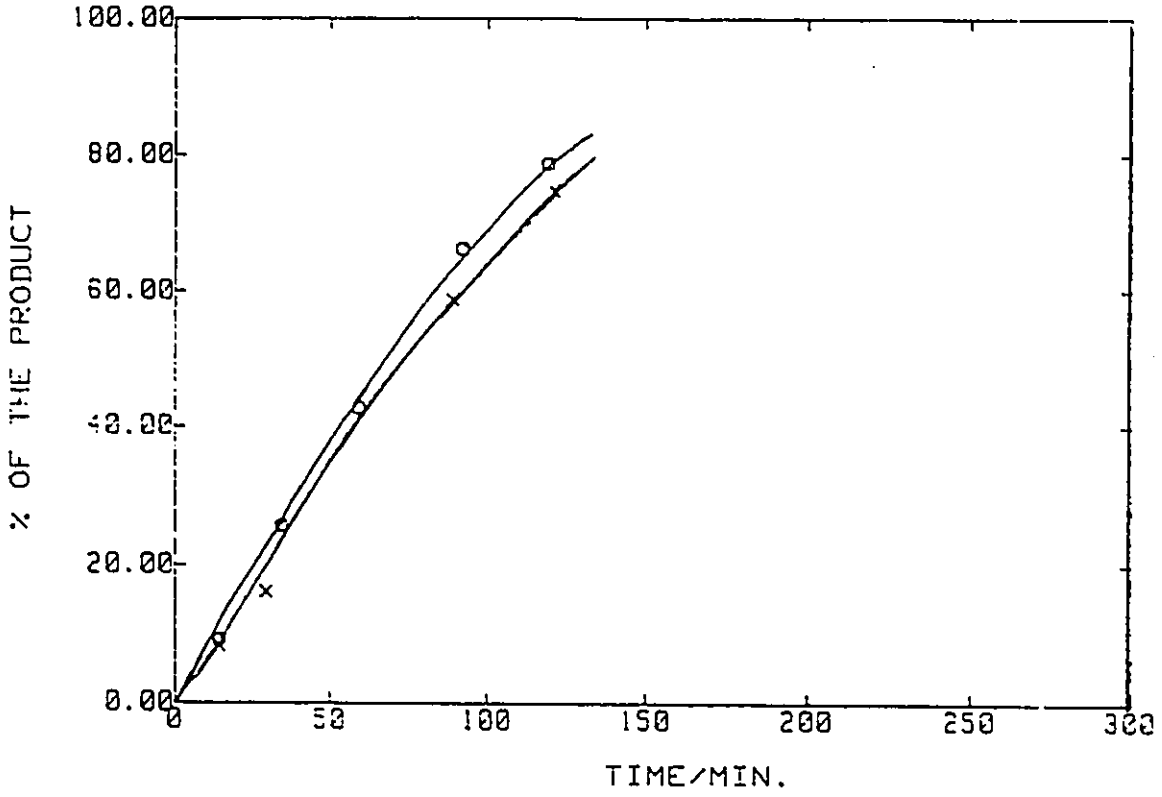
A minor product was observed in the gas chromatographic analysis of the reaction mixture formed on oxidation of isochroman. Its mass spectrum suggested that it might be the corresponding alcohol intermediate (m/e 150$[M]^+$, 149$[M-H]^+$). Unfortunately, it was not possible to isolate such a presumed hemiacetal.



In addition, during the oxidation of phenyl benzyl ether under standard reaction conditions, the rate of reaction was very slow. Two products were clearly observed in the GC. Their GC/MS. indicated that one was the desired product ($C_6H_5COOC_6H_5$), and another was probably the corresponding alcohol ($C_6H_5CH(OH)OC_6H_5$) (m/e 200$[M]^+$, 107$[C_6H_5CHOH]^+$, 77$[C_6H_5]^+$). Unsuccessful attempts were made to confirm the structure of this compound. Nevertheless, the mass spectrum of this product suggested the presence

of an alcohol intermediate.

At the end of the reaction, some pink precipitate was always observed. As discussed earlier, this pink precipitate is hydrated cobalt chloride resulting from complexation with water. In order to prove the formation of this complex, the oxidation of isochroman using commercially available hydrated $CoCl_2$ and this complex as catalyst were studied (Fig.[3.11]).

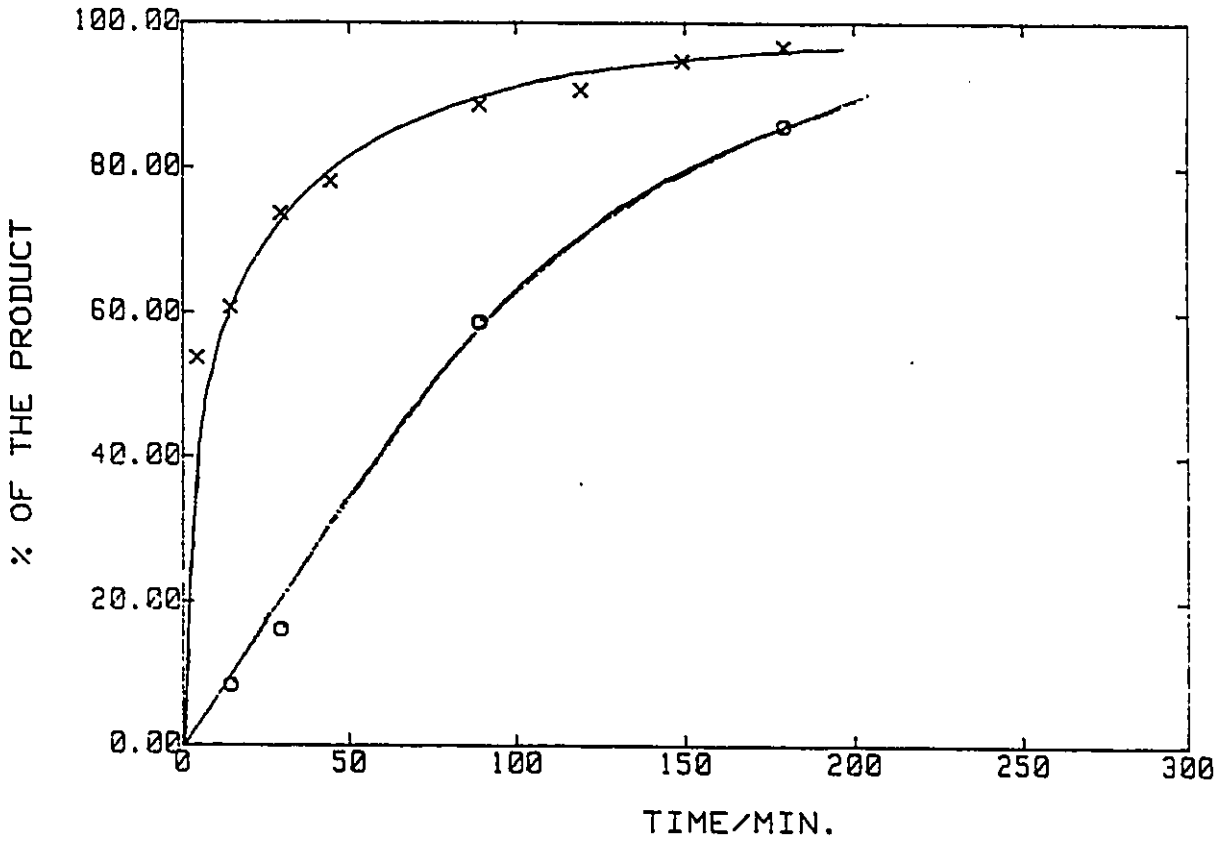


Reaction conditions: Isochroman(3 mmol), DME(5 ml), 80°C. o $CoCl_2 \cdot 6H_2O$ (0.03 mmol, 0.0071g); x Pink ppt. (0.0071g).

Fig. [3.11]

As can be seen from Fig.[3.11], both complexes gave similar results with respect to lactone formation. When the oxidation of isochroman using anhydrous $CoCl_2$ (blue) is compared with the use of this complex as catalyst (Fig.[3.12]), it was found that the reactivity of the pink complex in the oxidation was lower than that of anhydrous $CoCl_2$, especially in the initial stages. This result explains why the rate of reaction decreases

dramatically near the end when the color of the reaction passed from blue to pink. This is probably due to the formation of hydrated $CoCl_2$ (pink) which has a lower reactivity towards oxidation. Hence the above results clearly suppport the formation of water during the reaction.

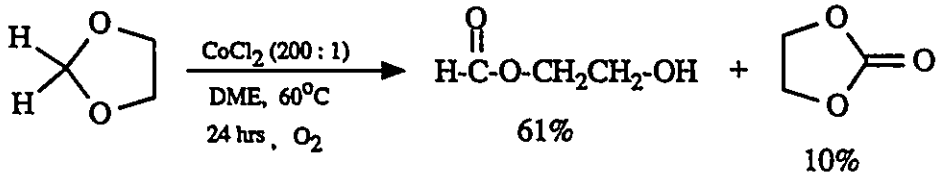


Reaction conditions: x isochroman (2.5mmol), $CoCl_2$(0.025mmol); □ isochroman (3mmol), pink ppt.(0.03mmol), 80°C.

Fig. [3.12]

3.2.2. OXIDATION OF 2-SUBSTITUTED 1,3-DIOXOLANES

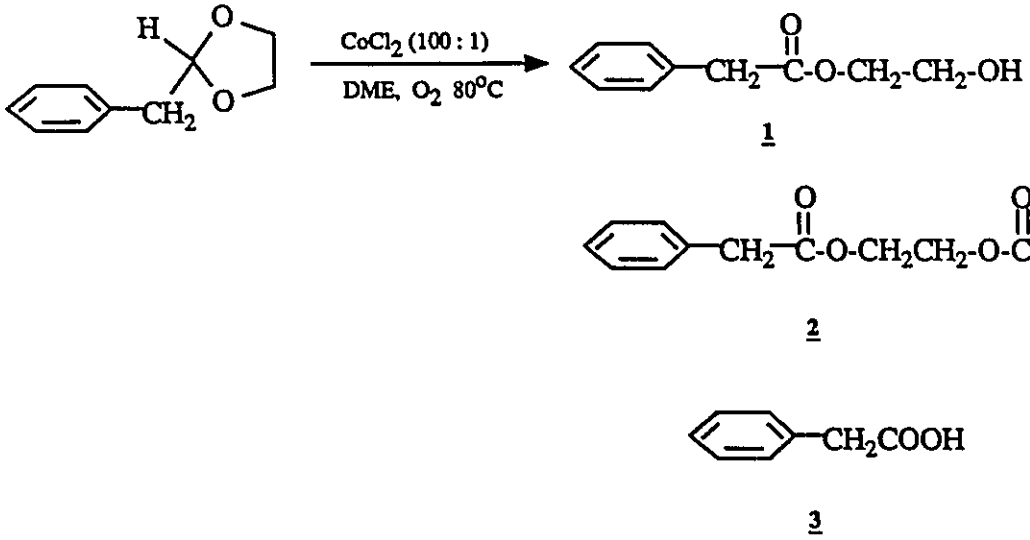
If the α-carbon of THF can be sucessfully oxidized to a carbonyl function when catalyzed by anhydrous $CoCl_2$ in the presence of DME, one should be capable of oxidizing 1,3-dioxolanes in a similar manner. The reactivity of the C-H bond of this carbon is higher than that of the α-C-H bond of THF resulting from the stablization by the two adjacent oxygen atoms. Hence the initial study of oxidation of 1,3-dioxolane was carried out in the presence of anhydrous $CoCl_2$ (substrate : Co^{2+} = 200:1) and DME. It was found that ethylene glycol monoformate was obtained as a major product (61% yield), and ethylene carbonate was isolated in 10% yield after 24 hours at 60°C (eq. [3.38]). This result indicated



[3.38]

that the oxidation of 1,3-dioxolane favors a ring opening reaction.

When the oxidation of 2-methyl-1,3-dioxolane was performed under similar reaction conditions, the expected product, ethylene glycol monoacetate ($CH_3COOCH_2CH_2OH$) was not the major product; instead, a new compound was observed. In order to understand the formation of this unexpected product, phenylacetaldehyde ethylene acetal which has a higher boiling point, was used to carry out this study. When the oxidation of this substrate was followed by GC, three products were observed during the reaction, and were identified as compound 1, 2, and 3 after isolation on TLC plates (eq.[3.39]). The formation of product 1 is not surprising. However, products 2 and 3 were completely unexpected since when counting the number of carbons in 2, one realizes that there is an additional carbon in the starting material. Where did this carbon come from? Was it from the reaction between



[3.39]

1

2

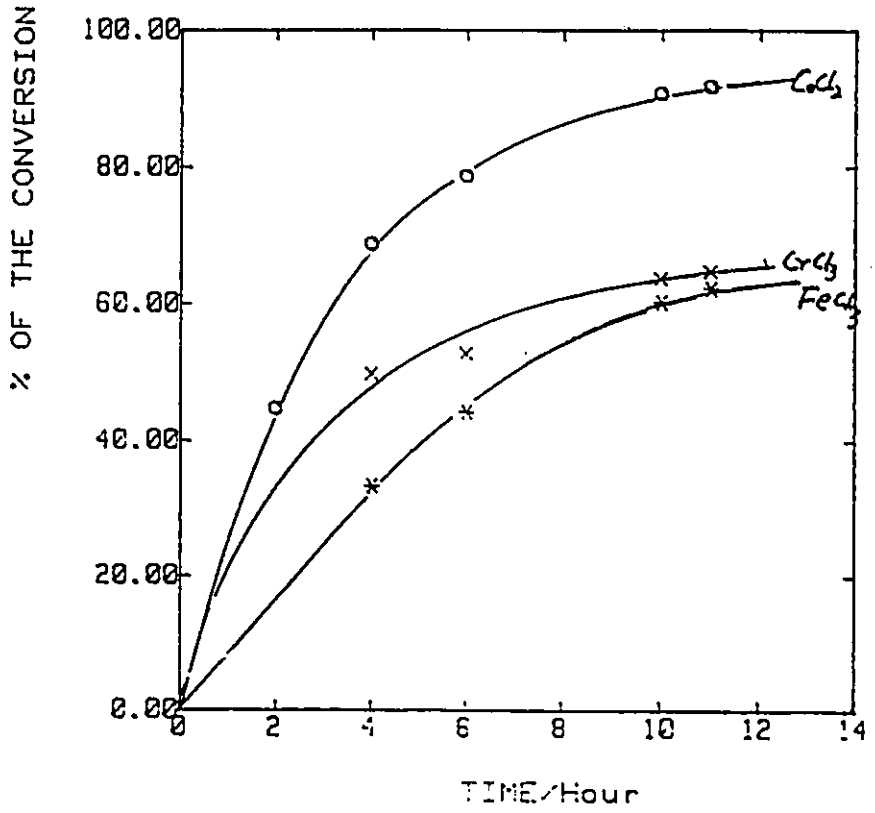
3

ethylene glycol monoacetate (1) and DME or from the reaction with itself? In order to clarify this point, the oxidation of phenylacetaldehyde ethylene acetal was carried out in the presence of 1,4-dioxane instead of DME. Since 1,4-dioxane has no primary methyl group, eliminating the possibility of reaction between ethylene glycol monoacetate and the solvent. It was found that 2 and 3 were now the major products after 42 hours at 85-90°C. This result clearly indicated that the extra carbon of compound 2 was not from DME.

During the reaction, 1 was observed to be the major product formed within 20 hours. It slowly disappeared with increasing reaction time, and after 56 hours, only 2 and 3 were present. This result indicates that phenylacetaldehyde ethylene acetal can be oxidized to compound 2 and 3 in a one-step reaction. Such an oxidation is very useful because 1) it results in homologation, 2) two functional groups are introduced simultaneously, one of which is the formate ester. Therefore, research was focused on determining the optimum reaction conditions to achieve a high yield of 2 and 3, and the use of such conditions to oxidize a variety of 2-substituted 1,3-dioxolanes to the corresponding formate esters and acids.

(A) Effect of Catalyst

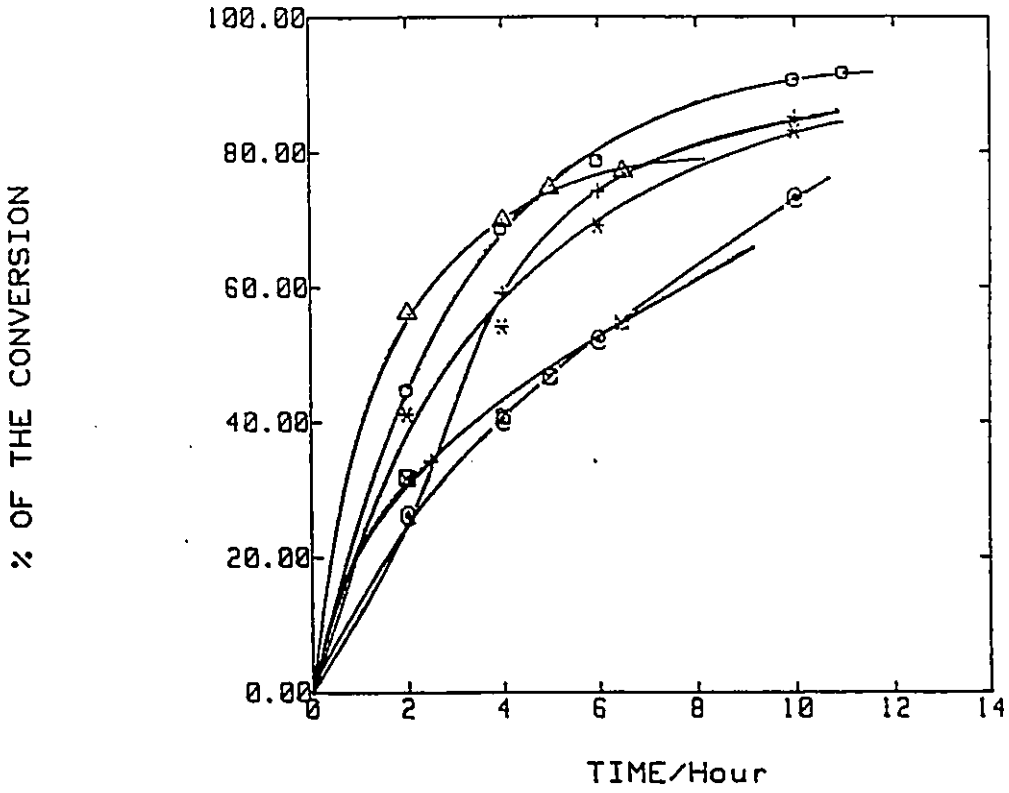
A series of metal catalysts were investigated for the oxidation of phenylacetaldehyde ethylene acetal to compounds 2 and 3. The first group of metal catalysts examined was $FeCl_3$, $CrCl_3$, and $CoCl_2$ (Fig.[3.13]).



Reaction conditions: Phenylacetaldehyde ethyleneacetal (2.5mmol), metal catalyst (0.1mmol), DME (15ml), at 90°C, t-butylbenzene as internal standard.

Fig. [3.13]

As shown in Fig. [3.13], the catalytic effect of these three metal complexes increases in the order $FeCl_3 < CrCl_3 < CoCl_2$. In other words, the cobalt complex has the highest reactivity towards oxidation. These results are consistent with results derived by Kuramshin.[183] The second group of metal catalysts examined were cobalt complexes containing a variety of ligands such as $Co(OAc)_2$, $Co(OCOPh)_2$, $CoCl_2(PPh_3)_2$, $CoBr_2$, $Co(NO_3)_2 \cdot 4H_2O$, and $CoSO_4 \cdot 7H_2O$ (Fig. [3.14]).



Reaction conditions: Same as Fig.[3.13], □ $CoCl_2$; @ $Co(OAc)_2$; * $Co(OCOPh)_2$; + $CoCl_2(PPh_3)_2$; Δ $CoBr_2$; ⊗ $Co(NO_3)_2 \cdot 4H_2O$.

Fig [3.14]

Anhydrous $CoCl_2$ is the most effective of the cobalt catalysts, with $CoSO_4 \cdot 7H_2O$ being inactive. It is noteworthy that the initial reaction with $CoBr_2$ is at a higher rate than that using anhydrous $CoCl_2$ as the catalyst. For example, after two hours, reaction in the presence of $CoBr_2$ reached 56% conversion, while the use of anhydrous $CoCl_2$ resulted in 45% conversion. However, the rate of reaction using $CoBr_2$ as the catalyst apparently decreased after 4 hours. As a result, considering the completion of the reaction, the catalytic effect of $CoCl_2$ is better than that of $CoBr_2$. Moreover, the catalytic activity of $CoCl_2$ is much higher than that of $Co(OAc)_2$. These results are different from those reported by Kuramshin. Consequently, anhydrous $CoCl_2$ was used for subsequent oxidation studies.

B) Effect of reaction temperature.

Increasing the reaction temperature dramatically increases the rate of reaction. This point is illustrated in Table [3.7]. Since the boiling point of DME is 85°C, the oil bath

Table [3.7] Effect of reaction temperature[a]

T (°C) (oil bath)	Time (h)	Conversion (%)
45-50	28	42
60-65	28	68
85-90	23	100

a) Reaction conditions: phenylacetaldehyde ethylene acetal (2.5mmol), anhydrous $CoCl_2$ (0.1mmol), DME(15ml).

temperature should not exceed 90°C. Otherwise, solvent loss may occur under a flow of oxygen.

C) Effect of concentration of $CoCl_2$

During the oxidation reactions, it was found that the starting material was completely converted after approximate one day at 85-90°C. However, the rate of disappearance of glycol ester 1 was quite slow, with 56 hours needed to achieve completion of the reaction. Thus it would be of interest to determine whether the concentration of $CoCl_2$ would influence the rate of disappearance of glycol ester 1. The result are listed in Table [3.8].

The results in Table [3.8] demonstrate that the concentration of cobalt chloride has no significant effect on the rate of further oxidation of glycol ester 1. Among these experiments, the use of a 25:1 ratio of substrate to $CoCl_2$ seemed to give the best ratio between 1 and 2. As a result, this ratio was used in subsequent studies.

Table [3.8] Effect of concertration of $CoCl_2$ [a]

Substrate / $CoCl_2$ (mmol)	Time (h)	Conversion (%)	Product Ratios[b] (1/2)
50 / 1	42	100	1 / 5
25 / 1	41	100	1 / 6
10 / 1	41	100	1 /5.3

a) Reaction conditions: acetal (5mmol), DME(15ml), 85-90°C

b) Product ratios were calculated in terms of peak area regardless of their response factors.

d) Effect of additives

Attempts were made to enhance the rate of oxidation of 1 to 2 by addition of Lewis acid ($ZnCl_2$), Lewis base (pyridine), or dehydration agents (2,2-dimethoxypropane or molecular sieves 4Å). The results are presented in Table [3.9]. It was observed that the

Table [3.9] Effect of additives for the further oxidation of glycol ester[a]

Additives	Substrate / Additives	Time (h)	Conversion (%)	Product Ratio[b] (1/2)
——	——	41	100	1 / 6
Pyridine	1 / 1.2 (mmol)	35	67	1 / 2
$ZnCl_2$	10 / 1 (mmol)	28	100	0 / 1
Molecular Sieves	1.6 / 1 (g)	28	100	1 / 3.3

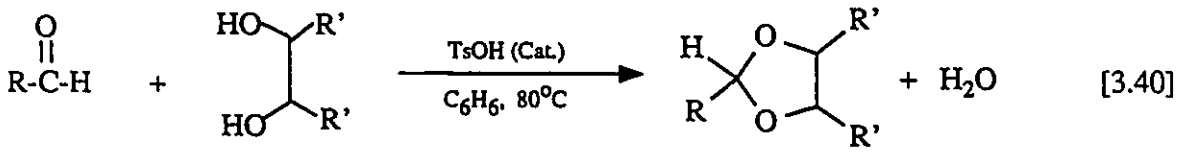
a) Reaction conditions: acetal(5mmol), $CoCl_2$(0.2mmol), DME(15ml), 85-90°C

b) Product ratios were calculated in terms of peak area regardless of their response factors.

addition of a catalytic amount of $ZnCl_2$ dramatically enhanced the rate of oxidation of

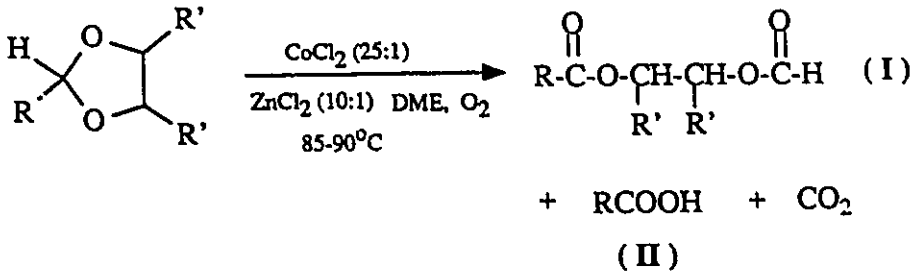
glycol ester. For instance, GC clearly showed that the glycol ester completely disappeared after 28 hours at 85-90°C. However, the addition of pyridine and molecular sieves either had no effect or led to negative results. At this point, it was necessary to determine whether the $CoCl_2$ or $ZnCl_2$ played an essential role in this oxidation. When the oxidation of phenylacetaldehyde ethylene acetal was catalyzed by $ZnCl_2$ (substrate : $ZnCl_2$ = 10:1) in the presence of DME, the rate of oxidation was much slower than that of the reaction catalyzed by $CoCl_2$. Only 21% conversion was obtained after 30 hours at 80-90°C. This result indicated that $CoCl_2$ was the key catalyst. The presence of $ZnCl_2$ promoted the rate of further oxidation of glycol ester.

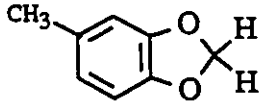
Having determined the optimal reaction conditions for the oxidation of phenylacetaldehyde ethylene acetal to the corresponding formate ester and acid using a mixed catalyst (substrate : $CoCl_2$: $ZnCl_2$ = 25:1:2.5) in the presence of DME under an oxygen atmosphere at 85-90°C, an investigation was undertaken of the conversion of a variety of 2-substituted 1,3-dioxolanes to the corresponding formate esters and acids. The results are illustrated in Table [3.10]. Some of the substrates were prepared according to the reaction shown below (eq.[3.40]).



[3.40]

Table [3.10] Oxidation of a variety of 2-substituted 1,3-dioxolanes to their formate esters and acids

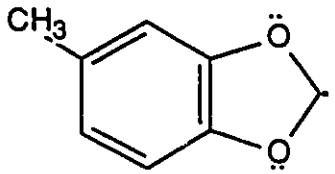


Substrates		T (°C)	Time (h)	Yield (%) [a]		Other products
R	R'			(I)	(II)	
C_6H_5	H	85	24	70	85	
$C_6H_5CH_2$	H	90	28	86	91	
n-C_7H_{15}	H	90	30	80	89	
CH_3	H	55	41	79	b	
n-C_7H_{15}	CH_3	85	29	38	42	$C_7H_{15}COOCH(CH_3)CH(CH_3)OH$ (34%)
n-C_7H_{15}	Trans-$COOCH_3$	90	48	No Reaction		
Trans-$C_6H_5CH=CH$	H	90	4	—	—	C_6H_5CHO (64%)
			24	—	—	C_6H_5COOH (92%)
		90	48	No Reaction		

a) Isolated yield was calculated in terms of 2 moles of substrate gave 1 mole of each product.

b) The yield of acetic acid is not available due to the losses incurred during the reaction and the work up.

The oxidation of 2-phenyl, benzyl, n-heptyl as well as methyl substituted 1,3-dioxolanes afforded formate esters and acids in high yields. Those 1,3-dioxolanes containing alkyl substituents such as R'=CH_3 underwent oxidation at a lower rate, and no reaction was observed when electron-withdrawing groups were present. Moreover, when the oxidation of trans-cinnamaldehyde ethylene acetal (R=C_6H_5CH=CH) was attempted, none of the desired products were observed. Instead, benzoic acid was obtained in 92% yield after 24 hours at 90°C. When this reaction was stopped after 4 hours, benzaldehyde was produced in 64% yield. Hence benzoic acid was formed as a result of further oxidation of benzaldehyde. Finally, oxidation of 3,4-(methylenedioxy) toluene did not occur at all, probably for the same reasons as those involved to account for the oxidation of 2,3-dihydrobenzofuran (chapter 3.2.1.2.).

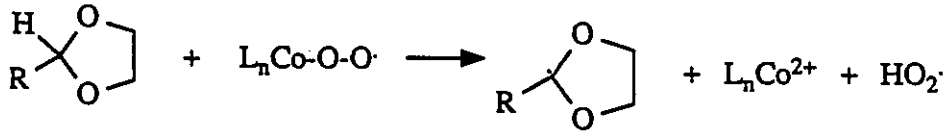


3, 4-(methylenedioxy) toluene

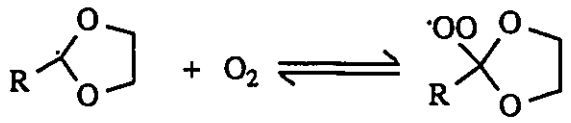
A possible mechanism for the reaction is outlined in (Scheme [3.15]):

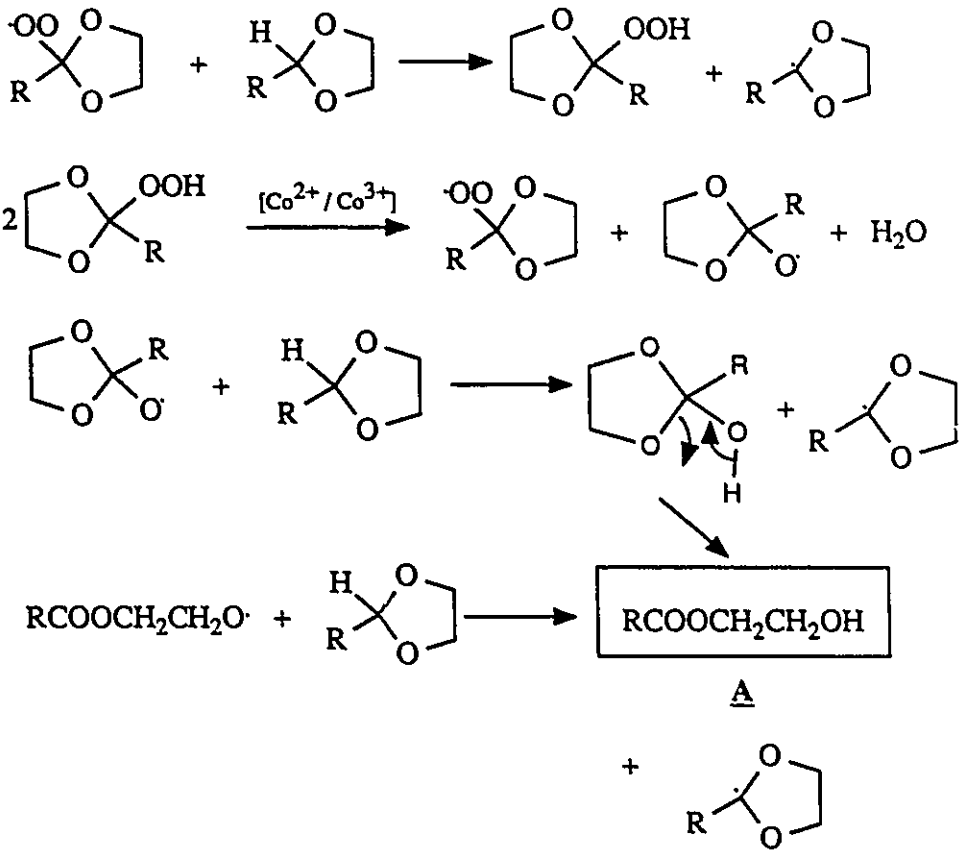
Scheme [3.15]
Process 1

Initiation: $L_nCo^{2+} + O_2 \xrightarrow{DME} L_nCo\text{-}O\text{-}O\cdot$ (L=ligand)

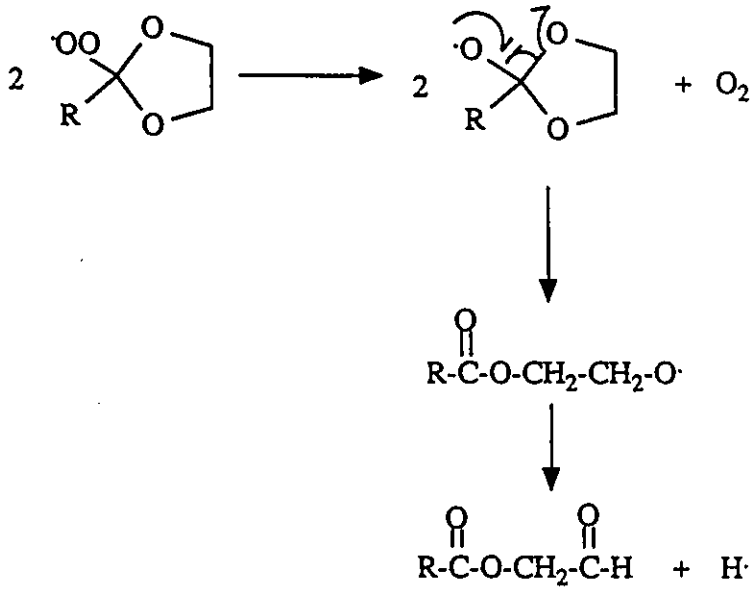


Propagation:

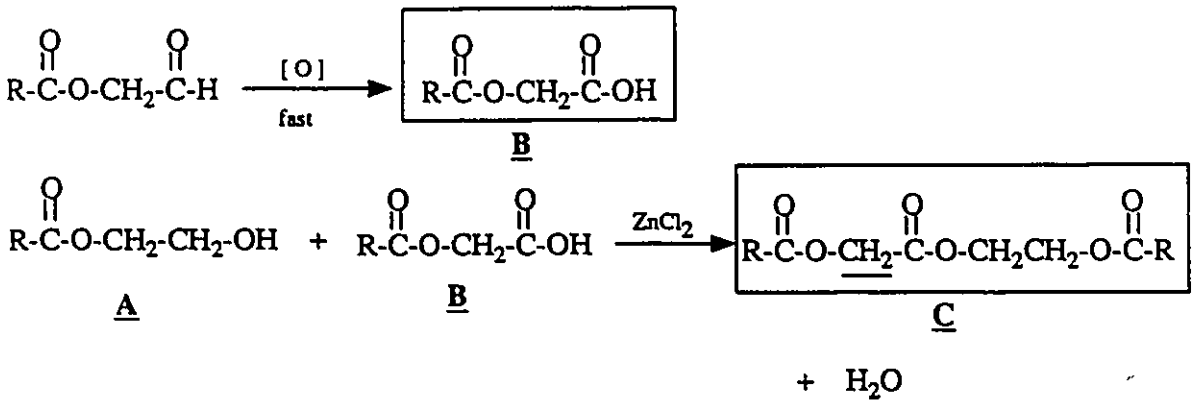




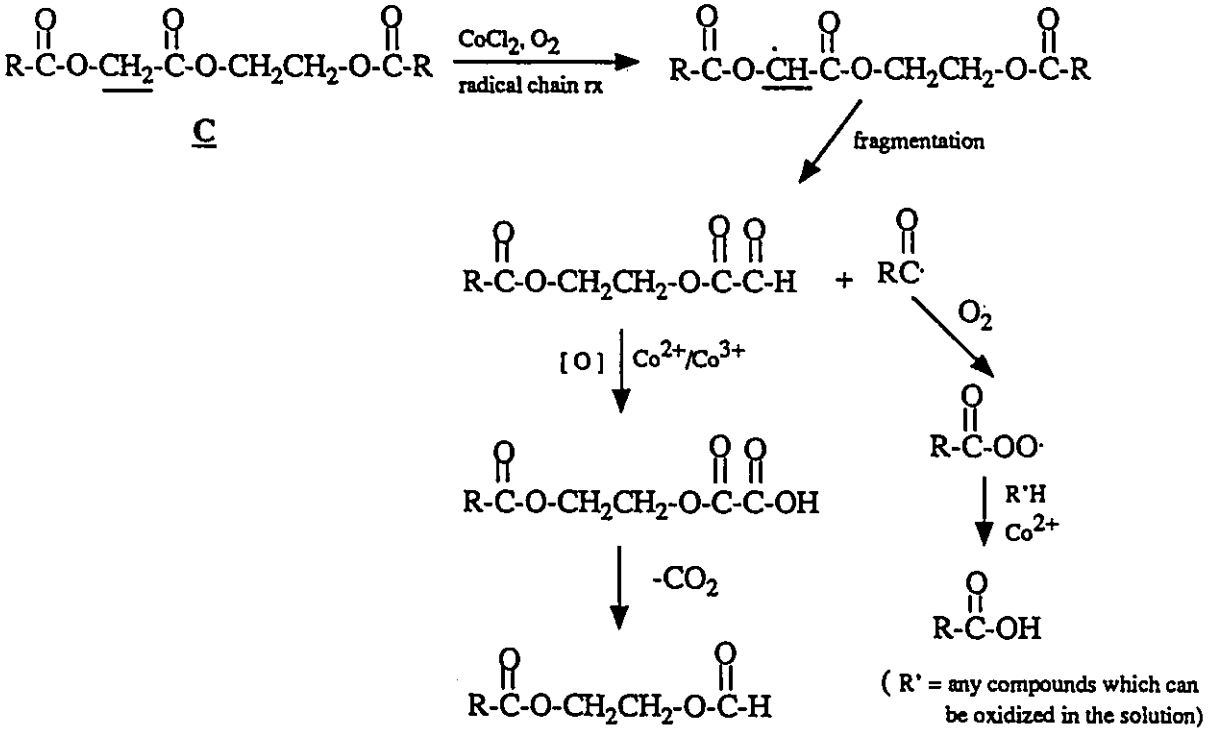
Termination:



Process 2



Process 3



The study of the course of these reactions was performed with phenylacetaldehyde ethylene acetal ($R=C_6H_5CH_2$) as substrate. The proposed mechanism receives support from

the following evidence:

1) Glycol ester $C_6H_5CH_2COOCH_2CH_2OH$ (A) was isolated as a primary product. When the reaction was carefully followed by GC, it was observed that the peak corresponding to the glycol ester decreased slowly while the peaks of formate ester and acid increased. That is, the glycol ester must be a intermediate and undergo further reaction to form the formate ester and acid.

2) Compound (B) was detected by GC/Mass Spec.. (m/e 194$[M]^+$, 119$[C_6H_5CH_2CO]^+$, 91$[C_6H_5CH_2]^+$, 59$[CH_2COOH]^+$, 45$[COOH]^+$).

3) Compound (C) was isolated and identified by IR, ^1H NMR and MS.

IR($CDCl_3$): $\nu_{C=O}$ 1738, 1730cm^{-1}, ν_{C-O} 1160, 1138,1028cm^{-1}.

^1H NMR($CDCl_3$): δ 3.63(s; 4H, $2C_6H_5\underline{CH_2}$), 4.23(m; 4H, -$COO\underline{CH_2CH_2}OCO$-), 4.58(s; 2H, -$OCO\underline{CH_2}OCOCH_2Ph$), 7.25(m; 10H, 2Ph).

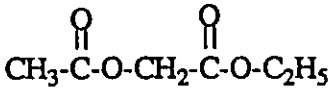
MS: m/e 193$[PhCH_2COOCH_2COO]^+$, 163$[PhCH_2COOCH_2CH_2]^+$, 118$[C_6H_5CHCO]^+$, 91$[C_6H_5CH_2]^+$.

4) Compound (B) and (C) disappeared at the end of the reaction.

5) The presence of $ZnCl_2$ greatly enhanced the rate of disappearance of glycol ester (A). This result indicated that glycol ester might react via an esterification process since $ZnCl_2$ is known to be a excellent promotor for the esterification step[190].

6) The underlined methylene group in compound (C) could be oxidized by this system. This was tested by the oxidation of a similar type of substrate (ethyl acetoxy acetate). During the oxidation, the decomposition of this compound to smaller molecules was observed with an alcohol intermediate analyzed by GC/Mass Spec. (m/e 89$[CH_3COOCHOH]^+$, 59$[CH_3COO]^+$). The reaction mixture was acidic and CO_2 evolution was determined.

7) Carbon dioxide evolution was determined by a simple test. A saturated $Ba(OH)_2$ solution was used as an exit bubbler to trap the evolved gas, and a white precipitate of



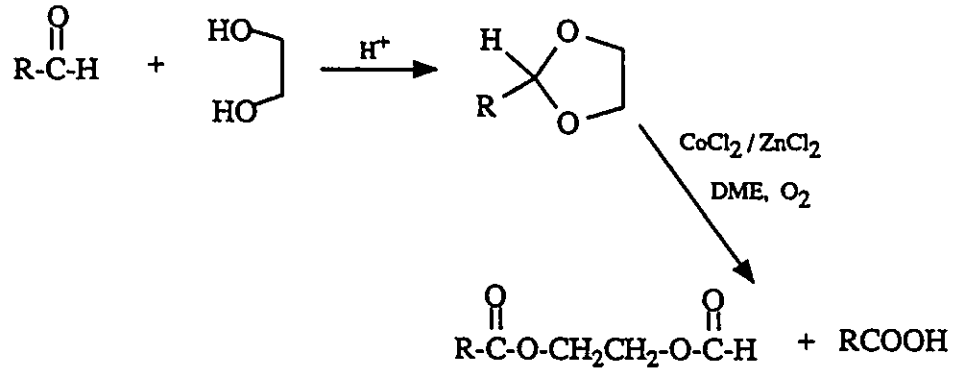
Ethyl acetoxy acetate

$BaCO_3$ was formed.

In conclusion, 2-substituted 1,3-dioxolanes can be oxidized to the corresponding formate esters and acids in high yields. This process is effectively catalyzed by anhydrous $CoCl_2$ and $ZnCl_2$ (substrate : $CoCl_2$: $ZnCl_2$ = 25:1:2.5) in the presence of DME, and has the following advantages:

1) Aldehydes can be converted to formate esters and acids via two step reactions: a) the preparation of the acetal from the aldehyde, and b) the oxidation of the acetal as described above (scheme [3.16]).

Scheme [3.16]



2) This oxidative cleavage of acetals is a novel method affording synthetically useful products.

3.3 Experimental Data

3.3.1. GENERAL COMMENTS

The general comments of chapter 2 are applicable here.

In addition, some proton and carbon magnetic resonance spectra were recorded with a Varian GEMINI 200 MHZ Proton NMR Spectrometer.

3.3.2. EXPERIMENTAL DATA FOR THE OXIDATION OF ETHERS

General procedure for the oxidation of ethers

A mixture of ether (5 mmol) and anhydrous $CoCl_2$ (0.0033 g, 0.025 mmol) in DME (10-15 ml) was stirred under an oxygen atmosphere for 3-72 hours at 40-90°C. The reaction was monitored by gas chromatography. Some pink precipitate was formed during the reaction. The following work-up was used in most cases: The reaction mixture was cooled to room temperature and filtered through a small silica column in order to remove the pink precipitate. The filtrate was concentrated by rotary evaporation. Distilled water (10ml) was added, and the products were extracted with ether (3 × 20 ml). The organic layer was washed with distilled water (50 ml), dried ($MgSO_4$), and concentrated. Pure products were isolated by thin layer or column chromatography of the crude material on silica gel, and were characterized by IR, ^1H NMR and mass spectrometry. The results and reaction conditions are listed in Table [3.5].

Oxidation of isochroman

Oxidation of isochroman afforded the corresponding lactone in 90% yield. Isolation of pure product was effected by column chromatography using 3:2 ether/hexane as the eluant.

IR(neat): $\nu_{C=O}$ 1720 cm^{-1}, ν_{C-O} 1241 cm^{-1}.

^1H NMR($CDCl_3$): δ 3.00(t, 2H, $C_6H_4C\underline{H_2}$), 4.47(t, 2H, $C_6H_4COOC\underline{H_2}$), 7.30(m, 3H, protons meta and para to carbonyl), 8.00(m, 1H, proton ortho to carbonyl).

MS: m/e 148$[M]^+$, 118$[M-H_2CO]^+$, 90$[C_6H_5CH]^+$.

A small amount of acetal by-product was detected by mass spectrometry.

MS: m/e 164$[M]^+$, 133$[M-OCH_3]^+$.

Oxidation of phthalan

Oxidation of phthalan afforded phthalide in 82% yield (isolation by TLC using 2:1 ether/hexane as the developer).

IR($CDCl_3$): $\nu_{C=O}$ 1758 cm^{-1}, ν_{C-O} 1055 cm^{-1}.

^1H NMR($CDCl_3$): δ 5.22(s, 2H, CH_2), 7.43(m, 3H, protons meta and para to carbonyl), 7.74(m, 1H, J=8Hz, proton ortho to carbonyl).

MS: m/e 134$[M]^+$, 105$[C_6H_5CO]^+$, 77$[C_6H_5]^+$.

A major by-product was identified as phthalic anhydride (5% yield).

IR(acetone-d_6): $\nu_{C=O}$ 1858, 1780 cm^{-1}, ν_{C-O} 1038, 1250 cm^{-1}.

MS: m/e 148$[M]^+$, 104$[M-CO_2]^+$, 76 $[C_6H_4]^+$.

Oxidation of 2,5-dihydrofuran

Oxidation of 2,5-dihydrofuran afforded 2(5H)-furanone in 63% yield. Product isolation was achieved by TLC using 9:1 methylene chloride/methanol as the developer.

IR ($CDCl_3$): $\nu_{C=O}$ 1760 cm^{-1}, ν_{C-O} 1170 cm^{-1}.

^{1}H NMR($CDCl_3$): δ 4.80(t, 2H, CH_2), 6.04(m, H, olefinic proton), 7.50(m, 1H, olefinic proton next to carbonyl).

MS: m/e 84$[M]^+$, 55$[M\text{-}CHO]^+$.

Oxidation of tetrahydrofuran

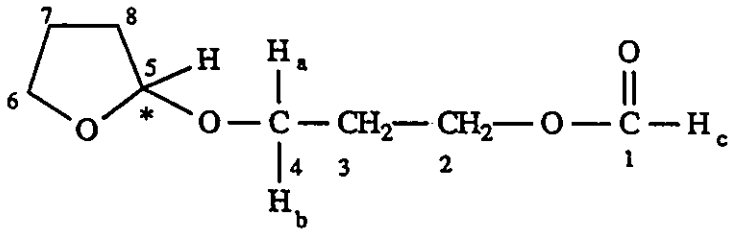
Oxidation of tetrahyrofuran in the absence of solvent (DME) afforded γ-butyrolactone in 34% yield. The pure product was obtained by vacuum distillation (44-45°C/0.1 mm Hg).

IR(neat): $\nu_{C=O}$ 1770 cm^{-1}, $\nu_{C\text{-}O}$ 1170 cm^{-1}.

^{1}H NMR($CDCl_3$): δ 2.32(m, 4H, -$OCH_2\underline{CH_2}\underline{CH_2}CO$), 4.32(t, 2H, -$O\underline{CH_2}CH_2CH_2CO$-).

MS: m/e 86$[M]^+$, 56$[CH_2CHCO]^+$, 42$[M\text{-}CO_2]^+$.

Another major product, isolated in 43% yield by vacuum distillation (76-78°C/0.1 mm Hg), was identified as



IR(neat): $\nu_{C=O}$ 1722 cm^{-1}, $\nu_{C\text{-}O}$ 1182 cm^{-1}.

^{1}H NMR($CDCl_3$): δ 1.87(m, 6H, protons on C_3, C_7, C_8), 3.43(m, 1H, H_a), 3.69(m, 1H, H_b), 3.81(t, 2H, protons on C_6), 4.10(t, 2H, protons on C_2), 5.06(m, 1H, proton on C_5), 7.98(s, 1H, H_c).

^{13}C NMR($CDCl_3$): δ 23.55(C_7), 28.98(C_8), 32.40(C_3), 61.28(C_4), 63.21(C_6), 66.96(C_2), 103.86(C_5), 160.95(C_1).

MS: m/e 174$[M]^+$, 128$[M\text{-}HCOOH]^+$.

Oxidation of methyl benzyl ether ($C_6H_5CH_2OCH_3$)

Oxidation of methyl benzyl ether afforded methyl benzoate in 84% yield.

IR (neat): $\nu_{C=O}$ 1726 cm^{-1}, ν_{C-O} 1282 cm^{-1}.

^1H NMR($CDCl_3$): δ 3.77(s, 3H, OCH_3), 7.30(m, 3H, meta and para protons), 7.81(m, 2H, ortho protons).

MS: m/e 136$[M]^+$, 105$[M-OCH_3]^+$, 77$[C_6H_5]^+$.

Some white precipitate was formed during the work-up procedure after addition of 10ml distilled water to the residue. The aqueous solution was basified by NaOH (5N) to pH 9-10, and then extracted with ether. The treatment of organic phase was the same as in the general procedure which affords methyl benzoate in high purity. The aqueous phase was acidified back to pH 2 with 5N HCl, extracted with ether (3× 20 ml), and then dried over $MgSO_4$. The dried ether phase was concentrated to afford a white solid. It was identified as benzoic acid (10% yield) by comparison of the GC retention time with that for the authentic compound, and further confirmed by mass spectrometry.

MS: m/e 122$[M]^+$, 105$[M-OH]^+$, 77$[C_6H_5]^+$.

Oxidation of ethyl benzyl ether ($C_6H_5CH_2OC_2H_5$)

Oxidation of ethyl benzyl ether afforded ethyl benzoate in 47% yield. This product was isolated following the work-up procedure described for the oxidation of methyl benzyl ether.

IR(neat): $\nu_{C=O}$ 1718 cm^{-1}, ν_{C-O} 1275 cm^{-1}.

MS: m/e 150$[M]^+$, 122$[M-CH_2{=}CH_2]^+$, 105$[C_6H_5CO]^+$, 77$[C_6H_5]^+$.

Benzoic acid was also obtained in 50% yield after work-up.

Oxidation of dibenzyl ether ($C_6H_5CH_2OCH_2C_6H_5$)

Oxidation of dibenzyl ether afforded benzyl benzoate in 13% yield. Benzoic acid was obtained as a major product in 85% yield.

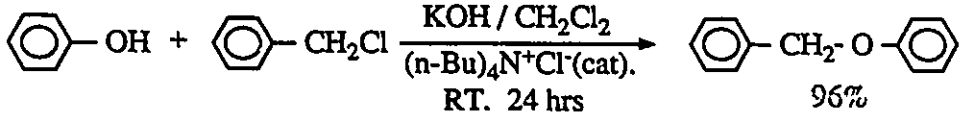
IR(neat): $\nu_{C=O}$ 1723 cm^{-1}, ν_{C-O} 1276 cm^{-1}.

^1H NMR($CDCl_3$): δ 5.17(s, 2H, -COOC<u>H</u>$_2$), 7.20(m, 8H, aromatic), 7.82(m, 2H, protons ortho to carbonyl).

MS: m/e 212$[M]^+$, 105$[C_6H_5CO]^+$, 91$[C_6H_5CH_2]^+$, 77$[C_6H_5]^+$.

Oxidation of phenyl benzyl ether ($C_6H_5CH_2OC_6H_5$)

a) Phenyl benzyl ether was prepared according to the reaction:



[3.38]

A mixture of phenol (1.41g, 15 mmol) and 5N KOH (15 ml) was stirred at room temperature for 30 minutes. A solution of benzyl chloride (1.58g, 12.5 mmol) and CH_2Cl_2 (15 ml) was then added dropwise to this mixture, followed by addition of $(n\text{-}Bu)_4N^+Cl$ (0.35g, 1.25 mmol). After stirring for 24 hours, the two phases were separated, and the organic phase was washed with distilled water (3 × 20 ml), and dried over $MgSO_4$. The dried organic phase was concentrated to give phenyl benzyl ether in 96% yield.

IR(neat): ν_{C-O} 1242 cm^{-1}.

^1H NMR($CDCl_3$): δ 4.90(s, 2H, CH_2), 7.00(m, 10H, 2Ph).

MS: m/e 184$[M]^+$, 91$[C_6H_5CH_2]^+$.

b) The oxidation of phenyl benzyl ether resulted in only 17% conversion after 42 hours at 90°C. Two major products were detected by GC. One of the products was identified as phenyl benzoate (7% GC yield) by comparison of GC retention times and mass spectrum with those of the authentic material.

MS: m/e 198$[M]^+$, 105$[C_6H_5CO]^+$, 77$[C_6H_5]^+$.

The other product (6% GC yield) was not characterized. The mass spectrum is consistent with the corresponding alcohol ($C_6H_5CH(OH)OC_6H_5$).

MS: m/e 200$[M]^+$, 107$[C_6H_5CHOH]^+$, 77$[C_6H_5]^+$.

Oxidation of dibutyl ether $(CH_3(CH_2)_3\text{-})_2\text{-O}$

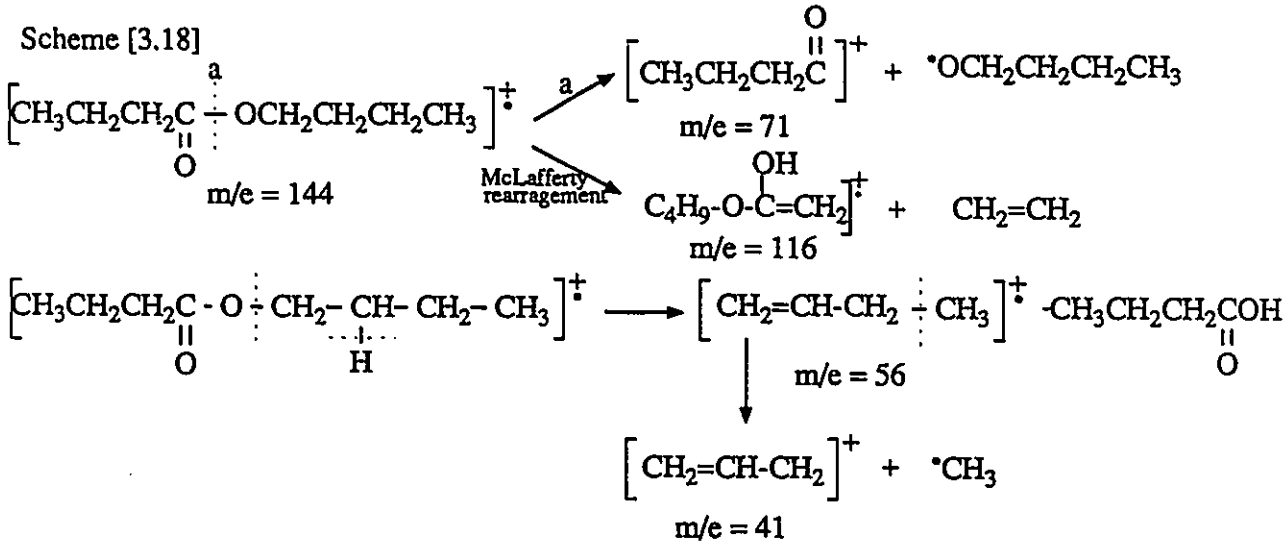
Oxidation of dibutyl ether was carried out in the absence of DME in order to avoid competition in oxidation of these two ethers. After 24 hours reaction at 80°C, 21% of the desired product, propyl butanoate, was detected by GC, as well as 7% of unknown product.

IR(neat): $\nu_{C=O}$ 1725 cm^{-1}, $\nu_{C\text{-}O}$ 1185 cm^{-1}.

MS: m/e 116$[M\text{-}CH_2{=}CH_2]^+$, 71$[CH_3CH_2CH_2CO]^+$,
56$[CH_2{=}CH\text{-}CH_2\text{-}CH_3]^+$, 41$[CH_2{=}CH\text{-}CH_2]^+$.

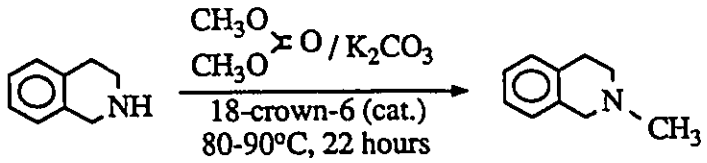
Although the molecular ion peak of propyl butanoate was not observed in the mass spectrum, the fragmentation was consistent with its structure (Scheme [3.18]).

Scheme [3.18]



Oxidation of N-methyl-1,2,3,4-tetrahydroisoquinoline

a) N-Methyl-1,2,3,4-tetrahydroisoquinoline was prepared according to the literature.[191] The reaction is presented below (eq. [3.39]).



[3.39]

IR(neat): $\nu(CH_3) = 1378cm^{-1}$, $\nu_{C-N} = 1100\ cm^{-1}$.

^1H NMR($CDCl_3$): δ 2.38(s, 3H, CH_3), 2.73(m, 4H, $C_6H_4C\underline{H_2}C\underline{H_2}N$), 3.49(s, 2H, $C_6H_4C\underline{H_2}N$), 6.92(m, 4H, ortho and meta protons).

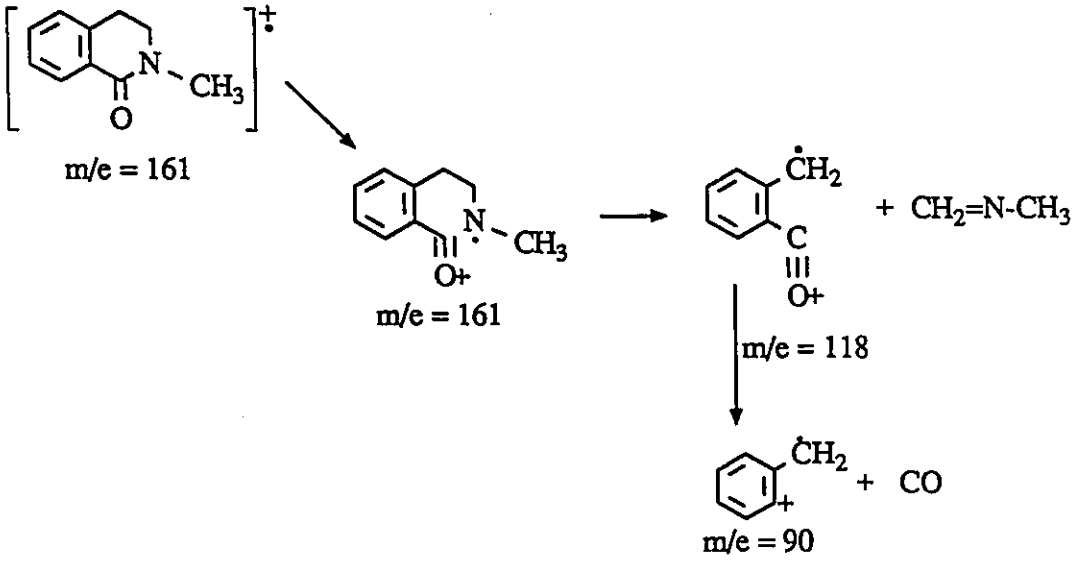
MS: m/e 147$[M]^+$, 104$[M\text{-}CH_2\text{=}N\text{-}CH_3]^+$.

b) Oxidation of N-methyl-1,2,3,4-tetrahydroisoquinoline (0.37g, 2.5 mmol) was catalyzed by anhydrous $CoCl_2$ (0.0017g, 0.0125 mmol) in the presence of DME (5 ml). Several products were observed after 36 hours at 80°C. 13% of the desired product, lactam, was detected by GC. Other by-products were unknown.

IR($CDCl_3$): $\nu_{C=O}$ 1660cm^{-1}

MS: m/e 161$[M]^+$, 118$[M\text{-}CH_2\text{=}N\text{-}CH_3]^+$, 90$[C_6H_4\text{-}CH_2]^+$.

Scheme [3.19]



Attempted oxidation of other cyclic ethers

2,3-Dihydrobenzofuran, tetrahydrothiophene and tetramethylene sulfone were not oxidized by this catalytic system. Oxidation of 2-methyltetrahydrofuran led to 65%

conversion after 48 hours at 60°C. However, many products were detected by GC, including the desired lactone, the latter not being isolable in pure form. When the oxidation of tetrahydropyran was carried out in this system, only 10% starting material was converted after 24 hours at 60°C. Six products were detected by GC.

3.3.3. VARIATION IN REACTION CONDITIONS

1. Synthesis of the 1-isochroman-d_2 (Scheme [3.12])

1,1-Dideuterated isochroman was prepared by reduction of the lactone.[192] The crude mixture was purified on TLC using 2:1 hexane/ether as the developer. 1-Isochroman-d_2 was isolated in only 8% yield.

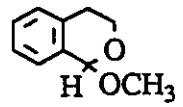
^{1}H NMR($CDCl_3$): δ 2.86(t, 2H, $C_6H_4C\underline{H_2}CH_2O$), 3.75(t, 2H, $C_6H_4CH_2C\underline{H_2}O$), 7.06(m, 4H, aromatic).

MS: m/e 136$[M]^+$, 106$[M-CH_2O]$.

The lactone used here was prepared according to the general procedure for the oxidation of isochroman.

2. Oxidation of isochroman in the presence of 2,2-dimethoxypropane (DMP) (eq. [3.33])

A mixture of 2,2-dimethoxypropane (0.52g, 5 mmol) and anhydrous $CoCl_2$ (0.033g, 0.025 mmol) in DME (10 ml) was stirred under O_2 at 80°C. Isochroman (0.335g, 2.5 mmol) was added dropwise to this mixture, and stirring was then continued for 2.5 hours. The work-up was the same as in the general procedure (by TLC using 1:2 ether/hexane) giving 0.17g (41% yield) of acetal, and 0.17g (46% yield) of the lactone.

Acetal 

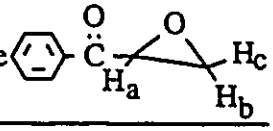
IR(neat): ν_{C-O} 1034 cm^{-1}, 1050 cm^{-1}, 1075 cm^{-1}, 1095 cm^{-1}.
note: acetals often give four or five strong bands, respectively, in the region from 1200 to 1020 cm^{-1}[193].

^1H NMR($CDCl_3$): δ 2.80(m, 2H, $C_6H_4C\underline{H}_2$), 3.48(s, 3H, OCH_3), 3.95(m, 2H, $C_6H_4CH_2C\underline{H}_2O$-), 5.33(s, 1H, $C_6H_4C\underline{H}(OCH_3)O$-), 7.05(m, 4H, aromatic).

MS: m/e 164$[M]^+$, 163$[M-H]^+$, 133$[M-OCH_3]^+$.

3. Oxidation of allylic benzenes

a) A mixture of allylbenzene (0.30g, 2.5mmol) and anhydrous $CoCl_2$ (0.0033g, 0.025mmol) in DME (10ml) was stirred under O_2 at 80°C for 18 hours, affording an epoxy ketone in 14% yield by TLC using 1:1 hexane/ethyl acetate as the developer. In addition, benzoic acid was also isolated in 47% yield.

Epoxide ketone 

IR($CDCl_3$): $\nu_{C=O}$ 1695cm^{-1}, ν_{C-O} 1250, 1234cm^{-1}.

^1H NMR($CDCl_3$): δ 2.96(dd, J=5; 2Hz, H_c), 3.11(dd, J=5; 4Hz, H_b), 4.22(dd, J=4; 2Hz, H_a), 7.49(m, 2H, meta protons), 7.61(m, 1H, para proton), 8.03(d, 2H, ortho protons).

MS: m/e 148$[M]^+$, 105$[PhCO]^+$, 77$[C_6H_5]^+$.

b) A mixture of 1-phenyl-2-butene (0.66g, 5 mmol) and anhydrous $CoCl_2$ (0.066g, 0.5 mmol) in DME (15 ml) was stirred under an atmosphere of oxygen for 21 hours at 80°C.

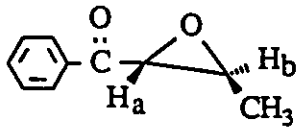
trans-4-Phenyl-3-buten-2-one and a epoxide ketone were isolated in 27% and 20% yield, respectively, by TLC using 4:1 hexane/ethyl acetate as the developer. Benzoic acid was also isolated in 44% yield from the aqueous phase.

trans-4-Phenyl-3-buten-2-one ($ArCH=CHCOCH_3$)

IR($CDCl_3$): $\nu_{C=O}$ 1672 cm^{-1}.

^1H NMR($CDCl_3$): δ 2.35(s, 3H, $COCH_3$), 6.69(d, 2H, J=16Hz $C_6H_5CH=CHCOCH_3$), 7.30(m, 6H, olefinic proton next to phenyl and Ph).

MS: m/e 146$[M]^+$, 131$[M-CH_3]^+$, 103$[M-COCH_3]^+$.

Epoxide ketone 

IR($CDCl_3$): $\nu_{C=O}$ 1692cm^{-1}, ν_{C-O} 1262, 1234cm^{-1}.

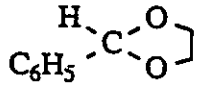
^1H NMR($CDCl_3$): δ 1.48(d, 3H, CH_3), 3.17(m, 1H, Hb), 3.94(d, 1H, J=2Hz, Ha), 7.45(m, 3H, meta and para protons), 7.98(d, 2H, J=8Hz, ortho protons).

MS: m/e 162$[M]^+$, 147$[M-CH_3]^+$, 105$[PhCO]^+$, 77$[C_6H_5]^+$.

3.3.4. SYNTHESIS OF VARIOUS 2-SUBSTITUTED-1,3-DIOXOLANES

General procedure (eq. [3.36])

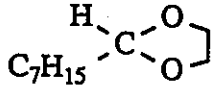
To a 250 ml three-necked round bottom flask, which was fitted with a Dean-Stark trap, was placed 0.5-1.0 mmol of p-toluenesulfonic acid, ethylene glycol (24-40 mmol), aldehyde (20 mmol) and benzene (100 ml). This mixture was stirred for 4-21 hours at reflux temperature (0.36-0.40 ml of water usually was collected from the Dean-Stark trap at the end of reaction). The following work-up of the reaction was used in all cases: The mixture was cooled to room temperature and washed with saturated sodium carbonate solution (2 × 20 ml), followed by saturated sodium chloride solution (1 × 20 ml), and then with water (20 ml) before being dried over $MgSO_4$. The dried mixture was concentrated under rotary evaporation and purified by column chromatography on silica gel. The pure products were identified by IR, ^1H NMR and mass spectrometry.

Synthesis of 

A mixture of p-toluenesulfonic acid (0.095g, 0.5 mmol), ethylene glycol (2.48g, 40 mmol), benzaldehyde (2.12g, 20 mmol) and benzene was stirred under reflux for 5 hours. Purification by column chromatography using 3:1 hexane/ethyl acetate as the eluant gave 2.7g (18 mmol, 90% yield) of the desired acetal.

^1H NMR($CDCl_3$): δ 4.17(m, 4H, -OCH_2CH_2O-), 5.94(s, 1H, C_6H_5CH-), 7.50(m, 5H, Ph).

MS: m/e 150$[M]^+$, 149$[M-H]^+$.

Synthesis of 

A mixture of p-toluenesulfonic acid (0.19g, 1.0 mmol), ethylene glycol (2.48g, 40

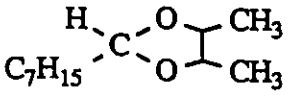
mmol), 1-octanal (2.56g, 20 mmol) and benzene was stirred under reflux for 15 hours. Standard work-up gave pure acetal (3.42g, 19.8 mmol) in 99% yield.

IR(neat): $\nu_{C\text{-}O}$ 1125 cm^{-1}, 1145 cm^{-1}.

^1H NMR($CDCl_3$): δ 0.83(t, 3H, $C\underline{H}_3CH_2CH_2$), 1.32(m, 10H, $(CH_2)_5$), 1.60(q, 2H, $C\underline{H}_2$-CH), 3.86(m, 4H, -OCH_2CH_2O-), 4.80(t, 1H, $CH_2C\underline{H}$-(O)(O)).

MS: m/e 172$[M]^+$, 171$[M\text{-}H]^+$, 73$[M\text{-}C_7H_{15}]^+$.

Synthesis of



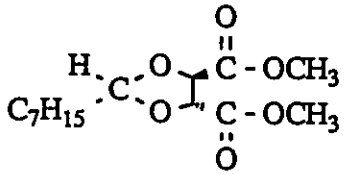
A mixture of p-toluenesulfonic acid (0.19g, 1.0 mmol), 2,3-butanediol (2.7g, 30 mmol), 1-octanal (2.56g, 20 mmol) and benzene was stirred under reflux for 7 hours. The acetal was isolated by column chromatography using 3:1 hexane/ethyl acetate as the eluant, affording the acetal (3.15g, 15.8mmol) in 79% yield.

IR(neat): $\nu_{C\text{-}O}$ 1082 cm^{-1}, 1120 cm^{-1}, 1150 cm^{-1}.

^1H NMR($CDCl_3$): δ 0.83(t, 3H, $C\underline{H}_3CH_2$), 1.26(m, 16H, $(CH_2)_5$, $2CH_3$), 1.58(q, 2H, $C\underline{H}_2$-CH), 3.56(m, 2H, -$OC\underline{H}(CH_3)C\underline{H}(CH_3)O$-), 4.99(t, 1H, $CH_2C\underline{H}$(O)(O)).

MS: m/e 200$[M]^+$, 199$[M\text{-}H]^+$, 101$[M\text{-}C_7H_{15}]^+$.

Synthesis of



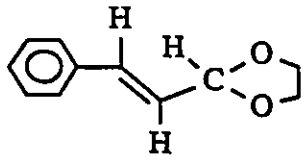
A mixture of p-toluenesulfonic acid (0.19g, 1.0 mmol), L(+) tartaric acid dimethyl ester (4.3g, 24 mmol), 1-octanal (2.56g, 20 mmol) and benzene was stirred under reflux for 21 hours. Purification by column chromatography using 10:1 hexane/ethyl acetate as

the eluant gave the acetal in 61% yield.

IR(neat): $\nu_{C=O}$ 1750 cm^{-1}(broad), ν_{C-O} 1220, 1149, 1120, 1090cm^{-1}.

^1H NMR($CDCl_3$): δ 0.83(t, 3H, $C\underline{H}_3CH_2$), 1.27(m, 10H, $(CH_2)_5$), 1.72(q, 2H, $\underline{CH}_2$-CH-), 3.76(s, 6H, $2OC\underline{H}_3$), 4.65(d, 1H, -OC<u>H</u>CHO-), 4.73(d, 1H, -OCHC<u>H</u>O-), 5.17(t, 1H, $CH_2\underline{CH}$(O)(O)).

MS: m/e 287$[M-H]^+$, 189$[M-C_7H_{15}]^+$.

Synthesis of 

A mixture of p-toluenesulfonic acid (0.19g, 1.0 mmol), ethylene glycol (1.86g, 30 mmol), trans-cinnamaldehyde (2.64g, 20 mmol) and benzene was stirred under reflux for 4 hours. Work-up by column chromatography using 4:1 hexane/ethyl acetate as the eluant gave 3.01g (17.1 mmol) of acetal in 86% yield.

^1H NMR($CDCl_3$): δ 4.00(m, 4H, -OCH_2CH_2O-), 5.41(d, 1H, J=5Hz, C<u>H</u>(O)(O)), 6.14(q, 1H, J=14Hz CH=C<u>H</u>-CH(O)(O)), 6.76(d, 1H, $C_6H_5C\underline{H}$=CH), 7.34(m, 5H, Ph).

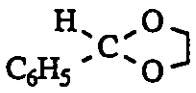
^{13}C NMR($CDCl_3$): δ 64.95(CH_2CH_2), 87.90(CH), 104.00(C_6H_5CH=C<u>H</u>-), 125.14($C_6H_5C\underline{H}$=CH-). 126.97, 128.39, 128.61, 134.97 (aromatic carbons).

MS: m/e 176$[M]^+$, 175$[M-H]^+$, 104$[C_6H_5CHCH_2]^+$, 103$[C_6H_5CH=CH]^+$

3.3.5. OXIDATION OF 2-SUBSTITUTED 1,3-DIOXOLANES

General procedure

A mixture of anhydrous $CoCl_2$ (0.027g, 0.2 mmol) and $ZnCl_2$ (0.068g, 0.5 mmol) in DME (15 ml) was stirred under an oxygen atmosphere at 85-90°C for several minutes. The 2-substituted 1,3-dioxolane (5 mmol) was then added, and stirring was continued until conversion of the substrate was almost completed (GC determination). The following work-up was used in all cases: The reaction mixture was cooled to room temperature, filtered through a small silica column to remove the pink precipitate, and the filtrate was concentrated by rotary evaporation. To the residue was added 20 ml distilled water, and the solution was basified with dilute NaOH(5N) solution. This solution was then extracted with ether (3 × 20 ml). The organic phase was washed with distilled water (50 ml), and dried ($MgSO_4$). The dried organic phase was concentrated and afforded an oily crude product which was purified by thin layer chromatography. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ether (3 × 20 ml). Drying and concentration of this ethereal extract yielded a white solid product. The white solid was purified by recrystallization. Pure products were characterized by IR, ^1H and ^{13}C NMR as well as by mass spectrometry. The results are listed in Table [3.10]. Products (I) and (II) generally refer to the corresponding formate esters and acids, respectively.

Oxidation of 

Oxidation of benzaldehyde ethylene acetal afforded (I) and (II) in 70% and 82% yield, respectively (purification of the formate ester (I) by TLC using 4:1 hexane/ethyl acetate).

(I) $C_6H_5COOCH_2CH_2OCHO$

IR: $\nu_{C=O}$ 1735, 1720cm^{-1}, ν_{C-O} 1282, 1170cm^{-1}.

^{1}H NMR($CDCl_3$): δ 3.95(t, 2H, -$CH_2\underline{CH_2}OCHO$), 4.45(t, 2H, $PhCOO\underline{CH_2}CH_2$-), 7.48(m, 3H, meta and ortho protons), 8.04(m, 2H, ortho protons), 8.10(s, 1H, -O$\underline{CH}$O).

MS: m/e 194$[M]^+$, 105$[C_6H_5CO]^+$, 77$[C_6H_5]^+$.

(II) C_6H_5COOH

The GC retention time of benzoic acid was compared with its authentic material, and confirmed by mass spectrometry: m/e 122$[M]^+$, 105$[C_6H_5CO]^+$, 77$[M\text{-}COOH]^+$.

Three other by-products were also isolated. They were identified as the following:

$C_6H_5COOCH_2CH_2OH$ (1% yield)

IR($CDCl_3$): ν_{OH} 3440 cm^{-1}, $\nu_{C=O}$ 1720 cm^{-1}, $\nu_{C\text{-}O}$ 1280, 1122 cm^{-1}.

^{1}H NMR($CDCl_3$): δ 2.40(s, 1H, O$\underline{H}$), 3.92(t, 2H, C$\underline{H_2}$OH), 4.43(t, 2H, COOC$\underline{H_2}$), 7.43(m, 2H, meta protons), 7.52(m, 1H, para proton), 8.03(m, 2H, ortho protons).

^{13}C NMR($CDCl_3$): δ 61.19 (-$\underline{C}H_2$OH), 66.53(COO$\underline{C}H_2$-), 128.43, 129.70, 129.84, 133.22, (aromatic carbons), 167.09(-$\underline{C}$OO-).

MS: m/e 148$[M\text{-}H_2O]^+$, 105$[C_6H_5CO]^+$, 77$[C_6H_5]^+$.

$C_6H_5COOCH_2CH_2OCH_3$ (1.5% yield)

IR($CDCl_3$): $\nu_{C=O}$ 1718 cm^{-1}, $\nu_{C\text{-}O}$ 1276 cm^{-1}, 1115 cm^{-1}.

^{1}H NMR($CDCl_3$): δ 3.42(s, 3H, OC$\underline{H_3}$), 3.72(t, 2H, C$\underline{H_2}$OCH$_3$), 4.46(t, 2H, COOC$\underline{H_2}$), 7.42(m, 2H, meta protons), 7.53(m, 1H, para proton), 8.05(m, 2H, ortho protons).

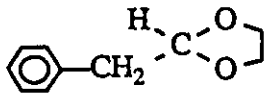
MS: m/e 105$[C_6H_5CO]^+$, 77$[C_6H_5]^+$.

$(C_6H_5COOCH_2CH_2\text{-}O)_2$ (6.5% yield)

IR($CDCl_3$): $\nu_{C=O}$ 1721 cm^{-1}, $\nu_{C\text{-}O}$ 1278, 1116 cm^{-1}.

^{1}H NMR($CDCl_3$): δ 3.80(t, 4H, $2CH_2\underline{CH_2}O$-), 4.56(t, 4H, $2COO\underline{CH_2}$-), 7.44(m, 4H, meta protons), 7.56(m, 2H, para protons), 8.05(m, 4H, ortho protons).

MS: m/e 122$[C_6H_5COOH]^+$, 105$[C_6H_5CO]^+$, 77$[C_6H_5]^+$.

Oxidation of 

Oxidation of phenylacetaldehyde ethylene acetal afforded (I) and (II) in 86% and 91% yield, respectively. The formate ester (I) was purified by TLC using 1:6 ether/benzene as the developer.

(I) $C_6H_5CH_2COOCH_2CH_2OCHO$

IR(neat): $\nu_{C=O}$ 1730, 1738 cm^{-1}, ν_{C-O} 1255, 1165 cm^{-1}.

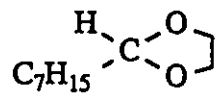
^{1}H NMR($CDCl_3$): δ 3.64(s, 2H, $C_6H_5\underline{CH_2}CO$-), 4.34(d, 4H, $COO\underline{CH_2}\underline{CH_2}O$), 7.29(m, 5H, Ph), 8.02(s, 1H, -O$\underline{C}$HO).

^{13}C NMR($CDCl_3$): δ 40.88($C_6H_5\underline{C}H_2$), 61.33, 62.05($COO\underline{C}H_2$, $\underline{C}H_2OCHO$), 127.23, 128.63, 129.29, 133.80 (aromatic carbons), 160.67(O$\underline{C}$HO), 171.50($ArCH_2\underline{C}OO$-).

MS: 208$[M]^+$, 162$[M\text{-}HCOOH]^+$, 119$[C_6H_5CH_2CO]^+$, 91$[C_6H_5CH_2]^+$.

(II) $C_6H_5CH_2COOH$

Phenylacetic acid was identified by comparing GC retention times and spectral data with those for the authentic compound.

Oxidation of 

Oxidation of 1-octanal ethylene acetal afforded (I) and (II) in 80% and 89% yield, respectively.

(I) $C_7H_{15}COOCH_2CH_2OCHO$

IR(neat): $\nu_{C=O}$ 1735 cm^{-1}, ν_{C-O} 1160 cm^{-1}, 1114 cm^{-1}.

^1H NMR($CDCl_3$): δ 0.84 (t, 3H, $C\underline{H}_3CH_2$-), 1.25(m, 8H, (-CH_2-)$_4$), 1.58(m, 2H, -$C\underline{H}_2CH_2COO$-), 2.30(t, 2H, -$CH_2C\underline{H}_2COO$-), 4.32(m, 4H, -$COOC\underline{H}_2C\underline{H}_2OCHO$), 8.05(s, 1H, -$OC\underline{H}O$).

^{13}C NMR($CDCl_3$): δ [13.82, 22.36, 24.62, 28.68, 28.83, 31.43, 33.87 ($\underline{C}_7H_{15}$)], [61.47, 61.53, ($COOC\underline{H}_2C\underline{H}_2OCHO$)], 160.70(O-$\underline{C}HO$), 173.7($C_7H_{15}\underline{C}OO$-).

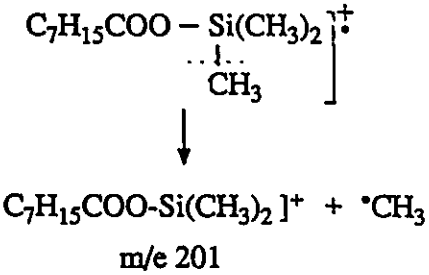
MS: m/e 127$[C_7H_{15}CO]^+$, 73$[CH_2CH_2OCHO]^+$.

(II) $C_7H_{15}COOH$

IR(neat): ν_{COO-H} 3500-2500 cm^{-1}, $\nu_{C=O}$ 1713 cm^{-1}, ν_{C-O} 1208 cm^{-1}.

MS: m/e 144$[M]^+$, 60$[CH_2=C(OH)_2]^+$, McLafferty rearrangement].

MS of trimethylsilylated derivative: m/e 201



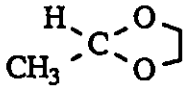
The intermediate glycol ester ($C_7H_{15}COOCH_2CH_2OH$) was isolated in 3% yield.

IR($CDCl_3$): ν_{OH} 3452 cm^{-1}, $\nu_{C=O}$ 1740 cm^{-1}, ν_{C-O} 1172, 1085 cm^{-1}.

^1H NMR($CDCl_3$): δ 0.84(t, 3H, -$CH_2C\underline{H}_3$), 1.25 (m, 8H, -(CH_2)$_4$-), 1.58(m, 2H, -$C\underline{H}_2CH_2COO$-), 2.11(s, 1H, -$O\underline{H}$), 2.30(t, 2H, -$CH_2C\underline{H}_2COO$-), 3.76(t, 2H, $COOCH_2C\underline{H}_2OH$), 4.16(t, 2H, -$COOC\underline{H}_2CH_2OH$).

^{13}C NMR($CDCl_3$): δ 13.81, 22.36, 24.68, 28.69, 28.86, 31.43, 33.98($\underline{C}_7H_{15}$), 61.14(-$\underline{C}H_2OH$), 65.77(-COO$\underline{C}H_2$), 174.43($\underline{C}OO$).

MS: m/e 84[CH_2=CH-$CH_2CH_2CH_2CH_3$]$^+$.

Oxidation of 

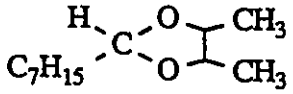
Oxidation of 2-methyl-1,3-dioxolane afforded (I) in 79% yield. The yield of product (II), acetic acid, could not be accurately determined due to the losses incurred during work-up. (I) was purified by TLC using 1:1 hexane/ether as the developer.

(I) $\underline{CH_3COOCH_2CH_2OCHO}$

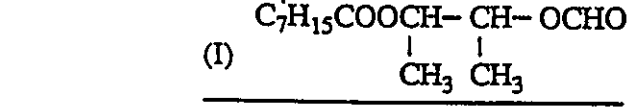
IR(neat): $\nu_{C=O}$ 1730, 1740 cm^{-1}, ν_{C-O} 1240, 1178 cm^{-1}.

^1H NMR($CDCl_3$): δ 2.06(s, 3H, -COC$\underline{H}_3$), 4.26(m, 2H, C$\underline{H}_2$OCHO), 4.34(m, 2H, CH_3COOC$\underline{H}_2$), 8.02(s, 1H, OC$\underline{H}$O).

MS: m/e 86[CH_2=CH-O-$COCH_3$]$^{\cdot+}$, 73[$HCOOCH_2CH_2$]$^+$, 43[CH_3CO]$^+$.

Oxidation of 

Oxidation of this substrate afforded (I) and (II) in 38% and 42% yield, respectively. The products were obtained by TLC using 6:1 hexane/ethyl acetate as the developer.

(I) 

IR($CDCl_3$): $\nu_{C=O}$ 1735, 1728 cm^{-1}, ν_{C-O} 1175, 1110 cm^{-1}.

^1H NMR($CDCl_3$): δ 0.83(t, 3H, $CH_2C\underline{H}_3$), 1.21(m, 14H, $(CH_2)_4$, 2C$\underline{H}_3$),

1.58(m, 2H, -C<u>H</u>$_2$CH$_2$COO-), 2.28(t, 2H, -CH$_2$C<u>H</u>$_2$COO-), 5.03(m, 2H, C<u>H</u>(CH$_3$)C<u>H</u>(CH$_3$)), 8.05(s, 1H, OC<u>H</u>O).

^{13}C NMR($CDCl_3$): δ [13.6, 21.2, 24.9, 28.5, 28.8, 31.5, 34.3, (C_7H_{15})], 15.8(2C<u>H</u>$_3$), 70.8, 71.3[C_7H_{15}COOC<u>H</u>(CH$_3$) and C<u>H</u>(CH$_3$)OCHO], 160.3(-OC<u>H</u>O), 173.1(C_7H_{15}C<u>O</u>OCH(CH$_3$)).

MS: 127[$C_7H_{15}CO$]$^+$.

(I). $C_7H_{15}COOH$

The GC retention time of this product was compared with pure octanoic acid. The structure was also supported by mass spectrometry: (m/e) 144[M]$^+$, 60[CH_2=C(OH)$_2$]$^+$.

The β-hydroxy ester [$C_7H_{15}COOCH(CH_3)CH(CH_3)OH$] was also isolated in 34% yield.

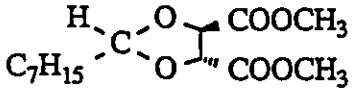
IR($CDCl_3$): ν_{OH} 3465 cm^{-1}, $\nu_{C=O}$ 1728 cm^{-1}, ν_{C-O} 1170, 1105 cm^{-1}.

^{1}H NMR($CDCl_3$): δ 0.83 (t, 3H, -CH$_2$C<u>H</u>$_3$), 1.13(m, 14H, (-CH$_2$-)$_4$, 2-CH$_3$), 1.56(m, 2H, C_5H_{11}C<u>H</u>$_2$CH$_2$COO-), 2.28(t, 2H, C_6H_{13}C<u>H</u>$_2$COO-), 2.26(s, 1H, O<u>H</u>), 3.69(m, 1H, -C<u>H</u>(CH$_3$)OH), 4.70(m, 1H, C_7H_{15}COOC<u>H</u>(CH$_3$)).

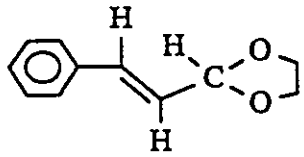
^{13}C NMR($CDCl_3$): δ [13.85, 22.45, 24.95, 28.86, 29.16, 31.46, 34.38 (C_7H_{15})], [16.05, 18.90, (2CH$_3$)], 69.97(C<u>H</u>(CH$_3$)OH), 75.54(C_7H_{15}COOC<u>H</u>(CH$_3$)). 173.89(C_7H_{15}C<u>O</u>O-)

MS: m/e 127[$C_7H_{15}CO$]$^+$.

Oxidation of



No oxidation occurred after 48 hours at 85-90°C.

Oxidation of 

Oxidation of trans-cinnamaldehyde ethylene acetal for 24 hours at 90°C gave benzoic acid in 92% yield after 24 hours at 90°C. When the reaction was stopped after 4 hours, benzaldehyde was isolated as a major product in 64% yield, along with small amounts of benzoic acid. Benzoic acid and benzaldehyde were characterized by comparison of GC retention times with those for authentic materials, and confirmed by IR and/or mass spectrometry.

C_6H_5COOH

IR($CDCl_3$): ν_{COO-H} 3400-2500 cm^{-1}, $\nu_{C=O}$ 1695 cm^{-1}, ν_{C-O} 1290 cm^{-1}.

MS: m/e 122$[M]^+$, 105$[M-OH]^+$, 77[M-COOH].

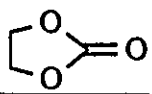
C_6H_5CHO

MS: m/e 106$[M]^+$, 105$[M-H]^+$, 77$[C_6H_5]^+$.

3.3.6. VARIATION IN REACTION CONDITIONS

1. Oxidation of 1,3-dioxolane (eq. [3.34])

A mixture of 1,3-dioxolane (7.4g, 100 mmol) and anhydrous $CoCl_2$ (0.066g, 0.5 mmol) in DME (5 ml) was stirred at 60°C for 24 hours. Work-up according to the general procedure (purification on colum chromatography using 4:1 ether/hexane as eluant) gave ethylene carbonate and glycol formate in 10% and 61% yield, respectively.

Ethylene carbonate 

IR($CDCl_3$): $\nu_{C=O}$ 1800 cm^{-1}, ν_{C-O} 1280, 1118 cm^{-1}.

MS: m/e 88$[M]^+$, 43$[COOH]^+$.

Glycol formate ($HCOOCH_2CH_2OH$)

IR(neat): ν_{OH} 3400 cm^{-1}, $\nu_{C=O}$ 1720 cm^{-1}, ν_{C-O} 1180, 1078 cm^{-1}.

^1H NMR($CDCl_3$): δ 3.42(s, 1H, O<u>H</u>), 3.84(m, 2H, C<u>H</u>$_2$OH), 4.33(m, 2H, HCOOC<u>H</u>$_2$), 8.14(s, 1H, <u>H</u>COO).

^{13}C NMR($CDCl_3$): δ 60.77(<u>C</u>H_2OH), 65.44(HCOO<u>C</u>H_2), 161.05(H<u>C</u>OO-).

MS(CI): m/e 91$[M+1]^+$.

2. When the oxidation of phenylacetaldehyde ethylene acetal was carried out for 27 hours according to the general procedure (except in the absence of $ZnCl_2$), glycol ester was isolated in 17% yield.

Glycol ester ($C_6H_5CH_2COOCH_2CH_2OH$)

IR($CDCl_3$): ν_{OH} 3440 cm^{-1}, $\nu_{C=O}$ 1735 cm^{-1}, ν_{C-O} 1161, 1080 cm^{-1}.

^1H NMR($CDCl_3$): δ 2.48(s, 1H, OH), 3.65(s, 2H, C_6H_5C<u>H</u>$_2$-), 3.77(t, 2H, -C<u>H</u>$_2$OH), 4.20(t, 2H, -COOC<u>H</u>$_2$-), 7.28(m, 5H, C_6<u>H</u>$_5$).

Mass Spec.: m/e 180$[M]^+$, 162$[M-H_2O]^+$, 118$[C_6H_5CHCO]^+$.

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Claims to Original Research

1. Oxidation using anhydrous $CoCl_2$, $CoCl_2/CrCl_3$, or $CoCl_2/ZrCl_4$ as the catalysts in a polar aprotic solvent (diglyme) under an atmosphere of oxygen for the selective conversion of substituted toluenes to the corresponding aldehydes.
2. Selective oxidation of a benzylic methylene group to form a carbonyl function induced by catalytic amounts anhydrous $CoCl_2$ catalyst in a mixed solvent of diglyme and methyl ethyl ketone (1:3) under O_2.
3. Oxidation of cyclic and acyclic ethers to the corresponding esters and lactones catalyzed by anhydrous $CoCl_2$ in DME under an atmosphere of oxygen.
4. Oxidation and esterification of 2-substituted 1,3-dioxolanes to formate esters and acids catalyzed by a mixture of anhydrous $CoCl_2$ and $ZnCl_2$ in DME.
5. Cobalt induced formation of a epoxy ketone and acid from the oxidation of allyl benzenes.