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STRATEGIES FOR THE IMPROVEMENT OF THE INDUSTRIAL OXIDATION OF CYMENE

by

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CONTENTS

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CONTENTS

SUMMARY

CHAPTER 1 INTRODUCTION

CHAPTER 2 PRODUCTION OF CRESOL VIA CYMENE HYDROPEROXIDE

CHAPTER 3 EXPERIMENTAL

CHAPTER 4 METHOD EVALUATION FOR ANALYSIS OF HYDROPEROXIDES

CHAPTER 5 THE CATALYTIC AIR OXIDATION OF *P*-CYMENE

CHAPTER 6 SUMMARY AND CONCLUDING REMARKS

REFERENCES

APPENDIX A : List of tables

APPENDIX B : List of figures

APPENDIX C : List of schemes

SUMMARY

The oxidation of cymene with dioxygen has been investigated in some detail with the view of establishing the feasibility of improving the efficiency of the oxidation process. Of particular interest were the rate of cymene oxidation and the selectivity of the oxidation process for the tertiary cymene hydroperoxide, especially at conversions above 15%.

In order to be able to evaluate the selectivity of oxidation processes, a reliable method for analysis of the individual hydroperoxides had to be established. Two methods were investigated, namely reduction of the hydroperoxides to alcohols using ferrous sulphate and reduction using triphenylphosphine, and analysing the reduction products by gas chromatography. Of these two methods, the triphenylphosphine method proved to be superior to the ferrous sulphate method and was used as the method of choice for this investigation.

A number of oxidation systems were evaluated in an initial screening experiment for the oxidation of *p*-cymene. The results of this screening experiment showed that three-phase oxidation systems, *i.e.* systems containing an organic phase, an aqueous phase and gas, gave significantly lower activities than two-phase oxidation systems. In addition, the use of a base in the aqueous layer does not improve the overall selectivity of the oxidation process, but improves the selectivity towards the tertiary hydroperoxide to some extent due to the decomposition and extraction of primary hydroperoxide into the basic aqueous phase. Oxidation systems using a non-autoxidation catalyst, *i.e.* a catalyst that does not catalyse the conventional autoxidation of organic compounds, gave by far the most promising results. These systems gave both a high selectivity as well as high reaction rate.

From the initial screening experiment, and using multi-factorial statistical techniques, two catalyst systems were selected for investigation, namely vanadium phosphate and boron phosphate. The results of these investigations showed that these two catalysts are remarkably active and selective for the oxidation of *p*-cymene, giving the cymene tertiary hydroperoxide in selectivities exceeding 85% and at substrate conversions as high as 25%. These results are a considerable improvement over currently known oxidation systems and may offer opportunities for further commercial exploitation.

CHAPTER 1

INTRODUCTION

1.1 GENERAL

The widespread commercial application of organic chemistry is generally considered to have started in the late 1850's, with the development of the synthetic dyestuffs industry. During the following 30 to 40 years the preparation of synthetic dyestuffs and the intermediates required for their manufacture became a major industry, and a number of other organic chemical products became commercially important. By 1900, the organic chemical industry was well established.[1]

During the twentieth century the industrial application of chemistry has developed rapidly, and chemistry has an all-pervading effect on our lives. The chemical industry is of major importance in all developed countries; in the UK, for example, its output is about 9% of total manufacturing industrial output,[1] while in the RSA this figure is close to 20%.[2] The products of the chemical industry make a major contribution to the present-day standards of living, and life as we know it today would be impossible without these products. Some of the more obvious examples of materials, which make life more pleasant and convenient for us are plastics, synthetic fibres, pharmaceuticals and dyes, but the products of the chemical industry cover a much wider range than this. It is, in fact, difficult to think of many consumer goods in modern society in the manufacture of which products of the chemical industry has played no part.

Competition for profit in the chemical process industry contributed to the development and manufacture of new and improved products. With the established companies developing new product lines, and new companies being created with new and /or improved technologies, cheaper and more efficient synthetic routes to established products needs to be developed for continuing economic viability. Consequently, the need exists for shorter, simpler and cheaper synthetic routes with improved selectivities and yields in order for the producers of bulk, commodity, speciality and fine chemicals to remain competitive and viable in an ever changing environment.[3]

1.2 A BRIEF HISTORY OF THE SOUTH AFRICAN (ORGANIC) CHEMICAL INDUSTRY[4,5,6]

The South African chemical industry has a relatively long history. Its origins may be traced back as far as 1896 when the first industrial manufacture of explosives (nitroglycerine) for the mining industry (diamonds and gold) was started. During the next fifty years, the industry grew from an almost entirely explosives industry to an industry producing both inorganic and organic chemicals. Inorganic chemicals included fertilizers, inorganic acids and a wide variety of mining chemicals. Apart from explosives, other organic chemicals of interest were ethanol that was obtained from the fermentation of molasses, and petrol from the distillation of torbanite shales.

Since South Africa has no oil reserves and little natural gas, the development of an organic chemicals industry was based primarily around the gasification of coal. Although negotiations aimed at the production of oil and petrol from South African coal was started in the early 1930's, it was only in 1950 that the Government-sponsored South African Coal, Oil and Gas Corporation Ltd. (acronym SASOL after the initial name, South African Synthetic Oil, Limited), was established. The initial activity of the new company focussed on the production of fuel and oil from coal, but as the supply of fuel increased, it was inevitable that a shift to the production of other chemicals, first from the by-products of the Fischer-Tropsch process, should occur. With increasing international political isolation during the three decades following the construction of the first Sasol plant, much emphasis was placed on the development of an organic chemical industry based on local raw materials derived from the oil-from-coal process. Since its establishment, SASOL has strived towards the continuous advancements of the Fischer-Tropsch process, firstly through the Synthol process and later the Sasol Advanced Synthol process. By the mid 1990's, SASOL had become South Africa's largest chemical company.

The primary organic products obtained from the Sasol Advanced Synthol process are almost exclusively aliphatic and include olefins (ethylene, propylene, 1-pentene, 1-hexene, 1-octene) and oxygenates (alcohols, ketones and carboxylic acids). Only small quantities of aromatic compounds such as phenols, cresols and xylenols are obtained as by-products of the gasification process.

1.2.1. Current Trends[7,8]

A number of issues may be identified that impacts directly on the South African chemical process industry, including government economic policies, changing labour legislation, and changing environmental standards. Although the first two are largely a South African issue, the third is a global issue. Trading partners expect their counterparts to comply with international standards that they themselves have to comply with.

Responsible Care,[9] which was initiated in Canada in 1984 and which is currently being supported by 120 South African companies, forms the backbone of the local industry's commitment to international environmental conduct. Responsible Care represents a public commitment to continuous improvement in the areas of health, safety and environment. It encompasses responsible management, but also a commitment to a cultural change, allowing the world to question and challenge common practices. These commitments have a direct influence on both the products produced by the industry, as well as the technologies used to produce them. The days are gone when economic considerations alone determined the success or otherwise of chemical production practises. Environmental considerations today may have an even larger influence on the success of chemical products and/or production processes.

Although the promotion of growth in the chemical process and related industries has been a high priority of government and industry leaders for a very long time, the rather sudden exposure of the SACPI to very competitive international chemical markets during the early 1990's called upon the entire industry to reflect on their available options. The SASOL-AECI joint venture, Polifin (1993), aimed at the production of monomers, polymers, chlor-alkali products, cyanide and peroxides, was one of the first results of the changing market conditions.

A number of factors, including a prolonged drought, high interest rates, increased international competition together with fluctuating market conditions and the devaluation of the Rand, resulted in financial difficulties for Sentrachem, one of the top three chemical companies in South Africa. During 1997, USA-based Dow Chemical Company acquired control of the financially struggling Sentrachem group. Since this take-over, Sentrachem's operations have seen major restructuring with the closing down of non-profitable production facilities and a subsequent loss in job opportunities. R&D activities into new production processes/businesses have also been halted and imports are rapidly replacing locally produced products.

Other international companies that are currently operating in South Africa, be it in manufacturing or sales, include Hoechst, Bayer AG, Hüls, BASF (Germany), Shell (Netherlands, and United Kingdom), ICI, Cookson, (United Kingdom), Unilever (Europe), Ciba Speciality Chemicals (India), Du Pont, CH Chemicals, Union Carbide, Monsanto, and Rohm and Haas (USA).

Between 1995 and 1996, annual imports of primary, secondary and formulated products increased by 27%, while annual exports increased by

29%. Based on statistics from The Central Statistical Services, the chemical industry contributed 21.3% of the revenue generated by the manufacturing sector, and 5.3% to the annual gross domestic product (GDP). The average value added by the chemical industry was 37% (1993 Industrial Census), which is substantially higher than the average estimated for the rest of the world (18%).

Forecasts on production volumes for 1997 indicated an increasing emphasis on organic chemicals as opposed to inorganic chemicals. Annual growth rates of between 4 and 11% were expected for the production of primary and secondary inorganic compounds in 1997. An analogous estimate for the production of primary and secondary organic compounds was around 17% and 19%, respectively. The trend towards downstream, value-added products is therefore obvious.

1.2.2 Coal Chemicals *versus* Oil Chemicals

The production of petroleum products from crude oil is a well-established and maturing industry and very little research has recently been aimed at improved oil refining processes, or finding replacements for oil as primary chemical feedstock. The recent instability in world crude oil prices, together with forecasts that prices will never return to the levels during the 99's may well increase interest in other potential feedstock such as coal and/or natural gas. Although oil provides 90% of the chemical raw materials for organic chemicals today, one does not need a too large a crystal ball to foresee a gradual shift to coal and natural gas in the light of the relatively high oil price predicted, coupled with the decline of the oil reserves of the world.

The major use of oil is for fuel and heating, and is responsible for 60% of the overall fossil fuel consumption in the world. Crude oil, however, contains between 5 and 10% (v/v) chemicals that are suitable for secondary applications in the chemical industry. The main component of these chemicals is naphtha, consisting mainly of paraffins, naphthenes and aromatics. Coal (and natural gas), on the other hand, while suitable as a direct fuel source, requires major transformations before it can become a chemical feedstock.

The primary processes for coal processing are:

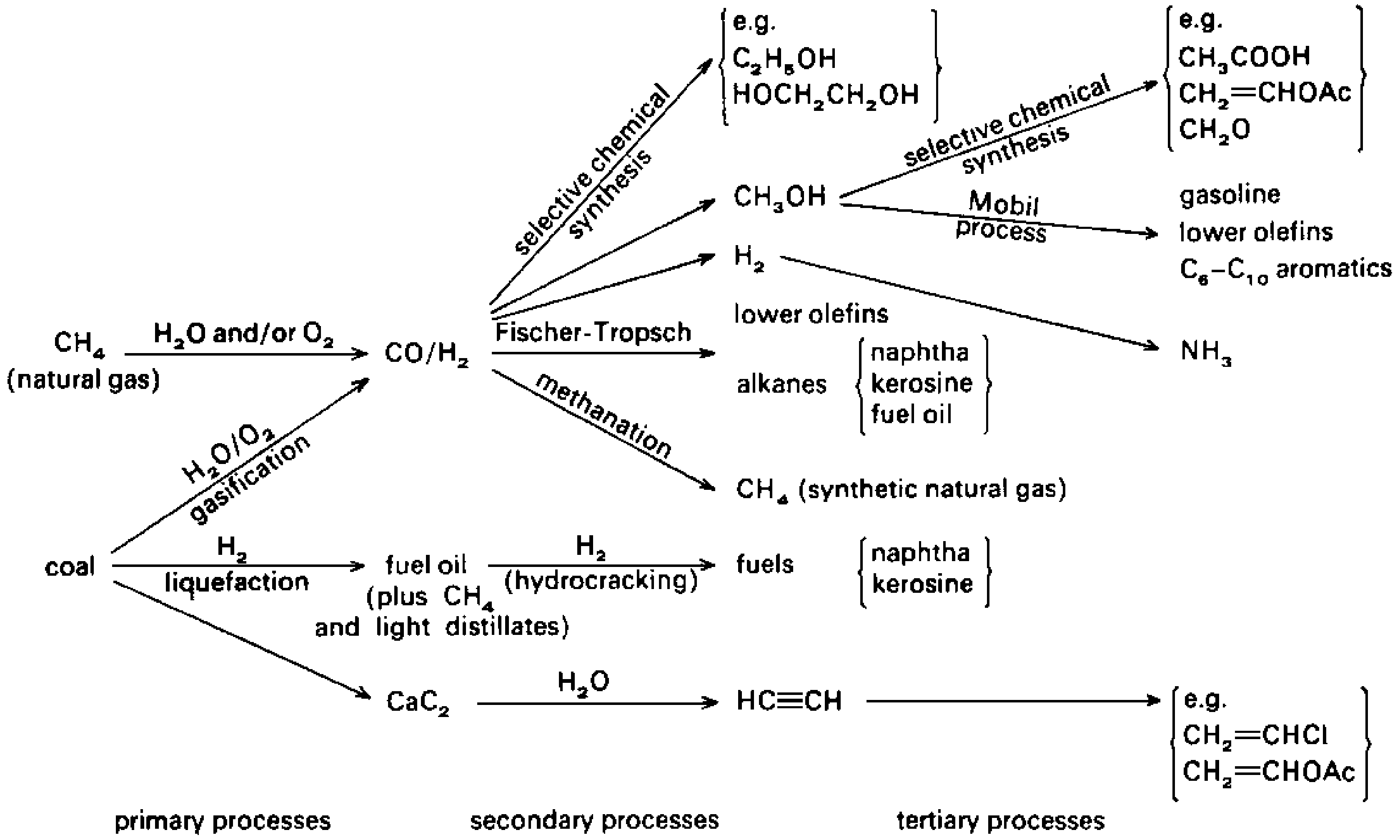
1 *Liquefaction* – in which lower molecular weight and more highly hydrogenated species are formed, and

2 *Gasification* – to form a gas mixture rich in carbon monoxide and hydrogen.

Refining of oil results in the distillation fractions shown in Table 1.1, while the various primary products possible from coal processing are indicated in Scheme 1.1.

Table 1.1: Oil raffination co-products

Oil Raffination[10]
- Natural gas
- Gasoline
- Naphtha: paraffins naphthenes aromatics
- Kerosene and Jet Fuel
- Diesel and Fuel Oil
- Atmospheric Gas Oil
- Heavy Fuel Oil
- Atmospheric Residue
- Vacuum Residue



Scheme 1.1 **Products obtained from Coal Processing**

Local South African chemical feedstock comes mainly from coal, the industry being in the advantageous position of having abundant coal supplies. There is, however, growing interest in the use of natural gas from local supplies and from neighbouring countries in the region. The viability of natural gas processing using locally developed technology (Sasol) has already been proven on a large production scale by Mossgas. Although the total of Mossgas's efforts is currently focussed on the provision of liquid fuels, there does not appear to be large technical difficulties should chemicals be the desired product.[11]

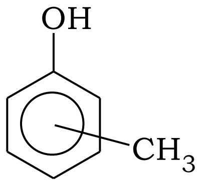
Oil suppliers from the USA, Asia and the Pacific Rim control a highly stable and secure chemical raw material market. It would be virtually impossible for a country like South Africa, despite its extensive coal supply, to attempt to enter or compete at such a high level of fuel and associated chemical feedstock supply. Therefore, it would be rational to follow the trends throughout the developed world, namely to abandon the stable feedstock areas for down-stream chemical products, and concentrate on value-added products. Moreover, given the specific nature of chemicals from coal, South African chemical industries should exploit the advantage of having unique chemicals at hand by securing specific downstream markets, both with respect to specific chemical products and the technologies required for the production of specific products.

One area where local (coal-based) companies have such an advantage is in the field of phenolic compounds, phenol, cresols, xylenols, etc. It is therefore not surprising that there should be considerable interest in the beneficiation of such compounds, together with an interest to be at the forefront of technology developments for the production of such compounds from other sources. This particular investigation addresses just one of the many existing opportunities, namely the development and evaluation of autoxidation technology for the conversion of iso-propyl-substituted benzenes and alkylbenzenes.

1.3 OVERVIEW OF CRESOLS

1.3.1 Introduction

Cresol, a member of the phenol group, contains one methyl group in addition to the hydroxy group. There are three possible cresol isomers: *ortho*-cresol, *meta*-cresol, and *para*-cresol, with the methyl groups in the 2-, 3-, and 4-positions, respectively. Dimethyl phenols (xylenols) exist as 2,3- 2,4-, 2,5-, 3,5-, and 2,6-isomers. There are also four possible trimethyl isomers representing the higher methyl phenols.



cresol

Cresols are highly corrosive and a mixture of the three isomers has been used as a disinfectant for a long time. The mixture has a sweet tarry odour and is occasionally referred to as tri- or *iso*-cresol in technical literature. Mixtures of *m*- and *p*-cresols are known as dicresol, and mixtures of the cresols, xylenols and higher alkylated phenols as cresylic acid, or tar acid when obtained from tar.

Mixtures of alkylated phenols, including the cresols, were originally only obtained from coal tar and later on from spent refinery caustic. Mixtures or specific isomers can also be synthesized via a number of production routes (see later). The operation of oil-from-coal processes on a large-scale (Fischer-Tropsch) results in a consistent supply of phenolic compounds, including cresols. Phenols and cresols are present in coal tar at concentrations ranging 0.5-4%. Of the phenols isolated in this manner, crude cresylic acid, purified phenol, dicresol mixture, and *o*-cresol are being marketed. However, current trends are towards value-added downstream products, which includes the separation of phenolic mixtures and the functionalization of specific compounds.[12-16]

1.3.2 Properties

Cresols form water-soluble salts in aqueous alkali solutions. The presence of the methyl group on the ring renders the cresols only slightly less acidic than phenol [$(pK_a)_{cresols}$ = 10.1 – 10.3; $(pK_a)_{phenol}$ = 9.9].[15,17] The cresols share the toxicity of phenol, and are labeled as hazardous air pollutants (HAPs).[16,18]

The presence of the methyl group on the ring results in higher boiling points compared to phenol (181.8°C).[18] The boiling points of *m*- and *p*-cresols are similar (202.2°C and 201.9°C, respectively),[12] making efficient separation through distillation impossible. Due to hydrogen bond formation between the two adjacent functional groups on the ring, *o*-cresol has a much lower boiling point at 191.0°C and is readily separated from the other two isomers in high purity.[19]

Cresols can be oxidized to hydroquinones, quinols, quinones, cyclic ketones, furans, dimeric and trimeric cresols, and tolyl ethers. Strong oxidizing agents can even break down the aromatic ring, and the specific oxidation products are dependent on reaction conditions, the oxidizing agent, and the position of the methyl group on the ring. Oxidation reactions normally occur *via* free radical mechanisms.

Protection of the phenolic hydroxyl group is achieved by esterification or etherification. The methyl group of such protected cresols can be selectively mono-, di- or tri-chlorinated, or selectively oxidized to a formyl group, or a carboxyl group. The phenoxy group is most commonly protected as a *tertiary*-butoxy[20] functionality.

Phenol-group protection can, alternatively, induce electrophilic ring substitution. Since the hydroxyl group is *ortho-para* directing, substitution of hydrogen atoms occurs on mainly the 2- and 4-positions of the ring. Isomerization to *m*-cresol, which is thermodynamically more stable, can also be achieved in the presence of a Friedel-Crafts catalyst, such as $AlCl_3$.[12]

1.3.3 Market Trends

Capacity in the three major producing and consuming regions – the United States, Western Europe and Japan – was 889 million pounds (404 thousand metric tons) in 1993.[21] Table 1.2 summarizes regional consumptions for cresols.[21]

Table 1.2: Consumption of Cresols by Major Region
(Millions of pounds)

	United States		**Western Europe**		**Japan**	
	1993	1998	1993	1998	1993	1998
Cresol						
o-cresol	5	5	45.5	39.6	20.2	23.8
m-cresol	14	17	8.6	13.2	8.4	7.5
p-cresol	26	28	25.5	19.8	13.9	13.4
(*m,p*)-cresols	8	8	3.1	2.6	18.9	15.4
Total	53	58	82.7	75.2	61.4	60.1

Pesticide production is the major market for o-cresol in Western Europe, while in the United States and Japan the principle application is for cresol-based resins. Japan consumes *m*-cresol primarily for pesticides, while the major outlet for *m*-cresol in Western Europe is antioxidants; US consumers use *m*-cresol for both categories. All three regions consume *p*-cresol for butylated hydroxytoluene (BHT) and for other oxidants. In Western Europe, tricresyl phosphate (TCP) is the primary outlet for (*m, p*)-

cresols, while cresol-based resins dominate Japanese consumption of this material.

1.3.4 Uses and Applications

Cresols are primarily used as intermediates in the manufacture of a variety of chemical products such as antioxidants, disinfectants, dyestuffs, optical brighteners, flavours and fragrances. The other major uses of cresols are summarized below.

1.3.4.1 Agricultural chemicals

o-Cresol is used in the manufacture of *p*-chloro-*o*-cresol, which is in turn used in the manufacture of phenoxyacetic acid (MCPA) and phenoxy propionic acid (MCPP or mecoprop) herbicides. *m*-Cresol can be converted to *m*-phenoxytoluene, which is oxidized to *m*-phenoxybenzyl alcohol and sold to manufacturers of pyrethoid insecticides.

1.3.4.2 Antioxidants

m-Cresol is used to produce 6-t-butyl-*m*-cresol (TBMC), an intermediate in the manufacture of hindered phenolic antioxidants. *p*-Cresol, pure or mixed with *m*-cresol is used mainly to produce 2,6-di-*tert*-butyl-*p*-cresol (BHT), a nonstaining and light-resistant antioxidant with a wide range of applications.

1.3.4.3 Flavours and fragrances

o-Cresol is used in the production of coumarin, which is used in the flavour and fragrance industry. *m*-Cresol is used to make several fragrances and flavours. For example thymol, 5-methyl-2-isoproprопylphenol, which can be synthesized by Friedel-Crafts alkylation of *m*-cresol with propylene or isolated from natural sources, is used in some liniments, balms and antiseptics, and as a precursor in the synthesis of L-menthol. *p*-Cresol is used as an intermediate to make *p*-methylanisole (*p*-cresol methyl ether), for the production of *p*-anisaldehyde, which is used in the fragrance industry. 6-Methylcoumarin, another flavour and fragrance chemical, can be synthesized by the addition of fumaric acid to *p*-cresol.

1.3.4.4 Pharmaceuticals

o-Cresol is used in the production of o-cresotinic acid, which is important in the pharmaceutical industry. The largest use of m-cresol is in the production of vitamin E. *m*-Cresol is methylated to form trimethylhydroquinone (TMHQ), followed by the reaction with isophytol to yield d-alpha-tocopherol (synthetic vitamin E).

1.3.5 Sources

1.3.5.1 Natural Sources

Natural cresol sources provide mainly *o*-cresol, and mixtures of *m*- and *p*-cresols. These mixtures can be separated indirectly to give the two isomers.

1.3.5.1.1 Coal Tar Acids

The oldest source of cresols is coal tar, obtained during the production of metallurgical coke by the coking of bituminous coal between 900 - 1300°C. The crude coal tar is distilled into four types of oil, namely light oil, middle oil, heavy oil (creosote oil), and pitch. Cresylic acid is primarily present in the light oil and middle oil fractions. Washing of these fractions with caustic soda solution removes the sodium cresylates, from which undesirable components can be removed by steam distillation. Stripping of the cresylate with carbon dioxide-rich gas ("springing"), followed by decanting of the liberated cresylic acid, allows recovery of the phenolic compounds. The crude cresylic acid can then be fractionated into various isomers or mixtures of isomers. Cresylic acid recovered from coal tar contains typically 45% phenol, 35% cresols, 15% xylenols, and 5% other phenolic homologues.[13]

1.3.5.1.2 Refinery Spent Caustic

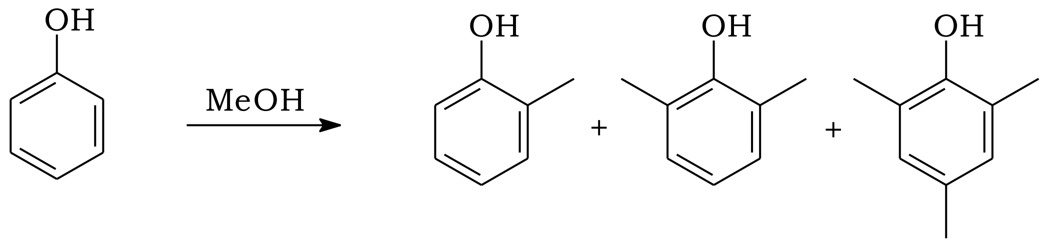
Cresol can be recovered from low-temperature coal tars obtained during the production of smokeless fuels (semicoke). Phenolic compounds are really coincidental components of the spent caustic that forms while thermally and catalytically cracked distillates are sweetened (caustic) to remove mercaptans. Cresylic acid is removed from the caustic by neutralization, followed by extraction.

1.3.5.2 Synthetic Sources

Specific cresol and xylenol isomers have been synthesized since 1965. These processes are based on either phenol or toluene, and are therefore more expensive compared to the isolation of cresol and xylenol as co-products. The synthesis of methylated phenols offers some control over regioselectivity and can lead to the synthesis of high purity products.

1.3.5.2.1 Phenol Methylation

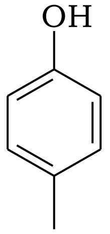
Alkylation of phenol with an excess of methanol is used to produce mainly *o*-cresol (**2**), 2,6-xylenol (**3**) and trace amounts of 2,4,6-trimethylphenol (**4**). Reaction conditions can, in some cases, be adjusted to promote the selectivity for one of the products. Gas phase-methylations, for example, produce mainly 2,6-xylenol (**3**), while liquid-phase methylations yield *o*-cresol as the main product. The latter route, however, also produces *p*-cresol (**5**) as well as 2,4- (**6**) and 2,6- (**3**) xylenols in a typical 7:5:2:1 ratio to *o*-cresol.



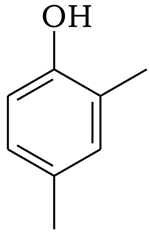
(**1**) (**2**) (**3**) (**4**)

Scheme 1.2 Alkylation of phenol

Yields of up to 98% (based on phenol) have been reported for the gas phase reaction. Common side products include water, methane gas, carbon monoxide and carbon dioxide. This process is currently used worldwide to produce almost the entire supply of 2,6-xylenol (**3**).[12,13,16]



(**5**)



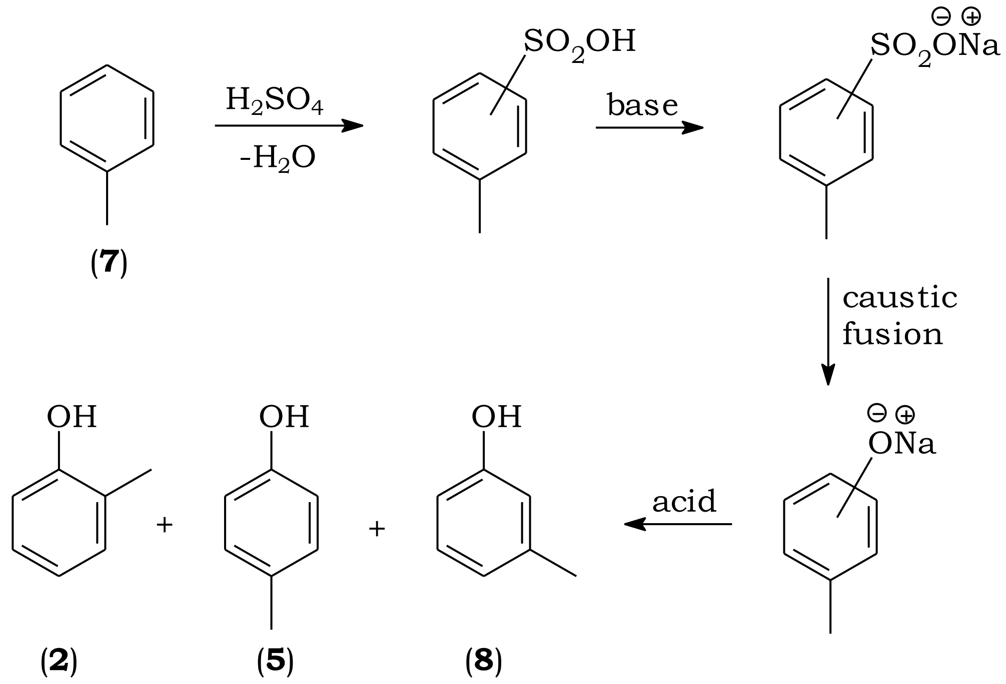
(**6**)

Addition of phenol to mixtures of the higher methylated products may result in the formation of *o*-cresol and *m*-/*p*-cresol mixtures by transalkylation at high temperatures (400 - 500°C) in the presence of an alkylation catalyst. Isomerization can also be achieved by this method.[19]

1.3.5.2.2 Toluene Sulfonation

Sulfonation of toluene (**7**), followed by neutralization, sodium hydroxide fusion and hydrolysis, is used to produce mainly *p*-cresol (Scheme 1.3). This process is analogous to the production of phenol from benzene through sulfonation, except that the rate of toluene conversion is far greater. A typical isomer distribution of 80-85% *p*-cresol, 6-12% *o*-cresol, and 6-12% *m*-cresol (**8**) is obtained. Milder reaction conditions can reduce the *m*-cresol content, while *o*-cresol is easily separated by distillation. Generally, *p*-cresol of up to 90% purity can be produced in this manner.

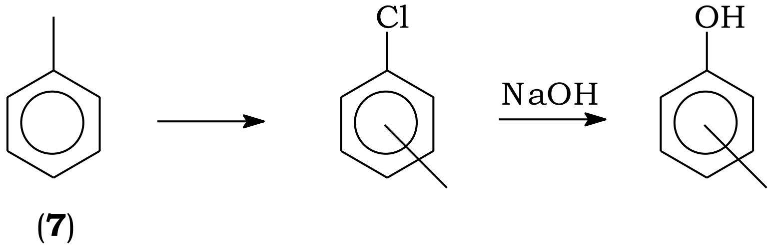
Sulfonation processes are, or was until recently, operated in the USA, Japan and the United Kingdom. Overall yields are typically around 80% and can be improved by altering the temperature and acid strength during the sulfonation step, and by using a stronger base in the fusion steps.[12,13,16,22]



Scheme 1.3 **Sulfonation of toluene**

1.3.5.2.3 Toluene Chlorination

A mixture of cresol isomers can be obtained by the chlorination of toluene and subsequent hydrolysis in the presence of sodium hydroxide at elevated temperature and pressure (Scheme 1.4). The basic reaction is analogous to the production of phenol from chlorobenzene. This process results in larger amounts of byproducts compared to the previous processes, including such compounds as dimeric and polymeric ethers, small amounts of toluene, phenol, benzoic acid, and methane and hydrogen gas. Yields are not higher than 70%. The resulting cresol mixture typically contains 60% *m*-cresol, the rest being *p*- and *o*-cresol in an approximate 1:1 ratio.

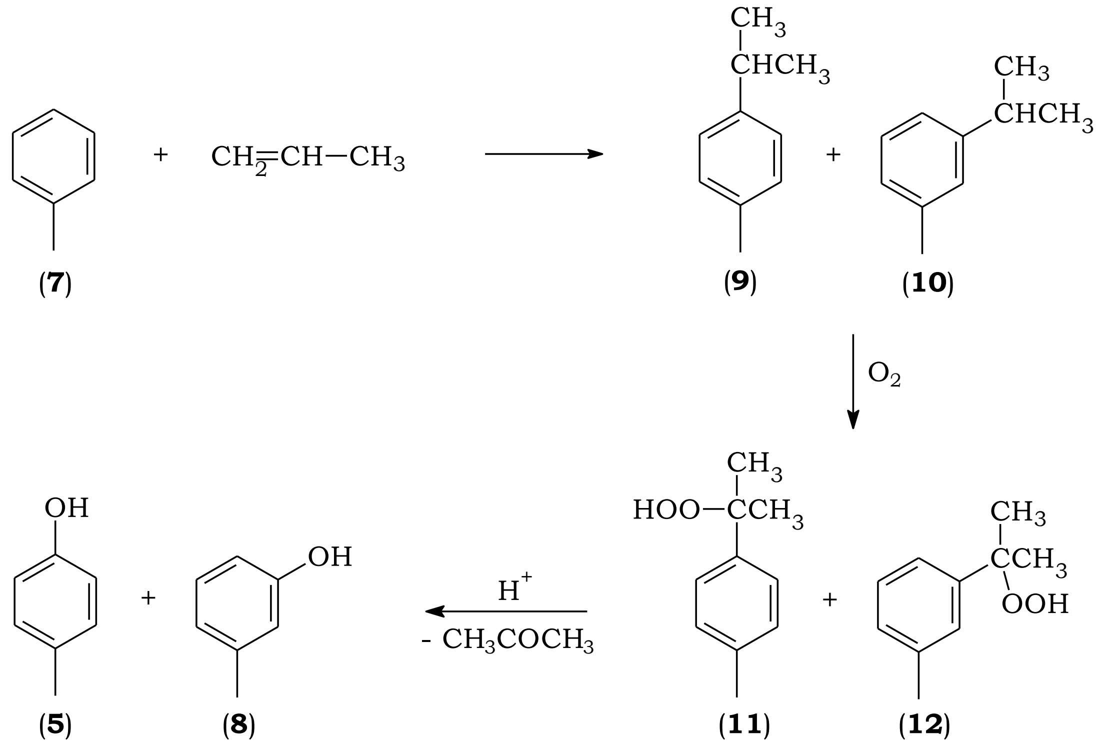


Scheme 1.4 **Chlorination of toluene**

When cresols are produced from pure *o*- or *p*-chlorotoluene a 1:1 mixture of the specific isomer with *m*-cresol is obtained. Different cresol mixtures are currently being produced according to this process in the United States, Japan, India and the United Kingdom.[12,13,16,22]

1.3.5.2.4 Cleavage of Cymene Hydroperoxide

Commercial processes based on the acid cleavage of cymene hydroperoxide produce cresol mixtures containing approximately 60% *m*-cresol and 40% *p*-cresol. Pure *m*- or *p*-cymene can also be utilized to produce pure *m*- or *p*-cresol, respectively. Cymene is first produced *via* the Friedel-Crafts alkylation of toluene with propylene (Scheme 1.5). All three cymene isomers are formed and the amount of *o*-cymene minimized (<10%) by isomerization, since it is not further oxidized and can even inhibit the oxidation of the other two isomers.

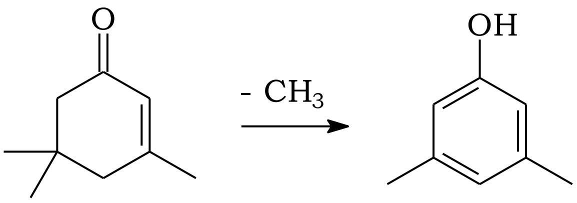


Scheme 1.5 Friedel-Crafts alkylation of toluene

Air oxidation of *p*- (**9**) and *m*-cymene (**10**) affords the corresponding cymene hydroperoxides (**11** and **12**), which are subsequently cleaved in an acid medium to yield the respective cresols and acetone. Cymene conversions are generally <20%, and the unconverted cymene returned to the reactor after separation. This process is discussed in greater detail in the next chapter. More than 95% of synthetic phenol is produced by the analogous cumene-phenol route.**[12,13,16,22]**

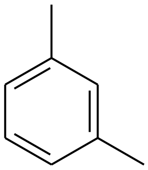
1.3.5.2.5 Demethylation of Isophorane

3,5-Xylenol (**14**) is produced in the United Kingdom by demethylation of isophorane (**13**) (Scheme 1.6). This reaction can yield up to 80% 3,5-xylenol, depending on the catalyst used. Side products include toluene, 1,3-xylene (**15**), mesitylene (**16**), *m*-cresol, 2,4- and 2,5-xylenol (**17**), and 2,4,6-trimethylphenol. After work-up, 3,5-xylenol is obtained in 99% purity.**[12,13,16,22]**

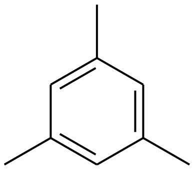


(**13**) (**14**)

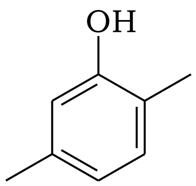
Scheme 1.6 **Demethylation of isophorane**



(**15**)



(**16**)



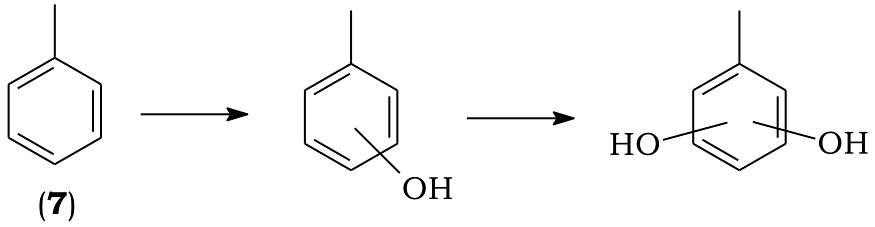
(**17**)

1.3.5.2.6 Hydroxylation of Toluene

The direct hydroxylation of toluene to form cresols has attracted considerable interest. The two routes currently receiving the most attention are based on catalysis and electrochemistry. Hydroxylations generally need to be carried out in dilute solutions since the resultant phenolic compound is generally susceptible to further hydroxylation.[22-25]

1.3.5.2.6.1 Catalytic Hydroxylation

Analogous to the large-scale industrial process for the direct hydroxylation of benzene to form phenol, toluene can be hydroxylated with hydrogen peroxide to form cresols (Scheme 1.7). Acid and transition metal catalysts can be used for this transformation. Side-chain oxidation occurs in competition with ring hydroxylation. However, the use of shape selective microporous catalysts like clays (copper modified), and titanium zeolites can result in largely controlled ring-hydroxylation reactions.



Scheme 1.7 Hydroxylation of toluene

Alcoholic media tend to favour *para*-selectivity. Although not yet optimized for large-scale application, this reaction can yield cresols in 80% selectivity (typically 1.33:1 *p*-:*o*-isomers) at 58% conversion of toluene in *tertiary*-butanol.[22,23,26-32]

The use of vanadium-based catalysts in acidic media for the hydroxylation of aromatics has recently been reported.[24] In this system hydrogen peroxide is generated *in situ* by the air oxidation of hydroquinone. The hydrogen peroxide subsequently oxidizes both the vanadium species to an active oxide species and simultaneously acts as the hydroxylating agent.

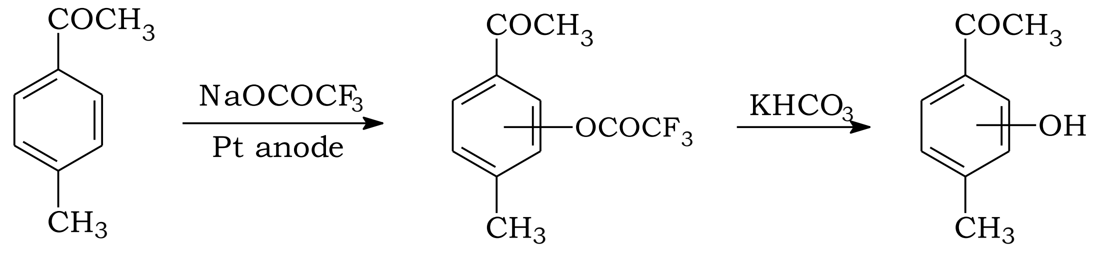
1.3.5.2.6.2 Hydroxylation with Nitrous Oxide

The catalytic transfer of an oxygen atom from nitrous oxide to the aromatic ring of a benzene derivative to afford the corresponding phenol derivative is an alternative to hydrogen peroxide hydroxylations. Apart from the preparation of phenol, little detail is known for the hydroxylation of toluene. Although other substrates are not as reactive as benzene, most derivatives can still be effectively hydroxylated in this way.

Solutia Ltd. is currently constructing a commercial plant for the hydroxylation of benzene using this technology. Nitrous oxide is obtained from an adjacent plant for the nitric acid oxidation of cyclohexanone/ cyclohexanol mixtures to adipic acid. A selectivity of 98% to phenol, at 0.33 mol benzene per gram catalyst converted, is claimed. Ruthenium- or aluminium-based zeolites are being used, although a variety of other catalysts may also be utilized effectively.[33]

1.3.5.2.6.3 Electrochemical Hydroxylation

The partial electrochemical hydroxylation of substituted aromatics has been achieved in high yield in a nitromethane/trifluoroacetic acid medium, using platinum electrodes. The absence of further hydroxylation products is ascribed to the relative inertness of the trifluoroacetate ester (**18**).



(**18**)

Scheme 1.8 **Hydroxylation of 4-methylacetophenone**

The hydroxylation of 4-methylacetophenone (Scheme 1.8) yields 73% phenolic products. Regioselectivity could, however, not be controlled, and the reaction was accompanied by the parallel hydroxylation of the benzylic methyl group (10%).[25]

1.3.5.2.7 Miscellaneous

There are several other methods for cresol synthesis that are not currently of any commercial interest.

The Gulf oxidation is based on the oxy-chlorination of toluene to prepare *o*- and *p*-chlorotoluene in a 2:1 molar ratio with higher than 95% selectivity at 80% conversion. This reaction is performed with aqueous hydrochloric acid and molecular oxygen in the presence of catalytic amounts of nitric acid and palladium or copper salts. Hydrolysis in the vapor phase (400 - 450°C) affords the corresponding cresols in 95% selectivity at 20% conversion.

Oxidative decarboxylation of methylbenzoic acids is achieved in the vapor phase in the presence of various catalysts. This reaction affords *m*-cresol in 90% selectivity at 80% conversion of *m*-methylbenzoic acid. Gas-phase decarboxylations always produce *m*-cresol, even from *o*- and *p*-methylbenzoic acids. Liquid-phase decarboxylation of *m*-methylbenzoic acid, on the other hand, affords a 1:2 molar mixture of *o*- and *p*-cresol.

The Baeyer-Villiger oxidation of *p*-methylbenzaldehyde yields 85% *p*-cresol at full conversion under the influence of zeolites or ion exchange resins. *o*-Cresol can also be prepared from *o*-methylbenzaldehyde. The oxidation utilizes performic acid, prepared from formic acid and hydrogen peroxide, to convert methylbenzoic acid to tolyl formate. Hydrolysis of tolyl formate affords the cresol and formic acid.

Besides the cymene process (refer to section 1.3.3.2.4), other toluene derivatives can also be subjected to the Hock reaction. The substrate is typically oxidized to the hydroperoxide which is subsequently cleaved to afford cresol and the corresponding carbonyl compound. Derivatives of toluene that can be used include ethylidene-*bis*-(*p*-methylbenzene) affording *p*-cresol and *p*-methylacetophenone, 4-methyl-cyclohexylbenzene affording *m*-cresol and cyclohexanone, and *p*-xylene affording *p*-cresol and formaldehyde.

Hydrogenation of *N,N'*-dialkylaminomethylphenols yield 90% *o*- and *p*-cresol (1:2 ratio). For example, a mixture of piperidinomethylphenols is prepared from phenol, paraformaldehyde and piperidine in methanol, and is subsequently hydrogenated to afford the cresols and piperidine.

Diels-Alder ring closure can give *p*-cresol in three steps using isoprene and vinyl acetate in the presence of hydroquinone. The reaction proceeds *via* 1-methylcyclohexen-4-yl acetate and 1-methyl-cyclohexen-4-ol intermediates. High yields are claimed and the starting material can be recycled.

Carbonylation of 2-methallylchloride, acetylene and carbon monoxide gives *m*-cresol in 74% yield. The reaction is catalyzed by tetracarbonylnickel, NaI, iron powder and thiourea. The hydrochloric acid formed is neutralized with magnesium oxide.

Extreme reaction conditions together with acid catalysts can lead to the hydrolysis of toluidine to the corresponding cresol. Thermal (600 - 700°C) or metal-oxide catalysed hydrodealkylation of xylenols with hydrogen under pressure, has also been performed.[22]

1.4 SUMMARY

The acid cleavage of cymene hydroperoxide remains the most important synthetic route to cresols despite some specific shortcomings. The technology and chemistry of this route will be reviewed in more detail in the following chapter with the view to identifying areas for possible improvement.

CHAPTER 2

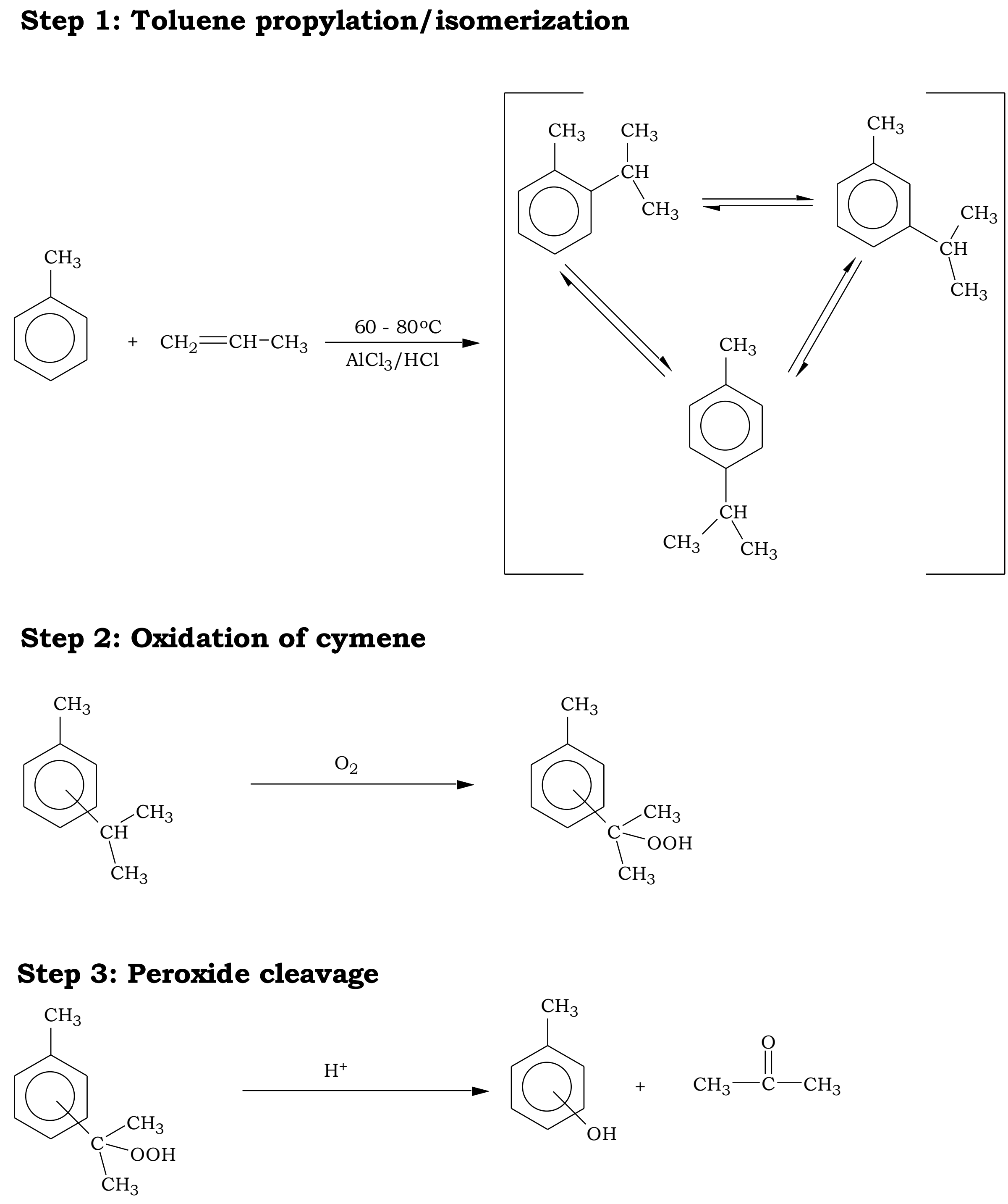
PRODUCTION OF CRESOLS VIA CYMENE HYDROPEROXIDE

2.1 INTRODUCTION

As discussed in the previous chapter, the synthesis of cresols via cymene hydroperoxide is one of the two most important production processes of *m*-, and *p*-cresols, either alone or in a mixture. This route is analogous to the phenol from cumene route, but results in considerably lower overall yields than the cumene route. In this section, a detailed overview of the cymene-cresol route is given and an attempt made at identifying areas where potential improvements may be sought.

2.2 OVERVIEW OF THE CYMENE-CRESOL ROUTE

The cymene-cresol process basically consists of three distinct steps, namely the propylation of toluene to cymene and the simultaneous isomerization of the cymene product mixture, the oxidation of cymene to cymene hydroperoxide and peroxide cleavage to give the reaction products (Scheme 2.1). In comparison to the corresponding cumene-phenol (Hock) process, the cymene-cresol process operates at considerably lower overall rates as a result of operating at significantly lower conversions. In addition, due to the lower substrate conversions and the formation of a number of byproducts, the cymene-cresol process also requires extensive distillation procedures and very costly wastewater treatment procedures. The main reasons for the above observations are briefly discussed below:



Step 1: Toluene propylation/isomerization

Step 2: Oxidation of cymene

Step 3: Peroxide cleavage

Scheme 2.1 **The cymene-cresol process**

2.2.1 Influence of *o*-cymene

The synthesis of cymene via Friedel-Crafts alkylation of toluene with propene results in the formation of all three isomers, *o*-, *m*-, and *p*-cymene. Of the three isomers, only *m*- and *p*-cymene can be oxidized to the cymene hydroperoxide. *o*-Cymene is not oxidized and, in fact, at certain concentrations (*ca.* 10%) actively inhibits the oxidation of the other two isomers.[34] This not only means that measures need to be taken to reduce the *o*-cymene content of new cymene batches, but in continuous cymene oxidation processes the *o*-cymene content of recycled substrate needs to be reduced by isomerization on a continuous basis to keep its concentration below *ca.* 10%, but preferably below 3%.[35,36]

2.2.2 Low oxidation rates and extent of oxidation

As stated before, the oxidation rates of cymene is lower than that of cumene and, in addition, the extent of oxidation needs to be restricted to below 20% to keep the formation of byproducts such dimethyl(tolyl)methanol and methylacetophenone, resulting from the oxidation of the isopropyl group, within reasonable limits. The result is that large amounts of unreacted cymene need to be recycled, adding to the complexity and cost of the process.

2.2.3 Oxidation of the methyl group

In contrast to cumene, which has only an isopropyl group attached to the ring, cymene contains a methyl group in addition to the isopropyl group. The methyl group, which also contains active hydrogen atoms, may also be oxidized to the corresponding primary hydroperoxide. It has been claimed that the ratio at which the methyl group is attacked relative to the isopropyl group may be as high as 1:4[37]. The primary hydroperoxide is much more reactive than the tertiary hydroperoxide, and is readily converted into such secondary products as isopropylbenzyl alcohol, isopropylbenzaldehyde, and cumic acid. In addition to these autoxidation products, Baeyer-Villiger re-arrangement of the primary hydroperoxide during the highly exothermic acid cleavage stage may lead to the formation of formaldehyde in a 1:1 ratio with the primary hydroperoxide present in the reaction mixture. Since formaldehyde is capable of binding cresol in a 1:2 ratio to form cresol-formaldehyde resins, cresol yield may be substantially reduced.[38]

2.2.4 Product separation

Reaction mixtures resulting from the autoxidation of cymene contain a wide range of reaction products that need to be separated. These products (see later), which result from the autoxidation of the isopropyl and methyl groups as well as from the acid cleavage of the primary and tertiary hydroperoxides, contain *inter alia* cymene, isopropenyltoluene, 2-tolylpropanol, isopropylbenzyl alcohol, isopropylbenzaldehyde, methylacetophenone, isopropylphenol, and numerous other compounds.[39] The separation of these compounds is relatively expensive because of their large number, their similar boiling points, and the formation of azeotropic mixtures.

2.3 CHEMISTRY OF THE CYMENE-CRESOL ROUTE

The basic chemistry used in the cymene-cresol process was illustrated previously in Scheme 2.1. Each of the three basic reactions will now be reviewed and recent developments highlighted.

2.3.1 Propylation of toluene

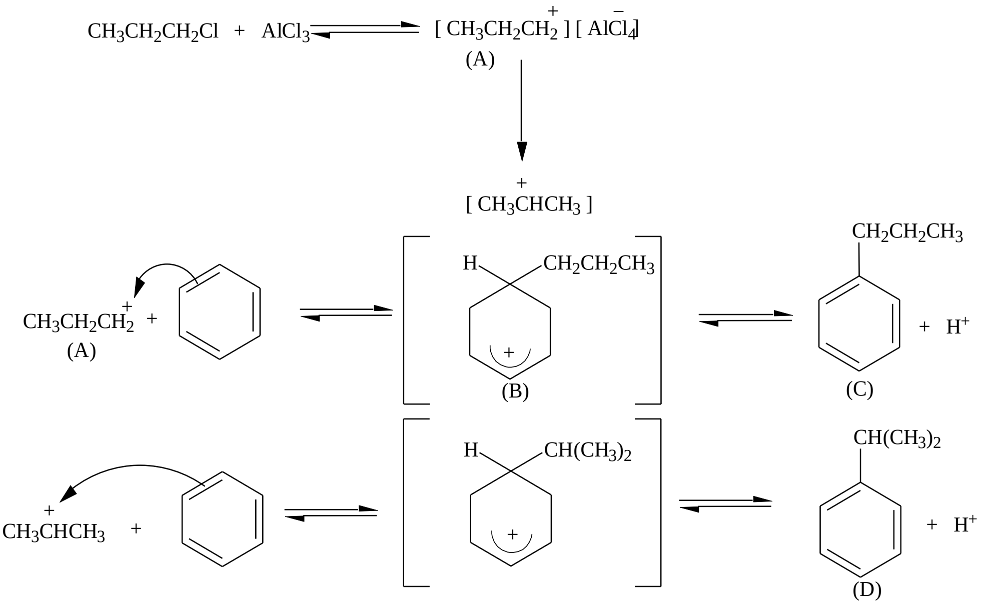
The Friedel-Crafts alkyation of toluene with propene results in the formation of *o*-, *m*-, and *p*-cymene, the relative amounts depending upon the activity of the Lewis acid catalyst and the reaction conditions (temperature and reaction time) used. As mentioned previously, the aim is to minimize the amount of *o*-cymene in the reaction product. The lowest amount of *o*-cymene that can be attained is that of a cymene mixture in thermodynamic equilibrium.[40] In order to achieve this equilibrium, extreme reaction conditions and very active Lewis acid catalysts are usually employed.[41] The use of $AlCl_3$, a strong Lewis acid, for example results in the formation of a cymene mixture containing approximately 3% *o*-cymene, 64% *m*-cymene and 33% *p*-cymene.

2.3.1.1 Alkylation of aromatic compounds

In the usual Friedel-Crafts alkylation of aromatics, a hydrogen atom of the aromatic nucleus is replaced by an alkyl group through the interaction of an alkylating agent in the presence of a Friedel-Crafts catalyst.[42] The overall reaction, using alkyl halides as alkylating agents, in the presence of $AlCl_3$ may be written as follows:

$$\mathrm{RX} \xrightarrow{AlCl_3} \mathrm{ArR} + \mathrm{HX} \qquad [2.1]$$

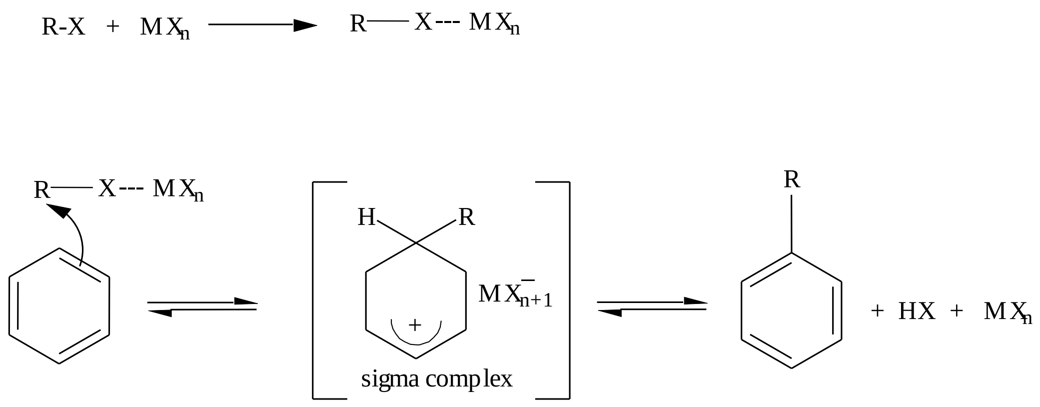
The mechanism[42] is best explained by the carbonium-ion concept. Consider for example the alkylation of benzene with n-propyl chloride (Scheme 2.2):



Scheme 2.2 Alkylation of benzene with n-propyl chloride

In Scheme 2.2, formation of a polarised complex between the Lewis acid and the alkylating agent produces the carbocation (A), which acts as an electrophile and attacks the benzene ring (or vice versa) to form an arenium ion (B). Loss of a proton from (B) produces the product n-propylbenzene (C). Rearrangement of the initially formed carbonium ion to the thermodynamically more stable secondary carbonium ion explains the formation of isopropylbenzene (D) in the alkylation.[42]

Friedel-Crafts alkylations do not necessarily proceed through a free carbonium ion. The polarised complex between the alkylating agent and the Lewis acid may be sufficiently polarised to act as the attacking electrophile. The complex behaves as a carbocation and transfers a positive alkyl group to the benzene ring. This is particularly the case when the alkylating agent is a primary halide.[43] C.R. Smoot and H.C. Brown proposed this type of displacement mechanism when they studied the gallium-bromide (weak Lewis acid) catalysed alkylation of benzene and toluene with ethyl bromide (Scheme 2.3).[44]



Scheme 2.3 Displacement Mechanism[45]

From the point of view of the alkyl halide, the above mechanism can be considered to involve nucleophilic attack by the electron rich aromatic ring on the alkyl group of the polarised complex. From the viewpoint of the aromatic ring however, the Friedel-Crafts reaction is considered as an electrophilic substitution regardless of the nature of the attacking electrophile. The ease of Friedel-Crafts alkylations varies with:

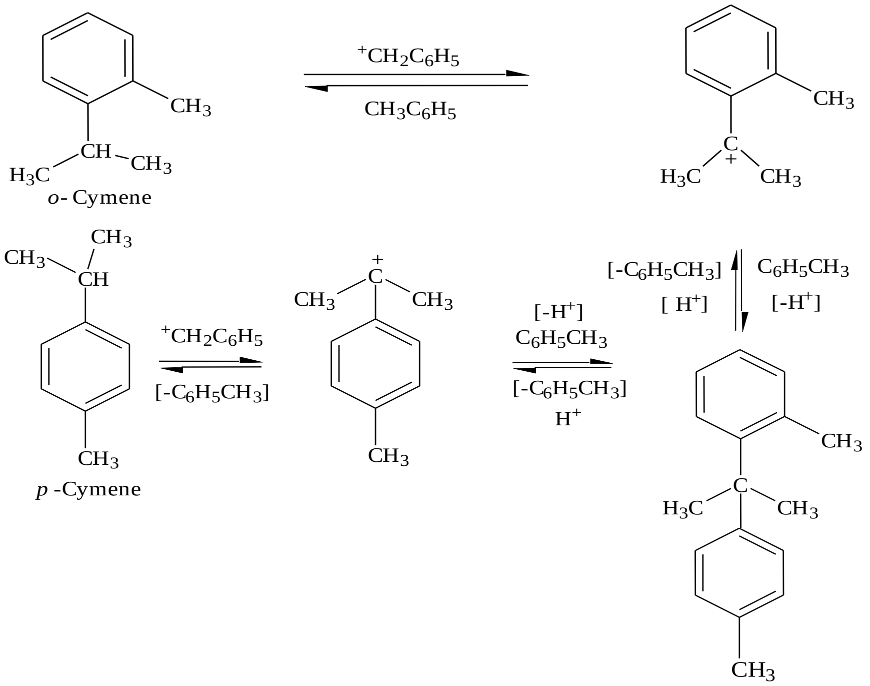
(a) The nature of the alkylating agent: the most frequently used alkylating agents are alkyl halides, alkenes and alcohols. Alcohols are more active than alkyl halides, although if a Lewis acid catalyst is used, more catalyst is required, since the catalyst complexes with the -OH group. For all types of reagents, the reactivity order is allyl > benzyl type > tertiary > secondary > primary. When alkyl halides are used, the reactivity order is F > Cl > Br > I.[46]

(b) The nature of the catalyst: Lewis acid type catalysts used include $AlCl_3$, $FeCl_3$, BF_3, $SbCl_5$, $ZnCl_2$ and $TiCl_2$. The common feature of these acidic halides is that they have an electron-deficient central metal atom capable of electron pair acceptance from the alkylating agent. Acid catalysts of the Brønsted-Lowry type include HF, H_2SO_4 and H_3PO_4.[42] The general order[47] of activity of the metal halides in alkylation reactions is reported to be $AlCl_3 > SbCl_5 > FeCl_3 > TiCl_2 > SnCl_4 > TiCl_4 > TeCl_4 > BiCl_3 > ZnCl_2$; the general order of activity of proton acid catalysts is $HF > H_2SO_4 > H_3PO_4$.

(c) The structure of the aromatic nucleus: electron-donor, *ortho-, para-* directing substituents, for example alkyl groups, generally enhance the rate of alkylation of aromatic rings. The additional electron density delocalised onto the ring enhances the ability of the ring to interact with a potential electrophile. Exceptions are -OH, -OR and -NH_2 groups, which do not facilitate the reaction, since the catalyst may coordinate with these groups. Electron-withdrawing, *meta-* directing substituents for example -NO_2, usually inhibit the rate of alkylation for reasons exactly opposite to those discussed for electron-donating groups.[46]

2.3.1.2 Dealkylation and transalkylmigration

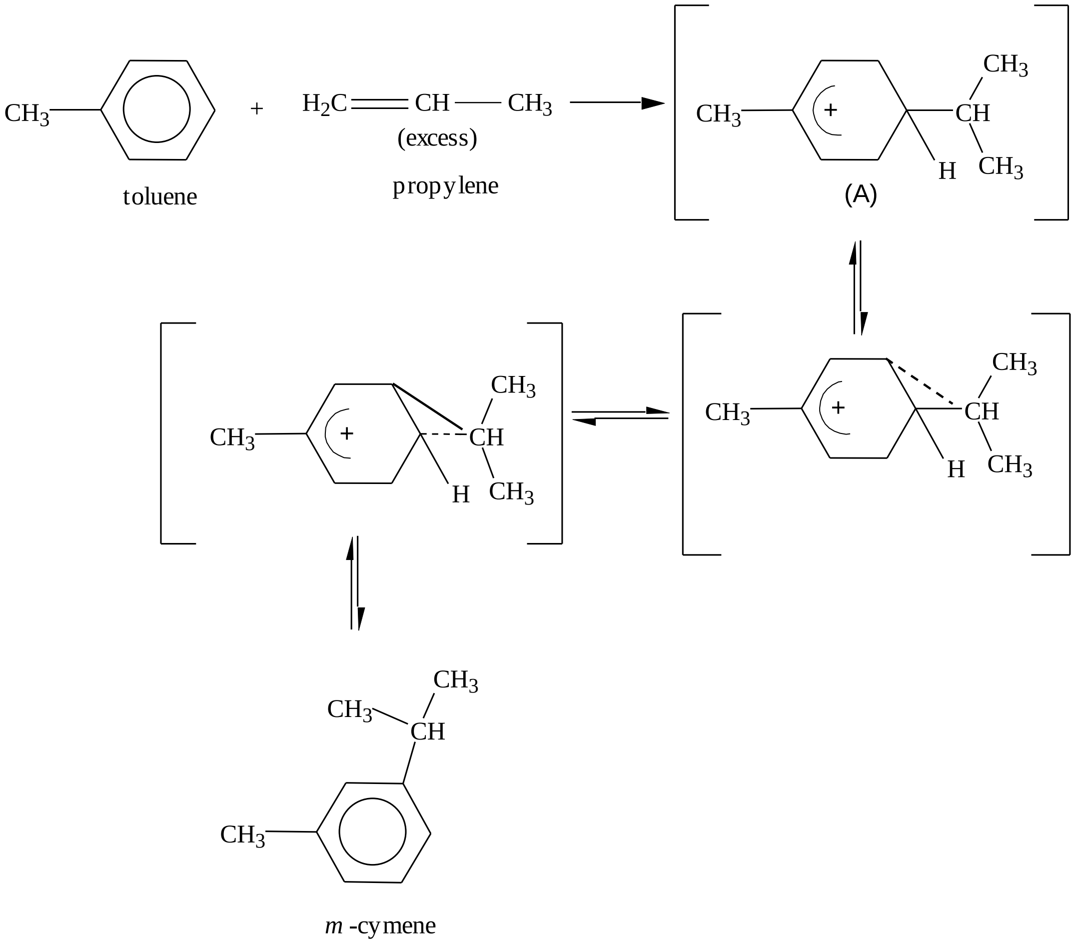
Lewis acid catalysts are not restricted to the introduction of alkyl groups into aromatics; they can also be used to remove alkyl groups from alkylbenzenes. When methylbenzenes are heated with aluminium chloride, dealkylation and alkylation proceed together so that the product is a mixture of hydrocarbons, some with fewer and some with more alkyl groups than the original alkylbenzene. Thus trimethylbenzenes yield xylenes and tetramethylbenzenes, as well as smaller amounts of toluene and benzene.[48] Similarly, stirring pure ethylbenzene with aluminium chloride at room temperature for a few minutes yields substantial amounts of benzene and polyethylbenzenes.[49] Streitwieser[50] proposed the following mechanism (Scheme 2.4). This mechanism was modified using cymene as starting material, for the sake of relevance.



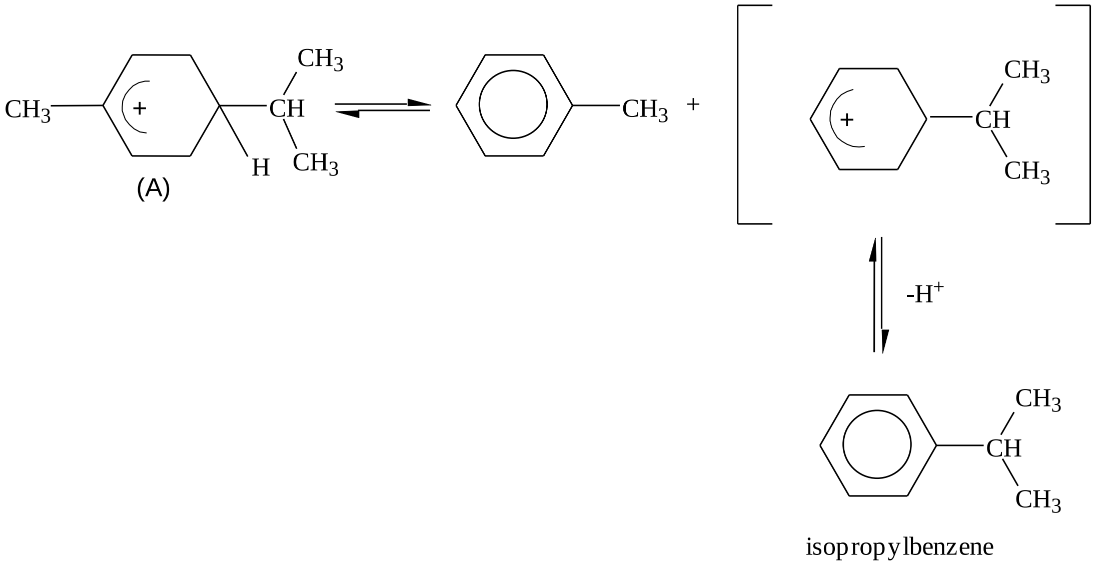
Scheme 2.4 Dealkylation and Transalkylmigration of cymene

2.3.1.3 Isomerisation

The migration of alkyl groups from one position on a ring to another position (intramolecular isomerisation) (Scheme 2.5), or from one ring to another (intermolecular isomerisation) (Scheme 2.6), is catalysed by Lewis acids.[42]



Scheme 2.5 Intramolecular isomerisation: 1,2-shift mechanism[51]



Scheme 2.6 **Intermolecular isomerisation: disproportionation (transalkylation)**

Both types of isomerisation involve protonation of *p*-cymene to the corresponding sigma complex[52] as a first step. Isopropyl group migration[51] produces *meta*-cymene. The disproportionation reaction (Scheme 2.6) can be viewed as an electrophilic transalkylation, which involves nucleophilic displacement on the intermediate complex (A) by a molecule of toluene. Thus the disproportionation (transalkylation) reaction is not considered to involve the cleavage of relatively unstable primary carbonium ions (CH_3-CH^+-CH_3) in any "free" state.[51]

2.3.1.4 Factors influencing mono- and polyalkylations

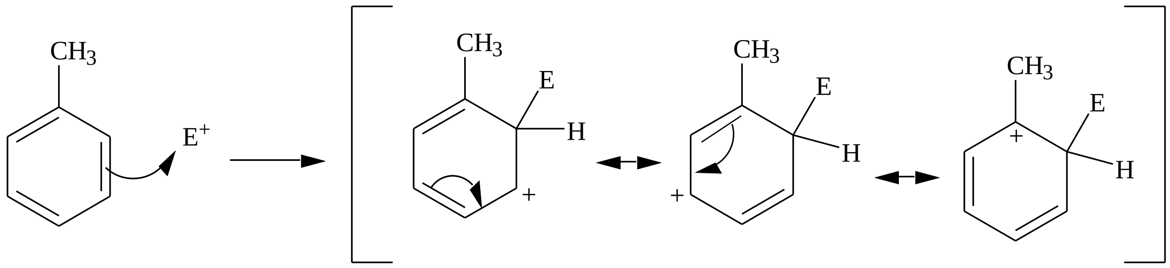
Friedel-Crafts alkylation is unusual among the principal aromatic substitutions in that the entering group is activating so that polyalkylation is frequently observed. However, the activating effect of simple alkyl groups, for example, ethyl, isopropyl etc., is such that compounds with these groups as substituents are attacked in Friedel-Crafts alkylations only about 1.5 to 3 times as fast as benzene. Thus, it is often possible to obtain high yields of the monoalkyl product.[46] The fact that polyalkyl derivatives are frequently obtained may not be due to the difference in reactivity but to the fact that alkylbenzenes are preferentially soluble in the catalyst layer where the reaction actually takes place.[49] This factor may be removed by the use of a suitable solvent, by high reaction temperatures or by very efficient mixing, especially when heterogenous catalysts are employed.[46]

2.3.1.5 Orientation

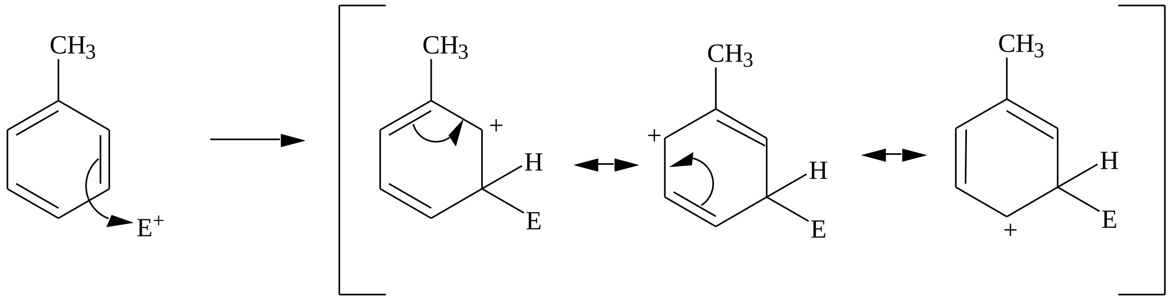
In most Friedel-Crafts alkylation reactions, the product distribution changes as a function of reaction time i.e. the contact with the catalyst. This is due to kinetic control of the initial reaction products followed by thermodynamic control of the final products.

Alkyl groups are *ortho-, para*-directors. This property is a result of the ability of an alkyl group to release electrons - an effect that is particularly important when the alkyl group is attached directly to a carbon that bears a positive charge. Consider the resonance structures for the arenium ions formed when toluene undergoes electrophilic substitution (Scheme 2.7):

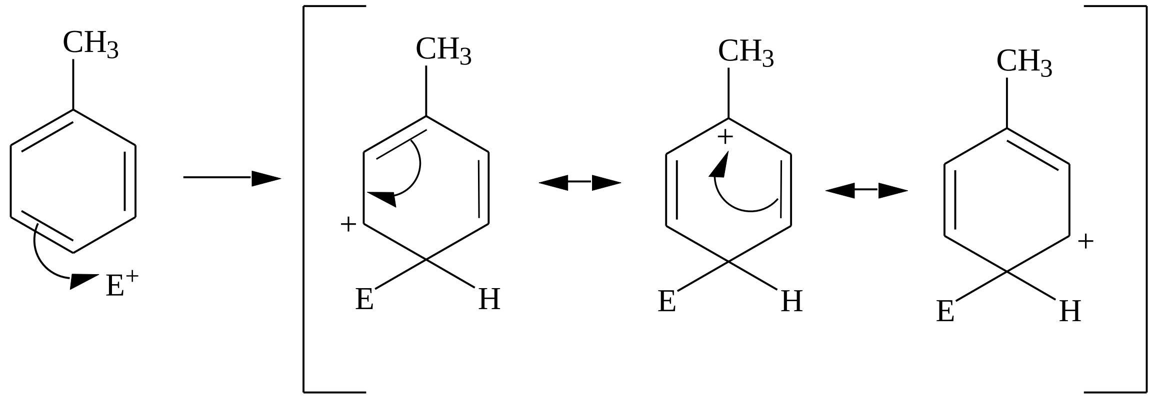
Ortho attack:



Meta attack:



Para attack:



Scheme 2.7 Electrophilic substitution of toluene

In *ortho* and *para* attack we can write resonance structures in which the methyl group is directly attached to a positively charged carbon of the ring. These structures are more stable relative to any of the other because, in them, the stabilising influence of the methyl group (by electron release) is most effective. These structures, therefore, make a large (stabilizing) contribution to the overall hybrid for *ortho*- and *para*-substituted arenium ions. No such relatively stable structure contributes to the hybrid for the *meta*-substituted arenium ion, and as a result, it is less stable than the *ortho*- or *para*- substituted arenium ion. Since the *ortho*- and *para*-substituted arenium ions are more stable, the transition states leading to them occur at lower energy and *ortho*- and *para*- substitution takes place most rapidly.

Thus, the initial products (mainly *ortho*- and *para*-) are formed in a fast step involving the energetically favourable intermediates, but the more stable *meta*-product is formed by a slower process from the *ortho*- and *para*- isomers (as illustrated in Scheme 2.5). In general, the more vigorous the conditions, with respect to activity of the catalyst, alkylating agent as well as reaction time, temperature and relative amount of catalyst, the greater is the tendency toward the formation of meta-derivatives.[42]

2.3.1.6 New developments and technical considerations in the industrial preparation of cymene

Due to the formation of all three cymene isomers during the propylation of toluene and the requirement for low *o*-cymene content, as well as the build-up of *o*-cymene in recycled reaction mixtures during continuous oxidation procedures, relatively expensive measures need to be taken for the isomerization of *o*-cymene over aluminium-based catalysts.[41] In addition, the formation of di-isopropyl substituted toluenes during the propylation step requires de- and trans-alkylation steps, also using aluminium-based catalysts. In view of these complications, it is not surprising that much effort has been extended in developing alkylation procedures that would circumvent these problems.

If pure *m*- or *p*-cymene is used for the production of the individual cresols, the need and high cost associated with the isomerization of *o*-cymene is eliminated. There has therefore been a number of reports dealing with the selective synthesis of individual *p*-/*m*-cymene isomers and/or the separation of *p*-/*m*-cymene mixtures. Owing to the close proximity of the boiling points of the cymene isomers (*m*-cymene 175.1°C, *p*-cymene 177.1°C, *o*-cymene 178.3°C at 101.3 kPa), the *m*-cymene, at most, may possibly be isolated at reasonable cost from the cymene mixture resulting from the propylation of toluene.[53] UOP has patented a process (Cymex process) for the separation of pure *m*-cymene and *p*-cymene from alkylation mixtures using 13X molecular sieves and toluene as desorption agent.[54] This process is similar to UOP's Parex process for the isolation of *p*-xylene from C_8 aromatics. The separation of individual cymene isomers in a process such as the cymex process allows the use of cheaper catalysts for the isomerization (and alkylation) steps (e.g. phosphoric acid on aluminium oxide)[54] since the residual cymene mixture from the separator may be returned to the isomerization step where the equilibrium mixture can be re-established.[55]

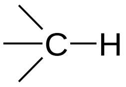
Similar to the developments for the production of cumene from benzene by propylation, several new catalyst systems were patented for the synthesis of cymene from toluene by propylation. These catalysts are invariably solid acid catalysts, and nearly without exception zeolite based.[56-59] In some cases, remarkable shape selectivity is claimed for the specific synthesis of *p*-cymene as illustrated by a Zn-based zeolite developed by Amoco that is claimed to give 98% *p*-cymene selectivity at 58% toluene conversion.[57] In addition, several processes were also patented for the selective production of specific cymene isomers using techniques involving selective de-alkylation (of di-isopropyltoluenes)[60] and transalkylation reactions between cumene and toluene.[61,62]

2.3.2 Oxidation of cymene

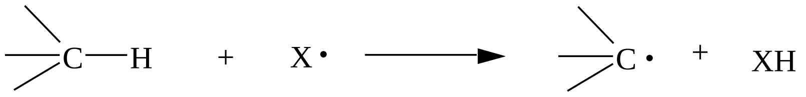
The liquid phase-air oxidation of cymene is a free-radical autoxidation, which is the atmospheric oxidation of a carbon- hydrogen bond (C-H) to a hydroperoxide moiety (C-O-O-H). Thermodynamically, the autoxidation of hydrocarbons containing carbon, hydrogen and oxygen to the stable end products carbon dioxide (CO_2) and water (H_2O), is very favourable. However, spontaneous oxidation is generally unfavourable at normal STP conditions due to the high activation energies required to initiate autoxidations. These oxidation reactions are therefore kinetically unfavourable for most compounds.

2.3.2.1 Generalised autoxidation mechanism

Discussion of this type of reaction is simplified by the fact that up to a point, the oxidation of a large number of compounds involves the same elementary steps. Consider, for example, a generalised substrate containing a carbon-hydrogen bond:

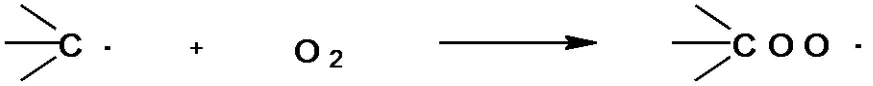


The first step in the oxidation of a particular substrate involves the cleavage of the “active” carbon-hydrogen bond. This cleavage is brought about by abstraction of the hydrogen atom by some free-radical species (usually an initiator like a hydroperoxide, since the O—O bond in hydroperoxides is weak and easily undergoes homolysis). Evidently, for any particular abstracting species, under a particular set of conditions, the ease with which this reaction occurs will depend on the strength of the carbon-hydrogen bond.[63] Strengths of carbon-hydrogen bonds vary considerably depending on the overall structure of the substrate.



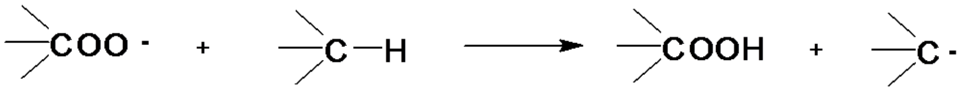
[2.1]

The free-radical produced in reaction (2.1) combines with oxygen, which itself is a bi-radical:



[2.2]

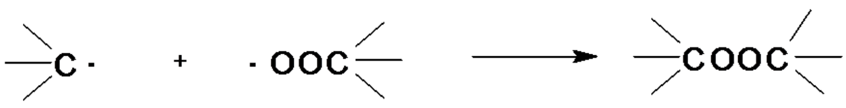
The product of this reaction, a peroxy radical, can abstract hydrogen from another substrate molecule to give a hydroperoxide and a substrate radical:



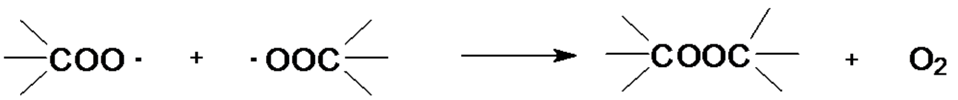
[2.3]

The substrate radical produced in reaction (2.3) can react with more oxygen to give another peroxy radical, resulting in a chain reaction in which (2.2) and (2.3) are the propagation steps, and the primary product is a hydroperoxide. As in all free-radical chain reactions, the number of times reactions (2.2) and (2.3) occur in any particular chain, i.e. the chain length, is limited by the occurrence of termination reactions in which free-radicals are consumed.

[2.4]



[2.5]



[2.6]

If the reaction is carried out in the presence of an excess of oxygen, reaction (2.2), the reaction of substrate radicals with oxygen is very rapid and consequently the concentration of substrate radicals is very low. Under such conditions reactions (2.4) and (2.5) are considered to be negligible as termination reactions compared with reaction (2.6). If reactions (2.1), (2.2), (2.3) and (2.6) were the only reactions occurring in the system, the products obtained would be hydroperoxide from reaction (2.3) and peroxide from reaction (2.6). The relative amounts of these products would depend on the chain length of the reaction, i.e. the number of cycles of reactions (2.2) and (2.3) which occur before termination of the chain, and, as most important oxidations have high chain lengths, the main product would be expected to be hydroperoxide.

The mechanism of autoxidation becomes more complicated at high hydrocarbon conversions and at elevated temperatures, the reason being the thermal decomposition of alkyl hydroperoxides to easily oxidized secondary products such as alcohols, aldehydes and ketones. Selective hydrocarbon oxidation is therefore often advantageously carried out at low conversions under mild conditions with the recycling of unreacted hydrocarbons.

2.3.2.2 Metal catalysis in autoxidations

The introduction of a metal catalyst into an autoxidation reaction mixture may influence the course of such reactions in two ways,[64] namely:

- chain initiation by facilitating radical formation, and
- chain propagation by participating in hydroperoxide decomposition.

From a cymene (to cymene hydroperoxide) oxidation point of view, the first of these is desirable so as to reduce reaction times, but the second is undesirable since this will reduce the yield of hydroperoxide and increase the yield of undesirable secondary oxidation products. The interest in metal catalysts for its effect on chain initiation lies in the possibility of influencing the position of attack in substrates with more than one “active” centre.

Although metal catalysts may actively participate in chain initiation, the most commonly accepted role ascribed to metal catalysts during autoxidation reactions is their participation in the decomposition of hydroperoxide or peroxide species.[65] When such species are added at the start of the reaction, the metal ions can induce their decomposition and reduce the induction period normally observed for uncatalyzed autoxidation reactions. In addition, if such species are formed during the course of the reaction, the presence of the metal catalyst may accelerate their decomposition and increase the overall reaction rate and/or moderate the course of the reaction.

Two basic reactions have been proposed for the decomposition of hydrogen peroxide by Fe(II)[66] and applied to the decomposition of hydroperoxides catalyzed by metal ions.[67-70]

$$RO_2H + M^{n+} \longrightarrow RO^{\bullet} + OH^{-} + M^{(n+1)+} \qquad [2.7]$$

$$RO_2H + M^{(n+1)+} \longrightarrow RO_2 + H^{+} + M^{n+} \qquad [2.8]$$

If a given metal ion is capable of affecting only one of the above reactions, then stoichiometric rather than catalytic decomposition of the hydroperoxide will occur. If the metal ion in question is a strong reducing agent, the decomposition will occur according to eqn. (2.7) and according to eqn. (2.8) if it is a strong oxidizing agent. When, however, a metal ion has two oxidation states (separated by one electron unit) of comparable stability, then both reactions can occur concurrently and a catalytic cycle is established. The overall reaction in such a situation then constitutes the decomposition into alkoxyl and peroxyl radicals (eqn. (2.9)).

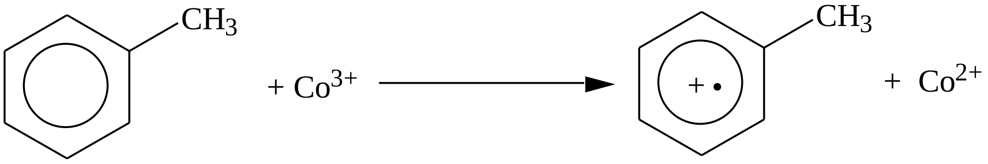
$$2RO_2H \longrightarrow RO_2^{\bullet} + RO^{\bullet} + H_2O \qquad [2.9]$$

It is believed that it is eqn. (2.9) that forms the basis for the effectiveness of catalysts such as cobalt and manganese in the oxidation of hydrocarbons to the corresponding carboxylic acids. It does not, however, explain the use of metal catalysts in the autoxidation of cumene and cymene to increase the selectivity to the corresponding hydroperoxide. One possible initiating mechanism, originally proposed for alkane oxidations, involves the participation of a high-valent metal ion in hydrogen abstraction as shown in eqn. (2.10).

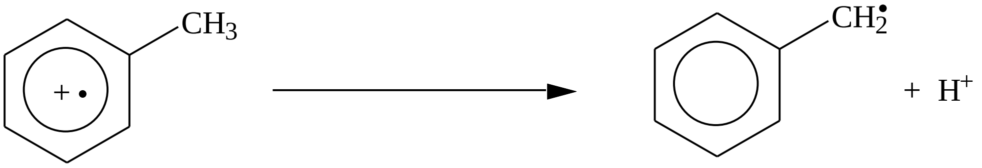
$$R\text{-}H + Co(III) \longrightarrow R^{\bullet} + Co(II) + H^{+} \qquad [2.10]$$

This type of participation in chain initiation is, however, not believed to be of any importance during the metal-catalyzed autoxidation of alkyl-aromatic compounds, except when using high metal concentrations (0.4 – 0.5mol/mol of substrate).[71]

An alternative mechanism that has been proposed for the participation of metal catalysts in chain initiation during the air oxidation of alkyl-aromatic compounds is the electron transfer mechanism.[72-74] This mechanism, which involves the removal of an electron from the aromatic ring (eqn's 2.11 and 2.12), is only applicable in cases where the aromatic ring is reasonably electron rich, and where the metal ion is a strong oxidizing agent in its high-valent state.



[2.11]



[2.12]

Metal ions typically associated with electron transfer oxidations include cobalt(III) and manganese(III). In the presence of dioxygen, the benzylic radical will give a peroxyl radical, which in turn may abstract a hydrogen atom from another substrate molecule to give the corresponding hydroperoxide. It is therefore clear that the electron transfer mechanism will only be significant in those cases where the metal ion is used in its high oxidation state, and will occur in conjunction with the classical autoxidation (free radical) mechanism.

In the presence of added halogens, and in particular bromide, as reaction promoters, the oxidation of alkyl aromatic compounds is dramatically enhanced.[75-78] It has been claimed that concentrations of at least 0.1 M are required for the cobalt acetate bromide system to be optimally active,[76] and that none of the other halogens approach bromide in activity.

In the presence of bromide ions, chain initiation is believed to be facilitated by the formation of bromine atoms, most probably in the form of a metal-bromine-atom complex (eqn’s 2.13 – 2.15).

$M^{n+} + Br^{-} \longrightarrow M^{n+}Br$ [2.13]

$M^{n+}Br \longrightarrow M^{(n+1)+}Br \longrightarrow M^{n+}Br^{\bullet}$ [2.14]

$M^{n+}Br^{\bullet} + R\text{-}H \longrightarrow R^{\bullet} + M^{n+} + HBr$ [2.15]

Oxidation of the metal ion from its low to its high oxidation state as represented in eqn (2.14) is most probably facilitated by peroxy radicals initially present in the reaction mixture.

2.3.2.3 Autoxidation of cymene

In discussing the free radical oxidation (autoxidation) of cymene with the view to identify possible areas for improvement, it is probably best to consider the entire process in different stages. These stages could be defined as follows:

- Free radical (arylalkyl) formation (according to eqn (2.1));
- Addition of O_2 (eqn (2.2));
- Reactions of peroxy radicals;
- Reactions of hydroperoxides; and
- Reactions of alkoxy radicals.

2.3.2.3.1 Free radical (arylalkyl) formation

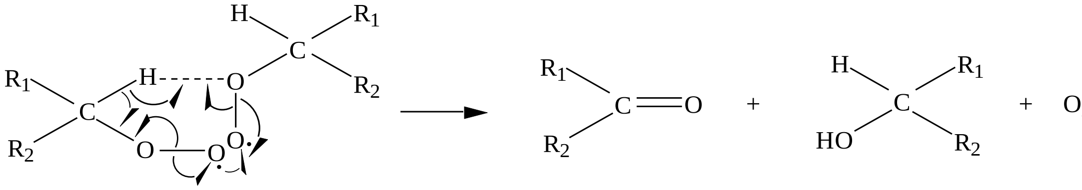
As stated previously, there are two possible positions of attack on cymene leading to the formation of either the tertiary radical or the primary radical as primary oxidation products. If one assumes that the primary hydrogen abstraction agent is a tertiary peroxy radical, formed from the deliberate addition of oxidized cymene, then the ratio of attack, according to eqn (2.3), on the isopropyl hydrogen as opposed to the methyl hydrogen will be in the order of 300:1.[79] This high preference for attack on the isopropyl group is due to both the weaker C-H bond in the isopropyl group, as well as the relatively low reactivity of the peroxy radical towards hydrogen abstraction.[80] However, due to the formation of other, more reactive radicals (e.g. $R^•$, $RO^•$, etc) during the radical chain oxidation, this ratio is much higher in practice and ratios as high as 4:1 have been reported.[37]

2.3.2.3.2 Addition of O_2

Because of the reactivity of alkyl and arylalkyl radicals, initially formed during autoxidation reactions, reaction (2.2) is so rapid that the concentration of aralkyl radicals will be too low to participate in any recombination reactions. In industry, however, oxidation reactions are normally run with an O_2 off-gas concentration near zero. This implies that the upper part of the oxidation reactor (bubble column) is O_2 deficient and some build-up of these radicals may occur in this zone. Thus, practically all industrial-scale autoxidations produce radical trapping products according to eqn's (2.4), (2.5) and (2.6).[81]

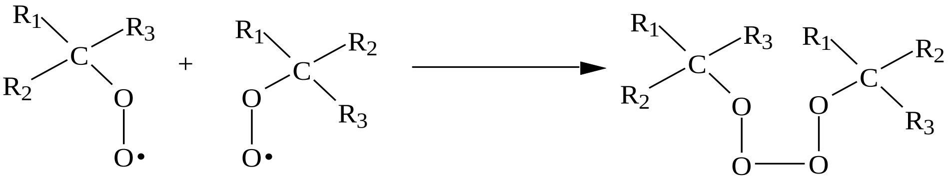
2.3.2.3.3 Reactions of peroxy radicals

The primary reaction of peroxy radicals, formed from the combination of dioxygen and alkyl or aralkyl radicals, is hydrogen abstraction as discussed in section 2.3.2.3.1. Because of their relatively low reactivity, peroxy radicals can accumulate in detectable concentrations. In the oxidation of cumene, for example, radical concentrations of up to 8×10^{-5} mol dm^{-3} were detected by ESR spectroscopy.[82] Peroxy radicals therefore frequently recombine, for example by reaction (2.16).

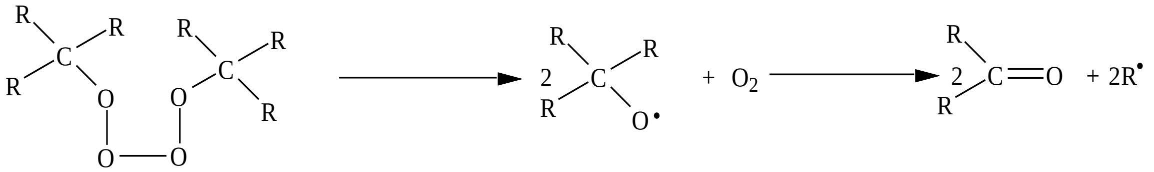


[2.16]

Lacking α-hydrogens, tertiary peroxy radicals cannot be stabilized in the same simple way as primary and secondary radicals, and they generally recombine to give tetroxides, which subsequently decompose to form very stable di-*tert*-alkoxy radicals (eqn (2.17)). The latter may either form tertiary alcohols or decompose further with cleavage of the carbon framework to form ketones, aldehydes, alkanes, or other decomposition products (eqn (2.18)).



[2.17]



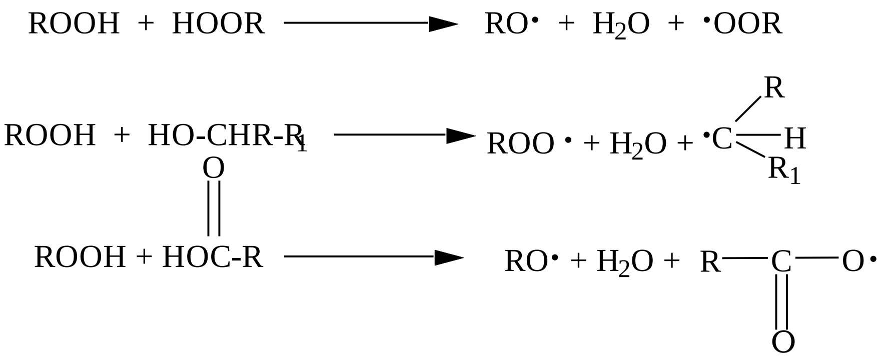
[2.18]

Because reactions of the type (2.18) have high activation energies, these reactions occur relatively slowly under mild conditions.[83]

2.3.2.3.4 Reactions of hydroperoxides

The stability of hydroperoxides depends on (1) the structure, (2) the surrounding medium, and (3) the active components in the medium. For aliphatic hydroperoxides, the stability decreases in the order: tertiary > secondary > primary, whilst hydroperoxides in a position α to a double bond or an aromatic ring (resonance stabilized) are fairly stable.[63] Because C-H bonds in such α-positions are weakened due to resonance stabilization of the incipient radical, these types of hydroperoxides (e.g. cumene hydroperoxide) are formed at lower temperatures than others, and can be obtained in high yields.[84]

The homolytic decomposition of hydroperoxides is catalyzed by compounds that form hydrogen bonds, for example by hydroperoxides themselves, alcohols, and carboxylic acids (eqn's (2.19) – (2.21)).



$$ROOH + HOOR \longrightarrow RO^{\bullet} + H_2O + {}^{\bullet}OOR \qquad [2.19]$$

$$ROOH + HO\text{-}CHR\text{-}R_1 \longrightarrow ROO^{\bullet} + H_2O + {}^{\bullet}C(R)(H)R_1 \qquad [2.20]$$

$$ROOH + HOC(=O)\text{-}R \longrightarrow RO^{\bullet} + H_2O + R\text{—}C(=O)\text{—}O^{\bullet} \qquad [2.21]$$

In hydrocarbon solvents the decomposition rate depends strongly on the C-H dissociation energy of the solvent (or the substrate in cases where the substrate acts as the reaction solvent): the lower the C-H dissociation energy, the faster the decomposition.[85]

Radicals also catalyze the decomposition of radicals, hence the addition of radical scavengers can reduce hydroperoxide decomposition. Although bases react with primary and secondary hydroperoxides according to eqn's (2.22) – (2.24), bases have practically no effect on tertiary hydroperoxides.

$$ROOH + B^{-} \longrightarrow ROO^{-} + B\text{-}H \qquad [2.22]$$

$$ROO^{-} + ROOH \longrightarrow RO^{-} + ROH + O_2 \qquad [2.23]$$

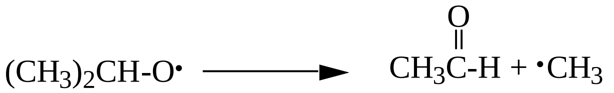
$$RO^{-} + ROOH \longrightarrow ROH + ROO^{-} \qquad [2.24]$$

The reaction of hydroperoxides in the presence of acids will be addressed under the heading of hydroperoxide cleavage (see later).

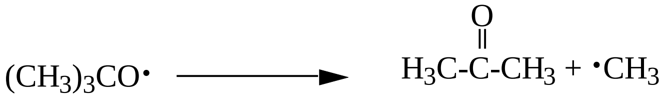
2.3.2.3.5 Reactions of alkoxy radicals

Although the alkoxy radicals formed in the decomposition of hydroperoxides are very reactive, only primary alkoxy radicals react predominantly by means of hydrogen abstraction to form alcohols (eqn (2.25)). Secondary and especially tertiary alkoxy radicals react via C-C fragmentation to give aldehydes or ketones, with only small amounts of alcohols (eqn's (2.26) – (2.27)).

$$H_3CO^{\bullet} + R\text{-}H \longrightarrow H_3COH + R^{\bullet} \qquad [2.25]$$



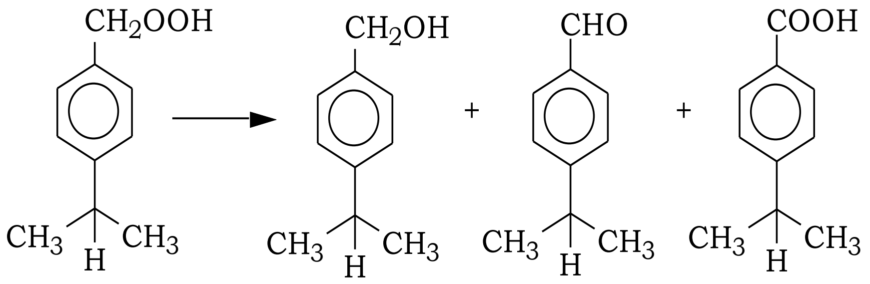
$$(CH_3)_2CH\text{-}O^{\bullet} \longrightarrow CH_3\overset{\overset{\displaystyle O}{\|}}{C}\text{-}H + {}^{\bullet}CH_3 \qquad [2.26]$$



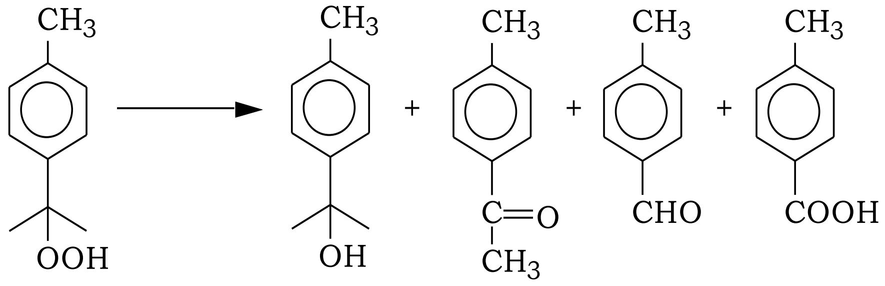
$$(CH_3)_3CO^{\bullet} \longrightarrow H_3C\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}CH_3 + {}^{\bullet}CH_3 \qquad [2.27]$$

2.3.2.3.6 Reaction products/by-products

Based on the considerations given above, the formation of oxidation products and by-products during the autoxidation of cymene can be rationalized entirely on the hand of the formation and reactions of the primary and tertiary hydroperoxides. (The formation of by-products arising from the autoxidation of impurities such as n-propyltoluene in the cymene mixtures is not considered here.) The major products/by-products arising from the autoxidation of the methyl group are illustrated in eqn. (2.28) while the products/by-products resulting from the oxidation of the isopropyl group are given in eqn. (2.29).



[2.28]



[2.29]

In terms of the optimization of the selectivity towards hydroperoxides (both tertiary and primary), the following strategies might be considered:

- Keep reaction temperatures as low as possible to minimize thermal decomposition of hydroperoxides according to eqn. (2.18).
- Avoid the use of solvents with C-H bonds that are active in radical abstraction processes.
- Use the substrate as reaction solvent where possible to ensure a low concentration of peroxy radicals (eqn. (2.3)). This will also minimize recombination reactions of the type shown in eqn. (2.17).
- Avoid the use of catalyst materials capable of forming acids during the autoxidation process, e.g. cobalt(II)bromide, as the formation of such acids may lead to hydroperoxide decomposition (see later).
- Consider the use of radical scavengers to minimize chain branching according to eqn's (2.19) and (2.20).

It is very difficult to see how the use of soluble metal catalysts can aid in the improvement of hydroperoxide selectivity (total hydroperoxide as well as tertiary hydroperoxide) in terms of the currently accepted explanations of the role of metal catalysts in autoxidation reactions. In terms of these explanations, the primary function of such catalysts is to aid in the decomposition of initially formed hydroperoxides, a role contradictory to that required for the selective oxidation of cymene to the tertiary hydroperoxide. Furthermore, the use of promoter substances such as bromides, which can be converted *in situ* to potential hydrogen abstracting bromine atoms, may also work against increased tertiary hydroperoxide selectivity in view of the high activity of such species towards hydrogen abstraction.

2.3.2.4 Technology Considerations

In view of the considerations given above, it is of interest to examine current industrial practices for the autoxidation of cymene. In Japan in particular, *m*-and *p*-cresol are synthesized by oxidation of cymene *(Sumitomo Chemical and Mitsui Petrochemical).* There are, however, a number of patent specifications that describe various approaches for the selective oxidation of cymene to the tertiary hydroperoxide.

2.3.2.4.1 Non-catalytic oxidation

Oxidation of cymene is normally carried out in industry in the absence of catalysts so as to minimize the formation of primary hydroperoxide. Oxidations are normally carried out in the presence of a base (pH 7-10) to neutralize acidic by-products during the oxidation process. Various radical initiators, including partially oxidized cymene oil can be used to initiate the oxidation process. Several problems are associated with the above oxidation, including:

- Poor selectivity to tertiary hydroperoxide. Provided that substrate conversions are restricted to below 20%, typical selectivities to tertiary cymene hydroperoxide range from 70-80 % based on cymene consumed.[86]
- Reaction control. Since reactions are carried out at elevated temperatures, careful control is required to prevent the formation of coloured reaction products and the formation of explosive gas mixtures.[86]
- Long reaction times. Autoxidations in the absence of metal catalysts are often difficult to initiate and reaction rates are normally low. In order to decrease initiation times and increase oxidation rates, initiator substances may be added to the substrate.[86]

Apart from the disadvantages referred to above, such oxidations suffer the additional drawback of forming significant amounts of primary hydroperoxide, which need to be extracted or decomposed in a separate step before the acid cleavage of the tertiary hydroperoxide. Cymene oxidations are therefore commonly carried out in the presence of a basic aqueous sodium carbonate solution to decompose and extract primary hydroperoxide oxidation products.[87] These by-products may be formed in quantities as high as 0.5kg per kg of cresol. The use of basic aqueous solutions decreases oxidation rates compared to oxidations in the absence thereof, making reaction times even longer.[87]

2.3.2.4.2 Oxidation using emulsifiers (stearic acid)

In this process, which is aimed at improving reaction rates, the reaction is done in the presence of an alkaline aqueous phase and oxidized cymene oil containing 60% *p*-cymene hydroperoxide as a reaction initiator, and stearic acid as an emulsifier.[88] This process can safely give a high quality hydroperoxide, but there are drawbacks too, such as a lower reaction rate and the difficulty of separating the oil and aqueous layers of the reaction mixture due to the emulsifier remaining therein, thereby causing a troublesome problem of after-treatment. In a variant of this process, *p*-cymene hydroperoxide was used as both the initiator and the emulsifier and by employing strong, mechanically forced mixing, this variant was claimed to show superior selectivity at comparable oxidation rates to the conventional processes using emulsifiers.

2.3.2.4.3 Oxidation using metal catalysts

In attempts to increase the rate of cymene oxidation while maintaining, or improving selectivity to the tertiary hydroperoxide, several metal catalysts have been investigated for the said oxidation. Metal catalysts investigated include copper, manganese, cobalt, nickel and iron. In most cases, the use of metal catalysts is only partially successful due to the lower selectivities (promotion of primary hydroperoxide formation), low reaction rates and catalyst deactivation. The most promising attempts appear to be the use of copper carbonate in basic solutions. In this process, the *p*-cymene is oxidized by air in the presence of a basic solution and a copper catalyst, wherein an aqueous solution containing (A) cupric carbonate and (B) an alkali metal carbonate is prepared outside the oxidation system.[89] According to this process, even under basic conditions, deactivation of the catalyst due to precipitation is prevented, and the p-cymene hydroperoxide can be obtained at high oxidation rates.

2.3.2.4.4 Comparison of different technologies

Table 2.1: Oxidation of Cymene

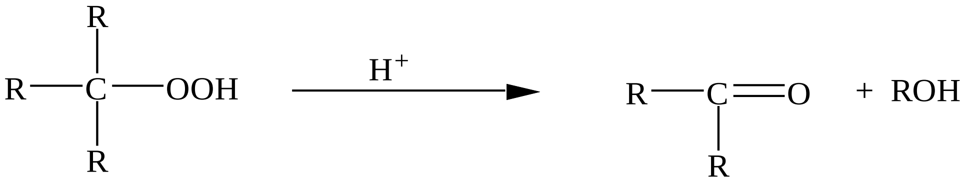
	Non-catalysed	Metal catalysed	Non-emulsified	Emulsifier
Substrate loading (%)	90	90	70	70
Solvent	9:1 Benzene/Na_2CO_3(aq)	9:1 Benzene/Na_2CO_3(aq)	NaOH(aq)	NaOH(aq)
Catalyst (ppm)	-	$Cu(SO_4)_2$ (0.5)	-	-
Emulsifier (ppm)	-	-	-	Stearic acid (0.8)
Temp. (°C)	120	120	100	100
Time (hrs)	Not specified	Not specified	10	8
Conversion (%)	14.7	15	19	24.6
Selectivity (%)*	69	42	78.3	62.8

*The ratio (%) of the mole of the formed cymene hydroperoxide to the consumed starting cymene

The data in Table 2.1 show that the conversion of cymene to the corresponding hydroperoxide is low for all the processes. Comparing the selectivities for the different processes, we can see that a higher selectivity towards the total hydroperoxide is obtained in the absence of a soluble metal catalyst and emulsifier. To improve the economic viability of the cymene route, a significant improvement in the selectivity to the tertiary hydroperoxide is required during the oxidation step.

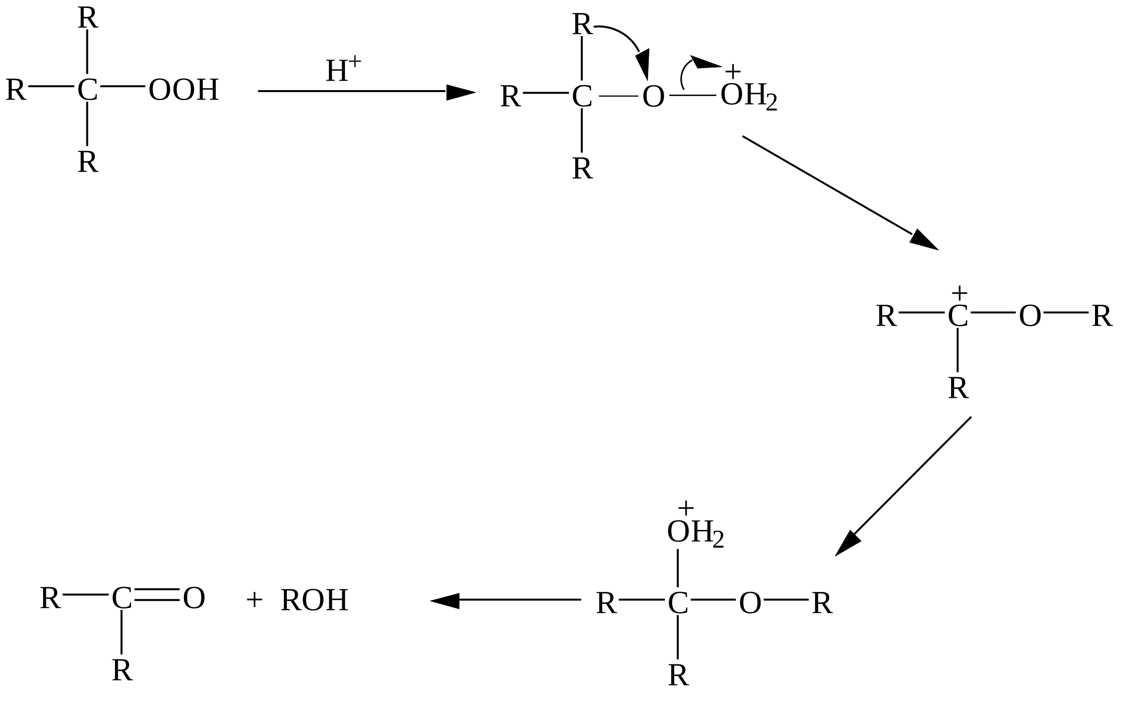
2.4 ACID CLEAVAGE OF CYMENE HYDROPEROXIDE

Hydroperoxides, R_3COOH (R = alkyl, aryl, or hydrogen) can be cleaved (eqn. (2.30)) by proton or Lewis acids in a reaction whose principal step is a rearrangement[90] resembling the rearrangement in the well-known Baeyer-Villiger rearrangement.



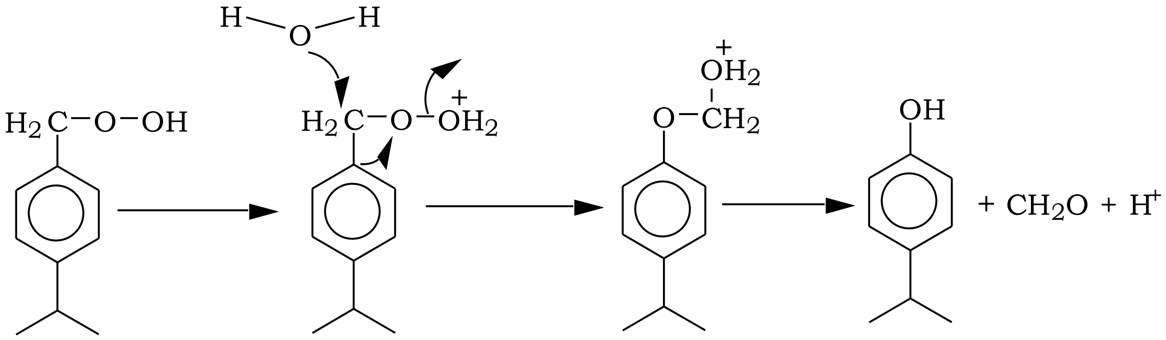
$$R_3C{-}OOH \xrightarrow{H^+} R_2C{=}O + ROH \qquad [2.30]$$

When aryl and alkyl groups are both present on the substrate, migration of the aryl group occurs preferentially. For alkyl groups the migratory order is tertiary > secondary > Pr ≈ H > Et > Me.[90] The most commonly accepted mechanism[90] is illustrated in Scheme 2.8.

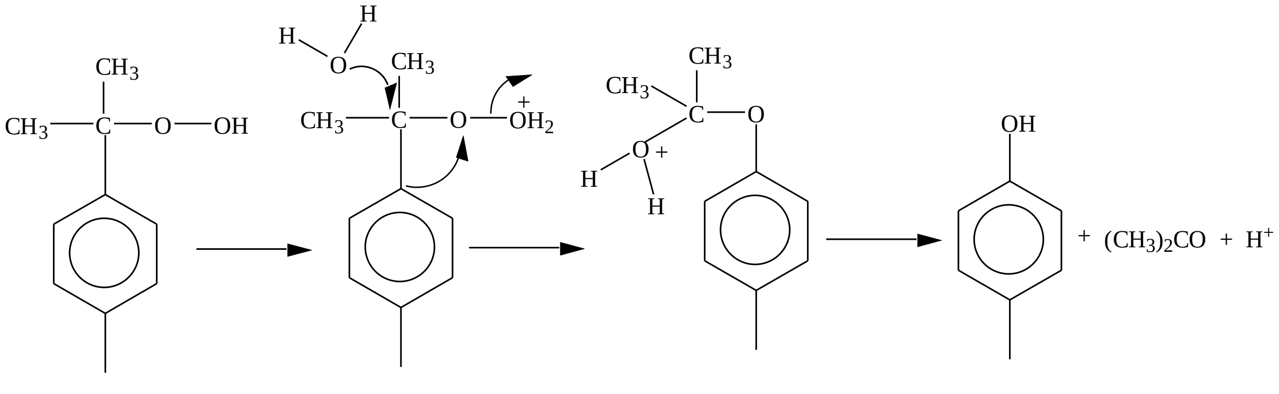


Scheme 2.8 Rearrangement of hydroperoxides

In the case of cymene, both the tertiary hydroperoxide and the primary hydroperoxide may undergo rearrangement as illustrated in Scheme 2.9 and 2.10.



Scheme 2.9 **Rearrangement of primary hydroperoxide**



Scheme 2.10 **Rearrangement of tertiary hydroperoxide**

2.5 SUMMARY

From the preceding discussion regarding the production of cresols from cymene it is possible to identify the following characteristics of this process:

The process is a three-step process, each particular step having its own difficulties that give relatively low selectivities for a particular step. The result is an overall process that gives rather poor yields. As example, if it is assumed that each of the individual steps give the desired product in 90% selectivity, the overall yield is $0.9^3 \times 100 = 72.9\%$.

Of the three steps, propylation, oxidation and hydroperoxide cleavage, oxidation offers by far the biggest challenge. A higher selectivity to the desired tertiary hydroperoxide will not only directly impact on the overall process yield, but lower amounts of primary hydroperoxide will considerably simplify the process. Of particular importance in this regard is the requirement to remove or destroy primary hydroperoxide prior to hydroperoxide cleavage, and the requirement for extensive separation and recycling facilities. As a result of primary hydroperoxide formation and hydroperoxide decomposition at higher concentrations of hydroperoxide, the overall conversion for the oxidation step must be kept low and conversions of *ca.* 15% is the rule. An improvement in the conversion of this step, whilst maintaining or, preferably, improving the selectivity to the tertiary hydroperoxide, will amount to a significant improvement in the economic viability of this process.

The main objective of this investigation is to evaluate different oxidation methodologies for the production of the tertiary hydroperoxide derivative of cymene. In the light of the considerations given previously in this chapter, the various specific objectives of the investigation may be summarized as follows:

- To evaluate various catalyst systems and oxidation systems for the oxidation of cymene with the view to increasing the selectivity to tertiary hydroperoxide at increased cymene conversions.

- To evaluate the impact of various reaction conditions on the selectivity to tertiary hydroperoxide and to determine a set of optimized reaction conditions.

The following will not be investigated during the course of the investigation:

- The extraction and/or selective decomposition of primary hydroperoxide;
- The acid cleavage of the tertiary hydroperoxide; and
- The isolation and purification of cresol products.

CHAPTER 3

EXPERIMENTAL

3.1 MATERIALS

3.1.1 Reagents for synthesis

All materials used in the oxidation procedures, together with their sources and respective grades, are listed in Tables 3.1a and b, and were used as received.

Table 3.1a Organic reagents for synthesis

CHEMICAL NAME	FORMULA	SOURCE	GRADE
p-Cymene	$CH_3C_6H_4CH(CH_3)_2$	Aldrich	CP
Dichloromethane	CH_2Cl_2	Merck	AR
Ethyl acetate	$CH_3COOC_2H_5$	Saarchem	AR
Ethanol	CH_3CH_2OH	Saarchem	AR
Methanol	CH_3OH	Saarchem	AR
Triphenylphosphine	$P(C_6H_5)_3$	Aldrich	AR
Acetic acid	CH_3COOH	ACE	AR

Table 3.1b Inorganic reagents for synthesis

CHEMICAL NAME	FORMULA	SOURCE	GRADE
Copper (II) sulphate	$CuSO_4$	Saarchem	AR
Cobalt (II) acetate	$Co(CH_3COO)_2$	Saarchem	AR
Sodium carbonate	Na_2CO_3	Saarchem	AR
Sodium bicarbonate	$NaHCO_3$	Merck	AR
Sodium iodide	NaI	Saarchem	AR
Boron phosphate	BPO_4	Aldrich	CP

Table 3.1b continued

CHEMICAL NAME	FORMULA	SOURCE	GRADE
Sodium thiosulphate	$Na_2S_2O_3$	ACE	AR
Sodium borohydride	$NaBH_4$	BDH	AR
Manganese sulphate	$MnSO_4$	Merck	AR
Medical air	21% O_2: 79% N_2	Air products	High purity

3.1.2 Reagents for analysis

The reagents used for gas chromatography (GC) standards are listed in Table 3.2, as well as their sources and grades.

Table 3.2 Reagents used as GC standards

Compound	Chemical formula	Source	Grade[a]
p-Cymene	$CH_3C_6H_4CH(CH_3)_2$	Aldrich	CP
Nitrobenzene	$C_6H_5NO_2$	Merck	CP
p-Isopropyl benzyl alcohol	$(CH_3)_2CHC_6H_4CH_2OH$	Aldrich	CP

[a] CP = Chemically pure

3.2 SYNTHETIC PROCEDURES

3.2.1 Synthesis of *p*-Cymenol

To a 250cm^3 glass reactor (Johannesburg Glassblowing Industries) was added *p*-cymene (35.0g; 261mmol) and cymene hydroperoxide initiator (2.0g; 12mmol). A reflux condenser was attached and the mixture was stirred vigorously (2000rpm) by means of an overhead stirrer fitted with a propeller-type stirrer head. The reaction temperature was controlled at 100^{0}C by passing heated oil through the thermostatic jacket of the reactor with a circulator. After equilibration (ca. 10 minutes), air was introduced through a gas inlet tube at the bottom of the reactor at a flowrate of 40cm^3/min. The reaction was heated and stirred in this way for 24 hours. After this the unreacted cymene was removed by high vacuum distillation. The residue was then washed with 0.5% Na_2CO_3 to remove the primary hydroperoxide. The tertiary hydroperoxide product was reduced with a 1:1 molar ratio of triphenylphosphine at room temperature to form *p*-cymenol. The mass spectrum of *p*-cymenol is shown in Fig 3.1 and displays the major characteristic fragmentations (m/z=43; m/z=91 and m/z=135).

3.2.2 Synthesis of cumic acid

To a 250mL glass reactor was added *p*-cymene (35.0g; 261mmol), 20cm^3 of a 0.5% Na_2CO_3 aqueous solution and 2.0g cymene hydroperoxide initiator. The reaction temperature was controlled at 100^{0}C. Air was introduced after equilibration at a flow rate of 40cm^3/min. After 24 hours, the aqueous phase was separated from the organic phase and acidified with HCl to pH 1. The white precipitate of cumic acid formed was filtered and washed three times with water and finally dried in an oven at 150^{0}C. The mass spectrum of cumic acid is shown in Figure 3.2 and shows the major characteristic fragmentations (m/z=77; m/z=105; m/z=149 and m/z=164).

3.2.3 Preparation of vanadium phosphate catalyst

To a 250mL three-necked round-bottomed flask was added V_2O_5 (35g; 82mmol), 90mL of benzyl alcohol and 60mL of iso-butanol. A reflux condenser was attached and the mixture was refluxed for 8hrs. It was then left stirring overnight without any heating. After this, 99% o-H_3PO_4 (28g; 286mmol) was added and the mixture refluxed for 4hrs. The product was cooled and the precipitate was separated by filtration under suction, and washed with three 25mL portions of water. The precipitate was dried overnight at 120^{0}C to give the precursor $VOHPO_4.0.5H_2O$. XRD analysis (Figure 3.3) confirmed the catalyst precursor $VOHPO_4.0.5H_2O$ (vanadyl hydrogen phosphate hemihydrate). This precursor was calcined to remove the water to afford the vanadium phoshate catalyst in the form $(VO)_2P_2O_7$.

Fig. 3.1 Mass spectrum of *p*-cymenol

Fig. 3.2 Mass spectrum of cumic acid

Fig. 3.3 XRD Scan of $(VO)_2P_2O_7$

3.3 EXPERIMENTAL PROCEDURE

3.3.1 Apparatus for oxidation procedures

Two different types of apparatus were used for the oxidation of cymene, namely a 100mL round-bottomed flask and a cylindrical reactor (250mL capacity) made by Johannesburg Glassblowing Industries. Air was supplied to the round-bottomed flask via a Pasteur pipette. Airflow was controlled by means of a pressure regulator connected to a needle valve, to allow fine setting of the airflow. For the round-bottomed flask, temperature control was achieved by immersing the flask into a thermostatically-controlled oil bath, both the oil bath and internal solution being stirred magnetically. For the glass reactor, temperature control was achieved by circulating heated oil through the thermostatic jacket of the reactor by means of a circulator. In this case, an overhead stirrer, fitted with a propeller-type impeller, was used for stirring at 2000rpm.

3.3.2 Oxidation procedure

The substrate, solvent and other starting materials were weighed directly into the appropriate glass reactor. Stirring was commenced at a rate of 2000rpm. The reactor and reaction mixture was allowed to equilibrate to the required temperature. Airflow was commenced at the required rate ($40cm^3$/min) and timing of the reaction commenced. Two aliquots ($2cm^3$) of the reaction mixture were removed from the reaction vessel at regular intervals and one portion was titrated iodometrically to determine the total amount of hydroperoxide. The hydroperoxide of the second aliquot was then selectively reduced using reduction methods to products, which could be analyzed on a GC. The internal standard (nitrobenzene) was weighed into these samples and the solvent dichloromethane was added for quantitative analysis.

3.4 ANALYTICAL TECHNIQUES

3.4.1 Iodometric titration

Total cymene hydroperoxide formed during oxidation reactions was determined by iodometric titration, which was performed by weighing 0.2g of the cymene hydroperoxide sample into 10mL of dichloromethane. The flask was flushed with nitrogen to remove any oxygen present. A saturated sodium iodide solution was added (2mL), followed by 15mL of glacial acetic acid. The flask was stoppered and allowed to stand in the dark for 5-10 min. Afterwards, 50mL of water was added and the solution was titrated to a starch endpoint with 0.05M $Na_2S_2O_3$ (previously standardized with a standard iodine solution).

3.4.2 G.L.C. – Mass Spectrometry

G.C. – Mass spectrometry was performed on a 5890 series II plus gas chromatograph coupled to a HP 5972 series mass selective detector. The G.C. was equipped with a HP-5 MS capillary column (30mm x 0.25mm i.d.). Data were acquired from the detector by means of a Hewlett Packard personal computer equipped with HP 61034 C software.

3.4.3 GC Analysis

GC Analysis was performed on a Varian 3400 Gas Chromatograph equipped with a 30m x 0.32mm i.d. SPB-20 column (Supelco) and a flame ionization detector (FID). Data were acquired from the detector by means of a Shimadzu C-R6A Chromatopac integrator connected to the GC system. The carrier gas flow rate was $30cm^3/min$ at a column head pressure of 12 psi. The injector was operated in split mode at a split ratio of 1:99 and an injection volume of 0.5μl was used. The injector and detector temperatures were 250^0C and 300^0C, respectively, for the analysis of *p*-cymene and the reduction products of the corresponding hydroperoxides. The column temperature programme used is summarized in Table 3.3.

Table 3.3: G.C. Temperature program for analysis of *p*-cymene

Column	SPB-20
Column Initial Temp. (^{0}C)	70
Initial Hold Time (min.)	5
Heating Rate (^{0}C min.$^{-1}$)	15
Column Final Temp. (^{0}C)	280
Final Hold Time (min.)	10

The internal standard method was used for all quantitative work, and nitrobenzene was employed as internal standard. Response factors for the compounds of interest were determined by means of calibration injections (x3) with known masses of standards and internal standard prior to each set of analyses.

CHAPTER 4

METHOD EVALUATION FOR ANALYSIS OF HYDROPEROXIDES

4.1 INTRODUCTION

Hydroperoxides, especially in a pure state, are known for their instability and decomposition at high temperatures, which makes it difficult for direct analysis using GC and HPLC instruments, since obtaining reference standards is problematic. While there are several potential methods for the estimation of the total amount of hydroperoxide in a particular sample, methods that can quantitatively discriminate between different types of hydroperoxides are not well described. Iodometric titration is the most widely used and most generally applicable method for analysis of hydroperoxides, but it cannot differentiate between different types of hydroperoxides. The objective of this particular part of the investigation was to establish a method whereby the primary and tertiary hydroperoxides, formed during the oxidation of *p*-cymene, could be determined separately and accurately.

4.2 OVERVIEW OF METHODS FOR THE DETERMINATION OF HYDROPEROXIDES

Hydroperoxides can be determined by various methods, i.e. physical and instrumental methods, chemical reduction methods, colorimetric and photometric methods.[79] These methods are discussed below and also the drawbacks associated with some of them.

(i) *Physical and instrumental methods*

- *Chromatography*: t-Alkyl hydroperoxides are the most stable members of this class; they can be determined by gas chromatography if they contain a maximum of about eight carbon atoms. Gas chromatography is widely used for the analysis of mixed alcohols obtained by the reduction of mixed hydroperoxides. Adsorption and liquid-liquid partition are mild and non-destructive techniques that have been used in the analysis of mono- and di-hydroperoxides, as well as hydroxyhydroperoxides. The column adsorbent is of prime importance in determining separation efficiency and hydroperoxide survival. Silicic acid and celite are frequently used, but alkaline alumina is often too destructive.
- *Polarography*: Hydroperoxides are readily reduced in a polarograph and they can be both qualitatively and quantitatively determined on a micro scale in aqueous or non-aqueous media. Polarography is better suited for distinguishing peroxide types than for identifying individual compounds.

(ii) *Chemical reduction methods*[79]

- *Iodometric methods*: Reduction of hydroperoxides by iodide ion is the most widely used and most generally applicable method for analysis of hydroperoxides. Iodide ion reacts rapidly and stoichiometrically with hydroperoxides in acidic solution, liberating iodine, which is determined by titration methods or colorimetrically. The major drawback of this method is that other classes of organic peroxides and hydrogen peroxide oxidize iodide ion; however, in the absence of interfering substances, hydroperoxides can be precisely and accurately determined by this method.
- *Stannous ion*: Reduction of hydroperoxides with stannous chloride and titration of the excess of stannous ion avoids the interference in the iodide methods by sulphur compounds that consume iodine. The method, although precise and accurate, is lengthy and complex

and requires careful purging with nitrogen and the absence of other reducible hydroperoxides.

- *Ferrous ion*: Reduction by ferrous ion is useful for the quantitative analysis of easily reduced peroxides, particular alkyl hydroperoxides formed in the development of fat rancidity and in other autoxidation processes. Unless ferrous ion reduction methods are conducted under carefully controlled conditions, results are irreproducible and inaccurate. Oxygen must be scrupulously excluded, solvent effects are serious and not understood, and chain reactions may consume peroxide without oxidizing ferrous ion.
- *Organic phosphines*: Tertiary phosphines reduce virtually every type of organic peroxide except the most unreactive ones. Hydroperoxides, as well as other easily reduced peroxides, are rapidly reduced and can be determined in the presence of dialkyl peroxides that are frequently formed in the preparation of hydroperoxides by displacement reactions.
- *Lithium aluminium hydride*: All classes of peroxides are reduced by lithium aluminium hydride. Organic hydroperoxides are smoothly reduced at room temperature to the corresponding alcohols with the evolution of two moles of hydrogen per mole of hydroperoxide; other peroxides form one mole of hydroperoxide. A drawback of this method is that interference by other reducible groups limits the utility of this reductant.

(iii) *Colorimetric and photometric methods*[79]

These methods are used to determine trace levels of peroxides, typically in rancid fats and other autoxidized natural products.

- *Aromatic diamines*: The best aromatic diamine reagents are 4,4’ diaminodiphenylamine and *N,N* - diphenyl-*p*-phenylenediamine, the oxidations of which produce highly absorbing blue dyes. The method is not specific for hydroperoxides.

- *Leuco Methylene Blue*: This reagent is not only one of the most sensitive colorimetric reagents, but it has an almost constant molar response for all reactive peroxide classes. Its main drawback is maintaining its analytical quality – the preparation and storage of the dye in benzene solution.

The ferrous ion and organic tertiary phosphine reduction methods were selected from the various methods and were investigated in detail.

4.3 METHOD VALIDATION

There are various definitions for the validation of an analytical method or testing procedure. For example, Chapman[91] defined the assay validation as establishing documented evidence that a process does what it purports to do. On the other hand, the USP/NF indicates that the validation of an analytical method is the process by which it is established, by laboratory studies, that the performance characteristics of the method meet the requirement for the intended analytical application. The two most important validation parameters of a method are its accuracy and precision. Accuracy is defined as the closeness of the assay result obtained by the assay method to the true value, while precision is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple sampling of a homogeneous sample. The method is applied to samples or mixtures of excipients. These excipients usually consist of known amounts of analyte, which are added both above and below the normal levels expected in the samples (% recovery studies), and this will be used to validate the selected method.

4.4 EVALUATION OF CHEMICAL REDUCTION METHODS

4.4.1 Iron (II) reduction

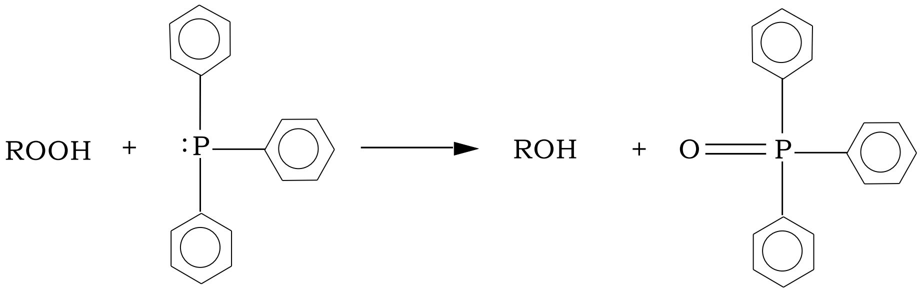
The hydroperoxide products were obtained by the oxidation of cymene with air at 100 ^{0}C for 24 hours. The tertiary and primary hydroperoxide were reduced with $FeSO_4$ to *p*-methylacetophenone and *p*-cumaldehyde respectively, and these compounds then analysed by GC as described in section 3.4.3. The total amount of hydroperoxide was determined by iodometric titration and compared to the total amount obtained from the $FeSO_4$ reduction and GC analysis. The results obtained (Table 4.1) show that the two values compare poorly, showing that the $FeSO_4$ reduction method will not be suitable for the simultaneous determination of the primary and tertiary hydroperoxide.

Table 4.1 Comparison of titration with GC results ($FeSO_4$)

Method	Total amount hydroperoxide	1° Hydroperoxide	3° Hydroperoxide
Titration	68.02%	-	-
GC Analysis	75.05%	15.02%	60.03%

4.4.2 Triphenylphosphine reduction

In the triphenylphosphine method, the hydroperoxides were reduced to their corresponding alcohols with formation of triphenylphosphine oxide in a 1:1 ratio (equation 4.1).



[4.1]

The primary and tertiary hydroperoxide from the oxidation of *p*-cymene were reduced to *p*-isopropylbenzyl alcohol and *p*-cymenol respectively. A reasonable mechanism for this reaction[92] involves attack by the phosphine on the hydroxyl oxygen of the hydroperoxide to give, in a smooth displacement reaction, the intermediate (A), which yields the products by a simple proton transfer.

$$[Ph_3P^+\text{-}OH \quad + \quad OR^-] \qquad (A)$$

The results obtain from this method are displayed in Table 4.2.

Table 4.2 Comparison of titration with GC results (triphenylphosphine)

Method	Total amount hydroperoxide	1° Hydroperoxide	3° Hydroperoxide
Titration	25.03%	-	-
GC Analysis	25.05%	1.80%	23.25%

The results obtained show a much closer comparison between the total hydroperoxide obtained from the iodometric titration and the total hydroperoxide obtained from the GC analysis following triphenylphosphine reduction. In view of the comparibility of the two results, it was decided to test the method further by means of a statistical analysis.

4.4.2.1 Statistical analysis of the triphenylphosphine reduction /GC-analysis method

A one-factor model with four different treatments was used to evaluate the method. In this evaluation, a sample of hydroperoxide (primary plus tertiary) was prepared by oxidizing cymene overnight as described previously. The total, primary and tertiary hydroperoxide amounts in this sample were determined by iodometric and GC-analysis after triphenylphoshine reduction. This sample was used as the standard sample in the series of analyses. The sample was then divided into several small samples. To each of the smaller samples were added cymene, *p*-isopropylbenzyl alcohol, *p*-cymenol, or a mixture of the two alcohols. Each of these samples was then subjected to triphenylphosphine reduction and GC analysis as described previously, and the percentage recoveries of the total amount of hydroperoxide, *p*-isopropylbenzyl alcohol and *p*-cymenol determined. The full design together with the responses obtained are given in Table 4.3.

Table 4.3 One factor factorial model

Std	Run	Block	Factor	Response		
				Sum (%)	Recovery 1^0 Alc. (%)	Recovery 3^0 Alc. (%)
10	1	1	3^0	90.00	80.00	93.19
5	2	1	Cymene	95.00	100.00	94.10
3	3	1	Standard	95.02	94.58	95.11
1	4	1	Standard	98.37	98.55	97.80
12	5	1	3^0 alc.	99.84	100.00	100.00
7	6	1	1^0 alc.	100.00	100.00	99.48
4	7	1	Cymene	90.00	100.00	92.93
13	8	1	Both alc.	98.92	100.00	96.96
11	9	1	3^0 alc.	95.00	90.00	95.00
8	10	1	1^0 alc.	100.00	100.00	99.50

Table 4.3 continued

Std	Run	Block	Factor	Response		
				Sum (%)	**Recovery 1^0 Alc. (%)**	**Recovery 3^0 Alc. (%)**
6	11	1	Cymene	98.06	93.86	99.18
15	12	1	Both alc.	97.95	93.27	99.78
14	13	1	Both alc.	99.95	100	98.5
2	14	1	Standard	97.16	97.24	97.14
9	15	1	1^0 alc.	95.54	99.54	97.68

1^0 alc. = *p*-isopropylbenzyl alcohol 3^0 alc. = *p*- cymenol

The responses for the sum and percentage recoveries for the individual alcohols in Table 4.3 were analyzed by means of analysis of variance (ANOVA). The results of these analyses are summarized in Table 4.4.

Table 4.4 Anova data

Source	**Sum of Squares**	**Degrees of Freedom**	**Mean Squares**	**F-Value**	$F^{Crit}_{4,10}$
Response: SUM					
Model	48.78	4	12.19	1.20	3.478
Residual	101.77	10	10.18		
Pure Error	*101.77*	*10*	*10.18*		
Cor Total	150.55	14			
Response: 1^0 Alcohol					
Model	171.66	4	42.92	1.63	3.478
Residual	263.65	10	26.37		
Pure Error	*263.65*	*10*	*26.37*		
Cor Total	435.32	14			
Response: 3^0 Alcohol					
Model	27.13	4	6.78	1.19	3.478
Residual	57.07	10	5.71		
Pure Error	*57.07*	*10*	*5.71*		
Cor Total	84.20	14			

The above analyses show that the model fit for each response is good since the F-values calculated for each model is smaller than the critical F-value with 4 and 10 degrees of freedom. It is now possible to compare the averages of the different treatments for each response. These averages are summarised in Table 4.5.

Table 4.5 Comparison of treatment averages

Treatment	**Sum**		**1° Alcohol**		**3° Alcohol**	
	Estimated Mean	**Std Error**	**Estimated Mean**	**Std Error**	**Estimated Mean**	**Std Error**
Standard	96.85	1.84	96.79	2.96	96.68	1.38
Cymene	94.35	1.84	97.95	2.96	95.40	1.38
p*-IPBA	98.51	1.84	99.85	2.96	98.89	1.38
***p*-Cymenol**	94.95	1.84	90.00	2.96	96.06	1.38
Both**	98.79	1.84	97.76	2.96	98.41	1.38

* -*p*-Isopropylbenzyl alcohol; ** - Adding both alcohols simultaneously.

The results are best viewed with the aid of response vs. treatment graphs as shown in Figures 4.1 - 4.3. The 95% confidence limits for the various treatments are also shown on these plots.

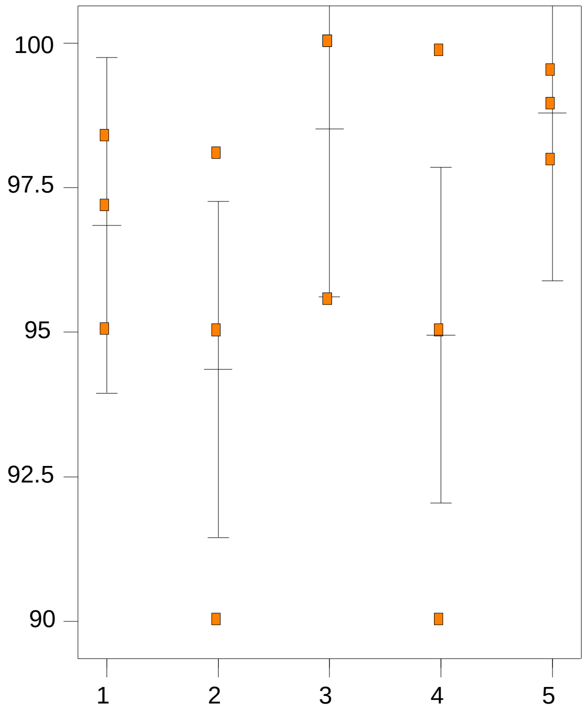


Figure 4.1 Response versus treatment plot for Sum

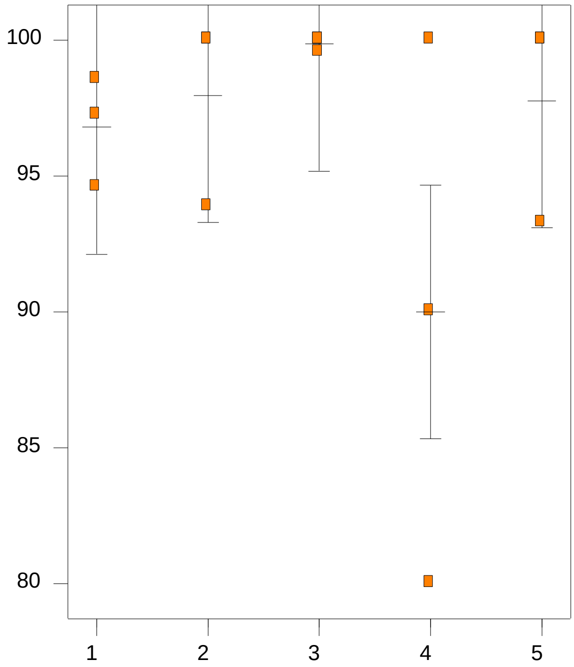


Figure 4.2 Response versus treatment plot for 1° alcohol

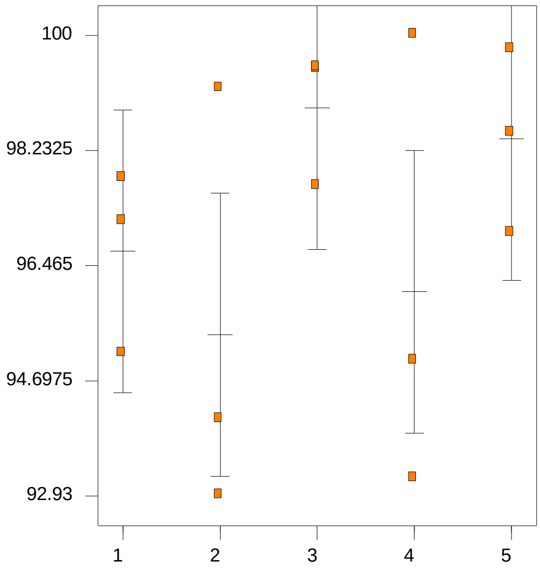


Figure 4.3 Response versus treatment plot for 3° alcohol

For an analytical method to be fully reliable, all the different treatments for a particular response should be close to 100% with the 95% confidence limits including the 100% recovery level. The response versus treatment plot for the sum response shows that this is only true for two of the treatments, while the 1° alcohol and 3° alcohol responses have four and two treatments adhering to this criterion. It would thus appear that the method gives consistently lower results than expected, but since the 95% confidence limits for all the treatments and all the responses overlap, the method is reproducible. The method will be used for the duration of this study, but it should be kept in mind that the values obtained may be slightly lower than the actual.

CHAPTER 5

THE CATALYTIC AIR OXIDATION OF *p*-CYMENE

5.1 GENERAL

As previously indicated in Chapter 2, the liquid-phase oxidation of *p*-cymene is currently one of the main production routes to *p*-cresol. It is well known from the open and patent literatures that the oxidation step of *p*-cymene to the hydroperoxide presents the most difficulties when striving for a high overall yield to the desired *p*-cresol. This is the result of two contributing factors, namely the co-oxidation of the methyl group present on the ring, and the over oxidation of the initially formed *tert*-hydroperoxide to secondary oxidation products from which the desired *p*-cresol cannot be prepared.

Many different variations of the cymene to *p*-cresol process have been reported in the patent literature that strive to minimize the shortcomings described above. For example, the secondary oxidation products resulting from the further oxidation of the reactive hydroperoxide may be continuously extracted into a basic aqueous-phase, as for example described in U.S. Pat. No. 2 728 797.[93] Alternatively, the primary hydroperoxide formed may be selectively reduced back to the methyl group using molecular hydrogen and solid noble-metal catalysts as for example described in JP-A 58-198468[94] and U.S. Pat. No. 5 399 791.[87] In yet another variation, the primary hydroperoxide may be selectively destroyed using specific organic acids or salts prior to the acid decomposition step, as for example described in U.S. Pat. No. 5 639 922.[95]

Several modifications of the actual oxidation step have also been reported, all of which strive to increase the oxidation rate and increase the selectivity of the oxidation to the tertiary hydroperoxide. These modifications include, *inter alia*, the use of a two-phase, aqueous-organic system incorporating an emulsifying agent, as for example described in U.S. Pat. No. 3 933 921, [88] the use of various oxidation catalysts such as cobalt in the presence of bromide ions (JP63170355A2),[96] copper in a basic aqueous phase (U.S. Pat. No. 4 293 720),[89] various metal ions complexed to chelate ligands (U.S. Pat. No. 4 013 725),[97] etc., and the use of radical scavengers to reduce free-radical chain reactions (EP 0 927 717 A1).[98] All of the modifications referred to above are only partially successful since the primary function of oxidation catalysts during the oxidation of organic substrates using dioxygen as primary oxidant is to decompose the initially formed hydroperoxides, thereby accelerating the oxidation process. Thus, at concentrations at which autoxidation catalysts become active during autoxidation procedures, such catalysts will become counterproductive when the initially formed hydroperoxide is the intended reaction product due to the decomposition of the initially formed hydroperoxides by the same catalysts. These effects become especially noticeable at higher conversions of substrate. This necessitates operation at low substrate conversions in order to ensure reasonable yields of desired hydroperoxide.

In order to establish whether an opportunity existed for the improvement of the actual oxidation process of *p*-cymene to cymene-*tert*-hydroperoxide, it was necessary to screen a large number of existing oxidation systems (catalysts) as well as other potential catalysts for the said oxidation. From the results of the screening experiments, the most promising systems were then selected for optimization on laboratory scale in order to evaluate the potential of the chosen systems in terms of potential commercial exploitation.

5.2 RESULTS AND DISCUSSION

5.2.1 Definitions

The following terms were employed for the discussion of results

$$\text{Conversion} = \frac{\text{moles of substrate consumed}}{\text{moles of substrate charged}}$$

$$\text{Yield} = \frac{\text{moles of product formed}}{\text{moles of substrate charged}}$$

$$\text{Selectivity} = \frac{\text{moles of product formed}}{\text{moles of substrate consumed}}$$

5.2.2 Typical reaction profile

The catalytic liquid-phase air oxidation of *p*-cymene gives rise to a reaction mixture containing the primary and tertiary hydroperoxide, and also other byproducts consisting mainly of cumic acid. A visual impression of the progress of the reaction may be obtained by using a product distribution diagram, which shows the change in reaction composition with time. During this investigation, these diagrams were also used for obtaining certain information such as the selectivity at a specific substrate conversion by regression methods. A typical product distribution diagram for the oxidation of *p*-cymene is given in Figure 5.1.

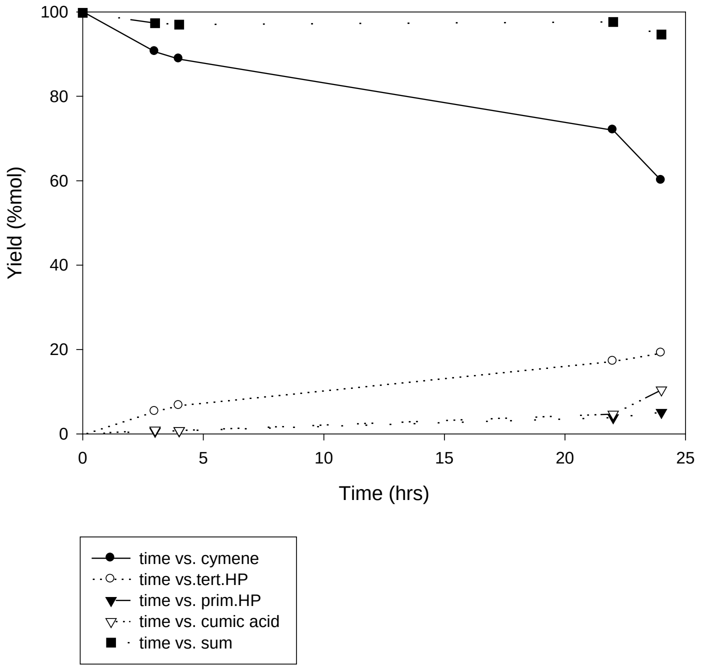


Figure 5.1 Product distribution diagram for the air oxidation of *p*-cymene

Reaction conditions: cymene (35.12g; 261.7mmol); hydroperoxide initiator (2.01g; 12.1mmol); temperature (100^0C); time (24 hrs)

5.2.3 Comparison of oxidation catalysts/systems

A total of eight different oxidation systems (catalyst and/or solvent) were screened for the oxidation of *p*-cymene. These oxidations were carried out in a 250 cm^3 all-glass slurry reactor using a total amount of 35g (260mmol) *p*-cymene and air (at a flow rate of $40cm^3/min$) as oxidant. Reactions were allowed to proceed for a period of six hours after which the reaction was terminated, and analyzed as described previously. The results of these comparisons are summarized in Table 5.1.

Table 5.1 Comparison of cymene oxidation systems

Exp. No.	Solvent	Catalyst	Conv. (%)	Total HP (%)	CA[a] (%)	Select. 1^{0}HP[b] (%)	Select. 3^{0}HP[c] (%)
1	None	None	10.00	2.51	3.00	5.02	20.10
2	None	None	12.00	2.62	7.76	3.49	17.42
3	None	None	11.11	2.38	7.48	4.15	17.27
4	B-aq[d]	None	12.61	7.54	4.24	21.05	38.28
5	B-aq[d]	None	12.41	7.53	4.08	21.08	39.66
6	B-aq[d]	None	12.65	7.14	4.13	19.43	37.02
7	B-aq[d]	Cu	13.40	9.54	2.14	22.52	45.38
8	B-aq[d]	Cu	14.92	9.69	3.42	19.56	48.78
9	B-aq[d]	Cu	13.49	9.28	3.48	21.53	47.28
10	B-aq[d]	Mn	12.20	3.48	8.10	6.62	21.92
11	B-aq[d]	Mn	12.30	4.04	7.64	9.89	23.36
12	B-aq[d]	Mn	11.92	4.09	7.48	10.57	23.66
13	B-aq[d]	Co	15.23	3.06	9.09	6.22	13.90
14	B-aq[d]	Co	15.97	3.42	8.35	7.33	14.09
15	B-aq[d]	Co	15.40	3.80	8.65	7.47	17.21
16	None	Charcoal	31.42	11.73	12.56	7.33	30.00
17	None	B-Phos[e]	30.05	24.77	1.45	2.86	79.56
18	None	B-Phos[e]	28.80	23.76	1.28	2.45	80.05
19	None	B-Phos[e]	25.35	20.45	1.01	2.12	78.56
20	None	V-Phos[f]	27.00	21.69	1.05	2.62	78.00
21	None	V-Phos[f]	24.52	21.04	1.01	2.53	83.28
22	None	V-Phos[f]	19.95	18.43	0.94	5.07	87.32

[a] = $(CH_3)_2CH(C_6H_4)CO_2H$; [b] = $(CH_3)_2CH(C_6H_4)CH_2OOH$;
[c] = $CH_3(C_6H_4)C(CH_3)_2OOH$; [d] = 1M 4:6 $NaHCO_3/Na_2CO_{3aq}$;
[e] = BPO_4; [f] = $(VO)_2P_2O_7$

Experimental details:

Exp. 1-3 *p*-cymene (35.0g; 260mmol); hydroperoxide initiator (2.0g; 12.0mmol); time (6 hrs); temp. (100^{0}C); air flow rate (40.0 cm3/min).

Exp.4-6 *p*-cymene (35.0g; 260mmol); hydroperoxide initiator (2.0g; 12mmol); 1M 4:6 $NaHCO_3/Na_2CO_{3aq}$ (10.0 cm^3); time (6hrs); temp. (100^{0}C); air flowrate (40.0 cm^3/min).

Exp.7-9 *p*-cymene (35.0g; 260mmol); hydroperoxide initiator (2.0g; 12mmol); 1M 4:6 $NaHCO_3/Na_2CO_{3aq}$ (10.0 cm^3); $CuSO_4$ (0.006g; 0.04mmol); time (6 hrs); temp. (100^{0}C); air flow rate (40.0 cm^3/min).

Exp.10-12	*p*-cymene (35.0g; 260mmol); hydroperoxide initiator (2.0g; 12mmol); 1M 4:6 $NaHCO_3/Na_2CO_{3aq}$ (10.0 cm^3); $MnSO_4$ (0.006 g; 0.04 mmol); time (6hrs); temp. (100^0C); air flowrate (40.0 cm^3/min).
Exp. 13-15	*p*-cymene (35.0g; 260.0mmol); hydroperoxide initiator (2.0g; 12mmol); 1M 4:6 $NaHCO_3/Na_2CO_{3aq}$ (10.0 cm^3); $Co(CH_3COO)_2$ (0.006 g; 0.04 mmol); time (6 hrs); temp. (100^0C); air flow rate (40 cm^3/min).
Exp. 16	*p*-cymene (35.0 g; 260.0 mmol); hydroperoxide initiator (2.0g; 12mmol); activated charcoal (0.20g; 17mmol); time (6 hrs); temp. (100^0C); air flowrate (40 cm^3/min).
Exp. 17-19	*p*-cymene (35.0g; 260mmol); hydroperoxide initiator (2.0g; 12mmol); $(V0)_2P_20_7$ (0.018g; 0.05mmol); time (6hrs); temp. (100^0C); air flowrate (40 cm^3/min).
Exp. 20-22	*p*-cymene (35.0 g; 260 mmol); hydroperoxide initiator (2.0g; 12mmol); BPO_4 (0.018 g; 0.17 mmol); time (6 hrs); temp. (100^0C); air flow rate (40 cm^3/min).

The following observations regarding the results given above may be made:

- Despite the fact that oxidation reactions, especially two- and three-phase systems, are notoriously difficult to replicate, reasonably good results were obtained for all replicate experiments, indicating that the results are reliable.

- The use of homogeneous catalysts such as $CuSO_4$, $MnSO_4$ and $Co(CH_3COO)_2$ result in improved oxidation rates, but increase the rate of hydroperoxide decomposition (both primary and tertiary) as indicated by the increase in secondary oxidation products.

- The use of activated charcoal in the oxidation of cymene results in a large increase in the conversion of cymene; however, the selectivity to the tertiary hydroperoxide is very low, which indicates the formation of a large amount of other byproducts.

- Solid phosphate catalysts improve both oxidation rates and oxidation selectivity remarkably in comparison to the other oxidation systems investigated. Selectivities to tertiary hydroperoxide in excess of 80% at conversions as high as 25% were obtained during these initial studies.

From the above results, it was decided to investigate the effect of the vanadium and boron phosphate catalyst systems in more detail using multi-factorial experimental designs.

5.3 MULTI-FACTORIAL INVESTIGATION OF VANADIUM/BORON PHOSPHATE CATALYSED OXIDATIONS

5.3.1 General

The production of interesting and important chemical compounds depends on the invention of new synthetic methods, which are economically viable. It is, however, rare that these new methods produce immediate satisfactory results. Much tedious work is often required before a new idea can be established as a synthetic method. It is necessary to explore the reaction conditions to determine how they should be adjusted to obtain optimal results. It is also interesting to find out whether the reaction can be used as a general method for a number of similar substrates. To this end, it is necessary to determine the scope and limitations of the reaction. This in turn calls for more experimentation. In chemical reactions, a number of factors are likely to be involved, and unfortunately their influence will depend on still other factors. Chemical phenomena are rarely the result of the influence of a single factor, or the individual effects of a number of factors. Interactions between different variables are often observed and in order to be able to take such interactions into account, it is necessary to use multivariate experimental methods, which allow all pertinent factors to be considered simultaneously, both for designing experiments and analyzing the results.

It is therefore surprising that so few synthetic methods are studied using such multivariate methods. New methods are often still investigated by so-called “systematic methods” where reaction variables are considered one factor at a time (OVAT), in spite of the fact that such methods have been shown by R. A. Fisher to be inappropriate when several factors are important.[99]

In this part of the investigation, the use of statistical experimental design methods will be used to investigate the oxidation of *p*-cymene in the presence of $(VO)_2P_2O_7$ and BPO_4 catalysts. The methods will be described in some detail for the sake of clarity.

5.3.2 Preliminary considerations

5.3.2.1 Identification of reaction variables

Since a certain amount of information pertaining to the procedures to be investigated was already known, an initial screening experiment to determine possible important reaction variables and critical steps was not required. From the existing knowledge, the following important reaction variables may be identified:

- *Reaction temperature:* In general, catalyst activity decreases with decreasing reaction temperature for a particular catalyst mass. On the other hand, the higher the reaction temperature, the more byproducts are formed, especially in the case of hydroperoxides, due to their instability and decomposition at high temperatures. The inclusion of reaction temperature in such a study would therefore be necessary to find an optimum between reaction rate and reaction selectivity.

- *Mass of catalyst:* In general, the rate of the reaction will increase with increasing catalyst amount. This is simply a direct result of an increase in the number of available active sites in the reaction medium. It should, however, be noted that the product yield may also be adversely affected by an increasing amount of catalyst, since byproduct formation may be affected by an increase in the amount of active (and other) catalyst sites. As in the case of reaction temperature, catalyst loading will need to be investigated so as to find an optimum compromise between reaction rate and reaction selectivity.

- *Reaction time:* Both conversion and selectivity (to products) will be critically affected by the reaction time. It might, however, be expected that factors such as amount of catalyst etc. will strongly interact with this parameter. In order to obtain an unbiased measurement of the selectivity and activity of the catalyst, a comparison of reaction selectivities at specific substrate conversions should be used instead.

- *Air flow rate:* The availability of air and its contact with the substrate is of crucial importance, especially for selectivity to the desired products. However, the rate and nature of air/oxygen supply to the reaction system is also dependent on the nature of the oxidation reactor used. Since the final reactor configuration will only be decided upon at a later stage, it would not make much sense to investigate this parameter without considering the reactor configuration.

Apart from the above list of rather obvious reaction variables, a number of others pertaining to the chemical engineering aspects of these oxidations may also be added. Some of these include reactor configuration, stirring mechanism, rate of stirring, heat transfer, etc. Since the objective at this stage was to evaluate the potential of two catalyst systems under laboratory conditions, chemical engineering parameters were not included, since these may better be evaluated from a process point of view. All the reactions were run in the same reactor, thereby ensuring constancy in these parameters.

5.3.2.2 Determination of the experimental domain

The experimental variables chosen for the two experimental designs, as well as the settings of the individual factor levels, are listed in Table 5.2 for vanadium and Table 5.3 for boron.

Table 5.2 Experimental domain – $(VO)_2P_2O_7$

Code	Variable	Unit	Variable level		
			Low (-)	Centre (0)	High (+)
T	Temperature	^{0}C	85	100	115
C	Catalyst loading	% m/m	0.03	0.05	0.07

Fixed variables		
Variable	Unit	Variable
Substrate loading	gram	35g (260mmol)
Initiator	gram	2g (12.03mmol)
Rate of stirring	rpm	2000
Air flow rate	cm^3/min	40

Table 5.3 Experimental domain – BPO_4

Code	Variable	Unit	Variable level		
			Low (-)	Centre (0)	High (+)
T	Temperature	^{0}C	80	100	120
C	Catalyst loading	% m/m	0.06	0.09	0.11

Fixed variables		
Variable	Unit	Variable level
Substrate loading	gram	35.0 g (260.0mmol)
Initiator	gram	2.0g (12.03mmol)
Rate of stirring	rpm	2000
Air flow rate	cm^3/min	40

5.3.3 Design and responses

The response variables selected for the optimization procedure were the selectivity towards the tertiary hydroperoxide product at 15% and 20% conversion. Tables 5.4 and 5.5 illustrate the individual designs for vanadium and boron phosphate respectively and also list the experimental responses obtained.

Table 5.4 Design and responses – $(VO)_2P_2O_7$

Run No.	Variable Settings*		3^0 HP Selectivity at 15% Conversion (%)	3^0 HP Selectivity at 20% Conversion (%)
	T (^{0}C)	C (%)		
1	0 (100.0)	0 (0.05)	82.90	81.05
2	1.4 (121.0)	1.414 (0.078)	87.55	86.89
3	0 (100.0)	0 (0.05)	83.78	83.5
4	0 (100.0)	0 (0.05)	81.37	81.37
5	-1.4 (79.0)	-1 (0.030)	75.23	73.56
6	-1 (85.0)	0 (0.05)	75.98	75.34
7	1 (115.0)	0 (0.05)	77.45	77.05
8	-1 (85.0)	-1 (0.03)	69.56	77.44
9	0 (100.0)	1 (0.07)	81.78	80.55
10	0 (100.0)	0 (0.05)	82.67	79.56
11	0 (100.0)	-1.414 (0.022)	77.45	76.98
12	0 (100.0)	1 (0.07)	81.76	79.89
13	1 (115.0)	0 (0.05)	78.22	77.67

[*] Natural values are given in parentheses

Table 5.5 Design and responses – BPO_4

Run No.	Variable Settings*		3^0 HP Selectivity at 15% Conversion (%)	3^0 HP Selectivity at 20% Conversion (%)
	T (^{0}C)	C (%)		
1	1.414 (128.3)	0 (0.09)	92.56	90.23
2	1 (120.0)	1 (0.10)	89.89	86.66
3	0 (100.0)	1.414 (0.11)	87.05	86.20
4	-1 (80.0)	1 (0.10)	86.54	85.12
5	0 (100.0)	-1.414 (0.06)	84.75	83.05
6	-1.414 (71.7)	0 (0.09)	82.45	81.33
7	0 (100.0)	0 (0.09)	85.85	84.05
8	-1 (80.0)	-1 (0.07)	84.12	83.22
9	0 (100.0)	0 (0.09)	87.78	85.55
10	0 (100.0)	0 (0.09)	88.12	86.34
11	0 (100.0)	0 (0.09)	87.34	85.57
12	1 (120.0)	-1 (0.07)	90.56	88.12
13	0 (100.0)	0 (0.09)	85.46	83.12

* Natural values are given in parentheses

The factor levels shown in Table 5.4 were coded using Equation 5.1:

$$X_i = \frac{(x_i - x_c)}{s_x} \qquad [5.1]$$

where: X_i = coded value of variable x_i,

x_i = natural value of variable x_i at a factorial point,

x_c = natural value of x_i at the design center, and

s_x = step size in the natural values of variable x_i.

5.3.4 Statistical analysis

5.3.4.1 Calculation of Response Surface Models

A second-order polynomial equation (response surface model) of the form

$$R = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2 + \beta_{11} x_1^2 + \beta_{22} x_2^2$$

(R = experimental response, x_1 = reaction temperature, x_2 = catalyst loading) was fitted to the experimental data by means of linear least squares regression. These calculations are briefly outlined below. A model matrix, **X**, is first constructed by augmenting the design matrix (Table 5.4, for example) with a column, ***I***, for the constant term (β_0), columns for the squared model parameters (β_{ii}), and columns for the two-factor interaction term (β_{ij}) in the model. The model matrices, **X**, were therefore as shown in Table 5.6 for vanadium and Table 5.7 for boron phosphate. (For this discussion, it will be assumed that the experimental settings of the reaction variables were exactly as specified by the design, *i.e.*, either +1, or –1).

Table 5.6 Model matrices – $(VO)_2P_2O_7$

Run	I	x_1	x_2	x_1x_2	x_1^2	x_2^2
1	1	0	0	0	0	0
2	1	1.4	1.414	1.9796	1.96	1.9994
3	1	0	0	0	0	0
4	1	0	0	0	0	0
5	1	-1.4	-1	1.4	1.96	1
6	1	-1	0	0	1	0
7	1	1	0	0	1	0
8	1	-1	-1	1	1	1
9	1	0	1	0	0	1
10	1	0	0	0	0	0
11	1	0	-1.414	0	0	1.9994
12	1	0	1	0	0	1
13	1	1	0	0	1	0

Table 5.7 Model Matrices – BPO_4

Run	I	x_1	x_2
1	1	1.414	0
2	1	1	1
3	1	0	1.414
4	1	-1	1
5	1	0	-1.414
6	1	-1.414	0
7	1	0	0
8	1	-1	-1
9	1	0	0
10	1	0	0
11	1	0	0
12	1	1	-1
13	1	0	0

The overall calculation may be summarized by the matrix equation 5.2 and illustrated in full by eqn's 5.3 and 5.4 for the selectivity responses at 15% and 20% conversion for the vanadium phosphate system, respectively.

$$y = Xb + e \qquad [5.2]$$

(y = the column vector of experimental responses, X = the model matrix, b = the column vector of model parameters, and *e* = the column vector of error terms associated with each model parameter.)

$$\begin{bmatrix} 82.90 \\ 87.55 \\ 83.78 \\ 81.37 \\ 75.23 \\ 75.98 \\ 77.45 \\ 69.56 \\ 81.78 \\ 82.67 \\ 77.45 \\ 81.76 \\ 78.22 \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1.4 & 1.414 & 1.9796 & 1.96 & 1.9994 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1.4 & -1 & 1.4 & 1.96 & 1 \\ 1 & -1 & 0 & 0 & 1 & 0 \\ 1 & 1 & 0 & 0 & 1 & 0 \\ 1 & -1 & -1 & 1 & 1 & 1 \\ 1 & 0 & 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & -1.414 & 0 & 0 & 1.9994 \\ 1 & 0 & 1 & 0 & 0 & 1 \\ 1 & 1 & 0 & 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \beta_{12} \\ \beta_1^2 \\ \beta_2^2 \end{bmatrix} + \begin{bmatrix} e_1 \\ e_2 \\ e_{12} \\ e_1^2 \\ e_2^2 \end{bmatrix} \qquad [5.3]$$

$$\begin{bmatrix} 81.05 \\ 86.89 \\ 83.50 \\ 81.37 \\ 73.56 \\ 75.34 \\ 77.05 \\ 77.04 \\ 80.55 \\ 79.56 \\ 76.98 \\ 79.89 \\ 77.67 \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1.4 & 1.414 & 1.9796 & 1.96 & 1.9994 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1.4 & -1 & 1.4 & 1.96 & 1 \\ 1 & -1 & 0 & 0 & 1 & 0 \\ 1 & 1 & 0 & 0 & 1 & 0 \\ 1 & -1 & -1 & 1 & 1 & 1 \\ 1 & 0 & 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & -1.414 & 0 & 0 & 1.9994 \\ 1 & 0 & 1 & 0 & 0 & 1 \\ 1 & 1 & 0 & 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \beta_{12} \\ \beta_1^2 \\ \beta_2^2 \end{bmatrix} + \begin{bmatrix} e_1 \\ e_2 \\ e_{12} \\ e_1^2 \\ e_2^2 \end{bmatrix} \qquad [5.4]$$

The procedure used during the least squares fit of the data is summarized by eqn 5.5, and is illustrated in full in eqns 5.6 to 5.9 for the vanadium phosphate system.

$$\mathbf{(X'X)^{-1}X'y = b} \qquad [5.5]$$

$$\mathbf{X'X} = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ 0 & 1.4 & 0 & 0 & -1.4 & -1 & 1 & -1 & 0 & 0 & 0 & 0 & 1 \\ 0 & 1.414 & 0 & 0 & -1 & 0 & 0 & -1 & 1 & 0 & -1.414 & 1 & 0 \\ 0 & 1.9796 & 0 & 0 & 1.4 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1.96 & 0 & 0 & 1.96 & 1 & 1 & 1 & 0 & 0 & 0 & 0 & 1 \\ 0 & 1.9994 & 0 & 0 & 1 & 0 & 0 & 1 & 1 & 0 & 1.9994 & 1 & 0 \end{bmatrix} \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1.4 & 1.414 & 1.9796 & 1.96 & 1.9994 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1.4 & -1 & 1.4 & 1.96 & 1 \\ 1 & -1 & 0 & 0 & 1 & 0 \\ 1 & 1 & 0 & 0 & 1 & 0 \\ 1 & -1 & -1 & 1 & 1 & 1 \\ 1 & 0 & 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & -1.414 & 0 & 0 & 1.9994 \\ 1 & 0 & 1 & 0 & 0 & 1 \\ 1 & 1 & 0 & 0 & 1 & 0 \end{bmatrix}$$

[5.6]

$$= \begin{bmatrix} 13 & 0 & 0 & 4.3796 & 7.92 & 7.9988 \\ 0 & 7.92 & 4.3796 & -0.18856 & 0 & 0.39916 \\ 0 & 4.3796 & 7.998792 & 0.399154 & -0.18856 & 0 \\ 4.3796 & -0.18856 & 0.399154 & 6.878816 & 7.624016 & 6.358012 \\ 7.92 & 0 & -0.18856 & 7.624016 & 11.6832 & 6.878824 \\ 7.9988 & 0.39916 & 0 & 6.358012 & 6.878824 & 11.9952 \end{bmatrix}$$

$$\mathbf{(x'x)^{-1}x'} = \begin{bmatrix} 0.2291 & 0.0356 & -0.0383 & 0.2662 & -0.2354 & -0.1601 \\ 0.0356 & 0.1945 & -0.1139 & 0.1144 & -0.0711 & -0.0500 \\ -0.0383 & -0.1139 & 0.1958 & -0.1295 & 0.0844 & 0.0495 \\ 0.2661 & 0.1144 & -0.1295 & 1.0351 & -0.6465 & -0.3592 \\ -0.2354 & -0.0711 & 0.0845 & -0.6465 & 0.5629 & 0.1792 \\ -0.1601 & -0.0500 & 0.0495 & -0.3592 & 0.1792 & 0.2794 \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ 0 & 1.4 & 0 & 0 & -1.4 & -1 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 1.414 & 0 & 0 & -1 & 0 & 0 & -1 & 1 & 0 & -1.414 & 1 \\ 0 & 1.9796 & 0 & 0 & 1.4 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 1.96 & 0 & 0 & 1.96 & 1 & 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 1.9994 & 0 & 0 & 1 & 0 & 0 & 1 & 1 & 0 & 1.9994 & 1 \end{bmatrix} \tag{5.7}$$

$$= \begin{bmatrix} 0.229 & -0.0298 & 0.229 & 0.229 & -0.0312 & -0.0418 & 0.0294 & 0.1026 & 0.0308 & 0.229 & -0.0367 & 0.0308 & 0.0294 \\ 0.0356 & 0.134 & 0.0356 & 0.0356 & -0.152 & -0.23 & 0.159 & -0.0518 & -0.129 & 0.0356 & 0.0966 & -0.128 & 0.159 \\ -0.0383 & 0.0874 & -0.0383 & -0.0383 & -0.0409 & 0.16 & -0.0677 & -0.116 & 0.207 & -0.0383 & -0.216 & 0.207 & -0.0677 \\ 0.266 & 0.3069 & 0.266 & 0.266 & 0.0584 & -0.495 & -0.266 & 0.3107 & -0.223 & 0.266 & -0.269 & -0.223 & -0.266 \\ -0.235 & -0.0338 & -0.235 & -0.235 & 0.157 & 0.397 & 0.256 & -0.153 & 0.0283 & -0.235 & 0.0035 & 0.0283 & 0.256 \\ -0.16 & 0.0387 & -0.16 & -0.16 & -0.0118 & 0.0692 & -0.0309 & -0.0602 & 0.169 & -0.16 & 0.329 & 0.169 & -0.0309 \end{bmatrix}$$

$$(\mathbf{X'X})^{-1}\mathbf{X'y}=\begin{bmatrix} 0.229 & -0.0298 & 0.229 & 0.229 & -0.0312 & -0.0418 & 0.0294 & 0.1026 & 0.0308 & 0.229 & -0.0367 & 0.0308 & 0.0294 \\ 0.0356 & 0.134 & 0.0356 & 0.0356 & -0.152 & -0.23 & 0.159 & -0.0518 & -0.128 & 0.0356 & 0.0966 & -0.128 & 0.159 \\ -0.0383 & 0.0874 & -0.0383 & -0.0383 & -0.0409 & 0.16 & -0.0677 & -0.116 & 0.207 & -0.0383 & -0.216 & 0.207 & -0.0677 \\ 0.266 & 0.3069 & 0.266 & 0.266 & 0.0584 & -0.495 & -0.266 & 0.3107 & -0.223 & 0.266 & -0.269 & -0.223 & -0.266 \\ -0.235 & -0.0338 & -0.235 & -0.235 & 0.157 & 0.397 & 0.256 & -0.153 & 0.0283 & -0.235 & 0.0035 & 0.0283 & 0.256 \\ -0.16 & 0.0387 & -0.16 & -0.16 & -0.0118 & 0.0692 & -0.0309 & -0.0602 & 0.169 & -0.16 & 0.329 & 0.169 & -0.0309 \end{bmatrix}\begin{array}{c}(15\%)\\ \begin{bmatrix} 82.9 \\ 87.55 \\ 83.78 \\ 81.37 \\ 75.23 \\ 75.98 \\ 77.45 \\ 69.56 \\ 81.78 \\ 82.67 \\ 77.45 \\ 81.76 \\ 78.22 \end{bmatrix}\end{array} \quad [5.8]$$

$$=\begin{bmatrix} 0.229 & -0.0298 & 0.229 & 0.229 & -0.0312 & -0.0418 & 0.0294 & 0.1026 & 0.0308 & 0.229 & -0.0367 & 0.0308 & 0.0294 \\ 0.0356 & 0.134 & 0.0356 & 0.0356 & -0.152 & -0.23 & 0.159 & -0.0518 & -0.128 & 0.0356 & 0.0966 & -0.128 & 0.159 \\ -0.0383 & 0.0874 & -0.0383 & -0.0383 & -0.0409 & 0.16 & -0.0677 & -0.116 & 0.207 & -0.0383 & -0.216 & 0.207 & -0.0677 \\ 0.266 & 0.3069 & 0.266 & 0.266 & 0.0584 & -0.495 & -0.266 & 0.3107 & -0.223 & 0.266 & -0.269 & -0.223 & -0.266 \\ -0.235 & -0.0338 & -0.235 & -0.235 & 0.157 & 0.397 & 0.256 & -0.153 & 0.0283 & -0.235 & 0.0035 & 0.0283 & 0.256 \\ -0.16 & 0.0387 & -0.16 & -0.16 & -0.0118 & 0.0692 & -0.0309 & -0.0602 & 0.169 & -0.16 & 0.329 & 0.169 & -0.0309 \end{bmatrix}\begin{array}{c}(20\%)\\ \begin{bmatrix} 81.05 \\ 86.89 \\ 83.50 \\ 81.37 \\ 73.56 \\ 75.34 \\ 77.05 \\ 77.44 \\ 80.55 \\ 79.56 \\ 76.98 \\ 79.89 \\ 77.67 \end{bmatrix}\end{array} \quad [5.9]$$

$$=\begin{bmatrix} \beta_o \\ \beta_1 \\ \beta_2 \\ \beta_{12} \\ \beta_1{}^2 \\ \beta_2{}^2 \end{bmatrix}$$

The two response surface models for the selectivity of the vanadium phosphate system to tertiary hydroperoxide at 15% and 20% conversion, respectively, are:

$$y^{15} = 81.554 + 2.195x_1 + 2.587x_2 - 4.550x_1^2 - 1.123x_2^2 + 4.686x_1x_2 \qquad [5.10]$$

$$y^{20} = 81.154 + 2.114x_1 + 1.308x_2 - 5.352x_1^2 - 1.457x_2^2 + 6.826x_1x_2 \qquad [5.11]$$

where y^{15} = the selectivity at 15% substrate conversion and y^{20} = the selectivity at 20% substrate conversion.

The corresponding response surface models for the boron phosphate system, calculated in a manner analogous to that described above are:

$$y^{15} = 87.113 + 3.011x_1 + 0.625x_2 \qquad [5.12]$$

$$y^{20} =85.274 +2.378x_1 + 0.612x_2 \qquad [5.13]$$

5.3.4.2 Statistical evaluation of results

Before using the response surface models determined above for comparison or optimization purposes, it is necessary to confirm that these models are indeed good descriptions of the actual response surfaces. Several statistical tests, both numerical and graphical,[99] have been described for evaluating experimentally determined response surfaces. Many of these have been applied to the response surface models given in eqns 5.10 to 5.13, and are briefly described below.

- **Analysis of variance (ANOVA)**

Analysis of variance is a powerful statistical technique that can be used to separate variances during the deliberate variation of experimental variances from pure experimental variance. The procedure used will be illustrated for the selectivity response at 15% conversion for the vanadium phosphate system.

Calculation of the total sum of squares, SST

From the series of *n* experiments used to determine a response surface model, the sum of squared responses, called the *total sum of squares, SST,* can be computed by simply obtaining the sum of squared responses (eqns 5.14 and 5.15). The values so obtained can be corrected for the mean by subtracting the quantity $\Sigma(x_iy_i)^2/n$ to give the total sum of squares corrected for the mean. The total sum of squares is calculated with (*n*-1) degrees of freedom, where *n* is the total number of experiments in the design.

$$SST = \Sigma y_i^2 = y'y \qquad [5.14]$$

$$SST^{corr} = [82.90^2 + 87.55^2 + 83.78^2 + 81.37^2 + 75.23^2 + 75.98^2 + 77.45^2 + 69.56^2 + 81.78^2 + 82.67^2 + 77.45^2 + 81.76^2 + 78.22^2] - \{(82.9 + 87.55 + 83.78 + 81.37 + 75.23 + 75.98 + 77.45 + 69.56 + 81.78 + 82.67 + 77.45 + 81.76 + 78.22)^2/13\}$$

$$= 257.6307 \qquad [5.15]$$

Calculation of the sum of squares due to regression, SSR

The sum of squares due to regression is calculated by first calculating predicted responses for every experimental point in the original design by substituting the individual model elements into the experimental response surface model (Eqn 5.10 in the present example), and then finding the sum of the squared predicted responses (Eqns 5.16 and 5.17). The sum of squares due to regression is calculated with (*p*-1) degrees of freedom, where *p* = the number of parameters in the response surface model. As in the case of *SST*, the sum of squares can be corrected for the mean by subtracting the quantity, $\Sigma (x_iy_i)^2/n$.

$$SSR = \Sigma y_i^{Pred} = \mathbf{Xb} \qquad [5.16]$$

$$SSR^{Corr} = [81.55^2 + 86.40^2 + 81.55^2 + 81.55^2 + 72.41^2 + 74.81^2 + 79.20^2 + 75.79^2 + 83.02^2 + 81.55^2 + 75.65^2 + 83.02^2 + 79.20^2] - \{(81.55 + 86.40 +$$

81.55 + 81.55 + 72.41 + 74.81 + 79.20 + 75.79 + 83.02 + 81.55 + 75.65 + 83.02 + 79.20)^2/13}

$$= 189.8323 \qquad [5.17]$$

Calculation of the residual sum of squares, RSS

The residual sum of squares is calculated by finding the sum of the squared differences between the experimental responses and the predicted responses (Eqn 5.18). Alternatively, the residual sum of squares can be obtained from the differences between SST and SSR (Eqn 5.19). The residual sum of squares is calculated with (*n-p*) degrees of freedom, where *n* = the number of experiments and *p* = the number of parameters in the response surface model.

$$\mathrm{RSS} = \Sigma(y_i - y_i^{\mathrm{Pred}})^2 \qquad [5.18]$$

$$\mathrm{RSS} = \mathrm{SST} - \mathrm{SSR} \qquad [5.19]$$

The residual sum of squares can be divided into two components, namely the sum of squares due to lack-of-fit and the sum of squares due to pure error. The residual sum of squares due to pure error is obtained as the sum of the squared differences between the experimental and predicted responses at the design centre (eqn 5.20), while the residual sum of squares due to lack-of-fit is obtained as the sum of squared differences between experimental and predicted responses for the factorial experiments. Alternatively, the residual sum of squares due to lack-of-fit may be obtained as the difference between the residual sum of squares (RSS) and the residual sum of squares due to pure error (Eqn 5.21).

$$\mathrm{RSS}^{\mathrm{Pure\ Error}} = \Sigma(y_{i0} - y_{i0}^{\mathrm{Pred}})^2 \qquad [5.20]$$

$$\mathrm{RSS}^{\mathrm{Lack\ of\ Fit}} = \mathrm{RSS} - \mathrm{RSS}^{\mathrm{Pure\ Error}} \qquad [5.21]$$

Statistical evaluation – Model

The goodness of fit of the experimentally determined response surface model is determined with the aid of an F-test by comparing the mean square for pure error to the mean squares of regression and lack-of-fit, respectively. For the comparison of pure error with regression, the *NULL*-hypothesis adopted is that there is no difference between the observed variation in the factorial points and that which is expected if pure experimental error were the only contribution to the observed variation. If the *NULL*-hypothesis is true, the calculated F-value for the corresponding number of degrees of freedom should not exceed the critical F-value obtained from standard F-tables. Also, if the *NULL*-hypothesis is true, the response surface must be rejected. In the case of the comparison of pure error with lack-of-fit, the *NULL*-hypothesis adopted is that there is no difference in the sizes of the experimental errors at the design center and the factorial points. In this case, the calculated F-value should be smaller than the critical F-value in order for the model to be valid. The results of *ANOVA* tests are best summarized in tabular form and these analyses for the different response surface models are given in Tables 5.8 – 5.11 for the four selectivity responses.

Table 5.8 ***ANOVA*** **– $(VO)_2P_2O_7$ (15% Conversion)**

Source of variation	Sum of squares	Degrees of freedom	Mean squares	F-value[a]
Total (SST)	257.63	12	21.47	
Regression (SSR)	189.83	5	37.97	14.15 $(9.01)_{5,3}$
Residuals (RSS)	67.80	7	9.69	
Lack-of-Fit	59.75	4	14.94	5.57 $(9.12)_{4,3}$
Pure error	8.05	3	2.68	

[a] – Critical F-values ($P = 0.05$) in brackets with the respective degrees of freedom as subscripts.

Table 5.9 ***ANOVA*** **– $(VO)_2P_2O_7$ (20% Conversion)**

Source of variation	Sum of squares	Degrees of freedom	Mean squares	F-value[a]
Total (SST)	149.76	12	12.48	
Regression (SSR)	134.69	5	26.94	9.97 $(9.01)_{5,3}$
Residuals (RSS)	15.08	7	2.15	
Lack-of-Fit	6.97	4	1.74	0.65 $(9.12)_{4,3}$
Pure error	8.10	3	2.70	

[a] – Critical F-values ($P = 0.05$) in brackets with the respective degrees of freedom as subscripts.

Table 5.10 *ANOVA* – BPO$_4$ (15% Conversion)

Source of variation	Sum of squares	Degrees of freedom	Mean squares	F-value[a]
Total (SST)	91.72	12	7.64	
Regression (SSR)	75.58	2	37.79	25.53 $(6.94)_{2,4}$
Residuals (RSS)	16.14	10	1.61	
Lack-of-Fit	10.23	6	1.705	1.15 $(6.16)_{6,4}$
Pure error	5.93	4	1.48	

[a] – Critical F-values ($P = 0.05$) in brackets with the respective degrees of freedom as subscripts.

Table 5.11 ANOVA – BPO$_4$ (20% Conversion)

Source of variation	Sum of squares	Degrees of freedom	Mean squares	F-value[a]
Total (SST)	67.62	12	5.63	
Regression (SSR)	48.25	2	24.13	12.46 $(6.94)_{2,4}$
Residuals (RSS)	19.37	10	1.94	
Lack-of-Fit	11.92	6	1.99	1.07 $(6.16)_{6,4}$
Pure error	7.42	4	1.86	

[a] – Critical F-values ($P = 0.05$) in brackets with the respective degrees of freedom as subscripts.

- **Graphical analysis**

Analysis of variance has been shown to give a good description of the actual response surface of a fitted response surface model, but this is normally not sufficient. To be completely trustworthy, a response surface model should be able to withstand all possible diagnostic tests that could indicate inadequacies in the model. In this work, only the two most important diagnostic tests, namely a normal probability plot of the residuals, and a plot of residuals versus predicted response, will be considered.

Normal probability plot of residuals

If a response surface is adequate, it can be assumed that the residuals will depend only on normally distributed random experimental error. A cumulative probability distribution plot of the residuals should therefore give a straight line. The residuals, calculated as the difference between experimental and predicted responses, are shown in Tables 5.12 and 5.13 for $(VO)_2P_2O_7$ and BPO_4 respectively, while Figures 5.2 to 5.5 illustrate the normal probability plots of the residuals for the selectivity at 15% and 20% for both catalysts respectively. All the figures show good normality.

Table 5.12 Calculated residuals - $(VO)_2P_2O_7$

Experimental responses[a]	Predicted responses[a]	Residuals[a] $e=R^{obs} - R^{pred}$
82.90 (81.05)	81.55 (81.15)	1.35 (-0.10)
87.55 (86.89)	86.40 (86.07)	1.15 (0.82)
83.78 (83.50)	81.55 (81.15)	2.23 (2.35)
81.37 (81.37)	81.55 (81.15)	-0.18 (0.22)
75.23 (73.56)	72.41 (74.50)	2.82 (-0.94)
75.98 (75.34)	74.81 (73.69)	1.17 (1.65)
77.45 (77.05)	79.20 (77.92)	-1.75 (-0.87)
69.56 (77.44)	75.78 (77.75)	-6.22 (-0.31)
81.78 (80.55)	83.02 (81.01)	-1.24 (-0.46)
82.67 (79.56)	81.55 (81.15)	1.12 (-1.59)
77.45 (76.98)	75.65 (76.39)	1.80 (0.59)
81.76 (79.89)	83.02 (81.01)	-1.26 (-1.12)
78.22 (77.67)	79.20 (77.92)	-0.98 (-0.25)

[a] – Values in brackets indicate the selectivity response at 20%

Table 5.13 Calculated residuals – BPO_4

Experimental responses[a]	Predicted responses[a]	Residuals[a] $e = R^{obs} - R^{pred}$
92.56 (90.23)	91.37 (88.64)	1.19 (1.59)
89.89 (86.66)	90.75 (88.26)	-0.86 (-1.60)
87.05 (86.20)	88.00 (86.14)	-0.95 (0.06)
86.54 (85.12)	84.73 (83.51)	1.81 (1.61)
84.75 (83.05)	86.23 (84.41)	-1.48 (-1.36)
82.45 (81.33)	82.86 (81.91)	-0.41 (-0.58)
85.85 (84.05)	87.11 (85.27)	-1.26 (-1.22)
84.12 (83.22)	83.48 (82.28)	0.64 (0.94)
87.78 (85.55)	87.11 (85.27)	0.67 (0.28)
88.12 (86.34)	87.11 (85.27)	1.01 (1.07)
87.34 (85.55)	87.11 (85.27)	0.23 (0.30)
90.56 (88.12)	89.50 (87.04)	1.06 (1.08)
85.46 (83.12)	87.11 (85.27)	-1.65 (-2.15)

[a] – Values in brackets indicate the selectivity response at 20%

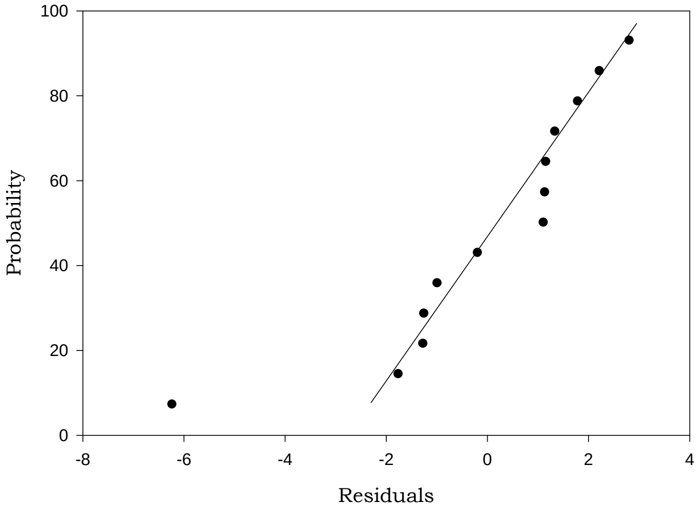
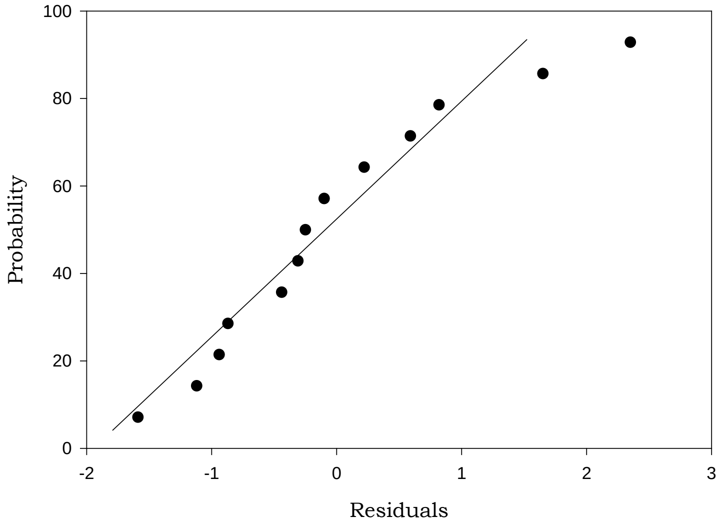


Figure 5.2 **Normal probability plot of residuals – $(VO)_2P_2O_7$ (15% Conversion)**



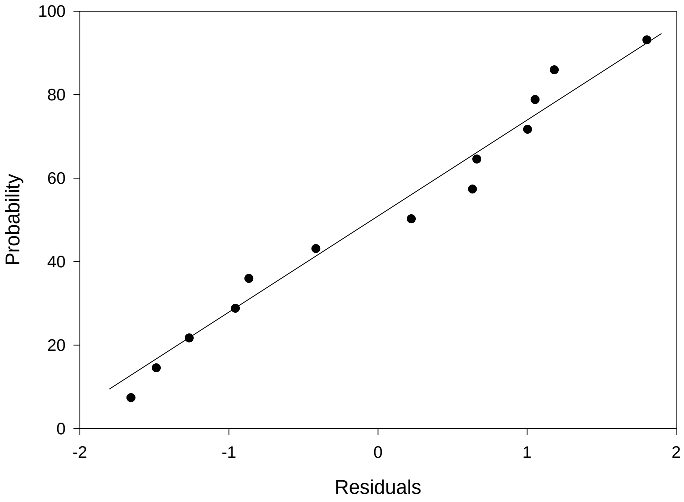


Figure 5.3 **Normal probability plot of residuals – $(VO)_2P_2O_7$ (20% Conversion)**

Figure 5.4 **Normal probability plot of residuals – BPO_4 (15% Conversion)**

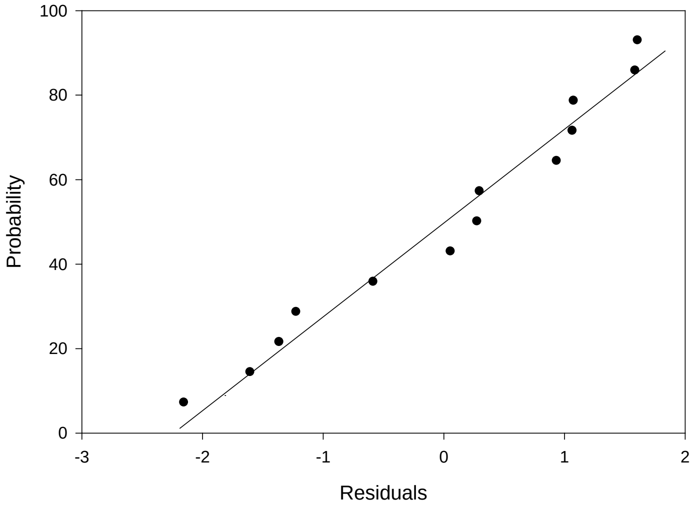


Figure 5.5 **Normal probability plot of residuals – BPO_4 (20% Conversion)**

Plot of residuals versus predicted responses

A second diagnostic test, which is always recommended[100], is to plot the residuals in each experiment against the predicted responses for the same experiment. This plot should not show abnormal behavior, i.e. the points should show a random scatter so that the upper and lower limits of the pattern in the plot form two parallel horizontal lines at approximately equal distances from the zero lines. Anomalous features[101] that can sometimes indicate problems with fitted response surface models include instances when:

(i) The upper and lower bonds diverge such that the pattern appears funnel-like. This is normally an indication that the experimental error differs in different parts of the experimental domain and, hence, the assumption of constant error variance is violated.

(ii) The upper and lower bonds are parallel, but not horizontal. This is normally indicative of the presence of systematic error.

(iii) The upper and lower bonds are bent so as to give a pattern that results in an arch. This could indicate that a second-order term has been left out of the response surface model.

These plots, shown in Figures 5.6 to 5.9 for 15% and 20% conversion, are satisfactory for both catalysts.

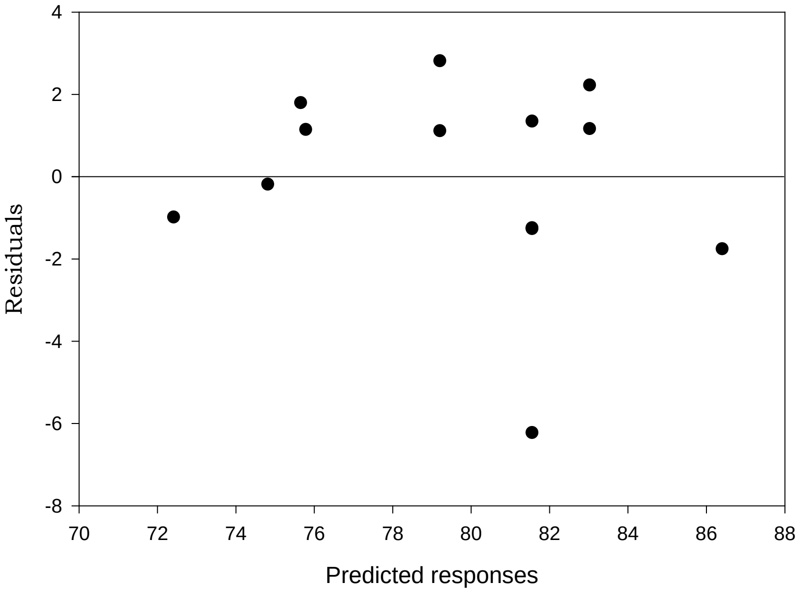


Figure 5.6 **Normal probability plot of residuals versus predicted response – $(VO)_2P_2O_7$ (15% Conversion)**

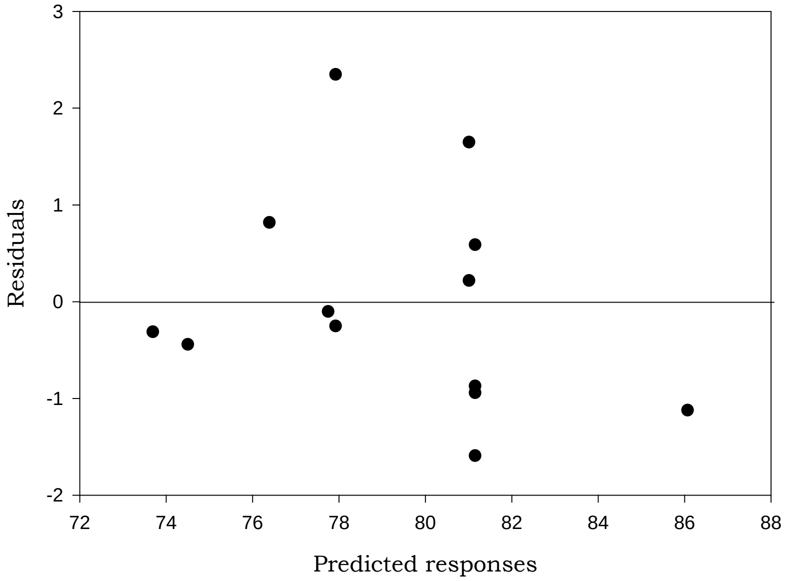


Figure 5.7 **Normal probability plot of residuals versus predicted response – $(VO)_2P_2O_7$ (20% Conversion)**

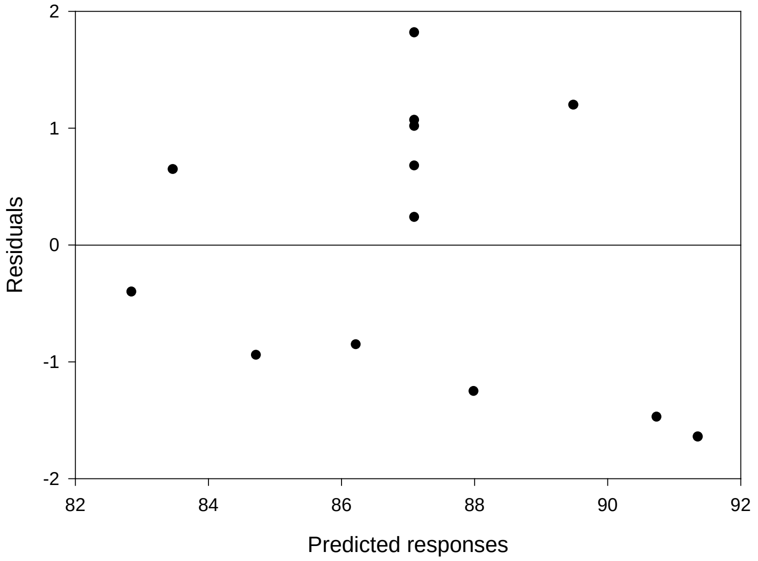


Figure 5.8 Normal probability plot of residuals versus predicted response – BPO_4 (15% Conversion)

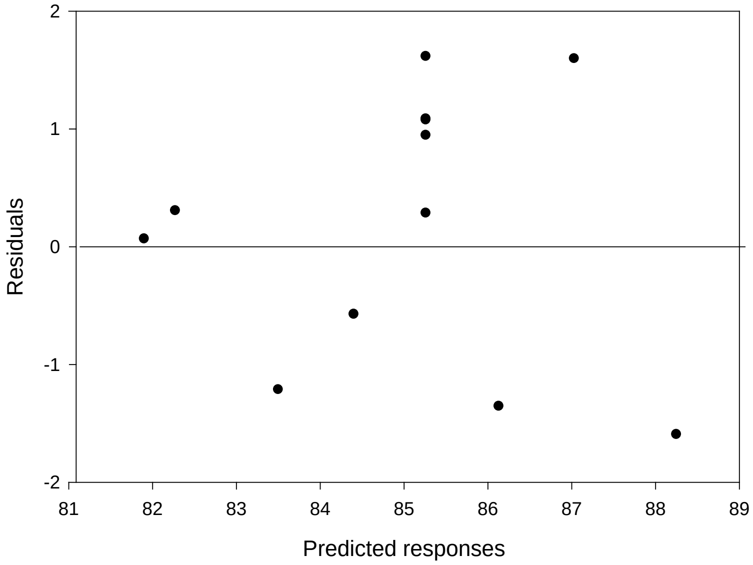


Figure 5.9 Normal probability plot of residuals versus predicted response – BPO_4 (20% Conversion)

5.3.5 Analysis of the fitted response

Having produced and evaluated the validity of a second-order response surface model, it becomes necessary to analyze this surface with the view to finding the optimum, or stationary point, on the response surface. The stationary point is defined as the point where there will be no change in the response with a variation in any of the factor levels, i.e., the point where for any factor x_i, the partial derivative $\partial y/\partial x_i = 0$. For a second-order response surface model in two experimental variables of the type

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2 + \beta_{11} x_1^2 + \beta_{22} x_2 \qquad [5.22]$$

partial derivation with respect to x_1 and x_2, respectively, gives the following two simultaneous equations:

$$\beta_1 + 2\,\beta_{11} x_1 + \beta_{12} x_2 = 0 \qquad [5.23]$$

$$\beta_2 + 2\,\beta_{22} x_2 + \beta_{12} x_1 = 0 \qquad [5.24]$$

Since the values of β_1, β_{11}, β_2, β_{22} and β_{12} are known from equations 5.10 and 5.11 for the selectivity responses at 15% and 20% conversion respectively in the case of $(VO)_2P_2O_7$, the positions of the stationary points on the response surfaces can be readily determined. The procedure may be illustrated by using the selectivity response at 15% conversion as an example for $(VO)_2P_2O_7$. The experimentally determined response surface model for 15% conversion (Eqn 5.10) was:

$$y^{15} = 81.554 + 2.195x_1 + 2.587x_2 - 4.550x_1^2 - 1.123x_2^2 + 4.686x_1x \qquad [5.25]$$

Partial derivation with respect to x_1 and x_2, respectively, gives:

$$2.195 - 9.100x_1 + 4.686x_2 = 0 \qquad [5.26]$$

$$2.587 + 4.686x_1 + 2.246x_2 = 0 \qquad [5.27]$$

These two simultaneous equations may be written in matrix format as in Eqn 5.28:

$$\begin{bmatrix} 9.100 & -4.686 \\ -4.686 & 2.246 \end{bmatrix} \begin{bmatrix} x1 \\ x2 \end{bmatrix} = \begin{bmatrix} 2.195 \\ 2.587 \end{bmatrix} \qquad [5.28]$$

Solving for x_1 and x_2 (Eqn 5.29) gives:

$$\begin{bmatrix} 9.100 & -4.686 \\ -4.686 & -2.246 \end{bmatrix}^{-1} \begin{bmatrix} 2.195 \\ 2.587 \end{bmatrix} = \begin{bmatrix} -0.1697 \\ -0.7979 \end{bmatrix} \qquad [5.29]$$

The values of x_1 and x_2 are in coded form, and may be decoded using eq. 5.1 to give:

x_1: Temperature = -11.2189 x 15 + 100 = 68.3^{0}C

x_2: Catalyst loading = -22.255 x 0.02 + 0.05 = -0.445 % m/m

The stationary points determined in this manner for $(VO)_2P_2O_7$ at both the conversions are given in Table 5.14. From the signs and magnitudes of the pure second order terms in the response surface models for the two conversions (Eqns 5.10 and 5.11), it can be deduced that these experimental response surfaces take the form of inverted, three-dimensional parabola opening downwards.

The BPO_4 catalyst was evaluated using a linear response surface model, since the interaction effects were negligible. In this case, there were no stationary points. From the signs and magnitudes of the pure first order terms in the response surface models for the two conversions (Eqns 5.12

and 5.13), it can be deduced that these experimental response surfaces take the form of a plane.

The 3-D Mesh plots and the contour diagrams for the response surface models at 15% and 20% conversion for both catalysts are shown in Figures 5.10 to 5.17.

Table 5.14 Stationary points on response surfaces - $(VO)_2P_2O_7$

Conversion	Response	Variable	Coded Value	Natural Value
15%	Selectivity (%)	Temperature	-0.17	97.5 ^{0}C
		Catalyst loading	-0.80	0.034%
20%	Selectivity (%)	Temperature	-0.98	85.3 ^{0}C
		Catalyst loading	-1.85	0.013%

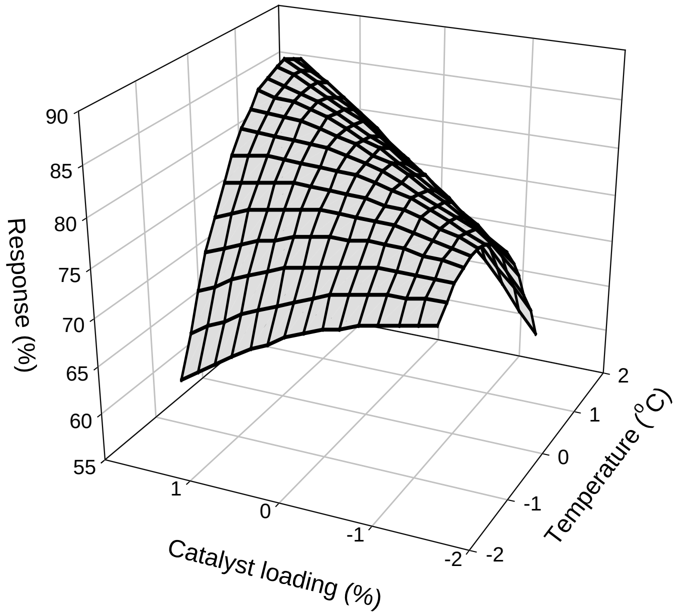


Figure 5.10 Three–dimensional response surface for the selectivity response for $(VO)_2P_2O_7$ (15% conversion)

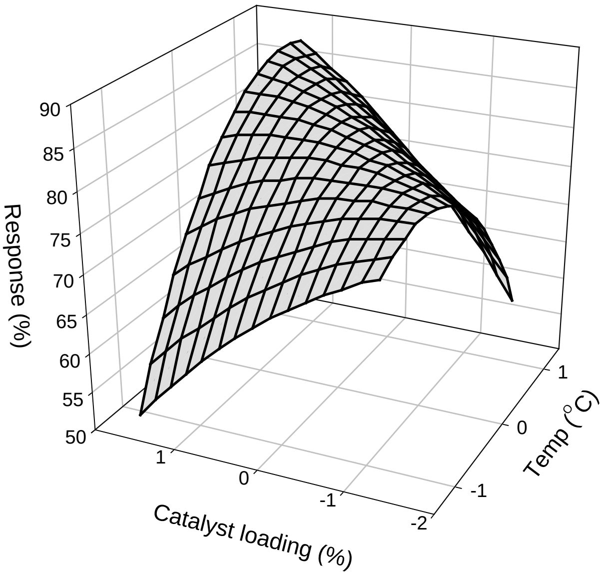


Figure 5.11 Three–dimensional response surface for the selectivity response for $(VO)_2P_2O_7$ (20% conversion)

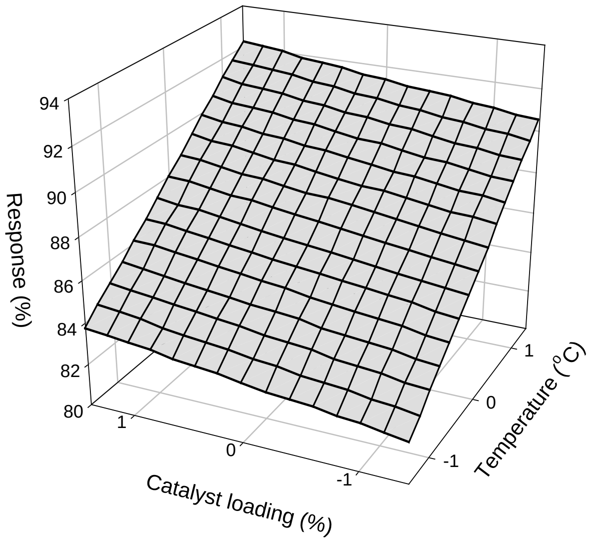


Figure 5.12 **Three–dimensional response surface for the selectivity response for BPO_4 (15% conversion)**

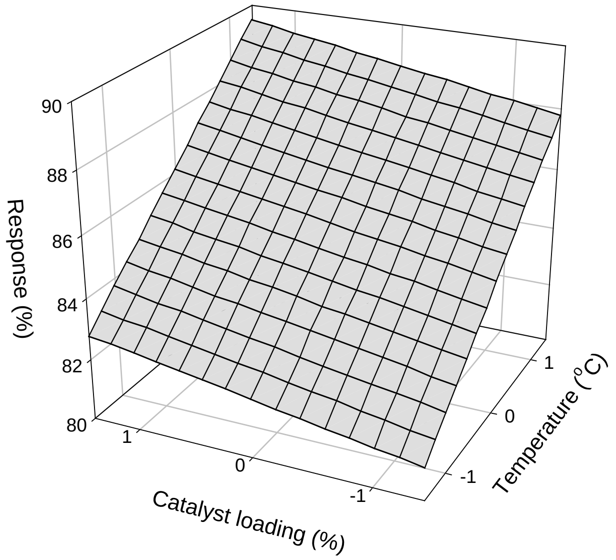


Figure 5.13 **Three–dimensional response surface for the selectivity response for BPO_4 (20% conversion)**

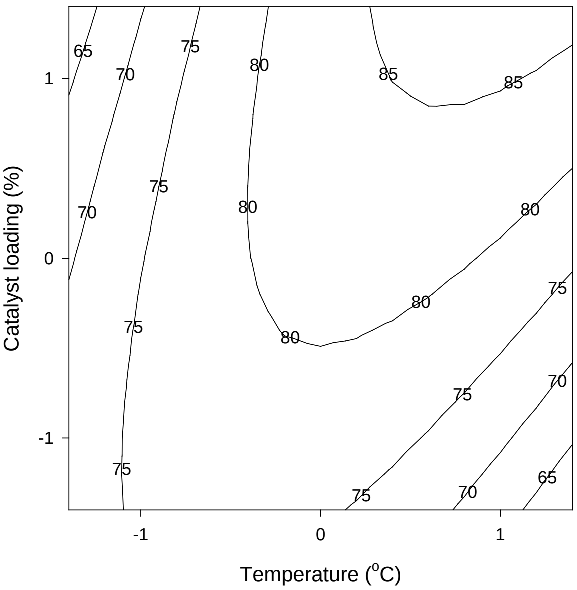


Figure 5.14 Contour diagram for the selectivity response for $(VO)_2P_2O_7$ (15% Conversion)

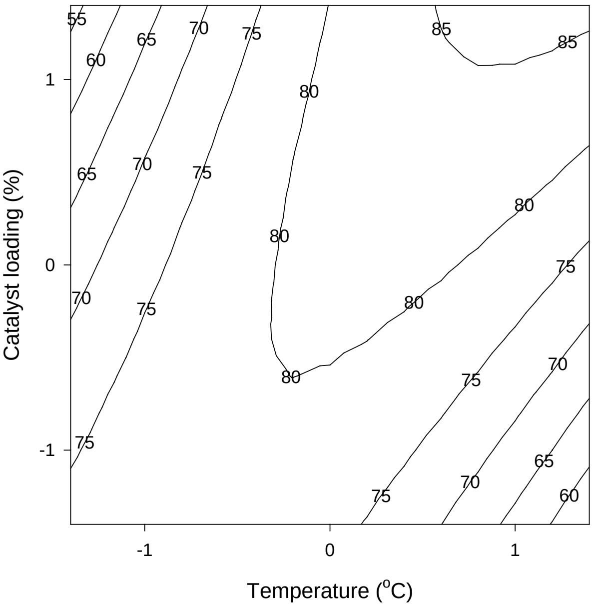


Figure 5.15 Contour diagram for the selectivity response for $(VO)_2P_2O_7$ (20% Conversion)

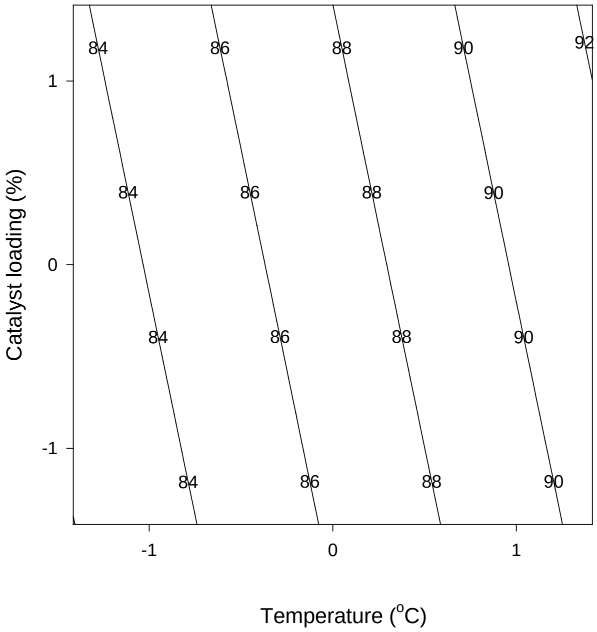


Figure 5.16 Contour diagram for the selectivity response for BPO_4 (15% Conversion)

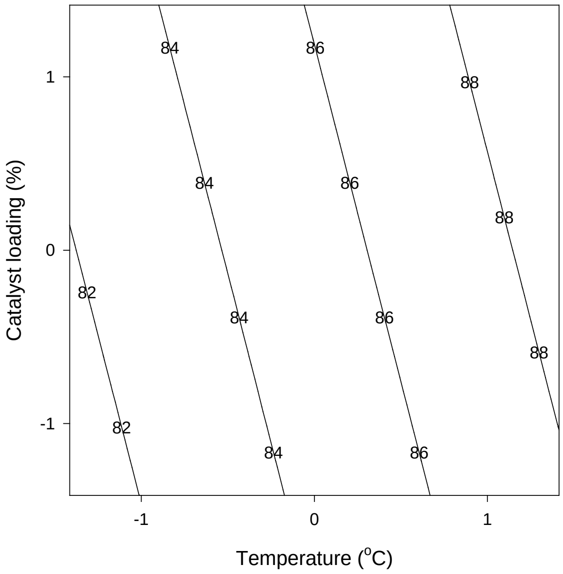


Figure 5.17 Contour diagram for the selectivity response for BPO_4 (20% Conversion)

5.4 DISCUSSION OF RESULTS

The use of the two-phase (organic liquid-gas) oxidation systems with the solid phosphate-based catalysts is remarkably efficient for the selective oxidation of *p*-cymene, increasing both the reaction rate and the selectivity to the tertiary hydroperoxide. Table 5.15 clearly illustrates the effect of the phosphate-based catalyst systems on the rate of oxidation, while the effect of these catalysts on reaction selectivity has been demonstrated in detail in the preceding sections.

Table 5.15 Comparison of reaction rates

Solvent	Catalyst	Reaction Rate[a] (mM s^{-1})	Ratio[b] (3^0 HP/1^0 HP)
None	None	1.720×10^{-5}	4.33
B-aq	None	1.300×10^{-5}	1.94
B-aq	Cu	2.533×10^{-5}	2.34
B-aq	Mn	1.489×10^{-5}	2.55
B-aq	Co	1.300×10^{-5}	2.15
None	V-Phos	7.220×10^{-5}	32.06
None	B-Phos	8.400×10^{-5}	24.32

[a] – Rate measured as the average rate of tertiary cymene hydroperoxide formation over the first hour of each reaction; [b] – Ratio of 3^0 HP/1^0 HP calculated from the averages of the runs given in Table 5.1.

The comparison in Table 5.15 shows that the rate of tertiary hydroperoxide formation is increased by a factor of between 3 and four when using the phosphate-based catalysts. To give an indication of the improvement in selectivity, the ratio of primary hydroperoxide to tertiary hydroperoxides has been calculated and shown in Table 5.15. From these comparisons it is clear that selectivities are improved by a factor of between 6 - 8.

It is not clear at this stage exactly how the phosphate-based catalysts are influencing the oxidation of the *p*-cymene substrate. Neither $(VO)_2P_2O_7$ nor BPO_4 are known catalysts for the liquid-phase oxidation of organic compounds. Vanadyl pyrophosphate ($(VO)_2P_2O_7$) and derivatives thereof are, however, the catalysts of choice for the gas-phase oxidation of *n*-butane to maleic anhydride.[102] In this case, catalytic activity has been ascribed to a combination of the presence of non-stoichiometric phophorus and oxidation state changes on the vanadium. However, no oxidation state changes are known for the boron phosphate catalyst. The latter has been reported as an efficient catalyst during the oxygenation of secondary and tertiary alkanes,[103] in which case the observed effect of the boron phosphate has been ascribed to the ability of phosphates to bind, hence deactivate, other metals capable of catalyzing unwanted autoxidation reactions. Such an explanation, however, fails to provide a ready answer for the observed increase in oxidation rates, even at very low levels of catalyst loadings. It is therefore clear that a considerable amount of work will need to be carried out to achieve some understanding of the mechanisms at work. The results of the multi-factorial experiments have shown that these catalysts are capable of giving high selectivities to the desired hydroperoxide, with values exceeding 85% not being uncommon. The results also show that the level of catalyst loading has a relatively small influence on the reaction outcome so that catalyst loadings as low as 0.03 % (m/m) are very effective. The main factor determining the reaction selectivity appears to be the reaction temperature, with increasing reaction temperature resulting in an increase in selectivity. Increasing the reaction temperature too far, however, promotes hydroperoxide decomposition giving rise to intensely coloured reaction mixtures. Preliminary experiments carried out at higher temperatures seem to indicate that a temperature of *ca.* 140°C might be the limiting reaction temperature under the conditions used during this investigation.

CHAPTER 6

SUMMARY AND CONCLUDING REMARKS

6.1 GENERAL OBSERVATIONS

The selective oxidation of *p*-cymene to the tertiary cymene hydroperoxide was investigated in some detail during the course of this investigation. The main objective of this study was to establish whether an improvement in the efficiency of the said oxidation process was possible, especially with respect to the following issues:

- Increasing the selectivity of the oxidation towards the tertiary cymene hydroperoxide.
- Increasing the level of substrate conversion whilst maintaining a high selectivity towards the desired hydroperoxide.
- Increasing the rate of the oxidation without affecting reaction selectivity.

The main findings of the work are summarized in the following sections.

6.2 ANALYTICAL PROCEDURES

A reliable method was required to quantify both the primary and tertiary hydroperoxides formed during the oxidation of *p*-cymene so as to be able to confidently evaluate reaction (catalyst) selectivity. Since the direct analysis of hydroperoxides is not feasible, a reduction method was required to convert the formed hydroperoxides to the corresponding alcohols, and analysing the alcohols by means of gas chromatography. Two reduction methods were considered, namely using ferrous sulphate and using triphenylphosphine. A comparison between the total hydroperoxide as determined by direct iodometric titration and reduction/GC analysis showed the triphenylphosphine method to be superior. The latter method was fully evaluated by means of recovery studies using statistical methods. The results of this showed that the method was consistent (with a confidence level above 95%), but it gave slightly lower recoveries than expected. This method of analysis was used during the study of the air oxidation of *p*-cymene.

6.3 SCREENING OF OXIDATION SYSTEMS

Eight oxidation systems were selected for an initial screening experiment to evaluate the type of system showing the most promise for possible improvement. These eight oxidation systems included five systems previously reported for the oxidation of cymene and three systems that have not previously been evaluated specifically for the oxidation of cymene. The main findings of these screening experiments may be summarized as follows:

- Three-phase oxidation systems, *i.e.* systems containing an organic phase, an aqueous phase and gas, with or without soluble or solid catalyst, gave much lower activities compared to two-phase oxidation systems consisting only of an organic phase (with or without catalyst) and gas.

- The use of a base in the aqueous layer improves the selectivity towards the tertiary hydroperoxide to some extent, but this effect is purely the result of the decomposition and extraction of primary hydroperoxide into the basic aqueous phase. Oxidation effectiveness does not appear to be improved by the use of a basic aqueous phase.

- The oxidation systems comprising only two phases and which use a non-autoxidation catalyst, *i.e.* a catalyst that does not catalyse the conventional autoxidation of organic compounds, gave by far the most promising results. These systems gave both a high selectivity as well as high reaction rate.

6.4 MULTI-FACTORIAL EVALUATION OF PHOSPHATE-BASED CATALYSTS

The solid metal phosphate catalyst systems, $(VO)_2P_2O_7$ and BPO_4, were investigated by multi-factorial techniques. The main results of these evaluations may be summarised as follows:

Comment [b1]: Formulas

- An increase in the reaction temperature appears to improve both the rate of oxidation and the selectivity towards the tertiary hydroperoxide for the two oxidation systems.

- An increase in the catalyst loading does not appear to have a marked effect on the activity or selectivity of the oxidation.

- Both catalyst systems give remarkably high selectivities towards the tertiary hydroperoxide (>85%), even at substrate conversions as high as 25%.

The effect of the phosphate-based catalysts on the oxidation of *p*-cymene is quite remarkable, improving both the rate of oxidation and the selectivity towards the tertiary hydroperoxide. As an example, the ratio of primary hydroperoxide to tertiary hydroperoxide, which has been reported to be in the region of 1:4, is improved markedly to ratios in the order of 1:15. It was, however, not possible to deduce any information regarding the mode of action of the phosphate catalysts during this study. The absence of a basic aqueous phase, of course, contributes to the improved selectivity as the decomposition of hydroperoxides in the presence of base is minimized. One possible explanation for the observed increase in selectivity worthy of further investigation is the possibility that the presence of the phosphate-based catalysts “bind” or deactivate metallic species capable of catalysing the normal autoxidation route. The effect of these catalysts on the rate of oxidation is unclear at this stage.

6.5 SUMMARY AND CONCLUDING REMARKS

The results of the present study have clearly shown that the improvement of the cymene oxidation route is clearly feasible, provided that the correct catalysts and reaction system are used. Current oxidation procedures typically give the desired products in the range 70 – 80% yield in terms of consumed substrate, while yields in excess of 85% have been obtained during this investigation. There are, however, a number of issues, which need to be addressed before the commercial viability of the present oxidation system can be fully evaluated. These include:

- Selecting the final production reactor configuration, and evaluating the oxidation system in that reactor under conditions as close as possible to actual production conditions.

- Performing a full mass balance on the oxidation reaction mixture, including identification and quantification of all by-products.

- Completing the work-up of the reaction mixture, including selective removal/decomposition of the primary hydroperoxide, acid cleavage of the tertiary hydroperoxide, and isolation of the reaction products (cresol and acetone).

Furthermore, only a limited number of catalysts and substrates were evaluated during the course of this investigation. It will hence be necessary to expand the scope of the investigation to include a wider range of catalysts, possibly together with other modifications such as the using a reaction solvent, or adding radical scavengers to the reaction mixture etc. Other substrates that could possibly be converted to specific phenolic compounds in a manner similar to the cymene must also still be evaluated. Examples of such substrates would include cumene, *o*-cymene, *m*-cymene, and substituted isopropylbenzenes such as 4-chloroisopropylbenzene and diisopropylbenzenes such as *m*-diisopropylbenzene.

CHAPTER 6

SUMMARY AND CONCLUSIVE REMARKS

The statistical analysis of the triphenylphosphine method proofed, that the method was reproducible within a 95% confidence limit for the analysis of the hydroperoxide products. This method of analysis was used during the study of the air oxidation of *p*-cymene.

The solid metal phosphate catalyst system were selected for the oxidation of cymene from the various catalyst and oxidation systems investigated. The use of solid metalphospate catalysts for the oxidation of cymene has been investigated by multi-factorial techniques. Two catalysts, namely vanadium and boronphosphate were selected for the investigation.

The results of the oxidation of cymene by the metal phosphate catalysts mat be summarised as follows:

- Increasing the reaction temperature for both catalysts results in an increase in the selectivity towards the tertiary hydroperoxide. This increase in activity with increasing temperature could possibly ascribed to more energetic reactive collisions between reacting molecules, as well as the increase in the activity of the of the metal catalysts.

- Increasing the amount of catalyst in the case of vanadium phosphate, results in an increase in the selectivity towards the tertiary hydroperoxide, in the case for boron phosphate, no significant improvement in the selectivity towards the tertiary hydroperoxide were observed.

- There were no significant difference between the results obtained for the two catalysts, both gave high selectivities towards the tertiary hydroperoxide (excess of 80%) at 25% conversion.

- The solid metal catalyst systems were successfully optimised using response surface techniques. For each catalyst one central composite design were run. A second-order response surface model was used for vanadium phosphate, while in case for boron phosphate a linear first-order response surface model was used, since the interaction effects were negligible. For vanadium phosphate, a inverted, three – dimensional response surface was obtained. For boron phosphate, the response surface obtained was a plane, since it was a first-order model.

The following conclusions may be drawn from this investigation.

- Solid phosphate catalysts improve both oxidation rates and oxidation selectivity remarkably towards the tertiary hydroperoxide in comparison to other oxidation systems investigated.

- The difference in selectivity with increasing conversion is relatively small, which is important from a reaction control point of view, reactions may therefore be controlled on reaction times rather then actual conversion.

- High temperatures increases the selectivity towards the tertiary hydroperoxide, in the oxidation of cymene with solid metal phosphate catalysts.

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System	[a]Rate (Mm/s) 10^{-5}
Uncatalysed	1.720
B-aq	1.300
Cu	2.533
Mn	1.489
Co	1.300
VPO_4	7.220
BPO_4	8.400

[a] – Rate based on 1 hr.

APPENDIX A

LIST OF TABLES

TABLE NO. **TITLE** **PAGE NO.**

APPENDIX B

LIST OF FIGURES

APPENDIX C

LIST OF SCHEMES