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THE ELECTROCHEMICAL SYNTHESIS OF 3-*tert*-BUTYL-4-METHOXYBENZALDEHYDE

By

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My mother and the rest of my family for all their support and guidance, I thank God for them.

The staff and my fellow students at the Chemistry department are also thanked for their assistance and friendship

SUMMARY

This project was concerned with the evaluation of three potential synthetic routes for 3-*tert*-butyl-4-methoxybenzaldehyde, a useful fine chemical intermediate and ingredient in many sunscreen agents. The three synthetic routes all involved the selective oxidation of the 3-*tert*-butyl-4-methoxytoluene to the desired benzaldehyde by (a) catalytic air oxidation, (b) direct electrochemical oxidation, and (c) indirect electrochemical oxidation.

In order to decide whether catalytic oxidation should precede the alkylation of 4-methoxytoluene, the selective oxidation using the well-known cobalt(II)-bromide catalyst system in acetic acid solutions were investigated with the view to determine whether increased electron density on the aromatic ring improves selectivity to the desired benzaldehyde or not. In addition, the effect of various important reaction variables was also investigated. These studies showed that increased electron density, hence increased substitution, increases the desired benzaldehyde selectivity. In addition, while reaction conditions such as reaction temperature, catalyst concentration, water concentration, etc. may be optimised for maximum 3-*tert*-butyl-4-methoxybenzaldehyde yields (~80%), such yields can only be achieved at relatively low (<40%) alkoxytoluene conversions.

The direct electrochemical oxidation of 3-*tert*-butyl-4-methoxytoluene was investigated in methanol solutions containing various supporting electrolytes and using constant current electrolysis with the intention of optimizing the production of 3-*tert*-butyl-4-methoxybenzyl dimethyl acetal which can later be hydrolyzed using sulfuric acid to the 3-*tert*-butyl-4-methoxybenzaldehyde. In this study, various parameters such as supporting electrolyte and electrodes were studied. Previous studies showed undoubtedly that methanol as a solvent gave better results amongst the rest of the solvents.

Indirect route was also studied as a method of synthesizing 3-*tert*-butyl-4-methoxybenzaldehyde and compared to the direct electro synthesis

KEY WORDS:
p-Methoxyanisole, 3-*tert*-butyl-4-methoxytoluene, 3-*tert*-butyl-4-methoxybenzaldehyde, Catalytic air oxidation, Electrochemical oxidation.

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Chapter 1

INTRODUCTION

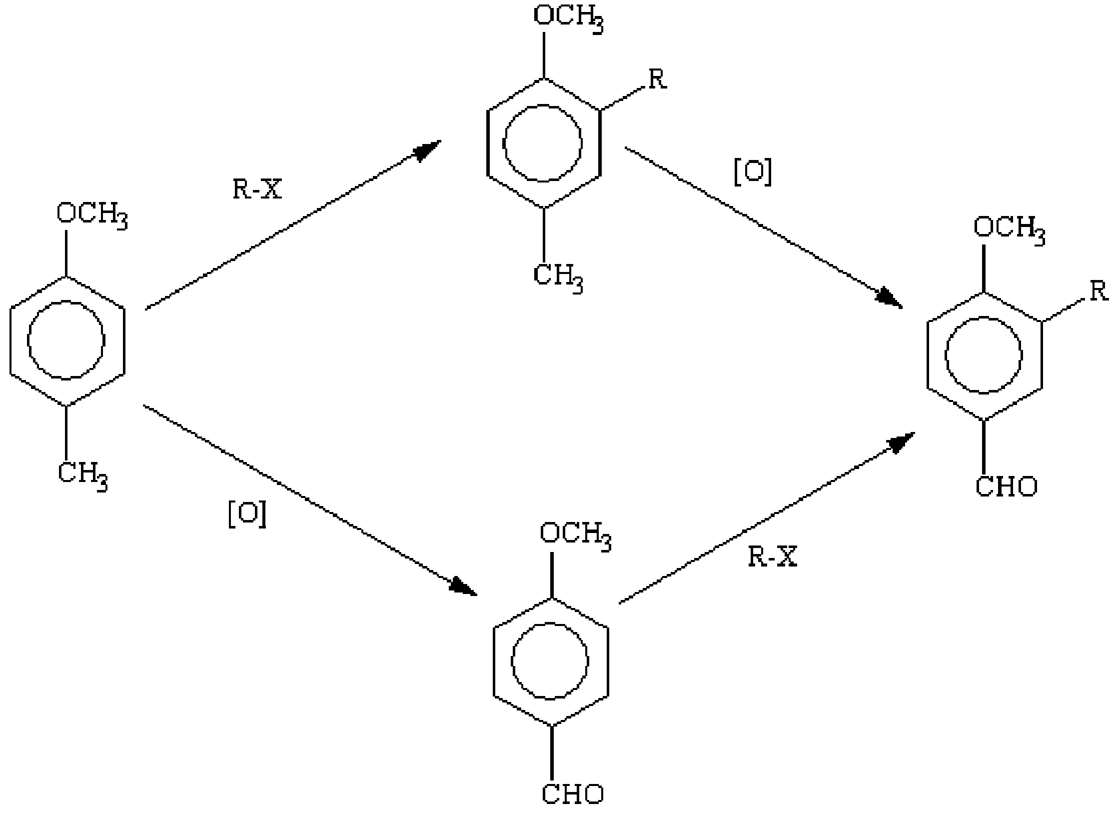
1.1 General

Apart from several notable exceptions, the South African chemical industry[1] has remained static over the last ten years. Indeed, in many cases, it has lost critical manufacturing capacity and skills; it has failed to expand and diversify significantly into higher value-added products; it has missed the opportunity to take a share of the high growth markets of the nineties, including such areas as electronic chemicals, speciality surfactants, active pharmaceutical ingredients, food and flavour additives and adhesives. Notwithstanding a number of strategic processes whose objectives were to increase downstream value-addition and integration, it remains predominantly an upstream, commodity-based industry that has not managed to break through its endemic growth barriers of a small local market, high cost of capital, distance from low-cost raw materials and inadequate human resources.

In early 2002, the Department of Trade and Industry published a document entitled Accelerating Growth and Development: The Contribution of an Integrated Manufacturing Strategy[2], the purpose of which was to ‘invigorate the production of goods and services and create the conditions necessary for the retention and growth of output and employment in other sectors of the economy’. The document identified a number of requirements for micro-economic reform in South Africa, including the promotion of competitiveness and the development of customised services. Furthermore, the chemical industry, in view of its potential for growth and development, was highlighted as worthy of increased attention and a number of specific objectives were defined. However, the Integrated Manufacturing Strategy (IMS)[3] will on its own not be able to achieve the desired outcomes of growth and development, as indeed is acknowledged in the document. For instance, the outcomes will also require appropriate and effective human resource development and technology strategies. The latter aspect has been a specific focus of the NACI, which is concerned that South Africa's R&D capability is lagging significantly behind competitor developing countries, and that this lag will reduce the country's competitiveness in world markets. In order to redress this situation, to underpin the new IMS and to stimulate investment in key technology, NACI commissioned an Advanced Manufacturing and Logistics Strategy with the requirement that the recommendations provide some radical, highly innovative and lateral solutions to leverage South Africa's manufacturing industry. In this context, the Chemical Sector Task Team (CSTT) proposed several strategic interventions[4], including:

- Establishment of a new technology platform that will develop technologies to decrease economies of scale for chemical plants and hence enable smaller production facilities to compete against the mega plants.
- Support for existing development efforts in low-cost diagnostics, aroma chemicals production, and development of biodegradable and high performance polymers, bio-diesel and products from alpha-olefins.

Towards the end of 2004 the Department of Science and Technology launched its "Research Centres of Excellence Program" including a Centre of Excellence in Catalytic Processing housed at the University of Cape Town. This Centre of Excellence, called "c*change" identified several major research programs with a view to support other initiatives such as the IMS referred to above. One of these programs, the Small Volume Chemicals Programme, specifically addresses the two strategic interventions highlighted above and this particular project forms part of this overall Small Volume Chemicals Program which focuses on "the development of chemical and technological expertise for the synthesis and/or production of phenolic chemicals, particularly chemical starting materials, intermediates and products". This particular project deals with the conversion of simple phenolic compounds to higher-value derivatives by catalytic oxidation technologies, e.g. phenols to hydroquinones/benzoquinones and alkylphenols to phenolic ketones or aldehydes and derivatives thereof. The latter group of compounds, which are of particular interest to the aroma (fragrance and flavour) industry, may be produced from locally (RSA) available feedstock from the company Merisol, the world's largest producer of phenolic compounds. More precisely, this project aims to evaluate various approaches to the synthesis of alkyl-substituted alkoxybenzaldehydes with the view to identify the most promising route for the production of the said aldehydes. Scheme 1.1 illustrates the two major options when using 4-methylanisole as starting material for this synthesis.



Scheme 1.1 Routes to alkyl-alkoxybenzaldehydes from 4-methylanisole.

As is illustrated above, the synthesis may involve either an alkylation or oxidation step as the initial reaction step. This choice is extremely important to optimize the selectivity of the final reaction product, particularly in view of the fact that partial oxidation reactions are particularly prone to undergo further oxidation reactions which lower the selectivity. Such further oxidation reactions will depend on the structure of the substrate being oxidized, for example in the above case the presence of the additional alkyl group may either promote selectivity, or decrease selectivity.

In view of the critical nature of the oxidation step to ensure high yields of final product, three oxidation technologies will be evaluated. These are: Catalytic air oxidation; direct electrochemical oxidations; and indirect electrochemical oxidations using a mediator substance.

1.2 Overview of the Flavour and Fragrance Industry

1.2.1 Introduction

Aroma chemicals are used as the foundation of flavour and fragrance for giving attractive taste and aroma to processed foods and beverages and contributing pleasing scents to perfumes, toiletries and detergents. The world-wide flavour and fragrance industry generally earns returns in excess of the chemical industry average. The relatively stable revenues, largely insensitive to commodity cycles and relatively recession-resistant come from the industry’s close unity with the health, personal care and food beverage markets.

The industry is comprised of the following broad segments:

- Isolation of synthetic and natural aroma chemicals or essential oils/ natural products (Aroma chemicals are single, chemically defined substances which act on the sense of smell and taste, and essential oils are naturally occurring, volatile products obtained from various parts of plants).
- Compounding of these products into flavour and fragrance formulations tailored to meet specific customer requirements. The formulation may

contain aroma chemicals as well as other essential oils and natural extracts.

- The sale and use of these formulations in the production of personal care and pharmaceutical active ingredients, food and beverage market etc.

The following schematic diagram (Figure 1.1) depicts the full flavour and fragrance value chain.

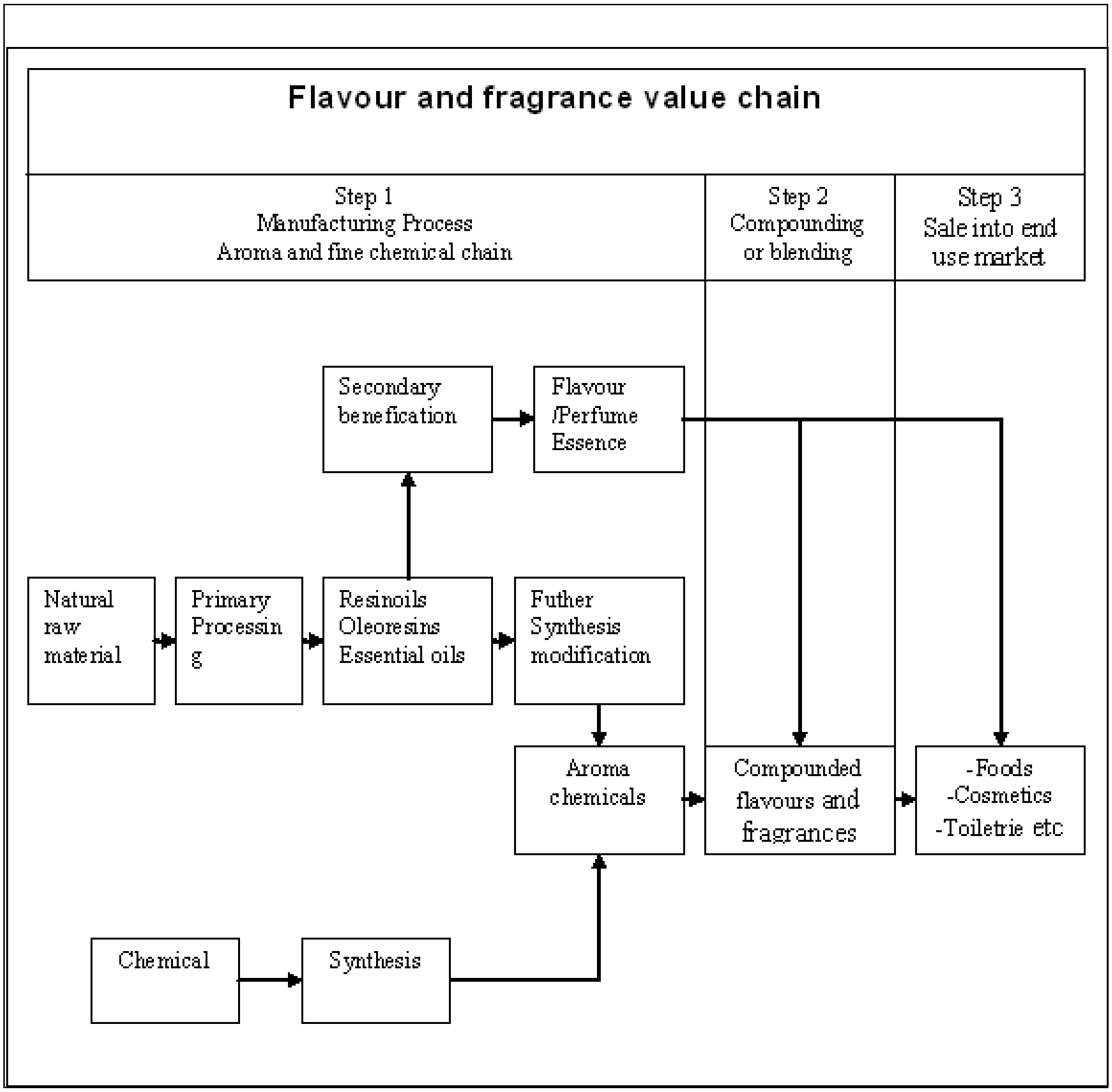


Figure 1.1: Flavour and Fragrance value chain

Approximately, 2,800 aroma chemicals are approved for use in flavour and fragrance formulations world-wide.

However, only a few hundred are produced in volumes over 50 tons for the merchant market.

There are various routes that can be used for the production of aroma chemicals:

I. **True synthetic chemicals**: It includes chemicals produced by synthesis from natural aromatic compounds and from synthetic feed stock such as petrochemicals.

II. **True Isolates**: Single aroma chemicals which are extracted from natural materials and subjected only to further processes of purification (e.g. camphor, citral and menthol).

III. **Chemically modified derivatives:** Made by converting isolate products into a specific chemical product by subjecting them to various chemical processes. This includes the conversion of crude sulfonated turpentine, a by-product of the kraft paper pulping process, into terpene aroma chemicals such as citral and linalool.

1.2.2 International Flavour and Fragrance Industry

Flavour and fragrance formulations are widely used globally to enhance, among other things, foods, beverages, detergents and pharmaceutical products. Compounded flavour and fragrance products are thus complex blends designed to impart either attractive taste or aroma to processed foods and beverages, or a pleasing scent to consumer products such as perfumes, toiletries, household cleaners etc. Other than the solvents, diluents and carriers, the formulation may contain other additives such as essential oils and natural extracts. Figure 1.2 illustrates a breakdown of the use of flavour compositions in consumer end products[5].

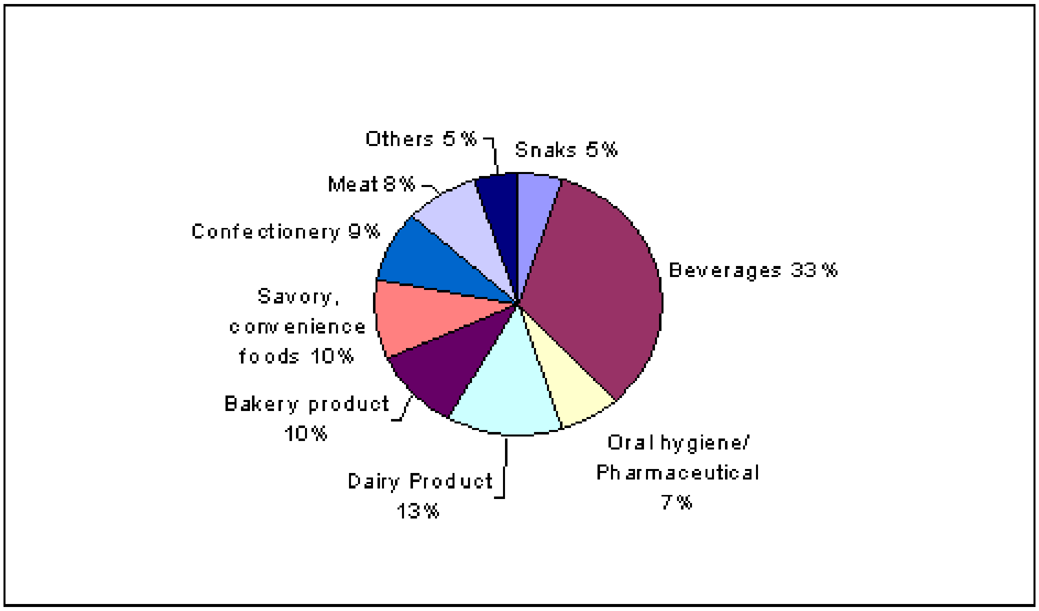


Figure 1.2: Flavours End-Use Market

Figure 1.3 illustrates a breakdown of the use of fragrance compositions in consumer end-products.

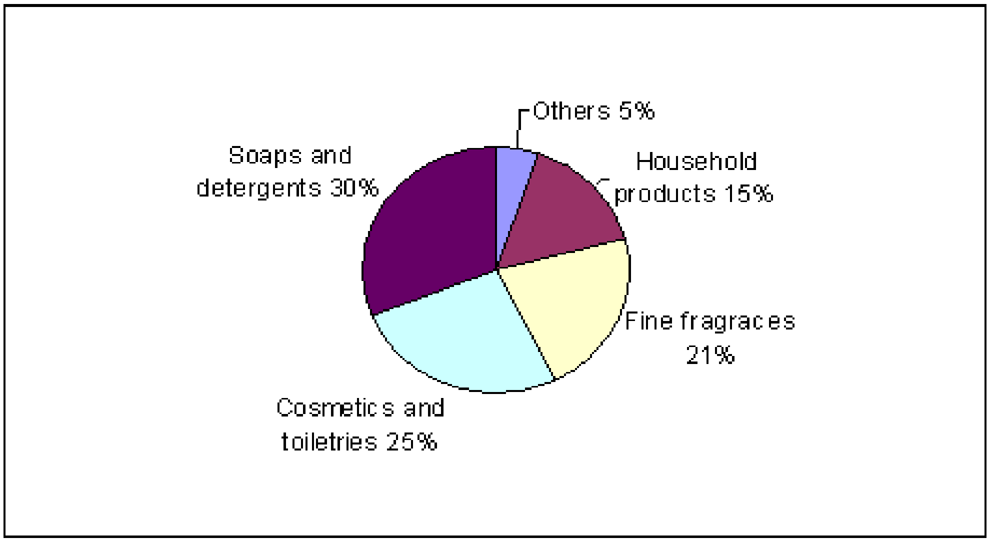


Figure 1.3: Fragrance End-Use Market

These end-use markets are typical of first world markets. This is confirmed by the global consumption usage of flavour and fragrances, which shows that the USA accounts for 31% of the market, with Western Europe representing about 29% of the world market and Japan with 12%.[6]

On the other hand, developing countries, which accounts for the rest of the market consumption, offer significant potential growth as use of the consumer products in these particular major end-use markets increase.

1.2.3 South African Flavour and Fragrance Industry

The South African market in 1999 was worth a total of $107.3 milllion. Flavour products were the largest application at about $56.7 million[7]. The market of flavour and fragrance in South Africa in 1999 and projected for 2004 is shown in the Table 1.1 below:[8]

Table 1.1: Market for flavour and fragrance in South Africa 1999-2004

End-use	**1999**	**2004**
Flavours	**Value ($ millions)**	
Beverages	18.1	21
Diary	9.3	10.9
Snacks/ Savoury/ Convenience	7.0	9.2
Bakery	6.4	6.7
Confectionary	5.2	5.6
Meat	5.1	6.4
Oral Hygeine/ pharmaceutical	3.0	4.6
Others*	2.6	3.1
TOTAL	**56.7**	**67.5**
Growth Rate		3.6
Soap/ Detergents	24.6	27.7
Cosmetics/Toiletries	12.0	14.7
Household cleaners	8.3	9.2
Fine fragrance	2.5	2.7
Others#	3.2	3.4
TOTAL	**50.6**	**57.6**
Growth Rate		2.70%
GRAND TOTAL	**107.3**	**125.3**

* Including pet food and tobacco; # including candles, aromatherapy, insecticides, etc.

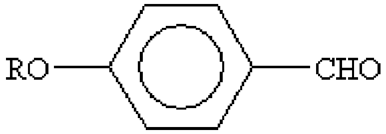
In S.A. the current emergence of the black middle class is having a positive impact on the consumption levels of flavour and fragrance containing compounds. Within the fragrance sector, the largest use is in soaps and detergents. Within this sector, washing soap is predominantly used in the less affluent regions, where the use of washing machines is at nominal levels. Many cosmetics and toiletries multinational companies have located production facilities in the South Africa as the production of base for the sub-Sahara region.

The total value of the South African market was predicted to be in the order of $125.3 million (R877 million at the exchange rate of R7/US $). Actual values for this market have not yet been reported for 2004. Any increase in the production of aroma chemicals and essential oils in South Africa would increase the participation in the regional flavour and fragrance market.

1.3 Overview of hydroxy- and alkoxybenzaldehydes

1.3.1 General

In this particular project we are considering the production of alkoxybenzaldehydes of the type:



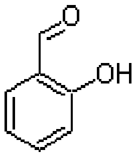
and where the aromatic ring may contain further substituents, for example linear or branched alkyl groups.

These types of aldehydes resemble their aliphatic counterparts, which mean that they are susceptible to further oxidation so that air must be excluded and/or stabilizers should be added during storage. Many of these alkoxybenzaldehydes and secondary products, such as the corresponding hydroxybenzaldehydes and their acetal derivatives, are used in the flavour and fragrance industries. In addition, they can be used as starting materials for pharmaceuticals, agricultural chemicals and fertilizers.[9]

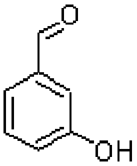
1.3.2 Uses

1.3.2.1 Hydroxybenzaldehydes

The two isomers that represent more than 99% of the hydroxybenxaldehyde market are 2- and 4-hydroxybenzaldehyde [(a) and (c)].[5] 3-Hydroxybenzaldehyde (b) is mainly used as an intermediate in the production of dyes and some pyrethroid pesticides.[10]



(a)



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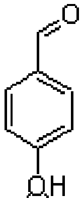
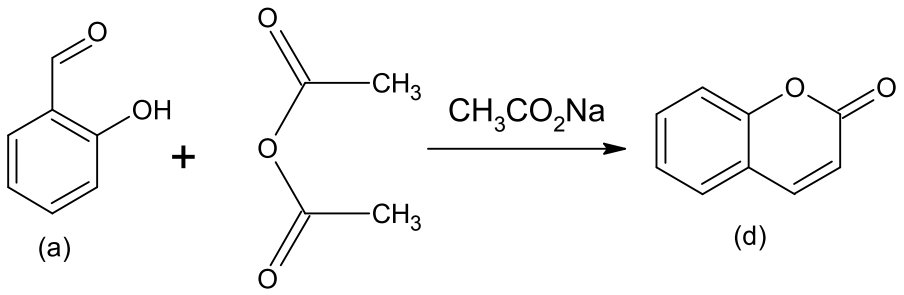


(c)

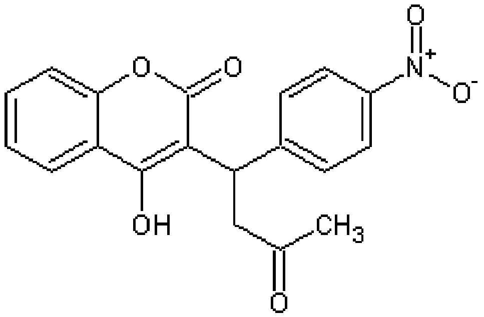
1.3.2.1.1 2-Hydroxybenzaldehyde

2-Hydroxybenzaldehyde, also known as salicylaldehyde, and its derivatives are used in applications such as agricultural chemicals, electroplating formulations, perfumes, petroleum chemicals, polymers and fibres. The largest use of salicylaldehyde is for the production of coumarin (d), an important commercial chemical used in soaps, flavours and fragrances and as a brightener and levelling agent in the electroplating industry. The synthesis of coumarin (Scheme 1.2), using the Perkin reaction (aromatic aldehyde condensation)[11] involves the reaction of salicyladehyde with acetic acid anhydride in the presence of sodium acetate. The anticoagulant, acenocoumarol (e),[12] can typically be prepared from 4-hydroxycoumarin.



Scheme 1.2: Coumarin Synthesis

Salicyladehyde itself has preservative and antibacterial properties, and can be used to form ultraviolet absorbing products upon interaction with compounds containing active ethylene groups. Derivatives of salicyladehyde are also used in photography, various polymer applications and for metal ion removal[13] (via chelating mechanisms).[5]

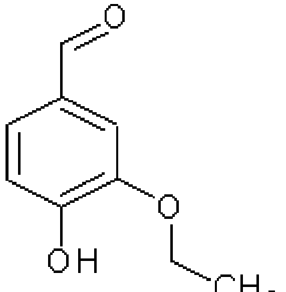


(e)

1.3.2.1.2 4-Hydroxybenzaldehyde

4-Hydroxybenzaldehyde is a colourless to tan-coloured solid that occurs in nature in small amounts in some plants. It has a slight aromatic odor and has a high melting point (117 °C), sublimes between 110 and 120 °C, and is sparingly soluble in water (0.81 g per 100 g water at 18 °C).

4-Hydroxybenzaldehyde is commonly used in food adulteration, being utilized to replace natural vanilla.[14] Other derivatives of this aldehyde that are generally used in the flavouring industry are 3-ethoxy-4-hydroxy-benzaldehyde (g), as well as sweet vanilla, 3-methoxy-3-hydroxybenzaldehyde (vanillin) (h) (as dry vanilla chocolate)[15], 4-acetyloxy-3-hydroxybenzaldehyde (i) (with a mild balsamic, floral odour), 4-isobutoxy-3-methoxybenzaldehyde, (j) (as heavy sweet vanillan nutmeg), 4-hydroxy-3-methoxybenzyl alcohol (k) (as mild sweet balsamic vanilla), and 4-(4-hydroxy-3-methoxyphenyl)-3-buten-2-one (l) (with a sweet, warm and long lasting odor).[16]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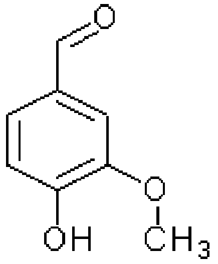
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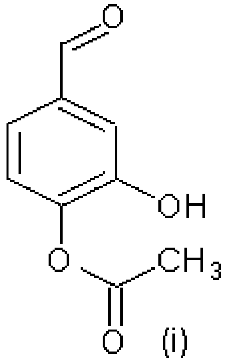
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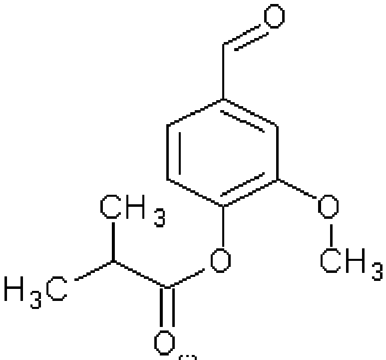
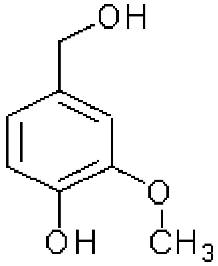
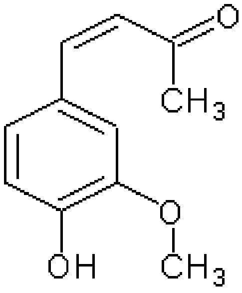
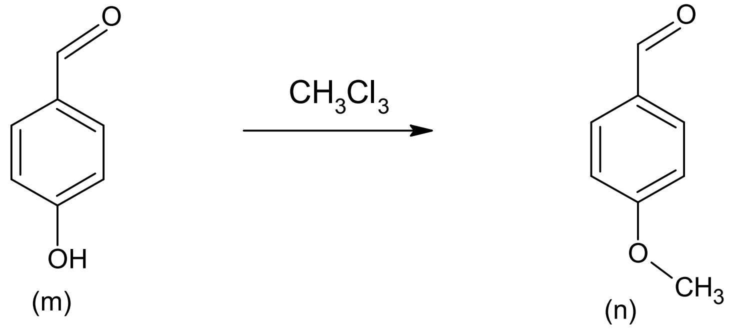

(j)


(k)

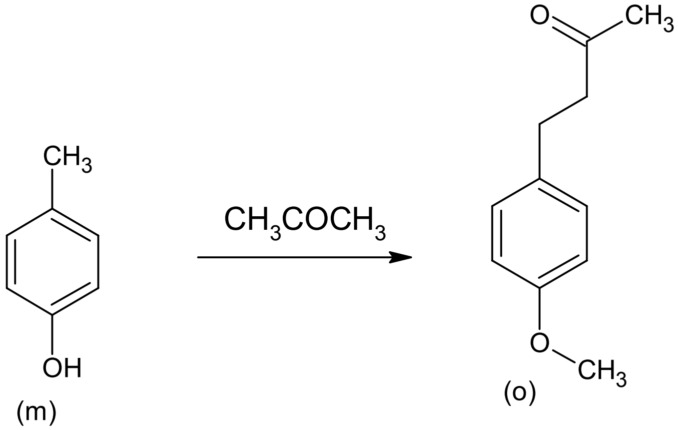

(l)

Despite an agreeable aromatic odor, 4-hydroxybenzaldehyde is not used as a fragrance, but rather as an intermediate in the synthesis of some fragrances. A methyl ether derivative, 4-anisaldehyde (n), is a commercially important fragrance, and is made in a simple one-step synthesis by reaction of 4-hydroxybenzaldehyde with methyl chloride (Scheme 1.3).



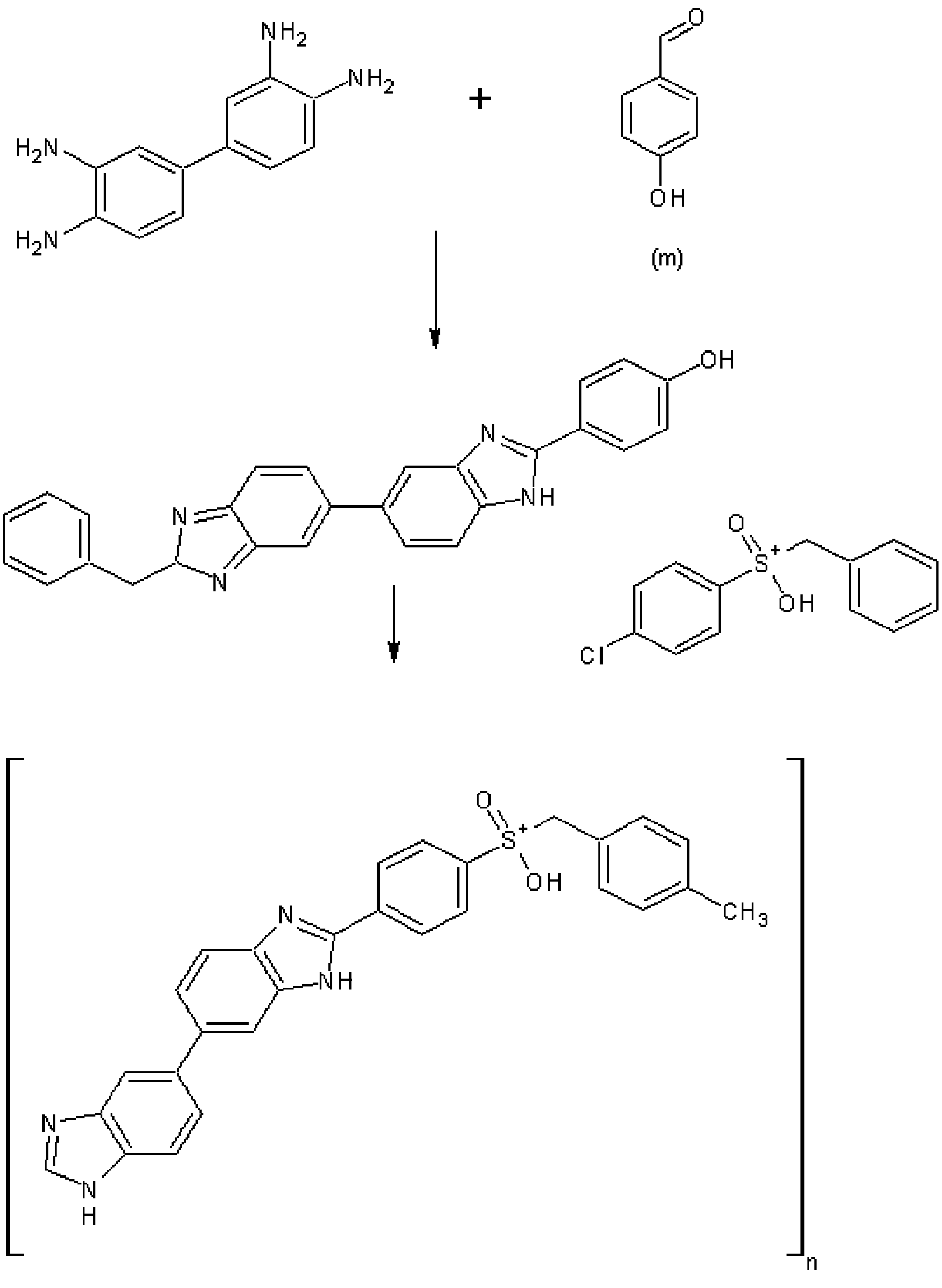
Scheme 1.3: Synthesis of Anisaldehyde

Another fragrance, 4-(4-hydroxyphenlyl)butanone (o) or raspberry ketone, is prepared from 4-hydroxybenzaldehyde and acetone (Scheme 1.4).[5]



Scheme 1.4: Synthesis of Raspberry Ketone

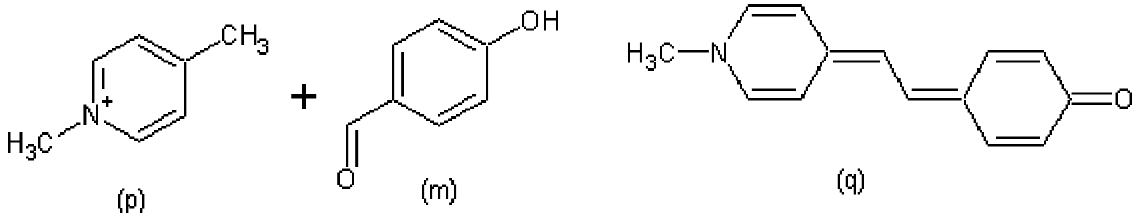
4-Hydroxybenzaldehyde is widely used as a starting material in the production of a variety of other useful products by various sectors in the chemical industry. One of its more recent uses is in the manufacture of a new range of polybenzimidazoles (PBI's), a type of polymer currently used in flame retardant fabrics or space craft parts which need to withstand extreme temperatures (Scheme 1.5). The PBI material manufactured from 4-hydroxybenzaldehyde imparts desirable handling characteristics to the material, along with thermal resistance.[17]



Scheme 1.5: Manufacture of a new range of polybenzimidazoles

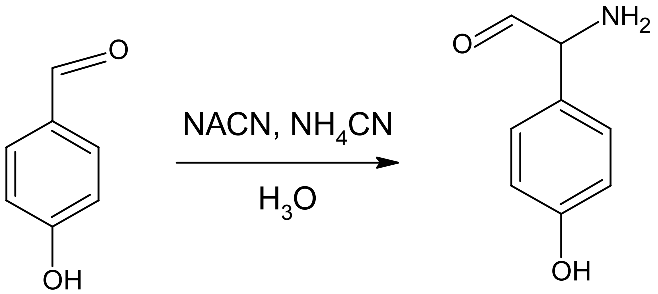
Other polymeric applications include the improvement of the resiliency and dyeability of poly (vinyl alcohol) fibres by incorporating 4-hydroxybenzaldehyde in the fibre itself. The hydroxyl group provide sites in the fibre for the formation of stable Mannich bases attached to the backbone of the polymer.[5]

The dye industry utilizes 4-hydroxybenzaldehyde in the synthesis of Merocyanine Dye. These dyes are known to display different colours, depending entirely on the solvent used. A single dye can therefore be purple, blue, green, red, green, orange or yellow, the colour being determined by the polarity and extent of hydrogen bonding in the medium. Its synthesis involves an Aldol condensation between 4-hydroxybenzaldehyde and a stabilized 1,4-dimethyl pyridinium carbocation **(p)** (Scheme 1.6). The resulting alcohol is dehydrated and deprotonated to form 1-methyl-4[(oxycyclohexadienylidine)-ethyllidene]-1,4-dihydropyridine **(q)**.[18]



Scheme 1.6: Aldol condensation between 4-hydroxybenzaldehyde and a stabilized 1,4-dimethyl pyridinium carbocation

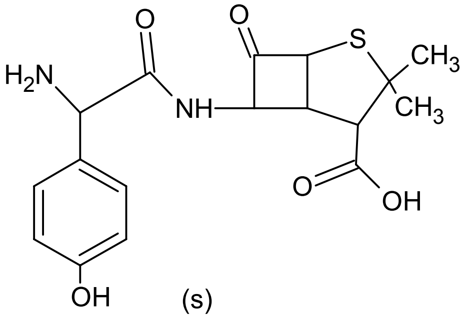
4-Hydroxybenzaldehyde is often used as a convenient intermediate in the pharmaceutical industry. Examples include the Strecker synthesis,[19] a special case of the Mannich reaction, to prepare alpha amino nitriles. 4-Hydroxybenzaldehyde is treated with NaCN and NH_4Cl, and after acid hydrolysis of the resulting cyano group, this affords 2-(4-hydroxyphenyl) glycine **(r)** (Scheme 1.7).[5] Compound **(r)** is an important commercial intermediate in the preparation of semi synthetic penicillin, amoxicillin **(s)**.



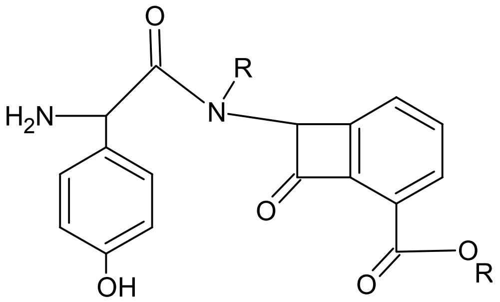
(m) (r)

Scheme 1.7: The Mannich reaction

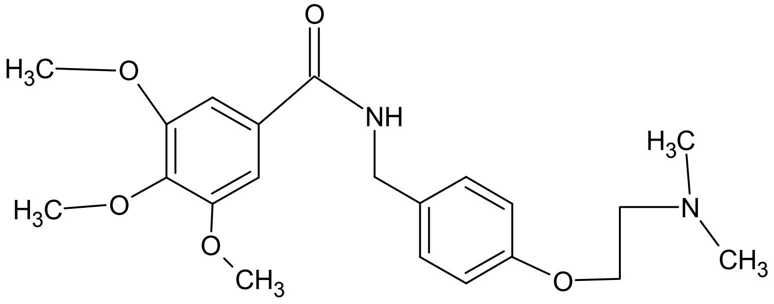
Many cephalosporin-type antibiotics (t) can also be made by this route.[20] Another pharmaceutical, trimethobenzamide (u), an antiemetic, is also prepared from 4-hydroxybenzaldehyde and 2-(4-hydroxyphenyl) glycine.[21,22]



(s)



(t)



(u)

4-Hydroxybenzaldehyde finds many applications in the agricultural industry. Mostly used as an intermediate in the synthesis of a variety of agricultural products, 4-hydroxybenzaldehyde is the most important isomer in the sector.

Herbicides like 3,5-dihalo-4-hydroxybenzonitriles are prepared via halogenation of 4-hydroxybenzaldehyde, followed by nitrile substitution for the aldehyde group. The most important herbicides of this type are bromoxynil (v) and ioxynil (w) although several other hydrazone derivatives also display herbicidal properties.[5]

[redacted]

1.3.2.2 4-Hydroxyacetophenone

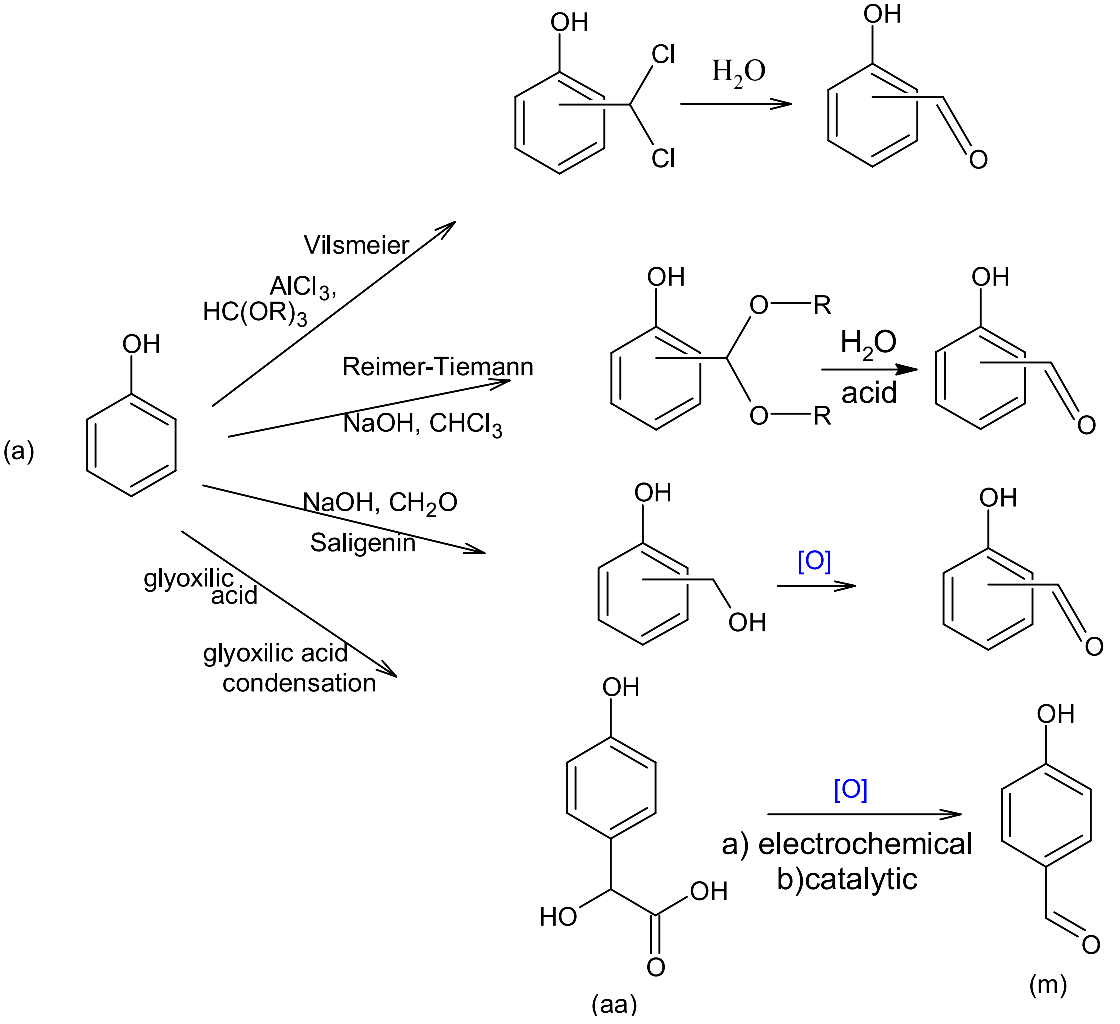
4-Hydroxyacetophenone (x) is mainly used for the preparation of pharmaceuticals. Amongst these is Salbutamol/Albuterol (y), the general bronchodilator used in most ventilators, and Atenolol (z), a β adrenergic blocking agent.[23]

[redacted]

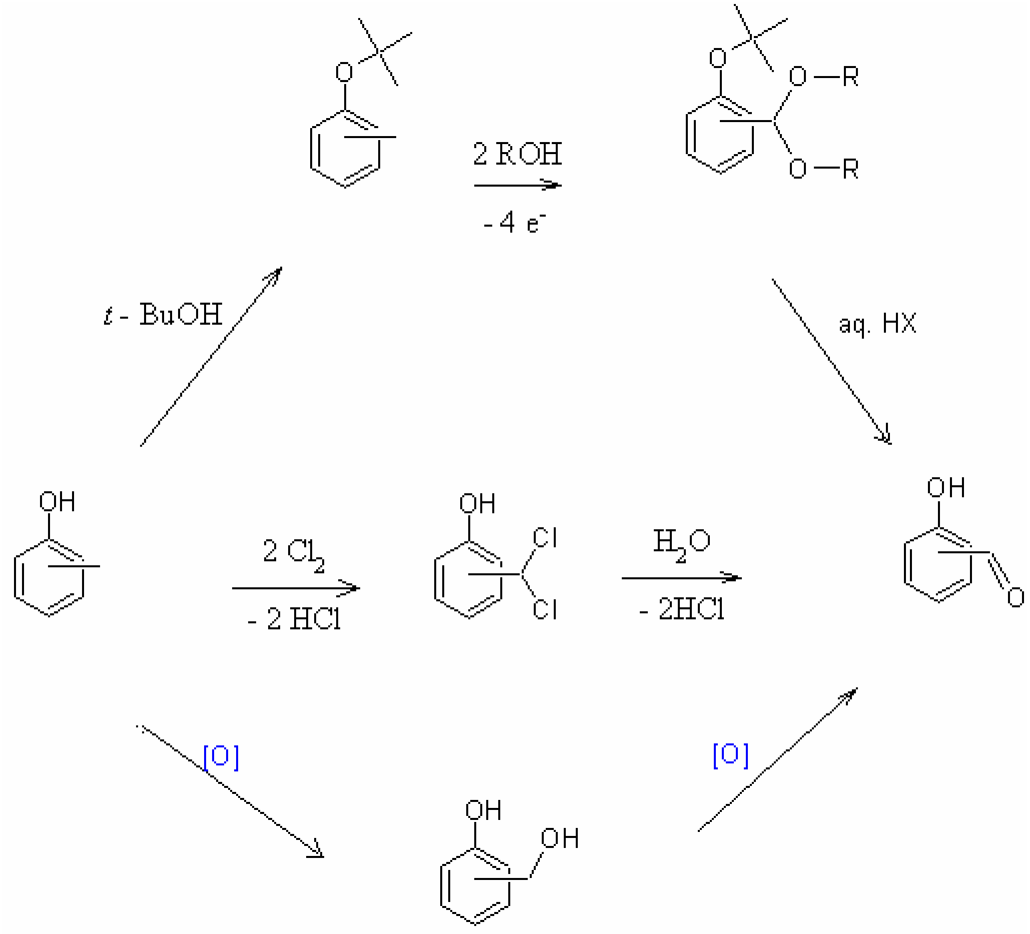
1.4 Overview of Synthetic Routes to Hydroxybenzaldehyde

1.4.1 Introduction

The main synthetic routes to hydroxybenzaldehydes are currently based on either phenol or cresol. The phenol-based routes (Scheme 1.8) have enjoyed most commercial success. Production routes from cresols (Scheme 1.9) have had only limited success, despite the potential advantage of regioselective-control. At present, Dow Chemical Company (USA) produces 4-hydroxybenzaldehyde from phenol using the Reimer-Tiemann reaction, BASF (Germany) produces 4-hydroxybenzaldehyde from p-cresol using an electrochemical route, and Rhône-Poulenc (USA) produces 2-hydroxybenzaldehyde from phenol using a process based on the Saligenin reaction.[24]



Scheme 1.8: 4-Hydroxybenzaldehyde - Routes from Phenol



Scheme 1.9: 4-Hydroxybenzaldehyde - Routes from Cresol

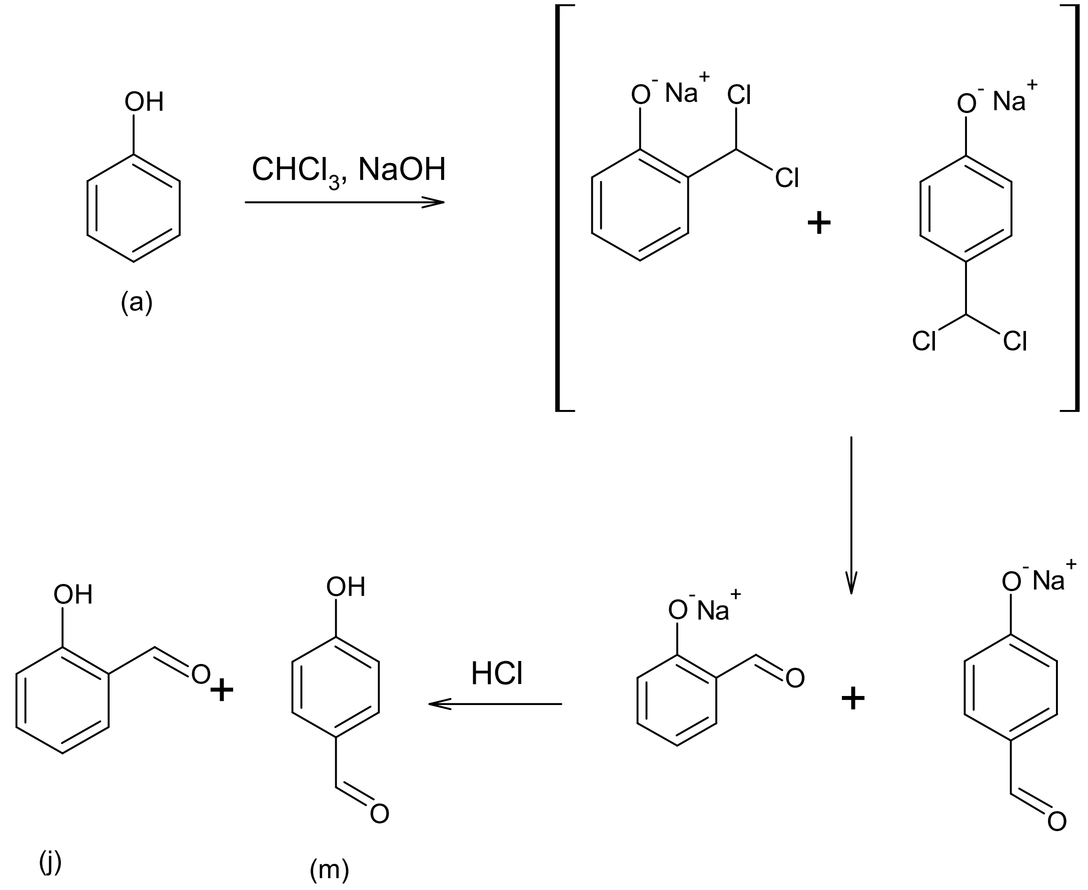
1.4.2 Routes from Phenol

1.4.2.1 The Reimer-Tiemann reaction

In this case phenol is reacted with chloroform in aqueous alkali to obtain an mixture of 2-hydroxybenzaldehde and 4-hydroxybenzaldehyde through hydrolysis of the resultant benzal chlorides (Scheme 1.10).

In most cases the aldehyde yield is moderately low, with a typical isomer ratio of 85 :15 in favour of 2-hydroxybenzaldehyde.[25] Other than low yields, this reaction suffer from other drawbacks such as the need for an excess of chloroform over phenol, and the expense of recovery and recyle of unreacted chloroform and phenol.[23] Distillation is normally used as a method of isolation, but not without difficulty, due to the sublimation of 4-hydroxybenzaldehyde.[26]

Dow Chemicals modified the reaction by adding 10 -75 % of aqueous methanol with the hope of improving the selectivity to 4-hydroxybenzaldehyde. However the difficulties of isolation and recovering the unreacted phenol still remains and the conversion is still low.[27]



Scheme 1.10: **Reimer-Tiemann Reaction**

Various reports in the literature suggests various approaches for improving the selectivity of 2-hydroxybenzaldehde, including:

- The addition of surfactants under anhydrous reaction conditions.
- The use of aprotic solvent catalysts like N, N-dimethylformamide in benzene.
- The use of various base and water loadings.
- Use of phase transfer catalysts etc.

The highest conversion reported (96 % with a selectivity of 63%) was reported for a process operated by Simutomo Chemical Company. The ratio of 2-hydroxybenzaldehyde to 4-hydroxybenzaldehyde for this process is reported to be typically 7.8:1.[5]

1.4.2.2 Vilsmeier Aldehyde Synthesis

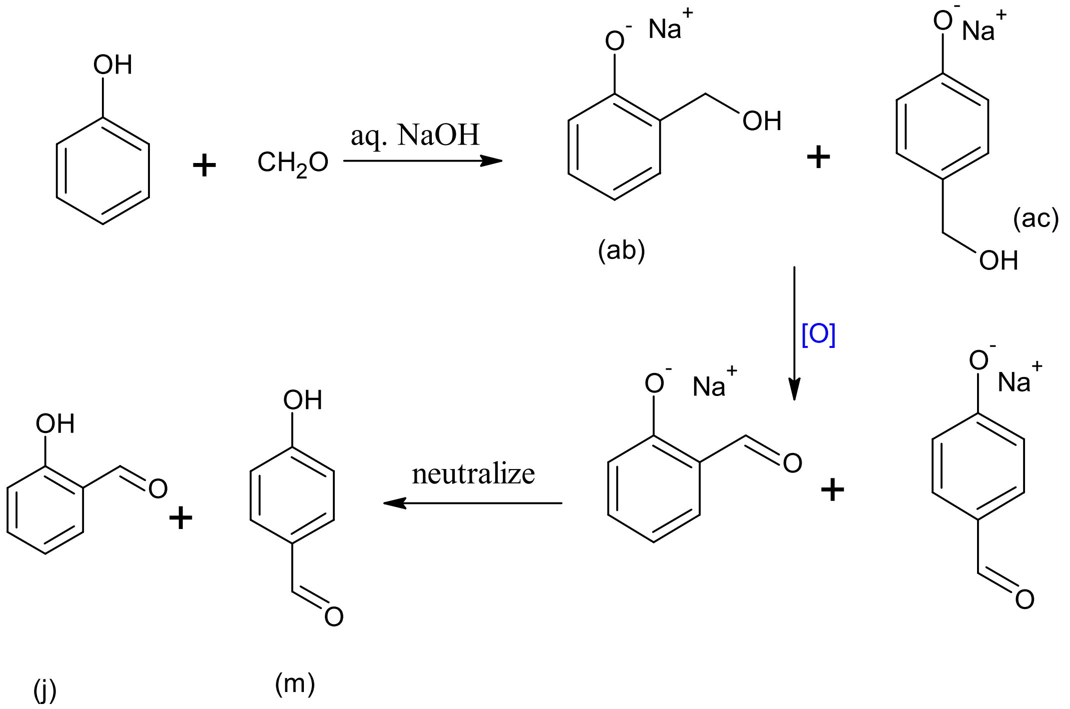
This method for the formation of hydroxybenzaldehydes (see scheme 7) used to be the preferred industrial method. This reaction uses disubstituted formamides in the presence of phosphorus oxychloride, and is applicable to activated substrates such as amines and phenols. Friedel-Craft catalysts such as aluminium chloride (instead of phosphorus oxychloride) and trialkyl orthoformate can also be used when performing these reactions. The resulting acetal is very unstable under acidic conditions, so it can be easily hydrolysed to the desired aldehyde. Regioselectivity to the 2-, and 4-hydroxybenzaldehydes is claimed to be about 50/50.[28,29]

1.4.2.3 Saligenin Reaction

The saligenin name was derived from the very first step of the reaction, formation of 2-hydroxybenzyl alcohol or saligenin. In this step, phenol is reacted with formaldehyde in the presence of aqueous base (ionic protection of the phonoxy group) to afford both isomers of the sodium salt of hydroxybenzyl alcohol (Scheme 1.11, (ab) and (ac)). Yields reported in the literature are about 85 %

and the ratio of 2-hydroxybenzyl alcohol to 4-hydroxybenzyl alcohol can be controlled by optimisation.[5,23]

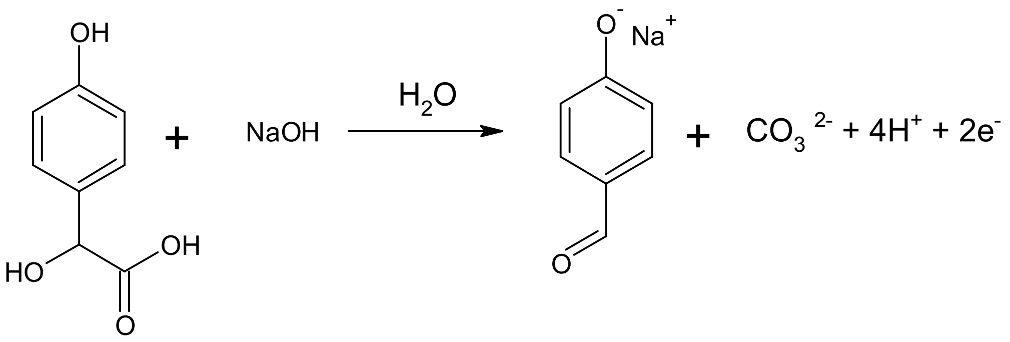
The catalytic air oxidation of the intermediate benzyl alcohol phenolates affords both hydroxybenzaldehyde isomers and it can be performed without a catalyst in an alkaline medium between 25 and 50 °C.[30] However the use of platinum, palladium, or activated carbon as catalysts is quite common for this conversion. Other mediators such as boron, bismuth, cadmium, cerium, indium, lanthanum, tellurium, lead, silver or tin to increase catalyst activity and stability has also been claimed.[31,32]



Scheme 1.11: Saligenin Reaction

1.4.2.4 Glyoxilic Acid Condensation

Condensation of phenol with glyoxilic acid affords mandelic acid (aa) with a yield of almost 77 %. Mandelic acid can in turn be oxidized to 4-hydroxybenzaldehyde in alcoholic medium using a copper catalyst and air. Literature reported yields are about 88%.[33] The disodium salt of mandelic acid can also be oxidized electrochemically using carbon felt electrodes, leading to a 90% yield (Scheme 1.12).[34]



(aa)

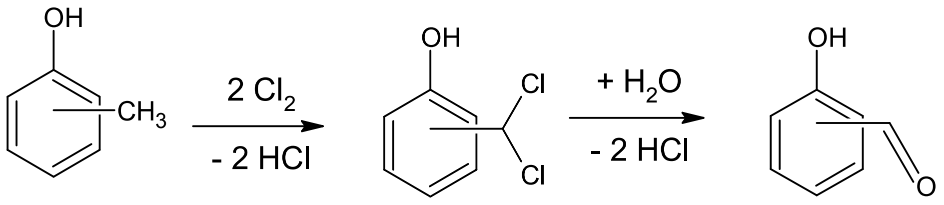
Scheme 1.12: Electrochemical Oxidation of Mandelic Acid

The reaction is performed under strong basic conditions and at temperatures between 30 and 60 ^oC.[33]

1.4.3 Routes from Cresols

1.4.3.1 Side-Chain Halogenation

Side-chain chlorination of cresol can be carried out to form the unstable dichloromethane intermediate **(ad)** which can be hydrolysed to the respective hydroxybenzaldehyde (Scheme 1.13). Esterification with an inorganic or organic acid chloride is used to protect the phenolic group prior to chlorination. Deprotection is by simple hydrolysis.[23]



(ad)

Scheme 1.13: Side chain halogenation

Chlorination is generally not very selective and a variety of ring chlorinated by-products often results.[35] Disposal of the chlorinated waste-streams, recovery of by-product hydrochloric acid gas, as well as separation of the large amounts of by-products, are expensive and difficult. Halogenations are in general being phased out due to environmental regulation and legislations globally.

1.4.3.2 Catalytic Air Oxidation

A significant amount of research on catalytic air oxidation of cresol to hydroxybenzaldehyde has been reported, but is not currently utilized on commercial scale. The following potential routes have been investigated:

- Oxidation under basic conditions.
- Oxidation under acidic conditions.

The reports on p-cresol oxidations focuses mostly on the catalytic air oxidation in alkaline media.[26,36] More than two and a half times the molar equivalent of base to cresol is required for reasonably successful oxidations. The most widely reported solvent for such oxidation reactions is methanol and the most widely used catalysts are based on cobalt. 4-Hydroxybenzyl alcohol and 4-hydroxybenzyl ether sodium salts are intermediates in the above process.[5,37] Conversions are typically in the order of 90% with selectivities to the aldehyde generally in the order of 80 – 85%. The methods based on the alkaline methanolic air oxidation of cresols in the presence of cobalt salts suffer several disadvantages, including:

- ➢ Slow reaction rates;
- ➢ High explosivity of methanol air mixtures; and
- ➢ Catalyst deactivation which results from the formation of hydroxyl-bridged cobalt complexes in aqueous media.

The very first patent on the air oxidation of *p*-cresol and its derivatives in alkaline methanolic medium using cobalt based catalysis was filed in 1979 by the Sumitomo Chemical Company.[38,39] Since this particular report, several modifications to the method have been claimed, including the use of water, the use of and inert organic co-solvent, the use of applied oxygen pressure, the use of activated carbon and three-dimensional silicate supports for oxidation catalysts, the use of chelated iron or manganese catalysts together with various co-catalysts, the use cobalt, manganese, chromium, nickel salts as catalysts in the presence of easily removed amines, and the use of platinum metal group (PMG) catalysts.

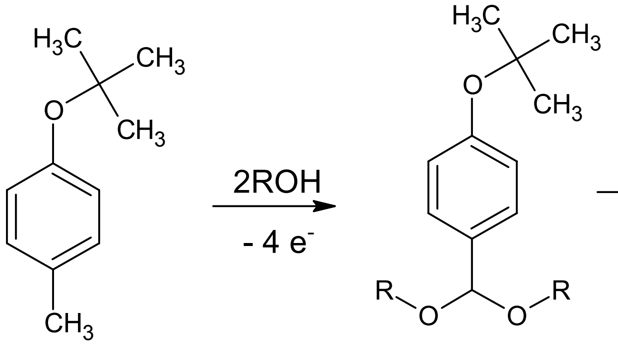
In contrast to the oxidation of *p*-cresol in alkaline methanolic solutions, researchers from the Port Elizabeth Technikon reported the oxidation of *p*-cresol [40] in an 80:20 ethylene glycol:water mixture using a copper(II)-cobalt(III) spinel catalyst. These procedures were reportedly much safer than similar oxidations in alkaline methanolic solutions, and also much more efficient with isolated yields of 4-hydroxybenzaldehyde >98% after recovery and recycling of reaction intermediates. In addition, substantially lower molar equivalents of base (even as low as 1:1) were found to be effective during these oxidations.

The isolation of 4-hydroxybenzaldehyde from oxidation mixtures is most commonly achieved by the addition of water to the mixture, filtration of the catalyst or hydrated metal species, followed by crystallization of the phenolate salt of 4-hydroxybenzaldehyde. Initial neutralization of the reaction mixture results in the co-precipitation of 4-hydroxybenzaldehyde, neutral by-products and unreacted substrate. Selective extraction with 3-methyl-2-butanone has been claimed to remove 4-hydroxybenzaldehyde at pH 10, while selective crystallization of by-products at pH 10, and 4-hydroxybenzaldehyde at pH 5 have also been reported.[26]

The oxidation of cresol in acidic medium (carboxylic acid) has been studied in lesser detail as indicated by the number of published reports in the literature compared to the oxidation in alkaline methanolic solutions. The most common solvent employed for these oxidations are mixtures of acetic acid and water, when using supported PMG catalysts. Side-products include 4-hydroxybenzyl alcohol, 4-hydroxybenzyl acetate, and 4-hydroxybenzoic acid, which is formed in significants amounts at high substrate conversions (at least 70%). Typical yields are about 75% 4-hydroxybenzaldehyde at 70% substrate conversion. These oxidations are generally performed in dilute solutions, and suffer from the formation of dimeric polymeric side products. Deactivation of the very expensive PMG catalysts are partially relieved by the use of transition metal promoters. However, regeneration of such catalyst could be problematic and therefore costly.

1.4.3.3 Electochemical Oxidation

The German company BASF[41] have been operating a process for the production of 4-hydroxybenzaldehyde based on a 4-electron oxidation of the protected cresol, 4-*tert*-butoxytoluene (ae) in methanol (Scheme 1.14), affording the dimethoxymethyl derivative (af)



(ae) (af) (m)

Scheme 1.14: Electrochemical oxidation of 4-*tert*-butoxytoluene

4-Hydroxybenzaldehyde is liberated in a separate step through treatment with an aqueous mineral acid. Reported yields approach 98%. The electrochemical oxidation of *p*-cresol as described above requires two additional steps *i.e.*, the protection and deprotection of the phenolic group.

CHAPTER 2

EXPERIMENTAL

2.1 Materials

2.1.1 Reagents for synthesis

All reagents used in alkylation, catalytic air oxidation, and electrochemical oxidation procedures, together with their sources and grades are listed in Table 2.1. Unless otherwise stated, all reagents were used as received,

Table 2.1 Reagents used for synthesis and oxidations

Chemical Name	Chemical Formula	Source	Grade ^{A}
3-*tert*-Butyl-4-methoxytoluene	$C_{12}H_{18}O$	Synthesized	CP
3-*tert*-Butylchloride	C_4H_9Cl	Saarchem	CP
4-Methoxytoluene	$C_8H_{10}O$	Merck	AR
Acetone	C_3H_6O	Saarchem	AR
Aluminium Oxide	Al_2O_3	Merck	CP
Ammonium bromide	NH_4Br	M&B	>98.7%
Ammonium ferrous sulfate	$Fe(NH_4)_2(SO_4)_2.6H_2O$	Minema	CP
Ammonium nitrate	NH4NO3)	Saarchem	CP
Barium chloride	$BaCl_2.H_2O$	Aldrich/Merck	CP
Benzene sulfonic acid sodium salt	C_6H_5 SO_3 Na	Aldrich	CP
Ceric ammonium nitrate	$(NH_4)_2Ce(NO_3)_6$	Fluka	CP
Cerium(III) carbonate	$Ce_2(CO_3)_3.3H_2O$	Aldrich	CP
Cerium sulfate	$CeSO_4$	Aldrich/Merck	CP
Cerium(II)acetate	$Ce(CH_3COO)_2.xH_2O$	Aldrich	CP
Chromium(III) chloride	$[CrCl_2(H_2O)_4]Cl.2H_2O$	Merck	CP
Cobalt(II) acetate	$Co(CH_3COO)_2.4H_2O$	Aldrich	CP
Copper(II) acetate	$Cu(CH_3COO)_2.H_2O$	Mallinckrodt	AR
Dichloromethane	CH_2Cl_2	SMM Instruments	AR
Diethyl Ether	$C_2H_5OC_2H_5$	Saarchem	AR
Di-oxygen	O_2	Air products	HP

Chemical Name	**Chemical Formula**	**Source**	**Grade** [A]
Ethyl acetate	$CH_3CH_2OCOCH_3$	Saarchem	AR
Ferrous sulfate	$FeSO_4$	Saarchem	CP
Glacial Acetic acid	CH_3COOH	Saarchem	AR
Hexane	$CH_3(CH_2)_4CH_3$	Saarchem	AR
Hydrobromic acid [B]	HBr	BDH	AR
Iso-Butyric acid	$(CH_3)_2CHCOOH$	ICN Biomedicas	CP
Magnesium Sulfate (Anh)	$MgSO_4$	Saarchem	CP
Manganese(II)acetate	$Mn(CH_3COO)_2.4H_2O$	Aldrich	CP
Methane sulfonic acid	CH_4O_3S	Aldrich	CP
Methanol	CH_3OH	Saarchem	AR
n-Butyric acid	$CH_3CH_2CH_2COOH$	Merck	Grade [A]
Nitrobenzene	$C_6H_5NO_2$	Saarchem	AR
Octanoic acid	$CH_3(CH_2)_3COOH$	Ega-Chemie	CP
Pentanoic acid	$CH_3(CH_2)_3COOH$	Saarchem	CP
Petroleum Ether		Saarchem	AR
Phosphoric acid	HP_3O_4	Skychem	CP
Potassium bromide	KBr	BDH	CP
Potassium carbonate	K_2CO_3	Aldrich/Merck	CP
Potassium chloride	KCl	Saarchem	AR
Propanoic acid	CH_3CH_2COOH	Saarchem	AR
Sodium carbonate	$NaCO_3$	Aldrich	CP
Sodium hydroxide	NaOH	Saarchem	CP
Sulfuric acid	H_2SO_4	Skychem	CP
Trimethyl othoformate	$CH(OCH_3)_3$	Aldrich	CP

[A]-AR = Analytical reagent, CP = Chemically pure, HPLC = HPLC grade, HP = High purity, B = (HBr concetraction = 45 % w/v)

2.1.2 Reagents for Analysis

2.1.2.1 Reagents for HPLC analysis

Additional reagents used in HPLC and GC analysis, together with their sources and respective grades, are listed in Table 2.2 and Table 2.3 and were used as received.

Table 2.2 Reagents for HPLC analysis

Chemical Name	Chemical Formula	Source	Grade ^{A}
4-Methoxytoluene	$C_8H_{10}O$	Merck	AR
Acetonitrile	CH_3CN	BDH	HPLC
Methanol	CH_3OH	Saarchem	HPLC
3-*tert*-Butyl-4-methoxy toluene	$C_{12}H_{18}O$	Synthesized	CP
3-*tert*-Butyl-4-methoxy benzyl dimethyl acetal	$C_{14}O_3H_{22}$	Synthesized	CP

^{A}-AR = Analytical reagent, CP = Chemically pure, HPLC = HPLC grade

Table 2.3 Reagents used as GC standards.

Chemical Name	Chemical Formula	Source	Grade ^{A}
4-Methylanisole	$CH_3C_6H_4OCH_3$	Merck	CP
p-Anisaldehyde	$CH_3OC_6H_4CHO$	Aldrich	CP
4-Methoxybenzyl alcohol	$CH_3OC_6H_4CH_2OH$	Aldrich	CP
p-Anisic acid	$CH_3OC_6H_4COOH$	Aldrich	CP
Nitrobenzene	C6h5NO2	Saarchem	AR

^{A}-AR = Analytical reagent, CP = Chemically pure, HPLC = HPLC grade

2.2 SYNTHETIC PROCEDURES

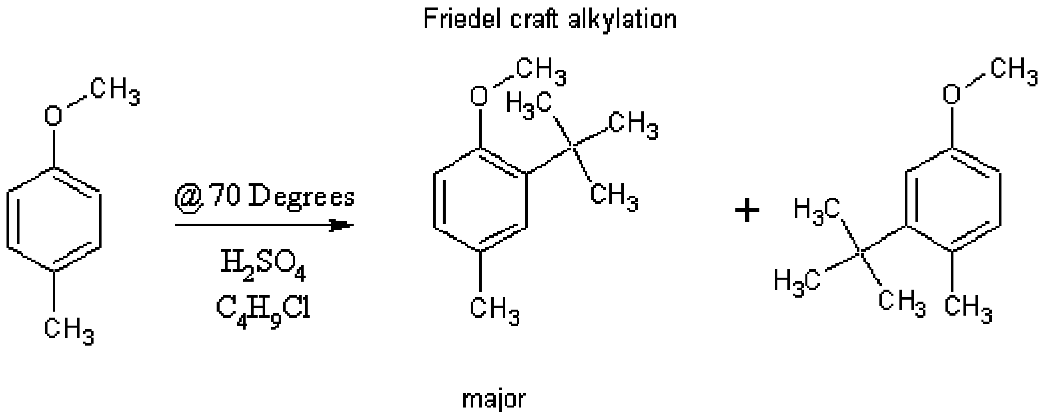
2.2.1 Catalytic air oxidation studies

A 250 cm^3 three-necked round bottom flask equipped with a double surface reflux condenser was used for all the oxidation experiments. Oxygen was delivered through a bent tip pasteur pipette through the side neck of the flask. Fine control of oxygen flow was maintained with a needle valve connected to the laboratory oxygen supply. The reaction temperature was controlled by immersing the reaction flask in an oil bath equipped with an external stirrer on a magnetic stirrer hotplate and closely monitoring the oil temperature. The external stirrer provided circulation to the oil, and ensured even distribution of heat from the hotplate.

All the starting materials, except the substrate and acid solvent, were weighed directly into the reaction flask. The required volume of solvent was added with a burette. The reaction flask was allowed to equilibrate to the required temperature. The required volume of substrate was added with a bulb pipette. A sample was taken by removing an aliquot (less than 0.15 cm^3) of the reaction mixture and diluting it with 3 cm^3 of diethyl ether in a vial containing some anhydrous sodium sulfate and oxalic acid. The samples were analyzed by means of a GC or HPLC.

2.2.2 Synthesis of 3-tert-butyl-4-methoxytoluene

4-Methoxytoluene (100 g, 0.858135 mole) was transferred to a 500 mL reaction vessel, sulfuric acid (8.0 mL, 0.09 M) was added as a catalyst and the mixture heated to reflux. *Tert*-butyl chloride (63.5 g, 0.648177mole) was added drop-wise with a dropping funnel over a period of 1 hour while stirring at a rate of 800 rpm. The mixture was then refluxed for 5 hours in an oil bath at 70 ^oC. Scheme 2.1 depicts the Friedel-Craft alkylation process.



Scheme 2.1 Friedal-Craft alkylation of 4-methylanisole

After 5 hours the mixture was allowed to cool and extracted with ethyl acetate (3 x 150 mL), and the ethyl acetate extracts washed with 3 x 100 mL distilled water, and once with 400 mL of a 10 % sodium carbonate solution. Samples were dried with anhydrous magnesium sulfate and analysed by GC-MS. The yield of of the desired isomer was 56 % based on GC-MS area percentage.

Vaccum distillation was used to separate the two isomers. Two fractions were collected, the first containing 4-methoxytoluene at a pressure of 9 torr in the temperature range 45 - 50 ^{o}C and the second fraction containing 3-*tert*-butyl-4-methoxytoluene at 9 torr in the temperature range 55 - 60 ^{o}C The sample was analysed by GC-MS, proton NMR spectrometry, and cosy and noesy analysis to confirm the structure of the resulting isomer. The following fragmentation patern was obtained from the GC-MS: (M_z = 178 (M^+), 163 (M_z – 15), 148 (M_z – 31), 105 (M_z – 15 – 57), 91 (M_z – 31 – 57),

NMR analysis gave: NMR (H^1, ppm) ($CDCl_3$), 7.15(2H, d, Ar), 6.85 (1H, d, Ar), 4 (3H, s, $ArOCH_3$), 2.4 (3H, s, $ArCH_3$), 1.5 (9H, s, Ar $C(CH_3)$)

From the noesy diagrams Figure 2.1 it can be seen that there is a definite interaction between the t-butyl group and the methoxy functional group, while the methyl group shows no interaction with any of these functional groups.

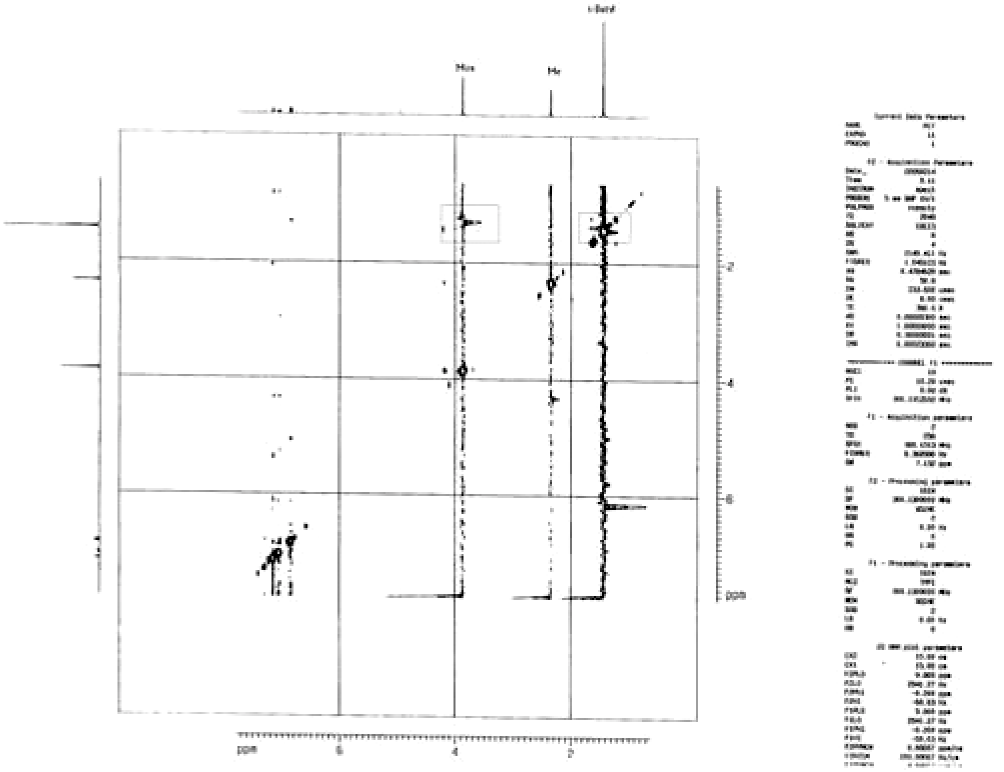


Figure 2.1 Noesy diagrams

If one studies the cosy diagram (Figure 2.2) and in particular a contour cut over the aromatic ring, it can be seen that there is a para hydrogen arrangement marked H1 and H3 at J = 1.5. There is also an ortho hydrogen arrangement marked H1 and H2 at J = 5.8. These measurements together with the Noesy diagram confirm the isolated product as the 3-*tert*-butyl-4-methoxytoluene isomer. The purity of 3-*tert*-butyl-4-methoxytoluene, determined using an HPLC internal standard method, was found to be 98 %.

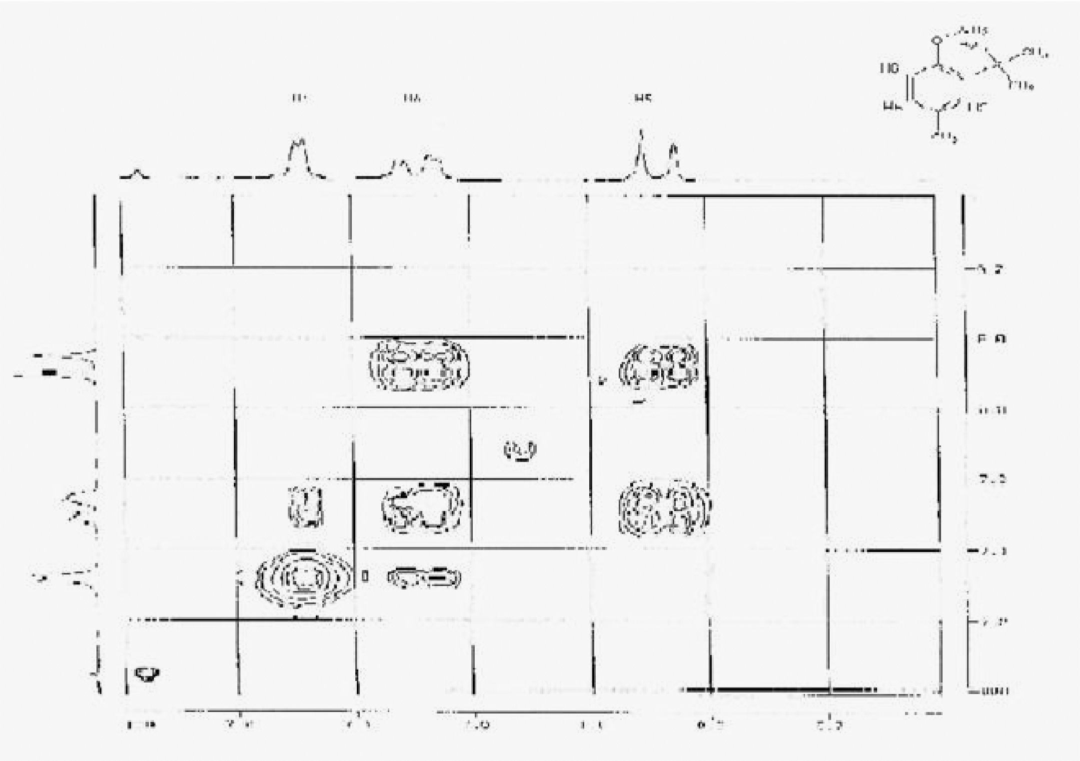


Figure 2.2 Cosy diagrams

2.2.3 Direct electrochemical synthesis of 3-*tert*-butyl-4-methoxy-benzaldehyde[42,43,44]

An ICI electrochemical processing laboratory package unit (Figure 2.3) was used for larger-scale electrochemical oxidation procedures. At the core of the process unit lays the FM-01 flow cell, which is based on the filter press or plate and frame arrangement. The electrochemical setup consists of a four neck 500 mL round bottom flask, a heating mantle, an Iwaki MD-30F impeller pump, precision glass flow indicator (2 L.min^{-1} maximum flow rate), the FM01-LC flow cell, and a Lorin SCT 20-30 galvanostat. The flask was fitted with a condenser in order to prevent a pressure build-up in the system in case of gas formation in the cell, an inlet tube from the electrolysis cell and an outlet tube to the impeller pump. The pump forced the liquid through the flow indicator into the flow cell, which was connected to the galvanostat. The flow cell outlet fed back into the round bottom flask in order to complete the loop.

Figure 2.3: Batch recirculation flow cell for scale-up

Electrolysis was carried out in the constant current mode using graphite electrodes as cathode and anode.

Apparatus : Undivided cell with 2 electrodes
Anode : Graphite
Cathode : Graphite
Current density : 1.5 A/dm^2
Electrolysis Temperature : Constant at 40 ^{o}C
Time : 2:30 hr

3-*Tert*-butyl-4-methoxytoluene (15 g, 0.084142 mol) was weighed and transferred to the 3 neck round bottom flask, $NaSO_3C_6H_5$ (10 g, 0.05556 mol) was added as a supporting electrolyte and 500 mL of methanol as solvent. The mixture was heated to 40 ^oC by adjusting the temperature of the heating fluid in the circulator bath while the mixture was pumped through the system at a flow rate of 0.8 L h^{-1}. Once the reaction mixture has reached the desired reaction temperature, the galvanostat was switched on and the current adjusted to provide a current density of 1.5 A dm^{-2}. The reaction was stopped after 2:30 hours. The reaction mixture was then transferred to a distillation flask together with 200 mL of methanol that was used for rinsing the reservoir and electrochemical cell. The methanol was distilled (recovered methanol was 700 mL) and the supporting electrolyte that precipitated (9.28 g) was filtered and washed with 2x100 mL of ethyl acetate. The ethyl acetate washings was combined with the filtrate and vacuum distilled. The acetal was hydrolysed to the corresponding aldehyde in a 10 % sulfuric acid with stirring for 1 hour.

The 3-*tert*-4-methoxybenzaldehyde was then extracted from the aqueous layer with ethyl acetate 3 x 25 mL. Dried and solvent evaporated on a rotator evaporator. The crude product was then recrystallized with petroleum ether (30 – 60 ^oC)

2.2.4 Indirect electrochemical synthesis of 3-*t*-butyl-4-methoxybenzaldehyde using Ce(IV)[45,46,47]

2.2.4.1 Cyclic voltammogram studies

Preliminary investigations were performed on a CV-50W instrument using a Pt – disk (5 mm) electrode versus a Ag/Ag^+ reference electrode to study the oxidation and reduction system of cerium (0.05 mM) in methanesulfonic acid (6 M). Figure 2.4 shows the cyclic voltammogram for this system.

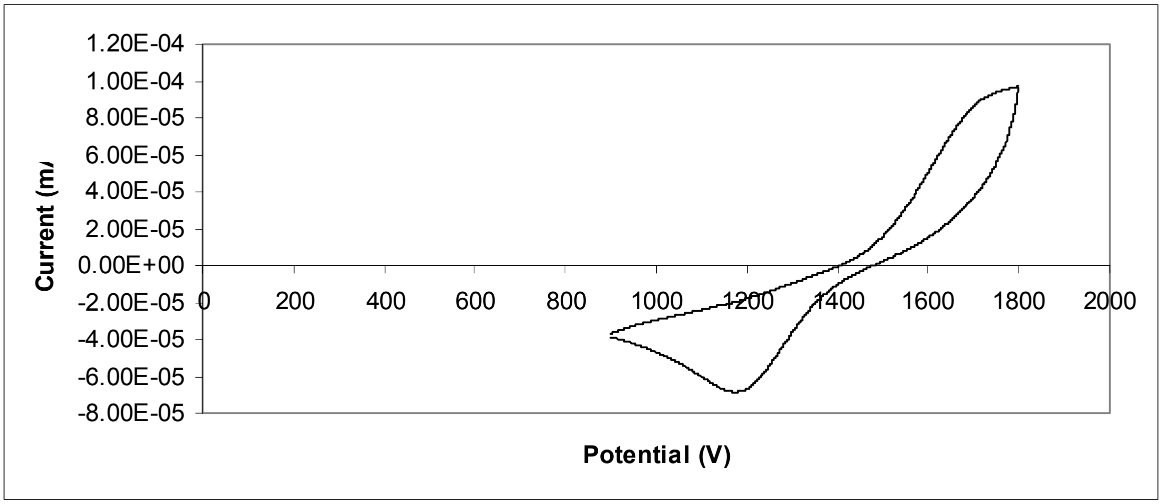


Figure 2.4: **Cyclic voltammegram for cerium (0.05 mM) in a methanesulfonic acid solution (6 M) using a Pt-disk (5 mm) electrode.**

A quasi-reversible system was obtained with an oxidation state of Ce^{III} to Ce^{IV} at 1.65 V which compares well with literature data[48]. From Figure 2.5 it can be seen that the current increases with increasing scan rates.

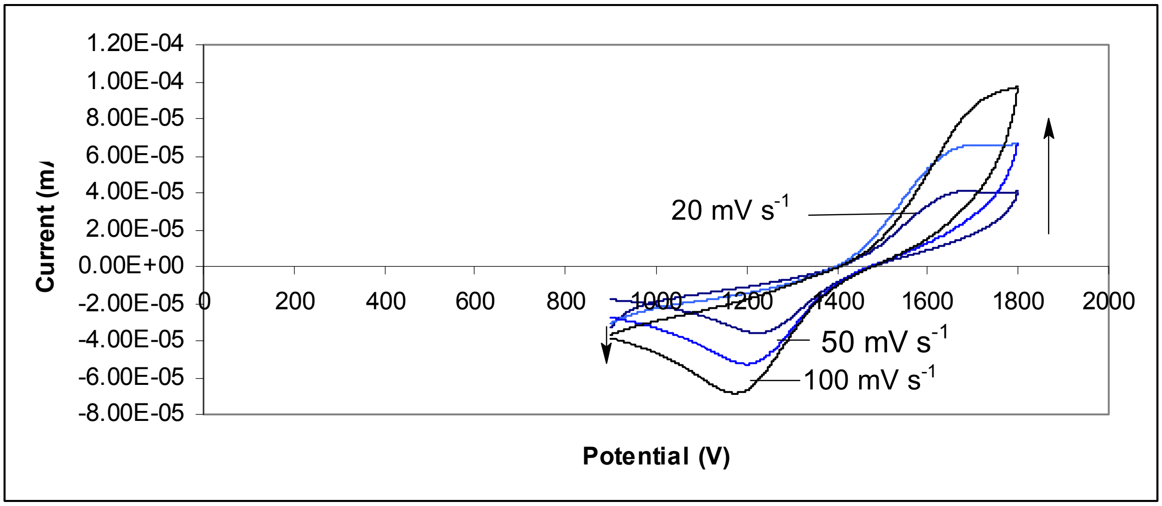


Figure 2.5: **Effect of scan rates on the quasi-reversible system of cerium methanesulfonate.**

This studies show the ease of oxidizing Ce(VI) in a methanesulfonic acid medium.

2.2.4.2 Synthesis of Ce(III) Carbonate

A solution of potassium carbonate (8.6502 g, 0.093445 mol) in 48 mL of water was added with vigorous stirring to a solution of ceric sulfate (10.1892g, 0.030668 mol) in 40 mL of water. A pale yellow precipitate of Ce(III)carbonate was produced. To this precipitate a solution of saturated barium chloride was added to ensure complete removal of sulfate ions as barium sulfate. The precipitate was collected with vacuum filtration, and washed with large amount of water to remove the barium sulfate and potassium chloride. The resultant yellow powder was then dried in air in an oven at 50 ^{o}C.

2.2.4.3 Synthesis of Ce(IV) methanesulfonate solution

Portions of the dry yellow powder (5.150 g; 0.01119 moles) was dissolved into 45 mL methane sulfonic acid solutions of varying concentrations of acid, *viz.* 2 M, 4 M, 6 M and 8 M to produce Ce(III) methanesulfonate solutions. These solutions were electrochemically oxidized using a platinum basket as the anode and a platinum electrode as the cathode at 1 A for six hours to produce solutions of Ce(IV) methanesulfonate. The actual concentration of Ce(IV) was determined by titrating against ferrous ammonium sulfate using ferroin as indicator.

2.2.4.4 3-*Tert*-butyl-4-methoxytoluene oxidation using Ce(IV) methane-sulfonate

The Ce(IV) solutions prepared as described above was used to oxidize 3-*tert*-butyl-4-methoxytoluene to 3-*tert*-butyl-4-methoxybenzaldehyde by stirring 3-*tert*-butyl-4-methoxytoluene (dissolved in various solvents) with 50 mL of the Ce(IV) solution at temperatures ranging from 20 – 80 ^{o}C for 6 hours.

2.2.5 Preparation of cerium(IV) methanesulfonate from commercial $Ce_2(CO_3)_3$

A commercial sample of (57.44015g; 0.1247966mol) cerium(III) carbonate (Aldrich) was dissolved in 500 mL of a 6 M methane sulfonic acid solution. This solution was oxidized using a platinum basket as the anode and a platinum electrode as the cathode at 1 A for six hours. The concentration of Ce (IV) was determined by titrating against ferrous ammonium sulfate using ferroin as indicator. The solution was used as described as for § 2.2.4.3.

2.2.6 Recycling of Ce (IV) in methanesufonic acid

After oxidation of 3-*tert*-butyl-4-methoxytoluene using cerium(IV) methansulfonate, the spent Ce(III) methansulfonate, appears as a white slurry in the aqueous phase. This slurry was collected, the methane sulfonic acid concentration adjusted to 6M and oxidised to cerium(IV) methane sulfonate as described in §2.2.4.2 above.

2.2.7 Oxidations using cerium(IV) ammonium nitrate

A solution of ceric ammonium nitrate (8.9567 g, 0.01634 mol) in 50 mL of methanol was transferred of a double walled reactor flask, 150 mL in volume, equipped with a heating jacket and connected to a Labcon circulator in order to effect either heating or cooling. The actual concentration of Ce(IV) in these solutions were determined by titrating the solution against ferrous ammonium sulfate using ferroin indicator and the substrate loading was calculated to correspond to a substrate:Ce(IV) mole ratio of 1:4.

The mixture was stirred at 30 ^{o}C for 30 minutes and extracted with 2 x 50 mL dichloromethane and washed with 2 x 50 mL deionised water. Samples were withdrawn from the reaction flask and analysed by either HPLC or GC. The spent cerium(III) salts was recovered by evaporating the bulk of the methanol to allow precipitation of the cerium(III) salts, filtering, and drying.[49]

2.2.7.1 Recycling of cerium ammonium nitrate

Recovered cerium salts from oxidation reactions using cerium(IV) ammonium nitrate were dissolved in 50 mL of methanol, ammonium nitrate (0.6g, 0.00749 mol) in 30 mL of methanol added as supporting electrolyte, and the solution electrolysed using two platinum electrodes in a divided cell. A constant current of 0.3 A at a cell potential of 9 -10 volts was passed through the cell for 1:30 - 2:00 hours till the concentration of Ce(IV) was constant. The concentration was determined by titrating against ferrous ammonium sulfate using ferroin indicator. These solutions were used for further oxidation reactions by adding the required amount of substrate, depending on the moles of Cerium, to the mixture as before.[50]

2.2.8 Direct electrolysis in an undivided electrochemical cell

The electrochemical cell shown in Figure 2.4 was used for direct electrochemical oxidation studies. The cell consists of a double-walled reactor flask, 150 mL in volume, equipped with a heating jacket, which was connected to a Labcon circulator in order to affect either heating or cooling. The top of the reaction flask was designed with a screw top and quick fit adapters for the insertion of electrodes, thermometer, and a condenser. The electrolysis was always carried out under constant current conditions, controlled by a Lodestar Instrument general purpose galvanostat.

Figure 2.4: Direct electrochemical oxidation setup

2.3 ANALYTICAL TECHNIQUES

Several analytical procedures were employed for the analysis of substrates, intermediates, products and supporting electrolytes.

2.3.1 Gas Chromatography – Mass Spectrometry

Gas chromatography-mass spectrometry analyses were performed on a Thermo Finning GC-MS fitted with a mass selective detector, a RTX 35ms column (length 30m x 0.25mm ID x 0.25 cm thickness). The GC-MS was connected to a PC equipped with Excalibur software, version 1.3. Table 2.3 below summarizes the GC-MS conditions used for analyses.

Table 2.4 GC-MS conditions

Initial column temperature	70 ^{O}C
Initial column hold time	5 min
Heating rate	10 ^{O}C/min
Final column temperature	210 ^{O}C
Final column hold time	5 min
Injector temperature	250 ^{O}C
Split flow	60 ml/min
Carrier gas	Helium at constant flow
Run time	24 min
MS-mass range	30 – 350 amu

2.3.2 High Pressure Liquid Chromatography

HPLC analyses were performed on a Hewlett Packard HP1100 HPLC system equipped with a UV-detector and connected to a PC equipped with a Hewlett Packard Chemstation, version 8.03. The HPLC conditions used are shown in Table 2.5. Nitrobenzene was used as internal standard and the internal standard method was used for all quantitative work. Response factors for the components of interest were determined by means of three calibration injections with known masses of standards and internal standard prior to analysis. Relative standard deviations for the three standard injections were typically within the range 0.2 – 0.5%.

Table 2.5 HPLC conditions

Injector Volume	25 µL
Column	µBondpak C_{18} (3.9x300 mm) (Waters)
Wavelength	280 nm
Flow rate	1 cm^{3} min^{-1}
Mobile Phase	MeCN : H_2O buffered to pH = 3 with H_3PO_4
Mobile phase composition	50 : 50

2.3.3 Conductivity Studies

A Metrohm 660 conductivity meter, equipped with two platinum black electrodes, was used to measure the conductivity and resistance of solutions containing substrates and supporting electrolytes. The cell constant was determined to be 0.986 cm^{-1}. The solvent used for conductivity measurements was dried before use by the addition of a water scavenger such as trimethyl orthoformate. The supporting electrolytes were used as received. The conductivity of a specific electrolyte was measured over a concentration range of 0.1 -0.5 mol dm^{-3} in methanol at 22^{o}C.

2.3.4 Cyclic voltammetry

Cyclic voltammetry was performed on a BAS CV-50 system consisting of the electrochemical cell, equipped with Pt and glassy carbon working electrodes, a Pt wire auxiliary electrode and a non-aqueous Ag/AgCl reference electrode linked to a PC. The potential of the working electrode was scanned over a range of 0 - 2.7V at a scan rate of 100 mV s^{-1} and sensitivity of 1 mA V^{-1}. Cyclic voltammograms were recorded for the substrate, intermediates and final products, so as to determine their oxidation potentials. Acetonitrile was used as solvent in CV studies of the reaction intermediates since methanol started to oxidize at potentials lower than that of the substrate.[51,52] Methanol was used as solvent for CV work dealing with different electrolytes.

2.3.5 Differential Scanning Calorimetry

DSC analysis was performed on Mettler Toledo DSC 820 and integrations performed using Stare software in order to determine the purity and melting point of the synthesized standards as well as their decomposition temperatures. The sample was placed in an aluminium sample pan (working range up to 400 ^{o}C) and sealed in a press.

2.3.6 UV/Visible Spectrophotometry

The optimum UV absorbance wavelength of samples for HPLC analyses was determined with the aid of Beckman DU® 7500 double beam UV/Visible spectrophotometer with Beckman DU series 7000 software. Data transfer and further manipulation of data was achieved using a personal computer equipped with PC Plus software. A quartz sample cell (cuvette) was used with samples dissolved in acetonitrile as solvent

2.3.7 pH Determinations

An Inlab level 1 digital pH meter with a WTW Sentix single glass pH electrode was used for all pH measurements.

2.3.8 Coulometric Analysis

Water in acetic solvent was determined by coulometric analysis, performed on a Metrohm 684 KF Coulometer.

2.3.9 NMR Spectroscopy

Proton NMR spectra were recorded on a Varian EM 360 A (300 MHz) spectrometer.

2.3.10 Fourier Transform Infrared Spectroscopy

Infra red spectra were recorded on a Bruker Tensor 27 FTIR spectrophotometer connected to a personal computer, equipped with Spectra file software. All samples were analyzed using KBr discs.

CHAPTER 3

RESULTS AND DISCUSSION

The following sections describe the results obtained for the evaluation of the various potential routes to convert alkyl-substituted methoxytoluenes selectively into the corresponding alkyl-substituted methoxybenzaldehydes. The routes that were evaluated through bench scale synthesis studies were:

- The catalytic air oxidation of the methoxytoluene;
- The direct electrochemical oxidation of the methoxytoluene; and
- The indirect electrochemical oxidation of the methoxytoluene.

The purpose of these investigations was to be able to identify the most efficient and selective route to produce the desired benzaldehydes in high yield.

3.1 Catalytic Air Oxidation

3.1.1 General

As discussed earlier, hydroxy-substituted benzaldehydes (or the corresponding alkoxy-substituted benzaldehydes) may be produced starting either with phenol as substrate (and introducing the aldehyde group), or from cresols or their alkyl ether derivatives by oxidation of the methyl group. Despite the disadvantage of the higher cost of cresol feed as opposed to phenol feed, there has been considerable interest in the use of oxidative technologies for the production of hydroxy-benzaldehydes in view of the potential advantages in respect of selectivity and decreased effluent problems. Current commercial oxidation routes include an electrochemical p-cresol oxidation process[53], and a phenol/glyoxilic acid condensation,[54] followed by oxidation of the resultant p-hydroxymandelic acid.

Studies on the partial air oxidation of substituted methyl phenols to phenolic aldehydes has been reported in considerable detail in the literature.[55,56,57]

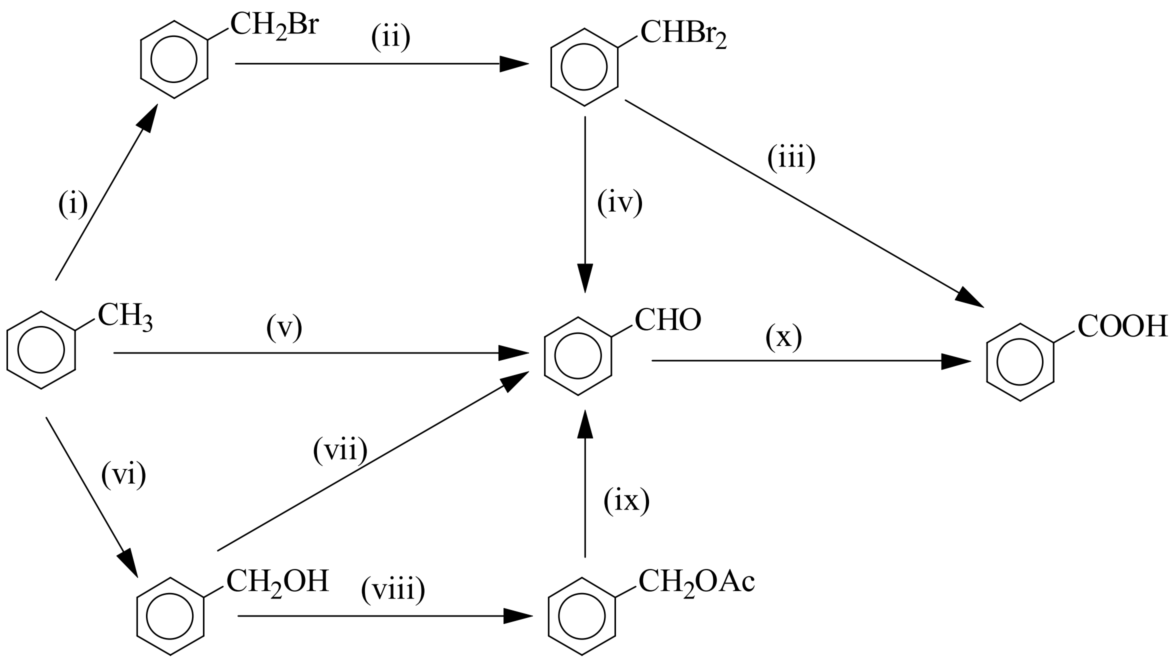
To avoid the formation of polymers and tars, the phenolic group is conventionally protected either as the acetate (acetic anhydride and acetic acid medium[58]) or phenolate (alcoholic based medium[59]).

Recently, it was shown that certain supported PGM catalysts could be used to afford benzylic oxidation of a cresol without protection of the phenolic group with reasonable success.[60] These procedures are supposed to be flexible enough, particularly with hindered cresols, to allow for the selective preparation of various oxidation products, including nucleophilic addition products and a range of coupled compounds.[61] However, most of these reactions are characterized by low yields of the desired aldehyde and the formation of further oxidized and/or oligomerization products. Deactivation of the very expensive PGM catalysts are partially relieved by the use of transition metal promoters. Regeneration of such catalysts is, however, problematic, and therefore expensive.[59,60]

In the case of the catalytic air oxidation of methoxytoluenes, the phenolic group is protected by the ether group and traditional oxidation methods and catalysts may be considered for these oxidations, including the well known cobalt(II) acetate/bromide or cobalt(II) acetate/manganese(II) bromide catalyst system.

3.1.2 Catalytic air oxidation: Nature of the substrate

Previous work in our laboratories has shown that the progress of the catalytic air oxidation of alkylbenzenes, using the well-known cobalt-bromide catalyst system, in acetic acid as reaction solvent, can best be described by the reaction sequence illustrated below in Scheme 3.1.



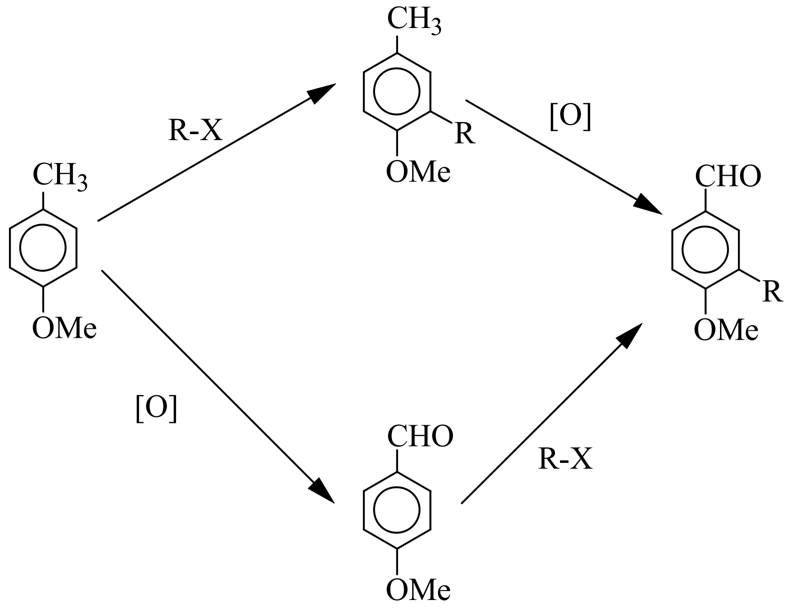
Scheme 3.1 Cobalt(II)-Bromide catalysed air oxidation of alkylbenzenes.

The starting alkylbenzene may be transformed into oxidised products in several ways (Reactions (i), (v) and (vi)), but only reaction (v) leads directly to the formation of the desired aldehyde. This process (reaction (v)) is, however, slow and requires the presence of significant quantities of Co(III) to proceed at any significant rate. The major route to the desired aldehyde is *via* reactions (vi) followed by (vii). This reaction sequence requires the catalyst system to remain in a form that contains bromide coordinated to cobalt(II). Unfortunately, bromide is slowly converted into an inactive form (through reactions (i) and (ii)). Thus, when approximately 70% of available bromide has been converted into organic bromide (essentially the benzylic bromide), the catalyst starts oxidising the aldehyde product at rates higher than the rate of formation of the aldehyde and, consequently, aldehyde selectivity decreases.

With the above in mind, the best approach to high aldehyde selectivities would be to restrict substrate conversion to a level where the aldehyde oxidation is still slow.

This level (of substrate conversion) will probably be different for different substrates, the main determining factor being the rate at which the substrate is converted into the corresponding benzylic bromide.

We have studied the catalytic air oxidation of several alkylbenzenes and substituted alkylbenzenes to determine the effect of substitution on the alkylbenzene ring, and to evaluate the feasibility of obtaining high benzaldehyde selectivity at restricted substrate conversions. The reasoning behind this approach was as follows. To produce alkyl-substituted methoxybenzaldehydes in high yield by means of catalytic air oxidation, one of two routes can be followed, namely initial alkylation of the aromatic ring followed by oxidation, or initial oxidation to form the benzaldehyde (or a protected form thereof) followed by alkylation (Scheme 3.2).



Scheme 3.2 Routes to alkyl-substituted methoxybenzaldehydes via catalytic air oxidation

The nature and extent of substitution on the ring will affect both the rate (and extent) of oxidation, as well as the rate (and degree) of substitution during alkylation reactions. Of these, the selectivity achievable during the catalytic air oxidation step would be the limiting factor due to the ease of further oxidation of the desired aldehyde product. It was therefore necessary to establish not only whether the oxidation step should come before or after the alkylation step, but also the selectivity to the desired aldehyde that could be expected from these oxidation reactions.

Before describing and discussing the results obtained, a few preliminary observations should be made. Firstly, catalytic homogeneous air oxidations of hydrocarbons are known to be affected by a number of chemical engineering parameters which influence mass transfer in the essentially two phase (gas-liquid) reaction system.[62] The most important of these are dispersion of gas in the liquid (number and position of gas inlets, size of air bubbles, etc.), reactor configuration (especially the height to diameter ratio of the reactor), and mixing method. Since all the catalytic air oxidation work described in this work was carried out in round-bottom flasks, not much control was available in terms of gas inlets, height/diameter ratio, etc. It was therefore necessary to eliminate mass transfer problems by manipulating stirring and oxygen supply to the reaction vessel. This can be achieved quite easily by stirring the solution magnetically at high revolutions (1000 rpm using a suitable size magnetic follower) and increasing the O_2 flow rate until no effect on the reaction rate (measured as the degree of substrate conversion after a predetermined, fixed reaction time – 15 minutes) is observed. Under these conditions, and using a 250 mL round-bottom flask as reaction vessel, an O_2 flow rate of 30 $mL.min^{-1}$ was found to give consistent conversions of substrate.

The second observation deals with the nature of the oxidation gas supplied to the reaction mixture. It has been claimed[63] that aldehydes could be isolated in good yields during electron transfer oxidation of alkylbenzenes under conditions of low temperature and oxygen starvation. In effect, such an approach is the equivalent of performing the oxidation reaction to restricted conversion, albeit at longer reactor residence times. In this investigation the approach was rather to perform oxidations under conditions of oxygen saturation and physically restricting conversion by fixing the reaction period. It is argued that this approach is closer to technical reality in the attempt to increase oxidation rates and decrease reactor residence times.

In the first series of reactions, a number of substituted toluenes (Table 3.1) were oxidised in order to establish the effect of substitution on the selectivity to the desired benzaldehydes at various substrate conversions. These oxidations were carried out using cobalt(II) acetate (0.48 g; 1.93 mmol) and NH_4Br (0.168 g; 1.72 mmol) in a 1:1 molar ratio as the catalyst, glacial acetic acid (50 mL) as the reaction solvent, a reaction temperature of 90 ^{o}C and dioxygen as the oxidation gas at a flow rate of 30 mL min^{-1}. Aliquots (0.5 mL) of the reaction mixture were withdrawn at regular intervals and analysed by gas chromatography. Figure 3.1 illustrates a typical product distribution diagram (*p*-xylene) obtained during this investigation and illustrates the typical progression of the oxidation through the aldehyde (4-methylbenzaldehyde) to the acid (4-methyl benzoic acid).

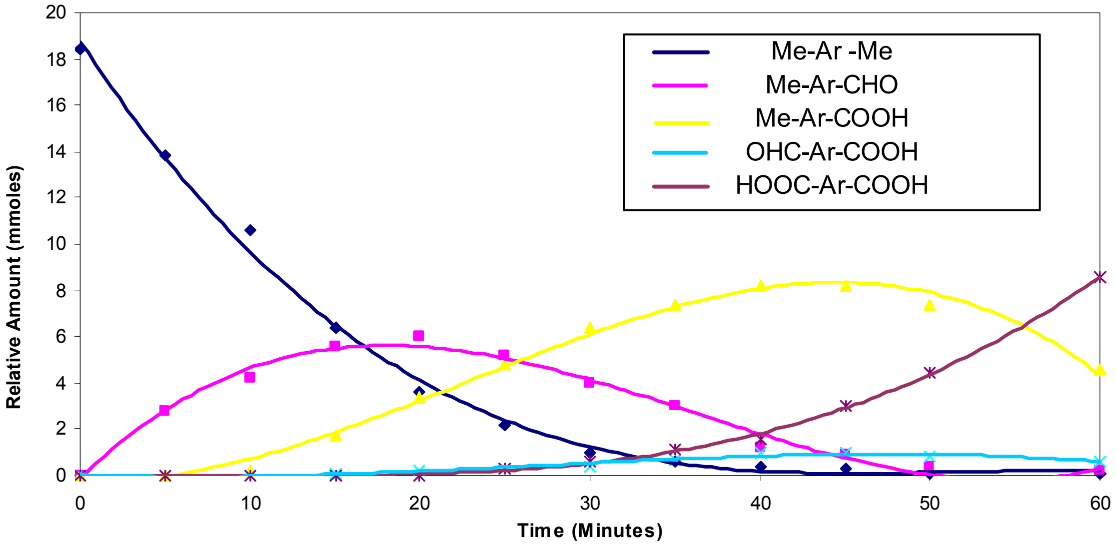


Figure 3.1 Product distribution diagram: *p*-Xylene oxidation

After construction of a product distribution diagram as shown below, a 3rd order polynomial was fitted to those intermediates of interest and the selectivity to aldehyde calculated from the polynomial equations as a function of substrate conversion. These results were used to determine the selectivity to aldehyde at specific substrate conversions as illustrated in Table 3.1.

Table 3.1: Catalytic air oxidation: Nature of the substrate.

Substrate	**Conversion (%)**		
	20	**40**	**60**
	Aldehyde Selectivity (%)		
$C_6H_5CH_3$[a]	67.8	56.8	44.3
4-$CH_3C_6H_4CH_3$[b]	70.0	61.7	49.9
4-$MeOC_6H_4CH_3$[c]	72.3	63.3	56.1
4-$ClC_6H_4CH_3$[d]	60.9	44.6	29.5
2,4-Cl_2-$C_6H_3CH_3$[e]	45.6	35.6	24.1

[a] - **$C_6H_5CH_3$** (2.40 g; 26.05 mmol); [b] - **4-$CH_3C_6H_4CH_3$** (1.95 g; 18.37 mmol); [c] - **4-$MeOC_6H_4CH_3$** (2.29 g; 18.77 mmol); [d] - **4-$ClC_6H_4CH_3$** (2.27 g; 17.93 mmol); [e] - **2,4-Cl_2-$C_6H_3CH_3$** (2.99 g; 18.58 mmol)

The results in Table 3.1 show that the aldehyde selectivity increases with increasing electron density on the aromatic ring. Thus, both *p*-xylene and 4-methoxytoluene, which contain electron donating groups on the aromatic ring, give higher aldehyde selectivities than toluene, while 4-chlorotoluene and 2,4-dichlorotoluene, containing electron withdrawing groups, give lower aldehyde selectivities. A comparison of the maximum aldehyde "yields" (determined at the point on the respective aldehyde curve where $\frac{\delta(aldehyde)}{\delta(time)} = 0$) for the above reactions are shown in Table 3.2. These results show exactly the same trend as observed above for aldehyde selectivities.

Table 3.2 Maximum amounts of aldehyde formed

Substrate	**Amount (%)**
$C_6H_5CH_3$	26.3
4-$CH_3C_6H_4CH_3$	34.4
4-$MeOC_6H_4CH_3$	36.2
4-$ClC_6H_4CH_3$	24.3
2,4-Cl_2-$C_6H_3CH_3$	15.1

It would not be unreasonable to expect 3-alkyl-4-methoxytoluenes to behave similarly to 4-methoxytoluene and other substrates containing electron donating groups on the aromatic ring to give somewhat higher aldehyde selectivities, or at least of the same order of magnitude as 4-methoxytoluene.

It should, however, also be noted that the results in Table 3.1 show that the benzaldehyde selectivity decrease as the substrate conversion increases. Thus, higher aldehyde selectivities will only be feasible at lower substrate conversions, which means that processes aimed at producing the aldehyde specifically will need to be run to limited substrate conversions (probably in the order of 20%).

3.1.3 Catalytic air oxidation: Reaction temperature

Being a free-radical reaction, catalytic air oxidation reactions can be expected to be influenced significantly by the reaction temperature at which oxidations are performed. In order to investigate the effect of reaction temperature on the oxidation of 4-methoxytoluene and the selectivity to 4-methoxybenzaldehyde, several oxidation reactions were performed at different reaction temperatures. These oxidations were carried out using cobalt(II) acetate (0.48 g; 1.93 mmol) and NH_4Br (0.168 g; 1.72 mmol) in a 1:1 molar ratio as the catalyst, 4-methoxytoluene (2.30 g; 18.85 mmol), glacial acetic acid (50 mL) as the reaction solvent, various reaction temperatures between 55 ^{o}C and 105 ^{o}C, and dioxygen as the oxidation gas at a flow rate of 30 mL min^{-1}. Aliquots (0.5 mL) of the reaction mixture were withdrawn at regular intervals and analysed by gas chromatography. Table 3.3 summarises the results obtained.

Before commenting on the results obtained, the “Rate” indicated in Table 3.3 refers to the rate of substrate consumption in the region 0 – 10 % of substrate conversion as measured by the slope of the substrate disappearance curve. This region was selected for measuring this rate so as to minimise interference of other reactions (e.g. further oxidation of intermediates such as benzylic alcohols and aldehydes) on the rate of substrate conversion. The results depicted in Table 3.3 show that as the reaction temperature is increased, the initial rate of substrate conversion increases substantially. This increase in rate is directly the result of the increase in the rate of initially formed peroxy ($RCH_2OO^{\bullet}$) or hydroperoxy ($HOO^{\bullet}$) radicals as the reaction temperature is increased, which result in the formation of more energetic radicals (e.g. alkoxy radicals – $RCH_2O^{\bullet}$) which increase the rate of hydrogen abstraction from substrate molecules. However, as the temperature and reaction rate increases, the selectivity to aldehyde decreases.

Table 3.3 Effect of Reaction Temperature on Oxidation Rate and Aldehyde Selectivity

Temperature (^{o}C)	Rate (mol dm^{-3} min^{-1})	Conversion (%)		
		20	40	60
		Selectivity (%)		
55	-0.47×10^{-2}	83.4	79.8	68.8
65	-0.77×10^{-2}	79.8	74.3	67.8
75	-1.33×10^{-2}	75.5	71.2	61.1
85	-1.85×10^{-2}	83.3	70.0	58.6
95	-1.82×10^{-2}	72.2	66.5	56.3
105	-1.81×10^{-2}	74.1	65.0	52.5

The optimum oxidation temperature (defined as the temperature at which the high aldehyde selectivities are achieved at acceptable rates of oxidation) will therefore be a compromise situation and is probably in the region of 85 – 90^{o}C.

3.1.4 Catalytic air oxidation: Effect of catalyst concentration

As discussed earlier, the active catalyst during the cobalt(II) acetate bromide catalyzed air oxidations of alkylbenzenes are thought to be a complex containing a direct Co(II) – bromide bond. It has, however, been shown[64] that bromide is converted into an inactive form, in particular benzylic bromides. This process destroys the initially active Co(II)-Br catalyst species and which is not readily converted back into an active form.[65] It has also been shown[66] that aldehyde oxidation starts to dominate once the bulk of “inorganic” bromide has been converted into “organic” bromide, and therefore aldehyde selectivity will decrease as a result of the conversion of the active catalyst species into a non-bromide containing form. In order to determine whether the use of a higher amount of catalyst concentration (while keeping the Co:Br ratio constant at 1:1) will improve aldehyde selectivity during these oxidation reactions, several reactions were carried out in which 4-methoxytoluene (2.30 g; 18.85 mmol) was oxidised using various concentrations of cobalt(II)acetate and NH_4Br in a 1:1 molar ratio as the catalyst, glacial acetic acid (50 mL) as the reaction solvent, a reaction temperature of 95 ^{o}C and dioxygen as the oxidation gas at a flow rate of 30 mL min^{-1}. Aliquots (0.5 mL) of the reaction mixture were withdrawn at regular intervals and analysed by gas chromatography. Table 3.4 summarises the results obtained.

Table 3.4: Initial catalyst concentration

[Co] (mol dm^{-3})	Conversion (%)		
	20	40	60
	Aldehyde Selectivity (%)		
0.01	38.8	35.8	32.7
0.02	72.4	63.1	49.6
0.04	79.9	69.3	52.8
0.06	78.7	67.0	54.1
0.10	82.5	67.9	49.8

The results clearly show an increase in 4-methoxybenzaldehyde selectivity as the catalyst concentration is increased from 0.01 M – 0.1 M during the Co-Br-catalysed air oxidation of 4-methoxytoluene. This effect is especially noticeable at lower conversion levels, but at higher conversion levels there is virtually no effect on the selectivity to 4-methoxybenzaldehyde once the cobalt concentration is raised above 0.02 M. The observed increase in selectivity is, however, probably not significant enough to warrant the large increase in catalyst concentration.

3.1.5 Catalytic air oxidation: Effect of water concentration

Water is continuously formed during the catalytic air oxidation of organic compounds and since the cobalt-bromide catalyst used during these oxidation reactions are susceptible to hydrolysis, it was important to investigate the effect of increasing water levels in the oxidation mixtures. Glacial acetic acid has been reported to contain about 0.1% water. [67] Coulometric analysis of the glacial acetic acid used during this investigation yielded an average value of 0.0933% (m/m). For the purpose of this investigation on the effect of water in the glacial acetic acid used as the reaction solvent during the oxidation of 4-methoxytoluene, increasing amounts of deionized water was added to a known mass of glacial acetic acid. The results obtained are depicted in Table 3.5.

Table 3.5: Effect of water concentration

$[H_2O]$ (mass %)	Conversion (%)		
	20	40	60
	Selectivity (%)		
0.1	79.9	69.3	52.8
2.0	87.8	76.4	66.1
4.0	70.7	66.9	58.2
6.0	66.7	59.3	54.4
8.0	62.2	54.9	51.1

The results obtained show an interesting trend (also observed with other substrates previously for rate enhancement)[65] in that the selectivity to 4-methoxybenzaldehyde improves as the water concentration is increased from 0.2% to about 2.5%. Thereafter, the reaction selectivity decreases significantly.

In previous studies into the effect of water concentration of the rate of substrate oxidation during the cobalt-bromide catalysed air oxidation of alkylbenzenes, it was shown that the observed increase in catalyst performance as the water concentration is increased to about 2.5%, is directly related to the ability of cobalt to coordinate bromide. Thus, in glacial acetic acid the cobalt(II) – bromide interaction is somewhat suppressed, but as the water concentration is increased (to about 2.5%), the extent of cobalt(II)-bromide coordination (as shown by UV-visible studies) increases. Above water concentrations of 2.5%, the cobalt(II)-bromide interaction decreases, mainly as a result of hydrolysis, and decreased aldehyde selectivities are observed.

3.1.6 Catalytic Air Oxidations: Concluding Remarks

The results on the catalytic air oxidation of various substituted alkyl aromatics, discussed in some detail in the preceding sections, suggest that high aldehyde selectivities (>70%) will only be achieved if:

- The substrate contains electron donating groups on the aromatic ring;
- The substrate conversion is restricted to <30%; and
- Other reaction variables that include reaction temperature, water content of the reaction mixture, etc, are carefully controlled.

While therefore not practically impossible to devise a process for producing, for example a 4-methoxy-2-alkylbenzaldehyde by means of a cobalt(II)acetate-bromide catalyzed air oxidation process, such a process will not be cheap or technically easy in view of the challenge to effect proper mass transfer at larger scales, and the large amounts of solvent and oxidation products that will need to be separated, and where feasible, recycled.

3.2 Indirect oxidation of 3-*tert*-butyl-4-methoxytoluene

3.2.1 Introduction

Oxidation and reduction processes in organic synthesis can be carried out effectively with traditional stoichiometric redox reagents,[68] a large number of which are amenable to electrochemical regeneration. Although there are exceptions, most suitable redox couples are inorganic reagents and examples of those which are commonly used are:

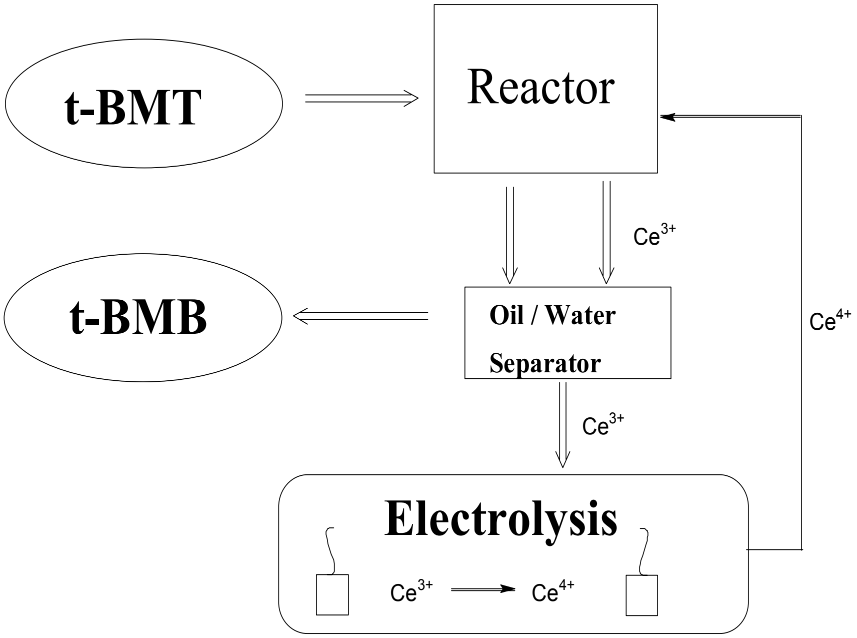
For oxidation: Ce^{3+} / Ce^{4+}; $Cr^{3+}/Cr_2O^{2-}_7$; Mn^{2+}/Mn^{3+}; Mn^{2+}/MnO_2; Br^-/ Br_2; Cl^-/ClO^-; $Ni(OH)_2/NiOOH$
For reductions: Sn^{4+}/Sn^{2+}; Ce^{3+}/Ce^{2+}; $Ti^{4+}/Ti^{3+;}$ Zn^{2+}/Zn, $Na^+/NaHg$

An advantage of using stoichiometric oxidation/reducing agents is the possible regeneration of these agents by electrochemical oxidation or reduction, which leads to simplification in the process operation, reduction in any problems of effluent treatment and eliminate the need for bulk storage of hazardous or toxic chemicals on the site. There are several requirements for successful electrochemical mediators, including:

- The oxidized and reduced forms of the mediator must be chemically stable and not undergo side reactions which are irreversible.
- The electron transfer with the electrode should ideally be fast and reversible; this reduces cell voltage and the possibility of undesirable side reactions.
- Redox reactions with species other than the target molecule should be minimal.
- The cycle time for recovery or regeneration of the mediator should be high.
- A high solubility in the aqueous supporting electrolyte is desirable to maximize the reaction rate with the organic species.

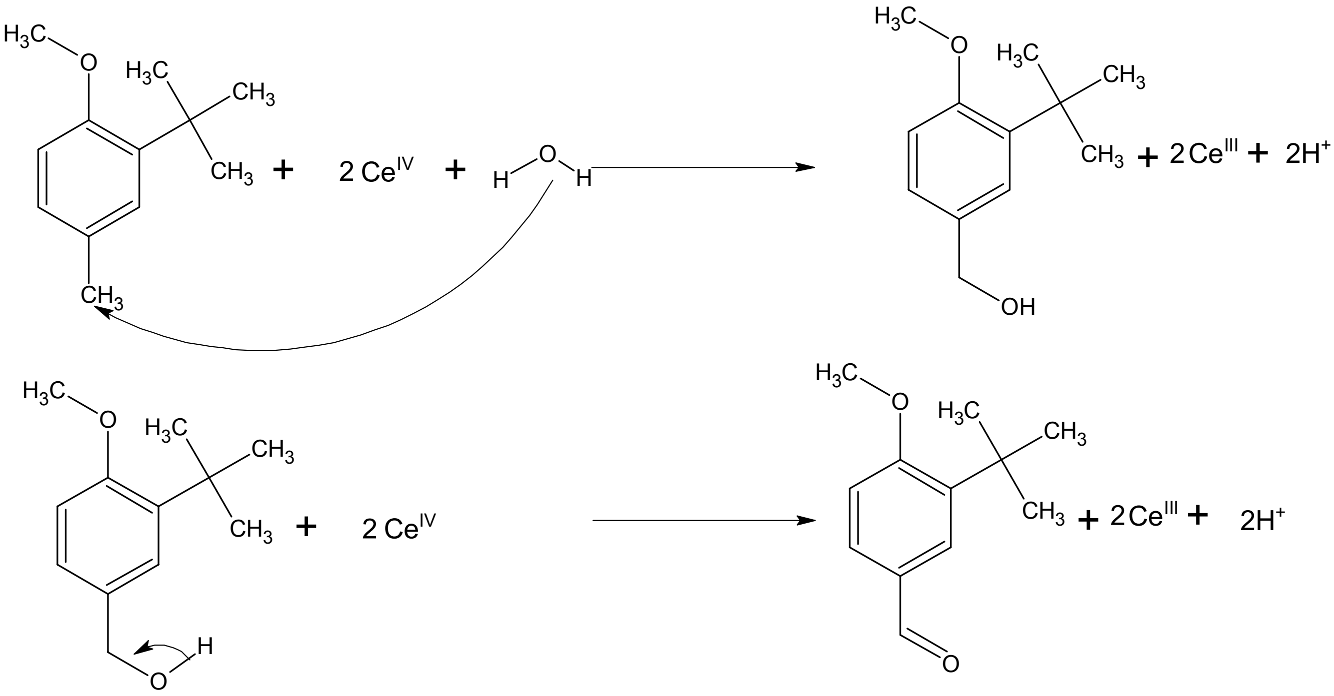
Many of these processes have been tested and developed to the pilot plant level, some even to full scale manufacturing plant especially in the fine chemical and pharmaceutical industries.[69]

Indirect electrochemical reactions are classified into two categories: In cell or Ex-cell processes. In the ex-cell process the reaction between a mediator and the substrate occurs in a chemical reactor separate from the electrochemical cell.[70] An example of such a process is shown in Scheme 3.2.



Scheme 3.2: Ex-cell method for indirect electrochemical oxidations

Scheme 3.3 shows the reactions involved in the Ce^{IV} methanesulfonate mediated oxidation of the 3-*tert*-butyl-4-methoxytoluene to the corresponding benzaldehyde. The first step involves a two electron oxidation of the methyl group of the toluene to the alcohol with a concurrent reduction of Ce^{IV} to Ce^{III}. This is then followed by a second two electron oxidation step from the alcohol to the benzaldehyde.

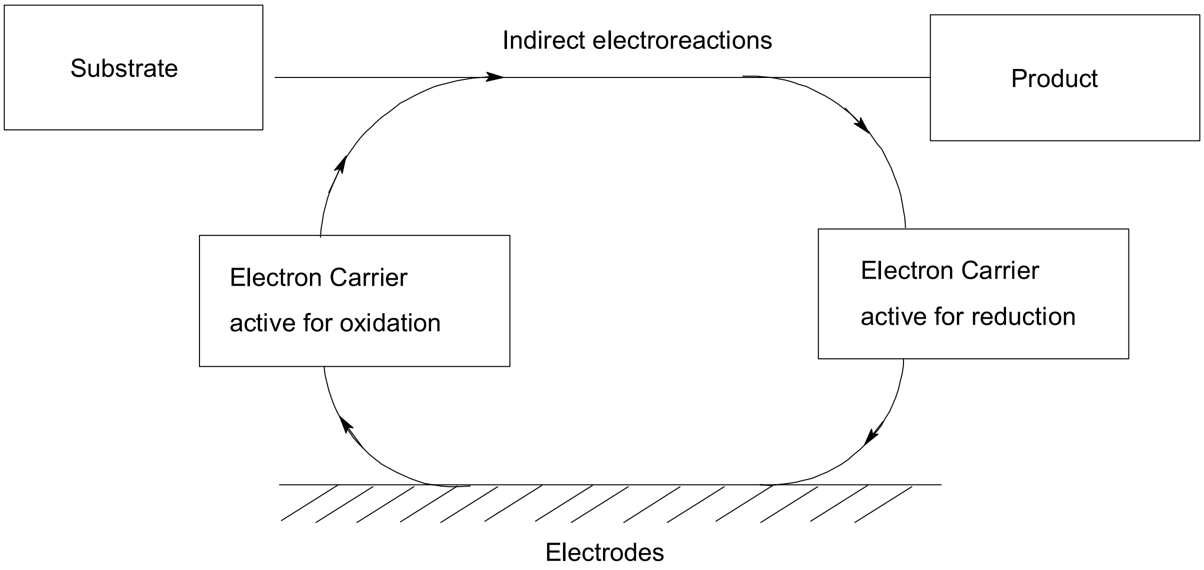


Scheme 3.3 Reaction sequence for the Ce(IV) oxidation of 3-*tert*-butyl-4-methoxytoluene.

After the reaction is completed, the mediator is separated from the organic products and returned to the electrochemical cell for regeneration. This is normally done in order to minimize contact of organic phase with the electrode surface, which can result in electrode fouling and deactivation.

With the In-cell process, however, the mediator and the reactant are placed in one electrochemical cell unit. This then generates the mediator at the surface of the electrode material which then oxidizes the substrate. The spent mediator is re-oxidized in situ and the cycle is repeated.

The regeneration is normally carried out on a continuous basis for as long as the reaction proceeds.[70]



Scheme 3.4: Recycling of the mediator in the electrochemical cell

3.2.2. Limitations in Solubility during Organic Electrochemical Processing

The commercial development of electro-organic synthesis in aqueous electrolyte media is frequently limited by low concentrations of organic reagent in the electrolyte and thus by a low value of diffusion limiting current density. The low amount of organic species in the electrolyte also limits the ability of the reactor to rapidly replenish the material consumed by the reaction in the aqueous phase.

These factors introduce mass transfer limitations to the electro-synthesis procedure. In terms of the mass transfer requirements at electrodes, calculations put limits of organic depolariser concentration at ~100 $mol.m^{-3}$ if a practical current density of ca $100A.m^{-2}$ is to be achieved.[70]

3.2.3 Ceric Ammonium Nitrate[71, 72]

The first mediator tested for the indirect electrochemical oxidation of 3-*tert*-butyl-4-methoxytoluene was ceric amminium nitrate. Table 3.5 lists the experimental conditions that were kept constant throughout this investigation.

Table 3.5: Constant conditions: Ceric ammonium nitrate method

Variable	Value
Methanol	50 mL
Stirring rate (rpm)	400
Temperature (^{o}C)	30
Substrate: Ce(IV) ratio*	1: 4
Time	30 min

* $(NH_4)_2Ce(NO_3)_6$ (8.9567 g, 16.337 mmol); 3-*tert*-butyl-4-methoxytoluene (0.6509g; 3.656 mmol).

The oxidation reactions with ceric ammonium nitrate were carried out as described previously in Section 2.2.7. After work-up (section 2.2.7.1), the precipitated cerium salts were recovered and the cerium(III) oxidised to cerium(IV) as described in section 2.2.7.1 After determining the actual concentration of cerium(IV) in the re-oxidised solutions, the relevant amount (Table 3.6) of 3-*t*-butyl-4-methoxytoluene was added and the solution oxidised as before. This procedure was repeated twice. The results of these experiments are summarised in Table 3.6 below.

Table 3.6 Indirect electrochemical oxidation of 3-*tert*-butyl-4-methoxytoluene using ceric ammonium nitrate.

Cycle No.	Ce(IV) (mmoles)	*tert*-BMT* (mmoles)	*tert*-BMB** (%)
1	16.01	4.003	73.18
2	9.98	2.496	80.42
3	11.11	2.779	76.89

* *tert*-BMT = 3-*tert*-butyl-4-methoxytoluene; *tert*-BMB = 3-*tert*-butyl-4-methoxybenzaldehyde

From Table 3.6 it can be seen that the amount of Cerium(IV), which were determined by titration against ferrous ammonium nitrate, varies between about 10 mmoles and 16 mmoles. This variation is probably the result of variations in the re-oxidation efficiency of the Cerium(III). What is important to note, however, is the observation that the amount of 3-*tert*-butyl-4-methoxybenzaldehyde formed during these oxidation reactions remain fairly constant (probably within experimental error) around the 75% mark during the 3 cycles.

3.2.4 Indirect electrochemical oxidation of 3-*tert*-butyl-4-methoxytoluene using Cerium(IV) Methanesulfonate

The next mediator system evaluated for the indirect electrochemical oxidation of 3-*tert*-butyl-4-methoxytoluene was cerium(IV) methanesulfonate, prepared as described previously in Section 2.2.4.3.

The first step on this section was to decide on the concentration of methane sulfonic acid to use in order to prepare a Ce(IV) methanesulfonate. Different concentration levels as shown in the table 3.7 below were evaluated and a decision was taken based on the results.

Table 3.7: Effect of Methane sulfonic acid concentration on the oxidation of 3-*tert*-butyl-4-methoxytoluene using Cerium(IV) Methanesulfonate.

Cerium(IV) methanesufonate concentration	*t*-BMT* Conversion %	*t*-BMB** Selectivity %	*t*-BMB** Yield %
8M	15.2889	32.9361	5.03558
6M	24.1832	73.7093	17.8253
4M	51.1543	3.9402	2.0156
2 M	0.0369	100	0.0369

* *tert*-BMT = 3-*tert*-butyl-4-methoxytoluene; *tert*-BMB = 3-*tert*-butyl-4-methoxybenzaldehyde

After the summarized (Table 3.7) trial reactions, 6M concentration was chosen as the better range of methane sulfonic acid concentration. Initial reactions were carried out by directly contacting the organic phase (3-*tert*-butyl-4-methoxytoluene) with the aqueous oxidation phase (cerium (IV) methanesulfonate typically in 6M methane sulfonic acid). These reactions gave rather disappointing results (typically 35 – 40% over a 6 hour reaction period), probably as a result of the poor mass transfer between the two immiscible phases. For this reason it was decided to rather perform these oxidations in the presence of co-solvents, namely acetone, acetonitrile and dichloromethane, to attempt improving the mass transfer between the two reaction phases.

The results depicted in Table 3.6 illustrate the effect of poor mass transfer even in reactions where a co-solvent such as acetone is used. These reactions were performed as described in Section 2.2.4.4 and where the 3-*tert*-butyl-4-methoxytoluene was dissolved in 10 mL of acetone.

Table 3.8 Effect of stirring rate on the cerium(IV) methanesulfonate mediated oxidation of 3-*tert*-butyl-4-methoxytoluene in the presence of acetone as co-solvent.

		1350 rpm	1500 rpm
Run 1 Ce[a] = 2.49 mmoles TBMT = 0.622 mmoles	TBMT* Conversion (%)	54.61	71.18
	TBMB** Selectivity (%)	100.00	100.00
Run 2 Ce[a] = 2.044 mmoles TBMT = 0.511 mmoles	TBMT* Conversion (%)	41.25	65.37
	TBMB** Selectivity (%)	100.00	100.00

[a] – Cerium (IV) methanesulfonate; Methanesulfonic acid [6M], at 21 °C

* TBMT = *Tert*.-butyl-methoxytoluene

**TBMB = *Tert*.-butyl-methoxybenzaldehyde

From the results depicted in Table 3.6 it can be seen that the rate of mixing significantly influences the degree of conversion of substrate, hence reaction rate, but has no influence on the reaction selectivity. All further investigations were carried out at the higher stirring rate of 1500 rpm.

In order to evaluate the effect of the selected solvent systems on the cerium(IV) methane sulfonate-mediated oxidation of 3-*tert*-butyl-4-methoxytoluene, several reactions were carried out at various reaction temperatures as described in section 2.2.4.4 and using cerium(IV) methane sulfonate (11.0 mmoles) in an aqueous methane sulfonate solution (6.3 molar) together with 10 mL of each solvent. The amount of substrate (3-*tert*-butyl-4-methoxytouluene) was kept constant (~2. 75 mmol) relative to the amount of cerium (IV) methane sulfonate

(1 : 4). The results obtained for these investigations are summarised in Table 3.7.

Table 3.9 Oxidation of 3-*tert*-butyl-4-methoxytoluene with cerium(IV) methane sulfonate in the presence of various solvents.

Solvent	**Temperature (^oC)**	**TBMT Conversion (%)**	**TBMB Yield (%)**
	21	95.21	95.21
Acetone	30	83.98	83.98
	Reflux	58.05	41.95
Dichloromethane	30	87.21	87.21
	Reflux	93.13	93.13
	40	98.15	66.60
	50	86.01	81.25
Acetonitrile	60	92.45	61.80
	70	99.51	55.72
	Reflux	97.21	53.90

From the results depicted in Table 3.7 it can be seen that the oxidations in the presence of acetone and dichloromethane are quite selective, resulting in the production of the 3-*tert*-butyl-4-methoxybenzaldehyde in near quantitative selectivity. Figure 3.2 illustrates a typical GCMS-chromatogram obtained for the oxidation of 3-*tert*-butyl-4-methoxytoluene (retention time = 8.54 min) in the presence of acetone and which only shows peaks for the starting material and product 3-*tert*-butyl-4-methoxybenzaldehyde (retention time = 12.37 min).

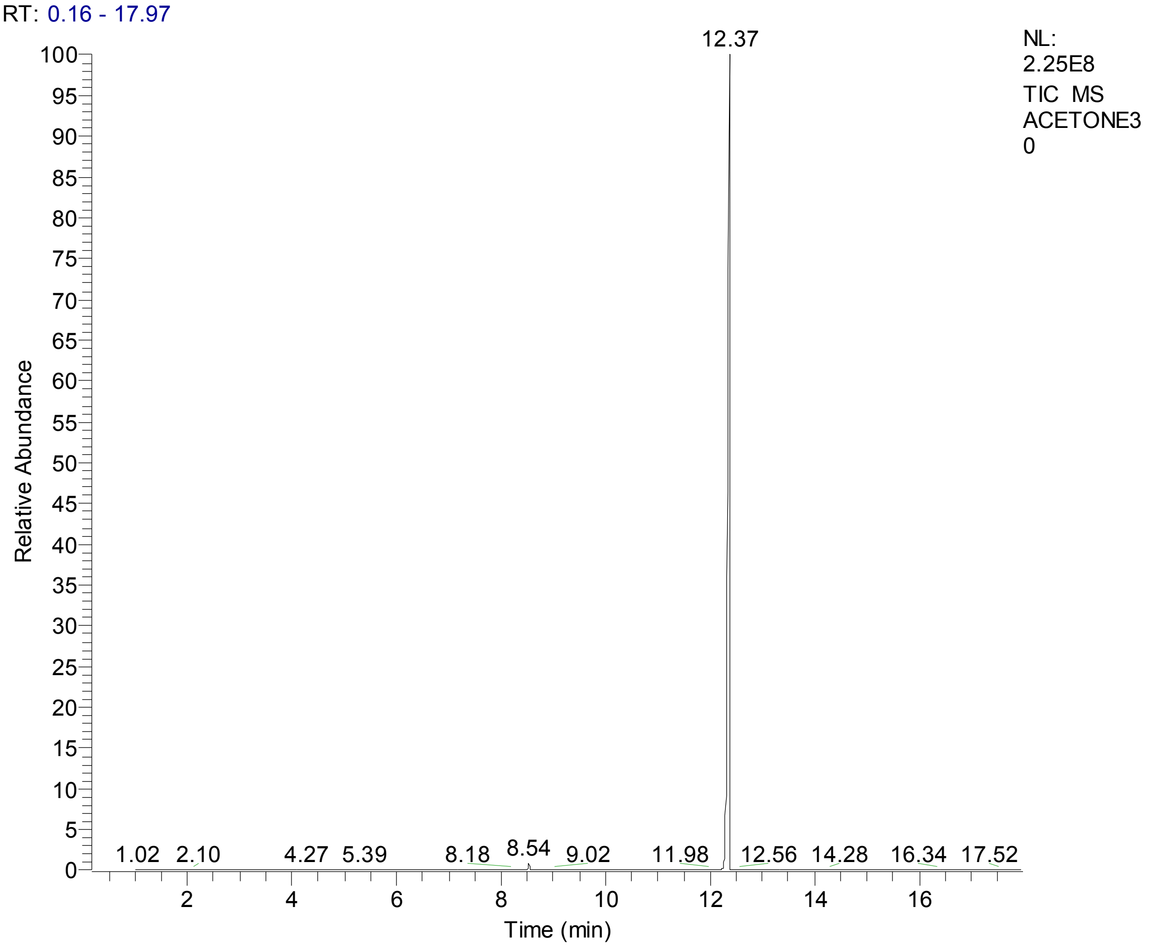


Figure 3.2 Typical GCMS-trace for oxidations in the presence of acetone.

In acetonitrile, however, over oxidation of the initially formed benzaldehyde to the 3-*tert*-butyl-4-methoxybenzoic acid (retention time = 14.13 minutes) readily occurs as the oxidation temperature is increased above 50 °C as shown in the GCMS-trace (Figure 3.3) for the oxidation of *t*-butyl methoxytoluene at 60 °C.

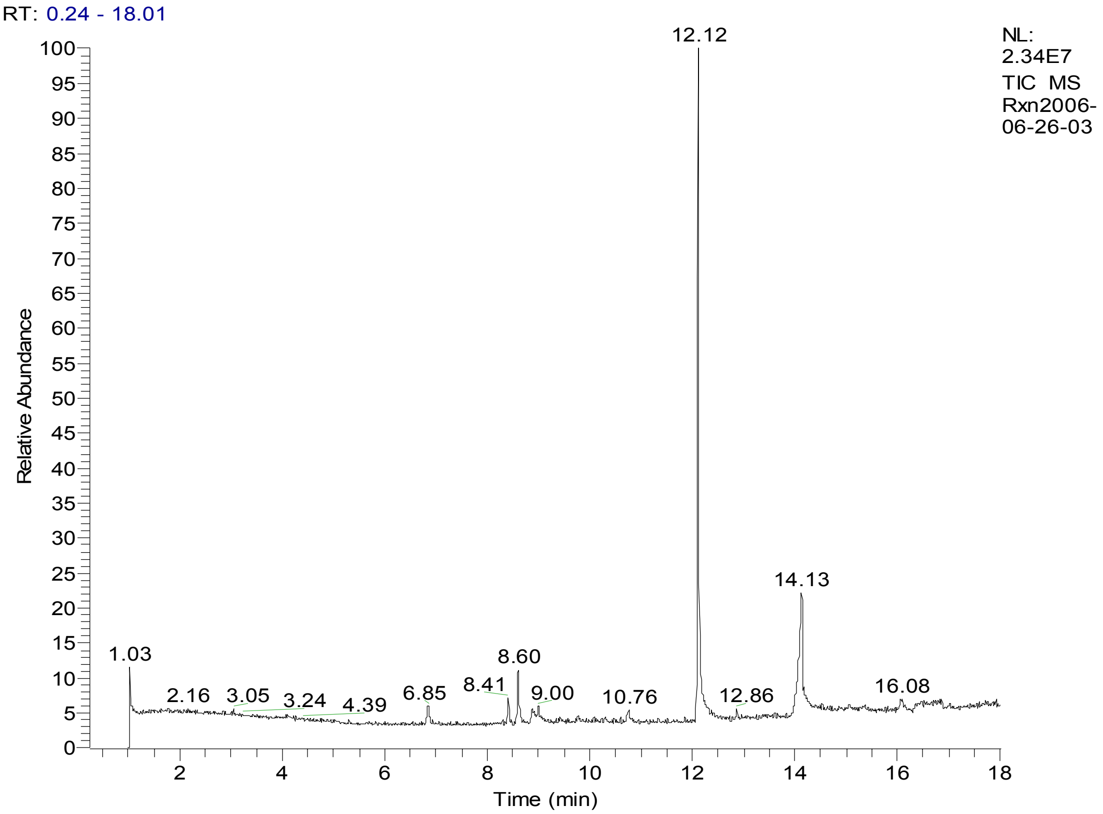


Figure 3.3 GCMS-trace for the oxidation of 3-*tert*-butyl-4-methoxytoluene in the presence of acetonitrile at 60 °C.

3.2.5 Indirect Electrochemical Oxidations: Concluding Remarks

Oxidations carried out using the inorganic mediators ceric ammonium nitrate and cerium(IV) methane sulfonate has shown that these methods are capable of producing significantly improved results compared to catalytic air oxidations. In particular, cerium(IV) methane sulfonate is capable of giving the desired product in near quantitative selectivity at substrate conversions as high as 90%. The low solubility of the substrate in the aqueous methane sulfonic acid solutions, however, results in slow mass transfer in these oxidations.

The use of polar solvents as co-solvents alleviates this problem only slightly, and in the case of acetonitrile, results in the further oxidation of the desired aldehyde through to the benzoic acid. While a reduction in the methanesulfonic acid concentration may reduce the oxidation strength of the cerium(IV), thereby reducing the extent of benzaldehyde oxidation, this will again reduce the rate of oxidation.

3.3 Direct Electrochemical Oxidations

3.3.1 Constant current and constant potential electrolysis

Electrochemical reactions are normally carried out using two of the following procedures: constant current or constant potential electrolysis.[73, 74]

Constant potential electrolysis: As the name suggests, the potential of the working electrode is kept constant with respect to a reference electrode. As the reaction proceeds (*i.e.* oxidisable material reduces), the current in the cell gradually decreases.

Constant current electrolysis: Throughout the reaction, the current is kept constant whilst the potential of the electrolysis system changes gradually as the reaction proceeds.

The following equations are used to determine the amount of charge passed through a reaction mixture during constant potential and constant current electrolysis respectively.[74]

$$Q = \int_0^\infty Idt = nFN \qquad (3.1)$$

$$Q = \int_0^\infty Idt = It = NFn \qquad (3.2)$$

In equations 3.1 and 3.2 the symbols used have the following meaning:

- Q is the number of coulombs consumed in an electrolysis;

- I is the current (Ampere);
- n is the total number of electrons involved per molecule for the oxidation/reduction process;
- t is the time (seconds);
- F is the Faraday constant, *i.e.* the charge needed (96500 coulombs) per mole of substrate to effect the electrochemical reaction, assuming there is a one electron change; and.
- N is the number of moles of substrate initially present.

The above processes have both advantages and disadvantages when compared to each other.[73]

3.3.2 Undivided vs Divided

Both direct and indirect electrolysis procedures can be carried out using undivided (one compartment) or divided (two compartments) cells. The difference between the two is explained below:[73, 75]

Undivided: Here there is no separation between the anode and the cathode, i.e. the two electrodes are immersed in one solution.[73]

Divided: Here there is a physical separation (micro-porous divider/membrane) between the anolyte and the catholyte. This prevents products, formed at one electrode, from migrating to the other where it can undergo additional redox reactions.

Each of these cells has its own advantages and disadvantages in electrochemical synthesis, which are mentioned below:[73,75]

Cell design: This is less complicated in an undivided process than it is in a divided process. The separator used in the divided cell can also cause problems:

the cell resistance is increased and this problem could be magnified if fouling of the separator occurs. When considering scaling-up, it is known that a undivided reactor is cheaper than a divided reactor by and order of magnitude.

Reactions: A divided cell prevents the occurrence of side reactions, which can occur at a counter electrode,. The divided cell does, however, facilitate the possibility of performing paired synthesis, where two distinctly separate reactions could be carried out in the same reactor at the same time.[76]

3.3.3 Mechanistic considerations

Even though there is a huge range and wide diversity of organic electro-synthesis processes, the mechanism by which the process occurs often start with the formation of radical ions, which then further form intermediate species which themselves may undergo further electron transfer. Here is an ideal direct electro organic synthesis reaction.

$$Organic + e^{-} \rightarrow (rad.ion) \xrightarrow{Fast} Intermediate + e^{-} \rightarrow \mathrm{Pr}oduct \qquad (3.3)$$

The final destination of the unstable ion radical, that is the type of product formed, totally depends on the surrounding homogeneous electrolyte (which is the solvent) and other species, the electrode surface and presence of the adsorbed species, if any.

The electron transfer process adds further control parameters in providing possible selective synthesis. On the other hand, the chemical reactivity of the radical ion is purely determined by the ionic character of the species and by the radical itself, which can undergo typical radical reactions such as hydrogen abstraction, radical addition, radical disproportionation and radical-radical dimerisation.

Radical cation, due to the positive charge, can also be expected to have the properties of electrophiles, adding to available nucleophiles. Radical cations may also add to unsaturated hydrocarbon molecules or can react further to give alkyl radicals. The reaction paths for radical anions obtained from unsaturated hydrocarbons, e.g. vinyl compounds, include hydrogen abstractions, radical reactions with the electrode material, radical anion disproportionation and radical dimerisation. Anionic reaction radical anions may be protonated to form radicals and undergo Michael additions of the radical anions. The radical cation reactions are more important than the radical anion reactions, except in the case of protonation to form the respective radical. This is due to the fact that proton donors cannot be completely eliminated from electrolytes. This often leads to undesirable electro-polymerisation.

The selection of a suitable supporting electrolyte and solvent type for a particular electrolytic oxidation, optimizing the reaction conditions and designing suitable process electrolysis cells requires, at least, a good working knowledge of the reaction mechanism. Naturally, the process of mechanism elucidation is also indispensable for the generation of new research ideas. Theoretically, elucidation of the reaction mechanism and optimising the experimental conditions in electrochemical reactions is not as complicated as in other heterogeneous reactions, for example, catalytic hydrogenation, which is routinely used in organic synthesis.[77]

In this section factors which could influence or have an impact on the mechanism of the direct electrochemical oxidation of substituted toluenes to the corresponding benzaldehydes will be considered, in order to facilitate the optimization of the selected oxidation reaction.

3.3.3 Electrochemical alkoxylation

Alkoxylation can be achieved by the anodic oxidation of the substrate in an alcohol medium such as methanol containing a suitable supporting electrolyte such benzensulfonic acid, sodium salt (BSANa)[78], KF[79], H_2SO_4, and $NaClO_4$.[80, 81] Both nuclear and side-chain methoxylation have been performed on aromatic compounds. Substrates that have been alkoxylated in this manner include aromatic compounds, alkenes and ethers.

Methanolic electrolytes have been shown to undergo oxidation at lower potentials than many organic substrates, which strongly suggests that an indirect mechanism operates in the α-methoxylation of alkyl aromatics such as toluene. The nature of the anion present in the supporting electrolyte greatly affects the yield of the α-methoxylated product, the effectiveness decreasing in the series.[82]

$$F^- \approx ClO_4^- > CN^- \approx OH^- > Cl^- \approx CH_3O^- > Br^-$$

The mechanism for the anodic methoxylation of alkyltoluenes is illustrated below:

$$CH_3OH \longrightarrow HOCH_2^{\cdot} + H^+ + e^-$$

or

$$CH_3O^- \longrightarrow CH_3O + e^-$$

$$ArCH_3 + X \longrightarrow HX + ArCH_2^{\cdot} \longrightarrow ArCH_2^+ + e^-$$

$$X = HOCH_2^{\cdot} \text{ or } CH_3O$$

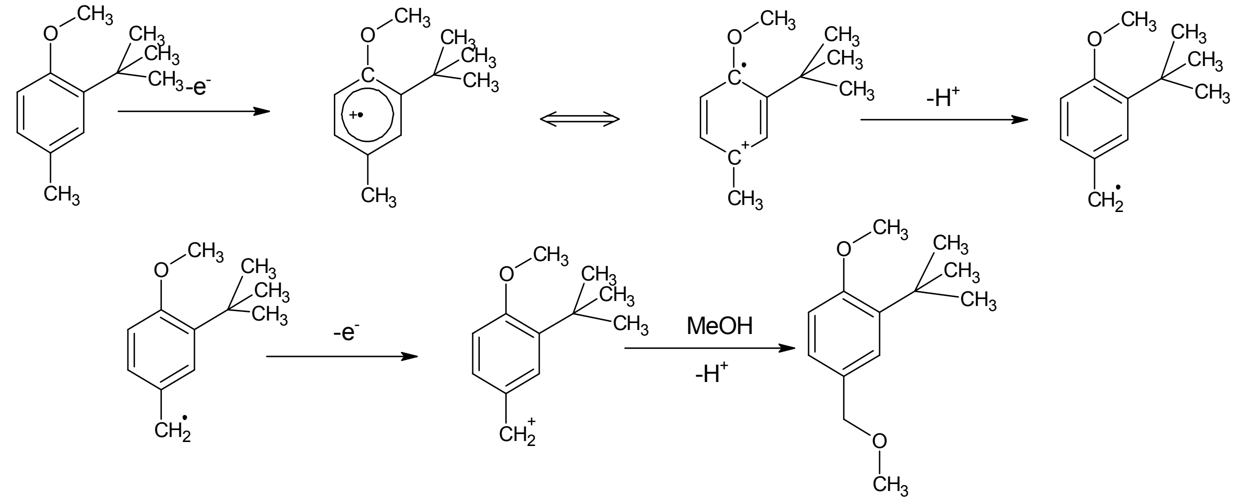
$$ArCH_2^{\cdot} + CH_3O \longrightarrow ArCH_2OCH_3$$

or

$$ArCH_2^+ + CH_3OH \longrightarrow ArCH_2OCH_3 + H^+$$

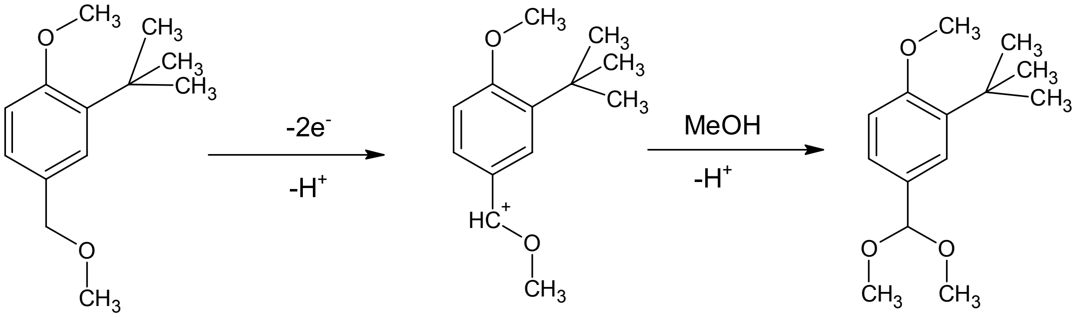
One would not expect F^- or ClO_4^- to be oxidized at all under these conditions, which suggest that methanol is the likely electroactive species, forming a radical intermediate that then functions as X in the above equations. The radical $HOCH_2^•$ is the most likely candidate since the O-H bond in MeOH is much stronger than the C – H bond.[83] In alkaline medium, MeO^- is probably the electroactive species, and $MeO^•$ would then be X.

The electrochemical oxidation of toluenes in dry methanol leads to methoxylation of the side-chain when non nucleophilic electrolytes were used.[84] Since side chain methoxylation during this investigation was investigated in dry methanol, using non-nucleophilic supporting electrolytes such as benzene sulfonic acid, sodium perchlorate, potassium fluoride and sulfuric acid, side chain methoxylation to produce the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether, as shown in Scheme 3.4, is expected.



Scheme 3.4: Side chain methoxylation of 3-*tert*-butyl-4-methoxytoluene to produce the 3-*tert*-butyl-4-methoxy benzyl methyl ether.

Further electrolysis should repeat the sequence of reactions to form 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal. This step should be easier than the first since the intermediate ether has a lower oxidation potential than the substrate. This follows an ECE (electrochemical chemical electrochemical) type reaction.



Scheme 3.5 **Formation of 4-methoxybenzaldehyde dimethyl acetal**

By controlling the potential of the oxidation system accurately at the cell potential values indicated by the cyclic voltammogram of 3-*tert*-butyl-4-methoxytoluene (Figure 3.11), it should be possible to accumulate the 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal and minimizes further oxidation to the corresponding benzoic acid.

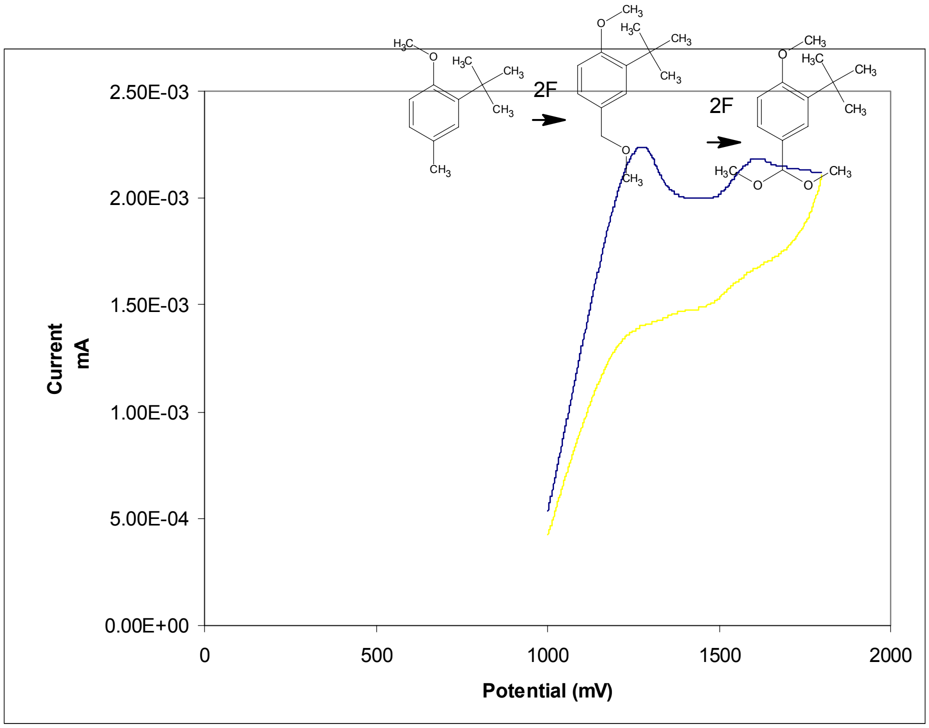


Figure 3.11 Cyclic voltammogram of the 3-*tert*-butyl-4-methoxytoluene on a graphite surface in a 0.5 M $NaClO_4$ / acetonitrile medium.

The cyclic voltammogram shows the anodic oxidation cycle for 3-*tert*-butyl toluene to produce the 3-*tert*-butyl-4-methoxybenzyl methyl ether at about 1193 mV, which is then further oxidized to the 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal at about 1653 mV. Figure 3.12 shows the cyclic voltammogram for 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal on graphite electrodes in a acetonitrile / sodium perchlorate medium.

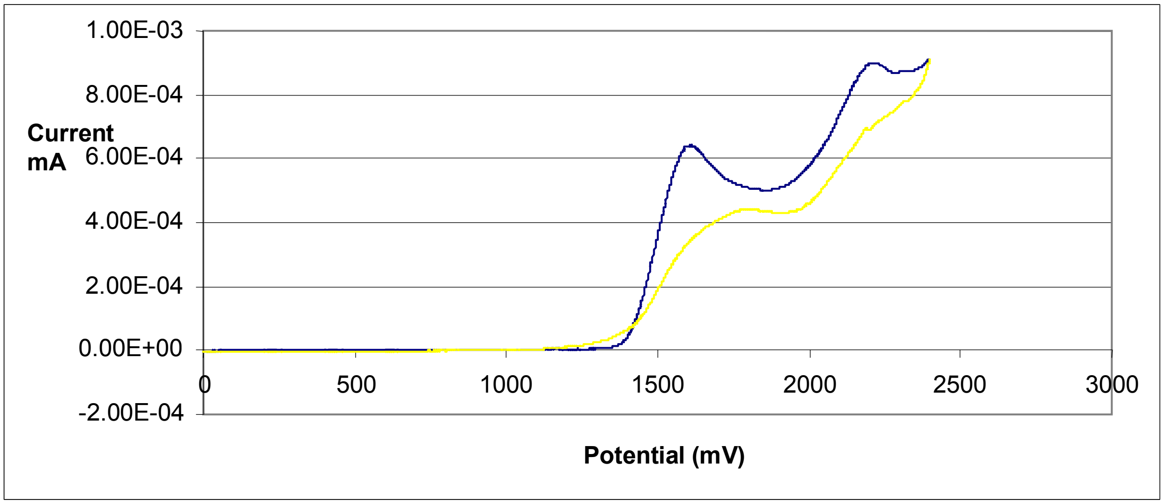


Figure 3.12 Cyclic voltammogram of 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal on a graphite surface in a 0.5 M $NaClO_4$ / acetonitrile medium.

From the cyclic voltammogram it can be seen that the 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal is oxidized at about 152O mV indicating that for the direct synthesis to be selective, the anodic oxidation must be performed at a slightly lower oxidation potential. It could also be seen that there is a second oxidation peak at 2200 mV which is quasi reversible.

3.3.4 Supporting Electrolyte Investigations

When selecting a suitable electrolyte, certain criteria have to be met. These are:

- Good solubility in the solvent to be used;
- Electrochemical stability;
- No reactivity towards the reaction intermediates;
- Ease of preparation; and
- Low cost.[85]

A supporting electrolyte is nearly always necessary during the electrolysis of an organic species, not only to provide a means of carrying the electrolysis current, but also to reduce the rather large electrical resistance encountered in organic solvents.[84]

Several supporting electrolytes were chosen for this part of the investigation, and they were as follows: benzenesulfonic acid, sodium salt (BSANa) sodium perchlorate ($NaClO_4$), potassium fluoride (KF), and sulphuric acid (H_2SO_4).

Two sets of experiments were conducted with each electrolyte, firstly to evaluate the conductivity of the electrolyte in methanol as a function of its concentration, and secondly to study the electrochemical stability of the electrolyte.

3.3.4.1 Conductivity Studies of the Supporting Electrolytes

Figure 3.13 shows a plot of conductivity (mS cm^{-1}) against concentration units for each supporting electrolyte in methanol at $22^{o}C$. H_2SO_4 shows the highest conductivity, followed by $NaClO_4$.

The electrolytes can be arranged in the following order according to their conductivity:

$$H_2SO_4 > NaClO_4 > BSANa > KF$$

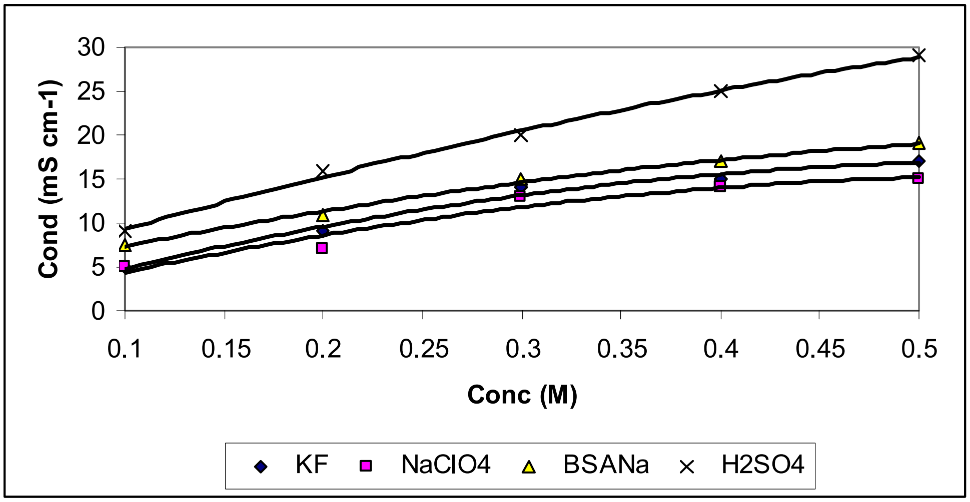


Figure 3.13 **Conductivity studies for different supporting electrolytes using Pt as electrode in a methanol medium**.

3.3.4.2 Stability Studies

Figure 3.14 shows the polarization curve for each supporting electrolyte at a constant concentration of 0.5 M in methanol, obtained from a linear sweep, using graphite as working electrode versus Ag / Ag^+ (0.1 mol dm $^{-3}$).

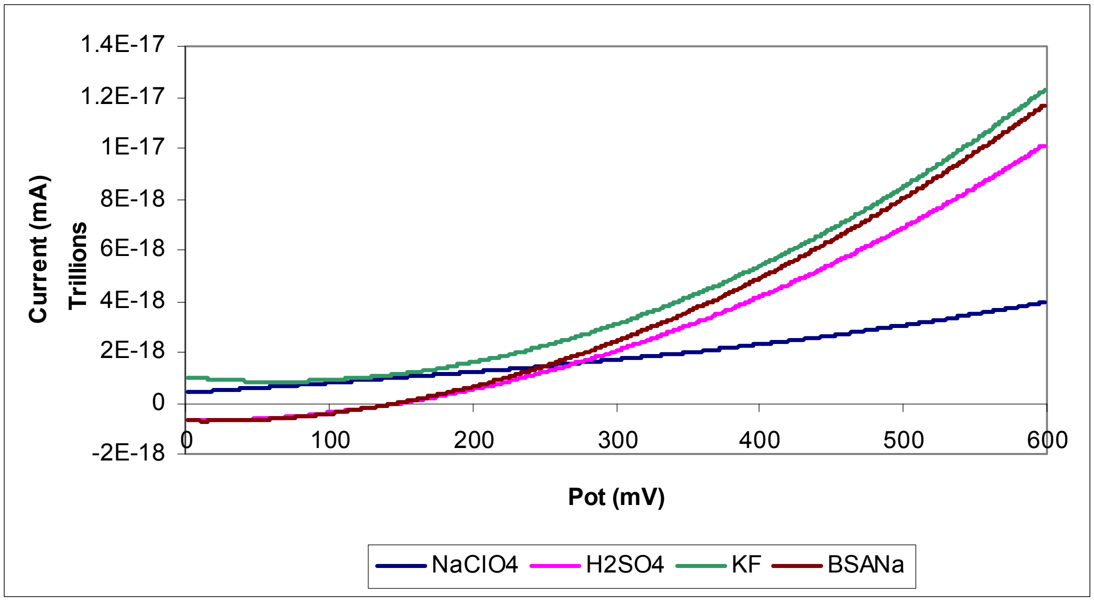


Figure 3.14: Polarisation curves for different supporting electrolytes (0.05 mol dm $^{-3}$) in acetonitrile medium.

From the above it can be seen that, for the linear sweep of all the electrolytes show good electrochemical stability in acetonitrile, with $NaClO_4$ showing the lowest current by-pass indicating that it can be the most stable supporting electrolyte.

3.3.5 Product distribution diagrams

Several reactions were carried out to investigate the effect of the different supporting electrolytes on the direct electrochemical oxidation of 3-*tert*-butyl-4-methoxytoluene in methanol. These reactions were carried out at four different reaction temperatures, using the following conditions: 3-*Tert*-butyl-4-methoxytoluene (2.5 g, 0.014 moles) in 150.00 mL methanol containing 0.5 M supporting electrolyte at a current of 1.5 A. The results obtained are summarised graphically in Figures 3.15 to 3.21.

3.3.5.1 Benzenesulfonic acid, sodium salt

Product distribution diagrams of the direct electrochemical oxidation of *t*-butyl methoxytoluene at four electrolysis temperatures, 30, 40, 50 and 60 ^{o}C, when using BSANa as the supporting electrolyte, are illustrated in Figures 3.15 to 3.18. These reactions were carried out using a stainless steel electrode for the cathode material and a graphite electrode for the anode material. Samples of (ca. 0.3 mL) were taken every 30 minutes and analysed by gas chromatography as described previously (section 2.3.1).

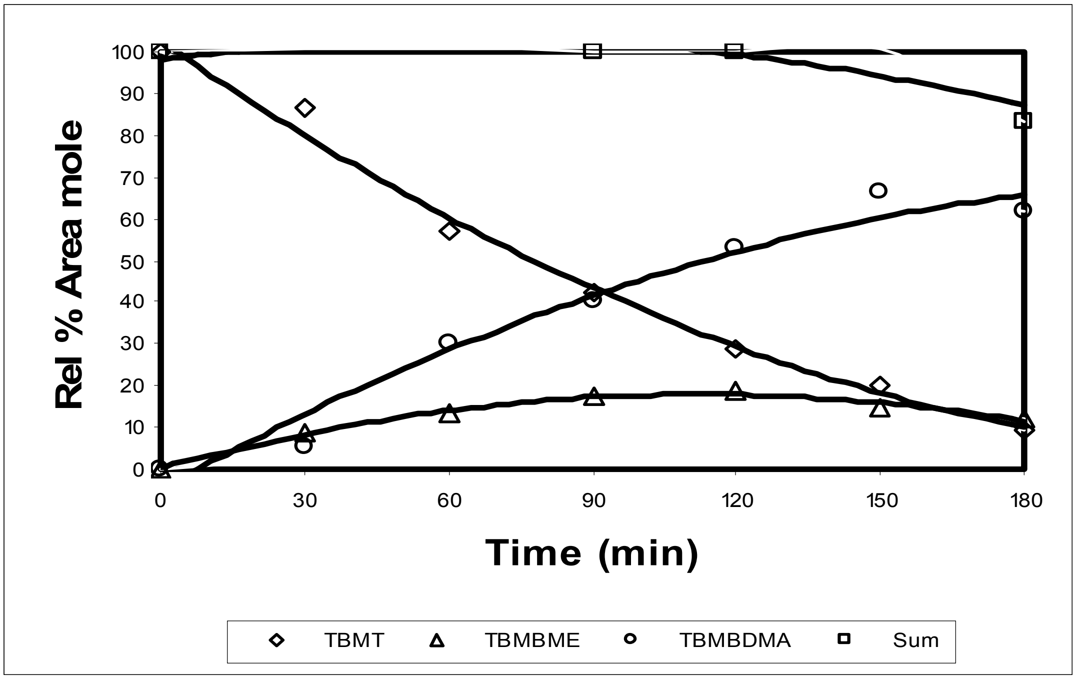


Figure 3.19 Shows the effect of the supporting electrolyte sodium benzene sulfonate at 30 °C

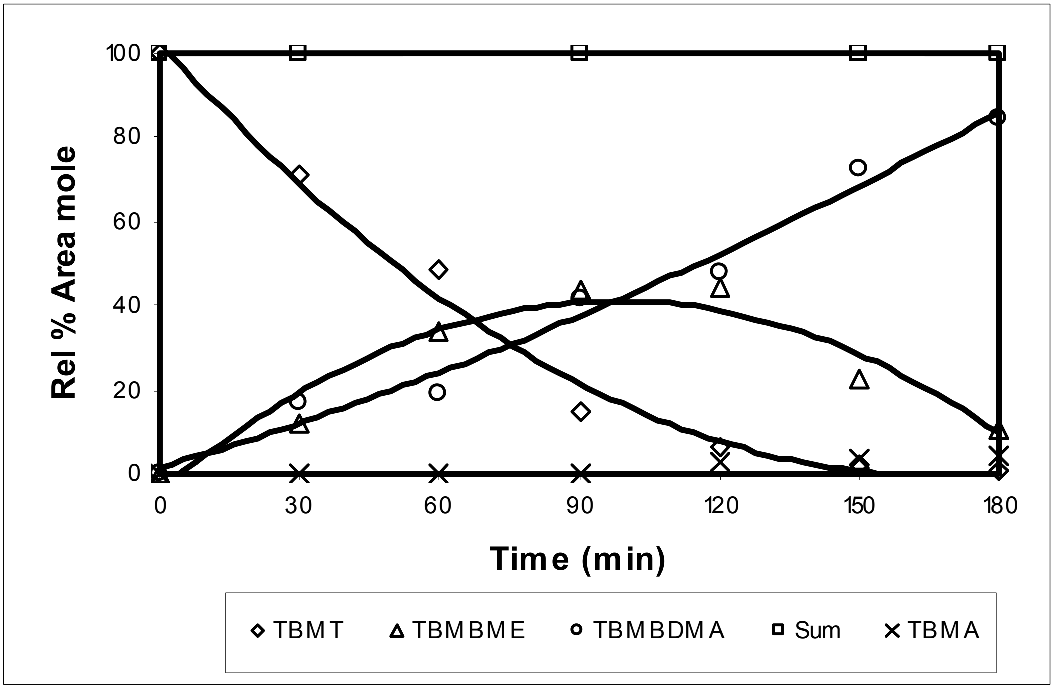


Figure 3.20 Shows the effect of the supporting electrolyte benzenesulfonate, sodium salt at 40 °C

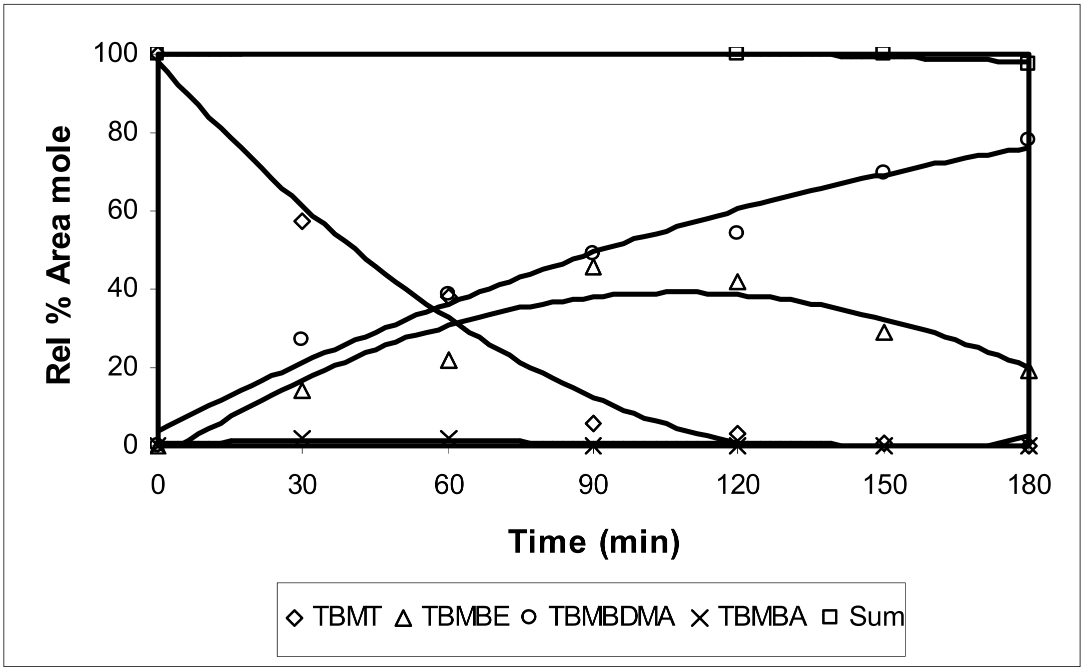


Figure 3.21 Shows the effect of the supporting electrolyte benzenesulfonate, sodium salt at 50 °C

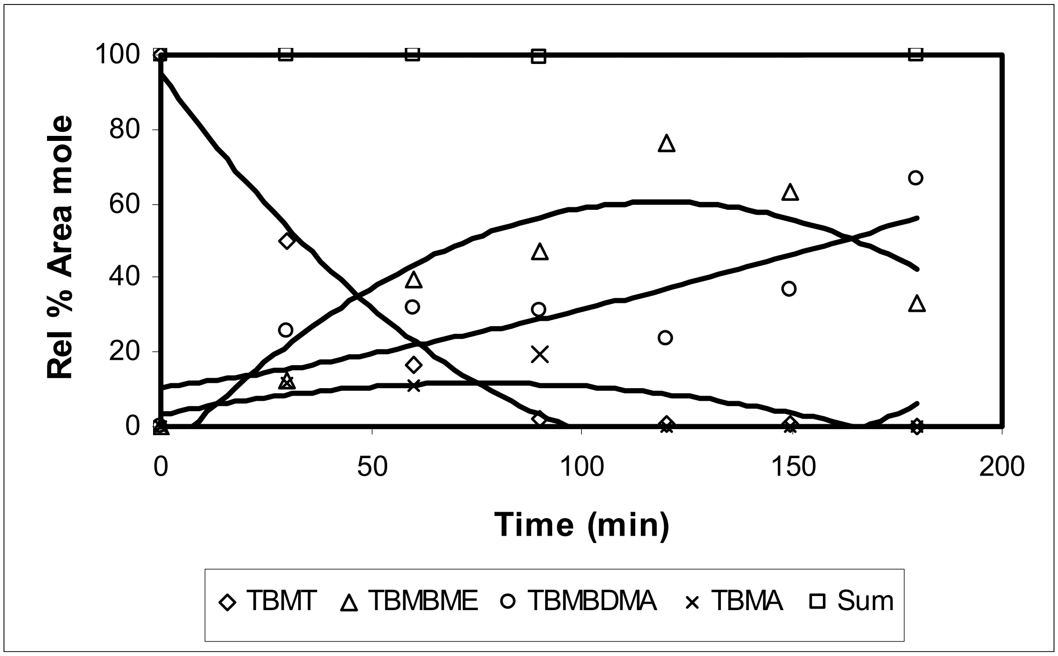


Figure 3.22 Shows the effect of the supporting electrolyte benzenesulfonate, sodium salt 60 °C.

The following observations can be made:

a) At 30 ^{o}C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 18 % after 90 minutes (or 2 Faradays of charge) and then continues to drag out over the duration of the time. The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal reaches a maximum of 66% at 150 minutes (3.3 F). The substrate 3-*tert*-butyl-4-methoxytoluene gradually decreased to zero at 180 min (4 F), the sum also decreases after 120 min to about 85 %.

b) At 40 ^{o}C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 46 % at 90 minutes (2 F) and then decrease to 11 % at 180 minutes (4 F). The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal reaches a maximum of 84 % at 180 minutes (4 F). It was also observed that some acetal 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal hydrolysed to form the 3-*tert*-butyl-4-methoxybenzaldehyde (4 %). The substrate 3-*tert*-butyl-4-methoxytoluene decreased sharply to 20 % and then more slowly to 0 %, whilst the easier oxidizeable species such as 3-*tert*-butyl-4-methoxy benzyl methyl ether is oxidized.

c) At 50 ^{o}C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 46 % at 90 minutes (2 F) and then decrease to 19 % at 180 minutes (4 F). The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal reaches a maximum of 78 % at 180 minutes (4 F). It was also observed that some acetal 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal hydrolysed to the 3-*tert*-butyl-4-methoxybenzaldehyde (2 %). The substrate 3-*tert*-butyl-4-methoxytoluene decreased sharply to 6 % after 90 minutes and then slowly to 0 %, while the easier oxidizeable species such as 3-*tert*-butyl-4-methoxy benzyl methyl ether is oxidized. The sum slightly decreases after 150 min to about 95 %.

d) At 60 ^{o}C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 76 % at 120 minutes (3 F) and then decrease to 33 % at 180 minutes (4 F). The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal stayed stable for the first 100 minutes at 30 % at this stage the substrate 3-*tert*-butyl-4-methoxytoluene been completely converted. And the next oxidizable species was the ether 3-*tert*-butyl-4-methoxy benzyl methyl ether showing a fast anodic oxidation to the acetal 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal. It was also observed an initial increase in 3-*tert*-butyl-4-methoxybenzaldehyde concentration.

3.3.5.2 Sulfuric acid

The effect of sulfuric acid as supporting electrolyte on the direct electrochemical oxidation of 3-*tert*-butyl-4-methoxytoluene at the four reaction temperatures (30, 40, 50 and 60 ^{o}C) is illustrated in Figures 3.23 to 3.26. These reactions were carried out in the same manner as described for BSANa above.

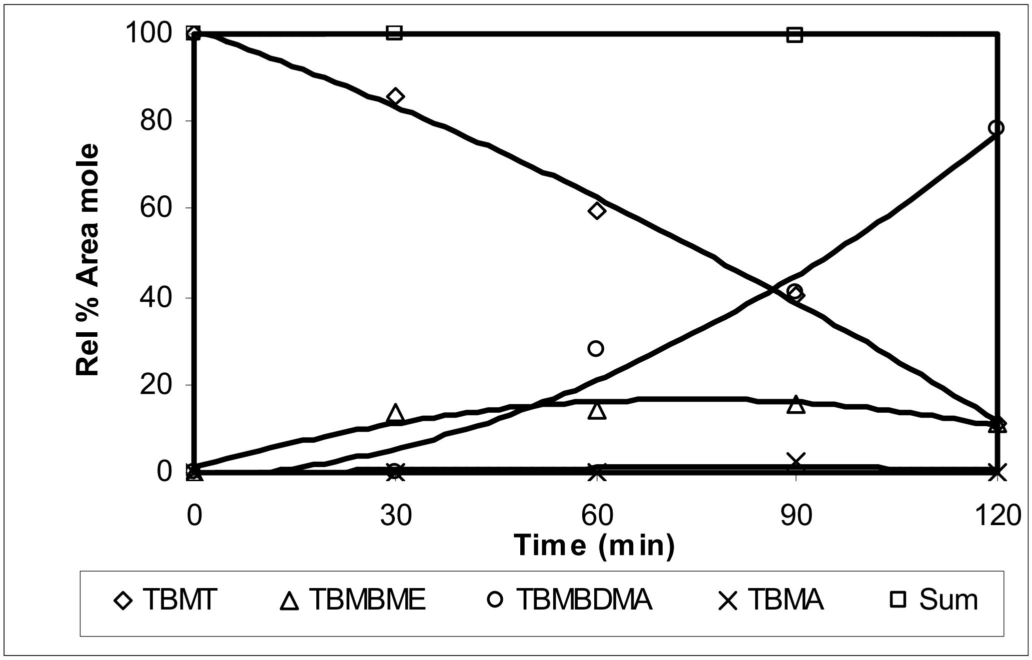


Figure 3.23 Shows the effect of sulfuric acid as the supporting electrolyte at 30 ^{o}C

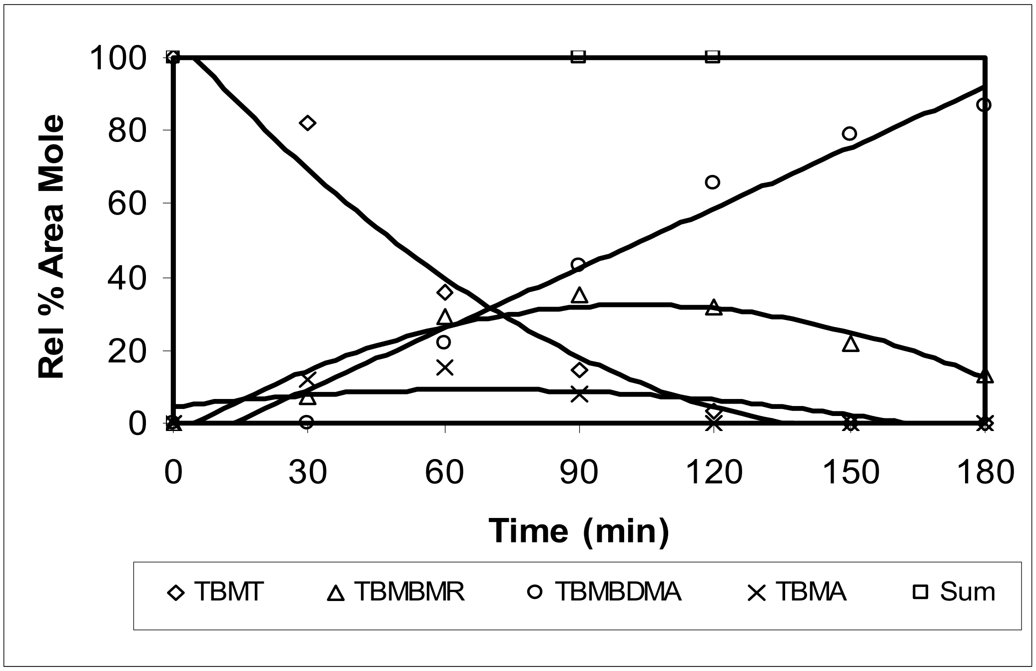


Figure 3.24 Shows the effect of sulfuric acid as the supporting electrolyte at 40 °C

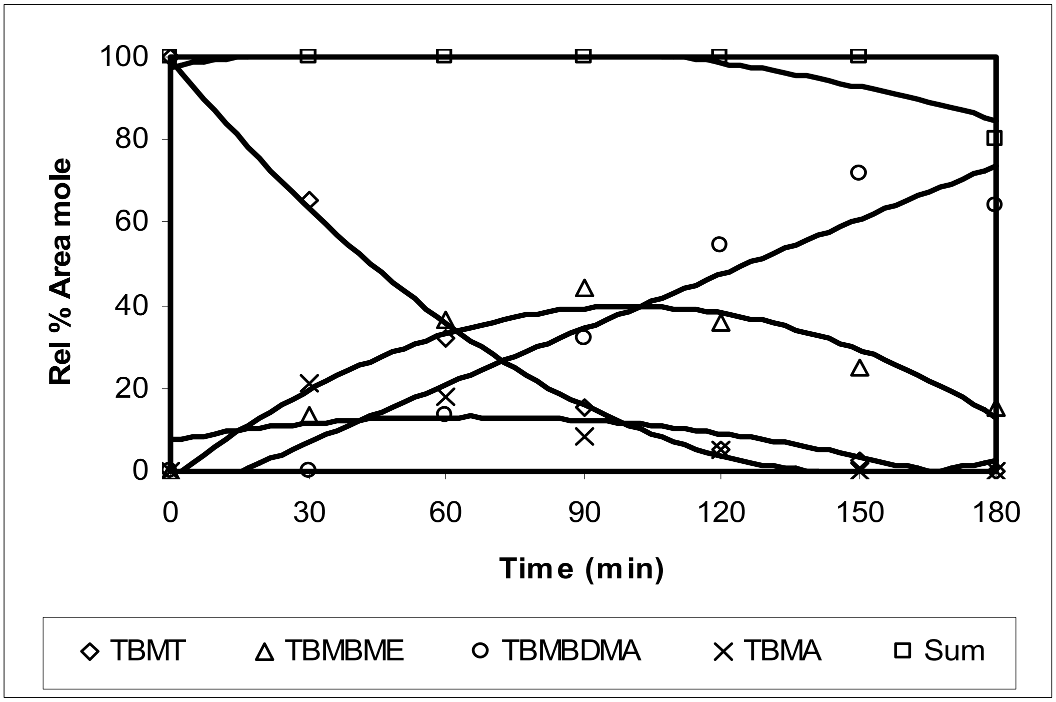


Figure 3.25 Shows the effect of sulfuric acid as the supporting electrolyte at 50 °C

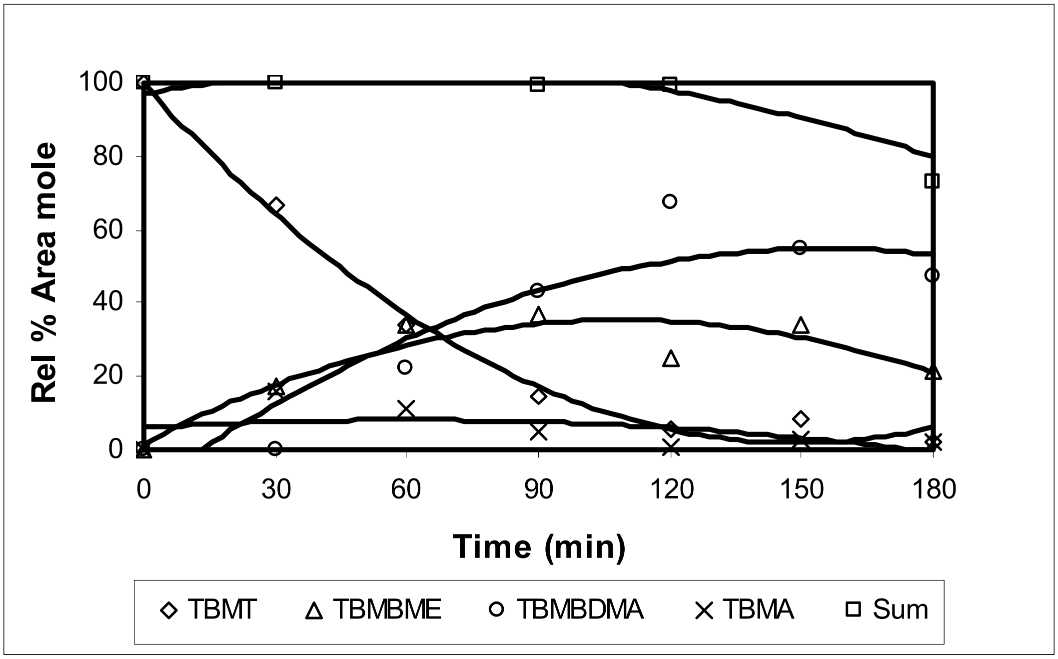


Figure 3.26 Shows the effect of sulfuric acid as the supporting electrolyte at 60 °C.

The following observations could be made:

a) At 30 °C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 15 % at 60 minutes (1.5 F) and then continue to drag out over the duration of the time. The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal reaches a maximum of 78 % at 150 minutes (3.3 F). The substrate 3-*tert*-butyl-4-methoxytoluene gradually decreased to 8 % at 180 min (4 F). Trace amounts of 3-*tert*-butyl-4-methoxybenzaldehyde (3 %) was observed.

b) At 40 °C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 44 % at 90 minutes (2 F) and then decrease to 15 % at 180 minutes (4 F). The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal reaches a maximum of 71 % at 180 minutes (4 F). It was also observed that some acetal (3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal) hydrolysed to the 3-*tert*-butyl-4-methoxybenzaldehyde (4 %). The substrate 3-*tert*-butyl-4-methoxytoluene decreased gradually to 0 %.

c) At 50 °C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 36 % at 90 minutes (2 F) and then decrease to 21 % at 180 minutes (4 F). The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal reaches a maximum of 71 % at 150 minutes (4 F). It was also observed that some acetal hydrolysed to the 3-*tert*-butyl-4-methoxybenzaldehyde (5 %). The substrate 3-*tert*-butyl-4-methoxytoluene decreased gradually to 0 %.The sum slowly decreases after 120 min to about 80%.

d) At 60 °C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 36 % at 90 minutes (2 F) and then stays constant for the remainder of the time. The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal reaches a maximum of 69% at 150 minutes. The substrate 3-*tert*-butyl-4-methoxytoluene decreased gradually to 2 %. The sum slowly decreases after 120 min to about 80%.

3.3.5.3 Sodium perchlorate

The effect of sodium perchlorate as supporting electrolyte on the direct electrochemical oxidation of 3-*tert*-butyl-4-methoxytoluene at the four reaction temperatures (30, 40, 50 and 60 °C) is illustrated in Figures 3.27 to 3.30. These reactions were carried out in the same manner as described for BSANa above.

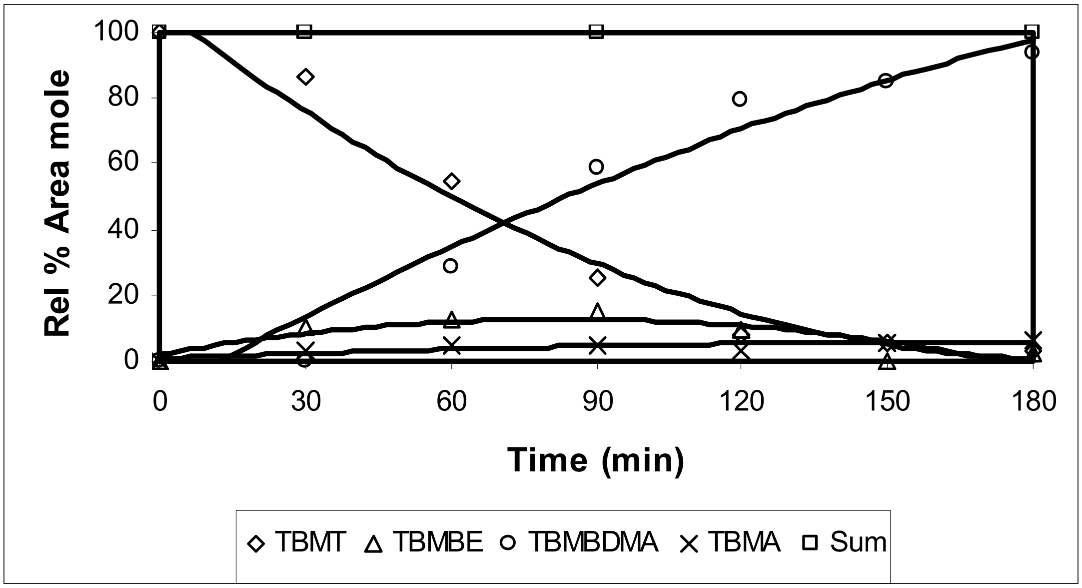


Figure 3.26 Shows the effect of sodium perchlorate as the supporting electrolyte at 30 °C

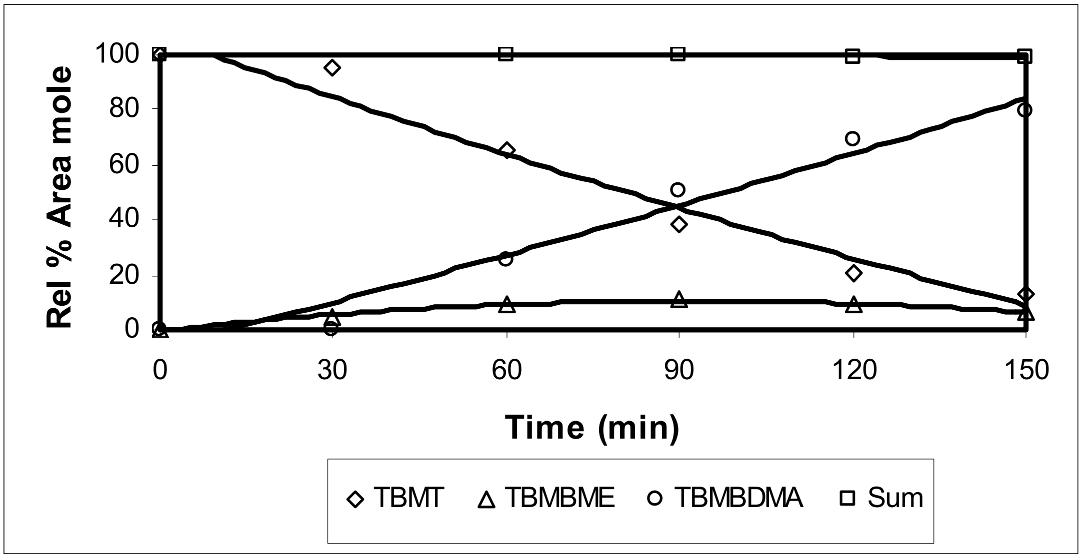


Figure 3.27 Shows the effect of sodium perchlorate as the supporting electrolyte at 40 °C.

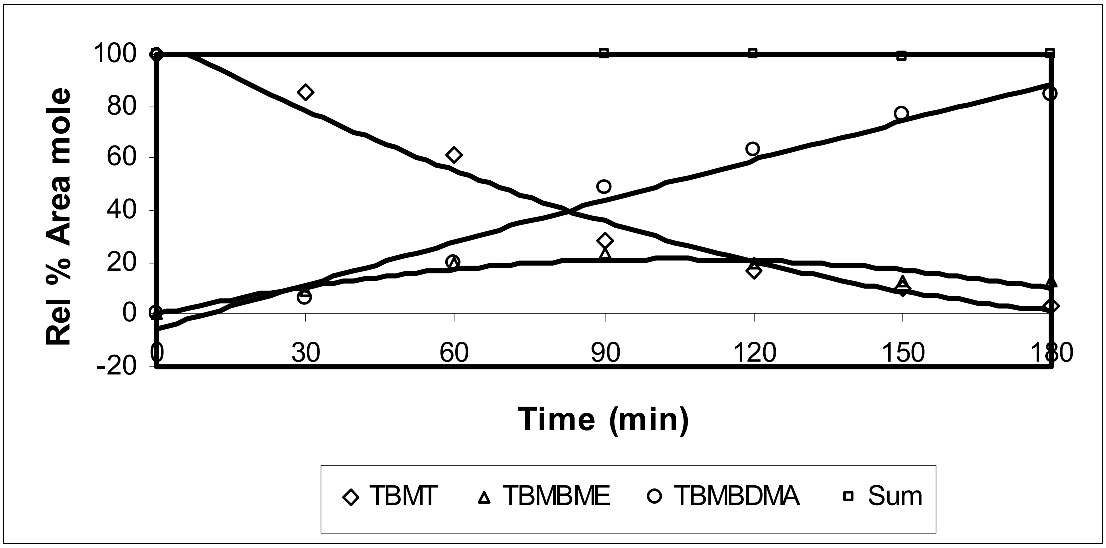


Figure 3.28 Shows the effect of sodium perchlorate as the supporting electrolyte at 50 °C.

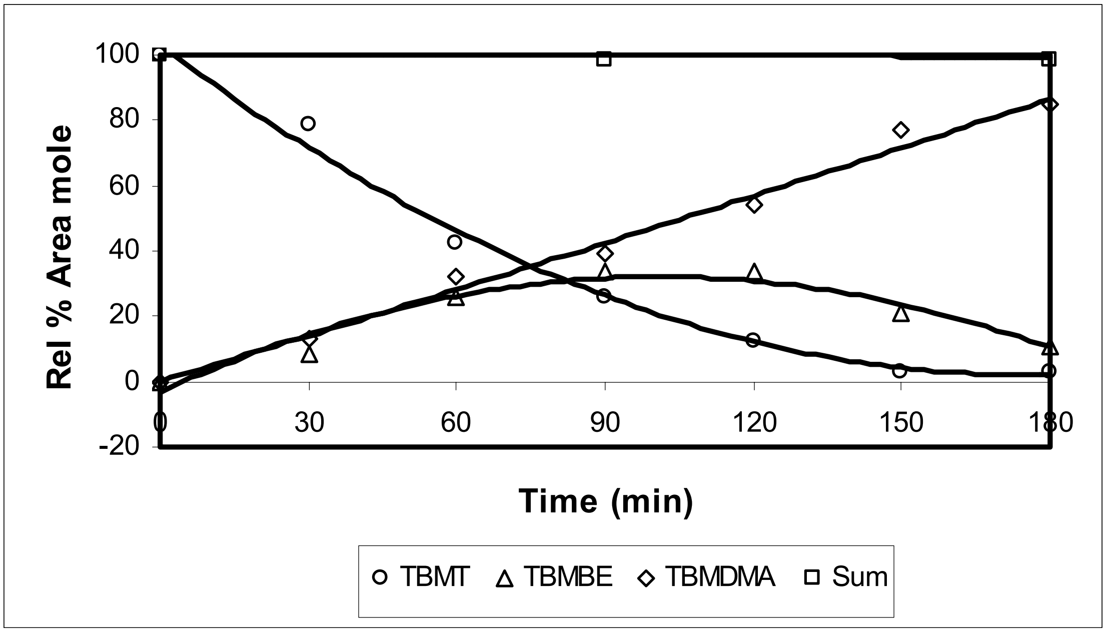


Figure 3.29 Shows the effect of sodium perchlorate as the supporting electrolyte at 60 °C

The following observations could be made:

a) At 30 °C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 15 % at 90 minutes (2 F) and then continues to drag out over the duration of the time. The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal reaches a maximum of 93 % at 180 minutes (4 F). The substrate 3-*tert*-butyl-4-methoxytoluene gradually decreased to 2 % at 180 min (4 F). Trace amounts of 3-*tert*-butyl-4-methoxybenzaldehyde (6%) was observed. The sum accountability stays at 100 %.

b) At 40 °C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 10 % at 90 minutes (2 F) and then stayed at 6 % till 180 minutes (4 F) passed. The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal reaches a maximum of 80 % at 180 minutes (4 F). It was also observed that some acetal 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal. The substrate 3-*tert*-butyl-4-methoxytoluene decreased gradually to 10 %. The sum accountability stays at 100 %.

c) At 50 °C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 23 % at 90 minutes (2 F). The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal reaches a maximum of 85 % at 180 minutes (4 F). The substrate 3-*tert*-butyl-4-methoxytoluene decreased gradually to 3 %. The sum accountability stays at 100 %.

d) At 60 °C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 33 % at 90 minutes (2 F) and then decreased to 11 % at 180 minutes. The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal reaches a maximum of 85% at 180 minutes. The substrate 3-*tert*-butyl-4-methoxytoluene decreased gradually to 3 %. The sum accountability stays at 100 %.

3.3.5.4 Potassium fluoride

The effect of potassium fluoride as supporting electrolyte on the direct electrochemical oxidation of 3-*tert*-butyl-4-methoxytoluene at the four reaction temperatures (30, 40, 50 and 60 °C) is illustrated in Figures 3.31 and 3.34. These reactions were carried out as described for BSANa above.

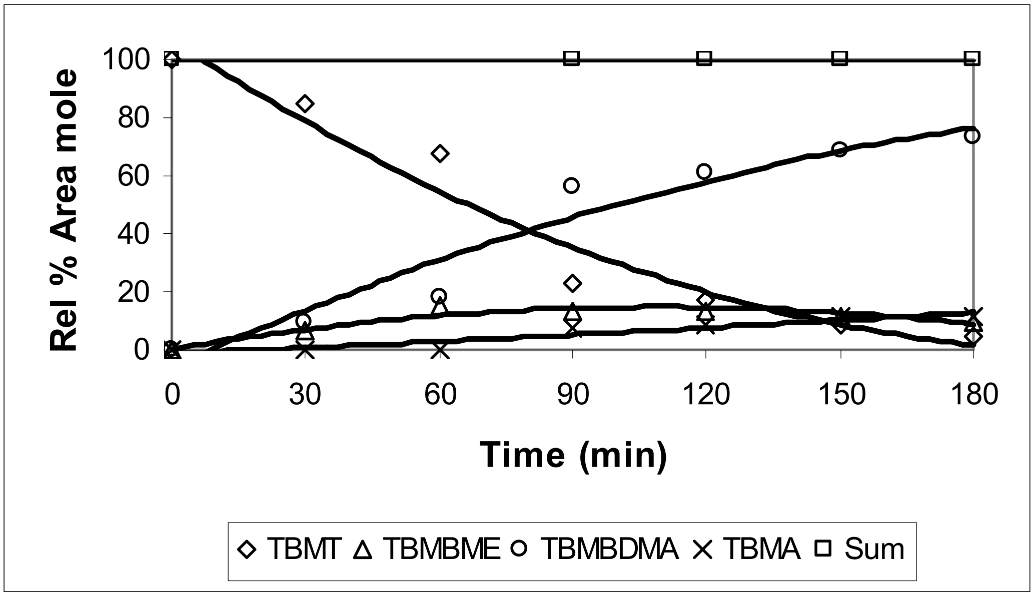


Figure 3.30 Shows the effect of potassium fluoride as the supporting electrolyte at 30 °C

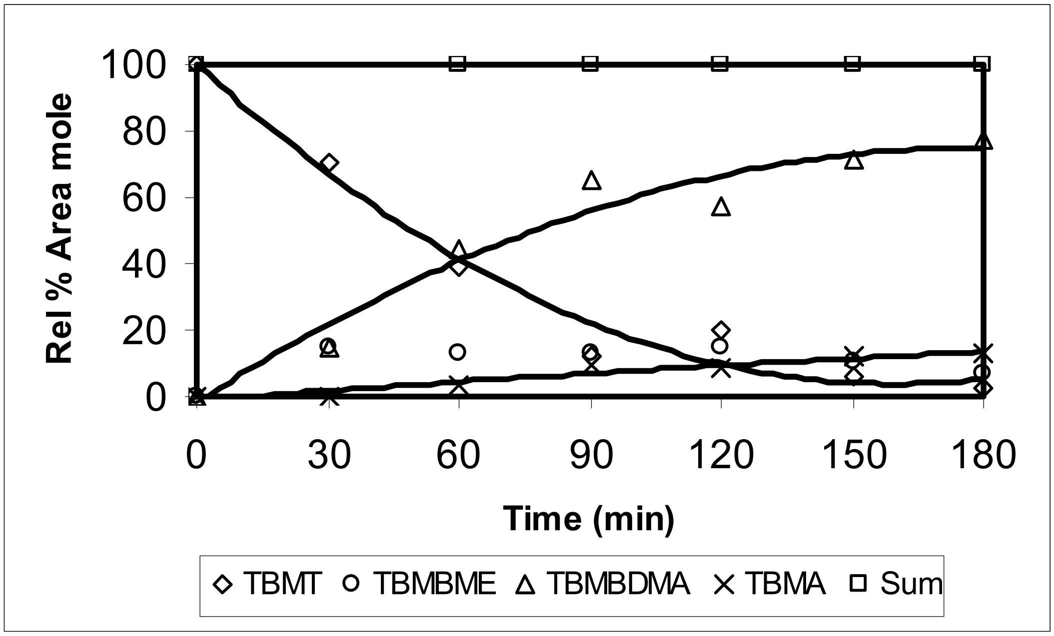


Figure 3.31 Shows the effect of potassium fluoride as the supporting electrolyte at 40 ^{o}C.

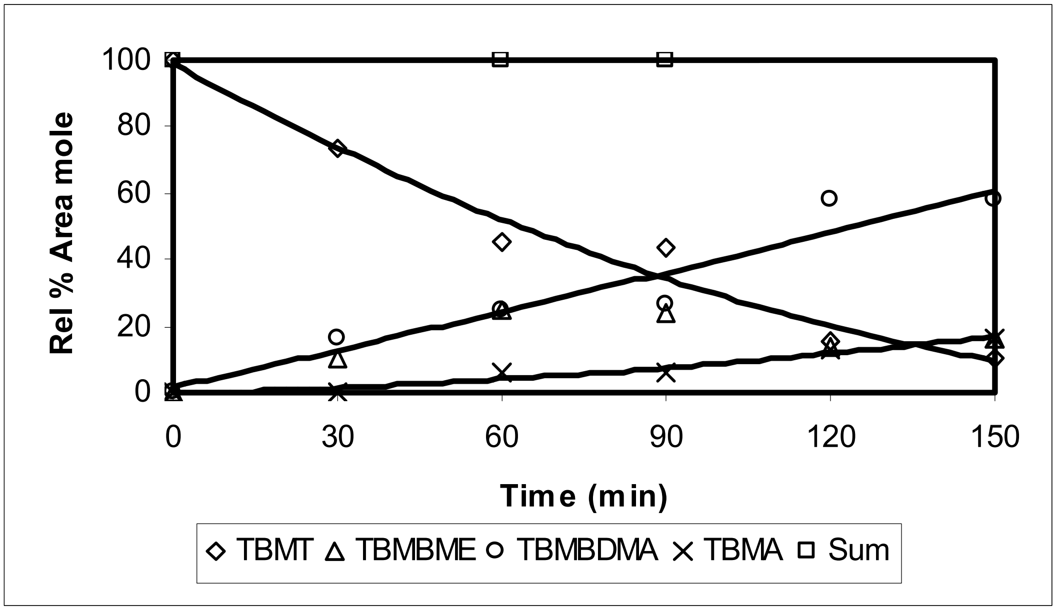


Figure 3.32 Shows the effect of potassium fluoride as the supporting electrolyte at 50 ^{o}C.

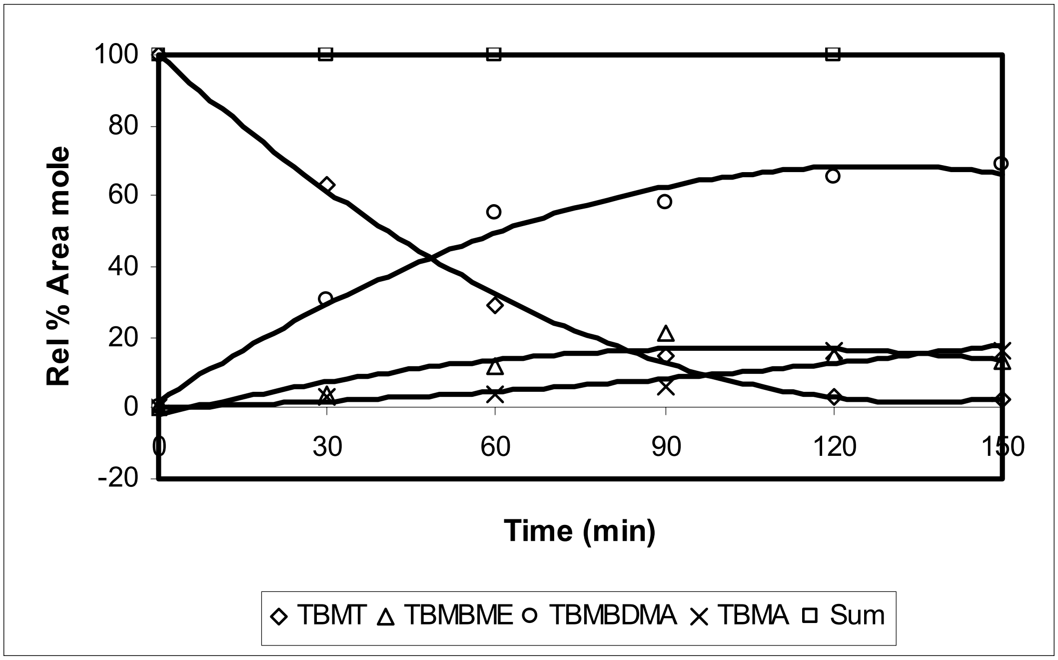


Figure 3.33 Shows the effect of potassium fluoride as the supporting electrolyte at 60 °C.

The following observations could be made:

a) At 30 °C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 13 % at 90 minutes (2 F) and then continues to drag out over the duration of the time. The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal reaches a maximum of 68 % at 120 minutes (3.3 F). The substrate 3-*tert*-butyl-4-methoxytoluene decrease rapidly to 90 min followed by a slow decrease to 5 % at 180 min (4 F). An amount of 11 % for the 3-*tert*-butyl-4-methoxybenzaldehyde was observed. The sum accountability stays at 100 %.

b) At 40 °C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 13 % at 60 minutes (1.5 F) and then stayed at 14 % till 180 minutes (4 F) passed. The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal reaches a 65 % at 90 minutes (2 F) and then continued to be formed with a maximum of 77% at 180 minutes.

The substrate 3-*tert*-butyl-4-methoxytoluene decreased gradually to 2 %. The sum accountability stays at 100 %.

c) At 50 °C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 23 % at 70 minutes (1.8 F). The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal reaches a maximum of 58 % at 120 minutes (4 F). The substrate 3-*tert*-butyl-4-methoxytoluene decreased to 10 %. An amount of 17 % for the 3-*tert*-butyl-4-methoxybenzaldehyde was observed. The sum accountability stays at 100 %.

d) At 60 °C the intermediate 3-*tert*-butyl-4-methoxy benzyl methyl ether reaches a maximum of 21 % at 90 minutes (2 F) and then decrease to 12 % at 180 minutes. The product 3-*tert*-butyl-4-methoxybenzaldehyde dimethyl acetal reaches a maximum of 65 % at 150 minutes. The substrate 3-*tert*-butyl-4-methoxytoluene decreased gradually to 2 %. An amount of 17 % for the 3-*tert*-butyl-4-methoxybenzaldehyde was observed. The sum accountability stays at 100 %.

3.3.6 Direct Electrolysis: Summary and concluding remarks

- Benzenesulfonic acid, sodium salt: At low temperatures the reaction is slow but results in a high yield of the desired acetal at 40 °C and 180 min. At high temperature, the reaction is faster and the intermediate ether reaches a maximum of 80%.
- Sulfuric acid: In this case we obtained better results at low temperatures compared to higher temperatures: At 30 °C the intermediate ether was 40 % at 90 min and the acetal was 90% at 180 min. At higher temperatures the acetal concentration reaches a maximum of only about 70%.

- Sodium perchlorate: The formation of the desired acetal seemed to be consistent in this case around the 80% mark, except at low temperature (30 °C) where the yield of acetal was about 90%.
- Potassium fluoride: In the presence of this electrolyte reactions were significantly faster, for example a 20% yield of the intermediate ether within 60 min and a yield of 60% of acetal was obtained at 40 °C within 90 min.

Chapter 4

SUMMARY AND CONCLUDING REMARKS

The following sections were described for the evaluation of the various potential routes to convert alkyl-substituted methoxytoluenes selectively into the corresponding alkyl-substituted methoxybenzaldehydes. The routes that were evaluated through bench scale synthesis studies were:

- The catalytic air oxidation of the methoxytoluene;
- The direct electrochemical oxidation of the methoxytoluene; and
- The indirect electrochemical oxidation of the methoxytoluene.

The purpose of these investigations was to be able to identify the most efficient and selective route to produce the desired benzaldehydes in high yield.

4.1 Catalytic Air Oxidation

The production of alkoxybenzaldehydes is currently based on two starting materials, namely cresol or phenol. The phenol-based routes have enjoyed most commercial success, and are currently the main route of hydroxybenzaldehyde production. Inherent to these reactions are the need for regioselective control, and most commercial processes are optimized in terms of the 2-hydroxybenzaldehyde isomer.

In the case of the catalytic air oxidation of methoxytoluenes, the phenolic group is protected by the ether group and traditional oxidation methods and catalysts may be considered for these oxidations, including the well known cobalt(II) acetate/bromide or cobalt(II) acetate/manganese(II) bromide catalyst system.

4.1.1 Nature of the substrate

We have studied the catalytic air oxidation of several alkylbenzenes and substituted alkylbenzenes to determine the effect of substitution on the alkylbenzene ring, and to evaluate the feasibility of obtaining high benzaldehyde selectivity at restricted substrate conversions. The reasoning behind this approach was as follows. To produce alkyl-substituted methoxybenzaldehydes in high yield by means of catalytic air oxidation, one of two routes can be followed, namely initial alkylation of the aromatic ring followed by oxidation, or initial oxidation to form the benzaldehyde (or a protected form thereof) followed by alkylation.

The nature and extent of substitution on the ring will affect both the rate (and extent) of oxidation, as well as the rate (and degree) of substitution during alkylation reactions. Of these, the selectivity achievable during the catalytic air oxidation step would be the limiting factor due to the ease of further oxidation of the desired aldehyde product. It was therefore necessary to establish not only whether the oxidation step should come before or after the alkylation step, but also the selectivity to the desired aldehyde that could be expected from these oxidation reactions. Results obtained clearly suggested that increased electron density on the aromatic ring improves the selectivity to the desired benzaldehyde. Thus, in terms of the present system, one may conclude that it would be desirable to first form the 3-*tert*-butyl-4-methoxytoluene before carrying out the air oxidation step.

4.1.2 Catalytic air oxidation: Reaction temperature

Being a free-radical reaction, catalytic air oxidation reactions can be expected to be influenced significantly by the reaction temperature at which oxidations are performed. In order to investigate the effect of reaction temperature on the oxidation of 4-methoxytoluene and the selectivity to 4-methoxybenzaldehyde, several oxidation reactions were performed at different reaction temperatures.

The results obtained showed that as the temperature increases, the selectivity to aldehyde decreases, especially as the substrate conversion increases.

4.1.3 Catalytic air oxidation: Effect of catalyst concentration

As discussed earlier, the active catalyst during the cobalt(II) acetate bromide catalyzed air oxidations of alkylbenzenes are thought to be a complex containing a direct Co(II) – bromide bond. It has, however, been shown that bromide is converted into an inactive form, in particular benzylic bromides. This process destroys the initially active Co(II)-Br catalyst species and which is not readily converted back into an active form. It has also been shown that aldehyde oxidation starts to dominate once the bulk of “inorganic” bromide has been converted into “organic” bromide, and therefore aldehyde selectivity will decrease as a result of the conversion of the active catalyst species into a non-bromide containing form.

The results obtained clearly showed an increase in 4-methoxybenzaldehyde selectivity as the catalyst concentration is increased from 0.01 M – 0.1 M during the Co-Br-catalysed air oxidation of 4-methoxytoluene. This effect is especially noticeable at lower conversion levels, but at higher conversion levels there is virtually no effect on the selectivity to 4-methoxybenzaldehyde once the cobalt concentration is raised above 0.02 M. The observed increase in selectivity is, however, probably not significant enough to warrant the large increase in catalyst concentration.

4.1.4 Catalytic air oxidation: Effect of water concentration

Water is continuously formed during the catalytic air oxidation of organic compounds and since the cobalt-bromide catalyst used during these oxidation reactions are susceptible to hydrolysis, it was important to investigate the effect of increasing water levels in the oxidation mixtures.

The results obtained show an interesting trend in that the selectivity to 4-methoxybenzaldehyde improves as the water concentration is increased from 0.2% to about 2.5%. Thereafter, the reaction selectivity decreases significantly.

4.1.5 Catalytic Air Oxidations: Concluding Remarks

High aldehyde selectivities of above 70 % could be achieved with the catalytic air oxidation on various substituted alkyl aromatics if the substrate contains electron donating groups on the aromatic ring, or when the substrate conversion is restricted to < 30 %, provided certain factors such as temperature, water content and other reaction variables could be carefully controlled.

4.2 Indirect Electrochemical Oxidations

4.2.1 Ceric Ammonium Reactions

It has been found that with the ceric ammonium nitrate oxidation reactions there are major factors that play a role on the rate of the product formation. Such factors are temperature, rate of stirring and time. Temperature was kept constant at 30 ^{o}C, stirring rate has to be fast enough to give good mass transfer between the mediator and the substrate. With these conditions an 85% conversion of the 3-*tert*-butyl-4-methoxtoluene, 85% yield and 95% selectivity for the 3-*tert*-butyl-4-methoxbenzaldehyde was obtained. Recycling of the cerium and re-using it to oxidized the substrate have shown no decrease in performance.

4.2.2 Methanesulfonic reactions and the effect of a co-solvent

Different concentrations of methanesulfonic acid were investigated i.e. 2M, 4M, 6M, 8M. The first two methanesulfonic acid concentrations did not have much effect on the substrate conversion, which is probably due to the low concentrations of Ce (IV) after electrolysis. At 8M concentration, the selectivity was low, probably due to over oxidation, which led to performing these oxidations at 6M concentration of methanesulfonic acid. Again there are several factors that played a role in these reactions, namely, solubility of the substrate, temperature and rate of stirring. When different organic solvents were used to improve mass transfer between the two reacting phases, reasonable results were achieved. Thus, acetonitrile performs best at 50 ^{o}C, dichloromethane at reflux, and acetone at 21 ^{o}C.

Oxidations carried out using the inorganic mediators ceric ammonium nitrate and cerium (IV) methane sulfonate has shown that these methods are capable of producing significantly improved results compared to catalytic air oxidations. In particular, cerium (IV) methane sulfonate is capable of giving the desired product in near quantitative selectivity at substrate conversions as high as 90%. The low solubility of the substrate in the aqueous methane sulfonic acid solutions, however, results in slow mass transfer in these oxidations. The use of polar solvents as co-solvents alleviates this problem only slightly, and in the case of acetonitrile, results in the further oxidation of the desired aldehyde through to the benzoic acid.

4.3 Direct Electrochemistry

In this method we used different supporting electrolytes i.e. benzene methane sulfonic acid sodium salt, sodium perchlorate, potassium flouride and sulfuric acid at different temperatures and different flow rates. The two electrodes used were graphite as the anode material and stainless steel as the cathode material,

- Benzenesulfonic acid, sodium salt: At low temperatures the reaction is slow but results in a high yield of the desired acetal at 40 ^{o}C and 180 min.

At high temperature, the reaction is faster and the intermediate ether reaches a maximum of 80%.

- Sulfuric acid: In this case we obtained better results at low temperatures compared to higher temperatures: At 30 °C the intermediate ether was ca 15 % at 90 min and the acetal was 80% at 180 min. At higher temperatures the acetal concentration reaches a maximum of only about 70%.
- Sodium perchlorate: The formation of the desired acetal seemed to be consistent in this case around the 80% mark, except at low temperature (30 °C) where the yield of acetal was about 90%.
- Potassium fluoride: In the presence of this electrolyte reactions were significantly faster, for example a 20% yield of the intermediate ether within 60 min and a yield of 60% of acetal was obtained at 40 °C within 90 min.

In conclusion, this work has clearly illustrated the potential advantages of electrochemical oxidations, either direct or indirect, for the production of high value fine chemicals over catalytic air oxidation routes.

REFERENCES:

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1. http://www.mbeni.co.za/indy/chem/ af/sa/p005.htm (2005)
2. http://www.dti.gov.za/downloads/ims.pdf (2002)
3. http://www.dti.gov.za/downloads/ims.pdf, pp.30 (2002).

4 W Basson, J Gordon Lennox, H Laing, D Walwyn, "*Chemical sector*", (2002).

5 K.E. Clonts, and R.A. McKetta, "*Hydroxybenzaldehydes*" in: *Kirk-Othmer, Encyclopedia of Chemical Technology*, Interscience, New York,3rd ed , Vol. **13**, pp. 70-79 (1978).

6 *Chemical and Engineering News*: (July 14, 2003)

7 IAL Consultants: 2000 Data; *C & EN* (July 2003)

8 IAL Consultants, *An Overview of the global flavour and fragrance market*: (2000)

9 D. Mcneil, "*Cresols*" in: *Kirk-Othmer, Encyclopedia of Chemical Technology*, Interscience, New York, 2nd Ed , Vol. 6, pp. 434-444 (1965).

10 "Cresols, xylenols and cresylic acid" in: Chemical Economics Handbook, SRI International, 637.5002 M (1994).

11 J.March, *Advanced Organic Chemistry. Reactions ,Mechanisms and Structure*, 4th ed., John Wiley & Sons, New York, pp.953 (1992)

12 K. Alive, R. A. Venkataraman, and P. Ratnasamy, *US Patent No. 5,811,599*, (1998).

13 D.P. Mellor, L. Maley, *Nature*, **159** (4037), pp.370-371 (1947).

14 Common Types of Food Adulteration, http://www.eurofins.com/ authetcity/common_foof_adulteration.asp.

15 TGSC Perfumery Raw Materials, 3-Ethoxy-4-hydroxybenzaldehyde, and 3-hydroxybenzaldehyde, htpp:// www.execpc.com,/~goofscnt/data/rw1002653.html,rw1011714.html

16 G.A. Burdock, *Encyclopedia of Food and Color Additives*, **3**, CRC Press, New York, pp 2485-2486, 371-376, and Tocopherols, pp.2800. (1997)

---

17 R.W. Thies, Synthesis of a Merocyanin Dye, http://www.ucs.orst.edu/~thiesr/rwtchem97.htm(1997)

18 Synthesis of a Merocyanin Dye, http://www.whitworth.edu/casses/Chem/ch278L/merocyan.htm

19 J.March, *Advanced Organic Chemistry. Reactions, Mechanisms and Structure*, 4th ed., John Wiley & Sons, New York, pp.1233 (1992)

20 R.D.G. Cooper, *US Patent No. 3,946,003* (1976).

21 M. Sittig, *Chemical Technology Review No. 124: Pharmaceutical Manufacturing Encyclopedia,* Noyes Data Corporation, New Jersey, pp.626 (1997)

22 "Timethobenzamide", in: Drug Information for the Health Care Professional, 12th ed., Arcata Graphics/Kingsport, Kingsport, 2705 (1992).

23 M. Sittig, *Chemical Technology Review No. 124: Pharmaceutical Manufacturing Encyclopedia,* Noyes Data Corporation, New Jersey, 40 (1997)

24 F.Bruhne, and W. Wright "*Benzaldehyde"*, in: Ullmann's Encyclopedia of Industrial chemistry, 5th Ed. W. Gerhards, (Eds.), VCH Verlagsgesellshaft, Vol. A3, pp. 463-474., (1985)

25 K. Homada, G. Shuzukamo, *European Patent No. 0,068,725*, (1986)

26 See Ref. pp. 25

27 B. M. Schoonees, "*The production of Hyrdroxy-substituted aromativa aldehydes and ketones by catalytic, liquid-phase oxidation*" D-Tech.: Chemistry Dissertation, P.E. Technikon (2000)

28 J .March, *Advanced Organic Chemistry. Reactions, Mechanisms and Structure*, 4th ed., John Wiley & Sons, New York, pp. 540-543 (1992)

K.E. Clonts, and R.A. McKetta, "Cresols and cresylic acids" in: Kirk-Othmer, Encyclopedia of Chemical Technology, Interscience, New York, 3rd ed , Vol. **3**, pp. 212-227 (1978).

30 Y. Christidis, and J. Valleros, *US Patent No. 4,481374* (1984)

31 H. Lefranc, *US Patent No. 5,811,559* (1998); H. LeFranc, *US Patent No. 5,689,009* (1997).

---

32 J.Le Ludec*, US Patent No. 4,026,950* (1977); K. Bauer, R. Molleken, H. Fiege, and K. Wedemeyer*, US Patent No. 4,119,671* (1978)

33 R. G. Kalikar, R.S. Deshpande, and S.B. Chandalia, *J. Chem. Tech. Biotechnology*, Vol. 36, pp. 38-46 (1986).

34 A. Gomis, V. Garcia-Garcia, J. Gonzalez-Garcia, V. Montiel, and A. Aldaz, *J. Appl. Electrochemistry*, Vol **29**, pp. 265-270 (1999)

35 J.March, *Advanced Organic Chemistry. Reactions, Mechanisms and Structure,* 4th ed., John Wiley & Sons, New York, pp. 689-694 (1992)

36 K.Nishizawa, K.Hamada, and T.Aratani*, European No. 0,012,939* (1979)

37 M. P. J. Peeters, M. Busio, and P. Leijten, *Appl. Catalysis A: General*, Vol. 118, pp. 51-62, (1994)

38 K.Nishizawa, K.Hamada, and T.Aratani, *European No. 4,429,163* (1984)

39 K.Nishizawa, K.Hamada, and T.Aratani, *European No. 0,012,939* (1979)

40 BM Schoonees and B Zeelie, *"Liquid-phase partial air oxidation of p-Cresol"*, 34th Convention of the South African Chemical Institute, Durban, 7 - 10 July 1998.

41 M. Barl, D. Degner, H. Siegel, and W. Hoffmann, *German Patent No. DE 2,935,398*, Vol **A1** (1979).

42 Yu. N. Ogibin,* A. I. Ilovaisky, V.M. Merkulova, *Russian Chemical Bulletin*, 44, **3**, pp. 507-510, (1995).

43 Kreh; Robert P.; Spotnitz; Robert M.; *US Patent, No. 4,639,298*, (1987)

44 Kreh; Robert P; Spotnitz; Robert M.*; US Patent, No. 4,670,108*, (1987)

45 J. Been. C.W. Oloman *J. Appl. Electrochemistry*, 23, pp. 1301-1309, (1993).

46 R. M. Spotnitz, R. P. Kreh, *J. Appl Electrochmistry*, 20pp.209-215, (1990).

47 G. Kreysa, H. Medin, *J. Appl. Electrochemistry*, 16, pp. 757-767(1986).

48 D.A. Skoog, D.M. West, and F.J. Holler, Fundamentals of Analytical Chemistry, Saunders College Publishing, 5th Ed. New York, 811, (1988).

49 Tse-Lok HO, Ceric Ion Oxidation in Organic Chemistry, Dept. of Chemistry, University of Manitoba, Winnipeg, Manitoba, Canada, pp. 347-354. (1972).

---

50 Sigeru Torri, *Hideo Tanaka, Tsutomu Inokuchi, *J. Org. Chem*., **47**, pp. 1647-1652, (1982).

51 J.W. Loveland, and G R Dimeler, *Analytical Chemistry*, pp.1196. (1961).

52 E.S. Pysh, and N C Yang, *J Amer. Chem. Soc*., 85pp. 2124, (1963).

53 M. Barl, D. Degner, H. Siegel, and W. Hoffmann, *German Patent No. DE 2,935,398,* Vol A1 (1979).

54 R.G. Kalikar, R.S. Deshpande, and S.B. Chandalia, J. Chem. Tech. Biotechnology, 36, pp. 38 - 46 (1986).

55 T. Yoshikuni, J. Molecular Catalysis, 72, 29 - 36 (1992)

56 M.P.J. Peeters, M. Busio, and P. Leijten, Appl. Catalysis A: General*,* 118, pp.51 - 62 (1994)

57 A, Vidyasagar, K.J. Nalawala, A.K. Varshney, C.S. Murthy, and M.H. Metha, *Indian J. Chem. Technol*., 3(5), pp. 295 - 297 (1996).

58 M. Constantini, D. Laucher, and E. Fache, US Patent No. 5,354,919c (1994).

59 S.N. Sharma, and S.B. Chandalia, *J. Chem. Tech. Biotechnol*., **49**, pp.141 – 153 (1990).

60 E. Fache, D. Laucher, M. Constantini, M. Beclere, and F. Perrin-Janet, in: *Industrial Chemistry Library*, Vol. **8**: "*The roots of organic development*", J. Desmurs, and S. Ratton (Eds.), Elsevier, Amsterdam, pp. 380 – 390 (1996).

61 T.R. Diephouse, and R.M. Strom, *US Patent No. 4,915,875* (1990).

62 P Raghavendrachar, and S Ramachandran, *Ind. Eng. Chem. Res.*, **31**, 453 (1992).

63 J. Imamura, M. Takehara, K. Chigasaki, and K. Kizawa. , *German Paternt DE 2,605,678*, (1975)

64 T. I.A. Gerber, A. Wiechers, A. T. Noah, and B Zeelie, S.A. J. Chem, 51, 178, (1998)

65 G.J. Powels, *The catalytic air oxidation* of chloro-substituted toluenes, M Dip. Tech Dissertation, P.E. Technikon (1994)

66 B. Zeelie, *Aspects of the Partial Oxidation of Alkyl-Aromatics: Catalysis by*

Cobalt and Bromide, Ph.D. University of Port Elizabeth, South Africa, (1996).

67 L.H. Sutcliffe, and J.R. Weber, *J. Inorg. amd Nucl. Chem*., 2, 281, (1960).

68 Sigeru Torii, Indirect Electrochemistry Reactions, in Hans J. Schafer, Organic Electrochemistry, Wiley-VCH, Weinheim, Vol **8**, pp 489 – 591(2004).

69 Derek Pletcher, and Frank C. Walsh, *Industrial Electrochemistry,* 2nd Ed., Chapman and Hall, New York, pp326 - 330(1990).

70 Keith Scott, *Electrochemical processes for clean technology*, The Royal Soceity of Chemistry, Newcastle , UK, 235, (1995).

71 Sigeru Tofii, *Hideo J. Org. 1982, 47, pp. 1647-1652

72 Tse-Lok HO; *Ceric Ion Oxidation*; pp. 347-354

73 T. Shono, "*Electrochemistry*" in *Ullmann's Encyclopedia of industrial Chemistry*, 5th Ed. W. Gerhards, (Eds.), VCH Verlagsgesellshaft, Vol A9, pp. 235, (1995).

74 Albert J. Fry, *Synthetic organic electrochemistry*, 2nd Ed. John WIiley & Sons, pp. 68-78, (1989).

75 J.Utley, *Chemistry & Industry*, 215, (1994).

76 M.M. Baizer, "*Paired Electrosynthesis*" in: *Organic Electrochemistry*, 3rd Ed. H. Lund and M.M. Baizer, (Eds.), Marcel Dekker, pp. 1421-1422 (1990).

77 L Eberson, and K Nyberg, *Tetrahedron*, 32, pp.2185, (1976).

78 Kreh; Robert P; Spotnitz; Robert M., *US Patent 4,639,298*, pp. 1-13, (1986).

79 D. Plecther and F.C. Walsh, Industrial Electrochemistry,2nd Ed., John Wiley & Sons, London, 324, (1990)

80 T. Shono, *Tetrahedron*, 40, pp.197, (1985)

81 S. Torii, *Electroorganic Synthesis, Part I, Oxidations*, VCH, Weinheim, (1985)

82 K Sasaki, H Urata, K Uneyama and S Nagaura*, Electrochim, Acta*, 12, 137, (1967)

---

83 P. Loyson, S. Gouws, and B. Zeelie, *S. Afr. J. Chem*, 51, pp.66, (1998).

84 A J Fry, Synthetic Organic Electrchemistry, 2nd Ed., John Wiley & Sons, New York, p105, (1991).

85 T. Shono, *Electroorganic Synthesis*, Academic Press, New York, p6 , (1994).